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Par
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Renforcement de la barrière épithéliale intestinale dans les maladies inflammatoires chroniques de l'intestin : une approche combinant nutrition lipidique et utilisation de bactéries propioniques probiotiques.

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Confucius

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- (Revue) **Mantel M**, Derkinderen P, Bach-Ngohou K, Neunlist M, Rolli-Derkindren M. Crosstalk between omega-6 oxylipins and the enteric nervous system: Implications for gut disorders? Front Med. doi: 10.3389/fmed.2023.1083351. 2023 March 28.

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- «Inhibitor function of bacterial EVs in the epithelial breakdown induced by inflammation: could it be use to treat IBD?» GO-EV. Octobre 2023, Nantes, France.
- «Combined effects of propionic acid bacteria and n-6 polyunsaturated fatty acids on the intestinal barrier» NutrEvent. Octobre 2023, Rennes, France.
- «Comment les bactéries propioniques laitières renforcent la BEI et préviennent de la colite.» GFNG. Juin 2023, Clermont-Ferrand, France.
- «Comment les bactéries propioniques laitières renforcent la BEI et préviennent de la colite.» CECED. Mars 2023, Strasbourg, France.

- «How could dairy propionic bacteria serve to strengthen the IEB and reduce colitis.» 7th IDF Symposium on Science and Technology of Fermented Milk. Novembre 2022, en ligne.
- «Role of bioactive lipids in the development of IBD» IBD Next Cluster Day. Septembre 2022, Nantes, France.
- « How could dairy propionic bacteria serve to strengthen the IEB and reduce colitis." Little Brain Big Brain (LBBB). Septembre 2022, Heiligkreuztal, Allemagne.
- « Effets protecteurs combinés des bactéries propioniques laitières et des dérivés AGPI n-6 sur la barrière épithéliale intestinale.» GFNG. Juin 2022, Grenoble, France.
- « Effets protecteurs combinés des bactéries propioniques laitières et des dérivés AGPI n-6 sur la barrière épithéliale intestinale.» CECED. Mars 2022, Lyon, France.
- « L'intestin : une zone de libre échange ? » Nuit Blanche des Chercheurs. Janvier 2022, Nantes, France.
- « Effets protecteurs combinés des bactéries propioniques laitières et des dérivés AGPI n-6 sur la barrière épithéliale intestinale.» Galactinov. Novembre 2021, en ligne.
- « Effets protecteurs combinés des bactéries propioniques laitières et des dérivés AGPI n-6 sur la barrière épithéliale intestinale.» BBA Milk Valley meeting. Octobre 2021, Rennes, France.

COMMUNICATIONS (POSTERS) :

- « Dairy propionic bacteria reduces colitis and promotes recovery through epithelial apoptosis inhibition and pro-resolving lipid production» NeuroGASTRO ESNM. Août 2023, Bucharest, Roumanie.
- « How could dairy propionic bacteria serve to strengthen the IEB and reduce colitis.» JFHOD. Mars 2023, Paris, France.
- « How could dairy propionic bacteria serve to strengthen the IEB and reduce colitis.» Société Française Microbiologie (SFM). Novembre 2022, Montpellier, France.
- « Combined protective effects of dairy propionic bacteria and n-6 polyunsaturated fatty acids on the intestinal epithelial barrier » Mibiogate meeting. Mars 2022, Nantes, France.

PRIX OBTENU :

- 1er prix de la meilleure communication orale lors du CECED en mars 2023 à Strasbourg.
- Prix des meilleurs posters lors des JFHOD en mars 2023 à Paris.
- 2nd prix du meilleur poster lors du congrès Mibiogate en mars 2022 à Nantes.

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LISTE DES ABREVIATIONS

- **5-ASA:** 5-aminosalicylate
- **6-kPGF1α :** 6-keto prostanglandine F1 alpha
- **11ßPGF2α** : 11beta-prostglandine F2 alpha
- **15-HETE** : 15-hydroxyeicosatetraenoic acid
- **15-HETrE** : 15-hydroxyeicosatrienoic acid
- **AA** : acide arachidonique
- **Ach** : acétylcholine
- **ACNQ** :2-amino-3-carboxy-1,4 napthoquinone
- **ADN** : acide désoxyribonucléique
- **AGCC** : acide gras à chaîne courte
- **AGCL** : acide gras à chaîne longue
- **AGPI** : acide gras poly-insaturés
- **AhR** : récepteur des hydrocarbures aromatiques
- **AIEC** : adhérent-invasive *Escherichia coli*
- **ALC** : acide linoléique conjugué
- **Alox** : arachidonate lipooxygenase
- **AOM** : azoxy methane
- **APS** : ammonium persulfate
- **ASCA** : anticorps anti-*Saccharomyces cerevisiae*
- **ATG16L1:** autophagy related 16 like 1
- **BA:** acide biliaire
- **BEI** : barrière épithéliale intestinale
- **BHE** : barrière hématoencéphalique
- **BIA** : bactéries d'intérêt alimentaire
- **BMP2** : protéine morphogénétique osseuse 2
- **BSH** : hydrolase des sels biliaires
- **CA** : acide cholique
- **CARD15** : caspase recruitment domain-containing protein 15
- **CC3** : caspase 3 clivée
- **CDAI** : Crohn's disease activity index
- **CDCA**: acide chénodésoxycholique
- **CEE** : cellules entéro-endocrines
- **CEI** : cellules épithéliales intestinales
- **CFU** : colonie formant unité
- **CGE** : cellules gliales entériques
- **CIRM** : centre international de ressources microbiennes
- **Cl-Gua** : chlorure de guanidium
- **CMV** : cytoplasmic membrane vesicle
- **COX** : cyclooxygénase
- **CPA** : cellule présentatrice d'antigène
- **CRC** : cancer colo-rectal
- **CRP** : protéine C réactive
- **CSI** : cellules souches intestinales
- **CYP450** : cytochrome p450
- **DC-SIGN** : dendritic cell-specific ICAM-grabbing non integrin
- **DC**: cellules dendritiques
- **DCA**: acide désoxycholique
- **DGLA** : acide dihomo-gamma-linoléique
- **DHNA** : 1,4-dihydroxy-2-acide naphtoïque
- **LfaT** : dihydrolipoamide acétyltransférase
- **DMEM** : Dulbecco's Modified Eagle Medium
- **DSS :** dextran sulfate de sodium
- **DTT** : dithiothréitol
- **ECEH** : *Escherichia coli* entérohémorragique
- **EDTA** : éthylènediaminetétraacétique
- **ELISA** : enzyme-linked immunosorbent assay
- **EPA** : acide eicosapentaénoïque
- **EPS** : exopolysaccharides
- **FADS1** : fatty acid desaturase 1
- **FAE** : épithélium associé aux follicules
- **FAK** : focal adhesion kinase
- **FFMD** : fast food mimicking diet
- **FMT** : transplantation fécale de microbiote
- **GALT** : tissu lymphoïde associé à l'intestin
- **GCA** : acide glycocholique
- **GC-MS** : chromatographie en phase gazeuse et spectrométrie de masse
- **GDCA** : acide glycodéoxycholique
- **GF** : germ free
- **GI** : gastro-intestinal`
- **GIP** : glucose-dependant insulinotropic peptide

- **GLA** : acide gamma-linoléique
- **GLP-1** : glucose like peptide-1
- **GP2** : glycoprotéine-2
- **GOS** : galactooligosaccharide
- **GRAS** : generally recognized as safe
- **GSDMB** : gasdermine B
- **GSR** : glutathione S reductase
- **GWAS** : genome-wide association study
- **HBD1**: human ß defensin 1
- **HDAC**: histone désacétylase
- **HFD**: high fat diet
- **HIF**: hypoxia inductible factor
- **HRP** : horseradish peroxidase
- **HYA** : 10-hydroxy-cis-12-octadecenoic acid
- **kDa *:*** kiloDalton
- **IgA :** immunoglobuline A
- **IL-10** : interleukine-10
- **IL-12** : interleukine-12
- **IL-17** : interleukine-17
- **IL-23R** : récepteurs à l'interleukine 23
- **ILC** : cellules innées lymphoïdes
- **ILF** : follicule lymphoïde isolé
- **IPAN** : neurones afférents primaires
- **IRM** : imagerie par résonnance magnétique
- **LA** : acide linoléique
- **LAB** : lactic acid bacteria
- **LCA** : acide litocholique
- **LFD** : low-fat diet
- **Lgr5** : récepteurs couplés à une protéine G contenant de répétitions riches en leucine
- **LOX** : lipoxygénase
- **LPS** : lipopolysaccharides
- **LspA** : large surface protein A
- **LTA** : acide lipoteichoïque
- **LxA4** : lipoxine A4
- **JAM** : molécules d'adhésion jonctionnelle
- **MAMP** : microbe associated molecular pattern
- **MC** : maladie de Crohn
- **MDP** : muramyl dipeptide
- **MEC** : matrice extracellulaire
- **MI** : microbiote intestinal
- **MICI** : maladie inflammatoire chronique de l'intestin
- **MLC** : chaîne légère de myosine
- **MLCK** : kinase des chaînes légères de myosine
- **MLNC** : mesenteric lymphe node cell
- **MMP** : métallo-protéase matricielle
- **MO** : microorganismes
- **MOI** : multiplicity of infection
- **MPO** : myélopéroxydase
- **MS/MS** : spectrométrie de masse en tandem
- **MTX** : méthotrexate
- **MUC2** : mucine 2
- **NAFLD** : non alcoholic fatty liver disease
- **NASH** : stéato-hépatite non alcoolique
- **NEC** : entérocolite nécrosante
- **NET** : neutrophile extracellular trap
- **NFkB**: nuclear factor-kappa B
- **NGS** : nouvelles méthodes métagénomiques
- **NK**: cellule natural-killer
- **NOD2** : nucleotide-binding oligomerization domain 2
- **NOS**: nitric oxide synthase
- **NT**: neurotransmetteur
- **OMV**: outer membrane vesicle
- **PAB**: propionic acid bacteria
- **PAM** : peptides antimicrobiens
- **p-ANCA** : anticorps périnucléaires anti-cytoplasme des polynucléaires neutrophiles
- **PBMC** : cellules mononuclées du sang périphérique
- **PBS** : tampon phosphate salin
- **PF** : Propionibacterium freudenreichii
- **PGD2** : prostaglandine D2
- **PGE2** : prostaglandine E2
- **PGI2** : prostacycline I2
- **pH** : potentiel hydrogène
- **PI3K** : phosphoinositide 3-kinase
- **PLA2** : phospholipase A2
- **Pmt1** : O-mannosyltransférase
- **PP** : plaque de Peyer
- **PRR** : Pattern Recognition Receptor
- **PS** : pénicilline/streptomycine
- **PTGIS** : prostacycline synthase
- **PTT** : purpura thrombotique thrombocy
- **PUF** : perméat d'ultra-filtrat de lait
- **PUF** : perméat de lait ultra-filtré
- **QPS** : qualified presumption of safety
- **RA** : acide ruménique
- **RCH** : rectocolite hémorragique
- **RCT** : randomize clinical trial

- **RE** : réticulum endoplasmique
- **RI** : réponse immunitaire
- **ROCK** : kinase associée à Rho
- **ROS** : espèces réactives de l'oxygène
- **SBA** : acide biliaire secondaire
- **SDS** : sodium dodécyl sulfate
- **SEM** : standard error of mean
- **SHU** : syndrome hémolytique et urémique
- **SI** : système immunitaire
- **SILT** : tissu lymphoïde secondaire isolé
- **SIgA** : IgA sécrétante
- **SLH** : domaines d'homologie de la couche superficielle
- **SLP** : surface layer protein
- **SNA** : système nerveux autonome
- **SNC** : système nerveux central
- **SNE** : système nerveux entérique
- **SPE** : extraction en phase solide
- **STD** : régime standard
- **SVF** : sérum de veau fétal
- **TA** : transit-amplifying
- **TAMP** : tight-junction associated MARVEL protein
- **TCA**: acide taurocholique
- **TCDA**: acide taurochénodésoxycholique
- **TDM** : tomodensitométrie
- **TEER** : résistance électrique trans-épithéliale
- **TEMED** : tétraméthyléthylènediamine
- **TFA** : acide trifluoroacétique
- **Th** : T helper
- **Th0** : lymphocyte T naïfs
- **TJ** : tight junction
- **TLR** : toll-like receptor
- **TNBS** : l'acide trinitrobenzène sulfonique
- **TNF** : tumor necrosis factor
- **TNFR** : récepteur au tumor necrosis factor
- **Treg** : cellules T régulatrices
- **Tris-HCl** : tris-hydrochloride
- **TSA** : troubles du spectre autistique
- **UCEIS**: Ulcerative Colitis Endoscopic Index of Severity
- **UDCA**: acide ursodésoxycholique
- **UHT** : ultra haute température
- **UV** : ultraviolets
- **VE** : vésicule extracellulaire
- **WD** : western diet
- **WFDC2** : WAP four-disulfate core domain protein 2
- **ZO** : zonula occludens

PREAMBULE

Le **tube digestif** joue un rôle fondamental pour notre organisme, assurant des fonctions vitales telles que la digestion, l'absorption des nutriments et la défense de l'hôte vis-à-vis des agressions mécaniques, chimiques et pathogènes extérieures. Ainsi, dans de nombreuses pathologies, qu'elles soient digestives, telles que les **maladies inflammatoires chroniques de l'intestin** (MICI) et le syndrome de l'intestin irritable, ou extra-digestives, comme la maladie de Parkinson, les fonctions du tube digestif sont perturbées.

Les MICI, qui comprennent principalement la **maladie de Crohn** (MC) et la **rectocolite hémorragique** (RCH), sont des pathologies digestives caractérisées par une **inflammation chronique** de la paroi de l'intestin. Elles touchent plus particulièrement les sujets jeunes, évoluent par poussées inflammatoires symptomatiques entrecoupées de périodes de rémission. Elles sont très invalidantes et altèrent grandement la qualité de vie des patients. Ces pathologies sont en constante augmentation et leur origine est complexe, impliquant à la fois des facteurs génétiques et environnementaux. En plus d'une dérégulation du système immunitaire, les patients atteints de MICI présentent une altération du **microbiote intestinal**, ou **dysbiose**, accompagnée d'une **augmentation** de la **perméabilité** et des **défauts** de **réparation** de la **barrière épithéliale intestinale** (BEI). Chacune de ces altérations joue un rôle crucial dans le développement de la maladie, mais les traitements actuels se concentrent principalement sur l'inflammation et le système immunitaire. De **nouvelles stratégies thérapeutiques** doivent être envisagées pour cibler et rétablir les fonctions des autres acteurs négligés de ces pathologies : la BEI et le microbiote intestinal. En ce sens, la question de l'utilisation d'une alimentation spécifique et/ou de bactéries probiotiques est à adresser. En effet, des **bactéries propioniques laitières**, telles que ***Propionibacterium freudenreichii*** ont des propriétés **probiotiques** qui incluent une diminution de l'inflammation et une modification du microbiote intestinal. Néanmoins, à ce jour, les **effets spécifiques** de *P. freudenreichii* sur la **BEI** demeurent largement méconnus. Concernant l'alimentation, alors qu'un ratio élevé d'acides gras polyinsaturés n-6/n-3 est associé à l'inflammation, ses effets propres sur le tube digestif, et sur la BEI en particulier, restent à préciser. Cela est d'autant plus important que *P. freudenreichii* étant une bactérie utilisée dans l'industrie fromagère, elle est intégrée avec des matrices riches en lipides.

Ainsi, le but de ce travail est d'étudier les propriétés de souches spécifiques de ***Propionibacterium freudenreichii,*** à **renforcer la BEI** soumise à un stress inflammatoire, et ainsi à déterminer si, associées ou non à certains lipides, elles pourraient être utilisées pour prévenir ou traiter la colite. Ce travail cherche à enrichir l'arsenal thérapeutique disponible dans le cadre des **MICI**, mais également plus largement pour toute autre pathologie associée à un défaut de BEI.

1. DEFINITION GENERALE DES MICI

1.1. SEMIOLOGIE ET DIAGNOSTIC

1.1.1 SEMIOLOGIE

Les MICI, qui regroupent la **maladie de Crohn**, la **rectocolite hémorragique** ainsi que des **colites indéterminées**, sont des pathologies digestives caractérisées par une **inflammation chronique** du tractus gastro-intestinal (GI). Ces maladies évoluent par **poussées inflammatoires** de durée et de fréquence de survenue variable, alternées par des périodes de **rémission**.

Bien que les MICI partagent des caractéristiques communes, la MC et la RCH sont tout de même bien différentes. En effet, la **MC** se traduit par une **inflammation transmurale**, c'est-à-dire potentiellement étendue à toute l'épaisseur de la paroi intestinale, et qui peut affecter tout le tractus GI de la **bouche à l'anus** de façon **discontinue** (Figure 1). La forme **iléo-colite** étant la plus fréquente, à savoir 50 % des patients Crohn (Gajendran et al. 2018). A l'inverse, la **RCH** est restreinte au niveau du **côlon** et du **rectum** avec des lésions plus **superficielles** qui touchent la muqueuse (Figure 1). Elle se développe de manière rétrograde et continue en partant du rectum pour s'étendre jusqu'à l'ensemble du côlon (Gajendran et al. 2019).

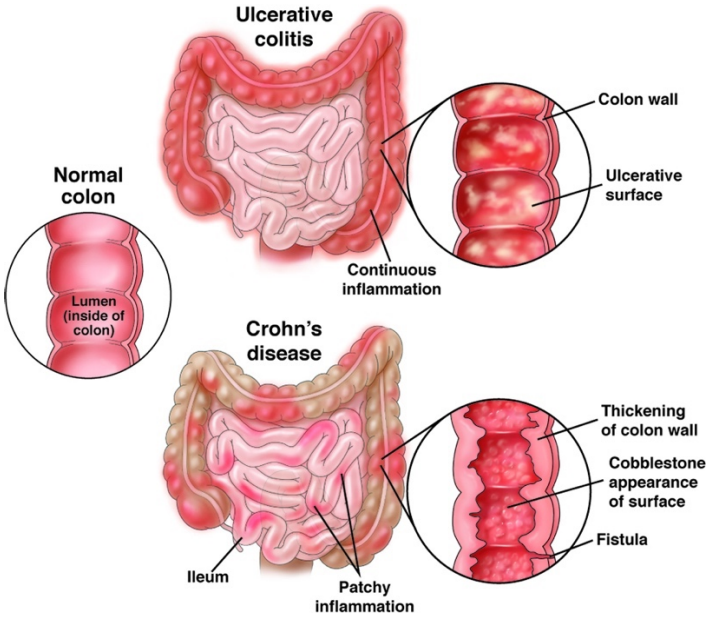

Figure 1. Localisation des atteintes dans la MC et la RCH (https://patient.gastro.org/inflammatory-bowel-disease-ibd/). La RCH est caractérisée par une inflammation superficielle, continue et rétrograde du rectum et du côlon, alors que la MC se caractérise par inflammation transmurale et discontinue de la bouche à l'anus avec un épaississement de la paroi, la présence de fistules et une apparence de surface en pavés.

Les MICI affectent considérablement la **qualité de vie** des patients, qui souffrent fréquemment de diarrhées parfois sanglantes, mais aussi de douleurs abdominales, nausées, vomissements, voire d'atteintes de la région anale (fissures, abcès). Ces **symptômes digestifs** s'accompagnent souvent de **symptômes systémiques** tels qu'une fatigue extrême, une perte de poids due notamment à une malabsorption des nutriments, de fièvre, d'anémie et parfois de **manifestations extra-intestinales** comme des atteintes musculo-squelettiques, cutanées, oculaires et hépato-biliaires (Rogler et al. 2021; Nocerino et al. 2020). De plus, les patients atteints de MICI présentent une prédisposition plus élevée à la dépression et l'anxiété par rapport à la population générale (Graff, Walker, et Bernstein 2009). Enfin, il est important de noter que les personnes touchées par ces pathologies sont généralement jeunes (15-35 ans pour la MC et 20-30 ans pour la RCH) et encourent un risque plus élevé de développer des **cancers colorectaux** (CRC) ou des **lymphomes** (Jess et al. 2005; Gajendran et al. 2019).

1.1.2 DIAGNOSTIC

L'endoscopie combinée avec des prélèvements de **biopsies** figure parmi les techniques les plus fréquemment utilisées dans le diagnostic et l'évaluation de score de sévérité des MICI (Gajendran et al. 2018). En complément de l'endoscopie, des **techniques d'imagerie** peuvent être utilisées, à savoir, l'imagerie par résonance magnétique (IRM), la tomodensitométrie (TDM), les ultrasons, l'endoscopie par capsule vidéo. Ces techniques permettent de confirmer la localisation de la pathologie ainsi que les complications intestinales. De plus, des **examens sérologiques** peuvent être effectués pour doser certains **biomarqueurs** permettant de suivre l'évolution de la pathologie de façon non invasive. C'est le cas de la protéine C réactive (CRP), qui est le marqueur de l'inflammation le plus sensible, mais aussi de la vitesse de sédimentation globulaire qui est un indicateur non spécifique de l'inflammation. De plus, les vitamines B12, D, ainsi que le fer peuvent être dosés, en raison de leur déficience chez les patients atteints de MICI (Gajendran et al. 2018). Enfin, d'autres marqueurs sanguins tels que les anticorps périnucléaires anti-cytoplasme des polynucléaires neutrophiles (p-ANCA) et les anticorps anti-*Saccharomyces cerevisiae* (ASCA) renseignent sur la nature de la MICI et permettent de discriminer les deux pathologies. En effet, un profil élevé en ASCA est associé à la MC alors qu'un profil élevé en ANCA est relié à la RCH. D'autre part, un autre moyen de détecter l'inflammation intestinale peut s'effectuer *via* la détermination de **marqueurs fécaux** dérivés des neutrophiles tels que la calprotectine et la lactoferrine, qui sont corrélées à l'activité endoscopique (Gajendran et al. 2018).

L'ensemble de ces mesures est utilisé pour définir un **score pathologique** permettant de suivre et d'évaluer la sévérité de la MICI. Des **scores endoscopiques** sont déterminés pour la MC et la RCH. Les critères de Rutgeert constituent le score de référence pour la récurrence endoscopique de la MC, et « l'Ulcerative Colitis Endoscopic Index of Severity » (UCEIS) celui de la RCH (Spiceland et Lodhia 2018; Pabla et Schwartz 2020; Hindryckx et al. 2015). De plus, le « Crohn's Disease Activity Index » (CDAI) pour la MC et le score de Mayo pour la RCH permettent de suivre et déterminer la réponse au traitement et la rémission du patient (Hindryckx et al. 2015). Enfin, d'autres scores sous forme de questionnaire prennent en considération la qualité de vie du patient (Gajendran et al. 2018).

1.2 Épidemiologie

Le nombre de patients atteints par ces pathologies est en constante augmentation ces dernières années, avec une prévalence élevée dans les pays industrialisés. En effet, les MICI touchent 3,7 millions d'individus aux Etats-Unis et en Europe (Ananthakrishnan 2015), c'est 0,2% de la population européenne en 2020 (Zhao et al. 2021). Globalement, la RCH est plus répandue que la MC (Feuerstein, Moss, et Farraye 2019).

Le pic d'incidence se situe entre 20 et 30 ans pour la RCH, avec un deuxième pic entre 50 et 80 ans (Gajendran et al. 2018). Concernant la MC, le pic d'incidence est entre l'âge de 15 et 35 ans (Saeid Seyedian et al. 2019). **L'âge** de survenue de la pathologie varie en fonction du **genre**, par exemple le risque de MC est inférieur chez les femmes durant l'enfance mais supérieur après l'adolescence (Zhao et al. 2021). Par ailleurs, le genre a un effet sur la localisation de la pathologie, sur les complications périanales dans la MC et l'extension de la pathologie dans la RCH (Khrom et al. 2023). Le genre influe également sur les facteurs psychosociaux, avec une qualité de vie rapportée plus faible chez les femmes par rapport aux hommes (Burisch et al. 2013).

Outre l'âge et le sexe, la **localisation géographique** influe également l'incidence et la prévalence des MICI (**Figure 2**). En effet, il existe un gradient Nord-Sud et Ouest-Est avec une prévalence plus élevée au Nord et à l'Ouest (Zhao et al. 2021). Toutefois, les pays d'Asie et d'Europe de l'est rencontrent une émergence rapide de la pathologie (Mak et al. 2020). L'incidence des MICI continue majoritairement d'augmenter dans le monde, cependant aux Etats-Unis et en Europe de l'Ouest leur incidence commence à se stabiliser au cours de ces dernières années (Kaplan 2015). De plus, l'incidence augmente plus rapidement dans les populations urbaines comparées aux populations rurales. **L'ethnicité** impacte également ce paramètre. En effet, l'incidence est plus élevée dans les populations blanches comparées aux populations afro-américaines et hispaniques aux Etats-Unis (Lewis et al. 2023).

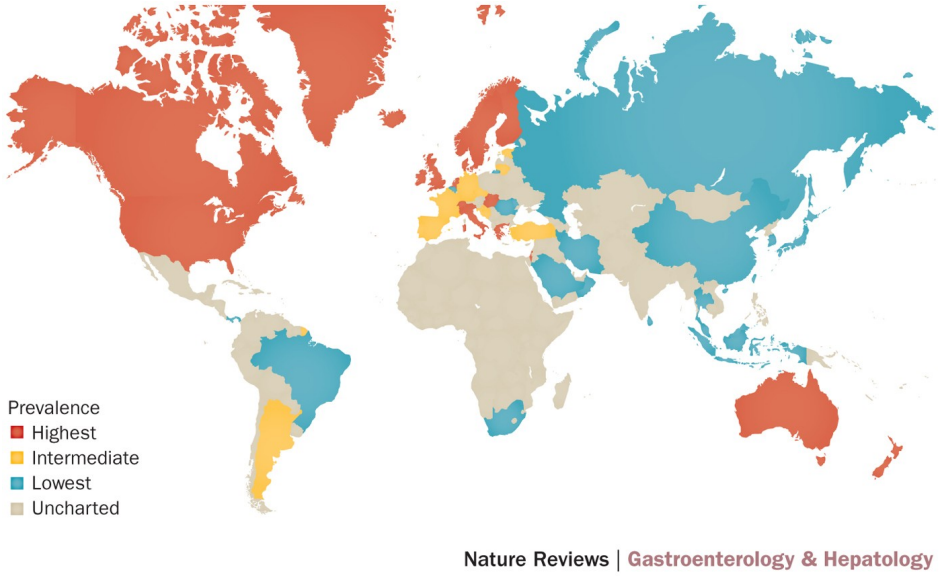

Figure 2. La prévalence des maladies inflammatoires chroniques de l'intestin dans le monde (Kaplan 2015). Il existe un gradient Nord-Sud et Ouest-Est des MICI, avec une prévalence plus élevée au Nord et à l'Ouest.

1.3 ÉTIOLOGIE

L'étiologie exacte des MICI est encore inconnue. Cependant, il est accepté que des facteurs de risques **environnementaux** (tabac, appendicectomie etc.) chez une personne prédisposée **génétiquement** favorisent le développement de la pathologie avec une altération de quatre acteurs clés de l'homéostasie intestinale (Ananthakrishnan et al. 2018). Ces acteurs incluent une inflammation chronique, une rupture de la BEI, des altérations du système nerveux entérique (SNE) et une dysbiose intestinale engendrant un **cercle vicieux** entre tous ces éléments (Figure 3).

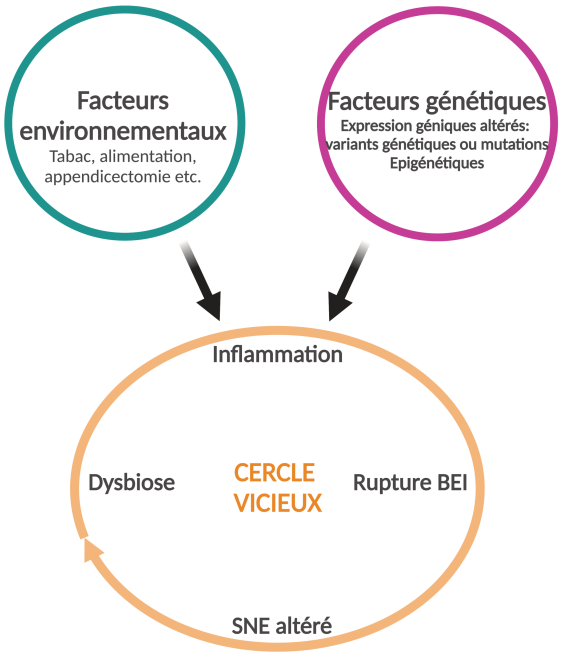

Figure 3. Étiologie des MICI (d'après Dalal et Chang 2014). Des facteurs environnementaux (tabac, appendicectomie etc.) chez un individu prédisposé génétiquement favorisent le développement des MICI, entraînant une altération de l'homéostasie intestinale : inflammation chronique, rupture de la BEI, altération du SNE et dysbiose intestinale.

1.3.1 FACTEURS GENETIQUES

Des **facteurs génétiques** ont une part de responsabilité dans ces maladies. En effet, environ 15% des patients Crohn ont un historique familial avec la pathologie (Gajendran et al. 2018). De plus, une étude souligne que les descendants directs de parents atteints de MICI présentent une perméabilité intestinale anormale (Chelakkot, Ghim, et Ryu 2018).

Des **gènes de susceptibilité** à la MC ou la RCH ont été décrits, 201 mutations génétiques ont été décrites comme étant associées au développement d'une MICI. Parmi ces mutations, 41 sont spécifiques de la MC et 30 de la RCH (Flynn et Eisenstein 2019). Les variants les plus connus sont ceux des gènes NOD2/CARD15 (NOD2 pour « nucleotide-binding oligomerization domain 2 », CARD15 pour « caspase recruitment domain-containing protein 15 »), le récepteur à l'interleukine 23 (IL23R) et ATG16L1 (pour « autophagy related 16 like 1 ») pour la

MC. Ces gènes sont impliqués dans la modulation du système immunitaire, des fonctions de la BEI telles que la perméabilité, la réparation et l'autophagie (Khor, Gardet, et Xavier 2011).

Les individus présentant une mutation hétérozygote du gène NOD2/CARD15 ont un risque 2 à 4 fois plus élevée de développer la MC et 20 à 40 fois lorsque c'est homozygote. NOD2 est un **PRR** (pour Pattern Recognition Receptor») intracellulaire, il reconnaît les agents pathogènes tels que les bactéries et active le système immunitaire dans le but d'éliminer les pathogènes intracellulaires. De façon intéressante, les patients présentant une mutation du gène *Nod2* ont des modifications caractéristiques du microbiote intestinal comparés à des individus sans la mutation (Zheng et Wen 2021). La mutation de ce gène est également associée à une apparition précoce de la pathologie.

Concernant l'IL23R, ce gène est impliqué dans la différenciation des lymphocytes T helper (Th) 17. La mutation entraîne une dérégulation de la production d'interleukine 17 (IL-17), une cytokine rapportée comme effecteur clé dans le développement de colite dans les modèles animaux (Gajendran et al. 2018).

Ensuite, en ce qui concerne le gène ATG16L1, impliqué dans l'autophagie, des études ont décrit qu'une délétion sélective du gène chez la souris entraîne une diminution du nombre de lymphocytes T régulateur (Treg) et Th2 (Zheng et Wen 2021).

Enfin, la majorité (80-90%) des *loci* identifiés sont non codants, suggérant qu'ils pourraient correspondre à des marqueurs épigénétiques, de l'ARN non codant ou des micro ARN (Flynn et Eisenstein 2019).

1.3.2 FACTEURS ENVIRONNEMENTAUX

En plus des facteurs génétiques qui ne sont responsables que d'un tiers des MICI (Ananthakrishnan et al. 2013), des **facteurs environnementaux** entrent également en jeu. C'est le cas de l'alimentation, du sommeil, de la consommation de tabac, l'appendicectomie, l'activité physique, l'hygiène, le stress, la vitamine D associée à l'exposition aux ultraviolets (UV), et la prise de médicaments qui vont jouer un rôle considérable dans la survenue de ces pathologies (Figure 4). Le point commun entre tous ces facteurs de risque est leurs effets sur le **microbiote intestinal**.

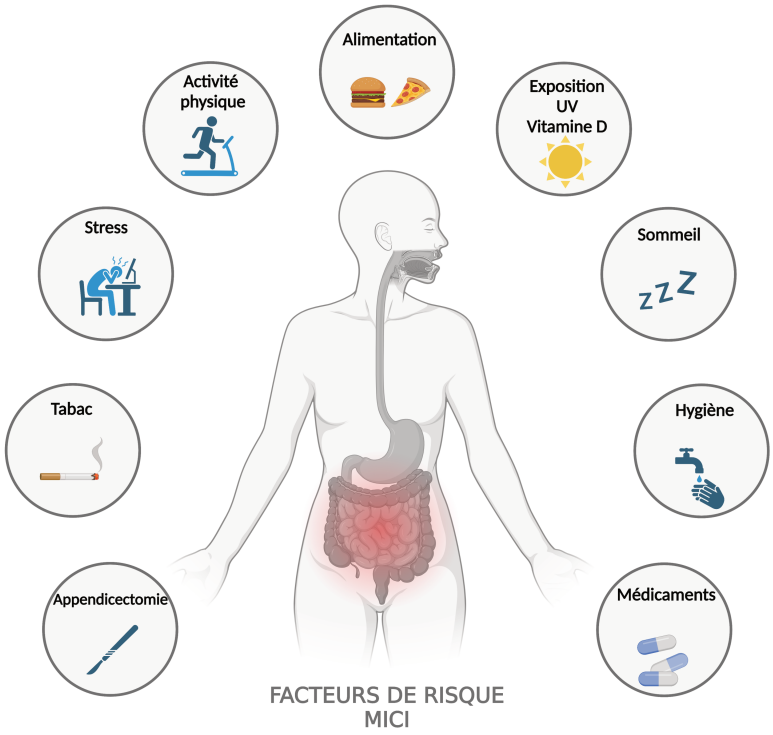

Figure 4. Facteurs de risque environnementaux des MICI (d'après Ananthakrishnan et al. 2015). Les facteurs de risque environnementaux des MICI sont : l'appendicectomie, le tabac, le stress, le manque d'activité physique, l'alimentation, une faible exposition aux UV, une déficience de vitamine D, une altération du sommeil, une hygiène excessive et la prise de médicaments.

L'appendicectomie constitue également un facteur de risque dans les MICI. L'appendice est un sanctuaire bactérien impliqué dans l'éducation du système immunitaire et la recolonisation du côlon en cas d'infection (Collard et al. 2022). Il permet le maintien de l'homéostasie du microbiote intestinal, et présente également des patchs caecaux, un tissu lymphoïde qui est le site majeur de génération de cellules productrices d'IgA qui migrent dans le côlon (Masahata et al. 2014). L'appendicectomie influe fortement la composition et la diversité du microbiote intestinal, notamment en favorisant le développement de pathogènes causant une déplétion des bactéries commensales bénéfiques (Shi et al. 2023). Encore une fois, les effets **divergent** entre la MC et la RCH. Deux facteurs semblent influer l'effet de l'appendicectomie sur la MICI : **l'âge** du patient et la **raison** de l'opération.

Les effets concernant la consommation de **tabac** sur l'apparition et le développement d'une MICI diffèrent entre la MC et la RCH. Concernant la MC, le tabac **augmente** d'un facteur de deux le risque de développer la pathologie (Ananthakrishnan et al. 2015). De plus, une méta-analyse rapporte que les patients Crohn fumeurs répondent moins bien aux traitements anti-TNF (TNF pour « tumor necrosis factor ») que les non-fumeurs (Lee et al. 2021). De façon surprenante, le tabac serait un facteur **protecteur** de la **RCH**. En effet, le risque de développer une RCH augmente 2 à 5 ans après l'arrêt du tabac, les études ne permettent pas d'expliquer ce phénomène. Toutefois certaines suggèrent que l'arrêt du tabac entraîne une modification rapide du microbiote intestinal (Ananthakrishnan et al. 2015). Il est important de noter que les patients RCH anciens fumeurs ont une augmentation du risque de subir une colectomie en comparaison aux non-fumeurs (Kuenzig et al. 2016). Globalement, le tabac affecte le microbiote intestinal et la composition en métabolites dérivés du microbiote intestinal, tels que les acides biliaires secondaires, favorisant ainsi le développement de pathologies telles que les MICI (Bai et al. 2022).

Le **stress** provoque des modifications à long terme du microbiote intestinal. Qu'il s'agisse du stress prénatal (Golubeva et al. 2015), du stress précoce, ou des divers stress physiques ou psychologiques qui surviennent tout au long de la vie, le stress induit des altérations du microbiote intestinal, par exemple en diminuant la présence de bactéries bénéfiques (Molina-Torres et al. 2019).

L'**activité physique** module positivement le microbiote intestinal en favorisant les bactéries bénéfiques productrices de butyrate, et en augmentant la diversité du microbiote intestinal. De plus, le sport réduit le temps de transit colique, limitant ainsi temps de contact de pathogènes avec la couche de mucus (Gubert et al. 2020). Le manque d'exercice, a contrario, ne bénéficie plus des effets positifs du sport sur le microbiote intestinal, ce qui favorise le développement des MICI.

Une carence en **vitamine D** est également l'un des facteurs de risque des MICI. La vitamine D apportée par l'alimentation, ou synthétisée par la peau à la suite de l'exposition aux UVB, impacte le microbiote intestinal. En effet, la supplémentation en vitamine D induit des changements dans la composition du microbiote intestinal, en particulier au niveau des phyla des *Firmicutes*, *Actinobacteria* et *Bacteroidetes*. De plus, la vitamine D possède des propriétés antimicrobiennes (Bellerba et al. 2021).

Une altération du **sommeil** cause également des altérations du microbiote intestinal, favorisant le développement des MICI. Par exemple, chez la souris, une déprivation du sommeil, réduit la concentration de mélatonine dans les selles et le côlon associé à une dysbiose intestinale. De façon intéressante, la supplémentation en mélatonine réverse les effets délétères de la privation de sommeil (Park et al. 2020).

La prise de **médicaments**, en particulier celle d'antibiotiques, contribue au développement des MICI, notamment en affectant le microbiote intestinal. Les antibiotiques diminuent la diversité du microbiote intestinal en éliminant les pathogènes, mais ils entrainent des dommages collatéraux, du fait de leur non-spécificité en tuant les bactéries bénéfiques (Ianiro, Tilg, et Gasbarrini 2016).

Enfin, un autre facteur de risque des MICI est **l'excès d'hygiène**, en particulier au cours des premières années de la vie. Comme Montesquieu l'a si bien dit « Le mieux est le mortel ennemi du bien », en voulant éliminer les pathogènes, les « microbes » pour prévenir les infections, nous avons restreint notre exposition aux micro-organismes qui nous entourent. Or, cette exposition durant les étapes précoces de la vie est essentielle à l'acquisition d'un microbiote intestinal sain (Schmidt et al. 2011; Penders et al. 2014).

2. PHYSIOPATHOLOGIE DES MICI

La physiopathologie des MICI est complexe et met en jeu 4 acteurs clés de l'homéostasie intestinale : la **barrière épithéliale intestinale**, le **système immunitaire**, le **microbiote intestinal** et le **système nerveux entérique**. Avant de s'intéresser à ces différents composants et comprendre leur implication dans la pathogenèse des MICI, un rappel sur la physiologie de l'intestin s'impose.

2.1. PHYSIOLOGIE GENERALE DE L'INTESTIN

2.1.1. ORGANISATION

Le tractus gastro-intestinal s'étend de la bouche à l'anus. Il comprend la **cavité orale**, **l'œsophage**, **l'estomac** puis **l'intestin grêle,** lui-même divisé en trois parties : le **duodénum**, le **jéjunum** et **l'iléon**. L'intestin grêle débouche sur le **gros intestin** qui comprend le **caecum**, **l'appendice**, le **côlon** qui forme un cadran, on l'appelle le cadre colique. Il est divisé en 4 parties : le **côlon ascendant**, le **côlon transverse**, le **côlon descendant**, le **côlon sigmoïde** puis le **rectum** et **l'anus** (Figure 5).

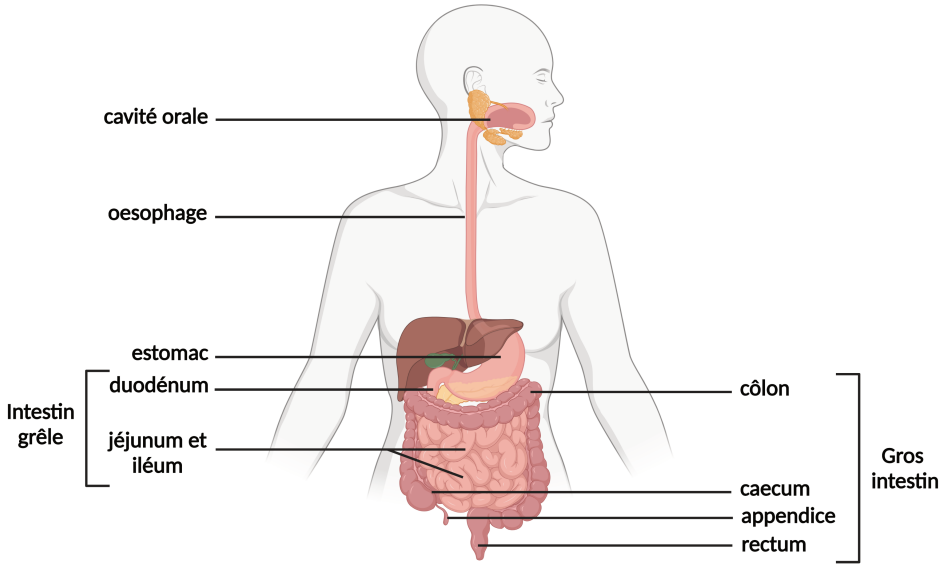

Figure 5. Structure anatomique du tractus gastro-intestinal.

La structure anatomique de l'intestin se décompose en plusieurs couches (Figure 6). La plus externe est le **mésentère** qui tapisse l'intestin, c'est un repli du péritoine, il permet le maintien de l'intestin dans la cavité abdominale. Ensuite vient la **séreuse**, constituée d'un mésothélium et d'un épithélium. La **musculaire**, plus interne, est composé d'une couche musculaire **longitudinale** qui permet de raccourcir et d'allonger l'intestin et d'une couche musculaire **circulaire** en dessous, qui permet la constriction. Sous la musculeuse se trouve la **sous-muqueuse** qui contient les vaisseaux sanguins, lymphatiques et le plexus sous-muqueux ou de Meissner. Enfin la dernière couche avant la lumière intestinale est la **muqueuse** intégrant la *muscularis mucosae*, la *lamina propria* et l'épithélium intestinal (Collins, Nguyen, et Badireddy 2023).

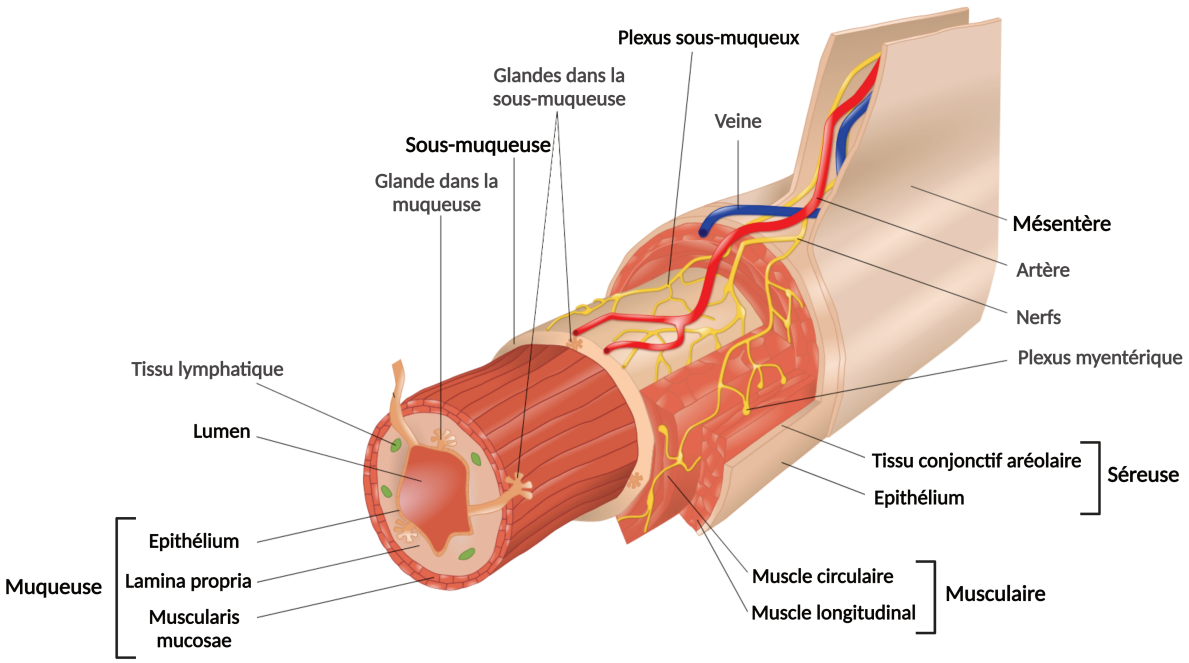

Figure 6. Structure anatomique de l'intestin. L'intestin de la couche la plus externe à la plus interne : le mésentère, la séreuse, la musculaire et la muqueuse.

2.1.2. FONCTION PRINCIPALE

Le tube digestif est un organe central dans la survie des organismes pluricellulaires. Ses mots d'ordre sont la **digestion**, **l'absorption** des nutriments provenant de l'alimentation, **l'élimination** ou la **transformation** des produits non assimilables et la **protection** vis-à-vis de l'environnement extérieur. Le bol alimentaire descend le long du tractus gastro-intestinal facilité par un processus de contraction **péristaltique** des muscles lisses. De plus, un processus de **segmentation** garantit une exposition suffisante du contenu luminal à l'épithélium (Greenwood-Van Meerveld, Johnson, et Grundy 2017). La durée du transit et les niveaux de pH (pH pour « potentiel hydrogène ») varient selon les compartiments intestinaux, ce qui permet une efficacité maximale de la digestion (Geerlings et al. 2018). Les fonctions du tube digestif sont assurées en s'appuyant sur 3 propriétés du tube digestif : la **motricité**, la **sécrétion** et la **perméabilité** intestinale.

2.2. LA BARRIERE EPITHELIALE INTESTINALE

La BEI est constituée d'une monocouche de **cellules épithéliales intestinales** (CEI) et de mucus recouvrant la majeure partie de l'appareil digestif. La lamina propria, une fine couche de tissu conjonctif, et les muscles lisses sont des éléments essentiels au soutien de la BEI. Grâce à ce système, une communication directe et/ou indirecte est établie entre le microbiote intestinal, les CEI et le système immunitaire sous-jacent (Chelakkot et al. 2018). Ses fonctions sont diverses avec un rôle d'absorption des nutriments, de sécrétion de mucus, d'enzymes, et de protection vis-à-vis du contenu luminal.

2.2.1. COMPOSITION

La BEI possède une organisation spatiale précise. Tout d'abord, il existe un **axe antéro-postérieur** (figure 7), caractérisé par une régionalisation des structures en fonction de leur localisation au sein du tractus gastro-intestinal (intestin grêle, côlon).

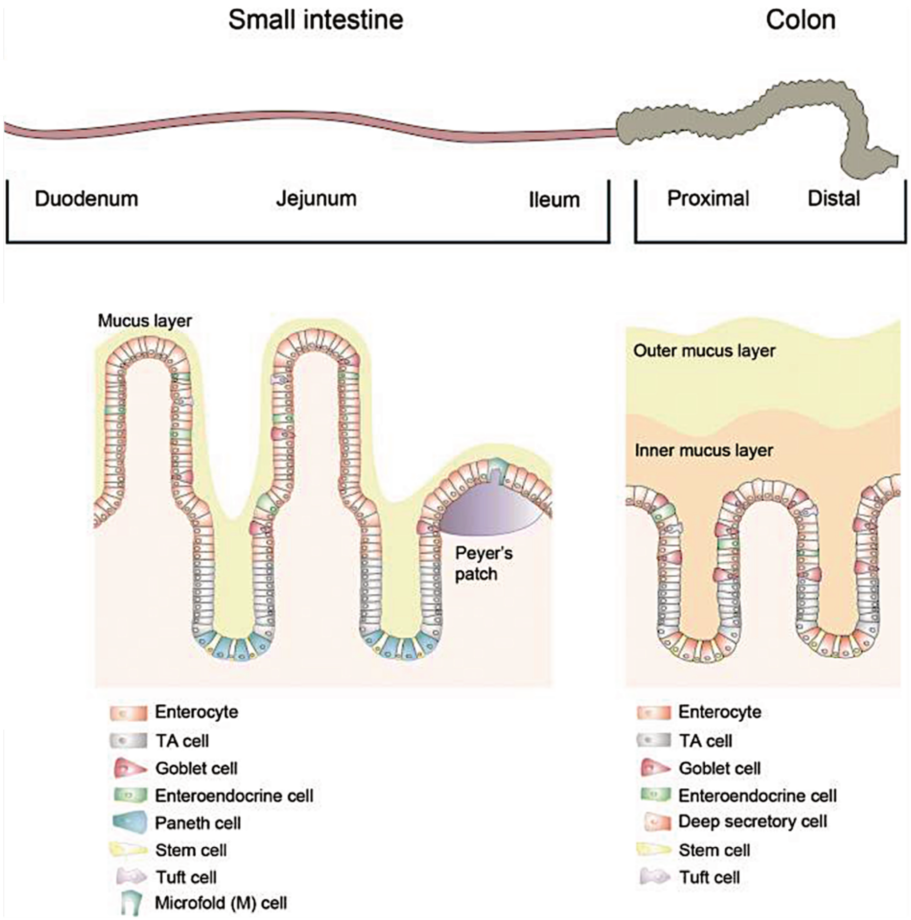

Figure 7. Axe antéro-postérieur de l'intestin (Kayisoglu, Schlegel, et Bartfeld 2021). L'intestin possède une régionalisation de l'axe antéro-postérieur. L'intestin grêle possède des villosités intestinales, une couche de mucus fine, des cellules de Paneth et Microfold. Le côlon est dépourvu de villosités, de cellules de Paneth et Microfold et présente une couche de mucus plus épaisse.

Bien que les deux régions possèdent les **cryptes de Lieberkühn** sous forme de structures invaginées, l'intestin grêle présente également des **villosités intestinales** qui sont des structures protubérantes (Allaire et al. 2018). A l'inverse, le côlon est dépourvu de villosités, mais possède un plus large éventail de types cellulaires. De plus, des types de cellules spécifiques sont exclusifs à l'intestin grêle. Les villosités, ainsi que les **microvillosités** situées au pôle apical des entérocytes, augmentent la surface d'échange des muqueuses et l'absorption des nutriments (Allaire et al. 2018).

De plus, un **axe crypto-villositaire** a été décrit avec une régionalisation des types et des activités cellulaires (Figure 8). En effet, la BEI est composée de différents types cellulaires issus de la différenciation des **cellules souches intestinales** (CSI) à récepteurs couplés à une protéine G contenant des répétitions riches en leucine (Lgr5+). Les CSI sont localisées au fond des cryptes (Poggi et al. 2019). Le renouvellement continu de la BEI, tous les cinq à six jours chez l'Homme, est assuré par l'équilibre entre **différenciation**, **prolifération** et mort par **apoptose** des CEI qui sont éliminées dans la lumière intestinale (Chelakkot et al. 2018; Allaire et al. 2018).

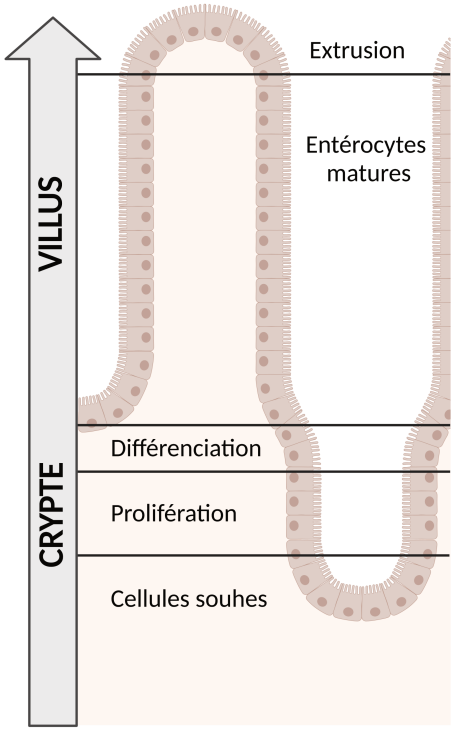

Figure 8. **Axe crypto-villositaire** (d'après Pageot et al. 2000). Au fond des cryptes on retrouve les cellules souches, puis un compartiment de prolifération, puis de différenciation. Au niveau des villosités, on retrouve les entérocytes matures puis en haut le compartiment d'extrusion.

2.2.1.1. CELLULES EPITHELIALES

La BEI est composée d'une population hétérogène de cellules qui se distinguent par leur localisation anatomique au sein des cryptes intestinales et des villosités ainsi que par leurs fonctions uniques. Ces cellules interagissent les unes avec les autres et travaillent ensemble pour maintenir l'intégrité structurelle et fonctionnelle de la BEI (Chelakkot et al. 2018). Les caractéristiques de chaque type cellulaire seront développées et leurs rôles respectifs, qu'ils soient individuels ou collectifs, seront discutés.

2.2.1.1.1. LES CELLULES SOUCHES INTESTINALES

Les CSI sont caractérisées par leur capacité **d'auto-renouvellement**, elles prolifèrent pour maintenir un pool constant de CSI. De plus, les CSI sont dotées de **multipotences**, c'est-à-dire qu'elles sont capables de produire des cellules filles, appelées progéniteurs TA (pour transit-amplifying) capable de générer tous les types de cellules intestinales matures (Figure 9). Les progéniteurs TA subissent 4 à 5 divisions et migrent le long de l'axe crypto-villositaire (Ellis et Fuchs 2022).

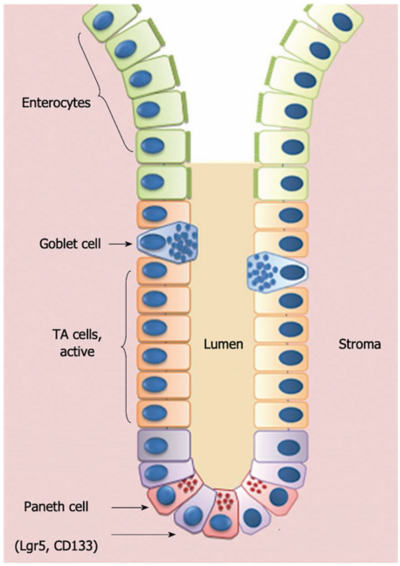

Figure 9. **Différenciation des CSI le long de l'axe crypto-villositaire** (Piscaglia et al. 2014). Les cellules souches intestinales (Lgr5+) au fond des cryptes sont entourées des cellules de Paneth. Les CSI donnent naissance à des progéniteurs TA capables de migrer vers le haut et de se différencier progressivement en entérocytes matures.

Ces cellules se différencient en plusieurs types cellulaires : les cellules caliciformes, les entérocytes, les cellules entéro-endocrines (CEE), les cellules Tuft afin d'assurer un renouvellement de la BEI (Barker 2014).

2.2.1.1.2. LES ENTEROCYTES

Les entérocytes sont des cellules **absorbantes** localisées au sommet des cryptes et des villosités. Ce sont les cellules les plus abondantes de la BEI, elles représentent 80% des cellules de la barrière. Ces cellules sont caractérisées par la présence de microvillosités à leur pôle apical, appelé **bordure en brosse**, permettant d'augmenter la surface d'échange avec la lumière intestinale, et ainsi favorisant l'absorption des nutriments. De plus, le pôle apical est recouvert d'un matériel fibrillaire riche en glycoprotéines, très adhérent à la cellule appelé le **glycocalyx**. Cette couche de mucines transmembranaires permet de poursuivre la digestion du fait de la présence d'enzymes facilitant la digestion et l'absorption des nutriments. En parallèle de leur rôle d'absorption, les entérocytes protègent la BEI *via* l'absorption et le traitement des antigènes, soit par la dégradation lysosomale, soit par la présentation aux cellules immunitaires (Snoeck, Goddeeris, et Cox 2005). Ces cellules sont également capables de sécréter des **peptides antimicrobiens** (PAM), tels que les β-défensines, qui favorisent les fonctions de barrière des CEI (Kopp et al. 2015).

2.2.1.1.3. LES CELLULES CALICIFORMES

Les cellules caliciformes, aussi nommées « goblet cells » en anglais, sont des cellules **mucosécrétantes**. C'est-à-dire, qu'elles sont capables de sécréter du mucus qui permet de protéger les CEI de la lumière intestinale. Ces cellules renferment, à leur pôle apical, des globules remplis de glycoprotéines appelés **mucines**. Il existe deux types de mucines : les mucines transmembranaires (citées ci-dessus) et les « gel-forming mucins » qui sont celles sécrétées par les cellules caliciformes. Ces cellules sont majoritairement retrouvées au niveau des cryptes et sont plus nombreuses au niveau du côlon. La couche de mucus produite permet la lubrification de l'épithélium dans le but de le protéger à la fois du bol alimentaire mais aussi des micro-organismes pathogènes et des toxines (*cf*. partie mucus).

2.2.1.1.4. LES CELLULES ENTERO-ENDOCRINES

Les cellules entéro-endocrines représentent entre 0.1 et 1% des CEI. Ces cellules ont pour but de produire des **hormones** indispensables à l'homéostasie intestinale. Il existe différents sous-types de CEE spécialisés dans un type d'hormone. Les cellules entérochromaffines vont sécréter de la sérotonine, un neurotransmetteur responsable de la régulation de la motricité intestinale. Les cellules D quant à elles sécrètent la somatostatine, qui inhibe les sécrétions acides gastriques. D'autres cellules sécrètent le GLP-1 (glucose like peptide-1) impliqué dans la régulation de l'appétit, mais aussi le GIP (glucose-dependant insulinotropic peptid) etc. (Haber et al. 2017). De plus, les CEE contrôlent la **motilité** intestinale, et orchestrent **l'immunité** de la muqueuse (Gribble et Reimann 2017; Worthington, Reimann, et Gribble 2018). Enfin, les CEE présentent un rôle majeur dans la communication entre l'intestin et le cerveau. En effet, ces cellules forment des **neuropodes** capables de faire des synapses avec le nerf vague. Ainsi, l'intestin envoie des informations à la milliseconde *via* des neurotransmetteurs au cerveau pour l'informer, par exemple, sur le type de nutriment ingéré (Kaelberer et al. 2018).

2.2.1.1.5. Les cellules M ou microfold

Les cellules M pour « microfold » sont un sous-type de CEI spécifique de l'intestin grêle. Découvertes dans les années 70 avec le développement de la microscopie électronique, ces cellules ont une morphologie particulière. En effet, elles sont dépourvues de microvili à leur surface apicale, mais présentent des micro-replis, ou microfold en anglais, leur permettant d'avoir une forte activité de **phagocytose** et **transcytose** (Ohno et al. 2016). Elles ont un cytoplasme fin et finissent avec un pôle basolatéral profondément invaginé, donnant un aspect de sacs permettant ainsi aux cellules dendritiques et aux lymphocytes de s'y installer. Ayant une activité lysosomale réduite et un nombre de lysosomes inférieur aux CEI, ces cellules sont capables de phagocyter les bactéries de la lumière intestinale et de délivrer des antigènes intacts aux cellules dendritiques (*cf. partie sur le système immunitaire*), qui vont permettre à ces dernières d'induire une **réponse immunitaire**. Les cellules M expriment de manière spécifique la glycoprotéine-2 (GP2). Ce récepteur reconnaît spécifiquement les pili de type I présent à la surface des bactéries Gram négatif de type Entérobactéries telles que des bactéries pathogènes comme *Escherichia coli* et *Salmonella enterica* (Terahara et al. 2008). De plus, ces cellules expriment des récepteurs aux Immunoglobulines A (IgA) et transportent les IgA sécrétoires (SIgA) associées aux antigènes dans les plaques de Peyer. Il a notamment été décrit que l'IgA sécrétoire associée aux antigènes via le récepteur Dectine-1 des cellules M est présentée aux cellules dendritiques par le biais d'un récepteur de type DC-SIGN (« dendritic cell-specific ICAM-grabbing non-integrin ») et ainsi permet d'induire une réponse immunitaire (Rochereau et al. 2013).

2.2.1.1.6. Les cellules de Paneth

Les cellules de Paneth sont retrouvées exclusivement au niveau des **cryptes de Lieberkühn** au niveau de l'intestin grêle. Elles sont de forme pyramidale, et présentent à leur pôle apical des granules de sécrétion. Ces cellules possèdent un réticulum endoplasmique et un appareil de Golgi volumineux leur permettant d'être les principales productrices de **PAM**. L'α-défensine régule la composition du microbiote intestinal, en effet elle possède une puissante activité antimicrobienne contre les bactéries pathogènes, alors que qu'elle est presque nulle vis-à-vis des bactéries commensales (Nakamura et al. 2016). Les cellules de Paneth sécrètent également du lysozyme C, de la phospholipase A2 (PLA2) capable de détruire la membrane des bactéries à Gram positif (Bevins et Salzman 2011).

2.2.1.1.7. Les cellules Tuft

Les cellules Tuft sont rares dans l'intestin. Elles sont impliquées dans la **réponse immunitaire** aux **helminthes** et **parasites protozoaires**, notamment *via* leur expression d'IL-25 qui augmente lors d'une infection d'helminthe (Schneider et al. 2018). L'IL-25 va activer les cellules lymphoïdes innées 2 (ILC-2) qui à leur tour produisent de l'IL-13 permettant aux progéniteurs de se différencier en cellules Tuft et caliciformes et d'engendrer une réponse de type « weep-and sweep » qui est un mécanisme de nettoyage et d'élimination des parasites (Von Moltke et al. 2016; Gerbe et al. 2016). Les cellules Tuft peuvent également sécréter des eicosanoïdes tels que la prostaglandine D2 (PGD2) impliquée dans l'allergie, et même des neurotransmetteurs tels que l'acétylcholine (Ach) (Schneider, O'Leary, et Locksley 2019).

2.2.1.2. JONCTIONS CELLULAIRES

Les jonctions cellulaires sont essentielles au **maintien de la BEI** en régulant les interactions des cellules entre elles, mais aussi avec la matrice extracellulaire. Les interactions **cellule-cellule** regroupent 4 types de complexes : les **jonctions serrées** (TJ pour « tight junction »), **adhérentes**, **communicantes** et les **desmosomes** (Figure 10). Les interactions **cellule-matrice** font appel **aux hémi-desmosomes** et aux **points d'adhésion focale**.

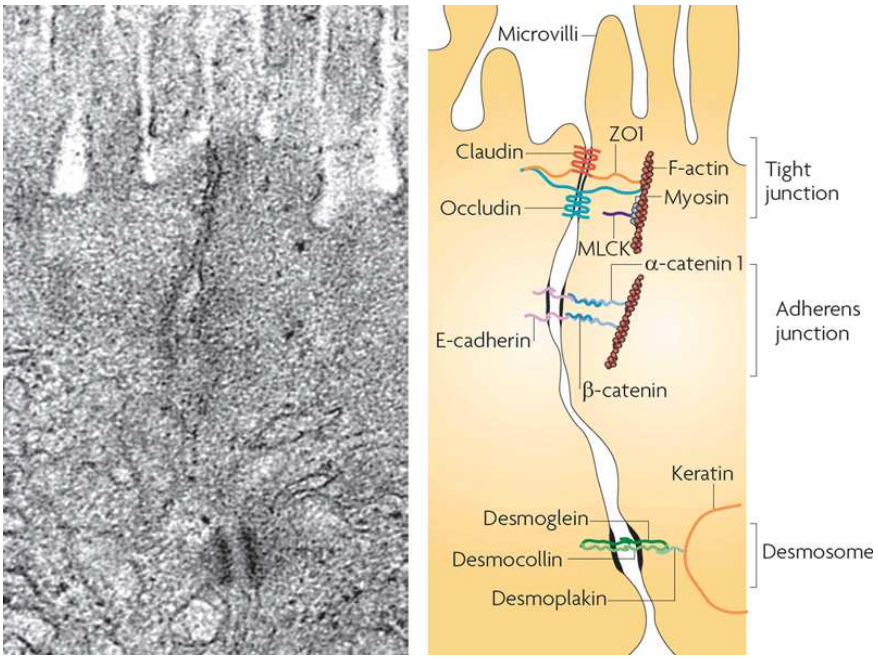

Figure 10. Les jonctions cellulaires cellule-cellule (Camilleri et al. 2012). Les jonctions cellulaires cellule-cellule regroupent 4 types de complexe : les jonctions serrées, adhérentes, communicantes et les desmosomes.

2.2.1.2.1. JONCTIONS SERREES

Les protéines des jonctions serrées constituent la structure la plus apicale des jonctions cellulaires. Elles participent à l'établissement de la **polarité** cellulaire et régulent principalement la **perméabilité paracellulaire** (Walsh et al. 2001). Ces fonctions sont sous le contrôle de deux familles de protéines transmembranaires : les **TAMPs** (pour « Tight Junction-Associated MARVEL Proteins » et les **claudines** qui interagissent avec d'autres protéines de la même famille située sur les cellules voisines.

Les **TAMPs** comprennent les **occludines**, **tricellulines** et **marvelD3.** Les protéines MarvelD3 régulent la résistance électrique trans-épithéliale (TEER) c'est-à-dire la perméabilité des ions, mais aussi la prolifération et la migration cellulaire. Les tricellulines n'affectent pas la perméabilité des ions, cependant elles permettent le passage de molécules de taille inférieure à <10 kiloDalton (kDa). Enfin, les occludines sont essentielles à l'assemblage des TJ (Figure 11). Les **claudines** régulent la fonction de passage des molécules selon leur taille (diamètre < 0,6 nm) et leur charge. Les claudines forment des canaux qui vont définir la **voie des pores** (Horowitz et al. 2023). C'est le cas de la claudine-2, majoritairement exprimée dans l'intestin avec la claudine-15, qui permet le passage de l'eau et de cations tels que le Na+. La claudine-2 ne permet pas le passage du dextran-4 kDa, un polysaccharide utilisé comme marqueur pour évaluer l'intégrité de la BEI. Le dextran-4kDa et les autres molécules > 0,6 nm vont utiliser

la voie du « **leak pathway** » permettant le passage des molécules entre 0,6 et 12,5 nm sans prendre en compte la charge des molécules.

Ces protéines transmembranaires sont en lien avec le cytosquelette *via* de grosses **protéines intra-cellulaires**. C'est le cas des **zonula occludens** (ZO) (**Figure 11**) (Walsh et al. 2001).

Enfin des **molécules d'adhésion jonctionnelles** (JAM) sont impliqués dans la fonction de barrière de la BEI et participent à l'établissement de la polarité cellulaire (**Figure 11**) (Campbell, Maiers, et DeMali 2017). Ces protéines sont également impliquées dans l'adhésion cellulaire des cellules endothéliales et à la migration des neutrophiles.

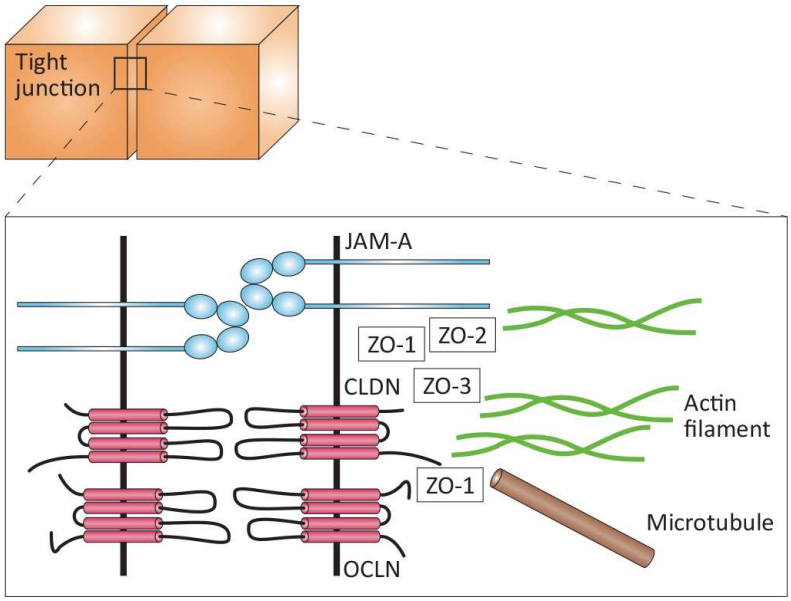

Figure 11. **Les protéines de jonctions serrées** (Zeisel, Dhawan, et Baumert 2019). Les TJ sont composées de protéines transmembranaires, tels que les claudines et les TAMPs (par exemple l'occludine (OCLN)), des molécules d'adhésion jonctionnelles (JAM, par exemple JAM-A), ainsi que des protéines cytosoliques (par exemple ZO-1, -2, -3), qui relient les composants transmembranaires au cytosquelette (filaments d'actine, microtubules).

Ces protéines sont en lien avec le **cytosquelette** d'actine et de myosine qui va permettre un phénomène de contraction de la CEI (**Figure 11**).

2.2.1.2.2. JONCTIONS ADHERENTES

Les **jonctions adhérentes** sont localisées directement en dessous des jonctions serrées (**Figure 12**). Elles comprennent deux sous-complexes : l'adhésion basée sur les **nectines** qui forment le premier attachement aux cellules voisines et celui basé sur les **cadhérines** qui permettent une forte adhésion entre les cellules. Ces deux protéines sont transmembranaires, la partie extracellulaire permet l'attache aux cellules voisines alors que la partie intra-cellulaire interagit avec d'autres protéines intracellulaires qui contrôlent l'assemblage des jonctions adhérentes en modulant les connexions avec le cytosquelette d'actine. Parmi ces protéines on retrouve les

caténines qui se lient aux cadhérines, notamment la E-cadhérine. Alors que les nectines se lient aux afadin (Campbell, Maiers, et DeMali 2017).

2.2.1.2.3. DESMOSOMES

Les **desmosomes** sont situés au pôle basolatéral des cellules. Les desmosomes sont constitués de protéines de type cadhérine : la desmocolline et la desmogléine (Figure 12). Ces protéines sont en lien avec des protéines de la famille des caténines telles que la plakoglobine et plakophiline, elles-mêmes reliées aux **filaments intermédiaires**. Les desmosomes représentent une structure d'adhésion robuste entre les cellules (Schlegel, Boerner, et Waschke 2021).

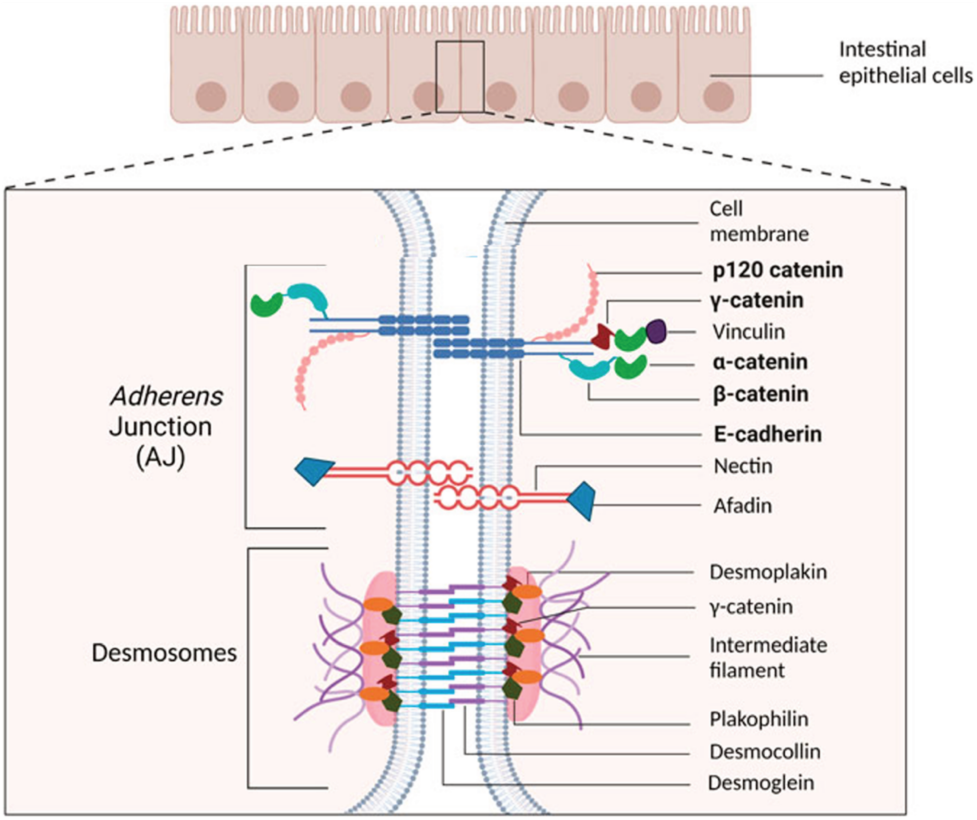

Figure 12. Les jonctions adhérentes et les desmosomes (d'après Lessey et al. 2022). Sous les TJ on retrouve les jonctions adhérentes, qui jouent un rôle-clé dans la médiation de l'adhérence cellulaire. Les desmosomes se situent sous les jonctions adhérentes et sont essentiels pour renforcer l'adhésion cellulaire et résister au stress mécanique.

2.2.1.2.4. JONCTIONS COMMUNICANTES

Les **jonctions communicantes** (ou gap junctions), tout comme les desmosomes, sont situées au pôle basolatéral des cellules. Les jonctions communicantes sont constituées de **canaux** eux-mêmes composés de **connexons** permettant le passage non spécifique de molécule entre deux cellules voisines. Chaque connexon est constitué de 6 **connexines** qui forment un pore de 2 nm de diamètre, sélectionnant les molécules selon leur taille (**Figure 13**) (Kumar et Gilula 1996).

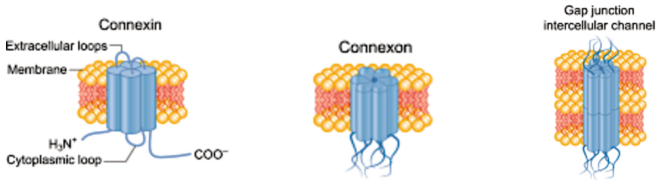

Figure 13. **Les jonctions communicantes** (Aasen et al. 2019). Les jonctions communicantes sont composées de connexines, des protéines transmembranaires avec des terminaisons N et C terminale cytosolique. 6 connexines s'oligomérisent pour former un connexon. A la membrane plasmique, le connexon d'une cellule s'associe avec celui de la cellule adjacente pour former un canal intracellulaire.

Les interactions suivantes permettent l'interaction avec la **matrice extracellulaire** (MEC) composée de la lame **basale** et la lame **réticulaire**. La MEC peut modifier les fonctions de la BEI, c'est le cas de la laminine 1 qui induit la différenciation des CEI (Turck et al. 2005).

2.2.1.2.5. POINTS D'ADHESION FOCALE

Les points d'adhésion focale sont des complexes protéiques qui transmettent des signaux externes à l'intérieur des cellules mais aussi dans l'autre sens en relayant les **signaux** intracellulaires afin d'activer les intégrines à la surface cellulaire (Mitra, Hanson, et Schlaepfer 2005). Ils permettent également **l'ancrage** des CEI à la MEC via des protéines transmembranaires, telles que les intégrines, ainsi que d'autres protéines cytoplasmiques de type vinculine et de signalisation via la FAK (Focal Adhesion Kinase) qui est un récepteur de type tyrosine kinase (Blikslager et al. 2007).

2.2.1.2.6. HEMIDESMOSOMES

Les hémidesmosomes favorisent la **cohésion** et l'**étanchéité** de l'épithélium. Ils mettent en jeu des **intégrines**, notamment la ß-intégrine, qui sont des protéines transmembranaires, associées à des glycoprotéines de la MEC, telles que la **laminine**, et au niveau intracellulaire aux filaments intermédiaires de **kératine** par le biais d'un ensemble de protéines adaptatrices (Walko, Castañón, et Wiche 2015).

2.2.1.3. LE MUCUS

Le mucus est un système de défense situé entre la lumière de l'intestin et les cellules épithéliales. Il est sécrété par l'épithélium, en particulier les cellules caliciformes. Le mucus est différent en fonction de la localisation dans l'intestin. Il est composé de **mucines** qui forment un gel, **MUC2** étant la mucine représentée de façon majoritaire

(Johansson et al. 2008). C'est une **glycoprotéine** de 5200 acides aminés, en particulier des acides aminés hydroxylés, décorés de 80% de **glycanes** qui sont des polysaccharides, majoritairement **O-glycosylée** au niveau des sérines et thréonines.

Dans **l'intestin grêle**, le mucus est formé d'u**ne couche fine** et lâche de mucus, qui n'est pas attachée à la muqueuse (Figure 14). Les cellules caliciformes le sécrètent en continu. Cette couche est hautement pénétrable, heureusement, les choses sont bien faites, l'intestin grêle de par son péristaltisme, sa forte concentration de peptides anti-microbiens et la présence des cellules de Paneth, empêchent les bactéries potentiellement pathogènes de rester longtemps en contact avec l'épithélium (Atuma et al. 2001).

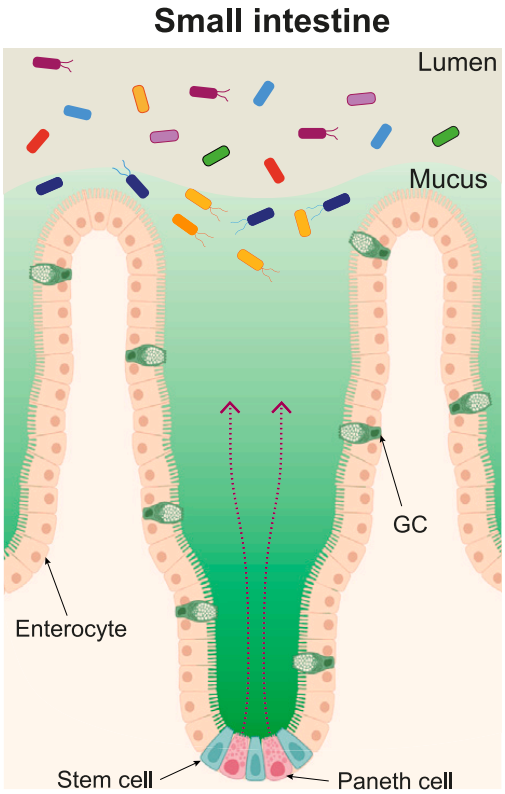

Figure 14. Le mucus dans l'intestin grêle (Luis et Hansson 2023). Le mucus de l'intestin grêle est formé d'une couche fine et lâche de mucus. Les composés antibactériens sécrétés par les cellules de Paneth, en association avec le mucus, maintiennent les bactéries à distance de l'épithélium dans l'intestin grêle.

Dans le **côlon**, là où réside la majeure partie du microbiote intestinal, le mucus est plus épais et formé de **deux couches** avec comme composant majeur la mucine 2, qui est lié par des isopeptides covalents, les transglutaminases-3 qui permettent de stabiliser le mucus (Luis et Hansson 2023). Les deux couches du mucus ont des propriétés différentes (figure 15), la **couche externe** est plus **lâche** que la couche interne, probablement dûe à des protéases cellulaires qui coupent MUC2. Elle abrite des **bactéries commensales** qui adhèrent aux glycanes *via* leurs adhésines, et qui les utilisent également comme source d'énergie. C'est le cas de la bactérie commensale, *Akkermansia muciniphila* qui dégrade le mucus grâce à ses glycoprotéases. Il existe une régulation

fine entre la production et la dégradation du mucus dans le côlon. En effet, dans le côlon, plusieurs sous-types de cellules caliciformes existent. On retrouve les cellules **caliciformes intercryptes**, qui comme leur nom l'indique sont entre les cryptes (Luis et Hansson 2023). Elles stockent transitoirement le mucus dans les granules et le sécrètent continuellement. A l'entrée des cryptes coliques, on retrouve les cellules **caliciformes sentinelles** qui sont sensibles à des niveaux élevés de toll-like receptor (TLR), en particulier TLR4 (Luis et Hansson 2023). Lorsque le niveau de TLR augmente, les cellules libèrent du mucus pour se débarrasser des bactéries présentes. Concernant la **couche interne**, elle est **dépourvue de bactéries** suggérant que les pores du gel sont plus petits pour bloquer le passage de ces dernières (Swidsinski et al. 2005; Johansson et al. 2008). De façon intéressante, lorsque le mucus est dépourvu de MUC2, les bactéries sont en contact direct avec les CEI (Johansson et al. 2008).

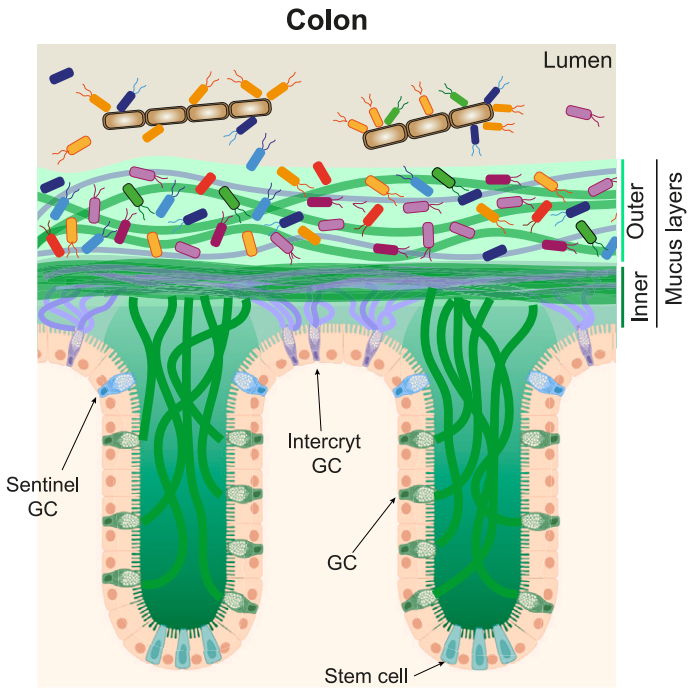

Figure 15. Le mucus dans le côlon (Luis et Hansson 2023). Le mucus du côlon est composé d'une couche interne, dépourvue de bactéries et d'une couche externe abritant des bactéries commensales. Les cellules caliciformes intercryptes et sentinelles sécrètent le mucus.

Les fonctions du mucus sont diverses, il sert de **lubrifiant** pour permettre le passage du bol alimentaire en protégeant l'épithélium contre les stress mécaniques. De plus, c'est à la fois une **barrière physique** contre les pathogènes et un **réservoir énergétique** pour les bactéries commensales. Il permet de créer un **gradient de pH** entre la lumière et la muqueuse, et de maintenir une **forte concentration d'IgA** et de **lysozymes**.

2.2.2. FONCTION

L'homéostasie de la BEI est en étroite relation avec le microbiote intestinal, le système immunitaire et le système nerveux entérique. La BEI présente trois grandes fonctions : la **perméabilité**, la **réparation** et la **défense**.

2.2.2.1. PERMEABILITE

La BEI agit comme une barrière pour séparer le corps de l'environnement extérieur. Une barrière fonctionnelle doit permettre le passage de molécules de manière **bidirectionnelle** tout en empêchant le passage de pathogènes et toxines. Pour cela la **perméabilité** de la barrière intestinale est finement **régulée** afin de permettre le déroulement de **processus métabolique** et la **tolérance immunitaire** tout en maintenant **l'intégrité de la barrière**.

2.2.2.1.1. PERMEABILITE PARACELLULAIRE

La **perméabilité paracellulaire** permet aux molécules hydrophiles (<4 kDa) non reconnues par des transporteurs de traverser la BEI de façon **passive** entre les cellules (Ward, Tippin, et Thakker 2000). Elle est régulée principalement par les **protéines de jonction serrées** qui vont sélectionner les molécules en fonction de leur taille et leur charge, par exemple les ions chargés positivement ont un passage facilité par cette voie (Schoultz et Keita 2020). La **voie des pores** est définies par les claudines (<0,6 nm) et la **voie « leaky »** dépend de l'occludine, la tricelluline, les ZO-1 et l'acto-myosine périjonctionnelle et est régulée par les kinases des chaînes légères de myosine (MLCK) (Figure 16) (Horowitz et al. 2023).

Pour rappel, les jonctions serrées et adhérentes vont former une seule unité fonctionnelle, appelée le **complexe jonctionnel apical** qui est en lien avec le cytosquelette formé de filaments d'actine et de chaînes légères de myosine (MLC).

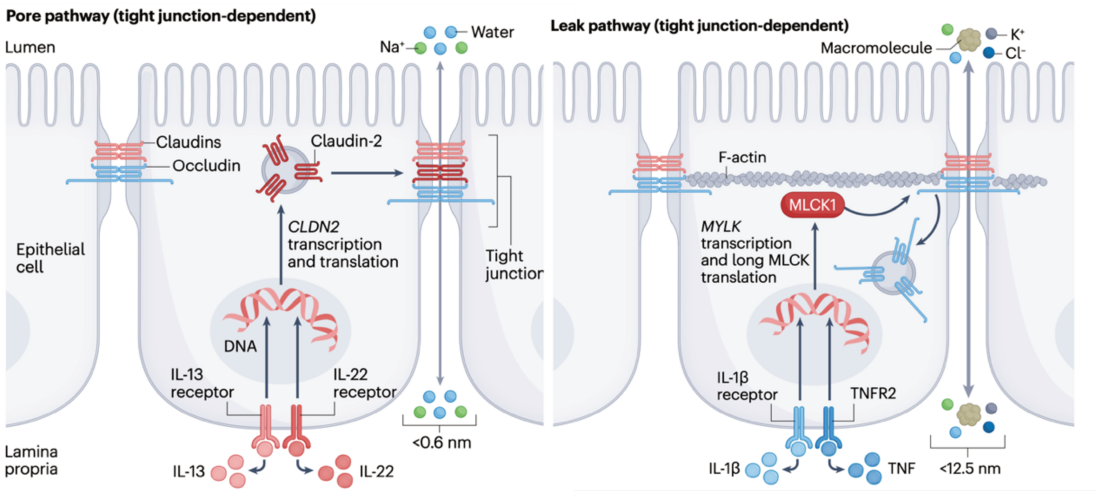

Figure 16. Régulation de la perméabilité paracellulaire : voie des pores à gauche et voie « leaky » à droite (Horowitz et al. 2023). La voie des pores, permettant le passage de l'eau et de cations inférieur à 0,6 nm, est définie par les claudines. L'Il-13 et l'IL-22 augmentent la transcription et l'expression de la claudine-2, augmentant le passage *via* cette voie. La voie « leaky » permet le passage de molécule inférieure à 12,5 nm et est régulée par les MLCK, notamment par l'IL1ß et le TNF.

Il existe 4 moyens de réguler la perméabilité paracellulaire, en conditions physiologiques et pathologiques. Tout d'abord, la **MLCK** peut être régulée, entraînant une phosphorylation des MLC qui affecte le cytosquelette d'actine, essentiel dans la régulation de la perméabilité intestinale. Les petites GTPase RhoA sont impliquées dans la régulation de l'anneau péri-jonctionnel F-actine, et l'induction de l'expression de la kinase associée à Rho (ROCK), également impliquée dans la phosphorylation des MLC (Schoultz et Keita 2020). De plus, l'expression des protéines de jonctions serrées peut être régulée, par conséquent la perméabilité paracellulaire sera modifiée. Par exemple, les cytokines régulent l'expression des TJ protéines comme illustrées sur la **figure 16**. Enfin, l'apoptose peut également impacter la perméabilité de la barrière (Ruder, Atreya, et Becker 2019).

2.2.2.1.2. PERMEABILITE TRANSCELLULAIRE

La **perméabilité transcellulaire** comprend une voie de diffusion **passive** au travers des cellules, et une voie de transport **actif**, c'est-à-dire utilisant de l'énergie.

Tout d'abord, la voie de diffusion passive concerne les lipides solubles et les petits composés hydrophiles, par exemple l'eau utilise cette voie *via* des canaux appelés **aquaporines**. Le passage de macromolécules (> 4 kDa) nécessite un transport actif par **endocytose**, c'est-à-dire une invagination de la membrane plasmique qui forme des vésicules puis un transport au travers du cytoplasme appelé la **transcytose** (Schoultz et Keita 2020). Il existe 4 types d'endocytose sélectifs et non sélectifs (**Figure 17**) :

- **L'endocytose dépendante de clathrine**, qui implique un manteau de clathrine suite à la liaison spécifique d'une molécule à son récepteur. Les immunoglobulines et virus utilisent cette voie (Sandvig, Kavaliauskiene, et Skotland 2018).
- **La phagocytose**, qui implique également la liaison spécifique d'une molécule à son récepteur. Cette voie est utilisée par les antigènes alimentaires et bactériens (Conner et Schmid 2003).
- **La micropinocytose**, qui est non spécifique. Les fluides extracellulaires sont invaginés dans la membrane plasmique, et les plis cellulaires sont libérés dans le cytoplasme sous forme de vésicules appelé macropinosome (Swanson et Watts 1995).
- **Les cavéoles**, sont des invaginations au niveau de microdomaines de la membrane plasmique enrichie en cholestérol et en cavéoline. Cette voie est utilisée par les entérotoxines et virus (Hommelgaard et al. 2005).

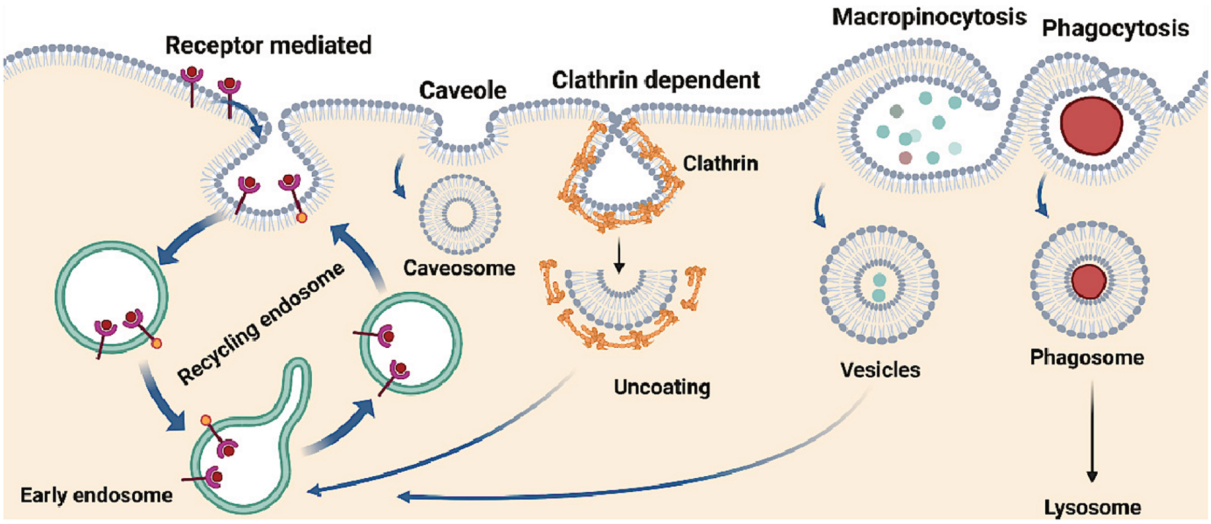

Figure 17. Perméabilité transcellulaire (Pathak et al. 2023). La perméabilité transcellulaire regroupe différentes voies d'endocytose. La phagocytose, la macropinocytose, la voie dépendante des clathrines, des cavéoles et l'endocytose médiée par les récepteurs.

La perméabilité intestinale peut être suivie en mesurant la **TEER** qui mesure la différence de charge ionique de part et d'autre de la barrière, mais aussi peut être mesurée en quantifiant le passage de molécules plus ou moins grosses au travers de la barrière.

2.2.2.2. REPARATION

À la suite d'une **lésion** dans l'épithélium intestinal, et **l'élimination** des cellules endommagées, un processus de réparation complexe se met en place pour restaurer la continuité de la paroi intestinale (**Figure 18**). Ce processus de réparation commence par une étape rapide appelée **restitution**, au cours de laquelle les CEI restantes se redistribuent pour combler les zones lésées. Les cellules adjacentes à la lésion **s'étalent** et **migrent** le long de la matrice extracellulaire, créant ainsi un environnement favorable pour l'étape suivante de régénération.

La **régénération** proprement dite implique la **prolifération** des CSI. Sous l'influence de facteurs de croissance, les cryptes intestinales s'agrandissent, fournissant ainsi l'espace nécessaire pour l'expansion et la multiplication des CSI. Le phénomène de prolifération est dépendant de la voie Wnt (Okamoto et Watanabe 2005).

La décision de la lignée cellulaire que prendront les CSI dépend de voies de signalisation telles que la voie Notch. Cette voie de signalisation joue un rôle crucial dans la régulation de la **différenciation** cellulaire et la **maturation** des CSI. En fonction des signaux perçus, les CSI donneront naissance aux différentes CEI (Okamoto et Watanabe 2005).

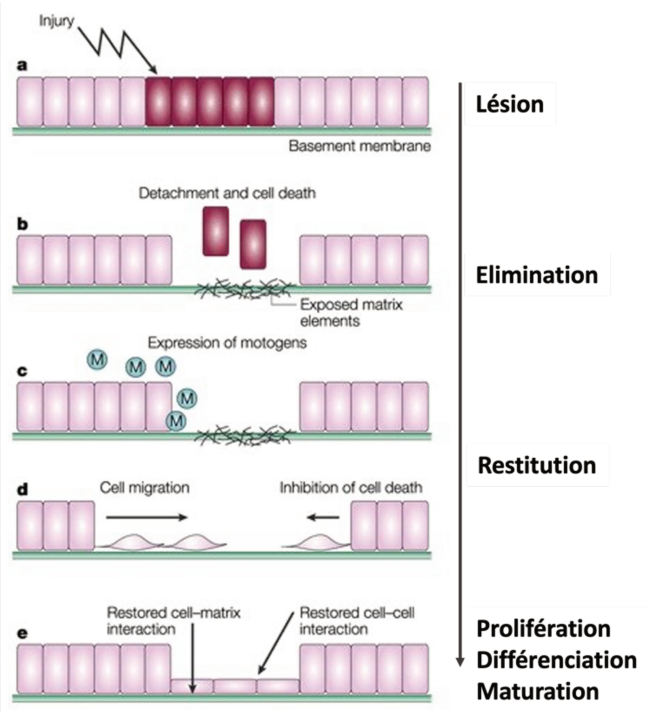

Figure 18. Processus de réparation de la BEI (Taupin et Podolsky 2003). La lésion des cellules épithéliales provoque leur détachement et la mort, créant un défaut épithélial exposant les éléments de la matrice. Il y a une expression rapide et une libération d'agents favorisant la réparation à partir des cellules adjacentes, suivies par la propagation et la migration des cellules épithéliales survivantes. La restauration de la continuité épithéliale est complétée par la restauration de la fonction de barrière.

2.2.2.3. DEFENSE

La BEI est le premier site de contact avec l'extérieur, de fait, elle présente un rôle majeur de défense contre les agents pathogènes et les toxines. La BEI représente une **barrière physique** avec son mucus qui protège les CEI. Le renouvellement régulier des CEI participe également à la défense de la BEI en limitant l'adhésion et la colonisation des pathogènes aux CEI (Takiishi, Fenero, et Câmara 2017). Certaines CEI sont capables de phagocyter les bactéries pathogènes, par phagocytose ou par séquestration et neutralisation des toxines bactériennes (Chelakkot, Ghim, et Ryu 2018).

La BEI est aussi une **barrière chimique** avec la production de **peptides anti-microbiens** par les entérocytes et cellules de Paneth. Les PAM, comprenant l'α-défensine, le lysozyme C, les lectines de type C, les phospholipases sont indispensables pour contrôler les potentiels pathogènes présents dans la lumière intestinale (Takiishi, Fenero, et Câmara 2017). De plus, les CEI, notamment les cellules M, en étant des cellules présentatrices d'antigènes (CPA) vont activer le système immunitaire (SI) et donc permettre une réponse efficace et rapide de l'organisme face à un corps étranger.

2.2.3. DEFAUTS DE LA BEI DANS LES MICI

La pathogenèse des MICI est complexe et mal connue à ce jour. Cependant, des études de GWAS ont mis en évidence qu'en plus des gènes impliqués dans l'inflammation, des gènes référant à des fonctions de barrière (perméabilité, réparation, autophagie) sont également impliquées dans la pathogenèse des MICI (Hampe et al. 2007). Une barrière **hyper-perméable**, des **défauts de réparation** et de **défense** vont faciliter le passage d'agents pathogènes au travers de la barrière et vont activer le système immunitaire de façon chronique.

2.2.3.1. DEFAUT DE PERMEABILITE

L'**hyper-perméabilité** semble être un facteur **aggravant** des MICI, par exemple, l'augmentation de perméabilité intestinale est corrélée avec une intensification de la sévérité de symptômes diarrhéiques (Chang et al. 2017). De plus, l'hyper-perméabilité semble être une caractéristique **précoce** de la pathologie avec une hausse de perméabilité généralement décrit avant l'apparition ou la rechute de la MC (Arrieta et al. 2006; Okamoto et Watanabe 2005; Irvine et Marshall 2000; Wyatt et al. 1993). De nombreuses études décrivent une augmentation de la perméabilité de la BEI chez ces patients (Arrieta et al. 2006), associée à l'apparition et la survenue de poussées inflammatoires chez les patients Crohn (Arnott, Kingstone, Ghosh 2000). Cependant, cette élévation de perméabilité intestinale peut apparaître dans des zones non inflammées (Söderholm et al. 1999) laissant supposer que l'altération de la BEI n'est pas dépendante de l'activation des cellules du SI et serait une cause de la hausse de l'inflammation. En effet, une barrière hyper-perméable permet le passage non sélectif et à haut débit de bactéries dans l'épithélium. D'ailleurs les patients atteints de MICI, en particulier de RCH, disposent d'une augmentation de bactéries associées à la muqueuse (Kleessen et al. 2002; Swidsinski et al. 2005). Un large spectre de bactéries sont présentes au contact de la muqueuse des patients RCH, allant des Protéobactéries (*Enterobacteriaceae*), aux Firmicutes (*Clostridium*) et aux Bacteroidetes (*Bacteroides* et *Prevotella*). Au niveau de la muqueuse colique des patients Crohn, les Protéobactéries, et les *Bacteroides*/*Prevotella* dominent, les bactéries Gram + sont quasi absentes. Le passage de ces bactéries participe à amplifier l'inflammation présente. De façon intéressante, une diminution de la perméabilité protège le développement de l'inflammation dans des modèles de colite (Arrieta et al. 2009).

Des défauts d'expression des protéines de **jonctions serrées** participent à l'hyper-perméabilité (**Figure 19**). De tels défauts d'expression sont classiquement décrits chez les patients atteints de MICI, avec une **augmentation** de la **claudine-2** (Weber et al. 2008) qui forme un pore et augmente le passage de molécules non sélectives. La hausse de l'expression de cette claudine est d'ailleurs associée à des symptômes de type diarrhéique (Amasheh et al. 2002). D'autres protéines sont également différentiellement exprimées chez les patients. Une **réduction** des **occludines**, **tricellulines** et **JAM-A** a été rapportée chez les patients (Vetrano et al. 2008; Aguanno et al. 2020; Barbara et al. 2021). De façon remarquable, des souris délétées de la protéine JAM-A entraînent une élévation de perméabilité colique due à une augmentation des claudines 10 et 15 (Laukoetter et al. 2007). Les claudines 5 et 8 sont diminués dans la MC (Zeissig et al. 2007), dans la RCH c'est la claudine 4 (Heller et al. 2005). Des mutations de la N-cadhérine chez la souris entraînent un accroissement de la perméabilité intestinale et de l'inflammation (Hermiston et Gordon 1995). Ces données supportent l'idée que l'augmentation de perméabilité

peut être indépendante de l'inflammation, et être une cause précoce dans le développement de la pathologie. Cependant, l'inflammation intervient dans la perméabilité de la BEI. Les patients atteints de MICI possèdent des augmentations de cytokines pro-inflammatoires au niveau de l'épithélium (Markus F. Neurath 2014). Une hausse de TNF-α en se liant aux récepteurs aux TNF (TNFR) des CEI active la MLCK, induisant l'expression de la claudine-2 (Su et al. 2013) et une diminution de la claudine-4 (Prasad et al. 2005), et par conséquent la perméabilité intestinale. La MLCK est par ailleurs sur-exprimée dans le côlon des patients MICI (Blair et al. 2006).

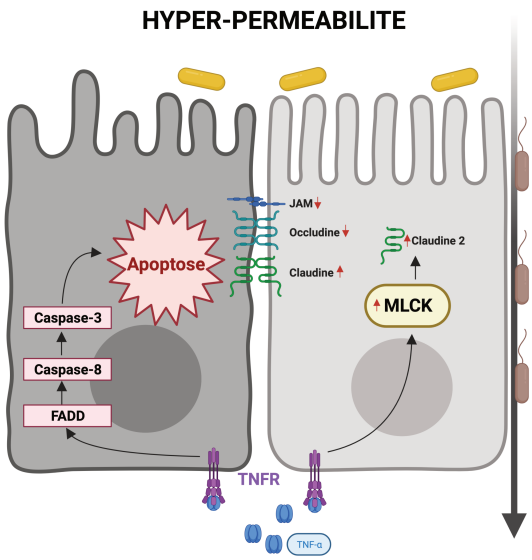

Figure 19. Hyper-perméabilité de la BEI dans les MICI (d'après Craig et al. 2022). Le TNFα en se liant à son récepteur, active la voie des caspases inductrices d'apoptose et la MLCK, altérant ainsi les protéines des jonctions serrées. Les dommages au niveau des protéines de jonctions serrées résultent en une augmentation de la translocation bactérienne.

Les patients atteints de MICI présentent une augmentation de **l'apoptose** au niveau de la muqueuse du côlon (**Figure 19**). En effet, une augmentation de la **caspase-3 clivée (CC3)** ainsi que de marqueurs de mort cellulaire M30 ont été reportée dans la muqueuse de patients MC et RCH par rapport à des patients contrôles (Pochard et al. 2021). L'apoptose peut causer une altération de la BEI. Il a été montré qu'une augmentation de l'apoptose à la suite d'un traitement au lipopolysaccharide (LPS) entraînait une élévation de la perméabilité paracellulaire (Yu et al. 2005). De plus, l'augmentation de la CC3 est associée à une hausse de perméabilité dans plusieurs modèles de colite (Pochard et al. 2021; Su et al. 2013).

2.2.3.2. DEFAUT DE REPARATION

En plus d'une barrière hyper-perméable, les patients atteints de MICI présentent des **défauts de réparation** de la barrière (Leoni et al. 2015). La réparation de la muqueuse intestinale est prédicteur de rémission à long terme (Baert et al. 2010), et est associée avec une diminution du risque de chirurgie (Markus F Neurath et Travis 2012).

L'inflammation entraîne des défauts de réparation de la BEI. En effet, une élévation de TNF-α augmente la desquamation de la BEI (Watson et Hughes 2012). Une hausse d'IL-13 est associée à un ralentissement du phénomène de restitution (Heller et al. 2005).

De façon intéressante, des études suggèrent que les dommages au niveau des **protéines de jonction** seraient une cause d'un défaut de réparation de l'épithélium de façon indépendante de l'inflammation. Effectivement, des mutations de la N-cadhérine chez des souris entraînent des défauts de prolifération et de migration (Hermiston et Gordon 1995), deux propriétés de l'épithélium impliquées dans la réparation. Curieusement, des souris ayant une délétion spécifique de ZO-1 dans les CEI présentent une augmentation de perméabilité intestinale mais ne développent pas de colites. En revanche, les souris développent une hypersensibilité aux agressions des muqueuses ainsi que des défauts de réparation. Effectivement, les processus de prolifération et de la voie de signalisation échouent à être activés en réponse à des dommages. De plus, ZO-1 est aux pôles mitotiques pendant la division cellulaire. En l'absence de ZO-1, le fuseau mitotique n'est pas correctement orienté entraînant une perturbation de la prolifération cellulaire (Kuo et al. 2021). Donc, la délétion de ZO-1 serait plutôt une cause de défauts de réparation de la BEI de façon indépendante de l'inflammation.

D'autres molécules, notamment impliquées dans les phénomènes de **prolifération** et de **migration**, tel que la gasdermine B (GSDMB), sont augmentées dans l'épithélium intestinal des patients MICI par rapport à des individus sains. Cette protéine est mutée chez des patients MICI entrainant des défauts fonctionnels perturbant la restitution et la réparation épithéliale. Cette étude établit GSDMB comme un facteur essentiel dans la restauration de la BEI (Rana et al. 2022).

2.2.3.3. DEFAUT DE DEFENSE

Les **défenses** de la barrière sont défectueuses chez les patients MICI. C'est le cas du mucus qui est anormal, la RCH est associée avec une couche de mucus plus fine et discontinue (Alipour et al. 2016). Les patients RCH présentent également une diminution d'expression de MUC-2, alors que les patients Crohn ont une augmentation de MUC-2 pouvant aller jusqu'à 70% pour les formes sévères (Liu et al. 2020). De plus, des souris déficientes de Muc-2 développent de façon spontanée des colites (Haskey et al. 2022).

Une diminution de l'expression de WFDC2 (pour « WAP four-disulfide core domain protein 2 ») est présente chez les patients RCH et dans le côlon de souris ayant une colite induite au DSS. WFCD2 est une molécule anti-protéase exprimée dans les cellules caliciformes situées au fond des cryptes intestinales, impliquée dans l'inhibition de la croissance bactérienne (Parikh et al. 2019; Chhikara et al. 2012). *In vivo*, cette molécule préserve l'intégrité des protéines de jonction serrées et prévient de l'invasion de bactéries commensales et de l'inflammation de la muqueuse (Parikh et al. 2019).

Une diminution de la sialylation, c'est-à-dire l'ajout de groupes d'acides sialiques sur les mucines, est décrite chez les patients MICI. La sialylation protège l'intégrité du mucus intestinal contre la dégradation bactérienne. Une diminution de la sialylation altère les mucines et par conséquent la muqueuse intestinale en étant plus pénétrable pour les bactéries (Yao et al. 2022). Par ailleurs, la glycosylation des mucines est également affectée, et cette altération est étroitement corrélée avec le degré d'inflammation et l'évolution de la maladie. La glycosylation des mucines participe à la sélection des bactéries commensales de l'hôte. En conséquence, les patients atteints de MICI présentent une dysbiose intestinale, pouvant expliquer les variations de la glycosylation

par rapport aux individus sains (Larsson et al. 2011). Cette altération de la glycosylation est vraisemblablement attribuable à la dégradation des glycanes par les bactéries intestinales. Enfin, des défauts de glycosylation favorisent le contact entre les bactéries et la BEI, alimentant ainsi l'inflammation (Theodoratou et al. 2014).

La production des peptides anti-microbiens par les cellules de Paneth est également anormale. HBD1 pour human ß-defensin 1, est exprimée de manière constitutive dans la muqueuse intestinale et n'est pas induite par l'inflammation alors que HBD2 et 3 sont inductibles. Dans la MC, on retrouve une diminution d'HBD1 dans le côlon, associée à une augmentation de bactéries épithéliales, ainsi qu'une induction défaillante d'HBD2 et 3 altérant la défense contre les pathogènes (Neurath et al. 2014; Wehkamp et al. 2002). De plus, une diminution des IgA spécifiques de bactéries commensales remplacée par une augmentation des IgG dans la muqueuse des patients MICI a été décrite (Ruthlein et al. 1992)

Enfin, une altération de **l'autophagie** (Hooper et al. 2019) avec notamment des mutations du gène ATG16L1 a été décrite chez les patients MICI. L'autophagie réfère à toute voie de dégradation cellulaire qui implique le transport de contenu cytoplasmique dans un **phagophore** puis un **auto-phagosome** pour être dégradé dans le lysosome. NOD2 recrute la protéine ATG16L1 à la membrane plasmique des cellules afin d'éliminer les bactéries intra-cellulaires (Iida, Onodera, et Nakase 2017). La stimulation des TLR conduit à une activité anormale de l'inflammasome dans les macrophages et d'autres cellules de l'immunité innée lorsque ARG16L1 est déficiente (Saitoh et al. 2008).

Au-delà de NOD2, la reconnaissance de pathogènes par d'autres PRR est dérégulée dans les MICI. C'est le cas du TLR4 qui reconnaît le LPS des bactéries à Gram négatif. Ce récepteur est augmenté dans l'épithélium de patients RCH avec une pathologie active, alors que le TLR3 est diminué chez les patients MICI (Lu et al. 2018).

Ces résultats suggèrent que l'altération de la BEI participe à la pathogenèse de ces maladies et notamment, qu'elle favorise la translocation de micro-organismes et de métabolites du microbiote intestinal au travers de la BEI induisant l'activation des cellules immunitaires et de l'inflammation intestinale.

2.3. LE SYSTEME IMMUNITAIRE INTESTINAL

2.3.1. COMPOSITION

Le système immunitaire intestinal est le plus vaste du corps humain, il contient 70% des cellules immunitaires du corps. Ceci est dû à son exposition importante aux antigènes et stimuli immunitaires (Jung, Hugot, et Barreau 2010). C'est au niveau de la muqueuse, c'est-à-dire l'épithélium, la *lamina propria* et la *muscularis mucosae* que se déroule la majorité des réactions immunitaires.

Le **tissu lymphoïde associé à l'intestin**, appelé le GALT (pour « gut-associated lymphoid tissue »), représente un organe lymphoïde secondaire composé **d'agrégats de follicules lymphoïdes** et de **tissus lymphoïdes solitaires isolées** (SILT) qui sont des sites **inducteurs** de l'immunité intestinale. Alors que l'épithélium et la *lamina propria* sont des sites **effecteurs** (**Figure 20**) (Mowat et Agace 2014).

Les agrégats de follicules lymphoïdes regroupent les **plaques de Peyer** (PP) dans l'intestin grêle (**Figure 20**), les **patchs caecaux** au niveau de la valve iléocæcale et les **patchs coliques**. Les PP sont visibles macroscopiquement, regroupent une centaine de follicules lymphoïdes et représentent la source majeure de plasmoblastes producteurs d'IgA pour l'intestin grêle alors que les patchs caecaux jouent un rôle dans la génération de plasmocytes sécréteurs d'IgA migrant dans le côlon en réponse au microbiote local. Les PP sont majoritairement localisées au niveau de l'iléon terminal, où l'on retrouve près de 45% des PP à ce niveau (Jung, Hugot, et Barreau 2010). Elles sont composées d'un **centre germinatif** contenant une condensation de **lymphocytes B** en maturation et prolifération entourée d'un **manteau** constitué majoritairement de **lymphocytes T** (**Figure 20**). Concernant les tissus lymphoïdes solitaires isolés, ils ont des tailles variées allant de la cryopatchs aux **follicules lymphoïdes isolés** (ILF), majoritairement concentrés dans le côlon. Ces follicules ont également une zone dense en lymphocytes B mais n'ont pas de « zone T » bien déterminée (Jung, Hugot, et Barreau 2010).

Les follicules lymphoïdes sont situés dans la muqueuse et la sous-muqueuse, entourés d'un **épithélium associé aux follicules** (FAE). Les FAE présentent une couche de mucus plus fine à leur surface, avec une glycosylation du glycocalyx spécifique. De plus, il contient des cellules M, décrites précédemment. La régulation de la perméabilité paracellulaire est également différente avec une augmentation de la claudines-3 et de l'occludine et une diminution de la claudine-2. De plus, la *lamina propria* ainsi que la gaine de myofibroblastes sous-jacente sont plus poreuses. La *lamina propria* contient des cellules de l'immunité innée telle que des cellules dendritiques, macrophages, éosinophiles et mastocytes, mais aussi des lymphocytes T et B. L'épithélium est riche en lymphocytes T (Mowat et Agace 2014; Jung, Hugot, et Barreau 2010).

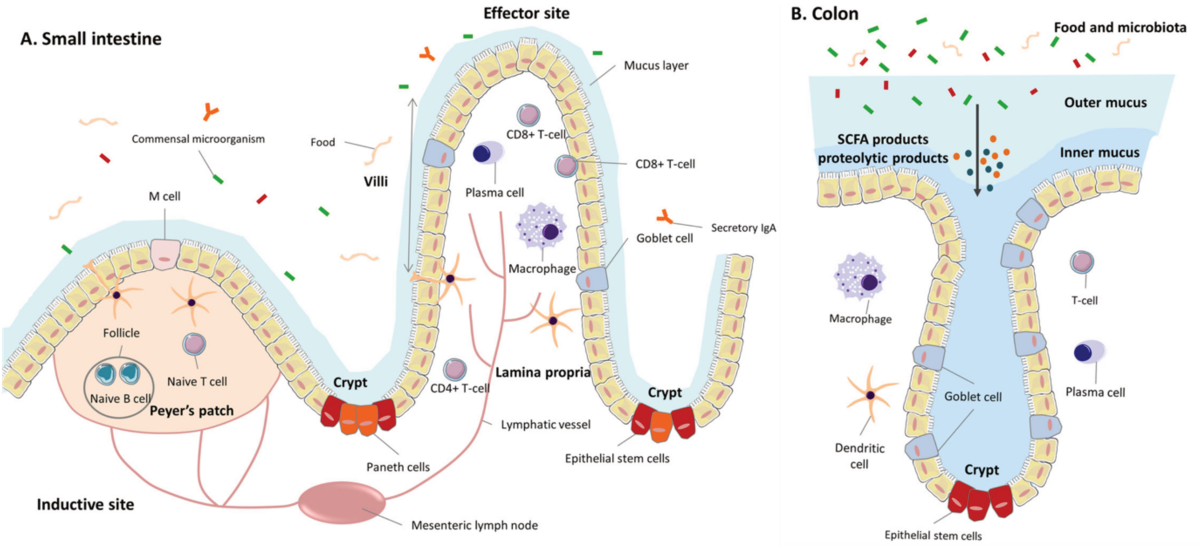

Figure 20. Le système immunitaire dans l'intestin grêle (à gauche) et le côlon (à droite) (Cheng et al. 2021).

Les composants immunitaires du tissu lymphoïde associé à l'intestin se situent au niveau des plaques de Peyer (site inducteur), de la lamina propria et de l'épithélium (site effecteur) alors que le côlon ne possède pas de plaques de Peyer.

De plus, l'intestin est pourvu de ganglions lymphatiques, les **ganglions mésentériques**, le drainent de manière différenciée en fonction de la localisation dans l'intestin. Le système lymphatique intestinal se distingue en deux compartiments distincts, avec un compartiment drainant la couche musculaire et l'autre la muqueuse. Cette vascularisation présente un rôle crucial dans l'élimination des antigènes et leucocytes des sites d'inflammation (De Souza et Fiocchi 2016).

2.3.2. INNEE / ADAPTATIF

2.3.2.1. SYSTEME IMMUNITAIRE INNEE

Le système immunitaire inné ou « passif » est la première ligne de défense de l'organisme, il comprend les cellules présentatrices d'antigènes (macrophages et cellules dendritiques), les cellules lymphoïdes innées, les mastocytes, les cellules natural-killer (NK), et les neutrophiles. Ces cellules identifient et éliminent les pathogènes sur le court terme, *via* des mécanismes non spécifiques (Kmieć, Cyman, et Ślebioda 2017).

2.3.2.1.1. LES CELLULES PRESENTATRICES D'ANTIGENE (CPA)

Les CPA regroupent les **cellules dendritiques** et les **macrophages**. Ces cellules connectent les deux types de réponses immunitaires (RI). Les DC sont les plus impliquées dans la présentation antigénique et jouent un rôle majeur dans la tolérance immunitaire en sécrétant de l'IL-10. Lorsqu'elles sont activées, elles migrent dans les ganglions lymphatiques. Les DC sont retrouvées à la fois dans les sites inducteurs et effecteurs des GALT. Ces cellules sont capables d'interagir avec le microbiote intestinal *via* la présence de TLR présent au niveau de leur dendrite qui s'insère entre les CEI jusqu'au lumen, mais aussi indirectement *via* les cellules M. Lorsque ces cellules ont phagocyté l'antigène, elles migrent dans les ganglions mésentériques où elles sécrètent des cytokines

ou des molécules de co-stimulation capables d'orienter la réponse immunitaire en activant des lymphocytes T naïfs (Th0) ou mémoire.

Les **macrophages** présentent une fonction phagocytaire majeure et sécrètent des cytokines pro- ou anti-inflammatoires en fonction de l'environnement inflammatoire. Les macrophages activent de façon locale la réponse immunitaire adaptative contrairement aux DC. Il existe deux types de macrophages : les macrophages de type M1 qui ont une activation classique et les M2. Les M1 sécrètent un panel de cytokines et chemokines pro-inflammatoires ainsi que des espèces réactives de l'oxygène (ROS) et NOS (« nitric oxide synthase ») au vu de leur activité anti-bactérienne majeure. D'autre part, les macrophages de type M2 jouent un rôle plutôt anti-inflammatoire en sécrétant de l'IL-10 qui active la polarisation des Th0 en Th2. De plus, *via* la sécrétion de chemokines anti-inflammatoires ils permettent le recrutement de basophiles et éosinophiles et jouent un rôle dans la réparation tissulaire et la fibrose (Kałużna, Olczyk, et Komosińska-Vassev 2022).

2.3.2.1.2. LES CELLULES LYMPHOÏDES INNEES (ILC)

Les ILC sont des cellules effectrices hématopoïétiques résidentes des tissus dérivant d'un progéniteur commun exprimant Id2. Elles présentent des caractéristiques communes telles qu'une morphologie lymphoïde, une lignée cellulaire négative (CD3-, B220-, GR1-, CD11b-, Ter119-) et l'absence de récepteurs d'antigènes dépendants de RAG. Les ILC sont impliquées dans l'élimination des micro-organismes intra- et extra-cellulaires, la protection de la BEI, la réparation et le remodelage tissulaire. On retrouve 3 types d'ILC détaillés dans le tableau suivant (**Tableau 1**).

Tableau 1. Les cellules lymphoïdes innées.

Cellules lymphoïdes innées	**ILC1**	**ILC2**	**ILC3**
Cytokines inductrices	IL-12	IL-33	IL-23, IL-1ß
Facteurs de transcription activés	Tbet	GATA-3, RORα	RORɣT
Cytokines synthétisées	IFN-ɣ	IL-5, -13, -4, -6, -8, -9, GM-CSF	IL-22, IL-17
Fonctions	élimination virus et bactéries	élimination parasites et allergènes, altération BEI	protection BEI

2.3.2.1.3. LES NEUTROPHILES

Les neutrophiles (ou leucocytes polymorphonucléaires) représentent près de 50-60% des leucocytes de la circulation sanguine (Fournier et Parkos 2012). Ces cellules limitent la translocation bactérienne lorsque la barrière est lésée en produisant des ROS (tels que l'H2O2), des composants granulaires comme des enzymes bactéricides (myéloperoxydase (MPO), PAM, métallo-protéase matricielle (MMP)) et des NET (neutrophil extracellular traps) (L. Kang et al. 2022). Les NETs sont des structures en forme de mailles contenant de l'acide désoxyribonucléique (ADN), de la chromatine condensée et des composants granulaires (Leppkes et al. 2022).

Ces cellules sont également impliquées dans la résolution de l'inflammation *via* la production de médiateurs lipidiques à l'instar des **résolvines E1** et **protectines D1**, capable d'inhiber le recrutement des neutrophiles et augmenter la phagocytose et l'apoptose des neutrophiles par les macrophages (Kang et al. 2022). De plus, les neutrophiles diminuent les débris cellulaires au site de l'inflammation par phagocytose. De façon intéressante, les études dévoilent la responsabilité des neutrophiles dans la **restitution épithéliale**. En effet, les neutrophiles libèrent des protéases et ROS impliqués dans la destruction de l'épithélium intestinal, mais aussi en consommant l'oxygène présent dans le micro-environnement épithélial lors de la phase aigüe de l'inflammation, les neutrophiles stabilisent les HIF (pour « hypoxia inductible factors ») qui favorisent la transcription de gènes impliqués dans la restitution épithéliale (Lin et al. 2018; Goggins et al. 2021).

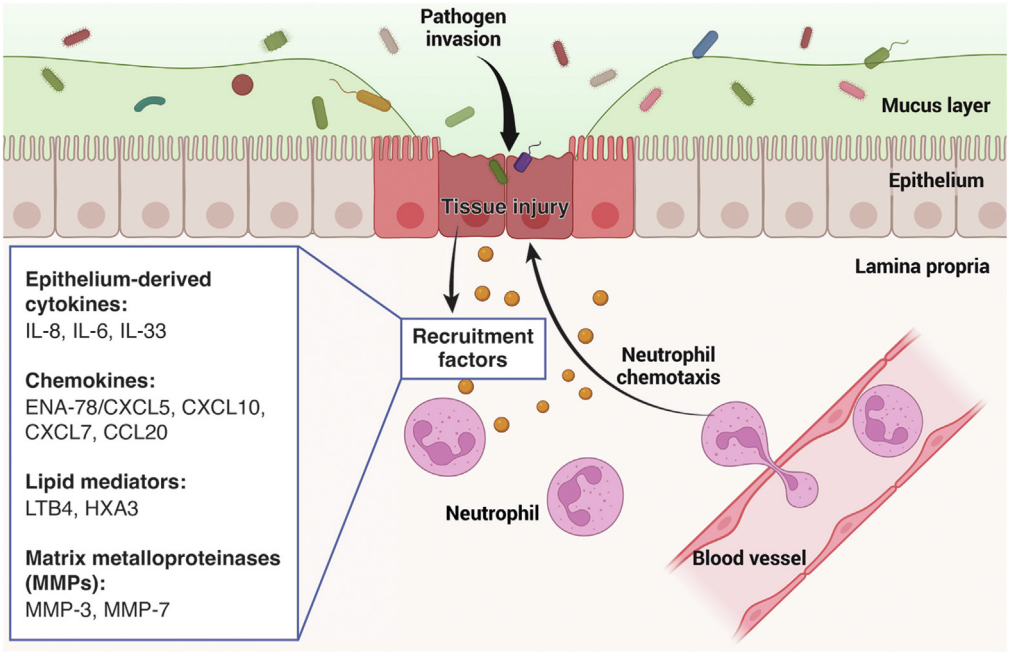

Figure 21. Recrutement des neutrophiles (Kang et al. 2022). Les cellules épithéliales inflammées attirent les neutrophiles à migrer des vaisseaux sanguins vers les sites d'inflammation à travers la *lamina propria*. Les chimiokines dérivées de l'épithélium comprennent des cytokines, des chemokines, des médiateurs lipidiques et des métalloprotéinases de matrice.

Le dialogue entre les neutrophiles et les cellules épithéliales est un aspect crucial lors de l'inflammation. En effet, la première étape qui est le **recrutement des neutrophiles** est favorisée par les cellules immunitaires et produits bactériens, mais aussi par les CEI (Figure 21). Ces dernières *via* la sécrétion de cytokines (IL-8, IL-33), chémokines (CXCl10/CXCR3), **LTB4** vont favoriser le recrutement des neutrophiles (Kucharzik 2005; Salem et al. 2018; Kang et Yu 2021). De plus, les CEI produisent des MMP qui sont des endoprotéases dépendantes du zinc ou du calcium capable de dégrader la MEC pour former des canaux facilitant la transmigration des neutrophiles (Phillipson et Kubes 2019). La deuxième étape est la migration transépithéliale qui comprend l'adhésion des neutrophiles à la surface basolatérale de l'épithélium *via* les intégrines ß2 puis la migration transépithéliale qui nécessite une fine coordination entre les CEI et les neutrophiles pour réguler les protéines de jonction cellulaires (Blake et al. 2004).

Enfin, les neutrophiles se retrouvent au pôle apical des CEI. Ce phénomène de transmigration a pour conséquence d'augmenter la perméabilité de la BEI, et modifie la prolifération et l'apoptose des CEI. La dernière étape consiste en l'élimination des neutrophiles par les macrophages et les CEI (Kang et al. 2022).

2.3.2.2. SYSTEME IMMUNITAIRE ADAPTATIF

Contrairement à la réponse immunitaire innée, le système immunitaire adaptatif est hautement **spécifique**, **adaptable** et confère une immunité de **longue durée**. En effet, la spécificité pour l'antigène est le résultat d'une maturation et d'un développement complexes des cellules immunitaires.

2.3.2.2.1. LES LYMPHOCYTES T

Les acteurs clés de la réponse immunitaire adaptative sont les **lymphocytes T**, **CD8+ cytotoxiques** et **CD4+ « helper »** ou Th. En condition physiologique, les composantes du SI adaptatif coopèrent les unes avec les autres et avec les molécules et cellules du SI inné pour monter une RI efficace, capable d'éliminer les agents pathogènes envahissants. Les lymphocytes Th0 peuvent être activés et se différencier en lymphocytes Th1, Th2, Th17 et Treg en fonction de l'environnement cytokinique (Geremia et al. 2014).

2.3.2.2.1.1. LYMPHOCYTES TH1

Les lymphocytes Th1 sont impliqués dans l'élimination des pathogènes intra-cellulaires. Les Th1 produisent de l'IFN-ɣ impliqué dans l'activation des macrophages ainsi que dans les réactions inflammatoires et auto-immunes. Les lymphocytes Th1 sont activés par l'IFN-ɣ et sont associés à une augmentation d'IFN-ɣ et de d'IL-12/IL-23 (Weigmann et al., 2002).

2.3.2.2.1.2. LYMPHOCYTES TH2

Les lymphocytes Th2 sont impliqués dans l'élimination des parasites, les réactions allergiques et le maintien de l'homéostasie de la muqueuse intestinale, notamment en régulant la réparation tissulaire. En sécrétant certaines cytokines (IL-5, IL-13, IL-21, IL-25), les Th2 inhibent l'activation des Th1 (Kałużna, Olczyk, et Komosińska-Vassev 2022).

2.3.2.2.1.3. LYMPHOCYTES TH9

Les lymphocytes Th9 sont activés par l'IL-4 et le TGF-ß. Ces lymphocytes sécrètent l'IL-9, une cytokine impliquée dans l'élimination des parasites, dans le recrutement des neutrophiles lors d'une réaction allergique mais également influe l'homéostasie de la BEI en induisant la synthèse de mucus et en régulant l'expression protéique des protéines de jonction serrées dans le but d'augmenter la perméabilité de la barrière (Kałużna, Olczyk, et Komosińska-Vassev 2022).

2.3.2.2.1.4. LYMPHOCYTES TH17

Les lymphocytes Th17 jouent un double rôle. D'une part, ils sécrètent des cytokines pro-inflammatoires afin d'éliminer les bactéries extra-cellulaires et les champignons. D'autre part, ils jouent un rôle protecteur sur la BEI. En effet, ils sécrètent des cytokines de la famille de l'IL17. L'IL-17 et l'IL-22 stimulent la sécrétion de mucus et de peptides anti-microbiens. De plus, l'IL-17A présente un rôle bénéfique sur la localisation de l'occludine (Kałużna, Olczyk, et Komosińska-Vassev 2022).

2.3.2.2.1.5. LYMPHOCYTES TH22

Les lymphocytes Th22 sont impliqués dans la défense anti-virale, anti-bactérienne et anti-fongique. De plus, *via* la production d'IL-10 et d'IL-22, ils présentent un rôle protecteur sur la BEI (Doulabi et al. 2022).

2.3.2.2.1.6. LYMPHOCYTES T REGULATEURS (TREG)

Les lymphocytes Treg sont essentiels dans la tolérance immunitaire envers le microbiote intestinal ainsi que la prévention du développement d'une réponse auto-immune. Ils vont permettre la sécrétion d'IL-10, d'IL-35 et de TGF-ß. Les lymphocytes Treg inhibent la polarisation des Th0 en Th17 (Kałużna, Olczyk, et Komosińska-Vassev 2022).

2.3.2.2.2. LES LYMPHOCYTES B

Les lymphocytes B sont responsables de la synthèse d'anticorps, de la présentation d'antigène aux lymphocytes T et à l'adaptation de la réponse immunitaire *via* la production d'IL-2, IL-4, IFN-ɣ, TGF-ß et de GM-CSF. Les lymphocytes B regroupent les **lymphocytes B effecteurs** capables de sécréter des anticorps et cytokines et les **lymphocytes Breg**, capables de sécréter des facteurs immunosuppresseurs tels que l'IL-10 permettant d'orienter une polarisation des lymphocytes T en Treg (Baba, Saito, et Kotetsu 2020).

Dans l'intestin, les lymphocytes B sont activés dans les ganglions mésentériques, et les nodules lymphatiques. Ensuite, ils migrent vers la *lamina propria* et se différencient en plasmocytes. Les plasmocytes, situés principalement dans la moelle osseuse et la *lamina propria*, constituent le stade final de différenciation des lymphocytes B. Les plasmocytes sécrétant de l'IgA sont majoritaires dans l'intestin, tandis que ceux sécrétant de l'IgG sont liés à l'inflammation (Baba, Saito, et Kotetsu 2020).

2.3.3. HYPERACTIVATION DU SI DANS LES MICI

Les patients atteints de MICI présentent une **hyperactivation** du système immunitaire caractérisée par un environnement cytokinique altéré et une infiltration de cellules immunitaires dans les tissus intestinaux. Les deux types d'immunité sont dérégulés dans les MICI et participent au développement et à l'exacerbation de la pathologie (**Figure 22**).

Concernant **l'immunité innée,** le nombre de DC pro-inflammatoire est augmenté dans la muqueuse des patients MICI. De plus, l'activité des DC est modifiée avec une augmentation des récepteurs de type TLR2 et -4 activant la voie NFkB (pour « nuclear factor-kappa B ») impliquée dans l'inflammation (Middel et al., 2006). La population de macrophages est également dérégulée, avec une balance M1/M2 pro-inflammatoire. L'augmentation des macrophages de type M1, et la diminution des M2 entrainent une augmentation de la sécrétion de cytokines pro-inflammatoires ainsi que l'augmentation de l'activité phagocytaire et de la cytotoxicité (Lissner et al. 2015; Kmieć, Cyman, et Ślebioda 2017). Les mastocytes sont retrouvés augmentés dans la muqueuse des patients MICI, associés avec une augmentation de leurs sécrétagogue à savoir les prostaglandines, leucotriènes, l'histamine, et des cytokines pro-inflammatoires (Nolte et al. 1990). Ces molécules sont notamment impliquées dans la neuro-inflammation présente chez les patients. De plus l'activité des mastocytes est associée à une dysbiose du MI, une réponse fibrotique augmentée et une altération du transport d'ions dans l'intestin (MacNaughton et al. 1994).

Un type cellulaire clé dans la pathogenèse des MICI est les **neutrophiles**. Les neutrophiles sont hyperactivés aboutissant à la déformation de l'architecture des cryptes intestinales. Effectivement, le sécrétagogue des neutrophiles, particulièrement des médiateurs pro-inflammatoires tels que la calprotectine, est associé à une déplétion des cellules caliciformes et la formation d'abcès (Kang et al. 2022). De plus, les neutrophiles libèrent des miRNA pro-inflammatoires inhibant la fermeture des lésions et recrutant des monocytes, lymphocytes T et neutrophiles (Butin-Israeli et al. 2019). L'infiltration des neutrophiles dans la muqueuse est due à une augmentation des enzymes impliquées dans la production de LTB4, telle que la 5-LOX et la LTA4 hydrolase (Kang et Yu 2021). De plus, une accumulation de NET est retrouvée chez les patients MICI. Cette hausse est également observée dans des modèles de colite et induit l'apoptose et la destruction des jonctions cellulaires et donc une élévation de la perméabilité intestinale (Kang et al. 2022). Dans la RCH, les neutrophiles sont les composants cellulaires majeurs des tissus intestinaux. Leur présence excessive est causée par un excès de TNF-α et de LPS, provoquant une production accrue de NET, MPO et ROS responsable des dommages tissulaires et de la formation d'ulcères. Enfin, les ILC jouent un rôle notable dans la pathogenèse des MICI. Dans la MC, l'élévation de la population ILC1 dans la muqueuse inflammée est corrélée avec la phase précoce de la pathologie. Les ILC1 et 2 sont augmentés dans la phase chronique de la RCH. De plus, les ILC3 sont diminués dans les deux pathologies aboutissant à une diminution d'IL-22 qui est bénéfique pour l'épithélium (Kałużna, Olczyk, et Komosińska-Vassev 2022). Cependant, d'autres études rapportent que la population d'ILC3 est dérégulée aboutissant à une production exacerbée d'IL-22 et d'IL-17 entraînant un recrutement accru de neutrophiles qui clivent les jonctions cellulaires et augmentent la perméabilité intestinale (Zeng et al. 2019). Cette altération serait due à l'expression du récepteur IL23R par les ILC3, qui à la suite de la présence excessive de l'IL-23 dans la muqueuse des patients, activerait de manière démesurée les ILC3 qui produiraient trop d'IL-12, IFN-y et d'IL-17.

En ce qui concerne **l'immunité adaptative**, l'inflammation est associée avec une activation et maturation accrue des lymphocytes T. En effet, il existe une augmentation de la réponse inflammatoire des lymphocytes T (Th1, Th2, Th17) et une réduction de cellules Treg (Tindemans, Joosse, et Samsom 2020). La MC est plus associée à une augmentation des cytokines de type Th1 (IFNɣ) alors que la RCH est plutôt de type Th2 (IL-5) (Weigmann et al. 2002).

Certaines études observent une hausse des Treg chez les patients RCH mais avec une diminution de leur activité immunorégulatrice. L'accumulation des Th1 et Th17 est observée dans la muqueuse des patients associés à une augmentation de l'IFN-y et l'IL-17 (Ueno et al. 2018). De plus, la plasticité des lymphocytes Th17 et Th1 est cruciale dans le développement des MICI. En effet, les lymphocytes IFN-y+ IL-17+ sont des lymphocytes Th17 qui se transforment en cellules progénitrices de Th1, ces cellules sont retrouvées de façon importante chez les patients. Les Th1 peuvent aussi se polariser en Th17. Chez les patients Crohn, l'IL-17 est fortement impliquée dans le développement de l'inflammation chronique. De plus, des souris déficientes pour le récepteur IL17RA soumise au TNBS ont une réduction de la sévérité de la colite, renforçant le caractère essentiel de l'IL-17 dans le développement de l'inflammation (Zhang et al. 2006). Un autre élément important est l'IL-23 qui est une cytokine indispensable pour la maturation et l'expansion des Th17. Cette cytokine est augmentée dans la muqueuse des

patients Crohn et RCH. Elle peut être produite par les macrophages CD14+, les DC, les CEI et active la voie pSTAT3 des lymphocytes T CD4+ leur conférant un signal de résistance à l'apoptose. En effet, les lymphocytes T TNFR2+ IL23+ qui libèrent des cytokines de type Th1 et Th17 sont accumulés chez les patients Crohn réfractaires aux anti-TNF. Les études de GWAS décrivent un polymorphisme du gène codant pour l'IL23R associé à la pathogenèse de la MC (Schmitt, Neurath, et Atreya 2021). En effet, ces patients sont caractérisés par une accumulation de cellules réactives à l'IL-23 dans la muqueuse. Les voies de l'IL-23 et l'IL-17 sont fortement impliquées dans la pathogenèse de la MC mais aussi dans le développement de la RCH avec une élévation de l'IL-23 chez les patients RCH qui entraine une hausse des Th17 et une baisse des Th22 favorisant l'inflammation chronique. Les patients RCH ont également une production exacerbée d'IL-33 dans les phases actives de la maladie. L'IL-33 est responsable de l'augmentation des Th2, caractéristique de la RCH, qui produit de l'IL-13 altérant l'intégrité de la BEI en augmentant la claudine-2, l'apoptose et en favorisant la fibrose tissulaire (Yang et al. 2013; Kobori et al. 2010). De plus, les Th9 sont accumulés dans la muqueuse des patients RCH provoquant une production exacerbée d'IL-9. L'IL-9 est une cytokine favorisant l'expression de la claudine-2 et donc la perméabilité intestinale. En effet, des souris déficientes en IL-9 développent une colite moins sévère caractérisée par une diminution de la claudine-2 (Gerlach et al. 2014).

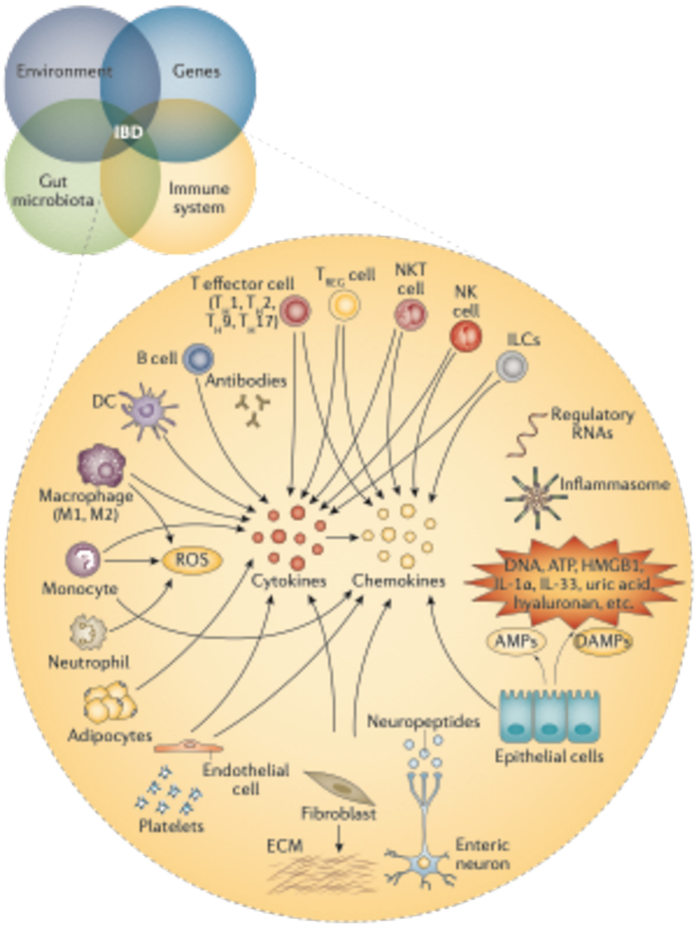

Figure 22. **L'immunopathogenèse des MICI** (De Souza et Fiocchi 2016).

2.4. LE MICROBIOTE INTESTINAL : FOCUS SUR LES BACTERIES

2.4.1. COMPOSITION

Le **microbiote intestinal** correspond à environ 10^{14} micro-organismes (mo), il est considéré comme un organe à part entière. Il existe un gradient de concentration croissante tout le long du tube digestif, avec également une augmentation des bactéries anaérobies à la fin du tube digestif. Le côlon est le segment d'intestin qui abrite la concentration la plus importante de bactéries, soit 10^{11} à 10^{12} bactéries/mL (Rinninella et al. 2019), avec un temps de transit plus long et un pH neutre à moyennement acide, ainsi que des conditions anaérobies, il représente un habitat idéal pour le MI. L'intestin grêle représente un environnement plus complexe à la colonisation du MI avec le court temps de transit, un pH plus faible et un potentiel RedOx plus élevé et la forte concentration d'acides biliaires (**Figure 23**).

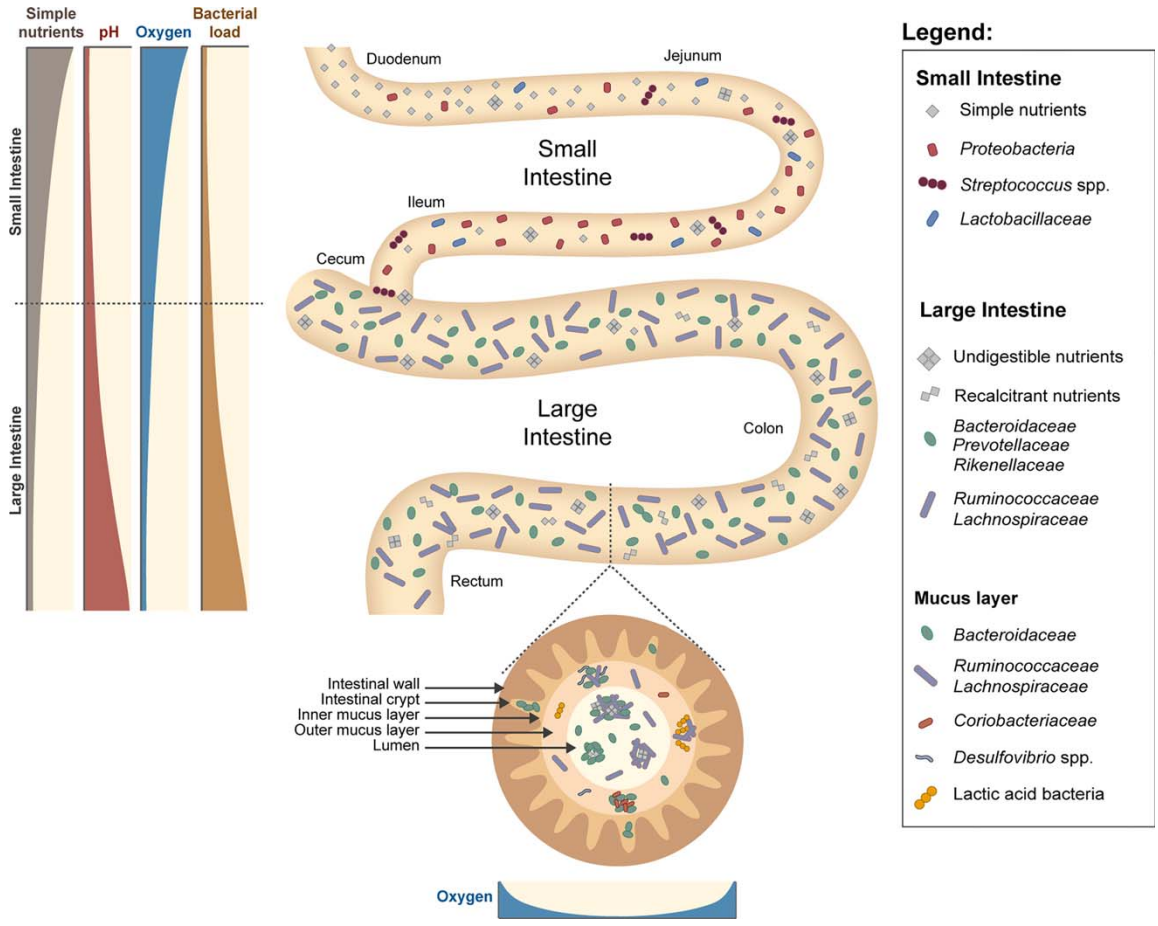

Figure 23. **Gradient de concentration bactérienne dans l'intestin** (Pereira et Berry 2017)**.** Les gradients de pH et d'oxygène le long de l'axe longitudinal limitent la charge bactérienne dans les régions proximales de l'intestin grêle, tandis que le côlon transporte de fortes charges bactériennes. Des nutriments simples sont abondants dans l'intestin grêle et sont métabolisés par des bactéries spécifiques. En revanche, le côlon est peuplé de bactéries capables de métaboliser des nutriments indigestibles. Il existe également une hétérogénéité spatiale le long de l'axe transversal de l'intestin, avec la

couche de mucus et la lumière abritant des populations bactériennes différentes en fonction des nutriments disponibles et de l'oxygène.

Le microbiote intestinal vit en **symbiose** avec l'hôte caractérisé par une grande diversité, stabilité et résilience et ayant des fonctions métaboliques et immunologiques. De façon surprenante, le microbiote intestinal est très bien **préservé** entre les individus mais, à l'instar de notre empreinte digitale, chaque individu est caractérisé par un microbiote intestinal **unique**. La composition du microbiote intestinal est très largement affectée par le mode de vie, l'âge, l'alimentation, l'utilisation d'antibiotique, la méthode d'accouchement etc. Le microbiote intestinal comprend des parasites intestinaux eucaryotes, le mycobiome, l'archéome, le virome et le bactériome. Nous nous concentrerons sur les bactéries du microbiote intestinal.

Avant tout, un rapide point de taxonomie. Les bactéries sont organisées en phylum, classe, ordre, famille, genre et espèces. Seuls quelques phyla sont présents dans le microbiote intestinal, regroupant plus de 160 espèces bactériennes. Les six phyla représentés dans le MI sont les suivants : Verrucomicrobiota (anciennement Verrucomicrobia), Actinomycetes (anciennement Actinobacteria) , Pseudomonadota (anciennement Proteobacteria), Fusobacteria, Bacillota (anciennement Firmicutes) et Bacteroidota (anciennement Bacteroidetes) (**Figure 24**). Ces deux derniers représentent 90% du microbiote intestinal.

Figure 24. Classification taxonomique des bactéries de l'intestin (Rinninella et al. 2019). Les *Firmicutes* et *Bacteroidetes* représentent 90% du microbiote intestinal.

2.4.1.1. BACILLOTA

Le phylum des Firmicutes est composé de plus de 200 genres différents, notamment les *Faecalibacterium*, *Lactobacillus*, et *Clostridium*. Les *Clostridia* représentent 95% des Bacillota, elles sont majoritairement commensales bien que certaines soient pathogènes, comme *Clostridium difficile* (Rinninella et al. 2019).

2.4.1.1.1. FAECALIBACTERIUM PRAUSTNITZII

F. prausnitzii est l'une des bactéries anaérobies les plus abondantes dans le MI (Leylabadlo et al. 2020). Cette bactérie est un membre important du MI, avec un impact considérable sur la santé de l'hôte. En effet, des changements d'abondance de *F. prausnitzii* sont généralement décrits dans des contextes pathologiques, en particulier dans les MICI. Le ratio *F. prausnitzii*/*E. coli* a été proposé comme marqueur de dysbiose, c'est-à-dire une altération de l'équilibre de la population en micro-organismes (Leylabadlo et al. 2020).

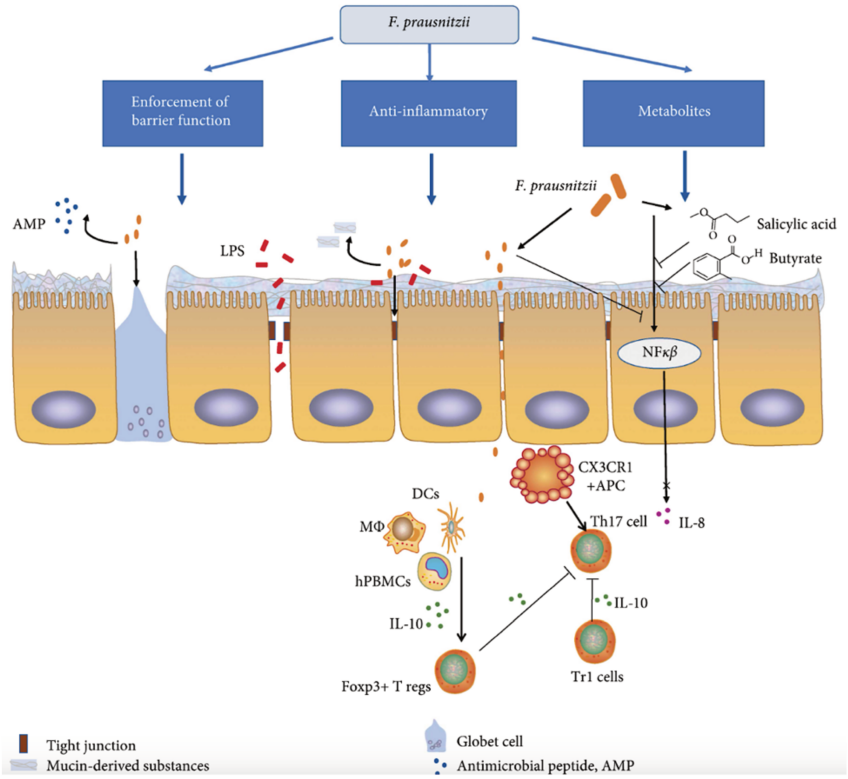

Figure 25. **Les différentes fonctions de *F. prausnitzii* sur l'homéostasie intestinale** (He, Zhao, et Li 2021). Les métabolites (butyrate) de *F. prausnitzii* stimulent la sécrétion d'IL-10 par les PBMCs, les DCs et les macrophages, diminuant ainsi les cytokines pro-inflammatoires. Les métabolites de la bactérie (butyrate, acide salicylique) inhibent la sécrétion d'IL-8 en bloquant la voie de NFkB. Les métabolites renforcent la BEI en fournissant des facteurs issus de la dégradation des mucines.

Cette bactérie est capable de fermenter des aliments non-digestibles, des prébiotiques, et de les métaboliser en produisant du **butyrate**, utilisé par les colonocytes en tant que source d'énergie. *F. prausnitzii* est en effet une bactérie productrice de butyrate, un acide gras à chaîne courte (AGCC), à partir d'acétate. Elle possède également des propriétés anti-inflammatoires en partie dues au butyrate mais également à d'autres métabolites tels que l'acide salicylique (Figure 25) (Quévrain et al. 2016). *F. prausnitzii* inhibe l'activation de NFkB pour bloquer la production d'IL-8 par les CEI (Sokol et al. 2008). De plus, elle stimule la production d'IL-10 par les cellules mononuclées du sang périphérique (PBMCs), les DCs et macrophages, favorisant ainsi la prolifération des Treg aux dépens des Th17 (Rossi et al. 2016; Sokol et al. 2008). Par ailleurs, *F. prausnitzii* influence la muqueuse en régulant la glycosylation des mucines et le développement des cellules caliciformes (Wrzosek et al. 2013). Cette bactérie, membre des clostridiales, est depuis peu considérée comme probiotique de nouvelle génération, jouant un rôle clé dans la régulation de l'inflammation et dans le maintien de l'homéostasie. En effet, elle diminue la perméabilité intestinale *in vivo* et *ex vivo*, permettant ainsi le renforcement de la BEI (Carlsson et al. 2013; Martín et al. 2015).

2.4.1.1.2. *LACTIPLANTIBACILLUS*

Les ***Lactiplantibacillus*** sont des bactéries lactiques à Gram positif, anaérobies mais tolérantes à l'oxygène. Ces bactéries sont présentes dans le MI, ainsi que dans le lait maternel. Parmi les espèces résidantes dans le MI on retrouve *: Lactobacillus crispatus, Lactobacillus gasseri, Ligilactobacillus ruminis, Limosilactobacillus reuteri, Lactobacilllus rhamnosus* etc. (Zheng et al. 2020). Les Lactobacilles sont généralement considérés comme non pathogènes, et même bénéfiques pour l'hôte. En effet, certaines espèces sont utilisées comme probiotiques en régulant le système immunitaire et l'intégrité de la BEI (Slover et Danziger 2008). De fait, plusieurs espèces de *Lactobacillus* présentent des **propriétés immunomodulatrices**. *Lactobacillus acidophilus* stimule la production par les DCs d'IL-10 et diminue l'IL-12 (Konstantinov et al. 2008). De façon intéressante, la modulation génétique de la paroi de cette souche, en supprimant l'acide lipoteichoïque (LTA) amplifie les effets anti-inflammatoires de la bactérie. Cette dernière diminue la sévérité de colite induite au DSS chez la souris en augmentant les lymphocytes Treg associés à une élévation d'IL-10 (Mohamadzadeh et al. 2011). D'autres espèces, telles que *L. paracasei* ou *L. rhamnosus* diminuent le niveau des cytokines pro-inflammatoires (IFN-ɣ, IL-6, IL-4) ainsi que le stress oxydant et augmentent l'IL-10 dans le côlon de souris (Laval et al. 2015; Simeoli et al. 2015). Les Lactobacilles améliorent la **défense** et modulent le **microbiote intestinal** de l'hôte. Elles produisent des peptides anti-microbiens tels que les bactériocines, et réduisent le pH intra-luminal, empêchant ainsi le développement de pathogènes (Slover et Danziger 2008; Wang et al. 2018; Simeoli et al. 2015). Des études *in vitro* exposent la capacité des Lactobacilles à inhiber la croissance de différents pathogènes notamment *Escherichia coli* EPEC (Piatek et al. 2020). De plus, *L. plantarum* favorise le développement de *Faecalibacterium in vivo*, associé à une augmentation d'AGCC tel que le butyrate et l'acétate (Wang et al. 2018). Les Lactobacilles **renforcent la BEI**. *In vitro*, elles inhibent la diminution d'expression de la claudine-1, de l'occludine et de ZO-1 causé par *E. Coli* ETEC (Wang et al. 2018) et augmentent la TEER des CEI (Laval et al. 2015). Dans des modèles de colite, *L. rhamnosus* diminue la perméabilité intestinale en restaurant l'expression d'occludine et de E-cadhérine (Laval et al. 2015). D'autres espèces comme *L. paracasei* freinent les dommages tissulaires au niveau du côlon, *via* un rétablissement des protéines de jonction serrées et une régulation du cytosquelette d'actine (Simeoli et al. 2015; Paveljšek et al. 2018). D'autres études soulignent une action anti-apoptotique des lactobacilles *via* la voie PI3K (phosphatidylinositol-4,5-bisphosphate 3-kinase)/Akt (Paveljšek et al. 2018). Par ailleurs, ces bactéries sont très utilisées dans l'industrie agro-alimentaire pour la production de produits fermentés tels que les yaourts et le fromage (Bernardeau, Gueguen, et Vernoux 2006).

2.4.1.1.3. *CLOSTRIDIA*

Les *Clostrida* regroupent des bactéries non pathogènes voire bénéfiques pour l'hôte, ainsi que l'espèce très connue *Clostridium difficile* réputée pour ses infections. Une grande partie des *Clostridia* produit des AGCC en particulier le butyrate. C'est le cas de ***Clostridium butyricum***, détecté chez 10 à 20% des adultes, elle fait partie des premières colonisatrices du microbiote intestinal (Stoeva et al. 2021; Mountzouris, McCartney, et Gibson 2002). *Clostridium butyricum* est un symbionte producteur de **butyrate**. Depuis environ une dizaine d'années cette bactérie est utilisée comme **probiotique** du fait de ses nombreux effets bénéfiques sur l'hôte (Stoeva et al. 2021). En effet, *Clostridium butyricum* présente des propriétés anti-inflammatoires, renforce la BEI en modulant

l'expression des TJ protéines associées à une augmentation de perméabilité. De plus, cette bactérie stimule la production de mucus, et ainsi augmente l'épaisseur du mucus (Stoeva et al. 2021). Enfin, elle modifie le MI en favorisant la croissance de bactéries bénéfiques telles que les Lactobacilles et les Bifidobactéries (Hagihara et al. 2018; 2020). De façon intéressante, une déplétion de *Clostridia*, causée par l'utilisation d'antibiotiques, perturbe le métabolisme énergétique du colonocyte. En effet, ce dernier en réponse à la diminution d'abondance du butyrate, favorise l'oxygénation qui permet l'expansion de pathogènes aérobies tels que Salmonella Typhimurium (Rivera-Chávez et al. 2016). Ces données soulignent l'importance des *Clostridia* productrices de butyrate dans le maintien de l'homéostasie intestinale. En ce qui concerne les *Clostridia* pathogènes, *Clostridium difficile* est de loin la plus célèbre. Cette bactérie est présente chez 5% des adultes et 15 à 70% des enfants, la prévalence de colonisation par *C. difficile* est augmentée chez les patients hospitalisés (Czepiel et al. 2019). Avant l'ère des antibiotiques, *C. difficile* était rarement décrite dans le MI mais elle pouvait être présente. A la fin du 20ème siècle, l'incidence des infections à *C. difficile* explose et son rôle dans la pathogenèse de pathologies intestinales suscite l'intérêt. A présent, les infections à *C. difficile* représentent l'infection nosocomiale la plus répandue dans le monde. Ces infections sont majoritairement le résultat de la transmission des spores de la bactérie. De façon intéressante, les individus caractérisés par une dysbiose du MI sont plus sujets à ces infections (Czepiel et al. 2019). D'ailleurs, la transplantation fécale de microbiote (FMT) est un des traitements les plus efficaces des infections à *C. difficile* (Hvas et al. 2019).

2.4.1.2. BACTEROIDOTA

Les Bacteroidetes colonisent majoritairement le côlon distal et fermentent les polysaccharides indigestibles en AGCC (McNeil et al. 1984). Les genres prédominants du phylum Bacteroidota sont les *Bacteroides* et *Prevotella*. Dans le côlon, ces deux genres peuvent être antagonistes. Les *Prevotella* sont associées à une consommation riche en fibres, comme c'est le cas dans les régimes végétariens, alors que les *Bacteroides* sont plus élevés chez les individus ayant adopté l'alimentation des pays industrialisés (Martínez et al. 2015; Wu et al. 2011).

Cette différence a permis notamment de classer les individus en fonction de leur **entérotype**. Il existe trois entérotypes, l'entérotype 1 caractérisé par un niveau élevé de *Bacteroides* qui présente comme source d'énergie majoritaire les carbohydrates, l'entérotype 2 où le microbiote est dominé par *Prevotella* et l'entérotype 3 où le microbiote est dominé par *Ruminococcus*. Les bactéries membres du microbiote des entérotypes 2 et 3 puisent leur énergie dans la muqueuse de l'intestin (Arumugam et al. 2011). Les entérotypes sont très dépendants du régime alimentaire de l'hôte.

2.4.1.3. ACTINOMYCETOTA

Le phylum des Actinomycetota est moins abondant, il est majoritairement représenté par le genre *Bifidobacterium*. Les *Propionibacteria*, sont également présentes dans le microbiote intestinal.

2.4.1.3.1. BIFIDOBACTERIA

Les *Bifidobacteria* sont responsables de la fermentation des galactooligosaccharides (GOS) pour produire des AGCC qui sont bénéfiques pour l'hôte (Bindels et al. 2015). En effet, elles sont régulièrement utilisées en tant

que probiotique. Ces bactéries favorisent la tolérance immunitaire en stimulant les macrophages, DC et lymphocytes T ainsi qu'en inhibant la production d'IL-8 par les CEI. De plus, elles inhibent le développement de pathogènes (Eichele et Kharbanda 2017). Enfin, les *Bidifobacteria* sont impliquées dans la régulation du cytosquelette d'actine et la diminution de l'apoptose, favorisant la régénération de l'épithélium intestinal *via* l'activation de PRR et la synthèse de facteurs de croissance (Paveljšek et al. 2018). *Bifidobacterium longum* subsp. *infantis* est décrit comme un champion primo-colonisateur de l'intestin du nouveau-né. Son implication précoce est favorisée par les HMO du lait humain qu'il utilise comme source d'énergie. Il possède de fortes propriétés anti-inflammatoires, limite la perméabilité intestinale, module le MI en la défaveur des entérobactéries, réduit le risque de développer une entérocolite nécrosante (NEC) chez le prématuré, et augmente la réponse vaccinale (Underwood et al. 2015).

2.4.1.3.2. PROPIONIBACTERIA

Les bactéries propioniques ne sont généralement pas considérées comme membres du MI humain. Leur détection par les nouvelles méthodes métagénomiques (NGS) est en effet difficile, ce qui explique qu'on les décrive rarement. Des travaux récents ont cependant montré leur présence dans le MI d'enfants allaités, et pas dans celui d'enfants recevant du lait maternisé (Colliou et al. 2017). Leur présence serait inversement corrélée au développement de la NEC.

2.4.1.3.3. CUTIBACTERIA

Les ***Cutibacteria*** sont composé d'espèces particulièrement présentes au niveau du microbiote de la peau, telles que *C. acnes*, mais d'autres espèces sont retrouvées dans le MI comme *C. granulosum* et *C. avidum* (Martin et al. 2019). Les Cutibacteria colonisent précocement le MI de l'hôte et le modifient. Peu d'études mettent en avant leurs effets bénéfiques, bien qu'une supplémentation en *C. avidum* lors de coliques chez l'enfant, diminue la production d'H_2 responsable de ballonnements et douleurs abdominales (Martin et al. 2022).

2.4.1.4. PSEUDOMONADOTA

Les Pseudomonadota sont peu représentées dans le MI d'un individu sain. Cependant, l'expansion des bactéries anaérobies facultatives, telles que les Pseudomonadota, est une signature d'une dysbiose du MI. Cette expansion est observée chez des patients souffrant d'inflammation intestinale sévère, telle que les MICI, le CRC, la NEC (Litvak et al. 2017). De plus, les Proteobacteria possèdent une version du LPS particulièrement immunostimulante, c'est-à-dire extrêmement puissante pour activer les TLR4 de l'hôte (Hemmi et al. 2000).

2.4.1.4.1. ENTEROBACTERIACEAE

La famille des *Enterobacteriaceae* comporte l'espèce *Escherichia coli* ainsi que les *Shigella*. Concernant les *E. coli,* il existe une distinction entre les commensales qui ne sont pas délétères, et les pathogènes opportunistes, voire les souches pathogènes mortelles. Dans la première catégorie, il y a la souche *E. Coli* Nissle 1917, isolée d'un volontaire sain, et qui est utilisée comme probiotique. Par exemple, dans un contexte de RCH, *E. coli* Nissle 1917 maintient la rémission de façon équivalente au traitement standard (Kruis et al. 2004). Cette bactérie protège de colite induite chimiquement, notamment *via* la production d'acides gras à chaînes longues (AGCL) tels que le C18-3OH (Pujo et al. 2021). La plupart des souches sont inoffensives, voire bénéfiques pour l'Homme, produisant

de la vitamine K3 ou empêchant la colonisation de l'intestin par des bactéries pathogènes, établissant alors une relation de type mutualiste. Dans la deuxième catégorie, on trouve des souches responsables d'infections intestinales ou extra-intestinales, en particulier les infections urinaires (colibacillose). On y trouve des AIEC (pour « adherent-invasive *Escherichia coli* »). Les AIEC génèrent une réponse pro-inflammatoire lors de l'interaction entre la flagelline de la bactérie et le récepteur TLR5. Comme leur nom l'indique, ces bactéries peuvent adhérer à l'hôte *via* leurs adhésines. L'adhésion est une des premières étapes de pathogénicité, elle permet de résister à l'élimination mécanique par l'intestin. L'adhésion entraîne la production d'IL-8 par les CEI, une cytokine pro-inflammatoire. De plus, les AIEC ont la capacité d'être internalisées par les CEI. Certaines souches peuvent survivre et se répliquer dans les macrophages (Palmela et al. 2018).

Dans la troisième catégorie, on trouve les dangereuses souches productrices de toxines. C'est le cas des souches de *E. coli* dites entérohémorragiques (ECEH). Ces dernières provoquent des diarrhées sanglantes et produisent une puissante toxine à l'origine du syndrome hémolytique et urémique (SHU). On peut citer le sérotype 0157H7 responsable de plusieurs pathologies, dont la colite hémorragique, le syndrome hémolytique et urémique (SHU) et le purpura thrombotique thrombocytopénique (PTT). Cette troisième catégorie n'est pas membre du MI humain, mais on trouve ces souches dans le MI d'autres animaux comme les bovins (Tarr et Neill 2001).

Les *Enterobacteriaceae* sont retrouvées localisées proches de la muqueuse intestinale à cause de leur tolérance relativement plus élevée à l'oxygène (Litvak et al. 2017). Les AIEC sont capables d'adhérer et d'infecter les CEI en recrutant les microtubules et les filaments d'actine. De plus, elles sont capables de survivre dans les macrophages et d'induire la production de TNF-α par les macrophages infectés (Baldelli et al. 2021). De façon intéressante, les *Enterobacteriaceae* font partie des premières colonisatrices de notre intestin, elles consomment l'oxygène pour créer un environnement idéal pour les anaérobies stricts tels que les Bifidobacteria.

2.4.1.5. VERRUCOMICROBIOTA

Akkermansia est l'unique genre du phylum *Verrucomicrobiota* retrouvé dans l'intestin. *Akkermansia muciniphila* dégrade les mucines, produits des AGCC, et contribue à l'expansion d'autres bactéries bénéfiques (Dao et al. 2016). De plus, elle peut stimuler la synthèse de mucines et renforcer la BEI en adhérant à l'épithélium (Geerlings et al. 2018). La présence de cette bactérie est associée à un intestin en bonne santé, et son abondance est inversement corrélé avec des états sévères de pathologies telles que les MICI (Geerlings et al. 2018). *Akkermansia muciniphila* est considérée comme un probiotique de nouvelle génération. Elle est immunomodulatrice, renforce la BEI via la production d'AGCC, module le MI. Les études pré-cliniques sont encourageantes quant à son utilisation chez l'Homme (Cani et De Vos 2017). Cette bactérie lors l'homéostasie intestinale, influence les réponses des lymphocytes T au microbiote intestinal et module la fonction immunitaire de l'hôte (Ansaldo et al. 2019). De façon intéressante, il a récemment été décrit qu'un phospholipide de la surface de la membrane cellulaire de la bactérie reproduit l'activité immunomodulatrice de la bactérie via l'hétérodimère TLR-2/TLR-1 *in vitro* (Bae et al. 2022).

2.4.2. FONCTION

Les principales fonctions du MI sont la **digestion** *via* l'extraction, la synthèse et l'absorption des nutriments et métabolites. Les bactéries du MI produisent des acides biliaires secondaires (SBA), des AGCC, des AA, des vitamines et des lipides qui vont avoir des effets sur l'hôte. De plus, le MI permet de **lutter** contre la **colonisation** de potentiels **pathogènes** via la production de PAM, la compétition sur les nutriments mais aussi en occupant le terrain des pathogènes. Par ailleurs, le MI est impliqué dans le maintien de **l'intégrité** de la **BEI** et la régulation du **système immunitaire** et du **système nerveux entérique**. Enfin, le MI peut agir à plus grande échelle sur le système nerveux central et sur d'autres organes.

2.4.2.1. IMPLICATION DANS LA DIGESTION

2.4.2.1.1. LES ACIDES BILIAIRES

Les acides biliaires (BA) sont produits dans le foie à partir du métabolisme du cholestérol, puis sont métabolisés par les bactéries intestinales. Les BA primaires, tels que l'acide chénodésoxycholique (CDCA) et l'acide cholique (CA), sont conjugués avec de la taurine, ou de la glycine pour former l'acide taurocholique (TCA), l'acide glycocholique (GCA), l'acide glycodéoxycholique (GDCA) et l'acide taurochénodésoxycholique (TCDA). Les BA primaires sont sécrétés dans la vésicule biliaire (**Figure 26**). Après un repas, ils sont libérés dans l'intestin où ils peuvent être métabolisés par les bactéries intestinales (Li et Chiang 2014). Les acides biliaires primaires, grâce à leurs propriétés détergentes, participent à l'émulsification et à l'absorption des lipides alimentaires ainsi que des vitamines liposolubles (Wahlström et al. 2016). Ensuite, les bactéries intestinales dé-conjuguent les acides biliaires d'origine hépatique. Grâce à l'action des hydrolases des sels biliaires (BSH) pour former leurs formes libres respectives d'acides biliaires. Les BSH sont exprimées par la plupart des bactéries intestinales, notamment les Firmicutes (30%), les Bacteroidetes (15%) et les Actinobacteria (9%). Cette dé-conjugaison microbienne empêche la réabsorption des acides biliaires par l'iléon. Ensuite, les bactéries anaérobies convertissent les acides biliaires primaires en acides biliaires secondaires (SBA) dans le côlon. Le CA est transformé en acide désoxycholique (DCA) et le CDCA en acide lithocholique (LCA) et acide ursodésoxycholique (UDCA).

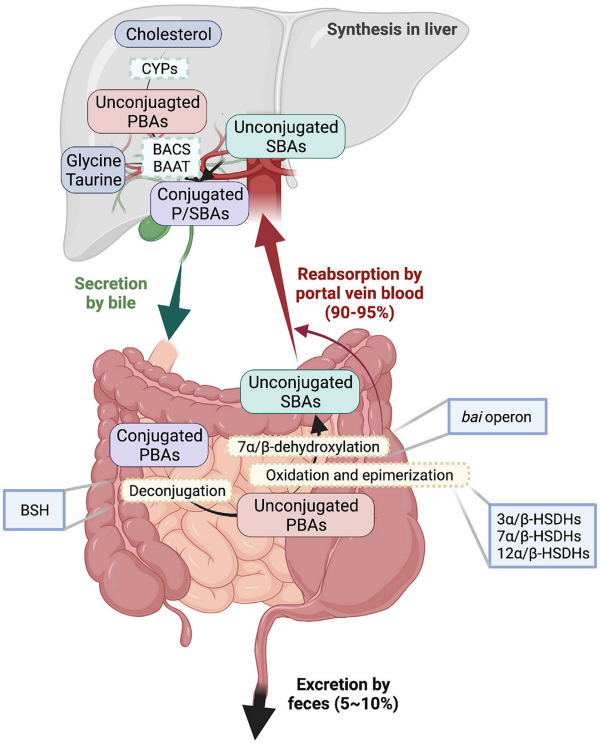

Figure 26. Voie de synthèse des acides biliaires primaires et secondaires (Cai, Sun, et Gonzalez 2022). Les acides biliaires sont synthétisés à partir du cholestérol dans le foie via l'oxydation catalytique du CYPs et la conjugaison catalytique. Les acides biliaires sont sécrétés dans l'intestin à la suite d'un repas. La plupart des acides biliaires (90-95%) sont réabsorbés dans le foie par la veine porte, et seulement une petite portion (5-10%) sont excrétés dans les selles. Le MI convertit les acides biliaires primaires en SBA. Les réactions de biotransformation microbiennes majeures comprennent la déconjugaison médiée par la BSH, la 7α/ß-déshydroxylation médiée par les produits géniques *bai* et l'oxydation et l'épimérisation médiées par les HSDH.

Les SBA exercent d'importantes fonctions biologiques pour le microbiote résident ainsi que pour le métabolisme de l'hôte. En effet, ils peuvent moduler le microbiote intestinal, ils sont d'ailleurs un indicateur de dysbiose (Cai, Sun, et Gonzalez 2022). De plus, ils ont un large éventail de fonctions sur l'hôte, notamment l'élimination du cholestérol et la régulation de l'homéostasie énergétique (MahmoudianDehkordi et al. 2019). Plusieurs études ont souligné le rôle des SBA dans la régulation de l'homéostasie du glucose et la sensibilité à l'insuline (Wahlström et al. 2016). Par ailleurs, les SBA peuvent moduler le système immunitaire (Jena et al. 2019). Par exemple, les dérivés du LCA favorisent la différenciation des Treg et inhibent celle des Th17 (**Figure 27**). Le DCA quant à lui peut orienter la différenciation des macrophages M1 en M2, pro-inflammatoires (Cai, Sun, et Gonzalez 2022).

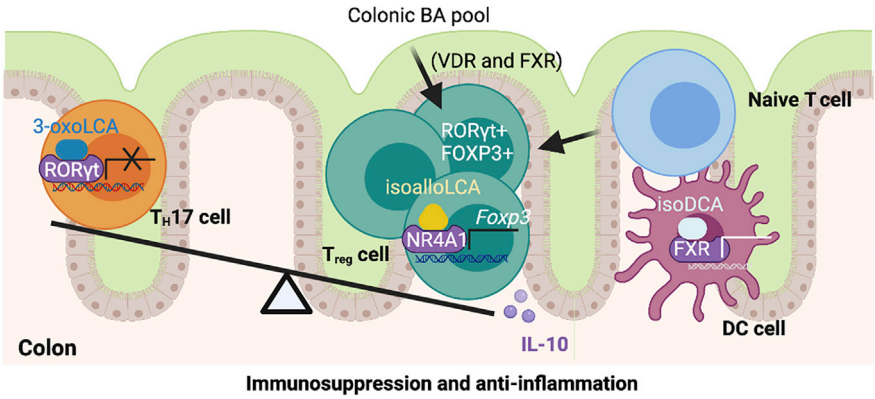

Figure 27. Effets anti-inflammatoires des SBA (Cai, Sun, et Gonzalez 2022). Les SBA contrôlent la différenciation des lymphocytes T dans le côlon et l'activité des DC. Par exemple, le 3-OxoLCA se lie à RORyt et inhibe directement la différenciation des lymphocytes Th17, tandis que l'isoalloLCA favorise la différenciation des Treg anti-inflammatoires en augmentant la liaison du récepteur hormonal nucléaire NR4A1 au locus Foxp3, entraînant une transcription accrue du gène Foxp3. De plus, l'isoDCA inhibe les propriétés immunostimulantes des DCs dépendantes de FXR se traduisant par l'expansion des Treg.

2.4.2.1.2. LES ACIDES GRAS A CHAINE COURTE

Les carbohydrates alimentaires complexes sont indigestibles pour l'Homme, ce sont les bactéries qui vont les dégrader à l'aide d'enzymes pour produire des acides organiques et AGCC. Les concentrations d'AGCC sont plus élevées dans le côlon, où la biomasse microbienne est la plus élevée. La fermentation des fibres alimentaires par le microbiote intestinal produit des AGCC tels que l'acétate (C2), le propionate (C3), le butyrate (C4) qui sont les principaux AGCC produits dans le côlon humain. Les AGCC jouent un rôle actif dans la communication entre l'hôte et le microbiote intestinal (Donohoe et al. 2011).

Le **butyrate** présente divers effets bénéfiques sur l'hôte. Le butyrate joue un double rôle sur les CEI. Tout d'abord, c'est la source principale d'énergie des colonocytes, qui en retour *via* leur métabolisme maintiennent l'hypoxie épithéliale (Donohoe et al. 2011). Cet environnement pauvre en oxygène favorise la croissance de commensaux anaérobies, notamment les bactéries productrices d'AGCC. Le butyrate favorise la différenciation cellulaire et inhibe la prolifération. Cependant, il est capable de réprimer l'expansion des cellules cancéreuses en favorisant leur apoptose. Par ailleurs, le butyrate possède des effets anti-inflammatoires *via* l'inhibition des HDAC (histone deacetylase) qui empêche l'activation des Th17 en faveur des Treg (Lavelle et Sokol 2020). Enfin, cet AGCC est impliqué dans le renforcement de la BEI. Le butyrate diminue la perméabilité en modulant l'expression de protéines de jonction serrées *in vitro,* il stimule la production de mucus et de PAM (Wang et al. 2012).

Le **propionate** *via* le récepteur GPR43 des CEI, inhibe leur prolifération en modulant la concentration intracellulaire d'AMPc. De plus, le propionate *via* ce récepteur induit la production de PAM Reg3 et promeut la prolifération de bactéries productrices d'AGCC telles que les Clostridia, *in vivo*. Le propionate prévient de la colite induite au DSS chez la souris, en augmentant l'expression de Reg3, une lectine de type C et en favorisant la prolifération des CEI dans un contexte inflammatoire (Bajic et al. 2020). Le propionate est également un inhibiteur des HDAC et participe au maintien de l'intégrité de la BEI.

Enfin **l'acétate** protège de la colite *in vivo*, améliore la production d'IL-10 et réduit les cytokines pro-inflammatoires (Masui et al. 2013).

2.4.2.2. MAINTIEN DE L'INTEGRITE DE LA BEI

Les interactions entre les MAMP des bactéries commensales et les PRR des CEI contribuent au maintien de l'intégrité de la BEI. Effectivement, cette interaction favorise l'expression de protéines des jonctions serrées, et par conséquent régule la perméabilité intestinale (Allaire et al. 2018). De plus, la signalisation induite par les TLRs régule la capacité de réparation de l'épithélium intestinal en stimulant des facteurs de protection tissulaire, et en inhibant l'apoptose (Nishida et al. 2018). L'interaction avec les TLR est également impliquée dans la production de mucus. Cette interaction peut être directe entre la bactérie et l'hôte, mais aussi indirecte *via* la production de métabolites tels que les AGCC qui stimulent la production de mucine (Barbara et al. 2021). Le microbiote intestinal est indispensable au maintien de l'intégrité de la BEI. En effet, la BEI de souris dépourvues de MI (GF pour « germ-free » en anglais) est différente de celles de souris conventionnelles, par exemple, la claudine-1 et l'occludine sont augmentées et la perméabilité paracellulaire du côlon est diminuée. Une transplantation fécale de microbiote provenant d'individus sains rétablit les caractéristiques de la BEI de manière similaire à celles observée chez les souris conventionnelles (Hayes et al. 2014).

2.4.2.3. MATURATION DU SYSTEME IMMUNITAIRE

Le MI est essentiel à l'éducation du système immunitaire et le conditionne de façon à ce qu'il tolère les microorganismes qui le constituent, c'est-à-dire ne pas reconnaître le MI comme un ennemi. Par exemple, les ILC3 sont responsables de l'immuno-surveillance du MI, facilitant la colonisation du MI chez le nouveau-né. Ce processus est régulé par des facteurs de transcription, qui à terme régulent l'IL-22 (Guo et al. 2015). De plus, le MI est crucial pour le bon développement du système immunitaire. L'absence de MI entraîne l'immaturité des tissus lymphoïdes, une diminution des lymphocytes intestinaux et de la sécrétion des PAM (Gensollen et al. 2016; Zheng, Liwinski, et Elinav 2020). La réintroduction du MI permet de restaurer un système immunitaire fonctionnel. Le MI stimule la production d'IL-22 par les ILC3, qui joue un rôle crucial dans le maintien de l'intégrité de la BEI (Guo et al. 2020). De plus, le MI peut directement initier et moduler la réponse immunitaire par le biais des TLR, induisant des modifications dans la population des lymphocytes T (Nishida et al. 2018). Certains genres bactériens, tels que les *Clostridia* ou les *Bacteroides*, favorisent l'expansion des Treg en stimulant la production de TGF-ß et d'IDO-1, réduisant ainsi l'inflammation (Cohen et al. 2019).

Enfin, il est important de noter que le microbiote intestinal provenant d'échantillons fécaux, correspondant au microbiote intestinal **luminal**, est considérablement différent en matière d'abondance, de fonctions métaboliques et de réplication, du microbiote intestinal **adhérent** au mucus. De plus, l'analyse du microbiote intestinal doit prendre en considération à la fois la présence et l'activité des micro-organismes de l'intestin, des bactéries d'espèces différentes peuvent avoir la même fonction métabolique.

2.4.3. DYSBIOSE DU MI DANS LES MICI

Le MI joue également un rôle non négligeable dans les MICI. Les patients présentent une dysbiose du MI, c'est-à-dire une différence de la composition et de l'abondance de certains micro-organismes présents dans le tractus GI, comparés à des individus sains.

Les patients atteints de MICI sont caractérisés par une diminution de la richesse du MI, des changements drastiques au niveau des espèces bactériennes et une diminution de métabolites bactériens, tels que les AGCC (Kowalska-Duplaga et al. 2019; Pascal et al. 2017; Lavelle et Sokol 2020). Les Firmicutes et Bacteroidetes sont diminués alors que les Proteobacteria et Actinobacteria sont augmentés, de façon corrélée à la sévérité de la MICI (Manichanh et al. 2012). De plus, les gènes bactériens impliqués dans la tolérance au stress oxydatif, et dans les systèmes de sécrétion, d'adhérence et d'infection sont plus élevés chez les patients atteints de MICI (Yang et Jobin 2014).

Dans la MC, la dysbiose serait plus particulièrement due à une diminution de bactéries bénéfiques qualifiée de **symbiontes**, plutôt qu'à une augmentation de **pathobiontes**, qui sont des micro-organismes commensaux qui peuvent devenir pathogènes dans un environnement spécifique chez des personnes prédisposées génétiquement (**Figure 28**) (Pascal et al. 2017). Les symbiontes comprennent *Faecalibacterium* et *Ruminococcus* qui apparaissent comme les genres qui influencent le plus la MC (Caparrós et al. 2021). En effet, *Faecalibacterium prausnitzii* est quasi absente du MI des patients Crohn (Pascal et al. 2017). Cette bactérie est également diminuée chez les patients RCH, ainsi que *Roseburia homonis,* par rapport à des individus sains, deux espèces bactériennes connues pour leur capacité à produire des AGCC (Machiels et al. 2014). De plus, une MICI active présente une concentration moins élevée de *F. prausnitzii* par rapport à un patient en rémission (Prosberg et al. 2016). Les patients RCH qui développent une pochite à la suite d'une colectomie présentent une diminution des *Ruminococcaceae*. Une autre bactérie bénéfique, ou symbionte, diminuée dans les MICI, est *Akkermansia muciniphila* connue pour sa capacité à dégrader les mucines. Les produits de cette dégradation sont utilisés par d'autres bactéries du MI (Rodrigues et al. 2022). De façon intéressante, le nombre de bactéries associés au mucus est augmenté dans la RCH, alors que *A. muciniphila* est diminuée, suggérant un rôle protecteur de cette bactérie (Png et al. 2010).

Cette perte de bactéries bénéfiques entraîne inévitablement une diminution de certains métabolites, tels que les AGCC et SBA (**Figure 28**). Effectivement, les SBA sont diminués chez les individus atteints de MICI alors que les PBA sont augmentées, indiquant que c'est le MI qui est en cause (Franzosa et al. 2019). Les patients RCH ayant une pochite présentent une diminution des SBA associée à une perte de *Ruminococcaceae*, l'un des rares groupes bactériens à contenir des bactéries productrices de SBA (Cai, Sun, et Gonzalez 2022; Loyd-Price et al. 2019). De plus, une augmentation des SBA dans le sérum est prédicteur de rémission précoce en réponse au traitement chez les patients atteints de MICI (Lee et al. 2021). De façon intéressante, l'abondance du cluster de gènes codant pour la BSH provenant du phylum des *Pseudomonadota* est plus élevée que celle provenant des Bacillota, ces résultats sont donc en accord avec l'augmentation des *Pseudomonadota* et la diminution des Bacillota dans les MICI (Jia et al. 2020). Ces données laissent supposer que les SBA seraient bénéfiques dans un

contexte de MICI. De fait, une supplémentation en SBA dans des modèles de colite induite favorise la diminution de la sévérité de la colite, *via* le récepteur TGR5 (Sinha et al. 2020). Les AGCC sont également altérés dans les MICI. Dans la MC, une diminution d'acétate et de butyrate a été décrite.

Par ailleurs, la **translocation bactérienne**, c'est-à-dire des bactéries ou produits bactériens qui vont du lumen vers les ganglions mésentériques ou les sites extra-nodaux, est augmentée dans les MICI (**Figure 28**). De fait, *E. coli* ainsi que des adhésines et facteurs de virulence voient leur translocation facilitée (O'Brien et al. 2014). Le MI lors des phases actives de la pathologie est instable avec une augmentation des *Pseudomonadota*, en particulier les *Enterobacteriaceae* (Mondot et al. 2016). En effet, les *Enterobacteriaceae* sont encore plus augmentées chez les patients RCH ayant une pathologie chronique par rapport à une phase aigüe, il existe une corrélation positive entre cette famille de bactéries et un stade sévère de la pathologie (Baldelli et al. 2021). De plus, une population élevée *d'Enterobacteriaceae* est associée à un risque élevé d'échec au traitement (Olbjørn et al. 2019). De façon intéressante, les AIEC associées aux patients Crohn adhèrent préférentiellement aux Caco-2 différenciées, qui sont à un stade de maturation avancé. Cette observation est d'autant plus intéressante, compte tenu de la constatation que les cellules présentes au niveau des cryptes, majoritairement immatures, sont rarement impliquées dans les lésions précoces de la pathologie (Palmela et al. 2018). D'autres pathobiontes sont caractéristiques d'une dysbiose chez les patients atteints de MICI. C'est le cas de *Fusobacterium nucleatum* qui a la capacité d'adhérer et d'être internalisé par la BEI, causant une exacerbation de la colite chez l'Homme et dans des modèles animaux. La détection de cette bactérie dans les selles a été proposée comme biomarqueur précoce des MICI et CRC (Strauss et al. 2011; Liu et al. 2020; Bashir et al. 2016). De plus, les lésions iléales chez les patients Crohn sont fréquemment colonisées par les AIEC. Les AIEC peuvent déclencher une inflammation chronique chez les hôtes susceptibles, en modifiant la composition du MI, lui conférant une capacité à activer le système immunitaire (Chassaing et al. 2014).

Le MI est clairement altéré chez les patients atteints de MICI avec une diminution des bactéries bénéfiques et de leurs métabolites et une augmentation des pathobiontes. Mais, est-ce que cette dysbiose est une cause ou une conséquence de l'inflammation ? Il est clair que l'inflammation perturbe la composition du MI. Des études chez la souris montrent que l'inflammation entraîne une dysbiose ainsi qu'une augmentation de la translocation bactérienne (Craven et al. 2012). L'inflammation favorise l'expansion des *Pseudomonadota* chez la souris (Jang et al. 2018). De plus, l'utilisation d'anti-TNF est associée avec une amélioration de la dysbiose, ainsi qu'une diminution de l'inflammation et une réparation épithéliale efficace (Lewis et al. 2015). Cependant, un transfert de microbiote de patients MICI chez la souris favorise le développement des symptômes de la colite (Weingarden et Vaughn 2017). De plus, une absence de microbiote protège du développement de colite spontanée chez des souris IL-10 -/- (Sellon et al. 1998). De façon intéressante, la FMT de patients sains diminue la sévérité de MICI dans des études cliniques (Weingarden et Vaughn 2017). La réponse à la question de la cause ou de la conséquence n'est pas évidente, mais ce qui est certain, c'est qu'il existe un **cercle vicieux** entre l'inflammation, l'altération de la BEI et la dysbiose.

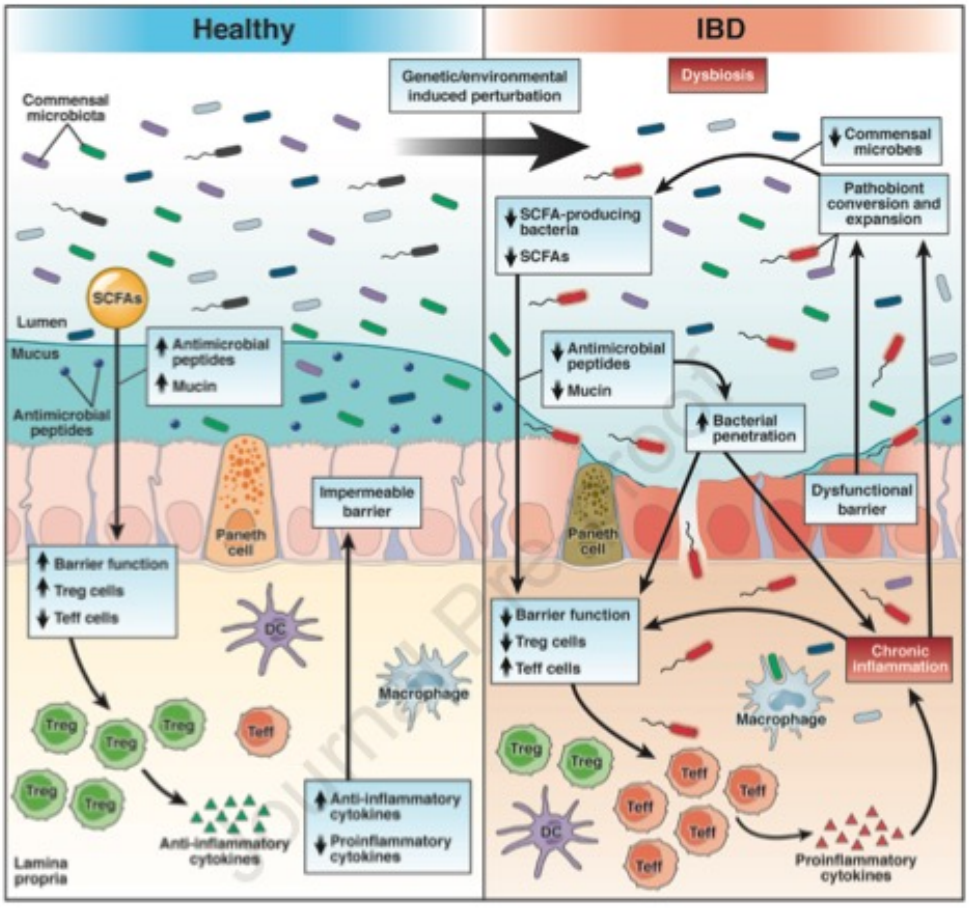

Figure 28. Dysbiose dans les MICI (Lee et Chang 2021). A gauche, les bactéries commensales fournissent des fonctions bénéfiques pour l'hôte sain. Certaines bactéries produisent des AGCC pour réguler l'homéostasie intestinale. Les cellules de Paneth et la couche de mucus préviennent de l'invasion bactérienne. Les AGCC servent de source énergétique aux colonocytes, sont anti-inflammatoires et favorisent la fonction de barrière. A droite, dans les MICI, les bactéries commensales ainsi que les AGCC sont diminués, entraînant une perte de leurs effets bénéfiques. Le déséquilibre entre les Treg et Teff cause une augmentation de l'inflammation qui perturbe la BEI favorisant la translocation bactérienne.

2.5. LE SYSTEME NERVEUX ENTERIQUE

2.5.1. DESCRIPTION

Le système nerveux entérique, aussi connu sous le nom de « deuxième cerveau », représente l'innervation intrinsèque du tractus gastro-intestinal, c'est la composante la plus importante du système nerveux autonome (SNA) (Fried et al. 2021). Ce système nerveux est indépendant du système nerveux central (SNC), bien qu'il existe une communication bidirectionnelle entre les deux qui participe à l'axe intestin-cerveau. Le SNE se compose de neurones entériques et de cellules gliales regroupés en ganglions reliés entre eux par des fibres inter-ganglionnaires (Costa 2000). Il est constitué de deux plexus : le **plexus myentérique** et le **plexus sous-muqueux** (Figure 29). Le plexus myentérique, le plus interne, contrôle la motilité intestinale. Le plexus sous-muqueux régule les activités sécrétoires et la perméabilité intestinale (Nezami et Srinivasan 2010). Les ganglions sont connectés par des interneurones, motoneurones et cellules gliales entériques (CGE) qui vont permettre de former un circuit réflexe qui médie le péristaltisme et les fonctions sécrétoires, tout en intégrant les signaux des neurones ortho- et para-sympathique.

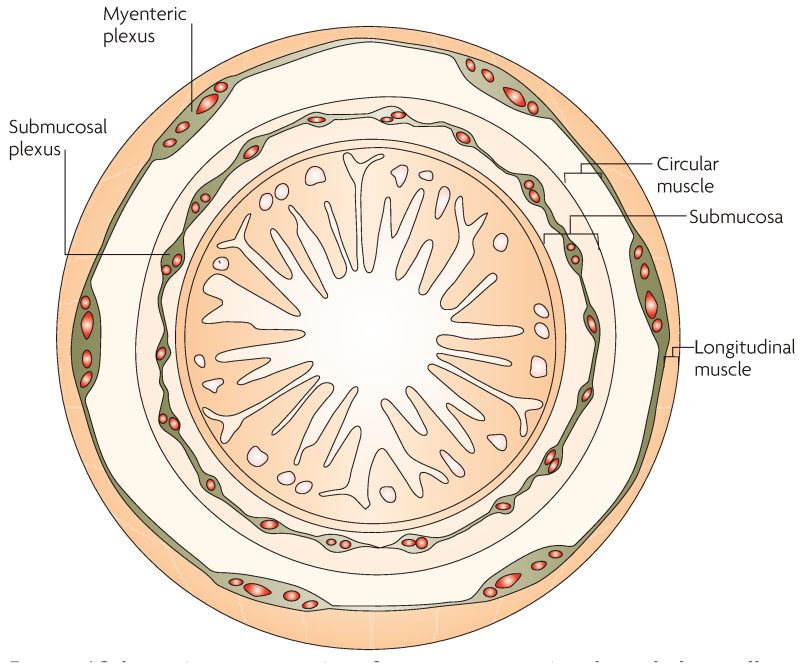

Figure 29. Organisation du système nerveux entérique (Heanue et Pachnis 2007). Le plexus myentérique est situé entre la couche musculaire longitudinale et circulaire. Le plexus sous-muqueux quant à lui est situé dans la sous-muqueuse.

2.5.1.1. LES NEURONES ENTERIQUES

Les neurones entériques comprennent les neurones afférents primaires (IPAN) qui sont connectés aux neurones moteurs et sécrétomoteurs par des inter-neurones (Sasselli, Pachnis, et Burns 2012).

Les neurones entériques peuvent recevoir des stimuli provenant du microbiote intestinal du fait de la présence de certains récepteurs à leur surface, notamment les récepteurs Ahr (pour récepteur des hydrocarbures aromatiques) et TLR4 (Anitha et al. 2012; Jacobson et al. 2021).

Les neurones sont en étroites communications avec les cellules immunitaires. Ils peuvent moduler l'inflammation *via* des neuro-transmetteurs (NT), neuromodulateurs et cytokines (Margolis et Gershon 2016). Par exemple, les macrophages muscularis sécrètent la protéine morphogénétique osseuse 2 (BMP2) qui est un facteur de croissance. BMP2 se lie à son récepteur sur les neurones entériques pour induire une contraction musculaire. En retour, les neurones entériques libèrent des facteurs de stimulation colonique 1 (Muller et al. 2014).

Les neurones entériques peuvent également réguler les CEI (**Figure 30**). Des études ont décrit des interactions entre les neurones et les cellules caliciformes. C'est le cas des neurones cholinergiques qui en libérant de l'Ach, régulent la formation de canaux de passage d'antigène associé aux cellules caliciformes, et donc réguler la présentation des Ag de la lumière intestinale aux cellules immunitaires. De plus, les neurones entériques sont impliqués dans le développement de l'immunité innée. Effectivement, les neurones entériques peuvent sécréter de l'IL-18, stimulant la sécrétion de PAM par les CEI et protégeant contre l'infection aux Salmonelles. Enfin, les neurones nocicepteurs provenant des DRG relâchent des molécules qui inhibent le développement des cellules M dans les plaques de Peyer, principale porte d'entrée aux infections de *Salmonella* (Jacobson et al. 2021).

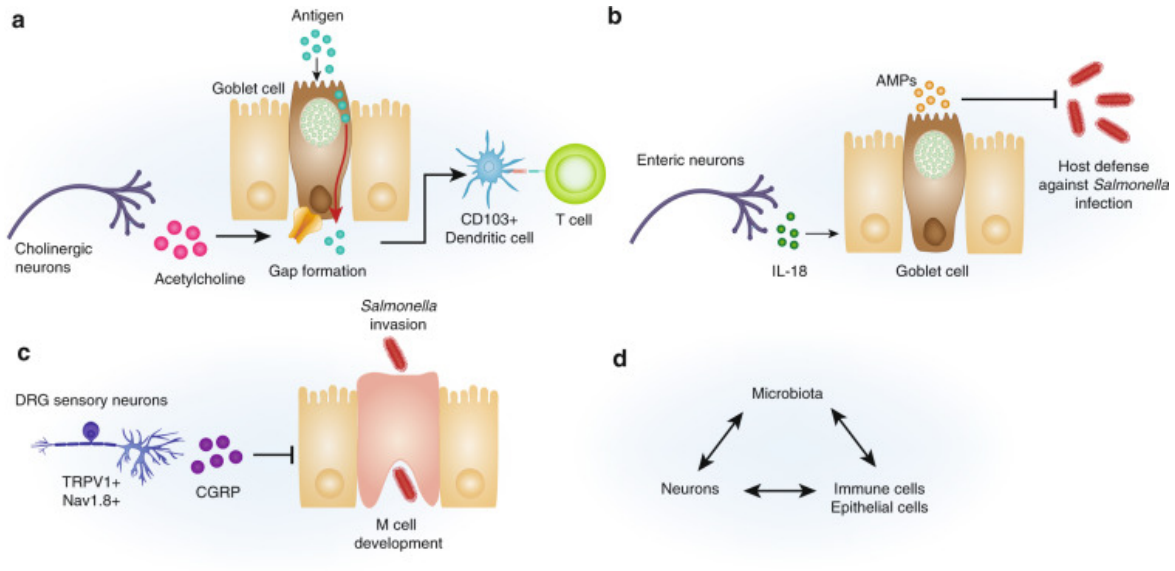

Figure 30. Régulation des CEI par les neurones entériques (Jacobson et al. 2021). A) L'Ach déclenche l'échantillonnage des antigènes luminaux par le biais des canaux de formation associée aux cellules caliciformes, entraînant la présentation d'Ag par les DC tissulaires. B) L'IL-18 neuronale régule l'expression des PAM sécrétés par les cellules caliciformes, essentielles contre la protection de pathogènes de type *Salmonella*. C) La libération de CGRP par les neurones sensoriels DRG limite le développement des cellules M des PP, réduisant ainsi l'invasion par les *Salmonella*. D) Le MI régule la communication neuro-immunitaire en influençant la fonction neuronale, immunitaire et épithéliale. Un MI sain favorise une signalisation neuro-immunitaire appropriée.

Dans les MICI, les neurones entériques sont altérés. On retrouve une augmentation du nombre de neurones, une altération de la synthèse de NT, du contenu et du relargage des neurones entériques (Margolis et Gershon 2016).

2.5.1.2. LES CELLULES GLIALES ENTERIQUES

Les cellules gliales entériques (CGE) sont 4 à 10 fois plus nombreuses que les neurones entériques (Neunlist et al. 2008), elles sont localisées dans différentes couches de la BEI. Les CGE intra-ganglionnaires sont présentes dans les deux plexi, les CGE interganglionnaires au niveau des fibres nerveuses entre les muscles lisses, où se trouvent les CGE intra-musculaires, et la *lamina propria* avec les CGE sous-épithéliales (Pochard et al. 2018). Ces cellules sont capables de répondre à un large panel de molécules : des cytokines, neurotrasmetteurs, des molécules provenant du MI et de l'alimentation (Pochard et al. 2018). Les CGE à l'instar des astrocytes dans le SNC ont une fonction protectrice des neurones entériques, mais leur activité ne peut être réduite à un simple protecteur des neurones entériques. Elles sont impliquées dans la modulation de **l'inflammation** ainsi que dans la régulation des **fonctions de barrière** (Neunlist et al. 2008; Pochard et al. 2018).

Les CGE peuvent renforcer la BEI (Flamant et al. 2011; Soret et al. 2013), notamment *via* le GSNO et le **15-HETE** (Savidge et al. 2007; Pochard et al. 2016). De plus, elles favorisent la réparation cellulaire *via* le pro-EGF (Van Landeghem et al. 2011), le **11ßPGF2a** qui est un dérivé des omégas 6 (Coquenlorge et al. 2016). Les CGE inhibent la prolifération des CEI *via* le TGFß1 (Neunlist et al. 2007), le **15dPGJ2**. Ce dernier régule également la différenciation des CEI (Bach-Ngohou et al. 2010).

2.5.2. OMEGAS 6 ET SNE : IMPLICATIONS DANS LES MICI

Les **oxylipines** sont des médiateurs lipidiques dérivés des acides gras polyinsaturés n-6, tels que l'acide arachidonique et sont impliqués dans divers processus biologiques. La présente revue écrite conjointement avec des membres du laboratoire Inserm U1235 synthétise les études récentes menées sur l'impact de ces oxylipines n-6 sur les fonctions digestives, leurs interactions avec le SNE et leur implication dans les processus pathologiques notamment les MICI. Les résultats majeurs mis en avant par la revue soulignent les effets des oxylipines sur les neurones entériques en modifiant l'activité neuronale, la neurotransmission et en favorisant la neuroprotection. Cependant, la présente revue fait le constat du manque d'études concernant les effets des oxylipines n-6 sur les CGE. Le SNE est également une source d'oxylipines n-6 qui régule les fonctions intestinales (barrière, sécrétion, motilité et régulation du SI). La déficience de certaines oxylipines n-6 pro-résolutives dans les MICI, en lien notamment avec l'altération du SNE dans ces pathologies, est associée avec l'inflammation chronique.

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Crosstalk between omega-6 oxylipins and the enteric nervous system: Implications for gut disorders?

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The enteric nervous system (ENS) continues to dazzle scientists with its ability to integrate signals, from the outside as well as from the host, to accurately regulate digestive functions. Composed of neurons and enteric glial cells, the ENS interplays with numerous neighboring cells through the reception and/or the production of several types of mediators. In particular, ENS can produce and release n-6 oxylipins. These lipid mediators, derived from arachidonic acid, play a major role in inflammatory and allergic processes, but can also regulate immune and nervous system functions. As such, the study of these n-6 oxylipins on the digestive functions, their cross talk with the ENS and their implication in pathophysiological processes is in full expansion and will be discussed in this review.

KEYWORDS

omega-3, omega-6, enteric nervous system, diet, inflammation

Introduction

The gastrointestinal tract (GI) fulfils complex tasks that are essential for survival including food digestion, absorption of nutrients and transit of luminal content. These processes are coordinated by a unique peripheral autonomic nervous system embedded in the gut wall and called the enteric nervous system [ENS; (1)]. The ENS consists of ganglionated networks organized in two main plexi, myenteric and submucosal, which regulate muscle and mucosal functions, respectively. Each ganglion is composed of neurons surrounded by enteric glial cells (EGCs) and these two cell types regulate GI functions *via* specific neuro- and glio-mediators. Regarding the enteric neurons, the most common neurotransmitters are acetylcholine, vasoactive intestinal peptide and nitric oxide while, among the numerous soluble mediators produced and released by EGCs, neuroptrophic factors such as glial derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF) and epidermal growth factor (EGF) have been by far the most widely studied. More recent observations showed that enteric neurons and glial cells are also capable of producing bioactive lipids such as polyunsaturated fatty acids (PUFAs) and in particular oxylipins (2, 3). Oxylipins are associated with a diverse set of inflammatory processes linked to various diseases, including inflammatory bowel diseases (IBD). The production of some n-6 pro-inflammatory oxylipins is increased in the lower GI tract of IBD patients compared to control subjects (4–7) or in inflamed mucosa relative to non-inflamed mucosa (8–11) and correlate with inflammation severity (12). These findings

support the idea of an imbalance between the n-6 pro-inflammatory and n-3 anti-inflammatory derivatives as pathological contributing factors, but this concept was challenged when it has been found for several derivatives that they could have pro- as well as anti-inflammatory properties (13–18). More importantly, recent findings define the importance of pro-resolutive properties of some n-6 derivatives (19) and their homeostatic functions (20, 21). In addition, we recently reported that EGCs produce mostly n-6 and little n-3 oxylipins and that some n-6 oxylipins that have a pro-resolutive and pro-homeostatic function are lacking in Crohn's disease patients. The general effects of n-6 oxylipins on the GI tract have been reviewed elsewhere (22, 23) but as far as we know there is no existing review on the links between n-6 oxylipins and the ENS. The current article fills that void and covers the research in this subject area over the past two decades. Here, we first provide a brief overview of n-6 oxylipins, before discussing the interplay between the compound and the ENS and their potential roles in GI pathophysiology.

n-6 oxylipins

The time is long gone when lipids represented only inert fats. In addition to their role in the formation of biological structures (e.g., cell membranes or organelles), lipids have metabolic energy storage and cell signaling function. Signaling lipids, from lysophosphatidic acid to endocannabinoids, regulate essential functions such as synaptic transmission, vasoconstriction or inflammation. Among the most important are the Omega-3 (n-3) and Omega-6 (n-6) oxylipins, the family of oxygenated products formed from n-3 and n-6 PUFAs. In both Omega families, many forms of PUFAs exist: α-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from the n-3 family and linoleic acid (LA), dihomo-γ-linolenic acid (DGLA), and arachidonic acid (ARA) from the n-6 family are the important PUFAs for human health.

n-6 Oxylipins are synthesized from ARA by cyclooxygenase, lipoxygenase, and cytochrome P450 (CYP) monooxygenase activities (24; Figure 1). Cyclooxygenases (COX), also known as prostaglandin-endoperoxide synthase (PTGS) are oxidoreductases that allow the synthesis of prostaglandins (PG) and thromboxanes (TX). In humans there are two isoforms of COX: COX-1 and COX-2. COX-1 participates in the basal synthesis of eicosanoids and is constitutively expressed in most tissues. In contrast, the expression of COX-2 is induced by stimuli such as inflammation (25). Their actions are carried out in two stages: first they subtract a hydrogen from the carbon 13 of the ARA and they add two molecules of oxygen, which allows the formation of prostaglandin G_2 (PGG_2). Second, this PGG_2 is reduced to PGH_2 by active peroxidase. The synthesis of PG and TX is then carried out thanks to specific isomerases. Thus, the PGD synthetases (L-PGDS and H-PGDS), the PGE synthetases (mPGES-1, mPGES-2, and cPGES3), the PGF synthetase (PGFS), the PGI synthetase (PTGIS and the TX synthetase (TXAS) that allow the synthesis of PGD_2 (which can give PGJ_2 following dehydration), PGE_2, $PGF_{2\alpha}$, PGI_2 (or prostacyclin), and TXA_2, respectively. The receptors for these compounds are G-protein coupled receptors, and a same eicosanoid can modulate its action depending on the targeted receptor subtype (26). The lipoxygenase (LOX) pathway allows the synthesis of hydroxyeicosatetraenoic acids (HETE) and leukotrienes (LT). These are non-heme iron enzymes that contain dioxygenases and are constitutively expressed in plants and animals. In the intestine we find the lipoxygenases 15-LOX (15-LOX-1 and 15-LOX-2), 12-LOX and 5-LOX which allow the synthesis of 15-HETE, 12-HETE, 5-HETE and LT, respectively. They will catalyze the reaction PUFA (ARA for example) + $O2^-$ > Hydroperoxyeicosatetraenoic acid (HpETE). These derivatives are then transformed into more stable one: HETE and LT (27). The LT receptors are well described, but little is known about those for HETE. However, it is recognized that they may be peroxisome proliferator-activated receptor (PPAR) agonists (28, 29). On the other hand, epoxy-PUFA are the oxylipins generated by CYP enzymes, later converted to their corresponding 1,2-diols by soluble epoxy hydrolase.

n-6 Oxylipins regulate ENS

Oxylipins play a major role in the regulation of inflammation not only in the central nervous system (CNS) but also in the GI tract. This prompted research on their potential effects on the ENS and numerous studies showed that n-6 oxylipins are indeed able to modulate neuronal activity and to exert neuroprotective effects. Regarding EGCs, although the data are still scarce, their phenotype and activity could be modified by oxylipins.

n-6 Oxylipins, enteric neuronal activity and neuroprotection

The first studies suggesting that n-6 oxylipins could modulate enteric neurotransmission and thus neuronal activity were performed in the myenteric plexus of guinea pig ileum and focused on the release of acethylcholine (Ach). Two independent groups showed that the release of Ach by either protein kinase C, DMPP (a nicotinic agonist) or neuronal activity was decreased in the presence of mepacrine, a PLA_2 inhibitor, and that the opposite was observed when samples of myenteric plexus were treated with either a PLA_2 activator (melittin) or ARA (30, 31). Additional pharmacological experiments allowed to identify the prostaglandins PGE_2, PGI_2 and PGF_2 as critically involved in the chemically or electrically-induced release of Ach by enteric neurons (32–35) (Figure 2). Regarding the LOX pathway, AA861, a selective inhibitor of 5-lipoxygenase, inhibited acetylcholine release

Abbreviations: 15d-PGJ2, 15-Deoxy-Delta-12,14-prostaglandin J2; Ach, acethylcholine; AKR1C3, aldo-keto reductase family 1 member C3; ARA, arachidonic acid; BDNF, brain-derived neurotrophic factor; S100b, calcium-binding protein S100b; CNS, central nervous system; CD, Crohn's disease; COX, cyclooxygenases; CYP, cytochrome P450; DGLA, dihomo-γ-linolenic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EGCs, enteric glial cells; ENS, enteric nervous system; EETs, epoxyeicosatrienoic acids; EGF, epidermal growth factor; GI, gastrointestinal tract; GDNF, glial derived neurotrophic factor; GFAP, glial fibrillary acidic protein; HpETE, hydroperoxyeicosatetraenoic acid; HETE, hydroxyeicosatetraenoic acids; IBD, inflammatory bowel diseases; IL-1b, Interleukin-1β; IBS, irritable bowel syndrome; LT, leukotrienes; LA, linoleic acid; LOX, lipoxygenase; LMMP, longitudinal muscle/myenteric plexus; oxoETE, oxoeicosatetraenoic acid; PPAR, peroxisome proliferator-activated receptor; PG, prostaglandin; PGDS, PGD synthetase; PGES, PGE synthetase; PGFS, PGF synthetase; PTGIS, PGI synthetase; PLA2, phospholipase A2; PUFAs, polyunsaturated fatty acids; PTGS, prostaglandin-endoperoxide synthase; PG, prostaglandins; NaCl, sodium chloride; TX, thromboxanes; TXAS, TX synthetase; UC, ulcerative colitis; VIP, vasoactive intestinal peptide; ALA, α-linolenic acid.

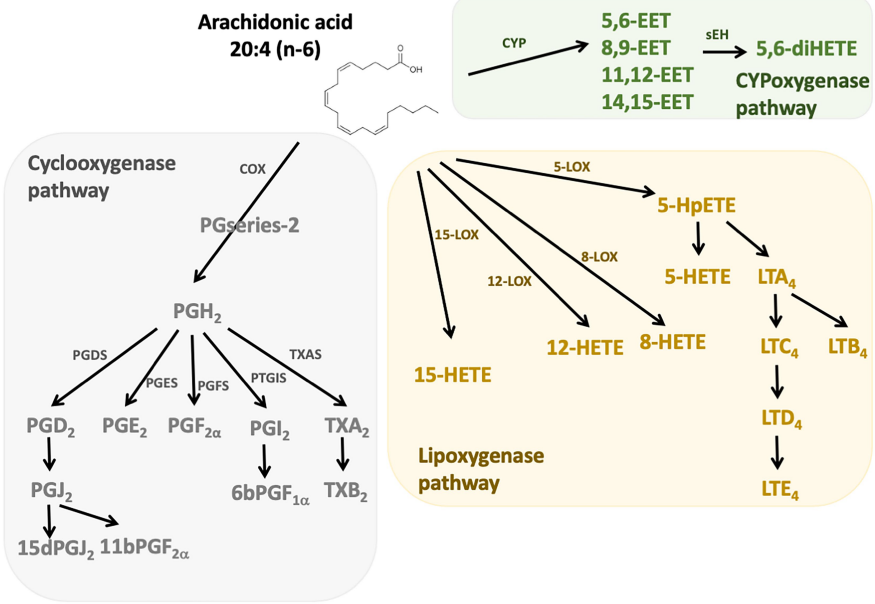

FIGURE 1
n-6 Oxylipins derived from arachidonic acid. The metabolism of PUFAs is a complex process involving several enzymes of desaturation, elongation, and β-oxidation. n-6 oxylipins are synthesized from arachidonic acid (ARA) through three major pathways, the first depending on cyclooxygenase (grey), the second on lipoxygenase (yellow), and the third on cytochrome P450 (CYP) monooxygenase activities (green). COX, cyclooxygenase; LOX, lipoxygenase; CYP, cytochrome P450; PGFS, prostaglandin F synthase; PGDS, prostaglandin D synthase, PGES, prostaglandin E synthase; PTGIS, prostaglandin I synthase; TXAS, thromboxane A2 synthase.

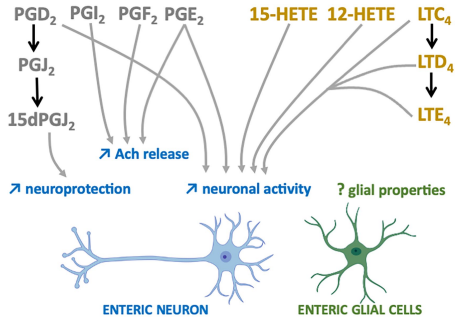

FIGURE 2
n-6 Oxylipins regulate the Enteric nervous system. COX-(grey) or LOX-(yellow) derived n-6 oxylipins increase (↑) different enteric neuron properties (blue) but their impacts on EGCs remain to be determined (?).

from the myenteric plexus induced by electrical field stimulation, an effect that was reversed by metabolites from the 5-lipoxygenase pathway, including 5-HETE, LT C_4, D_4 and E_4 (36) (Figure 2). Besides Ach, it has also been shown that prostanoid signaling, including PGE_2, regulated the cytokine-induced suppression of norepinephrine release in rat myenteric plexus (37). Although scarcer than for the myenteric plexus, some findings suggest that the n-6 oxylipins produced by the submucosal plexus might be also involved in the release of Ach. Interleukin-1β (IL-1β) potentiated the release of Ach induced electrical transmural stimulation in whole guinea pig ileum but not in longitudinal muscle/myenteric plexus (LMMP) only or in mucosal-free preparations and these effects were prevented with of PLA_2, COX or LOX inhibitors (38) (Figure 2). Taken as a whole, these findings suggest that IL-1β stimulates cholinergic enteric neurons *via* a cascade of ARA metabolites produced in tissues at the mucosal and submucosal level, but not in the myenteric plexus or longitudinal muscles.

Prostaglandins are also capable of directly modulating the electrophysiological properties of enteric neurons. Treatment of myenteric ganglia from the guinea pig colon or ileum with PGE_2 led to prolonged depolarization of enteric neurons with enhanced spike discharge together with an increased neuronal excitability (39–41) (Figure 2). More recently, myenteric neuron activity and contraction have been shown to depend on prostaglandin release (COX-2 pathway) from mucosal mast cells in a model of TNBS-induced colitis (42). Similar findings were observed when submucosal neurons of guinea pig colon were treated with PGD_2 (43). The application of leukotrienes C_4, D_4 and E_4 to myenteric and submucosal neurons of guinea pig resulted in slow depolarization of small intestine neurons, thereby suggesting that derivatives of the LOX pathway are also modulators of enteric neuronal excitability (Figure 2).

Oxylipins are well-known neuroprotectors in the CNS and this might be also the case in the ENS. 15-Deoxy-Delta-12,14-prostaglandin

J_2 (15d-PGJ_2), a PGD_2 metabolite produced by EGCs, has been identified as having neuroprotective effects (44) (Figure 2). Pretreatment of primary cultures of ENS with this n-6 oxylipin prevented the neurotoxicity induced by hydrogen peroxide. The involvement of EGCs in this beneficial effect was validated after glial genetic invalidation of the key enzyme involved in the synthesis of 15dPGJ_2, the L-PGDS. The neuroprotective effect of this glial mediator appeared to be due to increased expression in enteric neurons of both glutamate cysteine ligase and intracellular glutathione.

n-6 Oxylipins and EGCs

In sharp contrast with the regulation of enterics neuron properties described below, data on the effects of n-6 oxylipins on the EGCs are lacking. The observation showing that a high fat diet, which controls in a major way the GI oxylipin content, increased the number of EGCs in myenteric plexus in a juvenile mouse model (45), but alter submucosal glial density where the expression of the glial marker calcium-binding protein S100β (S100β) was also decreased (46), might suggest that EGC morphology and/or reactivity could be modified *via* oxylipins. But this is the few we know, and while many studies described the regulation of central glia (astrocytes or microglia) through oxylipin (mostly n-3 oxylipin), the impact of a specific oxylipin on EGC markers and functions remain to be addressed.

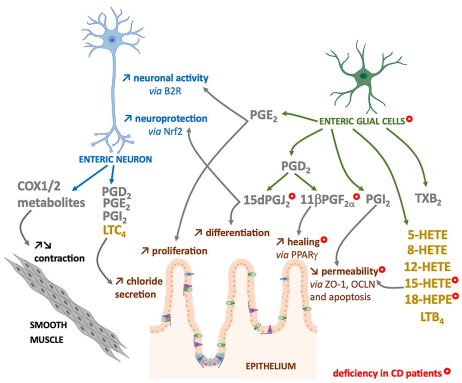

FIGURE 3
Enteric neurons and glial cells produce n-6 oxylipins to regulate the neighboring cells. Some n-6 oxylipin are to regulate glia or neurons, but also to control functions of smooth muscle or intestinal epithelial cells. COX-(grey) or LOX-(yellow) derived n-6 oxylipins produced by enteric neurons and/or glial cells can regulate different enteric neuron properties (blue), but also intestinal epithelial barrier properties (brown) or smooth muscle contraction (black). Marked with a (O) are cells, oxylipins or cellular functions deficient in chronic inflammatory disease that is Crohn's disease (CD).

The ENS is a source of n-6 oxylipins

While n-6 oxylipins can regulate the ENS, we could wonder whether ENS itself could be a source of n-6 oxylipins. Unlike other signaling, lipid messengers are produced on demand and degraded by metabolic enzymes to control their lifespan and signaling actions. The ENS contains the enzymatic machinery required for the production of n-6 oxylipins, and production of several have been measured in ENS or EGC in culture.

Secreted PLA2 (sPLA2-X) has been detected in the myenteric ganglia of small intestine and in neuronal fibers of the stomach, thereby suggesting that ARA-derived eicosanoids are produced by enteric neurons (47, 48). Regarding the cyclooxygenase pathway, both COX1 and 2 enzymes are found in the myenteric ganglia in both humans and mice (49–51). We further showed that both neurons and EGC from primary culture of rat ENS express the L-PGDS (52), and human EGC also express the aldo-keto reductase family 1 member C3 (AKR1C3) (53). The expression of these key enzymes is associated with the production of PGD_2, 15dPGJ_2, 11β$PGF_{2\alpha}$, PGE_2, PGI_2 (estimated by the measurement of its metabolite 6k$PGF_{1\alpha}$) and TXB_2 in primary culture of rat ENS, rat or human EGC (52–54). The LOX pathway is also active in ENS as we have shown that human submucosal plexus and human EGC express the 15-LOX-2 (54). The downstream mediator, 15-HETE, or oxylipins produced from other LOX pathways such as LTB_4, 5-HETE, 8-HETE and 12-HETE are also produced by rat and human EGC as demonstrated by the enlarged lipidomic analyzes (53, 54). No enzyme or specific metabolite from the CYP pathway has been specifically attributed to the ENS so far.

In an interesting way and comparable to what has been done in the CNS, the production of n-6 oxylipins by the ENS is regulated by inflammation. Seminal papers on the topic showed that COX2 and its downstream metabolites TXA_2 and TXB_2 were upregulated by TNF-α in isolated rat myenteric ganglia (55), while LPS induced COX-2 expression in enteric glial cells *via* autocrinal secretion of IL-1β (56). More recently, we showed that both neurons and EGC responded to LPS by increasing L-PGDS expression and its downstream metabolite PGD_2 (10).

Therefore, it appears that ENS, in the same way as immune cells, muscle cells or epithelial cells, could be a source of n-6 oxylipins, and thereby regulate its neighboring cells to participate in the control of digestive functions.

n-6 Oxylipins: ENS crosstalk and intestinal functions

The n-6 oxylipins can be produced by enteric nervous cells, both at the neuronal and glial level, but these lipid messengers regulate ENS properties, suggesting that they could also play a crucial role in the regulation of intestinal functions controlled by ENS (Figure 3).

Intestinal epithelial regulation

The intestinal epithelial barrier (IEB) represents a central actor of intestinal homeostasis. Intestinal epithelial barrier integrity is ensured by a constant renewal thanks to a balance between proliferation, differentiation, migration and elimination of cells, but also by a tight regulation of permeability and repair. The role of EGCs in controlling the properties of the IEB is quite well studied, and our laboratory has highlighted the crucial role of n-6 oxylipins in this regulation. Thus, the 15dPGJ_2 induced differentiation and inhibited the proliferation of epithelial cells

(52) (Figure 3). We also demonstrated the involvement of glial 11βPGF$_{2\alpha}$ in the control of IEB repair *via* an increase in intestinal epithelial cell spreading (53) (Figure 3). Finally, we have demonstrated that another glial mediator, the 15-HETE, controls IEB paracellular permeability, both *in vitro* and *in vivo* (54) (Figure 3). Thus, EGCs represent a source of n-6 oxylipins responsible for IEB strengthening.

Motility regulation

Inhibitors of both COX isoforms increased the contractions of human longitudinal muscles induced by electrical stimulation and are atropine-sensitive. It has been suggested that cholinergic neurons are thought to be primarily modulated by COX-1 activity, whereas COX-2 acts primarily at the muscular level to decrease muscarinic responses (50). Another study on rat duodenum also showed that inhibition of COX isoforms with indomethacin increased motility, probably *via* enteric nerve excitation (57). While the expression of COX1 and COX2 enzymes in neurons of myenteric ganglia of mouse or human colon, their role in the neuromuscular function is unclear. The inhibition of COX does not have the same effects on neuromuscular functions (peristalsis, spontaneous or Ach-induced activity, electrically-induced contractions, etc.…) depending on the species, but also according to the intestinal region (stomach, jejunum, distal colon, etc.) or the studied muscle layer (circular/longitudinal) (58). In addition, as enteric neurons can be the target but also the source of COX-pathway metabolites, and as many studies used COX inhibition or deletion without neuronal specification, it is difficult to conclude about the specific neuronal contribution (58) (Figure 3).

The LOX pathway has also been involved in motility regulation as a recent work demonstrate how the 12-HETE, can remodel the ENS and inhibit duodenal contraction (59).

Secretory regulation

The prostaglandins PGD_2, E_2, I_2 and F_{2a} as well as LTC_4 increased short-circuit current, which represents chloride secretion and activated submucosal enteric neurons. The secretory response was reduced by treatment with tetrodotoxin or atropine, suggesting an involvement of cholinergic submucosal neurons in this regulation (60–62). Nevertheless, the prostaglandin regulation of secretion through ENS could be more complex, being accelerated with high concentrations of PGE_2 (63) or sometimes presenting anti-secretory effect for rat colonic preparations treated with PGD_2 (64, 65).

Immune system regulation

Prostanoids and leukotrienes are mediator of communication between macrophages or mast cells and ENS, but the ENS to immune cell communication through n-6 oxylipins has not been described yet.

One study demonstrated that in a co-culture of mast cells with rat submucosal neurons, inhibition of 5-LOX, resulted in a reduction of the number of responding neurons (66). In the same way, in small intestine of guinea pig sensitized to cow's milk and exposed to beta-lactoglobulin, was observed an increase in neuronal excitability, both suppressed by treatment with a COX or 5-LOX inhibitors (67). Finally, one study suggests the involvement of macrophage-like cells found in rat myenteric plexuses in the effect of IL1β and IL-6 on the suppression of prostanoid-mediated norepinephrine release (37).

n-6 Oxylipins and ENS dysfunctions in gut disorders

In parallel to the involvement of the crosstalk between n-6 oxylipin and the ENS in the maintenance of intestinal homeostasis, increasing evidence suggest their dysregulation and role in different pathological conditions of the gut. Although numerous pre-clinical and clinical studies showed controversial results concerning the use of oxylipins or PUFAs, there is still much more to discover about the beneficial effects of these molecules, particularly in the field of IBD (68).

Inflammatory bowel diseases

The role of oxylipins in inflammatory bowel processes is multifaceted and unclear. Many studies associate n-6 with proinflammatory effects, and thereby an increased risk of developing IBD (8, 69–71). Conversely, many derivatives of ARA could also play an anti-inflammatory and pro-resolutive role (72), and treatment with COX inhibitors led to an exacerbation of the activity of the disease or induce relapse in IBD patients (73, 74). More recently, two eicosanoid synthesis pathway enzymes (PTGIS and PGD_2 synthase) were identified among genes dysregulated in fibrotic Crohn's disease (75). In the same manner, the concentration of a cluster of 10 eicosanoids ($PGF2_a$, 15-HETE, TxB_2, 11β $PGF2_\alpha$, PGE_3, $15dPGJ_2$, $6kPGF_{1\alpha}$, PGE_2, PGD_2 and 8 $isoPGA_2$) were decreased in biospie supernatant form UC or CD patients, when biopsies came from a non-inflamed areas (76). These studies suggest that, while upregulated by acute inflammation, the defects in expression of synthesis enzyme and/or the low production of n-6 oxylipins are associated with chronic inflammation.

These changes of n-6 oxylipins production could be related to alterations of EGCs and enteric neurons observed in IBD patients. Indeed, in addition to neuronal structural alterations (77), increase in neuronal degeneration (78–81), and changes in neurochemical coding (82–85), neurons of the myenteric plexuses from active IBD patients expressed high level of COX2 that could contribute to the dysmotility observed in patients (86). Indeed, a decrease in the number of myenteric neurons per ganglion was observed after the induction colitis with TNBS in guinea pigs and especially an increase in COX2 expression and release of PGE_2, TXA_2 and LTB_4 in the neuromuscular layer, was associated with a decrease in colonic propulsion and an increase in the excitability of myenteric neurons (87). In addition to neurons, EGCs from IBD patients present structural alterations (80), changes in glial marker expression (77, 88, 89) and a decrease in the production of four glial lipid mediators: the 15-HETE, 18-HEPE, $15dPGJ_2$ and 11βPGF$_{2\alpha}$ (53) (Figure 3). The defect in $15dPGJ_2$ and 11βPGF$_{2\alpha}$ production was explained by a decrease in L-PGDS and AKR1C3 synthesis enzyme expression by EGCs from CD patients (53). The functional consequences of the decrease of 15-HETE or 11βPGF$_{2\alpha}$ productions by CD EGC have been identified as a loss of control of the IEB permeability or healing, respectively (53, 54) (Figure 3). Similarly, the decrease of $15dPGJ_2$ could be linked to a loss of neuroprotection from oxidative stress (44) and a defect in the proliferation and differentiation of intestinal epithelial cells (52) (Figure 3).

Thus, while most of the studies are focused on an active role of n-6 oxylipins in the deleterious effect of intestinal inflammation, we have to reconsider their necessity in the resolution of inflammation (90, 91) and the possible involvement of their defects in the ENS as a contributing factor to the pathological mechanisms of IBD.

Infectious diseases

Other studies suggest a detrimental role of n-6 oxylipins that target the ENS in several infectious diseases, especially during parasitic infections.

The *Trypanosoma cruzi* infection leads to myenteric neuron cell death mainly in the esophagus and colon and results in megaesophagus and megacolon, respectively (92). A treatment with low-dose aspirin during the acute phase of infection, known to inhibit COX, reduced parasitemia and protects myenteric neurons from cell death and plastic changes, notably their hypertrophy. This protection of cholinergic neurons was also associated with a recovered transit time by the aspirin treatment. In addition, treatment with aspirin decreases substance P and increases vasoactive intestinal peptide (VIP) productions, and could therefore help to regulate inflammation in these animals.

The infection with the parasite *Cryptosporidium* in piglet, induces intestinal villous damages associated with malabsorption and reduced sodium chloride (NaCl) absorption due to prostaglandin released from the inflamed tissue. The prostaglandins alter NaCl transport in this infection primarily by stimulating cholinergic interneurons that innervate VIPergic and cholinergic motor nerves (93). The ENS may be a potential target for pharmacological control of the acute diarrhea in this infection.

Other intestinal disorders

The involvement of n-6 oxylipins has also been suggested in many other pathologies associated with intestinal disorders, particularly *via* their role on neuronal excitation or their inhibitory role on intestinal contractility.

Patients with irritable bowel syndrome (IBS) are characterized by abdominal cramps, diarrhea or constipation. Treatments with the PGD_2 antagonist BW A868C inhibited the longitudinal muscle contractions potentiated by supernatant of biopsies from IBS patient (94). In addition to this effect on motility, lipidomic studies have demonstrated that n-6 oxylipins can participate in visceral sensitivity. Quantification of the PUFA metabolites produced in biopsies from control and IBS patients have shown that 5,6-EET and PGE_2 production are increased in diarrhea-predominant IBS patients and 5-oxoeicosatetraenoic acid (5-oxoETE) in IBS with predominant constipation (95, 96). These productions are correlated with pain and bloating and these oxylipins can activate afferent sensory neurons but the contribution of ENS in these processes is not described.

In the same way, about half of the patients with slow-transit constipation exhibits an elongated colon and outlet obstruction. One study showed increased levels of COX2 in muscularis and mucosa of partially obstructed mice, associated with colon elongation, slowing of transit, and loss of mucosal reflexes. The expression of COX2 was also found in subpopulations of nNos myenteric neurons, and PGE_2 application completely abolished spontaneous inhibitory junction potentials and depolarize the circular muscle, suggesting that it was removing tonic inhibition. Removal of the obstruction or treatment with a selective COX2 inhibitor restored control parameters as spontaneous inhibitory junction potentials and mucosal reflexes (97). This study suggested that an increase in COX2 expression led to a hyperexcitable colon, largely due to suppression of inhibitory nerve pathways by prostaglandins.

In the case of food allergies, products of activated mast cells, including prostanoids and leukotrienes, are also known to stimulate nerve endings, to modulate neuronal excitability and to increase synaptic transmission, resulting in phenotypically and functionally altered submucosal secretomotor neurons (98).

In the context of postoperative ileus, a study showed, in the rat, that a bowel manipulation increased the expression of COX2, associated with an increased PGE_2 release in the immune cells but also in subpopulation of myenteric neurons. This associated with a decrease in contractile smooth muscle activity (99). COX2 metabolites such as PGE_2 produced by the ENS appear to be involved in enteric dysmotility, and administration of specific inhibitors could help to prevent the transit delay induced by bowel manipulation (58). The PGE_2 produced by the ENS is not only involved in smooth muscle control, but also in epithelial proliferation, and a study nicely shown how tumor cells can induce PGE_2 production by EGCs to activate colon cancer stem cells and stimulate tumorigenesis (100).

Finally, some ARA derivatives could also have an emetogenic role, and one study investigated the role of leukotrienes in this effect. Injections of different leukotrienes, such as LTC_4 and D_4 induced an increase in the frequency and percentage of least shrews receiving vomiting. Following LTC_4-induced vomiting, they showed increased labeling of nuclei for Fos in ENS, suggesting that leukotrienes modulate emetic activity in part *via* enteric nervous components activation (101).

Conclusion

Nowadays, the crosstalk between n-6 oxylipins and the ENS is mainly represented by n-6 oxylipins regulation of neuronal activity and the subsequent modulation of muscle contraction Nevertheless, first evidence shows that n-6 oxylipins could also have a broader impact through their production by enteric glia to the control of the intestinal epithelial properties. The EGC-derived n-6 oxylipins that strengthen the intestinal epithelial barrier and participate in gut homeostasis, are lacking in patients with Crohn's disease. We could speculate that they could also regulate other EGC neighboring cells such as ILC3, macrophages or T cells, and therefore could more broadly participate in pathological processes. New studies must go beyond the conventional wisdom of inflammatory prostaglandins, bring a better understanding of the kinetics, receptor type and cellular mechanisms regulated by specific n-6 oxylipins in order to elaborate new anti-inflammatory strategies, for example *via* supplementation with pro-resolutive mediators. Pharmacological approaches coupled with

tissue-specific gene invalidation might facilitate the translation of fundamental discoveries into clinical solutions for gut diseases with aberrant lipid signaling.

Author contributions

MR-D and PD directed, constructed and produced the final version of the review. MM wrote the first draft. MR-D produced the data. KB-N conducted a critical reading. MN participated in the reflexion and work funding. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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3. STRATEGIES THERAPEUTIQUES

Les stratégies thérapeutiques ont pour but commun **d'induire** la **rémission** à court terme et de **maintenir** la **rémission** à long terme. Une stratification des patients en fonction des facteurs de risque pronostique ainsi qu'une thérapie individualisée est conseillée. Il faut savoir que plusieurs facteurs influent sur le choix de la thérapie à entreprendre, à savoir la localisation, l'activité et la sévérité de la maladie, la réponse aux traitements antécédents ainsi que les potentielles complications, les caractéristiques individuelles des patients et la balance bénéfice / risque de chaque traitement. De plus, des marqueurs quantifiables sont utilisés pour suivre la thérapie, tels que la concentration de la CRP sanguine, et de la calprotectine fécale ainsi que de l'endoscopie et de l'imagerie. Les traitements médicamenteux combinés avec des mesures d'hygiène de vie sont utilisés dans un premier temps avant d'avoir recours à la chirurgie (Torres et al. 2020).

3.1. TRAITEMENTS MEDICAMENTS

Actuellement, il n'existe pas de traitements curatifs de ces pathologies. Cependant, des traitements symptomatiques existent, permettant de diminuer l'intensité et la durée des poussées inflammatoires et d'allonger la durée des périodes de rémission.

Plusieurs traitements sont utilisés pour **induire** la rémission. Lorsque l'activité de la pathologie est modérée, le 5-ASA (pour 5-aminosalicylate) ou mésalazine et le budésonide sont prescrits. Le 5-ASA réduit la synthèse de médiateurs pro-inflammatoires tels que les prostaglandines, leucotriènes et radicaux libres *via* une inhibition des enzymes LOX et COX (Gajendran et al. 2018). Cependant l'utilisation des 5-ASA dans la MC reste controversée (Torres et al. 2020). Quand la pathologie est plus sévère, des corticostéroïdes systémiques peuvent être utilisées. Les corticostéroïdes diminuent la production de cytokines pro-inflammatoires, inhibent les molécules d'adhésion et induisent l'apoptose de lymphocytes activés (Gajendran et al. 2018). De plus, des immunosuppresseurs tels que la thiopurine ou le méthotrexate (MTX) sont également prescrits. Le MTX est un analogue de la vitamine B9 et la thiopurine, un antagoniste des purines, inhibe la prolifération des lymphocytes T et B (Gajendran et al. 2018). Enfin, les thérapies basées sur l'utilisation d'anticorps monoclonaux peuvent être envisagées. C'est le cas des anti-TNFα (infliximab) ou des anticorps bloquant l'intégrine α4ß7 (vedolizumab), une molécule impliquée dans l'adhésion des lymphocytes à la *lamina propria* (Gajendran et al. 2018). Dans le but de maintenir la rémission, le 5-ASA peut être utilisé ainsi que les immunosuppresseurs décrits précédemment. En général, lorsqu'une thérapie fonctionne pour induire la rémission, elle est conservée pour la maintenir (Torres et al. 2020).

3.2. TRAITEMENTS CHIRURGICAUX

La chirurgie reste fréquemment nécessaire, malgré les avancées thérapeutiques pour les patients atteints de MICI. Environ 70 à 80% des patients atteints de MC et 30 à 40% des patients atteints de RCH subissent une intervention chirurgicale au cours de leur vie (Hancock et Mortensen 2008). Pour les patients atteints de RCH, la chirurgie est curative en cas d'échec de la prise en charge médicale ou de complications aiguës graves (Ferrari,

Krane, et Fichera 2016). Elle consiste généralement en une colectomie abdominale totale avec une iléostomie terminale. Cela implique l'ablation de côlon et du rectum, et la dérivation de l'intestin grêle vers l'extérieur du corps pour recueillir le contenu intestinal. En revanche, chez les patients atteints de MC, la chirurgie n'est pas curative mais nécessaire lorsque les traitements médicaux sont inefficaces ou en cas de complications telles que des fistules, des abcès ou des sténoses (Gardiner et Dasari 2007). Le type de chirurgie dépend de la localisation de la maladie et peut impliquer la résection d'un segment intestinal malade et une anastomose pour reconnecter les deux extrémités intestinales, ou d'autres options telles qu'un contournement intestinal, la création d'une iléostomie ou une stricturoplastie pour élargir les sténoses (Hwang et Varma 2008).

3.3. Nutrition et Modulation du microbiote intestinal

3.3.1. Nutrition : focus sur les omega 6

L'alimentation influe fortement notre santé, et en particulier l'homéostasie intestinale qui est en contact avec les nutriments. De plus, elle module de façon rapide et reproductible le microbiote intestinal (David et al. 2014). Au cours des 70 dernières années, notre alimentation s'est drastiquement détériorée. Nous consommons principalement des aliments ultra-transformés, comprenant des composants alimentaires raffinés et modifiés, tels que les huiles, les sucres et édulcorants, les protéines transformées et divers additifs alimentaires rendant la nourriture hautement appétissante mais dépourvue de nutriments essentiels (Fardet et Rock 2019). En conséquence, un tel régime entraine de nombreuses modifications dramatiques dans la qualité globale des aliments. On observe notamment une diminution des fibres, une déficience en vitamines, une augmentation des acides gras saturés et des sucres. Ces changements peuvent altérer la santé humaine à court terme en affectant particulièrement l'homéostasie intestinale, ce qui participe au développement de MICI.

1.3.2.1.1 Les fibres alimentaires

La plupart des études se concentrent sur les macronutriments, en particulier les **fibres alimentaires** principalement retrouvées dans les fruits et les légumes. Les fibres alimentaires sont largement considérées comme un facteur **protecteur** dans le développement des MICI (Khorshidi et al. 2020). Or notre alimentation s'appauvrit en fibres, les Français en moyenne consomment environ 17g de fibres par jour alors que les recommandations sont à 30g par jour. Une étude portant sur des adolescents de moins de 20 ans nouvellement diagnostiqués Crohn a révélé une diminution de la consommation de fibres avant le diagnostic (Amre et al. 2007).

1.3.2.3.2 Les acides gras poly-insatures (AGPI)

Outre les fibres, le **ratio oméga 6 / oméga 3** est un autre facteur important dans les MICI. Le ratio oméga 6 / oméga 3 doit être inférieur à 5. En 30 ans, ce ratio a augmenté de 1 :1 à 20: 1 favorisant le développement de pathologies chroniques (Mariamenatu et Abdu 2021). En effet, une diminution de ce ratio diminue le risque de développer une MICI (Amre et al. 2007; Chan et al. 2014; Ananthakrishnan et al. 2014; John et al. 2010).

Le métabolisme des oméga 3 permet la synthèse des acides eicosapentaénoïques (EPA) qui seront métabolisés par la voie des cyclooxygénase (COX) et leucooxygénase (LOX). Les oméga 6 dérivent de l'acide linoléique (LA) et

sont métabolisés en acide ɣ-linoléique (GLA) puis acide dihomo-ɣ-linoléique (DGLA) et enfin l'acide arachidonique (AA) (Saini et Keum 2018) (**Figure 31**).

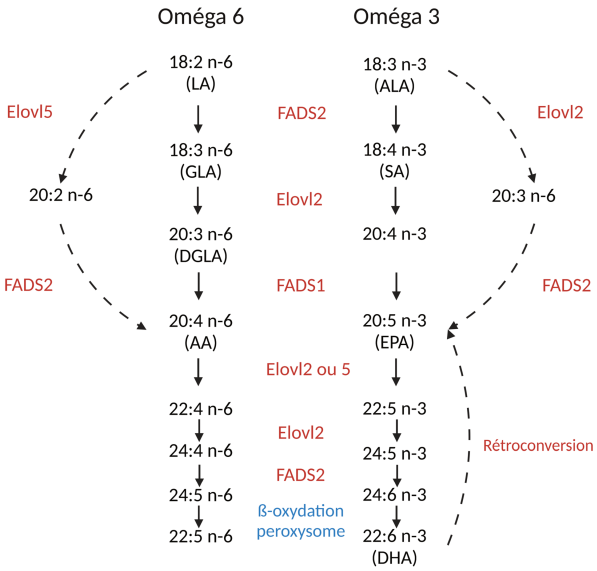

Figure 31. **Voie de synthèse des oméga 3 et oméga 6** (d'après Mokoena et al. 2020; Saini et Keum 2018).

L'acide linoléique est le précurseur des oméga 6 alors que l'acide α-linolénique celui des oméga 3.

L'AA peut également être synthétisé à partir des phospholipides membranaires via la phospholipase A2 (PLA2). L'AA va être métabolisé *via* la voie des LOX, COX ou cytochrome p-450 (CYP450) permettant la synthèse des **eicosanoïdes** (**Figure 32**).

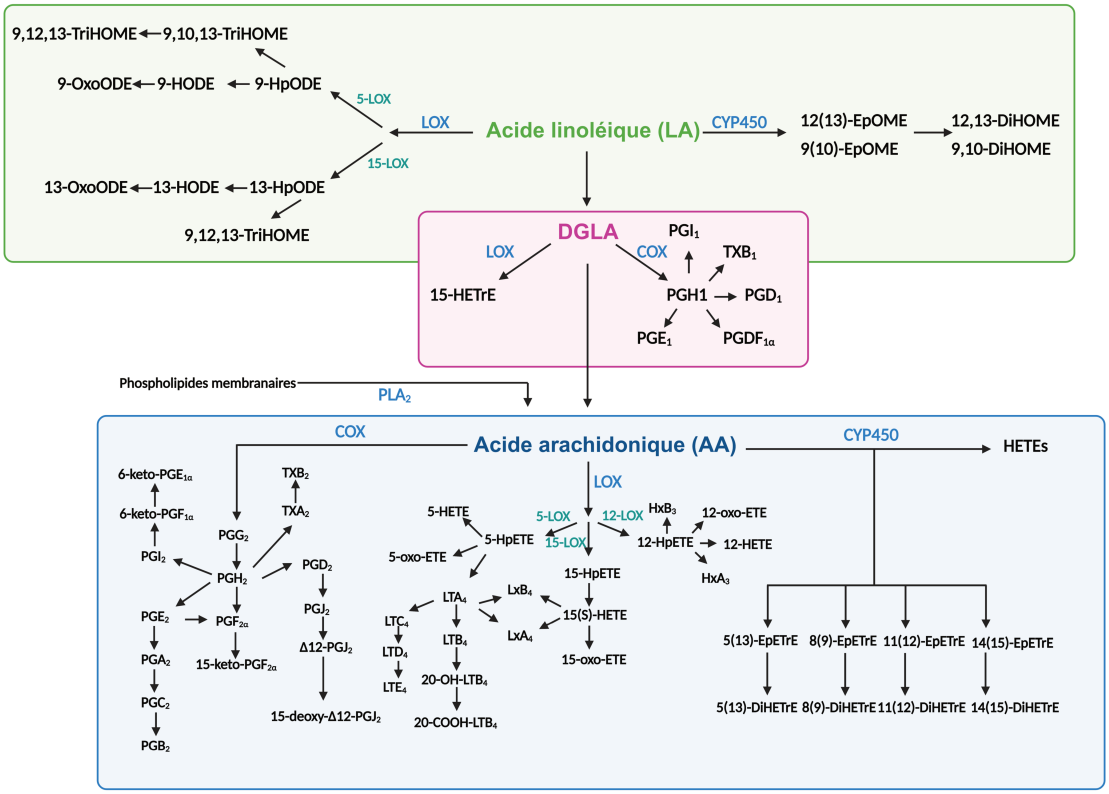

Figure 32. Voie de synthèse des oxylipines n-6 (d'après Strassburg et al. 2012).

Les **oméga 6** sont **pro-inflammatoires** et associés à un risque accru de développer une MICI (Shoda et al. 1996; Hou, Abraham, et El-Serag 2011). Dans des modèles de colites, un régime enrichi en **acide linoléique**, le chef de file des oméga 6, augmente la susceptibilité de la colite associée à une augmentation de perméabilité intestinale et une dysbiose du microbiote intestinal (Deol et al. 2023). Alors que les **oméga 3** sont connus pour avoir des effets **anti-inflammatoires** *via* la production de résolvines et de protectines (Barbalho et al. 2016). Les études *in vitro* et *in vivo* sont en accord, les oméga 3 sont anti-inflammatoires et capables de prévenir le développement de colite (Charpentier et al. 2018; Draper et al. 2011). En se basant sur ces données, il était clair que les oméga 3 devaient être testés chez l'Homme. Des études cliniques avec des régimes enrichis en oméga 3 ont donc été conduites chez des patients atteints de MICI. Mais, les résultats n'étaient pas concluants, bien que les patients présentaient une diminution des paramètres pro-inflammatoires, l'activité de la pathologie et le taux de rechute demeuraient les mêmes (Dixon et al. 2015).

En parallèle, les techniques de détection et de quantification des AGPI se sont perfectionnées (Le Faouder et al. 2013; Gobbetti et al. 2013), permettant une analyse plus fine des dérivés des AGPI n-6, aussi appelés **oxylipines n-6**. En effet, les oxylipines s'avèrent être des **médiateurs de l'inflammation** mais présentent également des effets de **résolution de l'inflammation** (Tableau 2).

Tableau 2. Action double des oxylipines n-6 dans l'inflammation.

	Médiation de l'inflammation	Références (DOI)
MICI	↑COX-2 dans les CEI des zones inflammées.	https://doi.org/10.1016/S0016-5085(98)70196-9
	↑PGE2, LTB4, 5-HETE.	https://doi.org/10.1016/S0016-5085(84)80015-3
RCH	↑PGD2 corrélée avec ↑ activité pathologie.	https://doi.org/10.1152/ajpgi.00351.2010
	↑PGE2, PGD2, TXB2, 5-HETE, 11-HETE, 12-HETE, 15-HETE dans la muqueuse inflammée corrélée avec sévérité de l'inflammation.	https://doi.org/10.1371/journal.pone.0076532
	↑PGE2, LTB4 luminal dans la RCH active *vs* rémission.	http://dx.doi.org/10.1136/gut.29.10.1316
in vivo	TNBS: ↑PGE2, LTB4.	https://doi.org/10.1016/S0016-5085(89)80016-2
	DSS: PGE2 aggrave sévérité inflammation colique.	https://doi.org/10.1084/jem.20082293
	Résolution de l'inflammation	**Références (DOI)**
MICI	Inhibition COX-1 et COX-2: ↓ synthèse PGs entraîne une ↑ activité pathologie.	https://doi.org/10.1016/S0002-9270(00)01054-6
	Inhibition COX-1 et COX-2: ↑ rechute.	https://doi.org/10.1016/S1542-3565(05)00980-8
MC	↓ AGPI n-6 dans le sérum associé à une ↓ des cytokines pro-inflammatoires et activité pathologie.	https://doi.org/10.1038/s41598-019-39232-z
RCH	↑ PGD2 chez RCH en rémission.	https://doi.org/10.1073/pnas.1004982107
	↓ expression 15-LOX2 muqueuse colique.	https://doi.org/10.1016/j.prostaglandins.2005.10.004
in vivo	PGE2: favorise la tolérance immunitaire.	https://doi.org/10.1038/ncomms1181
	PGD2 via synthèse 15dPGJ2 : résolution inflammation.	https://doi.org/10.1073/pnas.0707394104

De façon intéressante, les **oméga 6** se révèlent **bénéfiques** pour **l'intestin**. Un régime enrichi en oméga 6 pendant 9 semaines, mais pas en oméga 3, protège l'intestin de l'inflammation dans un modèle d'ischémie-reperfusion intestinale (Gobbetti et al. 2015). Le régime enrichi en oméga 6 permet de diminuer les dommages au niveau de la muqueuse, le recrutement des granulocytes et l'expression de certaines chemokines. Cette protection était associée avec une augmentation de l'expression génique de *alox5* (alox pour « arachidonate lipoxygenase »*)*, *alox12*, *alox15* (codants pour la 5-LOX, 12-LOX et 15-LOX), ainsi qu'une production plus élevée de Lipoxine A4 (LxA4). La LxA4 a été décrite comme un puissant lipide bioactif anti-inflammatoire (Serhan et Savill 2005). De plus certaines oxylipines n-6 renforcent de manière locale la BEI. Pour ne citer que quelques exemples (les oxylipines n-6 comptent plus de 100 médiateurs actifs …), la prostaglandine E2 (PGE2) a été décrite comme activatrice de la prolifération des CEI en réponse à des dommages de la muqueuse, et capable de supprimer la libération de TNF-α (Wallace et al., 2001). Le 11 beta-prostaglandine F2 alpha (11ßPGF2α) favorise la réparation épithéliale *in vitro* (Coquenlorge et al. 2016). Le 15-HETE (15-HETE pour « 15-hydroxyeicosatetraenoic acid »)

diminue la perméabilité *in vitro* et *in vivo* (Pochard et al. 2016). Le 6 keto prostaglandine F1 alpha (6kPGF1α) quant à lui, qui est la forme stable de la prostacycline I2 (PGI2), prévient de l'apoptose, la désorganisation architecturale de la muqueuse, augmente l'expression de l'occludine, une protéine de jonctions serrées permettant de diminuer la perméabilité intestinale dans des biopsies de patients Crohn. De plus, la PGI2 diminue la sévérité d'une colite induite au Dextran Sulfate Sodium (DSS) , associée à une diminution de la perméabilité intestinale (Pochard et al. 2021). Toutes ces données suggèrent que certaines oxylipines n-6 peuvent renforcer la BEI.

Or les patients atteints de **MICI** présentent une **déficience** de certaines **oxylipines n-6**, notamment celles identifiées comme renforçatrice de la barrière (Pochard et al. 2021). En effet, les 15-HETE, 11ßPGF2a, 6kPGF1a étaient diminuées dans le surnageant de biopsies de patients MICI. Mais alors pourquoi une supplémentation en oméga 6 dans l'alimentation ne permet pas d'avoir les effets bénéfiques attendus chez ces patients ?

Des études de GWAS ont mis en évidence une **altération du métabolisme des lipides** chez des patients atteints de MC fibrotique. Ces patients avaient une hyperméthylation de la région promotrice de la prostacycline synthase (PTGIS), une enzyme de synthèse de la PGI2, causant une inhibition de cette enzyme chez les patients et donc une diminution de la PGI2 (Sadler et al. 2016). De manière plus globale, le métabolisme de l'acide linoléique est altéré. Des variations du gène codant pour l'enzyme FADS1 (« Fatty acid desaturase 1 »), qui convertit le DGLA en AA, sont associées à une augmentation de susceptibilité des MICI (Diab, Hansen, et al. 2019). Les patients avec une RCH active présentent une augmentation de l'AA et de ses dérivés pro-inflammatoires, mais lorsque les patients sont en rémission le 15-HETrE (« 15-hydroxyeicosatrienoic acid ») augmente, suggérant que la **balance** entre les **médiateurs pro-inflammatoires** et **anti-inflammatoires** et/ou **renforçateur de BEI** est **dérégulée** (Diab, Al-Mahdi, et al. 2019; Diab, Hansen, et al. 2019).

En résumé, l'équilibre entre les AGPI n-3 et n-6 joue un rôle crucial dans la pathogenèse des MICI. Il est primordial d'éviter de réduire le message en affirmant que les oméga 6 sont uniquement pro-inflammatoires. Leur fonction est bien plus complexe, englobant à la fois un rôle dans la médiation et la résolution de l'inflammation, ainsi qu'un renforcement de la BEI. La seule complémentation en AGPI n-6 chez les patients devient compliquée en raison de l'altération du métabolisme de l'acide linoléique. D'autres études sont nécessaires sur la supplémentation avec les oxylipines renforçatrices de BEI ou bien l'utilisation de probiotique lipolytique. Dans l'ensemble, ces résultats soulignent l'importance d'une alimentation équilibrée et riche en fibres pour la santé intestinale et la prévention des MICI. Il est crucial d'intégrer ces connaissances dans les stratégies de traitement des patients atteints de MICI.

3.3.2. PRE-, PRO-, SYN- , POSTBIOTIQUES ET MICI

Un intérêt croissant se porte sur les thérapies ciblant le microbiote intestinal. En effet, certaines pathologies telles que l'infection à *Clostridium dificile* sont principalement soignées par la transplantation fécale de microbiote. Étant donné que les patients atteints de MICI présentent une dysbiose du MI et que la relation de causalité avec la pathologie reste encore indéterminée, il est tout à fait justifié d'envisager des thérapies visant à moduler le MI. Une méta-analyse d'études cliniques « RCT » indique qu'une préparation probiotique s'avère efficace dans le cadre des MICI, à induire ou à prolonger les rémissions (Sniffen et al. 2018).

Des prébiotiques, probiotiques, symbiotiques et postbiotiques sont donc considérées dans le contexte des MICI. La présente revue écrite conjointement par les membres du laboratoire TENS (U1235 INSERM/Nantes Université), BIA (U1268 INRAE) et STLO (U1253 INRAE/Institut Agro) synthétise les études récentes menées sur la modulation du microbiote intestinal dans un contexte de MICI. Cette revue aborde la question de quand les administrer, et dans quel but (préventif *versus* thérapeutique). Elle fait également le distinguo entre les études *in vitro,* précliniques et cliniques. Globalement, les effets des pre- pro- post- et synbiotiques *in vitro* et *in vivo* sont encourageants. Cependant, peu d'études cliniques ont été conduites. Pour le moment, l'utilisation de VSL#3, une association de bactéries probiotiques, est la formule la plus efficace pour maintenir et induire la rémission dans le contexte des MICI.

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REVIEW

Microbiome-Based Therapeutics and Their Physiological Effects

Inflammatory bowel disease therapeutic strategies by modulation of the microbiota: how and when to introduce pre-, pro-, syn-, or postbiotics?

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Abstract

Inflammatory bowel diseases (IBD), a heterogeneous group of inflammatory conditions that encompass both ulcerative colitis and Crohn's disease, represent a major public health concern. The etiology of IBD is not yet fully understood and no cure is available, with current treatments only showing long-term effectiveness in a minority of patients. A need to increase our knowledge on IBD pathophysiology is growing, to define preventive measures, to improve disease outcome, and to develop new effective and lasting treatments. IBD pathogenesis is sustained by aberrant immune responses, associated with alterations of the intestinal epithelial barrier (IEB), modifications of the enteric nervous system, and changes in microbiota composition. Currently, most of the treatments target the inflammation and the immune system, but holistic approaches targeting lifestyle and diet improvements are emerging. As dysbiosis is involved in IBD pathogenesis, pre-, pro-, syn-, and postbiotics are used/tested to reduce the inflammation or strengthen the IEB. The present review will resume these works, pointing out the stage of life, the duration, and the environmental conditions that should go along with microbiota or microbiota-derived treatments.

IBD; microbiota; n − 6; prebiotic; probiotic

INTRODUCTION

Inflammatory bowel diseases (IBD), a heterogeneous group of conditions that encompass both ulcerative colitis (UC) and Crohn's disease (CD), are complex chronic inflammatory disorders with increasing prevalence worldwide in the past decade (1). IBD are now a major public health problem that affects ~3.6 million people in the United States and Europe (2). IBD onset typically occurs between the second and third decades of life. A majority of affected individuals progress toward a relapsing and chronic disease, characterized by an immune activation and inflammation of the gastrointestinal (GI) tract that severely alters its function. Common IBD symptoms include bleeding, severe diarrhea, abdominal pain, and weight loss. In CD as well as in UC, inflammation of the gut is associated with the breakdown of intestinal epithelial barrier (IEB) integrity, abnormal secretions, and changes in motility patterns. UC features include diffuse mucosal inflammation that extends proximally from the rectum, whereas CD inflammation may be patchy and transmural. This uncontrolled chronic inflammation can result in a complicated disease course with undesirable abdominal abscesses, fistulae, strictures, subsequent bowel obstruction, and an increased risk for GI malignancy. As such, a greater understanding of IBD pathophysiological mechanisms is required.

IBD Etiology

IBD develop in genetically predisposed individuals under the influence of environmental factors. Family aggregation has long been recognized, and first-degree relatives of affected individuals have a relative IBD risk of fivefold or greater. More than 240 genetic risk loci have been associated with IBD (3). Despite susceptibility genes that are for the most part different between CD and UC, 30% of IBD-related loci are common to these two intestinal diseases. These genes are involved in the immune system modulation (immune cell recruitment, innate mucosal defense) as well as in the control of intestinal epithelial barrier (IEB) functions (permeability, repair, and autophagy). Most interestingly, many of

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the known IBD susceptibility genes are associated with recognition and processing of bacteria (4). Environmental factors are also involved, and potentially relevant environmental IBD risks factors encompass major life stressors, diet, and/or lifestyle. They span the spectrum of life from birth and early-life exposures (breastfeeding and antibiotic exposure in infancy) to exposures later on in adulthood (depression, physical activity, low-fiber diet, and low vitamin D) (2).

IBD Pathophysiology

Though the etiology of IBD has not been fully elucidated, it is currently known that IBD pathogenesis is sustained by aberrant immune responses and associated with alterations of the IEB, alterations of the enteric nervous system (ENS), and changes in microbiota composition (5). Patients with IBD are characterized by the infiltration of inflammatory $CD4^+$ T-cells in intestinal tissue encompassing an increase in inflammatory T cells (Th1, Th2, Th9, Th17, and $CD161^+CXCR3^+CCR6^+CD4^+$ Th17.1) response, associated with a reduced regulatory T cells (Treg and Tr1) response (6). In addition, the immune chronic activation in IBD involves a dysfunction of neutrophil granulocytes and phagocytes, T- and B cell selection and activation, and immune inhibitory mechanisms. Another common disease denominator is the defective IEB, that not only presents cell death abnormalities but also deregulation of the permeability, and clinical remission is linked to intestinal mucosal healing (7). In addition, widespread damage of the enteric nervous system (ENS) has been described for a long time in CD and its dysfunction has been recently demonstrated. Structural abnormalities of the ENS have consistently been observed in CD and, less frequently, in UC (8, 9). Coarse nerve fibers and axonal necrosis have been observed in CD ileum or colon (10, 11). In these segments, enteric glial cells have lost their control upon intestinal healing and permeability (12, 13). Finally, dysbiosis has been observed in patients with IBD and in mice models of colitis (14). Dysbiosis could be different between patients with UC and CD, but is observed in both pediatric and adult populations, in active or quiescent phases of the pathology and in treatment-naive patients with CD (15). The most consistent observation in IBD is a reduced bacterial diversity, with a decrease of *Firmicutes* phylum and *Bifidobacteriaceae* family, an increase of the *Enterobacteriacea* and *Akkermensia* genera (*Akkermensia muciniphila*). Periods of disease activity are also marked by increased transient microbial changes (16). The species *Faecalibacterium prausnitzii* is not only decreased in patients with CD compared with healthy subjects, but its absence is also correlated with the risk of relapse of ileal CD after surgery, and its recovery is associated with the maintenance of clinical remission (17–20). Increasing studies describe how *F. prausnitzii* can dampen the inflammation through reduction of proinflammatory cytokines production, regulation of Treg or intestinal epithelial cells (IEC) (21, 22). Altogether, these studies highlight the concept that host-microbiota interactions play a central role in IBD pathogenesis and are potential therapeutic targets (23, 24).

Treatments

At present, the mainstays of IBD treatment are immunosuppressive and immune-modulating agents. Therapeutic agents comprising anti-TNF demonstrated significant changes in our ability to induce and maintain remission but reached limitations. A significant percentage of patients with IBD do not respond primarily to the treatment or lose responsiveness over time (25). The inability to provide a surgical treatment due to physical extension and/or mislocalization of lesions represents as well a major challenge in the management of IBD (26, 27). Various new agents targeting cytokines, adhesion molecules, or tyrosine kinases are currently in clinical trials. Modulating the gut microbiota emerges as an attractive novel therapeutic approach for IBD, and therapies targeting/based on the gut microbiome are under extensive investigation with varying success.

Microbiota-Based Interventions

A microbiota is defined as an "assemblage of microorganisms (all the bacteria, archaea, protists, fungi, and viruses) present in a defined environment" found in all multicellular organisms (28). The gut microbiome, that encompasses ~600,000 microbial genes, contributes to trophic functions, metabolism, barrier function, and immune stimulation. Host-microbiota interactions play a key role in human health, with alterations of the microbiota associated with numerous neurological and chronic diseases (29, 30). The imbalance of the microbiota in its composition and metabolism is encompassed in a global concept of dysbiosis (31). This definition remains challenging as the definition of a healthy microbiota is complex and in constant need of refinement (32).

Resulting from this, different strategies are evaluated to compensate or restore the default observed in microbiota-host communication and treat dysbiosis and/or inflammation. Among many influencing factors, the diet is now well recognized for being able to rapidly and reproducibly modify or modulate the gut microbiota (33). In a more targeted way, the use of prebiotics aims at enriching the microbiome, and fecal transplantation or ingestion of microorganisms is under study in preventive as well as therapeutic strategies. Thanks to increasing knowledge on their function in host regulation, the use of products derived from or associated with the microbiota is being tested. The present review will examine the use of pre-, pro-, syn-, or postbiotics, fecal microbiota transplantation. and diet modification in the IBD patient care.

PREBIOTICS

Prebiotics Definition

A prebiotic is "a substrate selectively used by micro-organisms of the host conferring benefits for his health" (34). Prebiotics are found naturally in vegetables, fruits, and cereals but also in human milk as human milk oligosaccharides (35, 36). They mainly include oligosaccharides, nondigestible carbohydrates, and potentially polyphenols or polyunsaturated fatty acids (37). Because of their modulatory effects on the microbiota, fructans like the fructo-oligosaccharides (FOS) and inulin, but also galactans like galacto-oligosaccharides (GOS) represent the most studied prebiotics (35, 37).

Effects

Prebiotics can act on multiple organs/system apart from the gut (35). The functions of the prebiotics are supported by different mechanisms of action that may be direct,

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through interaction with cell surface receptors, or indirect through the products of their fermentation by specific commensal bacteria (35). Prebiotics contribute not only to the defense against pathogens but also to the enhancement of tolerance (e.g., Treg and dendritic cells promotion) (35). Prebiotics promote the growth of healthy bifidogenic strains populations like *Bifidobacterium* species (38). They also promote barrier integrity, so influencing as well functions such as wound repair and intestinal permeability (35, 37). Among the products of bacterial fermentation, short-chain fatty acids (SCFAs) are bioactive metabolites that can regulate epithelial and immune cells (35). They have a broader impact on gut functions through the regulation of the enteric nervous system and gut motility, and are thereby interesting in the context of IBD treatment (39).

In Vitro Studies

Different mixtures of prebiotics [GOS, GOS + FOS, GOS + FOS + acidic oligosaccharides (AOS)] were tested on primary equine peripheral blood mononuclear cells (PBMC) before and during inflammation (Table 1) (40). These prebiotics potentially enhanced inflammation and decreased tolerance by changing cytokines production. A second study used orange pectin and side chain-derived polysaccharides on the murine macrophage cell line RAW 264.7 before the induction of inflammation (41). Both prebiotics promoted anti-inflammatory effects by suppressing the IL-6 secretion induced by inflammation (41). The acidic fraction of human milk oligosaccharides reduced lymphocytes and neutrophils adhesion to human umbilical vein endothelial cells (HUVEC) and IFN-γ production (45, 46). Prebiotics like inulin increased on the contrary proinflammatory cytokines (47). Regarding T cells maturation, short chain GOS + long chain FOS treatment on dendritic cells led to Treg differentiation (48). In addition to the regulation of maturation and functions of the immune cells, prebiotics can regulate intestinal epithelial cells, mainly through decrease of cytokine production (42, 43).

Positive changes of microbiota activity through SCFA production and changes of composition were promoted in vitro by prebiotics. Indeed, apple pectin increased in vitro the abundance of butyrate-producing bacteria, including *F. prausnitzii,* and butyrate concentrations in feces from patients with UC and CD (49). Prebiotics modulated the expression of genes toward a decrease of potential barrier damage and of inflammation. Namely, an upregulation of MUC1 and Occludin expressions were induced by fermented chicory pulp supernatant in a GI tract model, while TNF and cyclooxygenase-2 (COX-2) were downregulated (44).

Preclinical Studies

FOS administration to Wistar rats promoted caecal SCFA production, which lowered the luminal pH (Table 1). Acidification of the luminal content may inhibit the development of pathogens and enhance the growth of lactic acid bacteria (52). GOS attenuated Citrobacter *rodentium* colitis severity (38). The decrease of clinical symptoms and colitis severity by prebiotics intake was linked notably to a decrease of immune cells gut infiltration and of proinflammatory cytokines secretion (41).

Prebiotics as early-life treatment was mainly investigated in postweaned rats and mice (Table 1). Disease severity and clinical symptoms were improved by prebiotics intake early in life for these animal models. FOS increased fecal *Bifidobacterium* spp. and decreased fecal *Enterobacteriaceae* in HLA-B27 TG rats, whereas inulin increased caecal butyrate concentration in 4-wk-old C57BL/6 mice. The production of proinflammatory cytokines was decreased by 3-sialyllactose human-identical milk oligosaccharide (HMO) intake in *IL-10*$^{-/-}$ mice (62). Germinated barley stuff reduced the dextran sulfate sodium (DSS)-induced disruption of collagen and reticulin fibers in the intestinal mucosa, so improving the IEB (66). In adult animal models, an overall improvement of colonic damages, histological scores, and disease index were observed following prebiotic treatment.

To this day, colitis prevention studies have been mainly performed in adult murine models, and while they show for the most part, protective effects (53, 76–78), two studies described how inulin supplementation potentiated the severity of colitis (63, 79). Recently, in line with our work, one study analyzed the effect of maternal intake of inulin on colitis development in rats, and described how it exacerbated intestinal damage and inflammation induced by DSS (80). The increased disease activity index, myeloperoxidase activity and IL-1β mRNA expression observed in this model were associated with an increase in the abundances of *Bacteroidetes*, Bacteroides, and *Parasutterella* (80).

Clinical Studies

Clinical studies were achieved in adults and exclusively used prebiotics to treat IBD (Table 1). Potential prebiotics such as oat and wheat bran were also tested as dietary fibers. They have interesting properties like the enhancement of immune and intestinal functions (81). The microbiota composition and metabolism were impacted, with an increase of fecal *Bifidobacteria* after the intake of the mix "Prebio 1" of FOS and inulin (71). Oat bran increased fecal butyrate concentrations (57). Immunological parameters were affected by prebiotics consumption, as evidenced by a change in dendritic cells cytokines production and populations (72). Prebiotics decreased inflammation markers and symptoms in patients, leading to the decrease of steroid medication, as seen with germinated barley foodstuff (GBF) for patients with UC in remission (60, 73). Even though the clinical disease activity index and recurrence rate might decrease with prebiotics intake (60), more withdrawals of patients were observed for supplemented groups (72, 82). Withdrawals took place mostly in studies where patients with CD had moderately active disease. This result underlined worsening symptoms and side effects that can accompany the supplementation in prebiotics.

Conclusion on Prebiotics

Promising results were achieved in vitro and in vivo, and showed beneficial effects of prebiotics on IBD prevention and treatment at early age and adulthood. However, more mitigated results were achieved in clinical trials that only focused on treatment of IBD. A better tolerance of prebiotics was observed in patients with UC in remission or with mild

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Table 1. *Prebiotic impact on colitis, prevention, and treatment of IBD*

Reference	Prebiotic Type	Model or Study Design	Age of Supplementation	Mechanisms/Global Impact on Colitis or IBD
		In vitro		
40	GOS, GOS/FOS, GOS/FOS/AOS	Primary equine PBMC ± LPS		Increase or decrease in IL-10 and TNF-α mRNA expression depending on the prebiotic used
38	GOS	Hep-2 cell line ± *Citrobacter rodentium*		Antiadhesive effect observed in vitro only
41	Pectin	RAW264.7 cell line ± LPS or Pam3CSK4		Suppressed IL-6 production
42	Oligosaccharides, α3-sialyllactose, or fructooligosaccharides	Caco-2 cells		Decrease TNF-α production and NF-κB activation through PGlyRP3 and PPARg
43	Galactosyloligosaccharides, human HMO	H4, T84, NCM-460 cell lines, immature human small intestinal tissue ± TNF-α, *S. enterica* or *L. monocytogenes*.		Decrease IL8 or MIP3A expression induced by stressors
44	4–25 HMO mix, filtered fermentation supernatant of inulin, chicory root, chicory or citrus pulp, rye bran, soya hulls.	PSIc1, IPEC-J2 cell lines, pig GI tract model ± LPS.		Reduced inflammation: change of cell proliferation and cytokines production, increased SCFA/Bifidobacterium
		Prevention		
38	GOS	*C. rodentium* infection ± GOS in drinking water	7-wo C57BL/6 female	In vivo reduction in disease severity independent of the antiadhesive effect observed in vitro only
41	Pectin	DSS or TNBS ± pectin supplemented in diet	7–8 wo C57BL/6 male	Amelioration of TNBS-induced Colitis by orange pectin, no effect on T cell differentiation or infiltration but decreased TNFa or IL17A concentrations
45–48	aHMO, nHMO, fucoidan, 3′NeuAc-Lac, 3′NeuAc-3Fuc-Lac, FOS, inulin, GOS, goat milk oligosaccharides, scGOS/lcFOS	HUVEC cell line, human/Wistar rat immune cells, TLR4$^{-/-}$ or mice splenocytes ± hrTNF-α, PMA/ionomycin, LPS		Influenced lymphocyte function, maturation and adhesion, and inflammatory cytokines secretion. Reduced adhesion and increased CD25 expression.
49	Grape-derived prebiotic, apple pectin	Healthy subjects, patients with UC and CD		Promoted SCFA production and SCFA-producing bacteria.
50	Glucan EPS P and L polymers	Colonic mucosa of patients with CD		Reduced proinflammatory cytokines production.
51	Potential prebiotic: feruloylated oligosaccharides of rice bran	Murine BMDC or T cells from: C3H/HeN, C3H/HeJ, C57BL/6, TLR2 KO or NF-κB/luciferase transgenic mice	C57BL/6	Induced maturation of dendritic cells, enhanced T cell immune response
52, 53	Inulin, FOS	Acute DSS and TNBS colitis induction	Male Sprague-Dawley and Wistar rats	Decreased colonic damages, body weight loss, and PGE2 release. Change of gut microbiota composition and SCFA
38, 41, 54, 55	GOS. Potential prebiotic: quinoa, orange, citrus pectin, native potato starch, pea starch, Chinese Yam starch.	Acute DSS and TNBS or *C. rodentium* colitis induction	6–8 wo C57BL/6 mice	Decreased clinical and histopathological parameters, changed gut microbiota composition, and SCFA. GOS increased *C. rodentium* number in distal colon and spleen.
56	Inulin or FOS	Spontaneous colitis. Before colitis induction	4–16 wo HLA-B27 TG rats	Reduced histological score and IL-1β, change of gut microbiota composition.
57	Potential prebiotics: oat bran	Controlled pilot trial: quiescent UC patients + oat bran	Adult patients (>18 yr)	No effect on SCFA concentrations. Could not demonstrate a benefit of oat bran.
58	Potential prebiotics: amylose-associated resistant starch (RS)	Remission UC patients + high and low RS/wheat bran (WB)		Decreased abdominal pain and gastroesophageal reflux for patients with UC, increased butyrate concentration. No impact of RS diet on UC, changed SCFA concentrations

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Table 1.— *Continued*

Reference	Prebiotic Type	Model or Study Design	Age of Supplementation	Mechanisms/Global Impact on Colitis or IBD
59	Potential prebiotic: curcumin (2 g/day)	Multicenter DB RPCT: quiescent UC patients UBT		Decreased the recurrence status, CAI and endoscopic index. 2/43 relapsed during 6 mo of therapy, whereas 8 of 39 patients in the placebo group relapsed ($P = 0.040$)
60, 61	GBF	Multicenter NC OLT, NR OLT, OLT, pilot OLT: patients with UC in remission		Lowered the cumulative recurrence rate. Maintained remission and anti-inflammatory.
		Treatments		
62, 63	2FL, inulin (ICD) or pectin	IL10$^{-/-}$ mice or C57BL/6J ± acute colitis	After weaning: 21 days to 6 wo	Decreased diarrhea, histological score and intestinal permeability. Impact on cytokines and SCFA production, gut microbiota composition. ICD worsened colitis: higher body weight loss, gut, and spleen remodeling.
64	Chondroitin sulfate, α-glucan butyrogenic resistant starch + β-glucans + mannaoligosaccharides	IBD dogs of different breeds.	Mean age = 4.85 yr old	No effect on IBD index score, decreased histological score
65	Purified soluble fibers (including inulin, arabinoxylan)	Mice colonized with a synthetic microbiota + *C. rodentium* colitis	8-9 wo Germ-free Swiss Webster mice	Did not prevent mucus barrier erosion, increased Bacteroides abundance
66, 67, 68	Raftilose Synergy 1, germinated barley foodstuff, Chinese Yam polysaccharides/inulin	Spontaneous colitis, acute colitis, "chronic" TNBS colitis	7–11 wo SPF housed HLA-B27 and Sprague-Dawley rats	Decreased DAI, histological scores, mucosal mast cells infiltration and damage. Changed proinflammatory cytokines and SCFA production, gut microbiota composition. Anti-inflammatory and improved gut microbiota
69	Potential prebiotics: wheat bran (WB)	Single-blind RCT: patients with active CD + wheat bran	Adult patients (>18 yr)	Increased IBDQ scores and decreased pHBI scores for patients with CD. No impact of WB diet on UC, changed SCFA concentrations. Improved quality of life and gastrointestinal function
70	GBF	Mild/moderately active UC and UBT		Improved the clinical activity index
71, 72, 73, 74	Prebio 1/Synergy 1, oligofructose-enriched inulin (OF-IN)	Pilot NC OLT, DB RPCT: patients with moderately active CD UBT + Prebio 1/Synergy 1. Pilot RPCT: mild/moderately active UC patients UBT and lower fiber diet + Synergy 1 DB RPCT: patients with inactive/mild/moderately active CD UBT + OF-IN.		Prebio 1/Synergy 1 increased flatulence, borborygmi and abdominal pain. Synergy 1 and OF-IN induced more withdrawals. Decreased DAI, changed cytokines and SCFA production, gut microbiota composition. Anti-inflammatory and improved gut microbiota
75	Lactulose	Prospective pilot RCT: patients with active UC and CD		No effect on UC or CD diseases, improved IBDQ for patients with UC. No effect on CD but improved quality of life

aHMO, acidic fraction of human-identical milk oligosaccharide (HMO); AOS, acidic oligosaccharides; BMDC, bone marrow-derived dendritic cells; CAI, clinical activity index; CBMC, cord blood mononuclear cells; CD, Crohn's disease; DAI, disease activity index; DB, double-blind; DSS, dextran sulfate sodium; EPS, extracellular polymeric substances; 2-FL, 2-fucosylated lactose; FOS, fructo-oligosaccharides; GBF, germinated barley foodstuff; GI, gastrointestinal; GOS, galacto-oligosaccharides; IBD, inflammatory bowel disease; IBDQ; inflammatory bowel disease questionnaire; HUVEC, human umbilical vein endothelial cells; ICD, inulin-containing diet; LPS, lipopolysaccharides; NC, noncontrolled; nHMO, neutral fraction of HMO; NR, nonrandomized; Olt, open-label trial; PBMC, peripheral blood mononuclear cells; PGlyRP3, peptidoglycan recognition protein 3; pHBI, Harvey–Bradshaw index; PMA, phorbol 12-myristate 13-acetate; PPARg, peroxisome proliferator-activated receptor gamma; RCT, randomized controlled trial; RPCT, randomized placebo controlled trial; SCFA, short-chain fatty acids; TLR, Toll-Like receptor; TNBS, 2,4,6-trinitrobenzenesulfonic acid; TSLP, thymic stomal lymphopietin; UBT, under baseline treatment; UC, ulcerative colitis; wo, weeks old.

active disease, accompanied by an improvement of clinical symptoms.

Additional homogenized studies, especially clinical trials, are needed to better understand the preventive effects of prebiotics and to determine the window of opportunity for the treatment of IBD with prebiotics. The age and stage of disease of the individual represent important parameters to take into account. Currently, it is too early to suggest this strategy. We have to understand more precisely the mechanisms of prebiotic interactions with the host at immune, microbial, metabolic, and transcriptomic levels and the part of these systems to explain the IBD treatment or prevention.

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Preclinical and in vitro studies will be crucial to treat these questions. New large interventional clinical studies with a homogenous design (same age, same prebiotic, same dose, and same duration of supplementation) using prebiotics on patients with IBD with different degree of disease severity have to be done. Only prebiotics from agricultural materials or enzymatically synthesized (lacking the structural complexity of dietary fibers) have been tested in this context. In the future it will be relevant to use synthetic glycans spanning the chemical and structural diversity of dietary glycans that can be efficiently and consistently produced. Synthetic glycans enable a wide range of targeted changes to the microbiome and potentially open new avenues for the prevention and treatment of disease (83). HMO are other new interesting prebiotics to test in the context of IBD by their natural properties to support the immune system maturation, the cognitive function, the digestive health, and the development of gut microbiome (84).

Key Ideas: Prebiotics

In vitro and in vivo reduction of inflammation with prebiotics: *1*) modulation of immune and intestinal epithelial cells functions/maturation and host genes expression; *2*) modification of microbiota activity/composition; and *3*) mitigated results for preclinical studies or clinical trials. Patients with UC in remission showed a decrease of clinical symptoms after prebiotics intervention but more withdrawals were observed in case of an active disease. Limitations: lack of harmonization of protocols and of studies on prevention and at early age.

PROBIOTICS

Probiotics and IBD Treatment

Probiotics are defined as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (85). Probiotics have different mechanism of action, including competitive interactions with deleterious bacteria via a production of antimicrobial metabolites such as bacteriocins and defensins. They have immunomodulatory properties mediated by anti-inflammatory molecules and may increase the mucus layer (86). Probiotics further show beneficial effects on the pathogenesis of IBD. The gut microbiota of patients with IBD is characterized by a lack of bacteria with anti-inflammatory activities such as *F. prausnitzii* (Firmicutes), together with an enrichment of bacteria with inflammatory functions (87). Consumption of probiotics with anti-inflammatory activities thus appeared as a promising strategy in the management of IBD. Pioneer in vitro studies identified immunomodulatory bacteria and their beneficial impact on colitis in vivo (88). Meta-analysis of clinical trials then indicated the beneficial effect of a selected probiotic preparation, in the context of IBD (89). This opens avenues for thorough characterization of the immunomodulatory role of such microorganisms, and of combinations thereof, from in vitro to clinical studies.

In Vitro Studies

VSL#3 is a probiotic mixture of four strains of *Lactobacillus*, three strains of *Bifidobacteria*, and 1 *Streptococcus thermophilus* strain (90). Pretreatment with VSL#3 on disrupted intestinal cell lines improved epithelial barrier integrity by increasing tight junction proteins (91) (Table 2). *Saccharomyces boulardii* pretreatment of inflamed colonic cells suppressed inflammation-mediated NF-κB activation (100). As for *Escherichia coli* Nissle 1917 (EcN1917), only one study showed that its treatment reverted the increased permeability and restored the disrupted epithelial barrier in Caco-2 cells challenged by proinflammatory cytokines. Other bacteria such as *Propionibacterium freudenreichii* showed anti-inflammatory effects, including on human PBMC by increasing the IL-10-to-IL-12 (IL-10/IL-12) ratio (121). Such effects in vivo reportedly coincide with a healing effect in preclinical models of IBD (88).

Preclinical Studies

Preclinical models of IBD, mainly murine models of spontaneous or induced colitis, revealed the protective effects of selected strains of probiotics (122). VSL#3 pretreatment reduced colonic inflammation and improved IEB function in wild-type (WT) and Muc2$^{-/-}$ DSS-treated mice (92) (Table 2). These effects are correlated with a restoration of antimicrobial peptide gene expression and an increase of commensal bacterial abundance, mediated by SCFAs (92). Pretreatment of mice with EcN1917 promoted recovery of inflammation by modulating tight junction proteins, decreasing proinflammatory cytokines secretion and increasing mucins expression (96, 97). Regarding *P. freudenreichii* CIRM-BIA (CB) 129, two studies highlighted its preventive effects on colitis models in mice by reduction of COX-2 expression and of proinflammatory cytokines levels (105, 106).

As treatment, VSL#3 probiotic mixture restored the loss of tight junction protein observed in DSS-treated mice (109). Another study however demonstrated no anti-inflammatory effects of VSL#3 in mice with colitis (110). *F. prausnitzii* as curative approach reduced colitis severity in mice and rats, associated with an increase of colonic tight junction (TJ) proteins, reduction of intestinal permeability, and levels of proinflammatory cytokines (107, 118, 119, 123). Besides, *F. prausnitzii* regulated Th17/Treg ratio and induced Treg cells (119).

Such promising in vivo results opened the way to clinical studies, provided that the safety of the implemented strain (s) was established.

Clinical Studies

Few studies investigated the ability of probiotics to maintain remission in children with CD (Table 2). No protective effect of *Lactobacillus rhamnosus* GG (LGG) was found in children with CD on standard therapy (108). Regarding adult patients with CD, *S. boulardii* showed encouraging effects in maintaining the remission in CD by reducing the Crohn's disease activity index (CDAI) and improving IEB integrity (101–103). LGG was tested on adult patients with active CD but failed to induce remission (120).

Children with acute UC and receiving the VSL#3 probiotic mixture exhibited reduced inflammatory markers levels, a modification of gut microbiota, but also adverse effects (124). Two clinical studies showed that VSL#3 supplementation was effective to induce remission in adult patients with mild to moderate UC (90, 125). In addition, mucosal healing rate was higher with VSL#3 (90, 93). For *S. boulardii*, a clinical trial showed that its supplementation to UC adult patients

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Table 2. *Prevention and treatment of colitis or IBD with probiotics*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
			Prevention		
91–95	VSL#3	IEC in vitro +/− inflammation		No effect on mucin secretion	
				Restored TJ proteins via an activation pf p38 and ERK pathways	Improved IEB integrity
				Attenuated ROS production by macrophages	Anti-inflammatory
		Colitis in mice (WT and Muc2$^{-/-}$)	10–12 wo	Increased abundance of gut commensal bacteria	Improved gut microbiota
				Increased expression of β2 defensin via the regulation of NF-κB and AP-1/restoration of antimicrobial peptide gene expression and VEGF	
		Patients with inactive UC	Adult patients (>18 yr)		Remission was higher in the VSL#3 group vs. placebo
96–99	*Escherichia coli* Nissle 1917 (EcN 1917)	IEC in vitro +/− inflammation		Restored the localization and altered distribution of claudin-1	Improved IEB integrity
		Induced colitis and mucositis in mice	7–9 wo	Ameliorated the decreased expression of TJ proteins	
				Inhibited the decrease of claudin-1 expression	
				Reduced the increase expression of ICAM-1	
				Restored the indices of richness and diversity to normal values	Improved gut microbiota
				Attenuated the increase of Firmicutes phylum and increased Cyanobacteria	
				Restored the of Firmicutes/Bacteroidetes ratio	
				Ameliorated expression of Muc-2 and -3	Effect on colonic mucosa
		Patients with inactive UC	Adult patients (>18 yr)		Efficacy and safety equivalent to the gold standard mesalazine in patients with UC
100–104	*Saccharomyces boulardii*	IEC in vitro +/− inflammation		Upregulated PPAR-γ, thus suppressed NF-κB activation leading to a decrease IL-8 expression	Anti-inflammatory
		Colon from patients with IBD		Enhanced E-cadherin delivery to the cell surface	Improved IEB integrity
		Patients with inactive CD	Adult patients (>18 yr)	Improved gut permeability	Clinical relapses were less frequent in patients receiving *S. boulardii* with current treatment
				Decreased lactulose/mannitol ratio	
105, 106	*Propionibacterium freudenreichii*	Human PBMC		Increased IL-10/IL-12 ratio	Anti-inflammatory
		Induced colitis in mice	8 wo	Modulated local and systemic inflammatory markers (proinflammatory cytokines, MPO, Cox-2)	
				Decreased secretory IgA concentration in small bowel	
				Increased zo-1 mRNA levels	Improved IEB integrity
				No effect on gut microbiota	
19, 107	*Faecalibacterium prausnitzii*	Induced colitis in mice	6–8 wo	Decreased proinflammatory cytokines and increased IL-10	Anti-inflammatory
				Corrected dysbiosis	Improved gut microbiota
108	*Lactobacillus rhamnosus GG* (LGG)	Children with inactive CD	5–21 yr		No extension of time before relapse in children with CD when given as an adjunct to standard therapy
			Treatment		
109–112	VSL#3		6–8 wo		

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Table 2.— *Continued*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
		Induced colitis in mice and rats		Decreased proinflammatory markers and increased IL-10 levels in colonic tissues and serum	Anti-inflammatory (controversial data)
				No effect on gut inflammation and severity of colitis	Improved gut permeability by preventing the decreased expression and distribution of TJ protein
				Improved IEB integrity	Prevented the increase in apoptotic cell level
				No effect on mucin secretion	
		Modulated the gut microbiota composition (increased Bifidobacterium spp. And Lactobacillus spp) and activity (increased capacity to ferment lactose, sucrose etc.)	Improved gut microbiota		
		Gastric ulcer in rats. Treatment after ulcer induction.	No data	Enhanced gastric ulcer healing	Improved IEB integrity
		Children with active UC	3–17 yr	Modification of the gut microbiota	Remission was achieved in 56% of children, response in 6% and bi change/or worsening in 39%
				Reduction of inflammatory markers	Adverse effects: 67% (bloating and flatulence)
Patients with active UC	Adult patients (>18 yr)	Mucosal healing rate was significantly higher in patients in the VSL#3 groups vs. placebo	Remission was achieved in >50% of patients		
113–115	EcN 1917	IEC in vitro +/− inflammation			Improved IEB integrity
		Induced colitis in mice (WT and TLR-2 and $-4^{-/-}$).	No data	Decreased proinflammatory cytokines via TLR-2 and -4 dependent pathways	Anti-inflammatory
		Patients with active UC	Adult patients (>18 yr)		Equivalent effect to the gold standard mesalazine in patients with UC
100, 116, 117	*Saccharomyces boulardii*	Induced colitis in mice.	8–12 wo	Decreased proinflammatory mediators via an upregulation of PPARγ Decreased proinflammatory mediators via an upregulation of PPARγ Limited the infiltration of lymphocyte T helper in inflamed colon	Anti-inflammatory
		Patients with active UC	Adult patients (>18 yr)		17/24 patients achieved clinical remission
107, 118, 119	*F. prausnitzii*	Induced colitis in mice and rats.	6–8 wo	Reduced proinflammatory cytokines and T-cell levels Induced Treg by inhibiting the IL-6/STAT-3/IL-17 pathway Secreted butyrate that regulated Th17/treg balance by inhibiting HDAC-1	Anti-inflammatory
				Improved gut permeability	Improved IEB integrity

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Table 2.— *Continued*

Reference	Probiotic Type	Model or Study Design	Age of Supplementation	Mechanisms	Effect on IBD
				Improved increased TJ proteins (claudin-4, occludin, ZO-1 and E-cadherin) in colonic samples No significant differences were observed in the passage of *E. Coli* K12	
120	LGG	Patients with active CD	Adult patients (>18 yr)		Could not demonstrated a benefit of LGG in inducing remission

CD, Crohn's disease; COX-2, cyclooxygenase-2; ERK, extracellular signal-regulated kinases; hDAC, histone deacetylase; ICAM-1, intercellular adhesion molecule; IBD, Inflammatory bowel diseases; IEB, intestinal epithelial barrier; IEC, intestinal epithelial cells; MPO, myeloperoxidase; PBMC, peripheral blood mononuclear cells; ROS, reactive oxygen species; TJ, tight junction; VEGF, vascular endothelial growth factor; TLR4, Toll-like receptor 4; UC, ulcerative colitis; wo, weeks old; WT, wild-type.

with clinical flare-up was effective to reach remission (116). EcN1917 efficacy in the treatment of UC is mitigated, with a study showing no difference between the EcN1917 group and the mesalazine control group and another presenting EcN1917 as an alternative to mesalazine for maintenance of remission in UC (113, 126). Meta-analysis of clinical studies dealing with IBD and probiotics concluded on a "strong evidence" for VSL#3 in the context of IBD, yet a "moderate" evidence for *S. boulardii* and a "weak to not effective" for *L. rhamnosus* GG and for *E. coli* Nissle 1917.

Conclusions on Probiotics

To conclude, in vitro studies suggested an action of probiotics on the IEB, gut microbiota, and anti-inflammatory effects. Animal studies supported the protective effects of probiotics against colitis development via a reduction of inflammation. However, knowledge about the role of probiotics on pediatric IBD at preclinical and clinical levels as well as data on CD is still missing. Beneficial effects of probiotics were more reported in UC than in CD. Larger clinical trials implementing probiotics are needed to confirm that they can favor remission in IBD.

Key Ideas: Probiotics

Actions of probiotics in vitro and in vivo: *1*) improved IEB via the regulation of tight junction proteins and mucin secretion; *2*) modification of gut microbiota composition and activity; and *3*) reduction of inflammation. VSL#3 appears to be the most effective probiotic for maintenance of remission in IBD and also in its induction at preclinical scale. Limitations: lack of preclinical studies and clinical trials both on probiotics as preventive and therapeutic strategies, especially at early age, on CD.

POSTBIOTICS

Definition of Postbiotics

Postbiotics refer to microbial components as well as microbial metabolites secreted by live bacteria or released after bacterial lysis (127). All these components may have local and systemic effects. Their advantages over probiotics include reduced risk of infection and side effects triggered by certain bacteria. Indeed, the administration of viable probiotics to individuals with weaker immune systems could enhance inflammatory responses and turn "generally recognized as safe" harmless probiotic bacteria into detrimental microorganisms. The inactivation of bacteria can be achieved by physical methods such as heat or chemical treatment, resulting in bacteria unable to grow but with maintained health benefits (127). Postbiotics can be divided in gut microbial components and metabolites.

Gut Microbial Components

Cell surface protein.

Surface-layer proteins (Slp) constitute a semipermeable cell envelope component in certain bacteria. Pretreatment with Slp from *Lactobacillus acidophilus NCFM* improved IEB in vitro by increasing transepithelial electrical resistance (TEER) and reducing permeability, which was partly due to a restoration of TJ proteins expressions (Table 3). Slp pretreatment also attenuated inflammation via the reduction of proinflammatory cytokines level (128). In a noninflammatory context, SlpA from *L. acidophilus* CICC 6074 increased proinflammatory mediators by activating MAPK/NF-κB pathway in a macrophage cell line. Regarding treatment, this protein suppressed Toll-like receptor 4 (TLR4) signaling activation triggered by LPS stimulation thus inhibited MAPK/NF-κB signaling (Table 3) (129). Furthermore, Slp from *P. freudenreichii* CIRM-BIA129 revealed anti-inflammatory properties, with SlpB inducing high IL-10 secretion in swine peripheral blood mononuclear cells (PBMC) and mesenteric lymph node immune cells (MLNC) under inflammation (149). Interestingly, pretreatment with SlpA from *L. acidophilus* NCFM in a DSS-induced colitis mouse model reduced inflammatory cytokines, as well as TLR4 and COX2 proteins, in colon tissues, demonstrating protective effects (129).

To conclude, Slp proteins can have anti-inflammatory effects on inflamed IEC, or and proinflammatory effects on immune cells in the absence of inflammatory stimuli (128–130, 149, 150, 175).

Peptidoglycan.

Peptidoglycans (PGN) are major cell wall components in both Gram-positive and Gram-negative bacteria (133). PGN

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Table 3. *Prevention and treatment of colitis or IBD with postbiotics*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
121, 128–132	Slp	IEC or immune cells in vitro +/− inflammation		Improved IEB integrity	Decreased TEER and permeability Restored TJ proteins
				Anti-inflammatory	Decreased proinflammatory cytokines and increased IL-10 via an inhibition of MAPK/NF-κB
				Proinflammatory	Increased proinflammatory mediators via an inhibition of PKC leading to an activation of MAPK/NF-κB pathway
		Induced colitis in mice. Before colitis induction.	No data	Anti-inflammatory	Reduction of inflammatory markers Inhibited the colitis-induced expression of TLR-4, iNOS and COX-2 in colon tissue
133	PGN	Induced colitis in mice. Before colitis induction.	6–7 wo	Protected against colitis, decreased inflammation parameters	Reduced IL-1β, IL-6 and TNF-α levels, reduced colonic gene expression but increased colonic IL-10 protein expression through NOD2 signaling
134–137	LTA	Goblet cells in vitro +/− inflammation		Effect on mucus secretion	Increased MUC-2 expression via TLR-2/NF-κB
				Anti-inflammatory	Decreased proinflammatory cytokines through TLR-2 leading to an inhibition of MAPK/NF-κB pathway
		IEC or immune cells in vitro +/− inflammation		Proinflammatory	Lactobacillus deficient in LTA: decreased proinflammatory cytokines and increased anti-inflammatory cytokines via TLR-2
		Induced colitis in mice. Before colitis induction.	No data	Proinflammatory	Lactobacillus deficient in LTA: reduced colitis score and increased colonic IL-10 level
138–146	SCFA	IEC or immune cells in vitro +/− inflammation		Anti-inflammatory	Decreased proinflammatory expression and increased IL-10 via different pathways: via MCT-1 and NF-κB pathway, by inhibiting HDAC through GPR109A and via ERK 1/2 pathway
		Induced colitis in mice. Before colitis induction.	6–9 wo	Anti-inflammatory	Decreased proinflammatory cytokines via an inhibition of NF-κB pathway Low concentration of acetate acted as a low chemotactic index for neutrophils Butyrate induced colonic IL-18 via GPR109A and regulated Treg and IL-10 producing CD4+ T cell frequency in the colon, thus increasing IL-10 secretion by macrophages Acetate activated NLRP3 inflammasome by binding to GPR43 on colonic epithelial cells lead to a K+ efflux and a hyperpolarization
				Proinflammatory	Increased ROS production and phagocytic activity

Continued

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Table 3.— *Continued*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
		Patients with inactive UC	Adult (>18 yr)	No change in the daily symptoms score and DAI	No change in the CRP, MPO and CAI Increased IL-10/IL-12 ratio
147, 148	MCFA/LCFA	IEC in vitro +/− inflammation		Anti-inflammatory Improved IEB integrity	Inhibited IL-8 secretion Suppressed the increased permeability and the decreased TEER Restored occludin, ZO-1/-2, claudin-1 and -3 expression and MLCK Decreased TNFR2 and increased GPR40
		Postbiotics before colitis induction in mice	6–10 wo	Improved IEB integrity Anti-inflammatory	Suppressed the increased permeability Decreased metabolites derived from $n-6$ PUFA known for their proinflammatory properties Increased PGE2 and 8-HETE
			Treatment		
129, 149–151	Slp	Piglets PMBC and MLNC, RAW 264.7 cells, HT-29 cells, Caco-2 cells, U937 cells		Anti-inflammatory Anti-inflammatory SlpB is involved in adhesion to HT29 cells. Anti-inflammatory properties on Caco-2 cells proinflammatory properties on U935 cells	Induced IL-10 secretion, inhibited TNF-α and IFN-γ release Decreased TNF-α, IFNa, IFNb, IL-10, IL-1β, COX-2 and iNOS levels, suppressed TLR4 signaling, attenuated NLRP3 inflammasome and NOD2 signaling Increased inflammation via TLR2, inhibition of NF-kB/p65 translocation into the nucleus
133, 152–154	PGN	RAW264.7 cells, colonic lamina propria monunuclear cells (LPMC) from colitis-induced mice, murine dendritic cells, Caco-2 cells with over- or underexpression of hPepT1		Anti-inflammatory Anti-inflammatory Anti-inflammatory Proinflammatory	Inhibited NO synthesis, iNOS and COX2 expression, decreased LPS-induced expression of TNF-α and IL-6 Inhibited IL-6 synthesis through inhibition of NF-kB Partial maturation of DC: increased IL-10/IL-12 ratio via NOD2 signaling Increased IL-8 expression through NF-kB pathway, activation of NOD1/2 signaling and increased IL-1β
142, 143, 155–157	SCFA	In vitro: human and mouse PBMC, macrophages, myofibroblast +/− IEC, HT-29, NMC460 cells		Anti-inflammatory properties M2 macrophage polarization and migration Induced mucoprotective prostaglandin profile NLRP3 inflammasome activation	Decreased NO, IL-6, TNF-α, and IL-12 release through GPR43 Decreased NO, IL-6, TNF-α, and IL-12 release due to an inhibition of HDAC Increased STAT-6 phosphorylation and decreased H3K9 deacetylase Increased CCL2 expression Increased PGE1/PGE2, promoted MUC2 expression in co-culture with IEC GPR43 signaling activation
157–160		SCFA after colitis induction in mice	No data	Limited colitis induction	Decreased colonic IL-6, IL-1β, and TNF-α increased colonic expression of Arg1 increased activation of the H3K9/STAT6 signaling pathway

Continued

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Table 3.— *Continued*

Reference	Postbiotic Type	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
					Promoted IL-10 production, activated Th1 cell STAT3 and mTOR
					Critical role for GPR43-mediated recruitment of PMN to contain intestinal bacterial translocation
161–166		Mild activate adult CD	Adult (>18 yr)	No difference	No difference in clinical, histological and endoscopic score
		Active UC		No difference	No difference in the endoscopic appearance of the mucosa
				Tend to improve pathological score	Improved DAI: 33% in the SCFA group and 20% in the placebo group
				Decreased DAI	Anti-inflammatory properties mediated by an inhibition of NF-kB in macrophages, reduced the number of neutrophils in epithelium
167–174	SBA	Rat IEC, Caco-2, and HT-29 cells, differentiated macrophages, Jurkat T cells		DCA: proinflammatory UDCA: no effect	DCA increased IL-8 secretion, 2 mM DCA cytotoxic UDCA: no effect on IL-8 secretion or capacity of enterocytes to limit bacterial translocation
				DCA proinflammatory	DCA increased IL-8 secretion via NF-κB activation
				Anti-inflammatory	Activated NF-κB pathway via TGR5-cAMP signaling and inhibited pro-inflammatory cytokines production
					Inhibited Th1 differentiation, inhibited ERK phosphorylation and decreased Th1 cytokines
		Induced colitis in rats. After colitis induction.	No data	Mitigated colitis severity	
		Induced colitis in mice. After colitis induction.	6–8 wo	Decreased colitis and colonic inflammation	Reduced leukocytes infiltration and promoted TGR5 pathway
			Postweaned mice	DCA exacerbated DSS-colitis	NLRP3 inflammasome activation, increased pro-inflammatory cytokines production by macrophages
					Promoted ileal and colonic inflammation, gut dysbiosis

CAI, clinical activity index; CCL2, chemokine ligand 2; DAI, disease activity index; DCA, deoxycholic acid; DSS, dextran sulfate sodium; HDAC, histone deacetylase; HETE, hydroxyeicosatetraenoic acid; IBD, inflammatory bowel diseases; IEB, intestinal epithelial barrier; IEC, intestinal epithelial cell; iNOS, inducible nitric oxide synthase; GPR, G protein-coupled receptor; LCA, litocholic acid; LTA, litocholic acid; LCFA, long-chain fatty acid; MCFA, medium-chain fatty acids; MCT1, monocarboxylate transporter 1; MLNC, mesenteric lymph node immune cells; mTOR, mammalian target of rapamycin; NLRP3, NOD-like receptor family, pyrin domain containing 3; PBMC, peripheral blood mononuclear cells; PGE2, prostaglandin E2; PGN, proteoglycan; PMN, polymorphonuclear leukocytes; PUFA, polyunsaturated fatty acids; ROS, reactive oxygen species; SBA, secondary bile acid; SCFA, short-chain fatty acid; Slp, surface layer protein; TGR5, Takeda-G protein receptor 5; TEER, electrical transepithelial resistance; TJ, tight junction; TLR, Toll-like receptor; UDCA = ursodeoxycholic acid; wo, weeks old.

have two main receptors, TLR2 and NOD1/2, which are expressed by antigen-presenting cells such as dendritic cells (DC), macrophages, and IEC (176, 177).

PGN from certain *Lactobacillus* strains decreased the expression of LPS-induced TNF and IL-6 through inhibition of the NF-κB signaling pathway in vitro and in colitis model (152, 178). Moreover, PGN from *L. acidophilus* inhibited inducible nitric oxide synthase (iNOS) and COX-2 expression (179, 180). Most of the studies dealing with PGNs nevertheless focused on their effects under physiological conditions to investigate their signaling pathway. Under basal condition, PGN increased the expression of proinflammatory cytokines in IEC and DC (153, 177). These studies suggested proinflammatory effects of PGNs. Nonetheless, murine DC underwent partial maturation when treated with *L. salivarius* 33 (Ls33) PGN, resulting in an increased IL-10/IL-12 ratio (133).

In vivo, PGN from *L. salivarius* Ls33 protected against 2,4,6-trinitrobenzenesulfonic acid (TNBS)-induced colitis induction by decreasing inflammatory parameters, but this protection was absent in IL-10-deficient mice or NOD2-deficient mice (Table 3) (133). No clinical data was found on Slp administration.

To conclude, in vitro studies indicated anti-inflammatory properties of PGN when cells were stimulated by an inflammatory stimulus, whereas PGN induced in basal condition a proinflammatory response.

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Lipoteichoic and teichoic acids.

Lipoteichoic acids (LTA) and teichoic acids (TA) are molecules anchored in the cell wall of Gram-positive bacteria. LTA belong to microbe-associated molecular patterns, which are recognized by pattern recognition receptors. One in vitro study used human monocytic THP1 cells stimulated with PGN from *Shigella flexniri* as an IBD model (Table 3) (181). Pretreatment with LTA from *L. plantarum* reduced proinflammatory cytokines in these inflamed cells (181). On the other hand, LTA from *L. acidophilus* NCFM decreased the IL-10/IL-12 ratio in cultured dendritic cells (134). In IEC, the immunomodulatory effects were also controversial. LTA from *L. paracasei* D3-5 decreased proinflammatory cytokines in murine intestinal goblet cells and increased MUC2 protein level expression (135). However, another study showed that LTA purified from *L. rhamnosus* GG increased *IL-8* mRNA expression in Caco-2 cells (136). Two studies demonstrated in a murine model of colitis that LTA-deficient *Lactobacillus* mutants were protective, with a rise of colonic IL-10 level and a reduced colitis score (Table 3) (134, 137).

The effects of LTA may differ within the same bacterial species. Therefore, screening for immunomodulatory properties in specific bacterial strains is essential. Preclinical studies suggested that LTA have proinflammatory properties on murine colitis models (134, 137).

Gut Microbial Metabolites

SCFAs.

In humans, SCFAs are found in different tissues but mostly within the colon lumen. They include acetate, propionate, butyrate, and valerate and are produced by anaerobic bacteria through the fermentation of dietary fibers. Butyrate is mainly produced by gut bacteria that belong to the phylum *Firmicutes*, such as *F. prautsnitzii,* whereas propionate and acetate production are mainly produced by *Bifidobacterium* bacterial species (182). SCFAs, the main energy source for colonocytes, participate in diverse intestinal functions, such as digestive motility, immunomodulation, and modification of gene transcription (35, 39, 183). SCFAs improve the gut barrier function and impact the intestinal microbiota (155, 184). Patients with IBD have reduced levels of SCFAs in the mucosa and feces (185). Most studies support anti-inflammatory benefits of SCFAs (63). All these data suggest an involvement of SCFAs in IBD pathogenesis.

Indeed, pretreatment with SCFAs reduced the inflammatory response on both IEC and immune cells (138–140). SCFAs inhibited IL-8 secretion induced by inflammatory stimulus in human fetal cell line, fetal intestinal organoids, and fetal mouse intestine (141). Regarding therapeutic effects, treatment of challenged-immune cells with butyrate or acetate reduced proinflammatory mediators release by interacting with the GPR43 receptor (Table 3) (142, 156). Butyrate facilitated M2 macrophage polarization after stimulation with both butyrate and IL-4, a Th2 cytokine (157). Besides, butyrate promoted migration of macrophages by increasing chemokine ligand 2 (CCL2) expression. Furthermore, treatment with SCFAs on cocultures of IEC and myofibroblasts induced a mucoprotective prostaglandin profile, reflected by an increased PGE1/PGE2 ratio in myofibroblast supernatants (155). Finally, acetate induced a NLRP3 inflammasome activation in colonic epithelial cells through GPR43 and Ca^{2+} signaling (143).

Acetate protected in vivo against colitis, improved IL-10 production, and reduced proinflammatory cytokines (Table 3) (142–144). Regarding treatment, SCFAs attenuated gut inflammation in DSS-treated mice (Table 3) (157, 158). Indeed, SCFAs stimulated colonic IL-10 secretion in mice with colitis (158). Butyrate decreased the histological score in DSS-treated mice by inducing M2 macrophage (158).

Only few studies have examined the therapeutic effect of SCFAs in active Crohn's disease and they are not conclusive about the efficiency of SCFAs to treat CD (Table 3). More literature exists on the preventive and therapeutic effects of SCFAs in UC. No differences in improvement of clinical, histological, and endoscopic scores were shown between butyrate and 5-aminosalicylate (5-ASA) supplementation (161). Butyrate combined with current treatments induced an increase of the IL-10/IL-12 ratio but did not change C-reactive protein, myeloperoxidase, or clinical activity index (186). Regarding curative effects of SCFAs on active UC, most studies failed to show a difference between SCFAs and current treatments (162–164). A study showed that butyrate enema improved disease activity index (DAI) in patients with UC, reduced both the number of neutrophils in crypt and surface epithelia (165).

To conclude, in vitro studies suggested an anti-inflammatory role of SCFAs on IEB via NF-κB pathway and the GPR43 receptor. Furthermore, in vivo studies suggested that SCFAs mitigated intestinal inflammation in induced-colitis model. Clinical studies are however not successful in terms of SCFA efficiency.

Medium-chain fatty acid/long-chain fatty acid.

Medium-chain fatty acids (MCFAs) and long-chain fatty acids (LCFAs) mostly derive from diet, but bacteria can also generate these lipids via the biohydrogenation pathway (187, 188). Recent evidence for their relevance in IBD is emerging with a recent study highlighting the possible use of bacteria-derived long-chain fatty acid that exhibited anti-inflammatory properties in colitis. Indeed, *E. coli* EcN1917 produced a high level of 3-hydroxyoctadecaenoic acid (C18-3OH) compared with other strains. Administration of C18-3OH in a mice model of colitis improved colitis and restored gut dysbiosis (147). Besides, 10-hydroxy-*cis*-12-octadecenoic acid (HYA), a derivate of linoleic acid ($n-6$), protected against inflammation by restoring tight junction proteins expression and modulating the expression of the TNF receptor TNFR2 in cultured IEC (148).

Secondary bile acids.

Bile acids (BAs) are produced in the liver from the cholesterol metabolism and are further metabolized by gut bacteria. Cholesterol is converted to primary BAs, such as chenodeoxycholic acid (CDCA) and cholic acid (CA) that are released after a meal in the intestine, where they are metabolized by gut bacteria. Gut anaerobic bacteria deconjugate the liver-derived BAs to their respective free BAs and then convert primary BAs into secondary BAs (SBAs) in the colon. CA is transformed into deoxycholic acid (DCA), and CDCA is

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transformed into litocholic acid (LCA) and ursodeoxycholic acid (UDCA). SBAs have different functions, including regulation of energy homeostasis, anti-inflammatory effects, and antimicrobial functions (189). Patients with IBD have reduced level of SBA in stools but not of total fecal BA concentrations, suggesting that this decrease is due to an impaired gut microbiota BA metabolism (190).

DCA increased in vitro IL-8 secretion by IEC, but high concentrations of DCA were toxic on Caco-2 cells (Table 3) (167–169). Furthermore, DCA and LCA inhibited TNF production in differentiated macrophages stimulated by commensal bacterial antigen or LPS. Pretreatment of $CD4^+$ Th cells with LCA inhibited Th1 differentiation (170).

Mice with DSS-induced colitis pretreated with LCA or UDCA displayed an improvement in the severity of colitis (147, 148). Colonic alkaline phosphatase (AP) activity, a marker of leukocyte infiltration, was significantly reduced by UDCA in rats with colitis. DCA exacerbated DSS-colitis and triggered NLRP3 inflammasome, therefore, increased proinflammatory cytokines production of macrophages (171). Regarding the curative mode, DCA and LCA improved colitis by decreasing colonic inflammation and disease parameters (Table 3) (191). UDCA also had beneficial effects on acute and chronic colitis induced by 2,4,6-trinitrobenzenesulfonic acid (TNBS) (172). SBAs reduced leukocytes infiltration and exerted an anti-inflammatory effect, in part dependent on the TGR5 bile acid receptor, in three murine colitis models (191). However, other studies did not show beneficial effects of SBAs.

To conclude, SBAs appeared to have beneficial effects in an inflammatory context. However, caution should be taken in the use of SBAs as DCA was toxic in some studies (167).

Key Ideas: Gut Microbial Components

Most of gut microbial components reduce inflammation. Limits: lack of in vivo studies and absence of clinical trials to conclude on their value in the prevention/treatment of IBD.

Key Ideas: Gut Microbial Metabolites

SCFAs are the most studied postbiotics in IBD; however, clinical studies are insufficient. The cited metabolites apart from SCFAs also showed promising results.

SYNBIOTICS

Definition

Synbiotics are products combining prebiotics and probiotics (192). Their benefit for the host relies on the synergic or additive action of both components to ensure an effective implementation of an improved microbiota by enhancing the survival of specific bacterial strains and/or their metabolism. Such strategy may help to preserve the intestinal functions and prevent diarrhea or constipation for the individual (193). Strengthening of the immune system and of the intestinal barrier is also investigated together with inhibition of pathogens (192). So synbiotics reportedly have a greater efficacy than pro-/prebiotics alone (193). Synbiotic administration may reduce cost and treatment duration, thus enhancing compliance (194). For all those reasons, synbiotics represent an attractive field of study for IBD care.

In Vitro Studies

Synbiotic supplementation was used only as treatment (Table 4). Altogether, in vitro studies underlined a positive effect of synbiotics via different mechanisms. An increased diversity of the microbiota and production of SCFA were observed after incubation of a synbiotic composed of *Bacillus* strains and a mix of FOS, xilooligosaccharides (XOS), and GOS in a synthetic human GI tract called M-SHIME (196). Human immune cells like PBMC were also impacted by the synbiotics, through the influence of the prebiotics part of synbiotic, for instance short-chain GOS and long-chain FOS (scGOS/lcFOS), which induce the production of IL-10 by dendritic cells (48). Metabolites derived from synbiotics like SCFAs also play a role, as seen with the SCFAs derived from the synbiotic inulin + *Lactobacillus rhamnosus* GG ATCC 53013 that reduced the production of inflammatory cytokines by LPS-stimulated human PBMCs (216).

Preclinical Studies

In general, the literature on synbiotics at preclinical level is scarce and seems to focus on the preventive aspect of synbiotics (Table 4). Promising results were achieved in the described preventive studies, with a reduction of the disease severity and colonic damages. The mechanisms found were the same as in in vitro studies: increased microbiota diversity, production of SCFAs, and secretion of IL-10 (199). Interestingly, a restoration of the gut barrier was seen after a supplementation by *Bifidobacterium infantis* + XOS in male C57BL/6 mice under acute DSS-induced colitis via the increase of tight junction proteins ZO-1 and claudin-1 expression (202). It appears that a supplementation of synbiotics mitigates the development of colitis in murine models.

Two other preclinical studies were found on the treatment of colitis with synbiotics. A synbiotic constituted of *L. paracasei* B21060 + FOS + arabinogalactan was given after DSS induction for 1 wk in male BALB/c AnNHsd mice. Another study used an acute DSS induction on C57BL/6 mice with a synbiotic composed of *Lactobacillus gasseri* 505 + *Cudrania tricuspidata* extract. Both studies showed anti-inflammatory effects, with a decrease of colonic damages and TNF production and a restoration of the gut barrier.

Clinical Studies

Surprisingly, more data were available on clinical trials but only for treatment with synbiotics. Indeed, no study was found with a use of synbiotics as preventive mean for IBD (Table 4). The heterogeneity of the studies is striking. Different types of synbiotics were used such as "Synbiotic 2000," which included inulin, β-glucans, resistant starch, and pectin. The recruited patients with IBD were mostly patients with UC (only 2 studies with patients with CD) with a broad range of disease severity, from remission to severe disease activity. The number of tested individuals is small (<50/condition) and underlines a need for clinical trials with a more consequent number of participants to ensure a relevant analysis of the effects of synbiotics.

One study focused on children with UC of ~12 yr old in remission for whom a synbiotic composed of *B. longum* R0175 + inulin was given for 10 mo (203). The result of this

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Table 4. *Studies of synbiotic uses as prevention and/or treatment for colitis or IBD*

Reference	Synbiotic	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
195	Oligoalternan + *B. breve* R0070 + *L. lactis* R1058	HT-29 cell line + LPS/IFN-γ		Improved IEB integrity	Inhibited cell proliferation
48	scGOS/lcFOS + *L. rhamnosus* or *B. breve*	Immature primary human immune cells + PMA/ionomycin		Anti-inflammatory	Induced IL-10 secretion
196	MegaSporebiotic + MegaPrebiotic	In vitro human gastrointestinal tract M-SHIME, each with fecal inoculum of a different human adult		Improved gut microbiota	Increased microbiota diversity and SCFA production
197	Synbiotic Multilac Baby	Pathogens culture: either *E. coli* EPEC, *Sh. sonnei*, *S. typhimurium*, *K. pneumonia*, and *C. difficile*			Higher growth inhibition of all pathogens with the synbiotic compared with probiotics alone
198	Synbiotic Instant Mixture = *Lactobacilli* + *Bifidobacteria* + inulin	HLA-B27–β2-microglobulin rats + spontaneous colitis. Synbiotic before colitis induction	2 mo old	Improved gut microbiota	Reduced histological score, increased microbiota diversity
199	*L. paracasei B21060* + FOS + arabinogalactan	BALB/c AnNHsd mice + acute DSS colitis. Synbiotic before colitis induction	10 wo	Improved IEB integrity	Reduced colonic damages. Restoration of gut barrier, increased IL-10
200	*L. rhamnosus GG* + tagatose	BALB/c mice + acute DSS colitis. Synbiotic before colitis induction	6 wo	Improved gut microbiota	Reduced clinical symptoms, recovery of gut microbiota dysbiosis
201	Green banana resistant starch + *Bacillus coagulans MTCC5856*, whole plant sugar cane fiber Kfibre + *Bacillus coagulans MTCC5856*	C57BL/6 mice + acute DSS colitis. Synbiotic before colitis induction	7 wo		Reduced disease and histological scores, increased SCFA production
202	*Bifidobacterium infantis* + xylooligosaccharide	C57BL/6 mice + acute DSS colitis. Synbiotic before colitis induction	6–7 wo	Anti-inflammatory and improved IEB integrity	Reduced DAI, inflammatory cytokines. Strengthened gut barrier
203	*B. longum R0175* + inulin	Single-blind RPCT: UC patients in remission	Mean age: 12.6 yr old.	Improved quality of life	Improved quality-of-life score
204	*B. longum* + psyllium	RCT: mild/in remission UC patients	Mean age (synbiotic, prebiotic, probiotic): 35, 37 and 36 yr old.		Improvement of IBDQ
205	Synbiotic 2000	DB RPCT: CD patients undergoing resection	Mean age at surgery (synbiotic, placebo): 36.1 and 34.7 yr old.	No effect	No effect on postoperative recurrence of CD
206	*B. breve Yakult* + GOS	Open-label RCT: patients with active/in remission UC	Mean age (synbiotic, control): 43.6 and 47.4 yr old.	Improved gut microbiota	Reduced endoscopic score, change of gut microbiota
			Treatment		
199	*L. paracasei B21060* + FOS + arabinogalactan	Male BALB/c AnNHsd mice + acute DSS colitis. Synbiotic after colitis induction	10 wo	Anti-inflammatory and improved IEB integrity	Reduced colonic damages. Restoration of gut barrier, increase of IL-10
207	*L. gasseri 505* + Cudrania tricuspidata extract	C57BL/6 mice + acute DSS colitis. Synbiotic after colitis induction	5 wo	Anti-inflammatory	Reduced serum TNF-α, nitric oxide
208, 209	*B. longum* + Synergy 1	DB RPCT: patients with active UC and CD.	Mean age (synbiotic, placebo): 45–46.3 and 38–49 yr old.	Anti-inflammatory and improved gut microbiota	Reduced disease activity, inflammatory cytokines. Increased regeneration of tissue and change of gut microbiota

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Table 4.— *Continued*

Reference	Synbiotic	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
210	*L. paracasei B20160* + arabinogalactan + XOS	RPCT: patients with mild/moderate UC UBT.	Mean age (synbiotic, placebo): 46 and 48 yr old.	Anti-inflammatory	Decreased serum IL-6, IL-8
211	Inulin + *L. plantarum, L. gasseri, L. casei, B. infantis, L. salivarius, L. acidophilus, S. thermophilus, L. sporogenes*	Randomized open-label trial: patients with mild/moderately active UC UBT		Increased remission.	
212	*Enterococcus faecium, L. plantarum, S. thermophilus, B. lactis, Lactobacillus acidophilus, B. longum* + FOS	RPCT: patients with mild/moderately active UC.	Mean age (synbiotic, placebo): 44.94 and 40 yr old.	Reduced DAI	
213	*S. faecalis T-110 JPC, C. butyricum TO-A, B. mesentricus TO-A JPC, L. sporogenes* + prebiotic	Open-label RCT: patients with moderately/severe active UC UBT.	Adult patients (>18 yr)	Increased remission.	Reduced relapse and disease severity. Increased remission duration, reduction of steroid dosage
214	Depending on parameter, 4–5 studies included	Meta-analysis of several diseases including IBD.	Depends on study	Anti-inflammatory	Reduced CRP and TNF-α
215	Lactocare	DB RPCT: patients with mild/moderately active UC UBT.	Adult patients (>18 yr)	Reduced SCCAI.	

CD, Crohn's disease; DAI, disease activity index; DB, double-blind; FOS, fructo-oligosaccharides; GOS, galacto-oligosaccharides; IBD, inflammatory bowel diseases; IBDQ, inflammatory bowel disease questionnaire; IEB, intestinal epithelial barrier; LAB, lactic acid bacteria; LPS, lipopolysaccharides; PMA, phorbol 12-myristate 13- acetate; RCT, randomized controlled trial; RPCT, randomized placebo controlled trial; SCCAI, simple clinical colitis activity index; SCFA, short-chain fatty acids; UBT, under baseline treatment; UC, ulcerative colitis; XOS, xilooligosaccharides; wo, weeks old.

study is encouraging as no severe symptoms were observed and an improvement of the quality of life was assessed.

Treated patients were aged of 18–60 yr old, and treatment time ranged from 4 wk to 1 yr. Apart from two studies where no effect of synbiotics were seen on CD recurrence or microbiota, and despite the heterogeneity of disease severity and disease type, the majority of the clinical trials presented a beneficial effect of synbiotic through a clinical improvement (205, 217). The tested synbiotics appeared also effective to reduce the production of inflammatory cytokines like IL-6 or IL-8 (210). For instance, two studies used *B. longum* and "Synergy 1," a preferential inulin/oligofructose growth substrate for this strain, on patients with either active CD or UC for 1 to 6 mo (208, 209). Both trials showed a reduction of disease severity after supplementation. This can be linked to a modulation of the microbiota and an enhancement of the tissue regeneration. Moreover, synbiotics contributed also to maintain remission and to reduce treatment dosage, as seen in a clinical trial with patients with active UC supplemented with a synbiotic containing patented *Streptococcus faecalis* T-110 JPC, *Clostridium butyricum* TO-A, *Bacillus mesentricus* TO-A JPC, *Lactobacillus sporogenes*, and a prebiotic (213).

Conclusions on Synbiotics

Few studies are available at in vitro and preclinical levels but all of them pointed out the beneficial effects of synbiotics on inflammation: reduction of colonic damages and inflammatory cytokines production, restoration of the microbiota diversity, and strengthening of the gut barrier. Synbiotics appeared to be more effective as pre- or probiotics alone. These observations were also seen at clinical level, with a reduction of disease activity and an extension of remission. However, robust homogenized clinical trials are lacking to fully characterize the effects of synbiotics and their design should be supported by preliminary data generated from preclinical studies. The distinctions of disease type and disease severity are also an important factor.

Key Ideas: Synbiotics

Beneficial effects observed at all levels for synbiotics: *1*) restored diversity of the microbiota; *2*) decreased anti-inflammatory cytokines production; *3*) strengthened the gut barrier; and *4*) improved disease severity, which led to an extended remission for patients with UC. Limitations: lack of robust in vitro/preclinical and clinical studies, especially for prevention; more data should be collected to describe precisely the effects of synbiotics for UC and CD, at different disease stages and different age of the individual.

FECAL MICROBIOTA TRANSPLANTATION

Definition

Because IBD is associated with alteration in the gut microbiota (reduced diversity, increased pathogens, and low commensals), fecal microbiota transplantation (FMT) is increasingly considered for the therapeutic treatment of IBD. FMT consists of the transfer of fecal material from a healthy donor to a recipient patient to restore the pathology-induced alterations of the intestinal microbiota. FMT can be administered through the lower gastrointestinal tract (enema, colonoscopy, and sigmoidoscopy) or upper gastrointestinal tract (endoscopy, nasoduodenal tube, and capsule ingestion). Although this method has been proven to be effective in cases

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of recurrence of *Clostridium difficile* infection (218), it is still under study for IBD.

Preclinical Studies

Few preclinical studies have investigated the role of FMT in the treatment of colitis (219–222). In a DSS-induced murine model of colitis, FMT of untreated mouse microbiota decreased weight loss and reduced colonic inflammation as measured by increased colonic length and fewer histological alterations (220–222). FMT also improved homeostasis of the gut microbiota with an increase in *Lactobacillus* and *Bifidobacterium* bacteria and restoration of tryptophan and SCFA levels similar to that of untreated mice (221, 222). Mechanisms by which FMT promotes the recovery of DSS-induced colitis may be mediated by the regulation of the immune system with higher IL-10 production as well as aryl hydrocarbon receptor (Ahr) activation (220). In another study, colonization of gnotobiotic mice with IBD donor-derived microbiotas induces an IBD-like phenotype characterized by abnormal immune cell profile (abundant Th17 cells and lower tolerogenic RORgt+ Treg cell) and higher susceptibility to colitis (219). Transplantation of healthy human donor microbiota in IBD mice favored a tolerogenic immune response with increased proportion of RORgt+ Treg cells that may protect from colitis. Thus, therapeutic effects of the FMT on IBD likely involve the remodeling of the gut microbiota and regulation of intestinal immunity.

Clinical Studies

Four studies have now been published on the treatment of IBD using FMT (223–226). They concern patients with UC in the active phase of the disease were intended to induce remission. Overall, 277 patients with UC receiving FMT (n = 140) or placebo treatment (n = 137) were followed over 8 to 12 wk posttreatment. Clinical remission was achieved in 28% of patients who received FMT compared with 9% in the placebo group. However, one of the randomized controlled trial (RCT) studies did not find any significant difference between FMT and placebo groups in improving remission (223). These discrepancies may rely on FMT frequency and mode of administration as well as donor microbiota. Microbial analysis of patients who achieved remission shows higher microbial diversity following FMT compared with those who did not and compared with placebo. Specific bacterial family (*Clostridium* clusters IV and XIVa or *Roseburia* species) were correlated with disease improvement while others (*Fusobacterium* or *Escherichia* species) were associated with the lack of remission. Specifically, better outcomes were observed for patients with UC who had a shift in microbiota composition toward the donor composition (223, 227). Microbial functional changes were also observed in patients who achieved remission following FMT with an increase in SCFA and secondary bile acid levels (227). One pilot RCT on pediatric UC population also suggests that FMT improves symptoms and inflammatory indexes through microbial changes and the regulation of mucosal inflammation (228).

In CD, fewer studies have been conducted and the results are scarce. One reason could be the heterogeneous nature of CD for which FMT advantage may not be observed in all phenotype. Only one randomized controlled study showed that the incidence of flare was lower following FMT compared with the placebo group despite no significant differences in clinical remission rate at 10- and 24-wk posttransplantation. However, patients who received FMT had a decrease in Crohn's disease endoscopic index of severity and, contrary to sham group, had no increase of C-reactive protein level after 6 wk (229). Similar to UC studies, maintenance of remission was associated with a greater colonization of the donor microbiota in patients.

Conclusions on FMT

To conclude, despite a small number of enrolled patients and short-term evaluation of clinical remission, the efficacy of FMT in improving clinical response and in the induction of remission in patients with UC are promising but larger studies are needed in patients with CD. Also, the few studies are encouraging regarding the safety of FMT treatment since the patients who had received FMT only had rare adverse events with mostly mild transient gastrointestinal symptoms (diarrhea, gas, or bloating). Overall, this suggests that FMT could be an effective therapeutic approach in IBD. However, several questions remain to be addressed. One is the definition of the material to be transplanted: how can we define a healthy microbiota? Should we prefer one donor or several? Is there a "super-donor"? Is there any donor-recipient matching required to improve FMT effects? Another question is about the FMT procedure: what is the best mode of delivery? Which frequency is needed? As Moayyedi et al. (224) observed that early diagnosed (<1 yr) patients with UC had a better FMT outcomes, should we determine any specific window of action during IBD course to favor FMT efficacy? Also, the question of the microbiota resilience arises: will the transplanted bacteria become sustainably established in the host? Is there a need for repeated FMT? The durability of therapeutic effects of FMT is still unclear but recent studies reported mid-term outcomes in patients with UC with remission greater than 6 mo up to over 1 yr when associated with a maintenance of FMT or dietary modification (228, 230). Finally, the main question concerns the active compounds of the FMT: what are the mediators (bacterial products, metabolites, bacteria) of the beneficial effects of FMT and mechanisms? These questions will need to be addressed in large clinical studies for patients with both UC and CD to demonstrate that FMT could be an effective (personalized) treatment for IBD.

Key Ideas: Fecal Microbiota Transplantation

Beneficial effects observed in preclinical and clinical studies: *1*) restored the diversity of the microbiota; *2*) restored an anti-inflammatory and tolerogenic immune profile; *3*) promoted clinical remission; and *4*) improved disease severity that led to an extended remission for patients with UC. Limitations: lack of randomized clinical studies, especially for CD; lack of reproducibility among studies (FMT procedure, donor type, etc.); more data should be collected to describe precisely the effects of FMT in UC and CD, at different disease stages and different patient phenotypes.

DIET

Several studies underline the protective effect of a healthy diet as well as the high consumption of fruits and vegetables

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against the risk of CD development (231, 232). On the contrary, diets enriched in fat and/or sugars constitute risk factors for IBD development (232, 233). The composition of the diet may influence several biological systems: the immune system, the microbiota, and the host response. Epigenetic effects can be induced by diet, as seen in an in vivo study where a methyl-donor maternal diet increases colitis susceptibility in offspring (234). Diet represents an interesting research field for IBD care, especially due to its ease of implementation. The impact of numerous types of diet or diet components have been tested on IBD or colitis model, from high salt to dietary fiber, high-fat, or spicy food, and we cannot be exhaustive in this review to summarize them. Nevertheless, we wanted to mention two particular supplemented diet: vitamin D and $n-3$ or $n-6$ polyunsaturated fatty acids (PUFA) enriched diet, because they represent diets tested long time ago and are among the most investigated nutrients with a potential association to IBD. In addition, they have a renewed interest especially because they regulate and/or are regulated by key elements of digestive homeostasis: lipids and microbiota (147, 235, 236).

Vitamin D

Vitamin D is a lipophilic compound that induces calcium absorption from the gut after binding to the vitamin D receptor (VDR). Deficiency in vitamin D is associated with increased IBD disease activity and clinical relapse (237).

Two in vitro studies on intestinal epithelial and immune cells studied the protective effects of vitamin D, while two others examined therapeutic effects. According to a study on Caco-2 cells challenged with adherent-invasive *E. coli* (AIEC) strain LF82, Vitamin D pretreatment protected against AIEC-induced IEB disruption by maintenance of the tight-junction distribution (Table 5) (273). In addition, pretreatment of immune and intestinal epithelial cells with vitamin D stimulated NOD2 expression, HBD2, and antimicrobial cathelicidin expression (274). In regard to treatment, Vitamin D3 downregulated claudin-1 and -2 and upregulated claudin-4 and -7 in colonic biopsies from patients with UC (Table 5). Besides, vitamin D3 inhibited IL-13 and IL-6 expression (267). Finally, another study found that vitamin D reduced permeability and increased TEER of disrupted IEB (268).

One in vivo study evidenced the protective effect of vitamin D toward colitis in early life. Vitamin D prevented the increase of intestinal permeability in DSS-treated mice as well as the disruption of IEB by AIEC *E. coli* (Table 5) (273). High dose of vitamin D was however deleterious, inducing a more severe colitis and an increase of proinflammatory cytokines expression. Furthermore, microbial composition of mice fed with high dose of vitamin D was similar to that of DSS-treated mice, indicating a negative impact of strong doses of vitamin D on the gut microbiota (275).

All clinical studies were performed in adults, and very few studies investigated the ability of vitamin D to maintain remission in patients with UC (Table 5). Vitamin D maintained gut permeability of patients with CD in remission, decreased C-reactive protein level, but did not change the CDAI score (276). Interestingly, a high dose induced a better rate of relapse than a low dose. Furthermore, vitamin D3 improved anxiety and depression scores (277). A pilot study exhibited the beneficial effects of vitamin D3 supplementation on patients with active CD with improved CDAI and quality-of-life scores (269).

Patients with UC in remission with low serum level of vitamin D (<35 ng/mL) have higher risk of clinical relapse (278). However, there is a lack of studies investigating the effects of vitamin D supplementation to sustain patients with UC in remission. Vitamin D supplementation reduced intestinal inflammation in patients with active UC (270). Besides, patients with active UC presented an increase of *Enterobacteriaceae* but no change in gut microbiota diversity (270). A decrease in UCDAI was observed correlated with an increase in serum vitamin D, a reduction in C-reactive protein, and calprotectin. Patients with active UC who received vitamin D presented decreased DAI, serum C-reactive protein, and TNF level (271). However, another study demonstrated no difference of DAI or inflammatory markers on patients with UC supplemented with vitamin D (272).

$n-3$ or $n-6$ PUFA Supplementation

Because of their attractive anti-inflammatory effects, diets enriched in $n-3$ PUFA and/or diet with an increased $n-3$-to-$n-6$ ($n-3/n-6$) ratio have been tested in different inflammatory digestive pathologies including IBD. In addition, association studies correlated high $n-3$ PUFA concentrations with a reduction of CD and protection from UC (279–281). $n-3$ PUFA modulate the microbiota, by increasing butyrate-producing bacterial genera but also by decreasing *Faecalibacterium*, for instance (282). $n-3$ PUFA are considered anti-inflammatory fatty acids and they may, for example, counter $n-6$ PUFA inflammatory effects by competition (283). Resolvins, protectins, and other proresolving molecules derived from $n-3$ PUFA modulate the immune response toward a resolution of inflammation, and strengthen the barrier by increasing epithelial proliferation (284, 285). Nevertheless, studies showing the protective effects of $n-6$ (12, 13, 286) or those highlighting defects in the metabolites of $n-6$ in patients with IBD (7), reshuffle the cards.

In Vitro Studies

Preincubating cells with $n-3$ PUFA resulted in anti-inflammatory effects, with a decrease of IL-17RA, IL-12B expression in monocytes, and an induction of tolerance by an increase of IL-10 production by dendritic cells (Table 5) (238, 241). A reinforcement of the gut barrier was achieved by increasing the transepithelial resistance, reducing the increase of permeability induced by inflammation, and by preventing barrier disruption (243). The duration of exposure to $n-3$ PUFA is heterogeneous, as well as the mean of inflammation. 15-Hydroxyeicosatetraenoic acid (15-HETE) or 11βPGF2α have $n-6$ PUFA metabolites presented also IEB strengthening properties as they decrease IEB permeability and increase IEB healing (12, 13). Thus, promising results were achieved in vitro for prevention.

Effects are more mitigated for in vitro of $n-3$ PUFA as a treatment (Table 5). Fish oil decreased the production of proinflammatory mediators like PGE_2 and the expression of COX_2, but induced at the same time apoptosis (261, 263). Interestingly, fish oil modified the composition of peripheral blood mononuclear cells and plasma phosphatidylcholine.

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Table 5. *Prevention and treatments studies with diet in IBD*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
			Prevention		
238	Krill oil (EPA + DHA)	THP1 cells + LPS, Citrobacter *rodentium*, PMA.	Before inflammation	Anti-inflammatory	Decreased inflammatory cytokines production, induced macrophages M2 differentiation and enhanced bacterial killing.
		White Yorkshire x Landrace pigs, C3H/HeNCr mice + *Trichuris suis* or *C. rodentium* infection	9–10 wo pigs5 wo mice	Anti-inflammatory and improved gut microbiota	Reduced the increase of crypts length, body weight loss, inflammatory cytokines expression. Improved spleen index, changed gut microbiota composition.
239, 240	EPA + DHA	DB RPCT: patients with CD in remission with 5-ASA	Mean age = 10.13 yr old	Reduced relapse.	
		DB RPCT: EPIC-1 (patients with CD in remission), EPIC-2 (patients with active CD UBT)	EPIC-1 mean age (placebo, $n - 3$): 38.2 and 40. 5 yr old. EPIC-2 mean age (placebo, $n - 3$): 40 and 38.5 yr old.	Failed to prevent relapse	No difference in CDAI or SF-36 scores
241, 242	EPA, PA or DHA	BALB/c mice bone marrow-derived DCs, primary HIMEC cells + LPS, IL-1β	Before inflammation	Anti-inflammatory	Increased IL-10 production, reduced VCAM-1 and VEGFR2 expression.
243–246	ALA, EPA, DHA, LA, GLA, AA, fat blend	RAW 264.7, 293 T, T84 cells lines + LPS, IFN-γ/TNF-α, IL4, heat stress		Improved IEB integrity	Reduced NF-κB activation, COX-2 expression. Reinforced the barrier by changing tight junction proteins distribution and morphology.
247–249	LA:ALA, LA:LC $n - 3$ PUFA, $n - 3/n - 6/n - 9$ diets at different ratios	Sprague-Dawley rats + acute DSS or TNBS colitis. Before colitis induction	Postweaning	Anti-inflammatory	Reduced DAI, colon histological score, pro-inflammatory cytokines expression, anemia and inflammatory cytokines. Changed colon phospholipid fatty acids profile.
242, 250, 251	ALA-rich oil, fish oil	Sprague-Dawley rats + acute TNBS colitis. Before colitis induction	7–8 wk inferred	Anti-inflammatory and improved IEB integrity	Decreased adhesion molecules, inflammatory cytokines expression. Anti-angiogenic effect.
252, 253	Extra virgin olive oil (EVOO), polyphenol extract (PE), EVOO + PE, fish oil	Wild-type or Rag2−/− C57BL/6 mice Acute T transfer or DSS colitis (induction + rest). Before colitis induction.	6–12 wo		Reduced DAI, colon histological score, inflammatory cytokines expression and cell proliferation. Fish oil: no effect on IBD score, modified lipid concentrations.
254	Fish oil (n-3 PUFA) + corn oil (n-6 PUFA)	C57BL/6 mice + acute *C. rodentium* colitis. Before infection	4 wo	Improved gut microbiota.	Protected against colitis but increased mortality with impairment of infection-induced responses. Increased Lactobacillus and Bifidobacteria abundances.
255	Fish oil or n-3 PUFA	Meta-analysis: CD and UC patients in remission	Depends on study	No effect	No benefit for UC. N-3 PUFA reduced risk of relapse for CD patients but heterogeneity. Risk of upper GI tract symptoms.

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Table 5.— *Continued*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
256	Atlantic salmon	Pilot study: UC patients UBT	Mean age = 50 yr old		Reduced SCCAI and increased AIFAI in plasma and rectal biopsies.
257–259	EPA-FFA	Controlled study: patients with CD and UC in remission UBT Pilot study, RCT: patients with UC in remission UBT.	Mean age-controlled study (CD, UC, healthy) = 39, 34, 28 yr old Mean age pilot study (control, EPA-FFA) = 22–48, 45 yr old Mean age RCT (placebo, EPA-FFA) = 42.7, 47.1 yr old	Anti-inflammatory and improved gut microbiota	Improved histological inflammation, maintained clinical remission, changed gut microbiota composition.
260	Grounded flaxseed (GF), flaxseed oil (FO)	Open-labeled RCT: patients with UC UBT	Mean age (control, GF, FO) = 32.52, 29.92, 32.30 yr old	Anti-inflammatory	Reduced inflammatory cytokines, Mayo score. Increased IBDQ-9 score.
			Treatment		
261, 262	Fish oil (EPA + DHA), extra virgin olive oil, OA-BSA, LA-BSA, AA, EPA	Caco-2, HT-29, NIH 3T3, RAW 264.7 cells + PMA		Improved IEB integrity	Induced apoptosis, cell differentiation. Decreased cell proliferation.
263, 264	Fish oil + vitamins A, C, E/selenium or enteral elemental diet EO28	CD patients PBMC, plasma phosphatidylcholine, Colonic biopsies of active UC and CD patients + LPS, ConA		Anti-inflammatory	Modified PBMC and plasma phosphatidylcholine compositions. Decreased cytokines and increased IL-1ra production.
265	Extra virgin olive oil	Chronic DSS colitis	6 wk old Sprague-Dawley rats		Decreased DAI and inflammatory cytokines expression, improved histological score.
266	Seal oil (EPA, DPA, DHA)	Pilot study: patients with CD and UC RCT: patients with IBD.	Pilot study age range (CD, UC, control): 27–42, 41–57, 50–67 yr old. RCT age range (CD, UC): 21–44 and 16–55 yr old.		Reduced of SF-36 assessed bodily pain.
267–272	Vitamin D	Inflamed or not biopsies of colon from active UC patients, Caco-2 cells	Adult (>18 yr)	Anti-inflammatory and improved IEB integrity	Anti-inflammatory, improved IEB (Downregulated claudin-1 and -2, upregulated claudin-4 and -7, inhibited IL-13 and IL-6 expression)
		Mild to moderate active CD			Improved IEB (reduced permeability and increased TEER restored expression and localization of ZO-1, claudin 1 and occludin 1)
		Active adult patients with CD		Improved DAI	Improved CDAI (improved of circulating vitamin D level, no change in cytokines level)
		Patients with active UC and inactive UC		Anti-inflammatory	Improved DAI (decreased fecal calprotectin levels and increased albumin increased Enterobacteriaceae but no change in gut microbiota diversity)
		Patients with active UC Patients with mild to moderate active UC			Improved DAI and anti-inflammatory properties (decreased of C-reactive protein and calprotectin, activation of NFκB pathway)

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Table 5.— *Continued*

Reference	Food Substrate	Model or Study Design	Age of Supplementation	Effect on IBD	Mechanisms
		Patients with active UC		No effect	No difference in DAI or inflammatory markers

AA, arachidonic acid; AIFAI, anti-inflammatory fatty acid index; ALA, linolenic acid; 5-ASA, 5-aminosalicylate; BSA, bovine serum albumin; CD, Crohn's disease; CDAI, Crohn's disease activity index; CLA, conjugated linoleic acid; DAI, disease activity index; DB, double-blind; DBP, diastolic blood pressure; DC, dendritic cells; DGLA, di-homo-gamma-linolenic acid; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; DSS, dextran sulfate sodium; EPA, eicosapentaenoic acid; EPA-FFA, EPA free fatty acid; EPIC, European Prevalence of Infection in Intensive Care; GLA, γ-linolenic acid; IBD, inflammatory bowel diseases; IBDQ-9 = inflammatory bowel disease questionnaire-short form; IEB, intestinal epithelial barrier; IEL, intestinal epithelial lymphocyte; LA, linoleic acid; LC $n-3$ PUFA (polyunsaturated fatty acids), C20:5 $n-3$ and C22:6 $n-3$; LPL, lamina propria lymphocyte; MLN, mesenteric lymph node; LBP, LPS binding protein; OA, oleic acid; PA, palmitic acid; PBMC, peripheral blood mononuclear cells; PBS, phosphate-buffered saline; PMA, phorbol 12-myristate 13- acetate; PG, prostaglandin; RBC, red blood cell; RPCT, randomized placebo controlled trial; RR, relative risk; SBP, systolic blood pressure; SI, small intestine; TEER, transepithelial electrical resistance; TNBS, 2,4,6-trinitrobenzenesulfonic acid; UBT, under baseline treatment; UC, ulcerative colitis; wo, weeks old.

Preclinical Studies

More in vivo data are available on the preventive effects of $n-3$ PUFA, including at early age (Table 5). Postweaning but also as adult, animals supplemented with $n-3$ PUFA showed a reduction of disease severity and improved clinical symptoms. Like in vitro studies, the supplementation modulated proinflammatory cytokines, with a reduction of IL-6 and iNOS (247). Gene expression was also impacted, with a decrease of the colonic NF-κB DNA binding activity (250).

Only one study investigated $n-3$ PUFA treatment at early age (Table 5). In postweaned mice, the $n-3$ diet ameliorated colitis but increased mortality by an impaired response to infection like LPS dephosphorylation ability (254). In adults, extra virgin olive oil reduced disease activity and abrogated DSS-induced gene expression of proinflammatory components like COX-2 and iNOS (265). To conclude on preclinical studies, $n-3$ PUFA intervention as prevention seemed effective, with an improvement of disease severity by similar mechanisms observed in vitro, i.e., a modulation of immune cytokines and gene expression. It should however be noted that the main model of inflammation induction was acute, so the chronic aspect of IBD is lacking and should be taken into consideration for future studies.

Clinical Studies

$n-3$ PUFA diet was mainly studied as treatment (Table 5). Clinical trials on the effects of $n-3$ PUFA at early age are scarce; only one study is enlisted and described the effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in 10-yr-old patients with CD in remission. As complement to 5-ASA, $n-3$ PUFA reduced the relapse risk. In adults, 10 studies including 1 meta-analysis and 2 robust studies (~190 CD patients/condition) were listed and comprised a consequent part of small studies (239, 255). EPA, EPA-free fatty acid, and DHA were the main $n-3$ PUFA analyzed. Patients in remission but also with moderately active disease presented decreased disease severity after $n-3$ PUFA consumption. The main effects were on the $n-3/n-6$ ratio, a decrease of proinflammatory cytokines production like IFN-γ and IL-17 by CD4+ and CD8+ T cells of peripheral blood (256, 287). However, in the EPIC-1 and -2 clinical trials that comprised the highest number of participants, $n-3$ PUFA diet failed to prevent relapse and to improve disease severity in patients with CD, active or in remission.

Conclusion on Diet Intake

In vitro and preclinical studies showed clearly beneficial effects of $n-3$ PUFA on inflammation, at different ages and both as preventive and therapeutic mean. However, at clinical level, the heterogeneity of $n-3$ PUFA intake duration and a lack of early age treatment studies do not allow full comparison. Especially, two clinical trials of great number of patients do not corroborate the positive results seen in smaller pilot studies. Also, preventive studies are needed at clinical level to complete the investigation of the potential of $n-3$ PUFA and predictive IBD markers (environmental factors, dysbiosis, etc.) should be taken into account for the recruitment of patients. Overall, diets rich in $n-3$ PUFA are disappointing due to their low efficiency. In view of their benefic effects on the digestive functions, diets rich in $n-6$ PUFA may be considered (7, 12, 13, 286). For example, the arachidonic acid metabolite 11β-PGF2α induces intestinal epithelial healing (13). Another arachidonic acid metabolite, the 15-HETE decreases IEB permeability, and the prostaglandin I2 supplementation alleviates colitis (7, 12). Altogether, implementing a supplementation with not only $n-3$ PUFA, but perhaps $n-6$ PUFA and/or their derived metabolites, represents a relevant direction of study for IBD treatment.

Concerning Vitamin D, the available clinical trials do not have standardization of doses and routes of administration. Despite its inflammatory processes, vitamin D presented opposite effect at different doses, underlining the need for standardized studies to establish how the supplementation should be performed and the doses to be administered.

Key Ideas: Diet

Lack of studies in general, both in prevention and treatment, with homogenized design and not only association studies. $n-3$ PUFA supplementation was beneficial in vitro and at preclinical level but failed to present any robust evidence in clinical trials. In contrast to diets that are globally enriched in $n-6$, recent studies focused on $n-6$ PUFA-metabolites and their interest as supplementation for patients with CD showed promising results.

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GENERAL CONCLUSIONS

From pre- to postbiotic, all levels of interventions have been or are being tested to reinforce and restore the microbiota, or mimic its effects. Although preclinical studies show very encouraging results, the transition to the clinic is less easy and will require many additional studies. Can all types of patients with IBD be treated and when? What is the better strategy? Prebiotics have a broad impact and up to now not entirely known. Their low specificity may lead to the fear of amplification of numerous physiological but also pathological processes, and thus the appearance of undesirable effects as recently described with inulin. Our knowledge has largely increased concerning probiotics or cocktails of probiotics, their interactions and their uses for the benefit of the host. They are relatively important means to restore digestive functions or reinforce the homeostasis of the digestive tract. Similarly, FMT is attractive, but many questions remain to be addressed to make progress on the subject. Better understanding of the effect of FMT, identification of super-donors, and of the protective members of their microbiota should lead to the development of next-generation probiotics (288, 289). In this respect, the present development of capsules containing freeze-dried raw microbiota of donors constitutes a first step (290). In general, the use of bacteria to treat is a concept that still needs to be promoted to many clinicians, in particular by demonstrating its safety and effectiveness. In this sense, postbiotics would be safer, but they are, to date, less effective. Nevertheless, we can suppose that a cocktail of postbiotics and means of administration that would allow to control and maintain their concentration would allow to improve this.

The development of bioinformatic modeling, the results of shotgun metagenomics, and metabolomics as well as the use of organoids or organ-on-chip human models should help us precise and define how microbiota-based strategies can improve host homeostasis. Even so, it seems reasonable to think that interventions improving the microbiota or using the microbiota should at least complete and improve the therapies used to treat patients with IBD.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

A.L. and M.M prepared figures; A.L, M.M., and J.M. drafted manuscript; J.M., M.B., G.J., and M.R.-D edited and revised manuscript; A.L., M.M., J.M., M.B., G.J., and M.R.-D approved final version of manuscript.

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Certaines souches de bactéries possèdent un potentiel immunomodulateur démontré. Par ailleurs, ce potentiel des bactéries probiotiques est favorisé par le rôle protecteur de la matrice alimentaire. Un aliment fermenté par ces bactéries peut s'avérer plus efficace qu'une préparation probiotique déshydratée. De plus, des souches immunomodulatrices sont identifiées dans un nombre croissant d'espèces bactériennes utilisées comme levains (starter) en fermentation alimentaire (fromages, laits fermentés).

3.3.3. ALIMENTS FERMENTES PAR DES SOUCHES SELECTIONNEES COMME VECTEUR DE PROBIOTIQUE

La présente revue écrite conjointement avec des membres des laboratoires STLO et TENS, discute des effets bénéfiques des **produits laitiers fermentés** sur l'homéostasie intestinale. Dans un contexte où notre mode de vie et notre alimentation se sont largement dégradées, renforcer l'homéostasie intestinale est cruciale. L'utilisation de probiotiques, comme décrit précédemment, présente des effets prometteurs sur la santé intestinale. Les probiotiques sont isolés à partir d'écosystèmes de bactéries commensales, c'est-à-dire présentes naturellement dans le MI humain, mais aussi à partir d'écosystèmes alimentaires. Les produits laitiers fermentés sont la **source majeure** de **bactéries vivantes** et **actives**, avec 10^9 bactéries par gramme de produit. La revue ci-dessous détaille les récentes études concernant les effets bénéfiques *in vivo* et les mécanismes d'action *in vitro* de différents levains tels que les LAB (pour « lactic acid bacteria ») qui englobent *Streptococcus thermophilus, Lactobacillus delbrueckii, L. helveticus* et *L. lactis*, ainsi que les PAB (pour « propionic acid bacteria ») qui concerne les propionibacteria dont *P. freudenreichii*. Enfin, les études cliniques sont rares, mais il est certain que les aliments fermentés modulent la physiologie et la santé de l'hôte, car une déprivation de produits fermentés dans l'alimentation impacte fortement le système immunitaire dans l'intestin, entrainant en particulier une chute de la réponse immunitaire innée (Olivares et al. 2006).

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Dairy starters and fermented dairy products modulate gut mucosal immunity

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ABSTRACT

The gut microbiota plays a crucial role in the regulation of mucosal immunity and of the function of the intestinal barrier. Dysbiosis is accordingly associated with rupture of mucosal immune homeostasis, leading to inflammatory intestinal diseases. In this context, probiotic bacteria, including a new generation of intestinal probiotics, can maintain intestinal homeostasis and promote health. Surprisingly, little is known about the impact of fermented dairy products in this context, while they represent our main source of live and active bacteria. Indeed, they provide, through our daily diet, a high number of bacteria whose effect on mucosal immunity deserves attention. Among bacteria ingested in fermented dairy products, *Streptococcus thermophilus, Lactobacillus delbrueckii, Lactobacillus helveticus, Lactococcus lactis* and *Propionibacterium freudenreichii* are on top, as they are ingested in high concentrations (close to 10^9 per gram of product) in fermented milks or cheeses. This review gives an overview of the potential immunomodulatory effects of these main dairy starters. It further explores studies dealing with fermented dairy products containing theses starters, in a context of inflammation.

Evolution of lifestyle leads to rupture of intestinal homeostasis and barrier function

Our lifestyle has changed dramatically since the last 70 years in terms of diet, medication, and increased sedentary lifestyle. One main point is the change in the food processing and eating habits associated with the worldwide Western diet, long-lasting settled in the everyday life. This western diet is mainly marked by ultra-processed foods, including refined and modified food components, as oils, fats hydrogenated or not, sugars and sweeteners, starch more or less modified, processed proteins, and various food additives, rendering the food highly palatable with empty and unnecessary calories [32]. As a consequence, such a diet leads to numerous dramatic changes in the overall food quality. Depletion of fiber, deficiency of vitamins, increase of saturated fatty acids and sugars, as well as the frequent addition of food additives, are particularly noticed. They can alter the human health in a short term, and particularly affect the intestinal homeostasis as illustrated in Fig. 1. The intestinal homeostasis is a fragile balance, finely regulated by complex interactions between the intestinal epithelial barrier (IEB), the gut microbiota, the immune system, and the enteric nervous system (ENS) [75]. In case of deregulation,i.e. dysbiosis, prevalence of inflammatory chronic diseases, diabetes and cardiovascular higher risks and obesity increase [62].

Fiber depletion can change the homeostasis by directly or indirectly influencing the gut microbiota. The richness of the microbiota can actually be decreased, with a higher Firmicutes to Bacteroidetes ratio observed [38] as well as the production of short chain fatty acids, which helps to lower the luminal pH and inhibit the growth of pathogenic bacteria [80], while a higher mucus degradation can be observed, lowering the overall mucosal protection [23]. For the food additives, the consequences are numerous and depend on the type of additives used. For example, maltodextrin, largely used as thickening agent, change bacterial mucosal colonization in mice, leading to higher levels of pathogenic bacteria as *Salmonella* and *Escherichia coli* [91,92]. Emulsifiers as polysorbate 80 and carboxymethylcellulose have a pro-inflammatory potential in human [14] and in colitis-induced context in mice [13]. Regarding the non-caloric artificial sweeteners, their short- or long-term use in humans or mice results in dysbiosis of the gut microbiota associated with glucose intolerance as shown for saccharin [130]. Prenatal exposure to sucralose resulted in altered

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composition and metabolism of the gut microbiota in pups [103], and changes in the tryptophan metabolism, essential for regulation of digestive functions, were notably observed in mice [7]. Another worrying feature of Western-diet is the presence of large quantities of micro-particles ($> 10^{12}$/day) derived from food additives, that can affect intestinal homeostasis. Among them, titanium dioxide (TiO_2) is one of the most widely used whitening food colorants. Studies support the pro-inflammatory effects of TiO_2, a shift in the gut microbiota as well as an alteration of the IEB with bacterial translocation [6,76,115]. In rats, TiO_2 accumulates in the liver and Peyer's patches following short-term exposure (7 days). Besides, a long duration of exposure contributed to a low-grade inflammation [6]. This inflammation can be explained by effects on the microbiota and the intestinal barrier. Indeed, rats exposed to TiO_2 had a decrease in SCFA as well as an increase in antimicrobial peptides. This suggests an alteration of the gut microbiota in rats. In addition, TiO_2 altered the IEB, decreased Muc-2 biosynthesis and altered colonic crypt length [76].

Western diet is also facing opposing disadvantages: excess of some components as fat and sugar and deficiency in vitamins. Excessively rich diet leads to an alteration of the IEB, which contributes to intestinal dysbiosis, inflammatory status, and even enhanced intestinal permeability [42,139]. Vitamin D deficiency is associated with IBD [34], while vitamin A therapies control intestinal inflammation [10]. In case of celiac diseases, the vitamin D deficiency can aggravate the reduction of bone mineral density, the increase in proinflammatory cytokines and the intestinal calcium malabsorption via a reduction of the vitamin receptor in the IEB and of some proteins involved in the tight junctions [2].

Finally, beside the role of the food component other parameters of our lifestyle, as sedentary lifestyle and medication with the increasing use of antibiotics, also negatively impacts the gut homeostasis (Fig. 1). Thus, sedentary lifestyle led to low intestinal motility, fecal diversity and higher inflammatory status in elderly population [18]. The physical activity has been proposed as a way to alleviate some intestinal bowel syndromes [51] and seems to positively affect the gut microbiota and promote an anti-inflammatory state [19]. Regarding the antibiotics, they directly act on the gut microbiota and an excessive use of antibiotics promotes the development of chronic diseases like IBD, IBS [47], causes impairment of IEB and increase inflammation. Actually, they induce a decrease in the microbial diversity by killing pathogenic as well as collaterally beneficial microorganisms, which in turn leads to a decrease in T cells in the gut. In addition, the use of antibiotics inhibits the expression of mitochondrial genes and the number of active mitochondria, which ultimately induced cell death in the GI epithelium [88].

Bacteria within the gut lumen modulate intestinal homeostasis and barrier function

The human gastrointestinal tract harbors about 10^{14} microbes belonging to 1000 species. This number is more than 10-fold the number of eukaryotic human cells [122]. This intestinal microbiota is crucial to human health since it influences host nutrition development and modulation of the immune system, and intestinal barrier function [39]. The results of various studies demonstrated a link between intestinal barrier dysfunction and human gastrointestinal diseases [52,95]. Furthermore, several studies have documented the beneficial effects of probiotics in diverse gastrointestinal diseases including IBD [39,118]. They provide the preservation of intestinal barrier by various mechanisms including (i) the decrease in pathogenic bacterial adhesion (ii) the increase of the

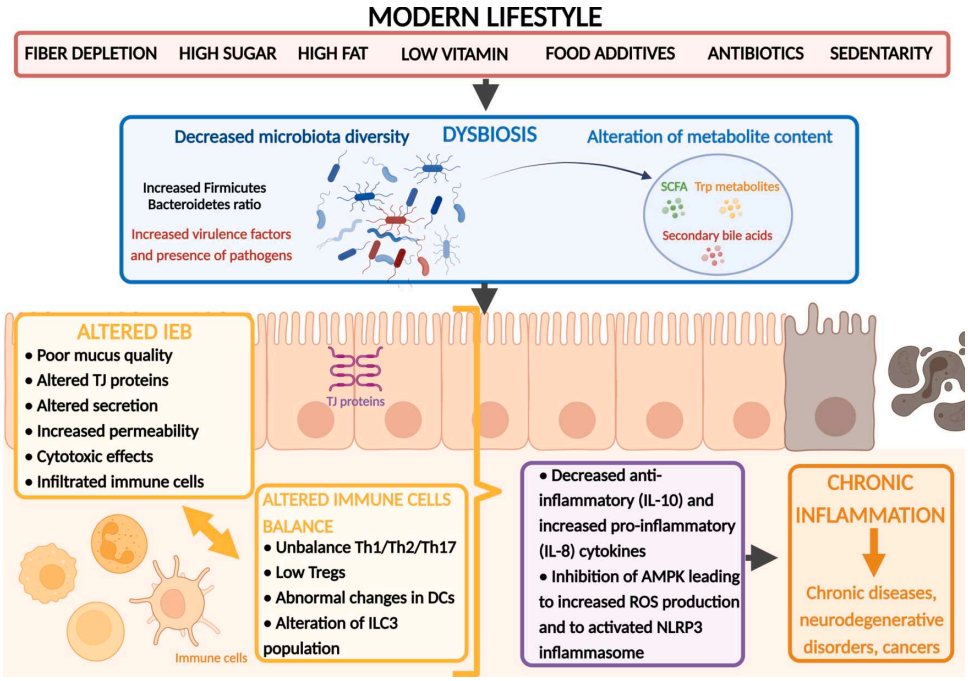

Fig. 1. Consequences of changes in modern lifestyle on the gut dysbiosis, intestinal epithelial barrier (IEB) and immune system. Changes occurring during transition to a modern lifestyle include modification of the eating habits, with reduced intake of fibers, of vitamin, yet enhanced intake of sugar, of food additives, and of fat. These changes also include sedentarity and medication, including the use of antibiotics. They favor dysbiosis, a dysregulation of the gut microbiota, with decreased microbial diversity and alteration of the content in microbial metabolites. This in turn leads to an altered intestinal epithelial barrier, which is involved in an altered balance of immune cells. All these changes finally favor chronic inflammation.
SCFA: short chain fatty acids; TJ: tight junction; IEC: intestinal epithelial cells; DCs: dendritic cells; ILC3: type 3 innate lymphoid cells; AMPK: Adenosine monophosphate-activated protein kinase; ROS: reactive oxygen species; NLRP3: Nucleotide-binding Oligomerization Domain-like Receptor Protein 3.

intestinal epithelial barrier function via inhibition of epithelial apoptosis, preservation of tight junctions protein expression, increase in mucus production and defensin secretion, and (iii) reduced proinflammatory cytokines [26,65,101]. These probiotics may be commensals, a fraction of the natural human microbiota, or provided by either fermented foods or food supplements [112,119]. They can interact with intestinal epithelial cells (IECs) and dendritic cells (DCs) in the mucus layer (Fig. 2A). Some surface components of probiotic bacteria, named microbe-associated molecular patterns (MAMPs), play an important role in these interactions (Fig. 2C). These components are recognized by the corresponding pattern recognition receptors (PRR), present at the surface of the host cells [65]. From the bacterial side, MAMPs include flagellins, pilins, surface proteins, lipoteichoic acid, peptidoglycan, and cell wall-associated polysaccharide (CPS). From the host side, PRRS include Toll Like Receptors (TLRs) and C-type lectin DC specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN). The interaction between a MAMP and a PRR allows the induction of signaling cascades which initiate a molecular response against the detected microorganism. This response leads particularly to the secretion of immunomodulatory cytokines and other immune mediators. Subtle structural variations exist between MAMPs found in different bacteria, while their basic structure remains similar. However, these variations do not allow discrimination between the functional classes of microorganisms [26,65,124]. Of note, interaction between host DC-SIGN and surface glycoproteins of probiotic gut lactobacilli was shown to induce an anti-inflammatory response [141].

Fermented dairy products constitute our main source of bacteria

Fermented dairy products exist since millennia as an outstanding way to preserve milk, provide safe food with desirable sensorial properties and numerous health benefits [78,79,116]. These fermented products are found worldwide and constitute an essential part of living bacteria arising from food in the everyday life diet [135,136]. Even if spontaneous fermentation exists, technical practices have largely evolved to use starters, either by back slopping of the previous batch of production, or by using commercial lyophilized direct-in-vat starters. The main bacteria, used as starters in many dairy processes, are lactic acid bacteria (LAB) required to produce yogurts, fermented milks, cream, butter, and cheeses. The main role of the LAB is to acidify the milk through the fermentation of lactose into lactic acid, which inhibits spoilage and/or pathogenic flora. Moreover, LAB are also responsible for the production of desirable aroma compounds such as diacetyl or acetoin for example. The presence of LAB is highly variable in the fermented dairy products, as shown for some examples in Table 1 and in greater details in the review of Rezac et al. [112]. It largely depends on the conservation time, the shorter time used the higher counts observed, and on the technological process used. Among LAB, the main species encountered in fermented dairy products are *Lactococcus lactis, Streptococcus salivarius* subsp. *thermophilus* (*S. thermophilus*) and lactobacilli such as *Lactobacillus delbrueckii* ssp in yogurts and fermented milks and *Lactobacillus helveticus* in Swiss cheeses. Many other microorganisms are also present within the cheeses such as propionibacteria (PAB) in Swiss-type cheeses, or at the surface of the cheeses, as moulds and yeasts (see for more details [8,81]). Among the internal ripening flora, PAB, and specially *Propionibacterium freudenreichii*, are generally growing after the LAB by using lactic acid as their main carbon source to produce propionic acid, acetic acid and carbon dioxide, visualized by holes in Emmental cheeses. Among other metabolites produced, PAB synthesize B_9 and B_{12} vitamins [11]. The propionic acid is often used for food

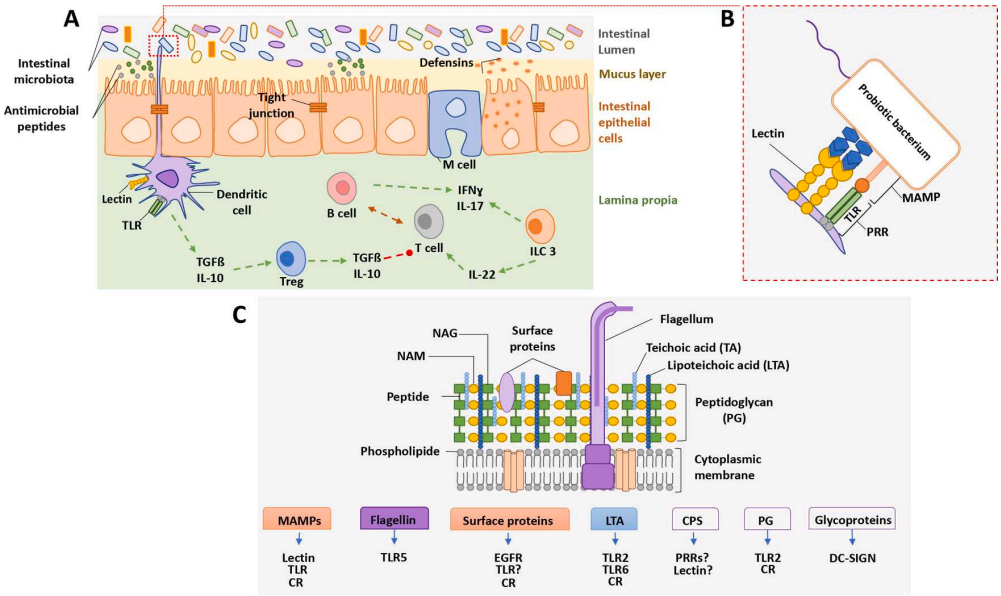

Fig. 2. Schematic view of possible interactions between ingested bacteria and the host. A: drawing of the key layers of the intestinal epithelial barrier. The intestinal barrier includes: (i) the intestinal lumen with the intestinal microbiota; (ii) the mucus layer that serves as a microbial and biochemical barrier; (iii) the intestinal epithelial cells (IECs) monolayer, maintained by tight junctions, forming a physical barrier; (iv) and the lamina propria which contains different immunological cells that interact together (DCs, T cell, or ILC3). Green arrows represent cytokine secretion or stimulation, brown represents interaction and red represents inhibition. **B: Focus on the interaction between a probiotic bacterium and dendritic cell (DC).** Probiotic bacteria interact with DC via microbe-associated molecular patterns (MAMPs) and pattern recognition receptors (PRR). **C: Schematic representation of the main surface components (MAMPs) of Gram-positive probiotic bacteria and the corresponding PRRs in IECs and DCs.** Host pattern recognition receptors (PRRs) that recognize probiotic MAMPs include Toll Like Receptors (TLRs), C-type lectin DC specific intercellular adhesion molecule 3-grabbing nonintegrin (DC-SIGN). CR, co-receptors; CPS, cell wall-associated polysaccharide; PG, peptidoglycan; TA, teichoic acid; LTA, lipoteichoic acid; EGFr, epidermal growth factor receptor; NAG, N-acetylglucosamine; NAM, N-acetylmuramic acid.

Table 1
Counts of some lactic acid bacteria and ripening flora in fermented dairy products.

Type of fermented milk products at the end of production	Species studied	Count range (log_{10} CFU.g^{-1} of product)	Reference
Plain yogurt ($n = 5$) Flavored yogurt ($n = 5$) Liquid yogurt ($n = 5$) Fermented milk ($n = 5$) Biogarde®3 ($n = 5$)	S. salivarius subsp. thermophilus *(S. thermophilus)*	8.20–8.36 8.34–8.60 8.41–8.56 8.34–8.59 8.45–8.53	[53]
Commercial yogurt	*S. thermophilus* *Lactobacillus delbrueckii*	7.54 ± 0.05-8.88 ± 0.06 6.90 ± 0.09 - 8.56 ± 0.01	[87]
Commercial Emmental cheeses (West part of France at 51 and 61 d of ripening)	Thermophilic streptococci including *S. thermophilus* Thermophilic lactobacilli including *Lactobacillus helveticus* Propionibacteria including *Propionibacterium freudenreichii*	Not detected 6.4; 5.7 8.0;8.6	[140]
Swiss Gruyère-type cheese manufactured with natural whey cultures (6-month ripening)	Thermophilic streptococci including *S. thermophilus* Thermophilic lactobacilli including L. *helveticus* *Lactobacillus helveticus* [2]	2.56 ± 0.07 −6.42 ± 0.01 3.0–7.86 ± 0.02 7.59 (±0.86)	[90]
Cantal cheeses (120 d of ripening)	Lactococci including *Lactococcus lactis* S. *thermophilus* Mesophilic lactobacilli Facultative heterofermentative lactobacilli Propionibacteria including *P. freudenreichii*	6.5 ± 0.5 6.3 ± 0.6 6.7 ± 0.3 7.4 ± 0.2 5.6 ± 0.3	[22]
Manchego cheese (150 d of ripening)	L. *lactis* subsp. *lactis* Commercial lactococci starter	~7 ~6	[108]

[1]CFU, colony forming unit.
[2] The quantitation of L. *helveticus* was performed by quantitative PCR, which specifically targets the *pheS* gene encoding the α-subunit of the phenylalanine-tRNA synthetase and expressed as log_{10} copies g^{-1}.

preservation in industry and has a positive role in the gut health [111].

Beyond their role in the genesis of the overall qualities of the fermented dairy products, LAB and PAB have also an essential role in the human health and the gut homeostasis as shown in the following sections. This review gives an overview of the potential immunomodulatory effects of these main dairy starters. It further explores studies dealing with fermented dairy products containing theses starters, in a context of inflammation.

Dairy starters as single strains: evidence *in vivo* and mechanisms *in vitro*

Streptococcus thermophilus, demonstrated effects in vivo

S. thermophilus strains have been mainly studied in colitis-induced context. As a now well-established animal model of immune homeostasis rupture, colitis can be induced in mice by introducing dextran sulfate sodium (DSS) into drinking water. This model of colitis, among various chemically-induced models, is widely used to investigate gut inflammation as well as means to counteract it. Indeed, it is simple to implement, rapid, reproducible, and controllable, and it shares many similarities with human ulcerative colitis [29].

Compared to a placebo, the consumption of *S. thermophilus* YIT2001, before colitis induction, was able to prevent colitis, to decrease the disease activity index, as well as the content of lipid peroxide in the colonic mucosa, as evaluated by quantifying the thiobarbituric acid reactive substance content [48]. Interestingly, other strains of *S. thermophilus* that were tested in this study, revealed no protective effect, which indicates the strain-dependent properties of immunomodulatory effects. These authors suggest that the antioxidative activity of active strains of *S. thermophilus* is involved in reducing colitis severity.

In the same model of DSS-induced colitis, other strains were tested: *S. thermophilus* ST28, [96] and *S. thermophilus* NCIMB 41,856 [3]. While DSS induced IL-17 in lamina propria lymphocytes, *S. thermophilus* ST28 consumption significantly decreased this production, as well as the percentage of Th17 cells in this lymphocytes population [96]. This strain thus suppresses Th17 response in the context of intestinal inflammation. The *S. thermophilus* NCIMB 41,856 consumption delayed onset of colitis, reduced bacterial translocation into the colon tissue, reduced clinical signs of the disease, including bodyweight loss and gastrointestinal bleeding. However, it had no effect on gross pathology, histopathology or cytokine production in either colitis or control animals [3]. Authors suggest that this strain promotes maintenance of mucosal barrier, preventing bacterial translocation, thus reduced immune stimulation and inflammation, allowing healing of colitis. In addition, Chen et al. [17] compared the effects of *S. thermophilus* MN-BM-A01 and of exopolysaccharides (EPS) produced by this strain. Isolated EPS, composed of rhamnose, glucose, galactose and mannose, alleviated the severity of colitis [17]. This included decreased disease activity index and colonic epithelial cell injury, reduced pro-inflammatory cytokines levels (tumor necrosis factor-α, interleukin-6, and interferon-γ) and restored expressions of tight junction protein (claudin-1, occludin, and E-canderin).

S. thermophilus CRL803 was tested in another model of colitis induced in mice by intrarectal administration of trinitrobenzene sulfonic acid (TNBS). Consumption of this strain is reported to lower macroscopic and histologic damage scores, microbial translocation to liver, $iNOs^{+}$ (inducible nitric oxide synthase positive) cells in their large intestines, and proinflammatory cytokines, compared with colitis mice without probiotic [66]. Authors report the same effect for other lactic acid bacteria (including L. *delbrueckii* subsp. *bulgaricus*) producing riboflavin, as well as for the administration of pure riboflavin. Authors suggest that riboflavin-producing lactic acid bacteria strains prevent intestinal damage and colitis.

S. thermophilus was also reported to mitigate another ailment characterized by an inflammation of the digestive tract, mucositis. This last is a painful inflammation and ulceration of the mucous membranes lining the digestive tract, usually as an adverse effect of chemotherapy and radiotherapy treatment for cancer. A now well recognized rodent model of mucositis is based on the injection of the cancer chemotherapy drug 5-fluorouracyl (5-FU) to rodents. In this model of intestinal digestive disease, consumption of *S. thermophilus* CRL 808 mitigated induced mucositis. This included reduction in diarrhea score and restoration of the intestinal architecture, while no effect was observed concerning blood levels of cytokines. By contrast, another strain of *S. thermophilus*, CRL 415, failed to exert similar protective effect [67]. Another consistent study reported the amelioration of 5-FU mucositis in mice as a result of consumption of *S. thermophilus* ST4, including reduction of body weight loss, of appetite loss and of diarrhea, as well as maintenance of the epithelium structure in small intestines and colons, and reduced intestinal inflammation [126]. These *in vivo* experiments suggested that protective mechanisms *of S. thermophilus*, in the context of intestinal inflammation, may involve the production of folate, riboflavin, of exopolysaccharide, modulation of the immune response, including suppression of Th17 response. Further molecular mechanisms of action were sought *in vitro*.

Streptococcus thermophilus, mechanisms elucidated in vitro

In order to explain the healing effect of selected strains of *S. thermophilus* in the context of intestinal inflammation, the mechanisms potentially involved in its immunomodulatory properties were sought. As an example, *S. thermophilus* ST28 was tested *in vitro* on murine splenocytes stimulated by TGF-β and IL-6. While these cytokines induced the production of IL-17, addition of ST28 repressed this induction, as well as the number of Th17 cells in the stimulated splenocytes. By contrast, the type strain *S. thermophilus* ATCC 19,258 failed to do so. Such an immunomodulatory property coincided with the healing effect of *S. thermophilus* ST28 in the context of DSS-induced colitis *in vivo* [96]. This suppressive effect of *S. thermophilus* ST28 was further characterised in murine splenocytes. It was shown to induce transcription of interferon (IFN)-γ mRNAs, and anti-IFN- γ antibodies suppressed the immunosuppressive effect of *S. thermophilus* ST28. Genomic DNA from this strain accordingly supressed IL-17 production. Authors hypothesized that this was mediated by the Toll-like receptor 9 and suggest that modulation of Th1/Th17 balance would be involved in ST28 anti-inflammatory effect [97].

S. thermophilus being shown to promote maintenance of mucosal barrier function [3], its effect on gut epithelial cells was further investigated. In cultured human intestinal epithelial cells (HIEC) Caco-2, barrier integrity was disrupted by the addition of pro-inflammatory lipopolysaccharide (LPS). By contrast, EPS isolated from *S. thermophilus* MN-BM-A01 protected Caco-2 cells barrier integrity from such disruption, in line with increased expression of tight junction proteins, and alleviated pro-inflammatory response in these cells [17]. *S. thermophilus* EPS were further shown to modulate the antiviral innate immune response in porcine intestinal epitheliocytes [86]. EPS more precisely increased the expression of interferon β (*IFN-β*), interleukin 6 (*IL-6*), and C-X-C motif chemokine 10 (*CXCL10*) in response to TLR3 stimulation in these cells. Monitoring of mucus biosynthesis and immune response in human colonic epithelial cells further indicated that *S. thermophilus* upregulates goblet cell activity [125]. *S. thermophilus* EPS were also shown to inhibit adhesion of the pathogen *Helicobacter pylori* to gastric AGS cells and to attenuate *H. pylori*-induced inflammatory response in these cells [77]. D-Alanylation of teichoic acid (TA), a component of bacterial cell wall, was also shown to play a role in gut barrier protection by *S. thermophilus*. Indeed, inhibition of TA D-Alanylation in *S. thermophilus* supressed its ability to maintain the trans epithelial electrical resistance (TEER) in Caco-2 cells, when challenged by TNF-α [85].

Lactobacillus delbrueckii, demonstrated effects in vivo

In a pioneer research work, the immunomodulatory properties of a series of strains of the dairy starter *Lactobacillus delbrueckii* were screened. Promising anti-inflammatory properties were evidenced, in a strain-dependent manner, in both the *bulgaricus* and the *lactis* subspecies, on cultured HIEC, by monitoring the Nuclear Factor NF-*κB* activity. A selected strain, L. *delbrueckii* subsp. *lactis* CNRZ327, was then shown to mitigate gut inflammation *in vivo* (Santos [121]). Its consumption reduced the macroscopic and microscopic symptoms of DSS-induced colitis in the mouse intestinal tract, diminished body weight loss, and improved survival (Santos [121]). The same authors then showed that it modulates the production of cytokines such as TGF-β, IL-6, and IL-12, at the colon level, as well as that of TGF-β and IL-6 in the spleen. It further caused an expansion of $CD4^{+}FOXP3^{+}$ regulatory T cells in the cecal lymph nodes (Santos [120]). In another study, L. *delbrueckii* subsp. *bulgaricus* was shown to inhibit colitis-associated cancer. It inhibited total tumor volume and mean size of tumors, attenuated the clinical signs of intestinal inflammation, and decreased intestinal and tumor levels of IL-6, TNF-α, IL-17, IL-23 and IL-1β, in an azoxymethane / DSS mice model [127].

Oxidative stress playing a role in the progression of IBD, L. *delbrueckii* subsp. *bulgaricus* A13, an exopolysaccharide-producing strain, was tested in a rat model of colitis induced by intracolonic administration of acetic acid, and oxidative stress markers were followed. Colitis caused oxidative damage, associated with enhanced level of malondialdehyde (MDA) activity and reduced antioxidant enzyme activities. Consumption of L. *delbrueckii* subsp. *bulgaricus* A13 restored antioxidant enzyme activities. It also improved the oxidative stress parameters [123]. In line with these *in vivo* studies, a clinical study reported the healing effect of a combination of L. *delbrueckii* with L. *fermentum*, in ulcerative colitis patients. Consumption of these probiotics for eight weeks ameliorated inflammation, decreased colonic concentration of IL-6, expression of TNF-α and NF-κ*B* p65, leukocyte recruitment and the level of fecal calprotectin, compared to the control group [43].

In germ-free mice, mono-association with L. *delbrueckii* UFV-H20b20 stimulates the immune system and protects towards experimental infections, including *Salmonella enterica* and *Listeria monocytogenes* (dos [28]). In influenza A virus-infected mice, L. *delbrueckii* feeding enhances humoral immune response [134]. In weaning piglets, L. *delbrueckii* improves intestinal integrity and antioxidant ability [15]. Accordingly, an immunobiotic feed developed with L. *delbrueckii* improves health and growth in piglets [129].

Lactobacillus delbrueckii, mechanisms elucidated in vitro

In the above-cited study by Santo Rocha et al., [121] the immunomodulatory properties, evidenced on cultured HIEC (HT29), were shown to be dependent on surface proteins. Indeed, shaving of the bacterial surface proteins by the protease trypsin suppressed these properties (Santos [121]). From a mechanistic point of view, they affect the central part of the NF-κ*B* activation pathway and reduce I-κ*B* phosphorylation (Santos [121]).

Exopolysaccharides produced by L. *delbrueckii* may also be involved in its immunomodulatory properties. Both L. *delbrueckii* and its exopolysaccharide attenuate enterotoxigenic *E. coli*-induced inflammatory response in porcine intestinal cells [143]. Such a treatment leads to enhanced resistance towards rotavirus infection [54]. In these porcine cells, L. *delbrueckii* exopolysaccharides differentially modulate immune response triggered by TLR3 activation. They enhanced the expression of interferon (IFN)-α and of IFN-β after the stimulation with the TLR agonist polyinosinic-polycytidylic acid (poly(I:C)), as well as the expression of the antiviral factors MxA and RNase L. They may thus improve intestinal innate antiviral response [55].

Considering immune cells, incubation of immature human dendritic cells with *Lactobacillus delbrueckii* ssp. *bulgaricus* induced secretion of the cytokines of IL-1β, IL-10, IL-12 and TNFα [30]. In such cells, generation of tolerogenic dendritic cells was stimulated by *Lactobacillus delbrueckii*, described as a tolerogenic probiotic [31]. In splenocytes isolated from C57BL/6 and BALB/c mice, L. *delbrueckii* modulated the production of interleukin 12p40 (IL-12p40), of tumor necrosis factor alpha and of IL-10. This effect was shown to depend, at least partly, on Toll-like receptor 2 (TLR2) and on phagocytosis [12].

Lactobacillus helveticus, demonstrated effects in vivo

L. *helveticus* NS8, isolated from Koumiss, a traditional fermented milk from Inner Mongolian pasturing area, revealed anti-inflammatory properties by protecting mice from TNBS-induced colitis. It limited in particular the weight loss induced by TNBS, and reduced the Wallace score, as well as damages seen at the histologic level [114]. The same strain was then shown to suppress colitis-associated colorectal tumorigenesis by modulating inflammatory development and microbial homeostasis [113]. In this azoxymethane + DSS-induced carcinogenesis mouse model, L. *helveticus* NS8 consumption reduced the tumor number and the degree of hyperplasia, enterocytes proliferation, while enhancing apoptosis, suppressed the activation of NF-κ*B*, upregulated the anti-inflammatory cytokine IL-10 and downregulated

IL-17-producing T cells [113].

Another strain, L. *helveticus* SBT2171, provided within a cheese, was tested in mice. In healthy mice, cheese induced regulatory T cells (Treg), which regulate immune and inflammatory responses, while suppressing production of IL-17, IL-4, and IL-10 in gut Peyer's patch cells. In mice with DSS-induced colitis, cheese alleviated the symptoms of colitis, prevented body weight loss and colon length shortening, and reduced the disease activity index, which includes diarrhea and fecal bleeding. It furthermore decreased production of proinflammatory cytokines (IL-17 and IL-6) and increased production of the anti-inflammatory cytokine transforming growth factor-β1 in Peyer's patch cells [45]. Its intraperitoneal administration moreover strongly alleviated symptoms of collagen-induced arthritis (CIA) in mice [46]. Such preventive effect towards induced arthritis was further evidenced as a result of oral administration of L. *helveticus* SBT2171, in line with its ability to downregulate the abundance of immune cells and the subsequent production of CII-specific antibodies and IL-6 [146].

Surprisingly, the strain-specific immunomodulatory properties of selected strains of L. *helveticus* prevented the anxiety-like behavior and negative effects on memory that were induced by a Western-style diet [98]. Furthermore, L. *helveticus* NS8 was shown to improve behavioral, cognitive, and biochemical aberrations caused by chronic restraint stress in rats [68]. This correlated with lower plasma corticosterone and adrenocorticotropic hormone ACTH levels, higher plasma IL-10 levels, restored hippocampal serotonin and norepinephrine levels.

Lactobacillus helveticus, mechanisms elucidated in vitro

In the above-mentioned study by Rong et al., L. *helveticus* NS8, in coculture with peripheral blood mononuclear cells (PBMCs), induced secretion of the immunomodulatory IL-10 [114]. It furthermore reduced the pro-inflammatory response elicited by lipopolysaccharide (LPS) in mouse macrophage cell line RAW264.7. Concerning the above-mentioned L. *helveticus* SBT2171, it was shown *in vitro* to inhibit lymphocytes proliferation (LPS-stimulated mouse T and B cells and Jurkat and BJAB human lymphoma cell lines) via regulation of the JNK signaling pathway [46]. It moreover induced A20 expression via Toll-Like Receptor 2 signaling and inhibited the lipopolysaccharide-induced activation of NF-κ*B* and mitogen-activated protein kinases in peritoneal macrophages [57]. This effect was also induced by a cell-wall fraction of the strain. The surface S-layer protein covering this strain was further shown to promote human β-Defensin 2 expression via TLR2-JNK signaling in Caco-2 HIECs [59]. In L. *helveticus* MIMLh5, S-layer protein SlpA mediates the stimulatory effect on innate immunity [138]. In murine bone-marrow-derived dendritic cells, L. *helveticus* MIMLh5 induced greater production of IFN-β, IL-10, and IL-12p70, compared to S-layer-depleted MIMLh5, and S-layer promotes endocytosis by these dendritic cells [137]. In stimulated human monocyte derived dendritic cells, different strains of L. *helveticus*, isolated from Italian hard cheeses, induced release of both the pro-inflammatory cytokine IL-12p70 and the anti-inflammatory cytokine IL-10, while corresponding cell-free culture supernatants triggered a dose-dependent decrease of IL-12p70 and an increase of IL-10 [149]. Accordingly, the suppression of intestinal epithelial cell chemokine production was shown to be mediated by secreted bioactive molecules in L. *helveticus* R0389 [49]. Different immunomodulatory compounds, with contrasted effects, are thus associated with the bacteria or secreted into the external medium.

Exopolysaccharide produced by L. *helveticus* KLDS1.8701, in addition, was shown to alleviate DSS-induced colitis in mice [70]. The immunomodulatory effect of L. *helveticus* R389 on murine IEC was shown to depend on TLR, as antibodies raised against TLR2 and TLR4 both supressed modulation by L. *helveticus*. In FaDu hypopharyngeal carcinoma cells, L. *helveticus* MIMLh5 antagonized the pro-inflammatory effect of *Streptococcus pyogenes*, reducing the induction of IL-6, IL-8, and of TNF-α [40].

Lactococcus lactis, demonstrated effects in vivo

Many studies dealt with recombinant genetically modified lactococci, expressing human or animal cytokines, in order to counteract inflammation, and will not be cited here, as this review only focuses on wild type, GRAS, safe bacteria that may be implemented in fermented food products As an example, L. *lactis* NCDO2118 was given in a curative way during the remission period following DSS treatment [71]. Its consumption resulted in a milder form of recurrent colitis than that observed in control diseased mice, together with an early increase in IL-6 production and sustained IL-10 production in colonic tissue, as well as an increase in regulatory CD4(+) T cells (Tregs) bearing surface TGF-β in its latent form (Latency-associated peptide-LAP) in the mesenteric lymph nodes and spleen. L. *lactis* healing effect was further shown to be more effective when administered in a preventive way prior to, than during and after DSS administration [5]. Such a preventive role towards DSS-colitis was confirmed by different teams [4,5,56,69,71], while another strain, L. *lactis* JCM5805, given at high doses to mice, worsened DSS-colitis, decreasing survival rate, increasing histopathological score, as well as levels of IFN-ɣ, TNF-α and IL-6 [60]. This evidences the strain-dependent immunomodulatory effects of lactococci.

In cyclophosphamide-immunosuppressed mice, consumption of L. *lactis* subsp. *lactis* GCWB1176 elevated natural killer (NK) cell activities; concanavalin A-induced T cell proliferation; and serum levels of TNF-α, IFN-γ, IL-2, IL-4, IL-10 and IL-12 [50]. This strain thus improved immune function through the activation of macrophages and NK cells (see below).

L. *lactis* subsp. *cremoris* ATCC 19,257 was shown to exert cytoprotective effects on the Drosophila intestine in response to oxidative challenge [21]. It induced activation of the Nrf2 signaling pathway in the Drosophila intestine, independently of reactive oxygen species. It further exerted a cytoprotective against radiological injury in mice and protected the murine intestine from DSS-induced colitis.

In healthy mice, administration of L. *lactis* MG1363 during five days triggered systemic immunomodulation. It reduced splenic T helper cell cytokine responses after *ex vivo* restimulation, as well as T helper 2 cell frequencies [128].

Lactococcus lactis, mechanisms elucidated in vitro

In cultured HIEC, L. *lactis* FC significantly down-regulated IL-8 mRNA expression and inhibited NF-κB nuclear translocation [94], while L. *lactis* NCDO2118 was able to reduce IL-1β-induced secretion of IL-8 [71]. L. *lactis* ML2018, which also prevented DSS-induced colitis in mice, prevented the release of nitric oxide (NO) and the production of inflammatory factors induced by lipopolysaccharides (LPS) in RAW264.7 cells [69].

The above-mentioned immunostimulatory strain L. *lactis* GCWB1176, in RAW264.7 macrophages, induced phagocytic activity, increased the production of nitric oxide (NO) and expression of inducible NO synthase. Moreover, it increased the production of TNF-α, IFN-γ, IL-1β, IL-10 and IL-12 from mouse splenocytes and RAW264.7 cells and increased the transcriptional activities of NF-κ*B* and iNOS [50].

The MAMPS responsible for potential interactions between L. *lactis* and host cells, leading to immunomodulation, are yet unknown. A surface proteome analysis of a natural isolate of this bacterium however revealed the presence of pili able to bind to cultured HIECs [82]. Inactivation of the corresponding pilin gene abolished adhesion of L. *lactis* both to culture HIECs ad to intestinal mucus [63,82]. Interestingly, adhesion of L. *lactis* to epithelial cells was shown to inhibit, in a strain-dependent manner, both adhesion and internalization of pathogens such as *E. coli* and *Staphylococcus aureus* [1]. Milk fermented by *Lactococcus lactis* ssp. *cremoris* JFR1 moreover inhibited Salmonella invasion into intestinal epithelial cells [151]. Competitive exclusion of pro-inflammatory bacteria, or of components thereof, by L. *lactis* may explain, at least partly, its immunomodulatory effect.

Finally, some strains of L. *lactis* were shown to produce exopolysaccharides, which display immunomodulatory properties and may also participate to this effect. EPS produced by L. *lactis* Z-2, composed of rhamnose, xylose, mannose, glucose, and galactose, was reportedly able to modulate the immune responses *in vitro* and *in vivo* [33]. *In vitro*, it enhanced proliferation and phagocytosis activities ($P < 0.05$), induced production of nitic oxide (NO), pro-inflammatory cytokines (TNF-α, IL-1β, IL-6), and anti-inflammatory cytokines (IL-10, TGF-β) ($P < 0.05$) in fish head kidney cells. In line with this, in cyclophosphamide-immunosuppressed mice, EPS from L. *lactis* increased macrophage phagocytosis, spleen and thymus indices and haemolytic complement activity (HC(50)) [41].

Propionibacterium freudenreichii, demonstrated effects in vivo

A first report on immunomodulatory properties of *Propionibacterium freudenreichii* strains evidenced a highly strain-dependent ability to induce the anti-inflammatory IL-10 in human peripheral blood monocytes cells (PBMCs) [36]. In the same report, the most IL-10-inducing strains were further shown to protect mice from TNBS-induced colitis. This included attenuation of weight loss, of macroscopic Wallace, of colonic MPO, and of histopathological score. Moreover, consumption of *P. freudenreichii* delayed and attenuated the onset of colitis induced by the pathogen *Citrobacter rodentium*. Further screening on PBMCs identified the *P. freudenreichii* CIRM-BIA129 strain as the most immunomodulatory one [35]. This strain was used to generate a model single-strain cheese, which protected mice against TNBS-induced colitis [107]. It was further associated with a strain of L. *delbrueckii* to generate a two-strain model cheese which displayed the same protective effect [106]. Consumption of both cheeses, in a preventive way, prior to TNBS-induction, alleviated severity of symptoms, modulated local and systemic inflammation, as well as colonic oxidative stress and epithelial cell damages. By contrast, the corresponding sterile cheese matrix failed to afford such protection. An Emmental cheese was finally manufactured in industrial conditions, using *P. freudenreichii* CIRM-BIA129 as a ripening starter. Its consumption was then shown to reduce severity of DSS-colitis in mice [109]. This included reduction weight loss, of disease activity index and histological score, of small bowel immunoglobulin A (IgA) secretion, restored occludin gene expression and reduced induction of TNFα, IFNγ and IL-17. Another strain, P. freudenreichii KCTC 1063, also protected rats from DSS-induced colitis, by stimulating MUC2 expression (mucin 2, a high molecular weight glycoprotein which forms an insoluble mucous barrier that protects the gut lumen) in intestinal goblet cell [73]. This included reduced mRNA levels of typical pro-inflammatory cytokines and decreased inflammatory state, yet increased expression of MUC2 gene and protein.

In the case of mucositis, *P. freudenreichii* CIRM-BIA129, given in a preventive way, prevented weight loss and intestinal damages, reduced inflammation and histopathological scores in mice receiving 5-FU [20]. Furthermore, it regulated key markers, including Claudin-1, as well as IL-17a, IL-12 and IL-1β cytokines levels, restored goblet cells and prevented a dramatic increase in gut permeability (do [25]).

Propionibacterium freudenreichii, mechanisms elucidated in vitro

The immunomodulatory effect of P. freudenreichii seems multifactorial, involving both surface proteins and secreted components. In *P. freudenreichii* CIRM-BIA129, guanidine-extraction of surface layer proteins, as well as proteolytic shaving thereof, supressed such activity [36, 64]. In line with this, the guanidine-extract, enriched in surface layer proteins, was shown to induce IL-10 in a dose-dependent manner in human PBMCs [64] and in porcine ones [110]. Several mutants, affected in various surface proteins, were constructed. *P. freudenreichii* ΔslpB, devoid of the SlpB surface layer protein, failed to induce IL-10, while the wild type (WT) parental strain did. In another *in vitro* assay, *P. freudenreichii* WT reduced expression of IL-8 and of TNF-α in LPS-stimulated HT-29 HIECs, while *P. freudenreichii ΔslpB* failed to do so (do [25]). In line with this, the mutant strain failed to adhere to cultured HIECs and to protect mice from 5-FU-induced mucositis [25,27]. Moreover, heterologous expression of *P. freudenreichii slpB* enhanced the protective potential of L. *lactis* in mice with DSS-induced colitis [4].

Secreted compounds are also involved in P. freudenreichii anti-inflammatory properties. Indeed, its culture supernatant reduced the disease activity in DSS-treated rats [73]. A bifidogenic secreted compound, called BGS, was identified in P. freudenreichii ET-3 [111]. It was identified as 1,4-dihydroxy-2-naphthoic acid (DHNA), a precursor of menaquinone (vitamin K2), which is responsible for the bifidogenic and for the immunomodulatory effects of P. freudenreichii ET-3 culture supernatants [44]. DHNA attenuated DSS- induced colitis by modulation of bacterial flora and lymphocyte homing in mice [99]. It furthermore reduced inflammation in IL-10-deficient mice with colitis by suppressing macrophage-derived proinflammatory cytokines [100]. It was moreover identified as an activator of the aryl hydrocarbon receptor (AhR), activating the AhR pathway in cultured HIEC and in the mouse intestine [37]. In mice, it induced anti-microbial proteins RegIIIβ and γ in the intestine, altered gut microbiota and inhibited DSS-induced colitis.

What clinical studies say

As recently reviewed, human studies confirming the health benefits of fermented foods in humans are rare [116]. This constitutes an apparent incongruity, when considering the numerous evidences obtained in preclinical studies (see above). This is complicated by the fact that fermented foods are various and contain a wide variety of microbial ecosystems, while all the health properties were shown to be strain-dependent, within each microbial starter species.

Nonetheless, a clinical study pointed out to the fact that deprivation of fermented foods from the human diet has strong impacts on the human immune system, including a fall in innate immune response [102]. In this study, the fall of in the immune response, provoked by a wash-out period, was counteracted by a daily consumption of a standard yogurt containing a conventional starter. This revealed the significant impact of the daily consumption of fermented foods on human physiology.

Looking for a beneficial impact of fermented foods ingestion in healthy subjects resembles the quest for a holy grail. Clinical studies however indicated effects of yogurt consumption in subjects with metabolic and cardiovascular disorders, including obesity and overweight. In obese Chinese women with non-alcoholic fatty liver disease and metabolic syndrome, yogurt consumption decreased serum LPS, lipids, and biomarkers of inflammation and oxidative stress [16]. In overweight and obese people, yogurt reduced PBMCs expression of ROR-γt and serum levels of high-sensitivity C-reactive protein (hs-CRP) [150]. In the same category of subjects, yogurt decreased plasma concentration of TNF-α, while increasing soluble TNF-α receptor-1 (s-TNFR-1), indicating an impact on low-grade systemic inflammation [142]. Concerning healthy subjects, consumption of yogurt reduced postprandial inflammation and markers of endotoxin exposure in healthy premenopausal women [104,105]. Yogurt consumption was further associated with lower levels of chronic inflammation, including serum levels of IL-6 and fibrin, in both normal weight and overweight volunteers, in the Framingham Offspring study [148].

While yogurt is fermented by 2 bacterial species, *S. thermophilus* and L. *delbrueckii*, cheeses constitute a much more complex ecosystem, so that every cheese will develop different effects. This may explain why meta-analyses fail to evidence significant immunomodulatory effect of dairy products taken together, including milk, yogurt and cheeses. A review of clinical evidence, based on 52 clinical trials, defined an inflammatory score (IS), and confirmed an overall anti-inflammatory property of dairy products, taken together, in subjects with metabolic disorders [9]. The IS of the product category "fermented dairy products" indicated a beneficial anti-inflammatory effect, whatever the subject

category. Authors conclude on the possible anti-inflammatory effect of bacteria present in such fermented products. Indeed, different components of fermented dairy products appear to supress inflammatory response.

A Randomized Controlled Cross-Over Trial (RCT) further aimed at evidencing the difference between fermented and unfermented dairy products, within high-fat meals, with respect to PBMCs' expression of inflammation-related genes, as well as circulating inflammatory markers and metabolites [117]. Based on 47 healthy subjects, this RCT evidenced that expression of genes related to lymphocyte activation, cytokine signaling, chemokine signaling, and cell adhesion was differentially affected, according to the kind of product. Fermented products cheese and sour cream reduced, while non-fermented products butter and whipped cream increased expression of these genes. Authors conclude that intake of fermented dairy products, especially cheese, induces a less inflammatory postprandial PBMC gene expression response than non-fermented dairy products.

Finally, a systematic review of the literature dealing with the effects of dairy products and proteins intake on inflammation reported contradicting results. In this review, 10 cited trials reported no effect of the intake of dairy products (milk, cheese, and yogurt) on low-grade systemic inflammation in adults without severe inflammatory disorder. By contrast, eight reported a reduction in at least one biomarker of inflammation [93]. More RCT are thus needed to specify the role of different fermented dairy products, and of the microorganisms contained therein, in the management of inflammation.

In order to elucidate beneficial effects of probiotic starters in humans, pure cultures thereof, including model fermented milks, were also implemented in clinical trials. As an example, a randomized, double blind, placebo-controlled clinical study, performed on 80 knee osteoarthritis subjects, tested the impact of *S. thermophilus* TCI633 oral intake. This probiotic improved serum collagen type II C-telopeptide and serum CRP [72]. In another clinical trial, topical application of *S. thermophilus* improved the signs and symptoms characteristic of atopic dermatitis [24]. In an RCT, oral supplementation with L. *delbrueckii* subsp. *bulgaricus* 8481 was shown to enhance systemic immunity in elderly subjects [89]. This included increased blood NK cells, decreased IL-8, yet increased antimicrobial peptide hBD-2. In the same category of patients, L. *delbrueckii* subsp. *bulgaricus* OLL1073R-1 fermented milk was shown to increase the concentration of saliva IgA [144,145]. It moreover reduced the risk of infection in the elderly, increasing NK cell activity as well as enhancing the quality of life score [74]. L. *helveticus* Lafti L10 was shown in an RCT, to modulate mucosal and humoral immunity in elite athletes, increasing anti-*Enterococcus faecalis* IgG, as well as total IgA [83]. It further reduced the duration of respiratory infection in the same population [84]. Another strain, L. *helveticus* SBT2171, alleviated perennial allergic rhinitis in Japanese adults by supressing eosinophils in an RCT [147]. Immunomodulation was also confirmed in humans for L. *lactis*. Consumption of milk fermented by L. *lactis* JCM5805-activated plasmacytoid dendritic cells in an RCT, while enhancing the ability to produce interferons [131]. It was further shown to modulate immunity, reduce symptoms such as sneezing, and reduce cumulative days of fatigue in a male athletes RCT [61]. Moreover, consumption of a fermented milk containing L. *lactis* 11/19-B1 mitigated the severity of atopic dermatitis in children in a clinical trial [133]. Concerning *P. freudenreichii*, a pilot clinical study, performed on 12 ulcerative colitis patients, indicated that the bifidogenic growth stimulator, consisting in a dried whey culture of the ET-3 strain, improved the clinical activity index, as well as the endoscopic index [132], in line with *P. freudenreichii* immumodulatory properties evidenced *in vitro* and *in vivo* (see above). Finally, an RCT conducted on 62 healthy adults showed that the consumption of milk fermented by *P. freudenreichii* JS reduced the serum level of hsCRP [58].

Conclusion

The healing effect of LAB and PAB strains was clearly evidenced through the numerous *in vitro* and *in vivo* studies shown in the review. However, only elected strains, within each species, are exerting positive action of gut homeostasis. This strain-dependency implies screening numerous strains to find the rare *gem* and to explore the mechanisms underlying the complex multi-facet interactions between bacteria and host gut system. These multi facets include different MAMPS on the bacterial side, that are recognised also by different receptors on the host side, leading to many different mechanisms of regulation of the gut homeostasis. This requires to develop preclinical and clinical studies using more complex associations of strains with well-known healing effects. The next challenge will be to enhance synergistic effects by wisely combining strains able to trigger adapted ways to alleviate specific inflammatory symptoms such as IBD or IBS that are one of the main consequences of the lifestyle changes. Knowledge of these strains and of their effects opens avenues for developing targeted functional fermented foods, namely fermented dairy products.

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4. *PROPIONIBACTERIUM FREUDENREICHII* : UN ELEMENT DE REPONSE FACE AUX MICI ?

4.1. DEFINITION GENERALE

4.1.1. HISTORIQUE

Propionibacterium freudenreichii (*Pf*) a été décrit pour la première fois dans **l'emmental**, un fromage Suisse, par Orla Jensen et von Freudenreich qui ont montré le lien entre, d'une part la production d'acide propionique ou propionate, par ces bactéries et, d'autre part la formation de trous dans le fromage. Cette bactérie est principalement utilisée dans l'étape d'affinage de l'emmental.

4.1.2. DESCRIPTION

Le genre *Propionibacterium* fait partie de la famille des *Propionibacteriaceae* qui regroupe des espèces **laitières** et des espèces **cutanées** (Figure 33). Au sein des *Propionibacterium* on retrouve *Propionibacterium freudenreichii* subsp. *shermanii* et subsp. *freudenreichii* (Scholz et Kilian 2016).

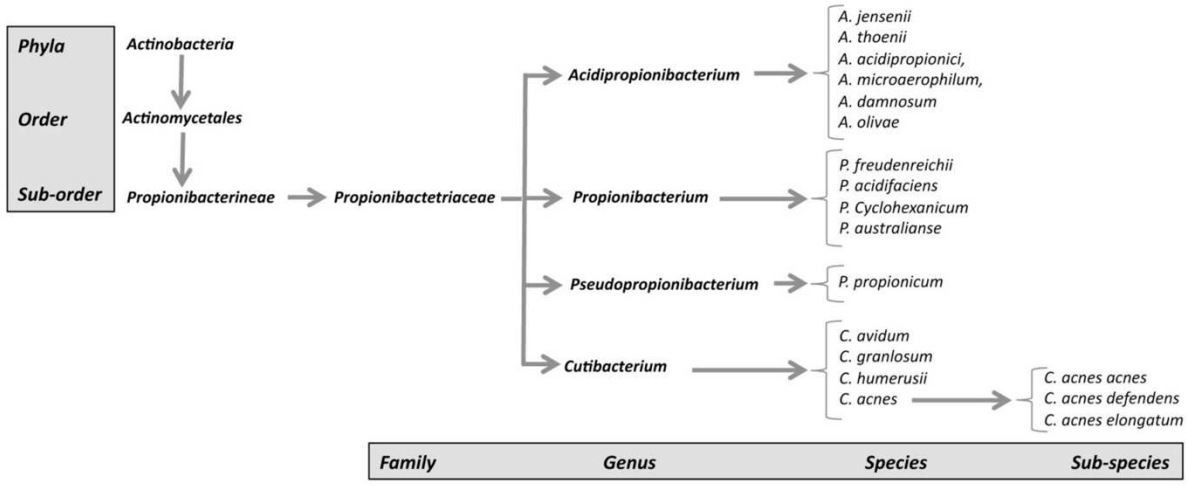


Figure 33. Taxonomie des *Proprionibacteriaceae* (Mayslich, Grange, et Dupin 2021).

Propionibacterium freudenreichii est une **actinobactérie** présente dans l'emmental, qui possède un statut GRAS (Generally Recognized as Safe) aux Etats-Unis, ainsi qu'un statut QPS (Qualified Presumption of Safety) en Europe. *Propionibacterium freudenreichii* est une actinobactérie à Gram positif, pléiomorphe, dont l'ADN présente un fort pourcentage en GC (caractéristique de l'ensemble des actinobactéries), mésophile, aérotolérante, non mobile et non sporulée, qui requiert de faibles besoins nutritionnels et survit dans des environnements hostiles (Rabah, Rosa Do Carmo, et Jan 2017). Elle est utilisée dans l'industrie comme levain d'affinage fromager, pour la production de vitamine B12, comme culture protectrice (antifongique en particulier) et comme bactérie probiotique.

4.2. PROBIOTIQUE

Comme indiqué précédemment, un **probiotique** est défini comme « un micro-organisme vivant qui, lorsqu'il est administré à des quantités adéquates, confère des effets bénéfiques sur la santé de l'hôte » (Sanders et al. 2019).

Certaines souches de *Propionibacterium freudenreichii* sont décrites comme des bactéries bénéfiques dites « **probiotiques** » ayant des effets sur le microbiote intestinal, ainsi qu'un potentiel anti-cancéreux et anti-inflammatoire. De plus, certaines souches survivent et restent métaboliquement actives dans le tractus gastro-intestinal (Lan et al. 2007; Huang, Kotula, et Adams 2003). *P. freudenreichii* est commercialisé comme constituant de compléments alimentaires probiotiques en France (Standa Industrie), en Finlande (Valio) et au Japon (Meiji).

4.2.1. MODULATION DU MICROBIOTE INTESTINAL

Propionibacterium freudenreichii peut agir directement sur le **microbiote intestinal** de l'hôte *via* la production de **facteurs bifidogènes** et la production de **bactériocines**.

Au Japon, des études sur des volontaires sains consommant quotidiennement un surnageant de culture de *P.freudenreichii* lyophilisé ont permis de montrer une amélioration de la constipation ainsi qu'une augmentation de la population de **bifidobactéries** dans les selles des individus (Hojo et al. 2002), sans favoriser la croissance d'aucune espèce considérée comme pathobiontes (Kaneko et al. 1994). De plus, aucun effet indésirable majeur n'a été rapporté lors d'une forte consommation (45 comprimés par jour !) de *P.freudenreichii* ni à court, ni à long terme, excepté une légère augmentation des ballonnements (Uchida et al. 2011). *In vivo*, la consommation de culture de *P.freudenreichii* semble également augmenter la population des bifidobactéries chez des porcelets sains (Rabah, Ferret-Bernard, et al. 2018). Les facteurs produits par *P.freudenreichii,* qui sont responsables de cet effet, sont l'acide 1,4-dihydroxy-2-acide naphtoïque (**DHNA**), un intermédiaire de biosynthèse de la vitamine K2, et la 2-amino-3-carboxy-1,4-napthoquinone (**ACNQ**). Le DHNA présente l'effet bifidogène le plus puissant (Isawa et al. 2002). De plus, le DHNA est un activateur du récepteur **AhR** impliqué dans la résolution de l'inflammation et sous-exprimé dans le côlon des patients atteints de MICI. L'activation de ce récepteur par le DHNA entraîne une production du **PAM de type lectine-C RegIII** dans le côlon de souris gavées avec du DHNA, expliquant également les effets décrits sur le microbiote intestinal (Fukumoto et al. 2014).

Cependant, les effets avancés de *P.freudenreichii* sur le microbiote intestinal sont modérés. Une étude chez la souris décrit une légère augmentation du phylum des Pseudomonadota après 5 jours de gavage avec du fromage contenant *Pf* CIRM-BIA 129 (Plé et al. 2015) et pas de changements au niveau de la richesse et la diversité du MI chez des porcelets sains (Cousin et al. 2012). Bien que des études aient montré quelques changements spécifiques dans la composition du microbiote intestinal, ceux-ci sont relativement limités. Néanmoins, dans des contextes pathologiques, *P.freudenreichii* semble avoir des effets positifs en contribuant à rétablir certaines populations bactériennes bénéfiques et en améliorant la diversité du microbiote. En effet, dans des modèles de colite, le contenu cécal de souris ayant reçu du DHNA dans l'eau de boisson permet de rétablir les populations de Lactobacillus, Enterobacteriaceae et de certains AGCC tel que le butyrate (Okada et al. 2006). De plus, *P.freudenreichii* améliore la diversité du microbiote intestinal en condition de CRC induites par l'azoxymethane

(AOM) chez le rat (Dikeocha et al. 2023). Enfin, *P.freudenreichii* induit l'augmentation de bactérie produisant des AGCC sur des dindonneaux infectés par la bactérie multirésistante Salmonella Heidelberg (Nair et al. 2021).

En somme, les résultats actuels indiquent que *P.freudenreichi* pourrait être un élément potentiellement bénéfique pour le microbiote intestinal, notamment en utilisant directement le DHNA qui serait alors un prébiotique. Cependant, il est important de noter que la majorité des études disponibles porte sur des modèles animaux, il reste un besoin crucial d'études cliniques sur l'Homme pour évaluer les effets spécifiques de *P.freudenreichii* et de ses métabolites sur le microbiote intestinal.

4.2.1. IMMUNOMODULATION

P. freudenreichii possède également des propriétés d'**immunomodulation**. Des études *in vitro* et *in vivo* suggèrent que cette bactérie module le système immunitaire intestinal et réduit l'inflammation dans un contexte de MICI. Dans des conditions physiologiques *in vivo*, *P.freudenreichii* entraîne un profil immunitaire de type **tolérogène** avec une augmentation du ratio Treg/Th17 et une diminution du ratio Th1/Th2 (Rabah et al. 2018). La consommation de ces bactéries dans des modèles de colite induite atténue la sévérité de la colite de manière **souche dépendante** en diminuant l'inflammation locale au niveau du côlon mais également systémique. De façon intéressante, les souches les plus aptes à induire la production d'interleukine-10 (IL-10), une cytokine anti-inflammatoire, chez des PBMCs sont les plus à même de protéger *in vivo* de la colite induite par le TNBS chez la souris (Foligné et al. 2010). C'est le cas de la souche CIRM-BIA 129.

4.2.2.1. PROTEINES DE SURFACE

Les propriétés d'immunomodulation de *P.freudenreichi* seraient en partie dues à ses protéines de surface, notamment les protéines de couche de surface, ou surface layer proteins, S-layer proteins (**Slps**). En effet, lorsque *P.freudenreichii* est privée de ces protéines, elle perd ses effets d'induction d'IL-10 sur les PBMCs. De plus, les Slp seules, extraites par la guanidine, sont capables d'induire la production d'IL-10 et d'IL-6 par les PBMCs (Le Maréchal et al. 2015; Rabah et al. 2018).

Les S-layer sont des structures paracristallines bidimensionnelles de macromolécules formées par des sous-unités de glycoprotéines, Slps, exposées en surface, présentes dans de nombreuses bactéries à Gram positif, négatif et archées (Assandri et al. 2023). Ces protéines sont très peu conservées et diffèrent entre les espèces. Elles ont un rôle dans la protection des bactéries contre les bactériophages, la résistance aux pH acides, l'adhésion etc. (Gerbino et al. 2015). Les Slps sont ancrées de manière non covalente à la paroi bactérienne, *via* des domaines d'homologie S-layer (SLH) pour les bactéries à Gram positif et sont associées au LPS pour les bactéries à Gram négatif (**Figure 34**). Les Slps font partie des MAMP qui sont reconnus par les PRR. Certaines études suggèrent que les Slps, qui sont glycosylées, sont reconnus par les récepteurs de type lectine-C (CLR), tels que SIGNR1, à la surface des cellules dendritiques (Colliou et al. 2017; Ge et al. 2020).

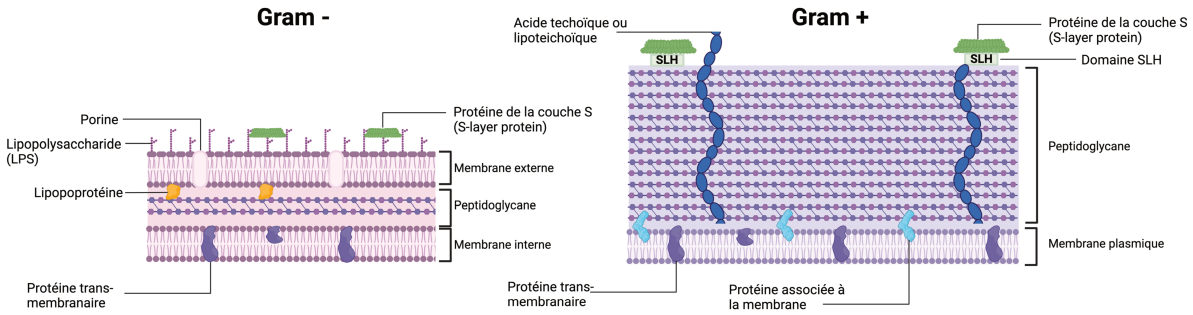


Figure 34. Les S-layer protéines chez les bactéries à négatif et positif (d'après Assandri et al. 2023). La paroi des bactéries à Gram négatif est composée d'une membrane externe reliée par des lipoprotéines à une fine couche de peptidoglycane. La membrane externe contient des porines, et des lipopolysaccharides qui sont exposés à la surface de la bactérie. Sous le peptidoglycane se situe la membrane interne. La paroi des bactéries à Gram positif est constituée de plusieurs couches de peptidoglycane, d'acide téichoïque et lipotéichoïque. Les Slp sont associées au LPS chez les Gram- alors que chez les Gram+ elles sont généralement associées à la couche de peptidoglycane ou à l'acide téichoïque via le domaine SLH.

Chez *P.freudenreichii* CIRM-BIA 129 il existe 7 gènes codants pour des protéines Slp putatives (Falentin et al. 2010), mais seules trois ont été identifiées par une analyse protéomique de la surface de cette bactérie (SlpA, SlpB et SlpE) (Le Maréchal et al. 2015). Lorsque les gènes codants pour SlpB et E sont inactivés la bactérie perd sa capacité à induire la sécrétion d'IL-10 par des PBMC humains, suggérant l'implication de ces protéines dans les effets immunomodulateurs de la bactérie (Deutsch et al. 2017). De plus, la souche 129 délétée du gène codant pour la protéine SlpB perd ses effets protecteurs dans un modèle de mucite. En effet, la souche mutante ne permet plus de diminuer le niveau d'IL-12 et d'IL1ß dans l'iléon des souris. Le ratio IL-10/IL-12 est considérablement diminué avec la souche mutante par rapport à la souche 129 sauvage dans l'iléon des souris ayant une mucite (do Carmo et al. 2019). Cependant, la mutation exerce des effets pléiotropes et affecte les propriétés (charge, hydrophobicité, tolérance au stress etc.) ainsi que le protéome de *P. freudenreichii* (do Carmo et al. 2018). Le clonage de la séquence codante pour la protéine SlpB dans *Lactococcus lactis* utilisé dans un modèle de colite lui confère un effet protecteur anti-inflammatoire caractérisé par une augmentation de l'IL-10, une diminution de l'IL-17, et de l'enzyme NOS (pour « nitric oxyde synthase ») induite par l'inflammation, dans un modèle de colite induite au DSS chez la souris. Ceci confirme le rôle majeur de SlpB pour contrer la colite *via* son action sur des marqueurs de l'inflammation et du stress oxydant (Belo et al. 2021). De plus, d'autres protéines de la couche de surface S-layer de *P.freudenreichii* ont été décrites comme ayant des effets immunomodulateurs. C'est le cas de la dihydrolipoamide acétyltransférase (**DlaT**), impliquée dans la décarboxylation du pyruvate. Cette protéine a été identifiée dans la souche commensale *Pf* UF1 isolée à partir des selles d'enfants prématurés nourris par allaitement. DlaT, ayant une forte affinité au CMH de classe II, favorise la différenciation des Th1 en Th17 en se fixant au CLR de type SIGNR1 à la surface des DC et protège contre l'infection à *Listeria monocytogenes*. De plus, *Pf* UF1 favorise la population des lymphocytes Treg et des ILC3 (Colliou et al. 2017). Enfin, **LspA** (pour large surface protein A), est une protéine de surface glycosylée par la

O-mannosyltransférase (Pmt1). Cette protéine, en interagissant avec SIGNR1 à la surface des DC protège contre une colite induite chimiquement chez la souris (Ge et al. 2020).

Il est important de noter que les propriétés anti-inflammatoires de *P.freudenreichii* résultent de la combinaison de composants de surface mais aussi intra-cellulaires tels que HsdM3. En effet, une inactivation du gène codant pour la protéine HsdM3, impliquée dans la modification de l'ADN, entraîne une réduction de la sécrétion de cytokines anti-inflammatoires par les PBMCs stimulées par la bactérie (Deutsch et al. 2017). De plus, la contribution relative aux effets anti-inflammatoires des protéines est souche dépendante. *P.freudenreichii* présente des propriétés anti-inflammatoires différentes entre les souches. Cette variabilité peut s'expliquer par le protéome différent entre les souches, la présence ou non d'exopolysccharides (EPS). En effet, les souches qui sont recouvertes d'une capsule expolysaccharidique n'induisent pas la libération d'IL-10 par les PBMC, globules blancs humains périphériques mononucléés. L'élimination de cette capsule par la mutation du gène *gtf*, impliqué dans sa biosynthèse, conduit à l'exposition de protéines de couche de surface et à la capacité à induire la libération d'IL-10 par ces cellules humaines (Deutsch et al. 2017). La variabilité inter-souche peut également s'expliquer par la capacité de production de **médiateurs solubles** (AGCC, vitamines etc.) par *P.freudenreichii*.

4.2.2.2. MEDIATEURS SOLUBLES

Le métabolisme fermentaire obligatoire de *P.freudenreichii* conduit à la production d'AGCC, en particulier **l'acétate** et le **propionate,** qui sont les métabolites primaires de cette fermentation. Ces deux AGCC ont la capacité d'augmenter l'apoptose de cellules cancéreuses de type HT-29 et sont des inhibiteurs des histone désacétylase (HDAC). L'inhibition des HDAC résulte en une augmentation de cytokines anti-inflammatoires et une inhibition de cytokines pro-inflammatoires (Cousin et al. 2016).

Comme décrit précédemment, *P.freudenreichii* produit également le métabolite secondaire **DHNA**, un activateur d'AhR. L'activation d'AhR par le DHNA diminue l'infiltration de macrophages dans le côlon de souris IL-10 -/- et réduit l'IL-6, une cytokine pro-inflammatoire (Okada et al. 2013).

P. freudenreichii peut également moduler l'activité métabolique par le biais d'une production d'autres métabolites bénéfiques. C'est le cas **des acides linoléiques conjugués** (ALC), qui sont des intermédiaires de bio-hydrogénation de l'acide linoléique (McIntosh et al. 2009). L'ALC naturellement présent de façon la plus abondante dans le lait est **l'acide ruménique** (RA). Le RA possède des effets anti-inflammatoires et anti-oxydants. En effet, une supplémentation en RA dans un modèle de colite induite chimiquement, diminue l'expression génique de l'IL-1ß dans le côlon et augmente la glutathion S réductase (GSR), une enzyme impliquée dans la production de glutathion essentiel à la résistance contre le stress oxydant et à la préservation du pH intracellulaire. Cette supplémentation protège les souris de la colite (Bergamo et al. 2017).

Propionibacterium freudenreichii est capable de produire certaines vitamines, notamment de la famille des vitamines B. En effet, elle synthétise de la **vitamine B12**, ou cobalamine, un co-facteur de la mutase methylmalonyl-CoA (Thierry et al. 2011). Les vitamines B sont hydrosolubles. Concernant la vitamine B12, une

déficience alimentaire de celle-ci résulte en une diminution des lymphocytes T cytotoxiques CD8+ ainsi qu'une suppression de l'activité des cellules NK chez la souris (Tamura et al. 2001).

4.2.2.3. VESICULES EXTRACELLULAIRES

Les vésicules extracellulaires (VEs) sont des structures sphériques nanométriques composées d'une bicouche lipidique, produites par tous types cellulaires. Ces VEs jouent un rôle crucial dans la communication inter-cellulaire *via* le transport de molécules bioactives telles que des protéines, acides nucléiques, lipides et métabolites (Rodovalho et al. 2020). Les VEs provenant des procaryotes sont de deux types. On distingue les vésicules membranaires externes (OMV pour outer membrane vesicles) produites par les bactéries à Gram négatif, et les vésicules cytoplasmiques (CMV pour cytoplasmic membrane vesicles) produites par les bactéries à Gram positif (Villard, Boursier, et Andriantsitohaina 2021). Les VEs de procaryotes sont impliquées dans la survie, la compétition, la pathogenèse et l'immunomodulation (Rodovalho et al. 2020).

Alors que le rôle des VEs a été principalement étudié dans le contexte des processus pathogènes, les recherches sur les VEs issues de souches probiotiques connaissent actuellement un essor prometteur. Pour citer quelques exemples, les VEs dérivés de *Bififobacterium longum* sont responsables de l'apoptose des mastocytes (Kim et al. 2016), tandis que celles dérivées de *Lacticaseibacillus rhamnosus* entraînent l'apoptose des cellules cancéreuses hepG2 (Behzadi, Mahmoodzadeh Hosseini, et Imani Fooladi 2017). La souche probiotique d'*E. coli* Nissle 1917 produit également des VEs impliquées dans la régulation de la réponse inflammatoire et l'homéostasie intestinale via la voie de signalisation NOD1 (Cañas et al. 2016).

Propionibacterium freudenreichii peut elle aussi produire des **vésicules extracellulaires**. C'est le cas de la souche CIRM-BIA 129 qui produit des VEs d'environ 85nm de diamètre. Ces VEs contiennent près de 319 protéines majoritairement cytoplasmiques, soit 11% du protéome de la souche 129. Parmi ces protéines, certaines protéines identifiées sont impliquées dans des fonctions immunomodulatrices, c'est le cas de SlpB, SlpE et InlA. Ces protéines de la couche de surface de Pf sont connues pour jouer un rôle clé dans l'interaction de ce probiotique avec l'hôte, y compris l'adhésion et la modulation de l'inflammation. Ceci suggère donc un rôle immunomodulateur des VEs de *Pf* CB 129. En effet, les VEs dérivées de *Pf* CB 129 inhibent l'activation de la voie de signalisation dépendante de NFkB, voie clé du processus inflammatoire. De plus, ces VEs inhibent la sécrétion d'IL-8 induite par l'inflammation dans les cellules épithéliales intestinales humaines HT-29 stimulées par du LPS, mais pas lors d'une stimulation par des cytokines pro-inflammatoires telles que le TNF-α et l'IL-1ß. De plus, les VEs dérivées de *Pf* CB 129 déficientes de la protéine SlpB, issue d'un mutant délété du gène *slpB*, réduisent partiellement l'activation de NFkB, suggérant l'implication d'autres molécules dans cet effet (Rodovalho et al. 2020). Ces résultats dévoilent les propriétés immunomodulatrices des VEs de *Propionibacterium freudenreichii*.

4.2.2. EFFETS SUR LA BEI

La plupart des études portant sur les propriétés protectrices de *P. freudenreichii* se concentrent sur ses propriétés immunomodulatrices et sa capacité à moduler le microbiote intestinal. La BEI est un acteur clé de l'homéostasie intestinale. Cependant, un nombre limité d'études abordent les effets de *P.freudenreichii* sur la barrière, mentionnant brièvement que l'administration *in vivo* de *P.freudenreichii* dans des modèles de colite entraîne une augmentation de l'expression génique de ZO-1, de l'occludine et des claudines-1 et -5 (Plé et al. 2015; Yang et al. 2022; Rabah et al. 2020; Belo et al. 2021). De plus, *P.freudenreichii* peut stimuler la production de mucus en augmentant la synthèse de la glycoprotéine MUC-2 et en préservant les cellules caliciformes (Belo et al. 2021; Ma, Yeom, et Lim 2020). Cette influence de *P.freudenreichii* sur le mucus semble être associée à la production de propionate par la bactérie. En effet, cet AGCC stimule la production de MUC-2 (Burger-van Paassen et al. 2009). Par ailleurs, *P.freudenreichii* CB 129 est capable d'adhérer aux cellules du côlon *in vitro* par l'intermédiaire de la protéine SlpB (do Carmo et al. 2017) suggérant un impact potentiel de la bactérie sur la BEI.

OBJECTIFS DE L'ETUDE

Les données de la littérature soulignent l'importance d'une **barrière fonctionnelle** dans l'homéostasie intestinale. Une **augmentation** de la **perméabilité** et des **défauts** de **réparation** de la BEI contribueraient à la pathogenèse des **MICI** en permettant le passage de molécules délétères qui alimenteraient l'inflammation, suggérant qu'un renforcement précoce de la BEI pourrait atténuer le développement de la pathologie. A l'heure actuelle, les traitements se concentrent sur le système immunitaire, c'est pourquoi de **nouvelles stratégies thérapeutiques** peuvent être envisagées pour réduire l'inflammation et moduler le microbiote en **ciblant la BEI**, en tant que premier point de contact avec l'environnement. En ce sens, des **bactéries propioniques laitières** sélectionnées sont capables de diminuer l'inflammation et réguler le microbiote intestinal, c'est le cas de souches **probiotiques** de l'espèce ***Propionibacterium freudenreichii***. En effet, cette bactérie est capable de prévenir l'apparition de colites chez la souris, notamment en diminuant l'inflammation et en modulant le microbiote intestinal. Toutefois, leurs **effets spécifiques** sur la **BEI** sont **inconnus**, à l'exception de leur aptitude à adhérer à des cellules épithéliales intestinales.

Ainsi, les **objectifs** de ce travail de thèse étaient :

1) De déterminer si des souches de ***P. freudenreichii*** étaient capables de **renforcer la BEI** dans un contexte d'inflammation, avec comme perspective son utilisation préventive ou thérapeutique dans les MICI.
2) D'investiguer les **mécanismes d'interaction** entre *P. freudenreichii* et l'hôte, en particulier avec la BEI.
3) De comprendre l'implication de la **matrice laitière** sur l'action du probiotique.
4) D'étudier les effets de **régimes** enrichis en **oméga 6** sur l'intestin et l'impact de souches lipolytiques de *P. freudenreichii* en combinaison avec de tels régimes.

Ce travail de thèse est présenté sous forme de trois articles. Le premier article a été publié dans *American Journal of Physiology-Gastrointestinal and Liver Physiology* en 2023, le second a été publié dans *Journal of Functional Foods* en 2023 et le troisième est en préparation.

Dans le premier article, nous avons démontré que la souche de référence *P. freudenreichii* CIRM-BIA129 protégeait contre une colite aigüe chimiquement induite chez la souris en diminuant la perméabilité intestinale. Nous avons identifié la protéine de surface SlpB comme un acteur clé dans la protection de la colite et le renforcement de la BEI *via* une restructuration des protéines des jonctions serrées. De plus, nous avons avancé que les vésicules extracellulaires de *P. freudenreichii* pourraient constituer un moyen efficace de fournir la protéine SlpB fonctionnelle pour réduire la perméabilité intestinale *in vitro*.

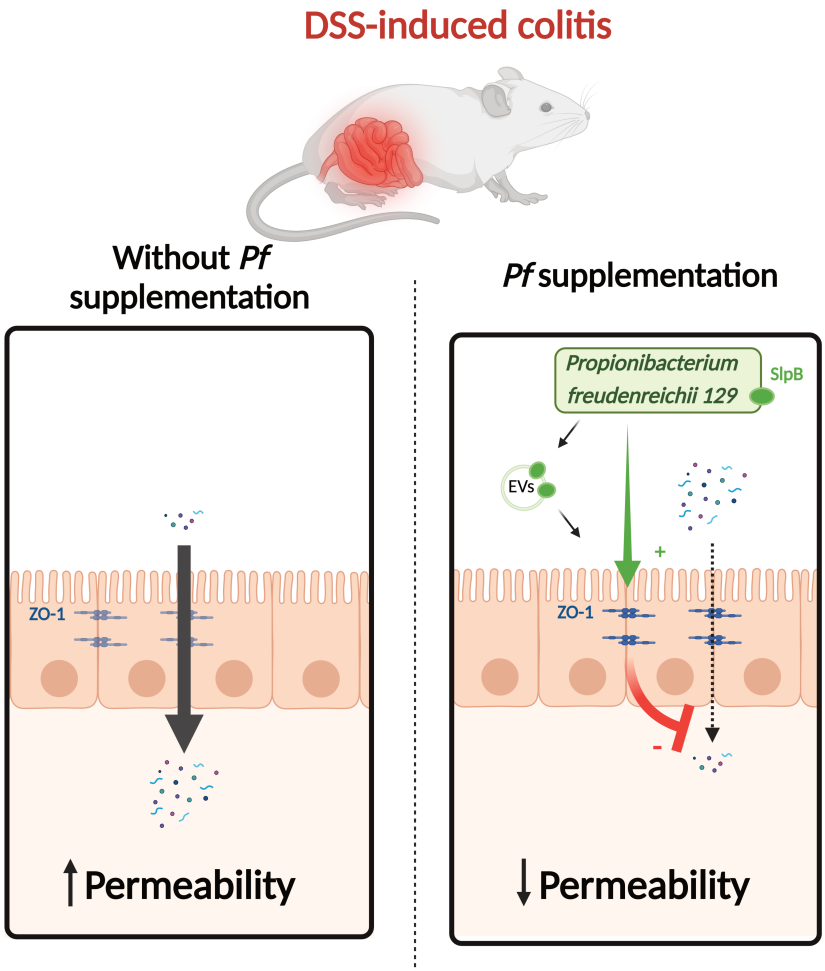
Dans le second article, nous avons mis en évidence que la matrice laitière renfermant le probiotique, et jouant le rôle de vecteur alimentaire de probiotique, avait un impact sur l'efficacité des effets anti-colite de *P. freudenreichii*. Nous avons étudié trois types de matrices laitières : i) le perméat d'ultrafiltration de lait, dépourvu

de protéines et de lipides, ii) le lait écrémé, dépourvu de lipides iii) et le lait entier, pourvu de protéines et de lipides, dans un modèle murin de colite. Les effets protecteurs de colite par *P. freudenreichii* étaient plus efficaces lorsque la bactérie était administrée dans du lait entier fermenté par cette bactérie.

Enfin, le troisième article a permis d'identifier une nouvelle souche de *P. freudenreichii* : CIRM-BIA508. Nous avons montré que cette souche protégeait les souris de la colite, améliorait la rémission en inhibant l'apoptose, modulant les protéines des jonctions serrées et favorisant les phénomènes de réparation. Tous ces éléments concouraient à la diminution la perméabilité et au renforcement de la BEI. De plus, nous avons mis en lumière que cette souche était capable de modifier le métabolisme lipidique de l'hôte en diminuant les médiateurs lipidiques pro-inflammatoires et en augmentant les médiateurs pro-résolutifs de l'inflammation. Enfin, notre étude a démontré que les effets protecteurs de la souche probiotique étaient perdus en présence d'un régime enrichi en oméga 6, soulignant l'importance de prendre en compte l'alimentation de l'hôte lors de la prise de probiotique.

Article 1

Propionibacterium freudenreichii CIRM-BIA 129 mitigates colitis through S layer protein B-dependent epithelial strengthening.



1. ARTICLE 1 : RENFORCEMENT DE LA BEI PAR *P. FREUDENREICHII* CIRM-BIA129 ET MECANISMES IMPLIQUES

Dans le contexte des MICI, l'homéostasie intestinale est altérée, les patients présentent une altération du SNE, une dysbiose du MI, une BEI fragilisée et un SI hyperactivé. Les traitements actuels ciblent préférentiellement le système immunitaire dans le but de réduire l'inflammation. Or, la BEI en tant que première ligne de défense de l'hôte est un élément majeur dans la pathogenèse des MICI. L'hyperperméabilité contribue aux MICI et est associée à une augmentation de la sévérité des symptômes (Chang et al. 2017). Il s'agit d'une caractéristique précoce de la pathologie qui peut survenir dans des zones non inflammées (Arrieta et al. 2006; Söderholm et al. 1999). Cette altération de la BEI n'est pas forcément dépendante de l'activation du SI, et permet le passage non sélectif et à haut débit des bactéries dans l'épithélium. Les défauts d'expression des protéines de jonction serrées contribuent à l'augmentation de la perméabilité. Comme discuté dans l'introduction, l'utilisation de probiotiques s'avère pertinente dans le contexte des MICI. *P. freudenreichii* module le microbiote intestinal, exerce une action anti-inflammatoire et protège de la colite et de la mucite *in vivo*, mais peu d'études s'intéressent à son impact sur la BEI (Rabah et al. 2020; do Carmo et al. 2019). Seules quelques études ont mis en évidence la capacité de la souche *P.f* CIRM-BIA129 à réguler des marqueurs de la BEI et à adhérer à des HT-29 *in vitro* (do Carmo et al. 2019; do Carmo et al. 2017).

Le but de ce travail était de savoir si la consommation quotidienne de façon préventive de *P. freudenreichii* CIRM-BIA 129 pouvait protéger de colite induite au DSS chez la souris, et plus précisément si elle pouvait protéger la BEI de l'inflammation.

Dans ce but, des souris C57Bl6 ont été gavées quotidiennement avec la souche *P.f* CIRM-BIA129 pendant 11 jours, au bout du 7ème jour de gavage, une colite aigüe a été induite au DSS 4% pendant 4 jours. Au 4ème jour la perméabilité intestinale a été évaluée et des marqueurs de l'inflammation et de la BEI ont été analysés au niveau du côlon des souris. Pour comprendre les mécanismes d'action de la souche *P.f* CIRM-BIA129 sur la BEI, des études *in vitro* ont été réalisés en utilisant des Caco-2.

Cette étude révèle que la souche de référence *P. freudenreichii* CIRM-BIA129 protégeait contre une colite chimiquement induite chez la souris en diminuant la perméabilité intestinale. Nous avons identifié la protéine de surface SlpB comme un acteur clé dans la protection de la colite et le renforcement de la BEI *via* une restructuration des protéines des jonctions serrées, en particulier ZO-1. De plus, nous avons avancé que les vésicules extracellulaires de *P. freudenreichii* pourraient constituer un moyen efficace de fournir la protéine SlpB fonctionnelle pour réduire la perméabilité intestinale *in vitro*.

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Propionibacterium freudenreichii CIRM-BIA 129 mitigates colitis through S layer protein B-dependent epithelial strengthening.

P. freudenreichii inhibits inflammation-induced epithelial break-down.

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ABSTRACT

The growing incidence of human diseases involving inflammation and increased gut permeability makes the quest for protective functional foods more crucial than ever. *Propionibacterium freudenreichii (P. freudenreichii)* is a beneficial bacterium used in the dairy and probiotic industries. Selected strains exert anti-inflammatory effects, and the present work addresses whether the *P. freudenreichii* CIRM-BIA129, consumed daily in a preventive way, could protect mice from acute colitis induced by dextran sodium sulfate (DSS), and more precisely whether it could protect from intestinal epithelial breakdown induced by inflammation.

P. freudenreichii CIRM-BIA129 mitigated colitis severity and inhibited DSS-induced permeability. It limited crypt length reduction and promoted the expression of Zonula Occludens-1 (ZO-1), without reducing *interleukin-1beta* mRNA (*il-1ß*) expression. *In vitro*, *P. freudenreichii* CIRM-BIA129 prevented the disruption of a Caco-2 monolayer induced by pro-inflammatory cytokines. It increased transepithelial electrical resistance (TEER) and inhibited permeability induced by inflammation, along with an increased ZO-1 expression. Extracellular vesicles (EVs) from *P. freudenreichii* CIRM-BIA129, carrying the surface layer protein (SlpB), reproduced the protective effect of *P. freudenreichii* CIRM-BIA129. A mutant strain deleted for *slpB* (ΔslpB), or EVs from this mutant strain, had lost their protective effects, and worsened both DSS-induced colitis and inflammation *in vivo*.

These results shown that *P. freudenreichii* CIRM-BIA129 daily consumption has the potential to greatly alleviate colitis symptomss and, particularly, to counter intestinal epithelial permeability induced by inflammation by restoring ZO-1 expression through mechanisms involving S-layer protein B. They open new avenues for the use of probiotic dairy propionibacteria and/or postbiotic fractions thereof, in the context of gut permeability.

NEW :
1. *P.freudenreichii* reduces DSS-induced intestinal permeability *in vivo*
2. *P.freudenreichii* does not inhibit inflammation but damages linked to inflammation
3. *P.freudenreichii* inhibits intestinal epithelial breakdown through S-layer protein B

NOTEWORTHY :
1. The protective effects of *P.freudenreichii* depends on S-layer protein B
2. Extracellular vesicles from P. freudenreichii CB 129 mimic the protective effect of the probiotic

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KEYWORDS
probiotic, inflammation, permeability, intestinal epithelium, zonula occludens-1

1. Introduction

Inflammatory bowel diseases (IBD) constitute a heterogeneous group of chronic inflammatory diseases including ulcerative colitis (UC) and Crohn's disease (CD), with a growing prevalence worldwide (Alatab et al. 2020). It involves immune response dysregulations, alterations of the enteric nervous system, gut microbiota dysbiosis, and intestinal epithelial barrier dysfunctions (Lê et al. 2022). Indeed, IBD patients exhibit aberrant immune responses such as infiltration of CD4+ T lymphocytes in the intestine, associated with a reduction in regulatory T (Treg) cells (Tindemans et al. 2020). The expression of enteric neuronal and glial markers is altered (Prigent et al. 2019; 2020; Le Berre et al. 2023) and glial cells have lost their functions in patients with CD (Pochard et al. 2016; Coquenlorge et al. 2016). In addition, a dysbiosis of the gut microbiota, characterized by a reduced bacterial diversity and alterations in the relative abundance of certain species were observed (Lê et al. 2022). At last, the intestinal epithelial barrier (IEB), serving as the first line of defense against the external environment, is failing. Indeed, there is increasing recognition of an association between disrupted IEB function and the development of inflammatory diseases. An increase in intestinal permeability occurs in IBD patients (Peeters et al. 1994; Pearson et al. 1982) and first-degree relatives of IBD patients (Munkholm et al. 1994). Increased permeability is often observed prior to relapse of CD (Wyatt et al. 1993). It is an aggravating factor in IBD, and the severity of symptoms is positively correlated with its extent (Chang et al. 2017). If increased permeability precedes inflammation (Arrieta et al. 2006), during inflammation, further barrier dysfunction can be induced by cytokines such as interferon-ɣ (IFN-ɣ) and tumor necrosis factor-α (TNF-α). This process is accompanied by changes in expression and/or redistribution of tight junction proteins such as the Zonula Occludens-1 (ZO-1), the occludin or the Claudin-2 (Turner et al. 2009). Interestingly, reducing barrier permeability prevents the development of inflammation in a genetic model of IBD (Arrieta et al. 2006). The strengthening or the re-establishment of IEB functions could therefore be interesting targets for approaches aiming at both prevention of relapses, and treatment of IEB-associated IBD dysfunctions.

Currently, the mainstays of IBD treatment are immunosuppressive and immune-modulating agents, and even protective functional foods are tested and developed for their anti-inflammatory properties (Lê et al. 2022). Beneficial bacteria, either ingested or members of the gut microbiota, may modulate gut inflammation through immunomodulation, engagement of an immune response and modulation of cytokines and of T-cells proliferation (Illikoud et al. 2022). Meta-analysis of clinical trials revealed the efficacy of selected probiotic strains, such as those constituting the VSL#3 product, in the context of IBD, while other strains failed to do so (Sniffen et al. 2018). In this context, promising immunomodulatory properties were reported for *Propionibacterium freudenreichii (P. freudenreichii),* an actinobacterium found in Swiss-type cheese, which holds a Generally Recognized as Safe (GRAS) status in the United States, as well as a Qualified Presumption of Safety (QPS) status in Europe. *P. freudenreichii* was shown to induce the modulatory cytokine IL-10 in human peripheral blood mononuclear cells, to mitigate the severity of TNBS-induced colitis and to counteract colonization of mice digestive tract by the rodent pathogen *Citrobacter rodentium* (Foligné et al. 2010). This property is highly *P. freudenreichii* strain-specific (Foligné et al. 2013), and depends on the presence of key surface layer proteins (Le Marechal et al. 2015), including SlpB, a main microbe-associated molecular patterns (MAMPs) involved in immunomodulation (Deutsch et al. 2017). In line with this, expression of *P. freudenreichii slpB* gene in *Lactococcus lactis* enhanced its ability

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to mitigate DSS-induced colitis in mice, further indicating the key role of the SlpB protein (Belo et al. 2021). More recently, *P. freudenreichii* was shown to prevent the inflammatory damages caused by the cancer chemotherapy drug 5-fluorouracyl, while the *slpB* mutant failed to do so. In this mucositis model, the wild-type *P. freudenreichii* reduced the dramatic increase in gut permeability which was induced by 5-fluorouracyl (do Carmo et al. 2019). SlpB is also involved in *P. freudenreichii* adhesion to intestinal HT-29 epithelial cells (do Carmo et al. 2017) suggesting that *P. freudenreichii* could exert a protective effect towards the gut epithelial barrier.

We thus investigated whether *P. freudenreichii* could mitigate mice colitis and in particular protect the intestinal epithelial barrier from damages induced by inflammation. We paid special attention to its protective effect towards tight junctions, and have analysed the involvement of the *P. freudenreichii* surface layer protein SlpB.

2. Materials and methods

Growth of dairy propionibacteria

The strain *Propionibacterium freudenreichii* CIRM-BIA 129 (*P. freudenreichii* CIRM-BIA129), was initially isolated from a Swiss-type cheese. It was provided by CNIEL (Centre National Interprofessionel de l'Economie Laitière) and maintained by the CIRM-BIA microbiological ressource center (Centre International de Ressources Microbiennes, Bactéries d'Intérêt Alimentaire, Rennes, France). Starting from a frozen stock, precultures were grown in liquid Yeast Extract Lactate (YEL) medium containing 0.1 M sodium DL-lactate (Sigma Aldrich, Saint Louis, USA) and 10 g/L yeast extract as described (Malik et al. 1968). *P. freudenreichii* CIRM-BIA129 was then grown at 30°C for 60 hours in milk ultra-filtrate (MUF) supplemented with 5 g/L casein peptone (casein peptone plus, Organotechnie, La Courneuve, France), 0.1M sodium DL-lactate filter-sterilized using a 0.2 µm NalgeneTop filter (Sigma-Aldrich, St. Louis, MO, USA). Propionibacteria were grown in agar-solidified media in anaerobic jars containing ATCO Biocult anaerobiosis generators (Laboratoires Standa, Cean, France). They were grown in liquid media in microaerophilic conditions in glass tubes with screw cap (2 thirds of volume occupied by liquid medium, one third by headspace air), at 30°C, without agitation. Regarding the knock-out strain *P. freudenreichii* CIRM-BIA129Δ*slpB*, YEL and MUF culture media were supplemented with chloramphenicol (10 µg/mL) as previously detailed in (do Carmo et al. 2018). For Caco-2 cells stimulation (see below), propionibacteria were centrifuged (10,000 x *g*, 10 min, 20°C), and resuspended in DMEM medium prior to addition to cell cultures.

DSS-induced colitis, *in vivo* DAI and permeability assessment

Eight-week-old C57Bl/6NRj male mice from Janvier Labs (Le Genest St Isle, France) were housed in a ventilated cage system under a 12-hours light-dark cycle and ad libitum access to food (SAFE A04) and drinking water. The experiments were carried out in strict accordance with the European Communities Council Directives 2010/63/UE on the use of laboratory animal. Mice were randomly divided into 4 groups of 14 animals: MUF, 129, DSS and 129DSS. Mice were gavaged daily either with 200 µL of MUF (MUF and DSS groups) or 200 µL of MUF fermented with *P. freudenreichii* CIRM-BIA129 at 1.10^8 CFU (129 and 129DSS groups) for 11 days. The last 4 days, colitis was induced by 4% (w/v) of Dextran Sulfate Sodium (DSS, colitis grade 36,000-50,000, MP Biomedicals, Eschwege, Germany) in drinking water renewed every day for the groups DSS and 129DSS. Animals were weighted daily and at the end of the protocol, mice received (5 µL/g of mouse) a solution comprising 30 mg/ml carmine red (cochineal carmine, Prolabo #22259), 10 mg/mL fluorescein-5,6-sulfonic acid (FSA, fluorescein-5-(and-6)-sulfonic acid, trisodium, F1130, In vitrogen), 100 mg

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Dextran TRITC (TRITC-dextran 4kDa, TdB Labs), and 10 mg/mL horseradish peroxidase (HRP; Peroxidase from horseradish, P8250, Sigma-Aldrich) resuspended in 0.5% carboxymethylcellulose in PBS (Sigma-Aldrich) *via* gavage, and then placed in individual cages. The Disease Activity Index (DAI) was determined as indicated in **Table 1**, according to the 3 main clinical symptoms of colitis: diarrhea, rectal bleeding, and weight loss, following a scoring previously described (Cooper et al. 1993). Four hours after gavage, blood was collected from the tail vein and permeability was evaluated in 5 µL of plasma. Paracellular permeabilities were evaluated *via* titration of FSA and TRITC-dextran fluorescence intensity measured at 487 nm and 520 nm, respectively, using an automatic microplate reader (BioTek Synergy H1, microplate reader). Transcellular permeability to HRP was measured using an enzymatic activity assay with 3,3′,5,5′-tetramethylbenzidine reagent (TMB Substrate Reagent Set, 555214, BD Biosciences). Mice were killed at the end of the protocol by cervical dislocation. Colonic tissues were collected and snap frozen for further quantification of gene transcripts and of proteins, or were also fixed for 24 hours in 4% paraformaldehyde for histopathological analysis. This procedure was repeated 3 times independently.

Histopathological score

After fixations, distal colons were dehydrated and embedded in paraffin. Sections of 5 µm were stained with haematoxylin–phloxine–saffron (HPS) or Alcian Blue (MicroPICell platform, Nantes, France) for histopathological analysis. Images were taken using a slide scanner (Nanozoomer; Hamamatsu). As previously described, distal colonic tissue damage was evaluated by two investigators in a blinded manner through the calculation of a micro disease activity index (mDAI) which reflects the destruction of mucosal architecture, the cellular infiltration, muscle thickening and goblet cells depletion (Pochard et al. 2021). The scoring for the destruction of mucosal architecture was as follows: 0-3 (0: none, 1: 1/3 basal, 2: 2/3 basal, and 3: loss of crypt and epithelium). The extent of cellular infiltration was rated on a scale of 0-3 (0: none, 1: infiltrate around crypt basis, 2: extensive infiltration reaching the muscularis mucosae, and 3: infiltration of the submucosa). The degree of muscle thickening was also ranging from 0 to 3, when the thickening was none, mild, moderate, or extensive thickening, respectively. The loss of goblet cell depletion was scored as 0 (normal presence) or 1 (massive depletion). A multiplication factor of 1–4 was applied for each measured criteria, depending on the extent of affected area (25, 50, 75, or 100%) of the considered sample. Crypt length was considered by measuring the length of 50 opened crypts/animal.

Lipocalin-2 enzyme-linked immunosorbent assay faecal quantification

The feces of each mouse were resuspended in a solution of PBS-Tween 20 0.1% protease inhibitor cocktail (1/2 tablet for 25 mL solution, cOmplete; Roche, France) to reach 100 mg feces/mL. Lcn-2 in the faecal solution was measured using an enzyme-linked immunosorbent assay (ELISA) kit (Mouse Lcn-2/NGAL DuoSet ELISA; Bio-Techne), according to the manufacturer's protocol.

Caco-2 culture

The human IEC line Caco-2 was obtained from American Type Culture Collection (Manassas, VA) and cultured in Dulbecco modified Eagle medium containing 4.5 g/L glucose (Gibco, Life Technologies, Carlsbad, CA) supplemented with 10% heat-inactivated fetal calf serum, 2 mmol/L glutamine, 100 IU/mL penicillin, and 100 µg/mL streptomycin. For treatments, transepithelial electrical resistance (TEER) and permeability experiments, 116.071 cells/cm^2 were seeded onto Transwell Permeable Supports (Costar, REF 3460) and grown for 21 days.

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Guanidine extraction and purification of surface layer proteins

Propionibacteria were cultivated in MUF as described above and harvested in late stationary phase, after 72 hours of culture. They were then harvested by centrifugation (10,000 x *g*, 10 min, 20°C), washed in PBS and resuspended in 5 M guanidine hydrochloride (20% of the initial culture volume). The bacterial suspension was incubated 15 min at 50°C prior to centrifugation (20,000 x *g*, 20 min, 20°C). The supernatant was then extensively dialyzed against distilled water (20 L) and then against PBS (5 L) using a Slide-A-Lyzer Dialysis Cassette (Thermo Scientific) with a 10 kDa Cut-Off.

Purification of EVs and Nanoparticle Tracking Analysis for EV size and concentration determination.

To extract and purify extracellular vesicles derived from *P. freudenreichii* CIRM-BIA129 and from its Δ*slpB* isogenic mutant (*P. freudenreichii* CIRM-BIA129 Δ*slpB*), the bacteria were pelleted by centrifugation (6,000 x *g*, 20 min, room temperature) of a 1 L culture and the supernatant fraction was filtered using a Nalgene 0.22 µm top filter (Thermo Scientific) to remove bacteria. Then, the supernatant was concentrated 1,000 times using Amicon ultrafiltration units with 100 kDa cut-off point through successive centrifugations at 2,500 g x *g*. The concentrated suspension of EVs was recovered in 500 µL of TBS buffer (Tris-Buffered Saline, 150 mM NaCl; 50 mM Tris-HCl, pH 7.5) prior to purification by size exclusion chromatography. Qevoriginal columns (qEV original 70 nm; iZON) were equilibrated with TBS and used according to the manufacturer's recommendations (Böing et al., 2014). The concentrated EV suspension (500 µL) was applied to the top of the chromatographic column and allowed to run into the column. 10 mL of TBS were then added on top of the column, prior to elution. Then, fractions of 500 µL were recovered in separate tubes. This chromatography step was conducted as previously described (Rodovalho et al. 2020) and EVs were reproducibly detected by NTA (see below) and by protein quantification in fractions 7 to 9. Finally, EVs-containing fractions (fractions 7-9) were pooled together, and the remaining fractions were discarded due to protein contamination or low EV content. To measure the size and concentration of EVs, nanoparticle tracking analysis (NTA) was performed at 25.0°C using a NanoSight NS300 instrument (Malvern Panalytical) with a CMOS camera and a Blue488 laser (Mehdiani et al., 2015). Samples were diluted to reach a concentration in the range 10^7 to 10^8 particles/mL, giving rise to 20 to 110 particles per frame. Samples were applied at 25°C in constant flux with a syringe pump speed of 50 µL/s. For each measurement, 5 x 60-s videos were recorded with camera level 15. Other parameters were adjusted accordingly to achieve image optimization.

Caco-2 treatments, TEER, and Permeability Measurement *In Vitro*

To determine the effect of propionibacteria, sodium-pyruvate (#11360070 ThermoFisherScientific), propionibacteria'supernatant, Slp, (enriched extracts of S-layer proteins), EVs or inflammation on intestinal epithelium, the TEER was measured before and after treatments with an epithelial voltohmmeter (EVOM; World Precision Instruments, Inc, Sarasota, FL). Caco-2 cells were stimulated for 24 hours with either *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129Δ*slpB* (MOI 1:100), or S-layer protein enriched extracts (10-200 µg/mL), and EVs from *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129Δ*slpB* at a concentration of 10^7 particles/mL in DMEM medium (0% FBS, 1% P/S) in the apical compartment or sodium-pyruvate (0.1-10 mM) in DMEM medium (10%FBS, 1% P/S) in the basolateral compartment. After 24 hours, an inflammatory stimulation was induced with a cytomix containing 50 ng/mL of TNF-α (human TNF-α, 50 µg, 130-094-017, Milteny Biotec) and 500 ng/mL of IFN-ɣ (human IFN-g1b, 1,000 µg, 130-

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096-486, Milteny Biotec) in 0% FBS in the apical compartment as well as in 10% FBS in the basolateral compartment, for 6 days with a renewal on day 3. To determine the effect of these treatment on permeability, 50 µL of the apical medium was replaced by 50 µL of 1 mg/mL of sulfonic acid FITC, 6 mg/mL of dextran 4 kDa TRITC and 3 mg/mL of HRP. The fluorescence level of basolateral aliquots (150 µL) was measured every 30 min for a period of 180 min using a fluorimeter (BioTek Synergy H1, microplate reader). Paracellular permeability was determined by averaging the slope change in fluorescence intensity over time by linear regression fit model. To assess transcellular permeability to HRP (Peroxidase from horseradish, P8250, Sigma-Aldrich), an enzymatic activity assay with TMB (TMB Substrate Reagent Set, 555214, BD Biosciences, France) was performed.

mRNA and protein extractions

Proximal colons from mice were lysed in RA1 buffer (Macherey-Nagel) with the Precellys 24 tissue homogenizer (Bertin Technologies, Montigny-le-Bretonneux, France), and total RNA and protein extraction was performed with a Nucleospin RNAII kit according to the manufacturer's recommendations. For Caco-2 filters, cells were lysed in ice-cold RIPA Lysis buffer (20-188, Merk) complete with protease inhibitor (66373700, Merk), a phosphatase inhibitor cocktail (P0044, Sigma) and sodium orthovanadate (S6508, Sigma).

Quantitative real-time PCR analysis

One microgram of purified mRNA was denaturated and processed for reverse transcription using Superscript III reverse transcriptase (Life Technologies). qPCR amplifications were performed using FastSYBR Green Master Mix kit (Applied Biosystems, Foster City, CA, USA) and run on a StepOnePlus system (Life Technologies). The primers used are listed in **TABLE S2** (DOI 10.6084/m9.figshare.24542629). Ribosomal protein S6 (RPS6) transcript was used as a reference gene. The relative transcript level of the gene of interest was measured by the $2^{-\Delta\Delta Ct}$ method.

Western Blot

For proximal colon, proteins were resuspended in 1:1 protein solving buffer and tris(2-carboxyethyl) phosphine-reducing agent (PSB-TCEP, Macherey-Nagel), sonicated and denatured for 5 min at 95°C. For Caco-2 filters, cells were washed with ice-cold PBS and lysed in ice-cold 1X RIPA buffer complete with protease inhibitor (Roche, France) and serine-threonine phosphatase inhibitor (Sigma-Aldrich) cocktails and completed with NuPAGE™ LDS Sample Buffer 4X (NP0008, Invitrogen) and NuPAGE™ Sample reducing agent 10X (NP0009, Invitrogen), sonicated and denatured for 10 min at 70°C. Fifteen micrograms of proteins were separated using NuPAGE™ 4-12% Bis-Tris or NuPAGE™ 3-8% Tris-Acetate gels (Life Technologies, Villebon sur Yvette, France) and transferred to nitrocellulose membranes (Life Technologies, Villebon sur Yvette, France). After blocking with Tris-buffered saline/0.1% Tween-20/5% nonfat dry milk for 30 min, blots were incubated overnight at 4°C with the primary antibodies (**Table S1**, DOI 10.6084/m9.figshare.24542629) diluted in Tris-buffered saline/5% nonfat dry milk.

Immunoblots were probed with HRP-conjugated anti-rabbit (Life technologies, 1:5,000) or anti-mouse secondary antibodies (Sigma, 1:5,000) and visualized by chemiluminescence (Clarity Western ECL Substrate, 170-5061, BioRad or Femto Maximum Sensitivity Substrate, 34095, Thermofisher) using a ChemiDoc MP Imaging System (Bio-Rad). Western Blot data are expressed as relative values to ß-actine and normalized to the control mean.

Organic acid quantification

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To identify whether soluble mediators are responsible for the *P. freudenreichii* CIRM-BIA129 effects dependent on the SlpB protein on the Caco-2 barrier, organic acids present in the apical and basolateral culture media at the end of the IEB-disruption protocol were analysed by High Performance Liquid Chromatography UltiMate 3000 (HPLC, Thermofisher, Les Ulis, France). Culture media were diluted 2-fold in 0.005 M H_2SO_4, prior to centrifugation (7500 × *g* for 15 min at 4 °C), and filtration (chromafil Xtra PVDF 45/13, Macherey Nagel, Düren, Germany). HPLC analysis was then conducted using a Rezek ROA organic acid H + column (300*7.8 mm, Phenomenex, California), with 0.005 M NH_2SO_4 as mobile phase, and a flow rate of 0.4 mL/min at 60°C. A UV detector (DIONEX-UVD 170U, Sunnyvale, California) operating at 210 nm, as well as a refractometer (RI 2103 Plus Jasco, Tokyo, Japan) were used. External calibration was used for quantification. Standards of lactic, citric, propionic, butyric, succinic, and pyruvic acids were purchased from Merck (St. Quentin Fallavier, France, and acetic acid from PanReac, Lyon, France).

Statistical analysis

Results were expressed as mean +/- SEM. Outliers were excluded using Grubbs' tests. Statistical significance was analyzed by an ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test, with a single pooled variance or a Kruskal-Wallis test, followed by a Dunn's multiple comparisons test (GraphPad Prism 9). Differences between experimental groups were considered significant at *p<=0.05, ** p<=0.01, *** p<=0.001 or p<=0.0001.

3. Results

***P. freudenreichii* CIRM-BIA129 reduces DSS-induced colitis severity and intestinal permeability *in vivo*.**

For *in vivo* assessment of *P. freudenreichii* CIRM-BIA129 ability to prevent colitis, acute colitis was induced by the addition of 4% DSS for 4 days to the drinking water of 8–10-weeks-old male supplemented, or not, with the *P. freudenreichii* CIRM-BIA129 for 11 days (Figure 1A). The colitis was characterized by an increased disease activity index (DAI) in the DSS as well as in the 129DSS groups compared to the MUF group (Figure 1B), but *P. freudenreichii* CIRM-BIA129 supplementation (129DSS group) significantly reduced the DAI score by about 50% compared to the DSS group (Figure 1B). The DAI was composed of three parameters: the bleeding and the stool consistency scores, and the weight change. *P. freudenreichii* CIRM-BIA129 supplementation inhibited DSS-induced increase in bleeding and stool consistency scores, but did not change the weight loss (Suppl Fig 1 ; DOI 10.6084/m9.figshare.24542629). The paracellular permeability measured *in vivo* by sulfonic acid (0.4 kDa) passage in mice plasma was also increased in the DSS and in the 129DSS groups compared to the MUF group, but again significantly less in the 129DSS group than in the DSS group (Figure 1C). The transcellular permeabilities measured *in vivo* by HRP (44 kDa) in mice plasma tended to be increased in the DSS group (p-value=0.0653) and was significantly lower in the 129DSS compared to the DSS group (Figure 1D). The histopathological score, reflecting the remodeling of the distal colon (cellular infiltration, muscle thickening, epithelial destruction), was significantly increased in the DSS as well as in the 129DSS groups compared to the MUF group (Figures 1E and F). The crypt length was reduced in the DSS group but not when mice were supplemented with the *P. freudenreichii* CIRM-BIA129 (Figure 1G). Under basal conditions, *P. freudenreichii* CIRM-BIA129 supplementation has had no impact on the measured parameters (Figures 1B-G). Altogether, these results show that *P. freudenreichii* CIRM-BIA129 is safe and has the potential to alleviate the severity of colitis and to maintain intestinal barrier function such as permeability.

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***P. freudenreichii* CIRM-BIA 129 promotes ZO-1 protein remodeling without reducing inflammation.**

To investigate in more details whether *P. freudenreichii* CIRM-BIA129 supplementation impacted the intestinal epithelium and/or inflammatory processes, the amount of tight junctions (TJ) proteins, as well as of inflammatory cytokines, were evaluated in the mice proximal colons and the release of a marker of intestinal injury (fecal concentration of Lcn-2 for neutrophil gelatinase-associated Lcn) was measured in stools. Western-blot analyses have shown that *P. freudenreichii* CIRM-BIA129 supplementation significantly increased the expression of the Zonula Occludens-1 (ZO-1) in the absence of colitis and through a tendency under DSS-induced colitis conditions with a noticeable variability within the samples (Figure 2A, 2B). Neither DSS nor 129 has modified the expression of occludin, another TJ protein (Figure 2A, 2C). Regarding the expressions of genes encoding pro- and anti-inflammatory cytokines, DSS treatment significantly up-regulated the level of *il-1ß* transcripts and tended to decrease *il-10* ones (Figure 2D, 2F), but had no impact on *tnf-α* transcripts (Figure 2E). Fecal Lcn-2 concentration was increased in the DSS and 129DSS groups compared to the MUF group (Figure 2G). *P. freudenreichii* CIRM-BIA129 supplementation did not modify these markers, neither in control, nor in DSS condition (Figures 2D, 2E, 2F, 2G). Overall, these findings support the hypothesis that *P. freudenreichii* CIRM-BIA129 mitigates the severity of DSS-induced colitis through its action on IEB, and in particular ZO-1 expression, rather than on inflammation.

***P. freudenreichii* CIRM-BIA 129 inhibits inflammation-induced IEB breakdown through S-layer protein B induction of ZO-1 expression.**

To analyse more specifically the regulation of intestinal epithelium permeability by the propionibacteria, an *in vitro* IEB model was challenged with inflammation with or without pre-treatment with the *P. freudenreichii* CIRM-BIA129 (Figure 3A). As *P. freudenreichii* CIRM-BIA129 anti-inflammatory effects (do Carmo et al. 2019) and it's adhesion to HT29 colonic cells (do Carmo et al. 2017) involved the S-layer protein B (SlpB), an isogenic mutant deleted for the *slpB* gene (*P. freudenreichii* CIRM-BIA129Δ*slpB*) was also tested in this protocol. After 24 hours of incubation with the bacteria and a full culture medium replacement, *P. freudenreichii* CIRM-BIA129 adhesion to Caco-2 monolayer was observed using Gram staining (Figure 3B). This adhesion was greatly reduced when using the *P. freudenreichii* CIRM-BIA129 Δ*slpB* (Figure 3B). No living bacteria have been observed at the end of the protocol (data not shown). Without inflammation, *P. freudenreichii* CIRM-BIA129 significantly lowered TEER compared to untreated cells, but has no impact on permeabilities (Figures 3C, 3D, 3E). After 6 days, inflammation significantly reduced the TEER (Figure 3C), increased the paracellular permeability to sulfonic acid-FITC (Figure 3D) and increased the transcellular permeability to HRP (Figure 3E). Pre-incubation with the *P. freudenreichii* CIRM-BIA129 prevented these three changes (Figures 3C, 3D, 3E). In contrast, *P. freudenreichii* CIRM-BIA129 Δ*slpB* failed to inhibit these inflammation-induced IEB failures (Figures 3C, 3D, 3E), and even increased the permeabilities induced by inflammation (Figures 3D, 3E). To investigate the molecular mechanisms sustaining these effects, the expressions of TJ proteins such as ZO-1 and occludin were analysed by western-blot. Inflammation significantly reduced both ZO-1 and occludin protein expression, while *P. freudenreichii* CIRM-BIA129 prevented the decrease of ZO-1 expression induced by inflammation but had no effect on occludin expression (Figures 3F, 3G, 3H). Conversely, *P. freudenreichii* CIRM-BIA129 Δ*slpB* was unsuccessful in restoring ZO-1 expression (Figures 3F, 3G). Taken together, these data provide evidence that *P. freudenreichii* CIRM-BIA129

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inhibits IEB breakdown induced by inflammation by maintaining ZO-1 expression in a SlpB dependent manner.

Organic acid productions do not explain the *P. freudenreichii* protective effect on inflammation-induced IEB breakdown.

To assess whether soluble factors such as short chain fatty acids could be involved in SlpB-dependent effect of *P. freudenreichii* CIRM-BIA129 upon intestinal epithelium, organic acid concentrations were measured in the apical (Figure 4A) and basolateral (Figure 4B) compartments of our *in vitro* model of inflammation-induced IEB disruption. Acetate and propionate concentrations are increased by *P. freudenreichii* CIRM-BIA129 Δ*slpB* but not *P. freudenreichii* CIRM-BIA129 in apical and basolateral compartments without impact of inflammation (Figures 4A and 4B). Glucose concentrations were decreased by *P. freudenreichii* CIRM-BIA129, *P. freudenreichii* CIRM-BIA129 Δ*slpB* or inflammation in apical and basolateral compartments (Figure 4A and 4B). Inflammation-induced lactate concentrations are inhibited by *P. freudenreichii* CIRM-BIA129 Δ*slpB* in apical and basolateral compartments (Figures 4A and 4B). Inflammation-induced decreased 2-pyrrolidone-5-carboxylic acid concentration is decreased by *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129 Δ*slpB* in apical compartment and increased by *P. freudenreichii* CIRM-BIA129 Δ*slpB* in the basolateral compartments (Figures 4A and 4B). Pyruvate concentration in the apical compartment was increased by *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129 Δ*slpB* and only by *P. freudenreichii* CIRM-BIA129 in the basolateral compartment (Figures 4A and 4B). None of the concentrations were correlated with the changes of permeability observed, but as pyruvate concentrations were increased in basolateral compartment by *P. freudenreichii* CIRM-BIA129 but not *P. freudenreichii* CIRM-BIA129 Δ*slpB*, we have tested if it could contribute to *P. freudenreichii* CIRM-BIA129 inhibition of inflammation-induced permeability. None of the tested concentrations were efficient in modulating Caco-2 permeability (Figure 4C). Beyond SCFAs, *P. freudenreichii* CIRM-BIA129 has the ability to generate other soluble mediators. To investigate the potential involvement of the bacterial-released soluble mediators, we evaluated *P. freudenreichii* CIRM-BIA129 supernatant in our *in vitro* model. The supernatant did not exhibit any protective effect against the inflammation-induced increase in permeability (Figure 4D). These data suggest that SlpB-dependent effect of *P. freudenreichii* CIRM-BIA129 upon epithelial permeability does not involve soluble mediators released by the bacteria.

Extracellular vesicles from *P. freudenreichii* CIRM-BIA 129 containing the SlpB protein are efficient to inhibit inflammation-induced IEB breakdown

To further explore the direct contribution of SlpB in reinforcing the IEB, enriched extracts of S-layer proteins (Slp) were tested in our *in vitro* model of inflammation-induced IEB disruption. Various concentrations of Slp, ranging from 10 µg/mL to 200 µg/mL, failed to inhibit the increase in paracellular permeability induced by inflammation, that remained significantly increased except for high concentration (Figure 5A). Nevertheless, this method is insufficient to conclude about the inability of isolated SlpB to modulate the permeability, as (i) guanidine chloride extraction samples also contain other proteins, and (ii) Slps are poorly soluble, forming aggregates in aqueous environments (do Carmo et al. 2018). Therefore we produced and tested extracellular vesicles (EVs) from *P. freudenreichii* CIRM-BIA129 that are known to contain the well-conformed SlpB protein (Rodovalho et al. 2020), and compared their effects to that of EVs produced from strain *P. freudenreichii* CIRM-BIA129 Δ*slpB*. The productions of EVs were verified by nanoparticle tracking analysis (NTA) to control the similar size profile and adjust the concentrations before treating Caco-2 cells (Figures 5B and

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5C). EVs derived from *P. freudenreichii* CIRM-BIA129, but not from *P. freudenreichii* CIRM-BIA129 Δ*slpB*, successfully inhibited the increase in paracellular permeability to sulfonic acid-FITC caused by inflammation (Figure 5D). These findings highlight the essential role of SlpB in barrier protection by *P. freudenreichii* CIRM-BIA129.

Deletion of SlpB surface protein exacerbates colitis.

To confirmed the necessity of SlpB in *P. freudenreichii* CIRM-BIA129 protective effect *in vivo*, induction of colitis was induced by DSS in mice supplemented with *P. freudenreichii* CIRM-BIA129 Δ*slpB*. The mutant strain had no effect on DAI score increased by DSS (Figure 6A). It exhibited a tendency to raise paracellular permeability to sulfonic acid-FITC compared to DSS condition (Figure 6B) and significantly elevated the transcellular permeability to HRP compared to the DSS condition (Figure 6C). Moreover, *P. freudenreichii* CIRM-BIA129 Δ*slpB* did not changed the level of *il-1ß* transcripts and exacerbated the increase in transcript levels of *tnf-α* mRNA induced by DSS (Figures 6D and 6E). Surprisingly, *il-10* transcripts were increased in the presence of *P. freudenreichii* CIRM-BIA 129Δ*slpB* compared to the DSS condition (Figure 6F). These data show *slpB* deletion not only abrogated *P. freudenreichii* CIRM-BIA129 protection but also exacerbated colitis through an increased inflammation and permeability.

4. Discussion and conclusion

Disruption of intestinal epithelial barrier (IEB) plays a central role in the pathogenesis of IBD and stands as a pivotal target for effective IBD therapies (Chang et al. 2017). This study demonstrated that the anti-inflammatory dairy bacterium *P. freudenreichii* CIRM-BIA129 strain can counter inflammation-induced barrier disruption *in vitro* and *in vivo*. It revealed that through the expression of the surface protein SlpB, the *P. freudenreichii* CIRM-BIA129 maintains the expression of the tight junction protein ZO-1, thereby strengthening the IEB *in vitro* and *in vivo*.

P. freudenreichii is widely recognized for its anti-inflammatory properties (do Carmo et al. 2019; Ma et al. 2020), both *in vitro* and *in vivo*, through the regulation of immune cells but also epithelial cells. Indeed, probiotic bacteria can interact with dendritic cells and with intestinal epithelial cells, leading to anti-inflammatory effects of specific strains (Sniffen et al. 2018). *P. freudenreichii* enhances the production of IL-10 by human peripheral blood mononuclear cells and reduces the levels of TNF-α and IL-8 induced by lipopolysaccharide stimulation of epithelial HT-29 cells (do Carmo et al. 2019; Foligné et al. 2010). In the present study, *P. freudenreichii* CIRM-BIA129 exerted no significant effect on inflammation *in vivo* in a mice model of acute colitis, but had a major impact upon the gut barrier function. *P. freudenreichii* CIRM-BIA129 was shown to specifically target the intestinal epithelium to enhance one of its major function, the control of permeability. This complements previous studies showing the adhesion of *P. freudenreichii* CIRM-BIA129 to HT-29 cells and describing its capacity to protect the IEB in a mucositis model (do Carmo et al. 2019). Other probiotic such as *Lactiplantibacillus plantarum* (formely *Lactobacillus plantarum*) may also protect the intestinal epithelial barrier through the regulation of the expression of key tight junction proteins such as claudin-1, occludin, and ZO-1 (Wang et al. 2018). *P. freudenreichii* CIRM-BIA *129* can also enhance the mRNA expression of ZO-1 (Deutsch et al. 2017; Le Maréchal et al. 2015; Rabah et al. 2018; do Carmo et al. 2017) and we have further demonstrated here that *P. freudenreichii* CIRM-BIA129 also induces ZO-1 protein expression.

The IEB cytoskeletal integrity, survival and apoptosis are regulated by probiotics through key bacterial surface components named microbe-associated molecular patterns

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(MAMPs), which are recognized by corresponding host pattern recognition receptors (PRR) (Lebeer et al. 2010) as well as soluble factors (Capurso et al. 2019; Yan et al. 2012). The mechanism by which *P. freudenreichii* strengthens IEB seems to exclude soluble factors, as bacterial supernatants did not reproduce the bacterial effect, and none of the organic acid present in apical or basolateral epithelial sides were correlated with the permeability observed. Surprisingly, the supernatant contains EVs, although in all likelihood, their quantity is insufficient to mediate the protective effects of *P. freudenreichii.* However, we have demonstrated that *P. freudenreichii* CIRM-BIA129 adheres to Caco-2 cells, and induces ZO-1 protein expression in a SlpB-dependent manner. It should be noted that this *in vitro* effect relies on propionibacteria and on their surface components, yet not on an active metabolism, which is not possible in the conditions of these *in vitro* co-incubations. Other bacterial probiotic species, including lactobacilli, were already shown to possess surface layer proteins involved in probiotic/host interactions. As an example, *Lactobacillus acidophilus* binds to dendritic cells C-type lectin SIGNR3 and, regulates immature dendritic cells and T cells functions, mitigating gut inflammation as well as mucosal barrier function in mice, thanks to a specific surface layer protein (Konstantinov et al. 2008; Lightfoot et al. 2015). We previously showed that SlpB was involved in and necessary to the *P. freudenreichii* probiotic effect (Deutsch et al. 2017; Le Maréchal et al. 2015; Rabah et al. 2018; do Carmo et al. 2017). Herein, we focused our study on IEB and showed that SlpB reinforces the barrier, as strain lacking *slpB* gene have lost their protective effect upon inflammation-induced IEB disruption. However, it is important to acknowledge that the mutant strain exhibits pleiotropic effects on the bacteria itself (do Carmo et al. 2018). In the present study, in addition to the loss of SlpB, we evidenced the remodeling induced by SlpB deletion through the major change induced in organic acid productions. The increased production of acetate and propionate by the *P. freudenreichii* CIRM-BIA129 Δ*slpB* in comparison to the wild type strain *P. freudenreichii* CIRM-BIA129 could explain the aggravating effect of the bacteria upon permeability and inflammation. But to focus and identify whether isolated SlpB could be responsible of the probiotic effect of *P. freudenreichii* CIRM-BIA129, we have treated epithelial monolayer with a guanidine extract enriched in *P. freudenreichii* surface layer proteins, but it had no effect. This observation does not imperatively mean that isolated SlpB are not enough to induce the probiotic effect, but rather than SlpB, although it is not a transmembrane protein, must interact with a lipid bilayer to be well conformed and operational. Slps are known for their capacity to aggregate, after extraction, forming paracrystalline structures different in the guanidine extract than on the surface of propionibacteria envelope (do Carmo et al. 2018). In a consistent manner, the heterologous expression of *slpB* in *Lactococcus lactis* NCDO 2118 that confers probiotic potential to the strain to alleviate DSS-induced colitis in mice (Belo et al. 2021).

Our work mainly observed the regulation of the IEB by *P. freudenreichii*, shedding light on the significant role of epithelium dysfunction into colitis development. However, it is equally surprising to note the absence of any discernible anti-inflammatory effects, emphasizing the crucial role of the matrix. Indeed, we have already demonstrated the role of the dairy matrix in the modulation of *P. freudenreichii* probiotic activity. The cheese matrix was shown to protect the immunomodulatory SlpB protein from digestive proteolysis (Rabah et al. 2018), and the presence of dairy fat in the fermented product potentiates the anti-colitis effects of the probiotic strain (Mantel et al. 2023). In the present work we gave *P. freudenreichii* in milk ultra-filtrate supplemented with casein peptone and sodium DL-lactate, that seems unsuitable to support anti-inflammatory effect. Further studies are necessary to determine to which extend the matrix composition is crucial for the bacterial strain, or for the host, to obtain optimal effects. Another strategy could be to deliver and to trigger of the probiotic effects in a matrix-independent-way. Our study also shows that EVs

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are efficient vehicles to mimic the protective effect of *P. freudenreichii* upon inflammation-induced IEB disruption. They have previously been shown to reduce inflammation in cultured human intestinal cells by modulating the NF-κB pathway (Rodovalho et al. 2020), and could be efficient to protect the IEB as well as to damper inflammation. It opens new avenues for the definition of preventive strategies against chronic diseases involving intestinal barrier hyperpermeability and inflammation, avoiding the drawbacks associated with the use of live bacteria.

Finally, the research work presented here was performed on model systems which are still distant from clinical situations. The Caco-2 cell line is a cancer cell line different from healthy human colon epithelial cells and DSS-colitis in mice only mimics inflammatory conditions. However, this work, in addition to previous data using human PBMCs, HT-29 cells, Caco-2 cells, TNBS-colitis, DSS- colitis and 5-FU mucositis constitute a body of converging indications pointing at the anti-inflammatory potential of selected strains of *P. freudenreichii*. Pilot clinical studies further suggest the interest of this probiotic bacterium in the context of inflammatory conditions (Suzuki et al. 2006). However, further clinical investigations are needed to precise the future use of propionibacteria in live biotherapeutic applications.

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LEGENDS TO THE FIGURES

Figure 1. *P. freudenreichii* CIRM-BIA129 mitigates DSS-induced colitis severity and reduces intestinal permeability *in vivo*. (A) Eight-week-old C57BL6 mice were gavaged during 11 days with milk ultra-filtrate (MUF) or MUF fermented by *P. freudenreichii* CIRM-BIA129(129) containing 1.10^8 CFU. At day 7, 4% DSS was added to drinking water or not. On day 11, permeabilities were measured, mice sacrificed, and the tissues collected. (B) Disease activity index (DAI) of the 4 groups: control (MUF) or *P. freudenreichii* CIRM-BIA129 (129) in control conditions (grey) or with DSS (DSS and 129DSS in orange) at day 11. (C) Paracellular and (D) transcellular permeabilities evaluated by measurement of sulfonic acid and HRP in animal plasma 4 hours after mice gavage, respectively. (E) Representative images of Alcyan Blue staining of the distal colon. (F) Histological scores (mDAI) quantifying the destruction of mucosal architecture, cellular infiltration, muscle thickening and loss of goblet cells. (G) Crypts length measured for 50 opened crypts per animal. Data represent mean +/- SEM of 14 mice per group.

Figure 2. *P. freudenreichii* CIRM-BIA 129 promotes tight junction protein remodeling without reducing inflammation. (A) Representative Western blot analysis of ZO-1, occludin (OCLN) and ß-actin. (B) Quantification of ZO-1, and (C) occludin expression normalized to β-actin and relative to control mean. Quantification of transcript levels of (D) *il-1ß*, (E) *tnf-α,* and (F) *il-10* measured at day 11 in the proximal colon of the four groups. Relative expression

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was determined using *Rps6* as reference gene. Both protein and transcript levels were normalized to control mean. (G) Fecal lipocalin contents were measured at day 11.

Figure 3. *P. freudenreichii* CIRM-BIA129 inhibits inflammation-induced IEB breakdown through S-layer protein B induction of ZO-1 expression. (A) Caco-2 cells grown on transwell for 21days were left untreated or pre-treated with *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129 Δ*slpB* (MOI 100:1) for 24 hours before removal and treatment with an inflammatory cytomix containing TNF-α and IFN-ɣ was added for 6 days, with a renewal at day 3. (B) Gram staining of *P. freudenreichii* CIRM-BIA129 culture. The top-left image showed the bacteria in its fresh state; top right showed Caco-2 cells without any bacteria were the pore filter are visible; down-left, Caco-2 cells after 24hours with *P. freudenreichii* CIRM-BIA129; down-right, Caco-2 cells after 24hours with *P. freudenreichii* CIRM-BIA129 Δ*slpB*. (C) Trans-epithelial electrical resistances (TEER), (D) Sulfonic acid-FITC diffusion (E) HRP diffusion were measured at the end of the experiment. (F) Representative western blot analysis of ZO-1, occludin (OCLN) and ß-actin amounts. (G) Quantification of ZO-1 and (H) OCLN expressions normalized to β-actin and relative to control mean (Ct grey). Values are expressed as means +/- SEM.

Figure 4. Organic acid productions do not explain the *P. freudenreichii* CIRM-BIA129 protective effect on inflammation-induced IEB breakdown. Caco-2 cells grown on transwell for 21 days were left untreated or pre-treated with *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129 Δ*slpB* for 24 hours before removal and treatment with an inflammatory cytomix containing TNF-α and IFN-ɣ was added for 6 days, with a renewal at day 3. Impact of *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129 Δ*slpB* on the concentrations of different SCFAs was measured (A) at the apical and (B) basolateral compartments at the end of the experiment. Caco-2 cells grown on transwell for 21days were left untreated or pre-treated with the indicated concentrations of sodium-pyruvate at the basolateral side for 24 before removal and treatment with an inflammatory cytomix described above was added for 6 days, with a renewal at day 3. (C) Sulfonic acid-FITC diffusion was measured at the end of the experiment. Caco-2 cells were left untreated or pre-treated with the *P. freudenreichii* CIRM-BIA129's supernatant for 24 h before removal, and treatment with an inflammatory cytomix described above was added for 6 days, with a renewal at day 3. (D) Sulfonic acid-FITC diffusion was measured at the end of the experiment. Data are expressed as means +/- SEM.

Figure 5. Extracellular vesicles from *P. freudenreichii* CIRM-BIA 129 containing the SlpB protein are efficient to inhibit inflammation-induced IEB breakdown. Caco-2 cells grown on transwell for 21days were left untreated or pre-treated with the indicated concentrations of S-layer protein extracts from *P. freudenreichii* CIRM-BIA129 for 24h before removal and treatment with an inflammatory cytomix containing TNF-α and IFN-ɣ was added for 6 days, with a renewal at day 3. (A) Sulfonic acid-FITC diffusion was measured measured at the end of the protocol. (B) Size distribution (nm) and concentrations (particle/mL) of purified EVs from *P. freudenreichii* CIRM-BIA129 and (C) *P. freudenreichii* CIRM-BIA129ΔSlpB measured by nanoparticle tracking analysis. (D) Caco-2 cells grown on transwell for 21days were left untreated or pretreated with EVs from *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA129ΔSlpB (10^7 particles/well) for 24 hours on the apical side and then challenged or not with TNF-α and IFN-ɣ on the apical and basolateral side for 6 days, with a renewal at day 3. Sulfonic acid-FITC diffusion were measured at the end of the experiment. Data are expressed as means +/- SEM and normalized to control mean.

Figure 6. Deletion of SlpB surface protein exacerbates colitis. (A) Disease activity index (DAI) of the 3 groups (control, DSS and *P. freudenreichii* 129ΔSlpB+DSS) at day 11. (B) Paracellular and (C) transcellular permeabilities evaluated by measurement of sulfonic acid and HRP in animal plasma 4 hours after mice gavage. (D) Quantification of transcript levels

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of *il-1β* (E) *tnf-α*, and (F) *il-10* measured at the end of the protocol in proximal colon of the four groups. Relative expression was determined using *Rps6* as reference. Values are expressed as means +/- SEM.

Supplemental Figure 1. *P. freudenreichii* CIRM-BIA129 mitigates DSS-induced colitis severity *in vivo*. Eight-week-old C57BL6 mice were gavaged during 11 days with milk ultra-filtrate (MUF) or MUF fermented by *P. freudenreichii* CIRM-BIA129(129) containing 1.10^8 CFU. At day 7, 4% DSS was added to drinking water or not. On day 11, permeabilities were measured, mice sacrificed and the tissues collected. (A) Bleeding score (B) stool consistency and (C) weight change before/after DSS of the 4 groups: control (MUF) or *P. freudenreichii* CIRM-BIA129 (129) in control conditions (grey) or with DSS (DSS and 129DSS in orange) at day 11.

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Table 1. Disease Activity Index.

Score	Weight loss (%)	Stool consistency	Occult/Gross bleeding
0	<1%	Normal	Negative
1	1-5%		Stain
2	5-10%	Loose	Occult blood
3	10-15%		
4	>15%	Diarrhea	Gross bleeding

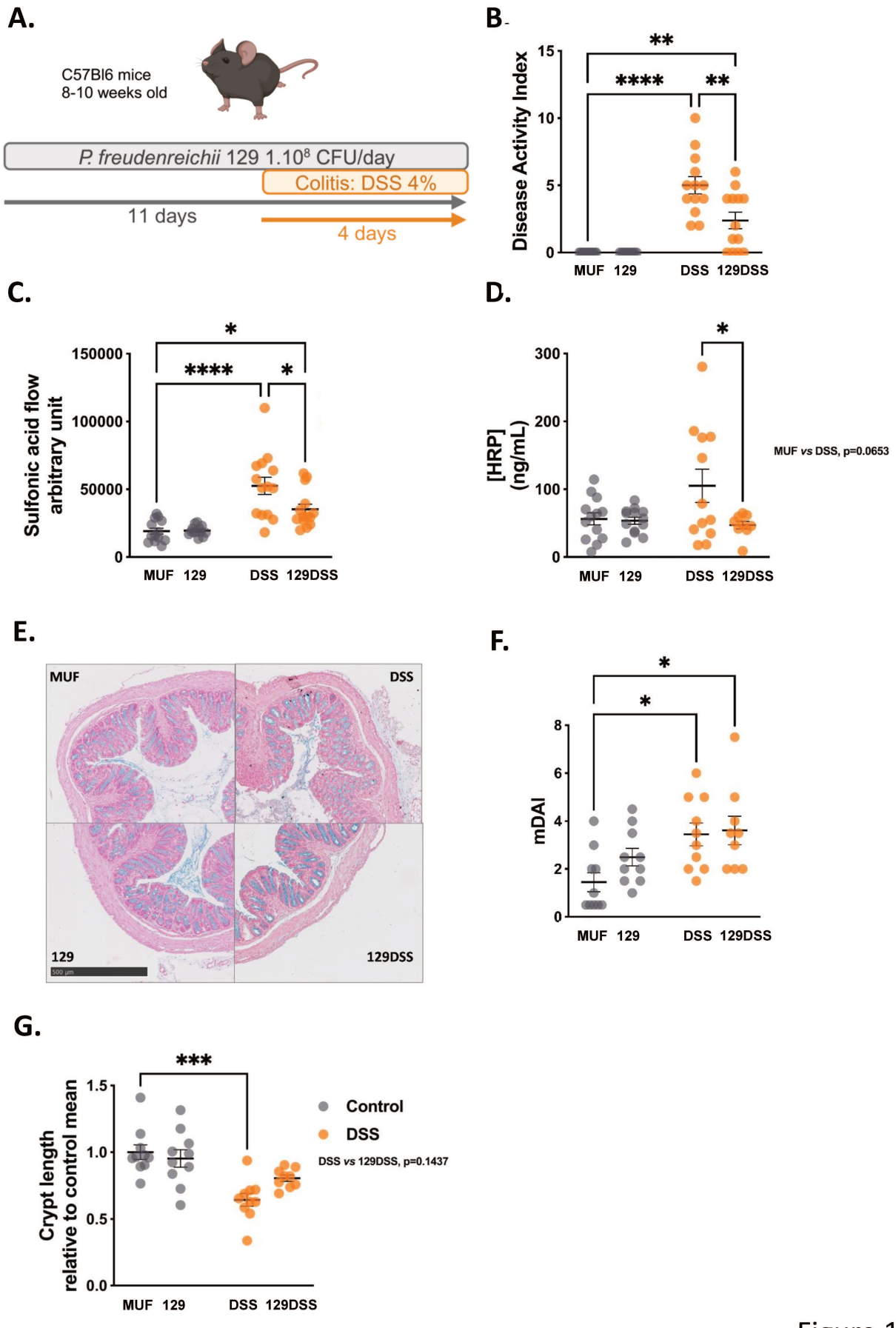
A.
C57Bl6 mice
8-10 weeks old
P. freudenreichii 129 1.10⁸ CFU/day
Colitis: DSS 4%
11 days
4 days
B.
Disease Activity Index
MUF 129 DSS 129DSS
C.
Sulfonic acid flow arbitrary unit
MUF 129 DSS 129DSS
D.
[HRP] (ng/mL)
MUF vs DSS, p=0.0653
MUF 129 DSS 129DSS
E.
MUF
DSS
129
129DSS
F.
mDAI
MUF 129 DSS 129DSS
G.
Crypt length relative to control mean
Control
DSS
DSS vs 129DSS, p=0.1437
MUF 129 DSS 129DSS

Figure 1

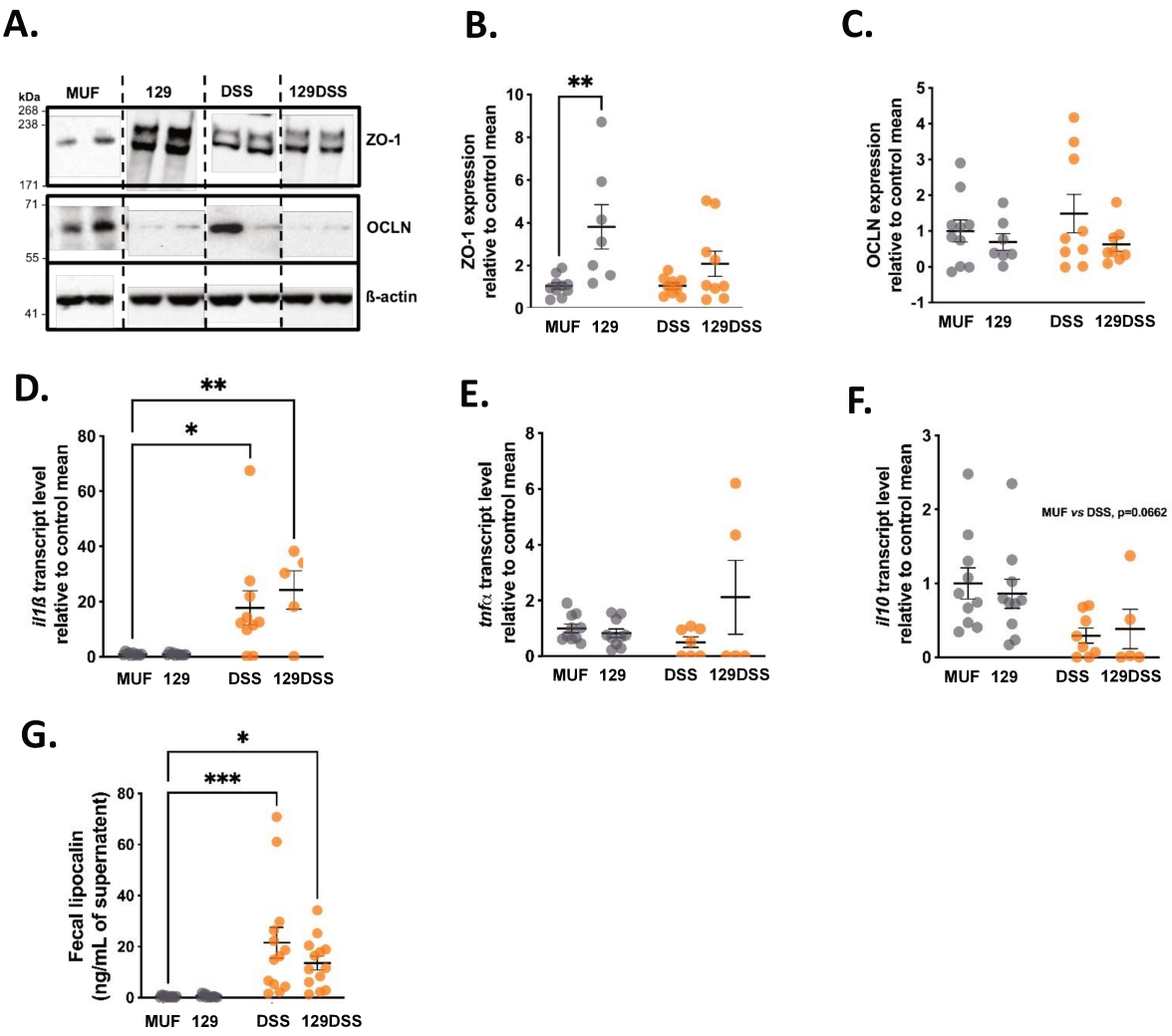

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Figure 2

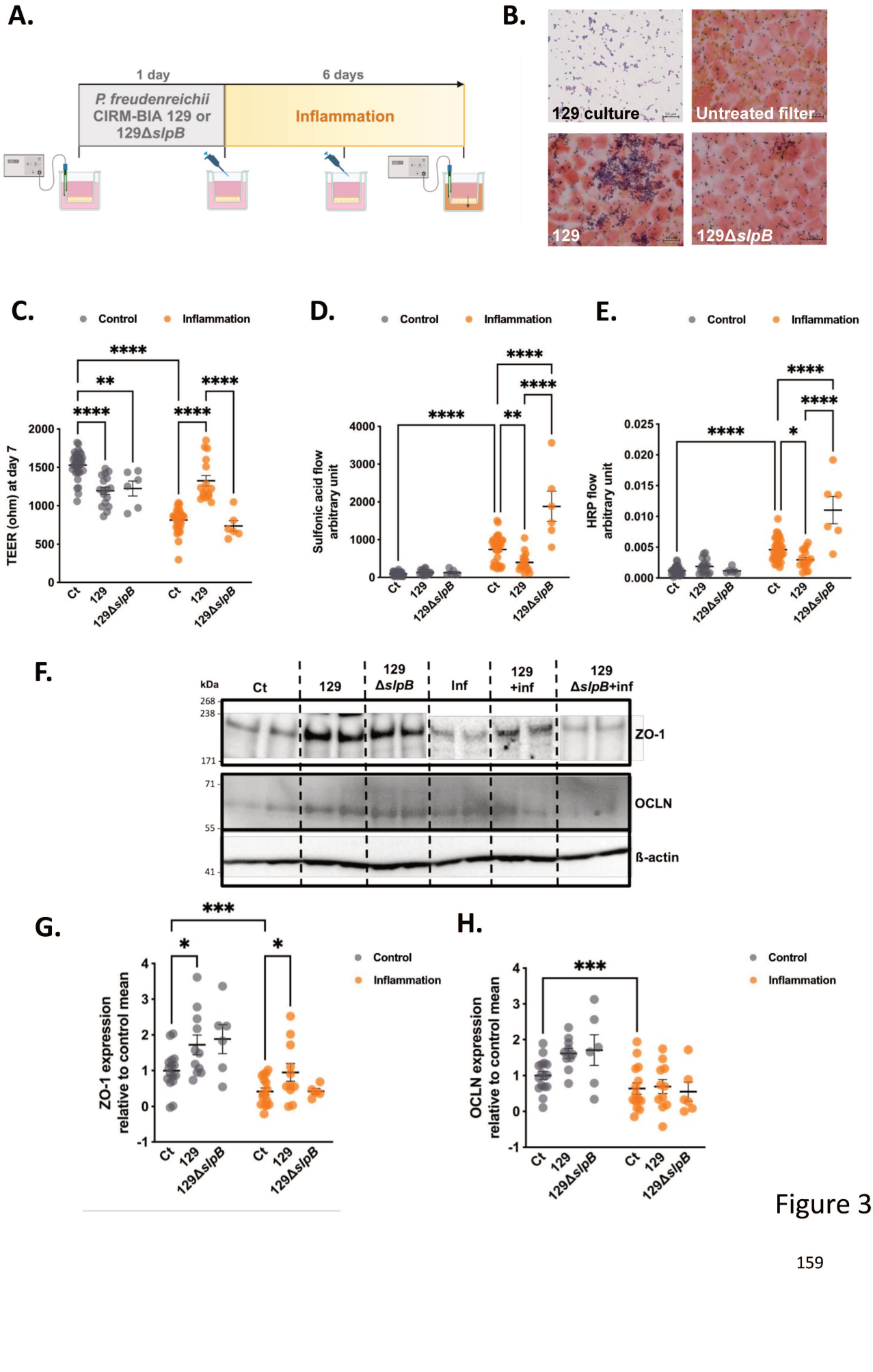

A.
1 day
6 days
P. freudenreichii CIRM-BIA 129 or 129ΔslpB
Inflammation
B.
129 culture
Untreated filter
129
129ΔslpB
C.
Control
Inflammation
TEER (ohm) at day 7
Ct
129
129ΔslpB
D.
Sulfonic acid flow arbitrary unit
E.
HRP flow arbitrary unit
F.
kDa
Ct
129
129 ΔslpB
Inf
129 +inf
129 ΔslpB+inf
ZO-1
OCLN
ß-actin
G.
ZO-1 expression relative to control mean
H.
OCLN expression relative to control mean

Figure 3

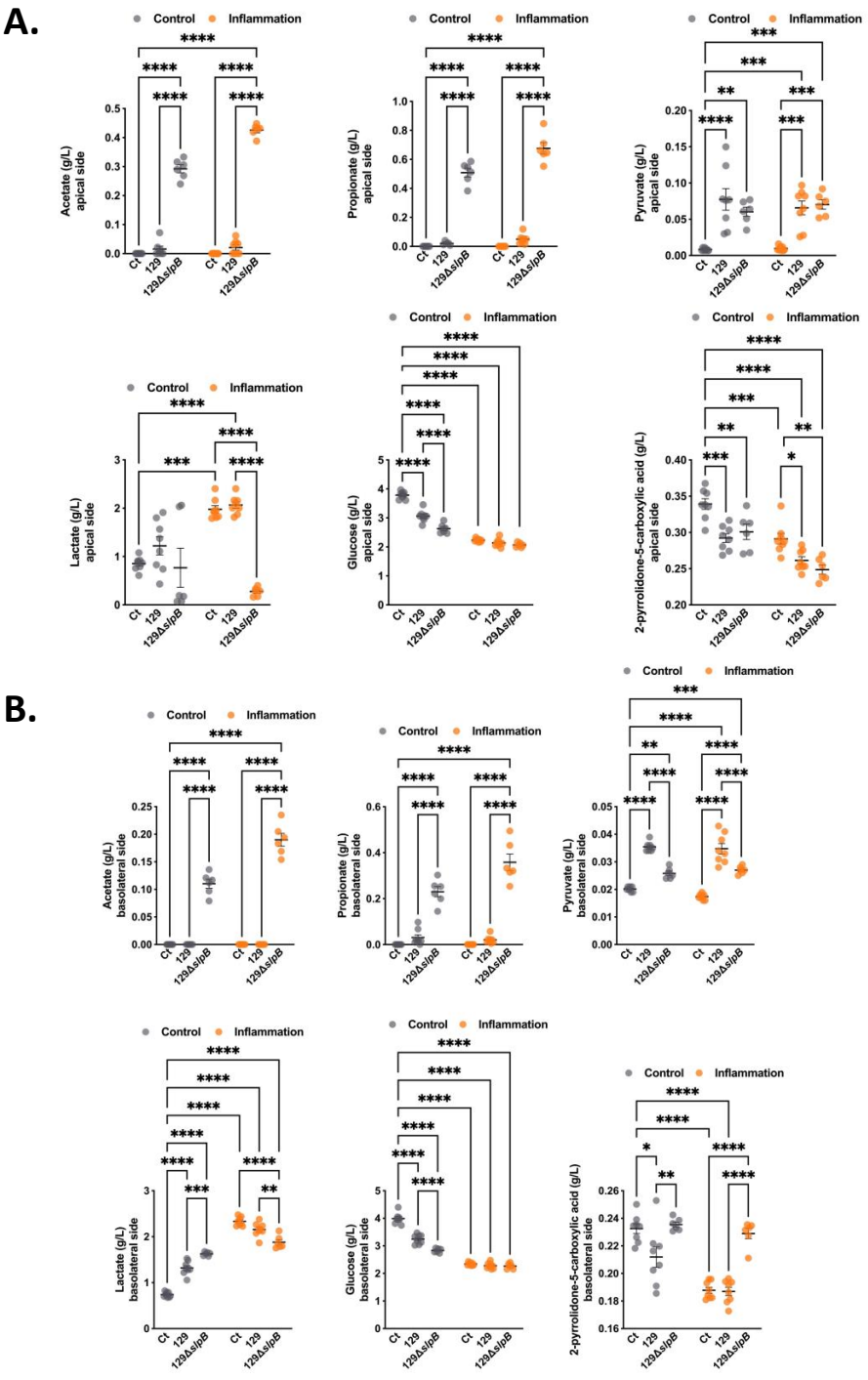

A.
Control
Inflammation
Acetate (g/L) apical side
Propionate (g/L) apical side
Pyruvate (g/L) apical side
Lactate (g/L) apical side
Glucose (g/L) apical side
2-pyrrolidone-5-carboxylic acid (g/L) apical side
B.
Acetate (g/L) basolateral side
Propionate (g/L) basolateral side
Pyruvate (g/L) basolateral side
Lactate (g/L) basolateral side
Glucose (g/L) basolateral side
2-pyrrolidone-5-carboxylic acid (g/L) basolateral side
Ct
129
129ΔslpB
C.
Sulfonic acid flow arbitrary unit
CT
INF
Pyruvate 0.1mM INF
Pyruvate 1mM INF
Pyruvate 10mM INF
D.
Sulfonic acid flow arbitrary unit
Ct
129sup

Figure 4

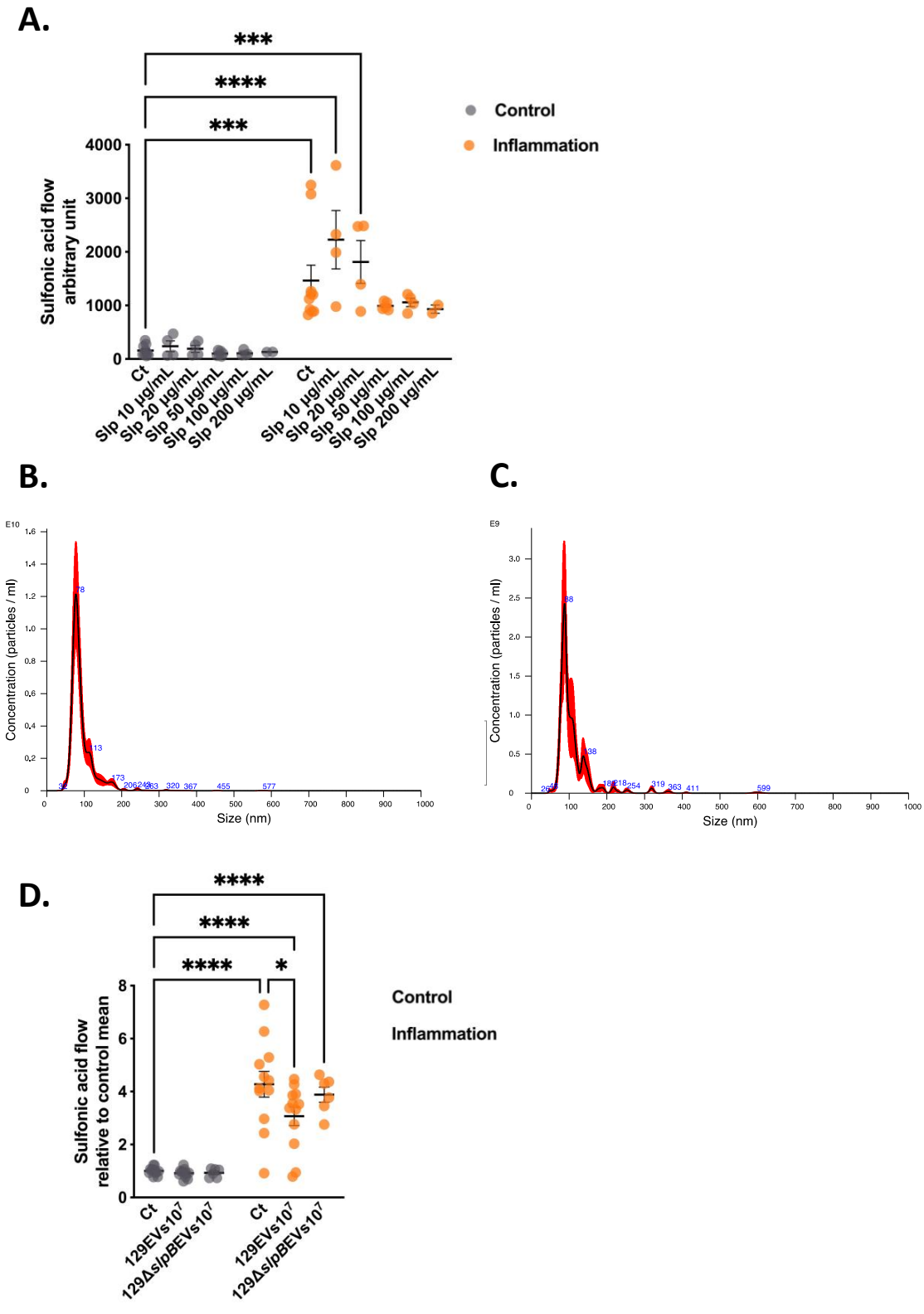

A.
***
****
***
Control
Inflammation
Sulfonic acid flow arbitrary unit
4000
3000
2000
1000
0
Ct
Slp 10 µg/mL
Slp 20 µg/mL
Slp 50 µg/mL
Slp 100 µg/mL
Slp 200 µg/mL
B.
C.
Concentration (particles / ml)
Size (nm)
D.
****
****
****
*
Control
Inflammation
Sulfonic acid flow relative to control mean
Ct
129EVs10^7
129ΔslpBEVs10^7

Figure 5

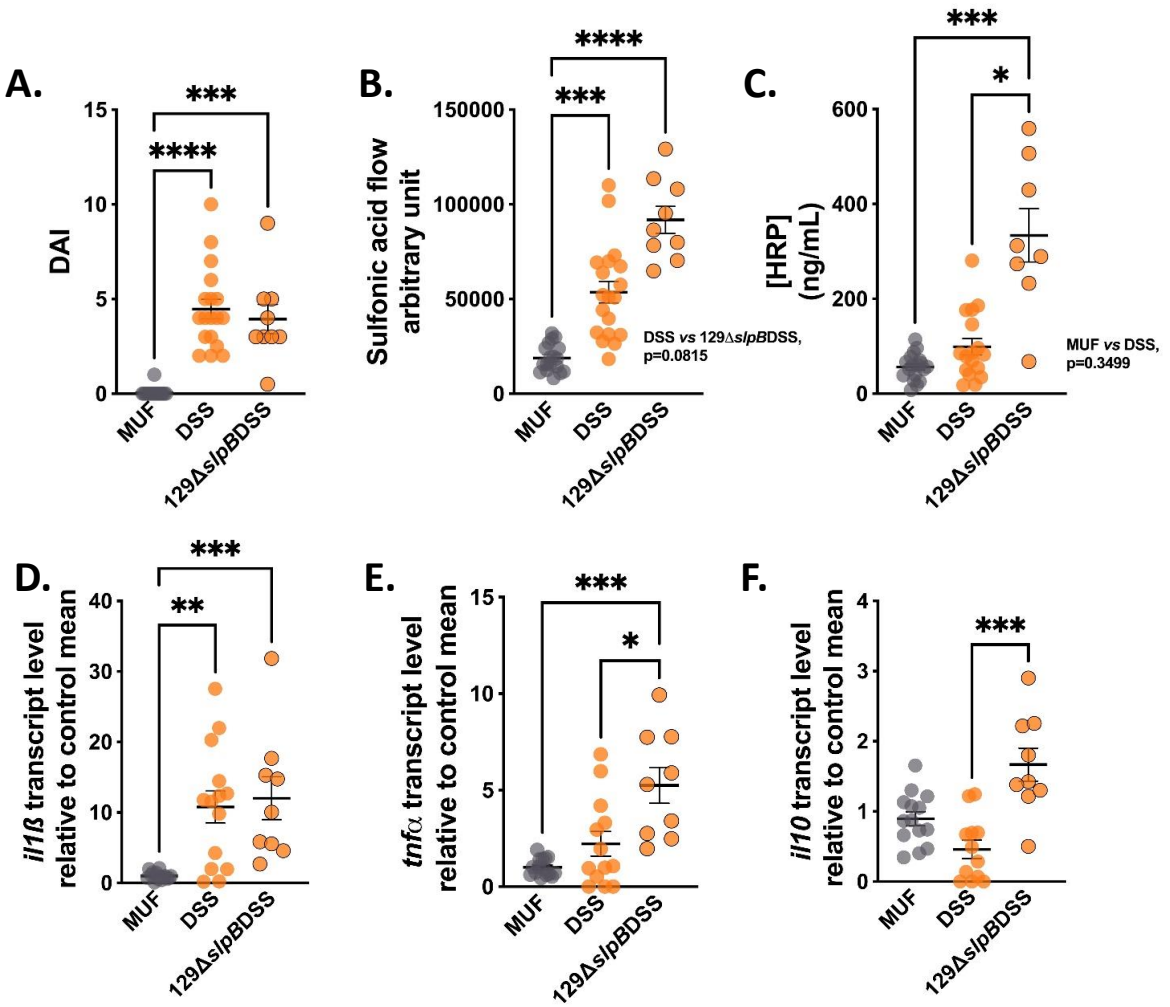
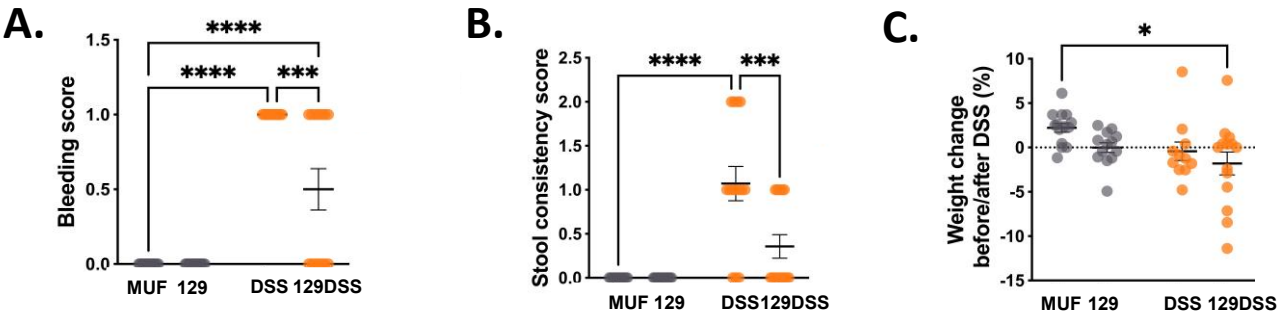


Figure 6



Suppl Figure 1

Table S1- Antibodies

REAGEANT or RESOURCE	SOURCE	DILUTION and SPECIES	IDENTIFIER
Antibodies for Western-Blot			
anti-ZO-1	In vitrogen	1:500; rabbit	40-2200
anti-occludin	Abcam	1:500; rabbit	Ab31721
anti-cleaved-caspase-3	Cell signaling	1:500; rabbit	9661S
anti-ß-actin	Abcam	1:1000; mouse	Ab227387
anti-mouse	Sigma-Aldrich	1:5000	A9044
anti-rabbit	Thermo-fisher	1:5000	31460
Antibodies for IHC			
ZO-1	In vitrogen	1:500; rabbit	40-2200
Occludin	In vitrogen	1:200; rabbit	71-1500
DAPI	Sigma-Aldrich	1:2000	D9542
Cy-5 anti-rab	Jackson ImmunoResearch	1:500	111-175-144

Table S2- Primers

Interleukin 1 beta (IL1ß) #NM_008361.4
Forward Primer: 5'-GCCTCGTGCTGTCGGACCCATA-3'
Reverse Primer: 5'-TTGAGGCCCAAGGCCACAGGT-3'

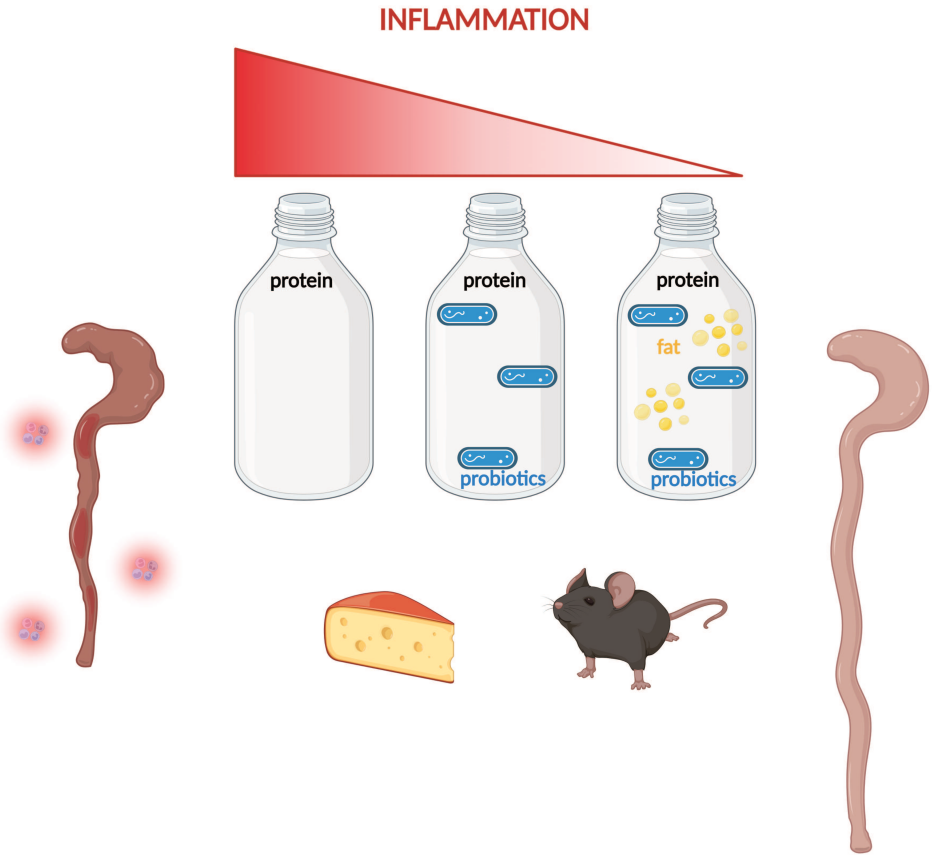
Tumor necrosis factor alpha (TNFα) #NM_013693.3
Forward Primer: 5'-GAACTTCGGGGTGATCGGTC-3'
Reverse Primer: 5'-GCCACTCCAGCTGCTCCTCC-3'

Interleukin 10 (IL10) #NM_010548.2
Forward Primer: 5'-GACTTTAAGGGTTACTTGGGTTGC-3'
Reverse Primer: 5'-AGAAATCGATGACAGCGCCTC-3'

Ribosomal protein S6 (RPS6) #NM_001010.2
Forward Primer: 5'-CCAAGCTTATTCAGCGTCTTGTTACTCC-3'
Reverse Primer: 5'-CCCTCGAGTCCTTCATTCTCTTGGC-3'

Article 2

Fat matters: Fermented whole milk potentiates the anti-colitis effect of *Propionibacterium freudenreichii*



2. ARTICLE 2 : LA MATRICE LAITIERE IMPACTE LES PROPRIETES ANTI-COLITE DE *P. FREUDENREICHII* CIRM-BIA 129

L'article précédant montre qu'une consommation quotidienne de *P.freudenreichii* CIRM-BIA129 protège de la colite *in vivo*, en particulier, en inhibant l'augmentation de perméabilité induite par l'inflammation *via* la restauration de l'expression protéique de ZO-1 par le biais d'un mécanisme impliquant la protéine SlpB. Cependant, *Pf*CIRM-BIA129 est une bactérie présente dans l'emmental. Envisager son utilisation en tant que probiotique pourrait impliquer l'incorporation de produits laitiers fermentés dans l'alimentation. Cette approche soulève ainsi la question de l'influence de la matrice laitière sur l'effet du probiotique. L'impact de la matrice a déjà été abordé par le passé, la matrice fromagère module les propriétés immunomodulatrices de *P.freudenreichii* CIRM-BIA129 chez des porcelets par rapport à un milieu liquide. Cette matrice favorise le développement des lymphocytes Treg et Th2 dans des PBMC et MLNC provenant des porcelets (Rabah et al. 2018). De plus, cette matrice protège la protéine SlpB de la protéolyse dans un système de digestion gastro-intestinale *in vitro* et préserve la viabilité de la bactérie, contrairement à une culture liquide (Rabah et al. 2018). Cependant, l'action propre des deux principaux types de nutriments du lait, à savoir les lipides et les protéines, sur les effets immunomodulateurs de *P.freudenreichii* CIRM-BIA129 demeure inconnue.
Le but de ce travail était de comprendre le rôle respectif des protéines et des lipides du lait sur les effets protecteurs de colite de *P.freudenreichii* CIRM-BIA129.

Pour ce faire, trois matrices laitières différentes (lait entier, lait écrémé, perméat d'ultrafiltrat de lait), fermentées ou non par la propionibactérie *P.freudenreichii* CIRM-BIA129, ont été testées dans un modèle de colite au DSS chez la souris. La sévérité de la colite, la perméabilité intestinale, l'expression génique de marqueurs inflammatoires et de la BEI ont été étudiées.

Cette étude dévoile les lipides du lait comme constituants qui boostent les effets anti-colite de *P.freudenreichii* CIRM-BIA129. En effet, le lait entier fermenté favorise la protection de la colite avec des effets majeurs au niveau de la perméabilité intestinale, du score histopathologique, de l'expression des claudines 1- et 5- ainsi que de l'il1ß.

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Fat matters: Fermented whole milk potentiates the anti-colitis effect of *Propionibacterium freudenreichii*

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ABSTRACT

Inflammatory bowel diseases (IBD) constitute a growing concern in western countries. They coincide with gut microbiota dysbiosis, including a loss of immunomodulatory bacteria. Accordingly, probiotic products containing selected immunomodulatory bacterial strains mitigate IBD. Selected strains of *Propionibacterium freudenreichii* display promising modulatory properties and prevent colitis in animal models. Dairy matrices protect propionibacteria immunomodulatory surface antigens during digestive transit. However, the functional role of the dairy matrix components in such fermented dairy products remains unknown. In the present workthis study, *P. freudenreichii* CIRM-BIA129, a probiotic strain known for its anti-inflammatory properties, was used to ferment whole milk, skim milk or skim milk ultrafiltrate. The preventive potential of fermented products was tested in DSS-induced mice colitis, in comparison with their unfermented counterparts. *P. freudenreichii*-fermented milk prevented colitis. Dairy fat in the fermented product potentiated the anti-colitis effects of the probiotic. This work opens new perspectives for developing immunomodulatory functional fermented foods.

1. Introduction

1.1. Inflammatory diseases constitute a growing concern.

Many developed countries presently experience an epidemic of chronic inflammatory disease, which can be, at least in part, attributed to a deleterious shift in lifestyle and in diet. Indeed, consumption of Western diet combined with overnutrition and sedentary lifestyle evoke a state of chronic metabolic inflammation, referred to as meta-flammation (Christ et al., 2019). This in turn contributes to an increased incidence of non-communicable diseases, which include inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC). This constitutes a rising public health problem with global epidemic dimensions responsible for a growing burden of care. The causes of such an epidemic are complex. Dietary factors such as over-consumption of fat and protein, yet low intake of fruits and vegetables, are probably involved (Hou et al., 2011). Indeed, high-fiber and fruit intakes are associated with decreased risk of IBD, including CD and UC (Hou et al., 2011). By contrast, a review of clinical evidence associated fermented dairy products with an anti-inflammatory activity. This association was particularly significant in subjects with metabolic disorders (Bordoni et al., 2017). In addition to the diet, dysbiosis of the gut microbiota may also play a key role in such inflammatory ailments. Indeed, exacerbated immune response in IBD involves an interplay between the gut microbiota, host genetic factors, and environmental factors.

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[2] These authors shared senior authorship.

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1.2. Dysbiosis coincides with inflammatory ailments.

In many inflammatory diseases, including IBD, the gut microbiota is modified, in comparison to that of healthy volunteers. This modification constitutes dysbiosis, which can be defined as "a disturbance to gut microbiota homeostasis due to an imbalance in the flora itself, changes in their functional composition and metabolic activities, or changes in their local distribution" (DeGruttola et al., 2016). Indeed, dysbiosis of the gut microbiota was described in IBD patients, including in CD (Sokol et al., 2008) (Matsuoka and Kanai, 2015)and in UC (Zhang et al., 2007) (Kostic et al., 2014). Dysbiosis is more pronounced in CD patients than in UC ones, with a more reduced diversity and a less stable microbial community (Pascal et al., 2017). Indeed, increasing human diseases are often associated with a modern western lifestyle and with a reduction in the intestinal microbiota diversity (Mosca et al., 2016). This includes metabolic diseases and cancer, but also immune disorders such CD, UC, allergy and celiac disease. Loss of microbial diversity in this context is characterized by a reduction of the population of commensal bacteria with a recognized immunomodulatory role. This includes reduced population of *Faecalibacterium prausnitzii*, a butyrate-producing bacterium with immunomodulatory anti-inflammatory properties (Quévrain et al., 2016); (Touch et al., 2022). This also includes species of Bifidobacteria, also recognized as key immunomodulators (Tojo et al., 2014). In line with this, a meta-analysis of available clinical data indicated that the consumption of a mix of 8 stains of probiotic bacteria, VSL#3, which includes bifidobacteria and lactic acid bacteria, mitigates the symptoms of IBD in humans (Sniffen et al., 2018). This evidences the key importance of a research work aimed at the identification of food-grade bacteria able to down-regulate inflammation in the context of colitis.

1.3. Propionibacteria exhibit promising immunomodulatory properties.

Dairy propionibacteria, including the main species *Propionibacterium freudenreichii*, are generally recognized as safe (GRAS) bacteria, with the qualified presumption of safety (QPS) status, which are consumed both in Swiss-type cheeses and in probiotic food supplements. They constitute promising immunomodulatory probiotic candidates that may be useful to mitigate symptoms of colitis. In a pioneer study, selected strains of *P. freudenreichii* were shown to induce the modulatory IL-10 in human immune cells *ex vivo* (PBMC). These strains, when administered in a preventive way, were further shown to prevent acute colitis induced by TNBS in BALB/c mice (Foligné et al., 2010). A wider screening of *P. freudenreichii* strains then revealed that this ability is highly dependent on the strain, with a great variability of the immunomodulatory properties (Foligné et al., 2013). These last depend on the presence of specific key immunomodulatory surface proteins, and extraction of such proteins suppresses propionibacteria ability to induce IL-10 (Le Marechal et al., 2015). Moreover, mutational inactivation of key genes (*slpB*, *slpE*) encoding such surface layer proteins also suppresses this immunomodulatory ability (Deutsch et al., 2017). The *P. freudenreichii* CIRM-BIA129 was thus selected as the most modulatory one, exposing SlpB and SlpE proteins at its surface. It prevents acute colitis induced by TNBS (Plé et al., 2015), as well as colitis induced by DSS (Rabah, 2020) and mucositis induced by the cancer chemotherapy drug 5-fluorouracyl (2018). Inactivation of the *slpB* gene in this strain suppresses adhesion to human intestinal epithelial cells, as well as protective effect towards colitis and mucositis (do Carmo et al., 2017); 2019). In line with this, cloning and expression of this gene in *Lactococcus lactis* confers to this lactic acid bacterium enhanced anti-inflammatory properties (Belo et al., 2021). In humans, a clinical study revealed that propionibacteria were members of the gut microbiota of breast-fed preterm infants, while they were absent of that from formula-fed ones, in which necrotizing enterocolitis (NEC), a leading and intractable cause of mortality in preterm infants, is more frequent (Colliou et al., 2017). Accordingly, these authors isolated a *P. freudenreichii* strain from a healthy infant and described its ability to confer protection against pathogen infection and to increase intestinal Th17 cells in mice. In line with this, a pilot clinical study indicated that the consumption of whey cultures of *P. freudenreichii* improved the clinical activity index score in patients with active UC (Mitsuyama et al., 2007). These authors suggested that this healing effect was mediated by a secreted compound, found in culture supernatant and referred to as bifidogenic growth stimulator (BGF), produced by *P. freudenreichii* (Suzuki et al., 2006). These data strongly suggest that, in addition to being a GRAS and QPS dairy starter with a long history of safe use, *P. freudenreichii* also constitutes a human symbiont and a promising immunomodulatory probiotic.

1.4. The dairy matrix may play a role in the modulatory effect.

We previously addressed the role of the dairy matrix in the modulation of *P. freudenreichii* probiotic activity. Using an *in vitro* gastrointestinal digestion system, the cheese matrix was shown to protect the immunomodulatory SlpB protein from digestive proteolysis (Rabah, Ménard, et al., 2018). Both the viability of the propionibacterium and the integrity of the SlpB were preserved during digestion of the cheese, by contrast with a liquid culture. In young weaned piglets, the cheese matrix modulated *P. freudenreichii* immunomodulatory properties (Rabah, Ferret-Bernard, et al., 2018). Compared to liquid cultures, cheese containing *P. freudenreichii* enhanced Treg and Th2 cells in piglets PBMC and MLNC. Consumption of such a cheese reduced severity of subsequent DSS-induced colitis in mice, including weight loss, disease activity index, score, as well as induction of Tumor Necrosis Factor α (TNFα), Interferon γ (IFNγ) and Interleukin-17 (IL-17) (Rabah, 2020). Such data indicate the interest of using a fermented dairy product such as cheese for the vectorization of propionibacteria to the gut. It is easy to hypothesize that the dairy constituents, including proteins and lipids, protect these bacteria from the insults of low gastric pH, of digestives enzymes and of bile salts. However, the precise role of these constituents in the overall probiotic effect of the fermented food remains elusive. Do dairy lipids and proteins play a role, *per se*, as immunomodulators? Indeed, bioactive milk proteins reportedly exert anti-inflammatory effects (Chatterton et al., 2013) and so do casein hydrolysates (Chen et al., 2022). Dietary fats, depending on their structure, may exert opposite effects on intestinal inflammation (Basson et al., 2020).

We therefore assessed the question of the respective role of propionibacteria, of milk protein and of milk fat in the anti-colitis effect of *P. freudenreichii*-fermented milk. To do so, whole milk, skim milk and milk ultrafiltration permeate were fermented by *P. freudenreichii* CIRM-BIA129. These fermented products, as well as their unfermented control, were administered to mice prior to colitis induction. The research work indicate that the most protective product is the whole milk fermented by *P. freudenreichii* CIRM-BIA129, suggesting a protective role of milk fat.

2. Materials & methods

2.1. Growth of dairy propionibacteria

The strain *Propionibacterium freudenreichii* CIRM-BIA129, equivalent to ITG P20, was initially isolated from a Swiss-type cheese. It was kindly provided by CNIEL (Centre National Interprofessionnel de l'Économie Laitière) and maintained by the CIRM-BIA microbiological resource center (Centre International de Ressources Microbiennes, Bacteries d'Intérêt Alimentaire, Rennes, France). Starting from a frozen stock, precultures were grown in liquid Yeast Extract Lactate (YEL) broth containing 0.1 M lactate and 10 $g.L^{-1}$ yeast extract as described (do Carmo et al., 2017); 2019)(Malik et al., 1968). CIRM-BIA129 was incubated at 30 °C during 3 days, without agitation, until stationary phase was reached.

2.2. Preparation of fermented dairy products

Dairy media for propionibacteria growth were prepared as previously described (Cousin et al., 2012). Milk ultrafiltration (UF) permeate was prepared as follows. Raw cow milk was skimmed using a cream separator (Westfalia, Chateau-Thierry, France). It was then separated using an UF pilot equipment (T.I.A., Bollene, France) equipped with an organic spiral membrane with a molecular weight cut-off of 5 kDa (Koch International, Lyon, France). The temperature during the ultrafiltration process was maintained at 55 °C. The collected UF permeate was supplemented with 0.1 M food-grade sodium lactate (Sigma-Aldrich, St. Louis, MO, USA) and 10 $g.L^{-1}$ food-grade grade casein hydrolysate (Casein Peptone Plus, Organotechnie, La Courneuve, France) prior to sterilization using a 0.2 μm filtration unit (Nalgene, Roskilde, Denmark) and stored at 4 °C. UHT skim milk and whole milk (Agrilait, France) were purchased from a local supermarket and supplemented with 0.1 M food-grade sodium lactate (Sigma-Aldrich) and 10 $g.L^{-1}$ food-grade grade casein hydrolysate, as was UF permeate. Starting from YEL precultures, UF precultures were grown prior to inoculation of dairy media (UF, skim milk, whole milk). Growth was at 30 °C during 3 days, without agitation, until stationary phase was reached, corresponding to bacterial densities of 10^9 CFU $g.L^{-1}$, as described previously (Cousin et al., 2012).

2.3. Animal experiments

C57Bl/6 mice ($n = 80$), male, 6 weeks old, were obtained from the "Biotério central" of the Federal University of Minas Gerais (Belo Horizonte, Minas Gerais, Brazil). They were randomly divided into 8 groups of 10 animals. They were kept in microisolators at a controlled temperature (25 °C +- 1), with a 12 h/12 h light/dark cycle and *ad libitum* access to food (standard chow pellets – Nuvilab Brazil) and autoclaved drinking water. During 14 days, mice received treatments indicated in Table1. They were daily gavaged with 200 μL of sterile phosphate buffered saline (PBS), filter-sterilised milk UF, UHT sterile skim milk, UHT sterile whole milk, or with 200 μL of *P. freudenreichii* culture in milk UF, in skim milk, or in whole milk. During the last 7 days, colitis was induced, in all groups except the negative control (NC) group, by replacing drinking water by a 2.5% dextran sulphate sodium (DSS) solution in autoclaved water (DSS 40 kDa, TdB Consultancy, Uppsala, Sweden). On the 15th day, animals were euthanized by anesthetic overdose (Ketamine 270 mg/Kg and xylazine 30 mg/Kg). The Ethics Committee on Animal Experimentation of the Universidade Federal de Minas Gerais (CEUA-UFMG, Brazil) approved all experimental procedures realized in this work by the protocol no. 148/2020. Total blood was collected for permeability assay. The colon was collected and measured, washed with sterile PBS, and divided into 2 sections for histology and for gene expression analysis.

2.4. Intestinal permeability

Intestinal permeability was assessed as described previously (do Carmo et al., 2019). On the last day, mice were gavaged with 100 μL of a solution of radiolabelled Diethylenetriamine Pentaacetic Acid (DTPA) containing 18.5 MBq of ^{99m}technetium (^{99m}Tc-DTPA). After 4 h, the animals were anesthetized as described above and blood was collected. The radioactivity was counted in a gamma radiation counter (Wizard, PerkinElmer) according to the instructions of the manufacturer. Results were expressed as a percentage of dose per g of blood, using the following equation: % dose = (cpm in blood/cpm in administrated dose) × 100 (cpm: counts per minute) (Generoso et al., 2011).

Table 1
Groups codes and treatment description.

Group code	Treatment administered	Colitis induction
NC	PBS	No
DSS	PBS	DSS 2.5%
DSS-PUF	Milk Ultra Filtrated	DSS 2.5%
DSS-SM	Skim Milk	DSS 2.5%
DSS-WM	Whole Milk	DSS 2.5%
DSS-UF129	Fermented milk Ultra Filtrated	DSS 2.5%
DSS-SM129	Fermented Skim Milk	DSS 2.5%
DSS-WM129	Fermented Whole Milk	DSS 2.5%

2.5. Assessment of colitis severity

Food and liquid consumption were daily measured for each isolator and animals were weighed individually. During the last three days, feces were analyzed for consistency and for the presence of blood using the Feca-Cult test, (Inlab, Brazil). The disease activity index (DAI) was determined as indicated in Table 2, according to the 3 main clinical symptoms of colitis: diarrhoea, rectal bleeding, and weight loss, following a scoring previously described (Murthy et al., 1993). The size of PBS-washed colons was measured.

2.6. Histology

Colon sections were gently washed in PBS, rolled in a distal-proximal configuration, fixed in neutral buffered 10%(v/v) formalin solution (Sigma-Aldrich) and processed for histological analysis. Hematoxylin phloxine saffron (HPS) and Alcian Blue stained sections of the paraffin-embedded proximal colonic tissue were used for histological analysis. Tissue damage was determined by two blinded investigators quantifying the destruction of mucosal architecture, the presence and degree of cellular infiltration, the extent of muscle thickening and the goblet cell depletion. The destruction of mucosal architecture was scored as 0–3 (0: none, 1: 1/3 basal, 2: 2/3 basal and 3: loss of crypt and epithelium). Then, presence and degree of cellular infiltration was rated as 0–3 (0: none, 1: infiltrate around crypt basis, 2: extensive infiltration reaching the muscularis mucosae and 3: infiltration of the submucosa). Next, the extent of muscle thickening was scored as 0–3 (0: none, 1: mild, 2: moderate and 3: extensive thickening). Finally, presence or absence of goblet cell depletion was determined as 0: goblet cells presence and 1: loss of goblet cells. An extension factor of 1–4 was implemented when the criteria measured reached 25, 50, 75 and 100% of the tissue evaluated.

Furthermore, the crypt depths and the number of goblet cells per crypt were determined based on histology images. Five pictures from random sections of the colon were collected per animal. For the crypt measurements, 20 crypts were measured from each image and the mean was determined for each animal. The number of goblet cells crypt was counted on 10 crypts per image, and the average was used for the analysis.

2.7. Gene expression analysis

After collection, colon samples were stored in RNAlater RNA-latter (Invitrogen, USA) at −20℃ until further RNA extraction. The RNA extraction was performed using the RNeasy Mini Kit (QIAGEN, USA) according to the manufacturer's instructions. Purified RNA (1 μg) was then used to produce the cDNA with the QSCRIPT cDNA synthesis kit (Quantabio, USA) for a final volume of 20 μL. The cDNA incubation program consisted of 5 min at 22℃, 30 min at 42℃, and 85℃ for 5 min.

Table 2
Disease Activity Index.

Score	Weight loss (%)	Stool consistence*	Occult/Gross Bleeding
0	None	Normal	Absent
1	0–5		
2	5–10	Loose	Occult blood
3	10–15		
4	>15	Diarrhea	Gross bleeding

Both the RNA and the produced cDNA were quantified in a nanodrop spectrophotometer (Thermo Scientific, USA). qPCR was carried out in a 16 µL volume containing 15 ng cDNA, specific primers (300 nM), and 8 µL IQTM SYBR Green Supermix (Bio-Rad). Reactions were run on a CFX96 real-time system (Bio-Rad, France) using the following cycling parameters: DNA polymerase activation and DNA denaturation 95 °C for 5 min, 40 cycles of denaturation at 94 °C for 15 s, and extension at 60 °C for 30 s. Melting curve analysis was included to check the amplification of single PCR products. The primers used are listed in Table 3. All genes were analysed in duplicate and the amount of mRNA was normalized by using the geometrical mean value of four reference genes: *actB* (beta-actin), *gapdh* (glyceraldehyde 3-phosphate dehydrogenase), *ppiA* (peptidylprolyl isomerase A) and *tuba* (beta-tubulin). The online tool RefFINDER (https://www.heartcure.com.au/reffinder/) was used to identify the most stably expressed genes in the experimental conditions tested from a panel of six gene candidates. The values corresponding to the amount of amplified gene compared to the NC control group (2-ΔΔCT) were expressed as mean ± SEM. The differences among the groups were assessed by the Kruskal-Wallis test followed by Dunn's multiple comparisons test performed using GraphPad Prism version 9.5.1 for macOS, GraphPad Software, San Diego, California USA, https://www.graphpad.com.

3. Results

3.1. Consumption of *P. freudenreichii*-fermented milk attenuated the clinical signs of DSS-induced colitis.

The animal study is depicted in Fig. 1A. We first explored macroscopic markers of DSS-induced colitis, in the presence or in the absence of the administration of the probiotic *P. freudenreichii* CIRM-BIA129 (Fig. 1A). This last was consumed either under the form of a fermented milk ultrafiltrate (DSS-UF129), of a fermented skim milk (DSS-SM129), or of a fermented whole milk (DSS-WM129). In addition, to evaluate the impact of the fermentation by CIRM-BIA129 versus that of the vehicle food matrix, mice were also treated with the unfermented dairy products (DSS-UF, DSS-SM and DSS-WM). As expected, addition of 2.5 % DSS to the drinking water led to clinical signs such as an increased disease activity index (DAI) score, taking into account weight loss, stool consistence and gross bleeding (Fig. 1B), as well as colon shortening (Fig. 1C and D). Consumption of the unfermented sterile dairy products tested here had no significant effect on the clinical signs of DSS-induced colitis. Indeed, DAI remains increased, in the context of colitis, whether mice consumed sterile UF, skim milk, or whole milk. Nevertheless, consumption of the *P. freudenreichii*-fermented dairy product alleviated the clinical signs of DSS-induced colitis, as indicated by a DAI score intermediate between the NC and the DSS, and no significant difference between the DSS-UF129, the DSS-WM129 groups, and the NC groups (Fig. 1B). In the same manner, colon shortening was not modified by the unfermented sterile dairy products tested, but significantly decreased in DSS-UF129 and DSS-SM129 groups when compare to the DSS group (Fig. 1C and D). These data show that consumption of *P. freudenreichii*-fermented dairy products reduced colitis and lowered colon damage.

Table 3
Primers used in this study.

Gene	Primer	Sequence	Reference
*ACTB**	Forward	CCTTCTTGGGTATGGAATCCTGT	https://doi.org/10.3390/ijms21124403
	Reverse	CACTGTGTTGGCATAGAGGTCTTTAC	
*GAPDH**	Forward	TGACCTCAACTACATGGTCTACA	https://doi.org/10.1186/s12867-016-0065-9
	Reverse	CTTCCCATTCTCGGCCTTG	
*TUBA**	Forward	TGTCCTGGACAGGATTCGC	https://doi.org/10.1080/21541264.2022.2079184
	Reverse	CTCCATCAGCAGGGAGGTG	
*PPIA**	Forward	GGCAAATGCTGGACCAAAC	https://doi.org/10.1038/srep38513
	Reverse	CATTCCTGGACCCAAAACG	
TNF	Forward	CTGTAGCCCACGTCGTAGC	https://doi.org/10.4049/jimmunol.0802948
	Reverse	TTGAGATCCATGCCGTTG	
IL6	Forward	GAGGATACCACTCCCAACAGACC	https://doi.org/10.1038/aps.2013.54
	Reverse	AAGTGCATCATCGTTGTTCATACA	
IL1B	Forward	GCAACTGTTCCTGAACTCAACT	https://doi.org/10.1128/IAI.00721-13
	Reverse	ATCTTTTGGGGTCCGTCAACT	
NOS2	Forward	CAGCTGGGCTGTACAAACCTT	PMID: 28,559,977
	Reverse	CATTGGAAGTGAAGCGTTTCG	
PPARG	Forward	CAGGCTTCCACTATGGAGTTC	https://doi.org/10.1172/jci.insight.127551.
	Reverse	GGCAGTTAAGATCACACCTATCA	
OCLN	Forward	CAGCCTTCTGCTTCATCG	112030.2/rs.3.rs-885593/v1
	Reverse	GTCGGGTTCACTCCCATTA	
CLDN1	Forward	ATCCATAGGAAAGGCCCTTCAGCA	https://doi.org/10.1093/ecco-jcc/jjab044
	Reverse	TACATGTAGGGCAACCAAGTGCCT	
CLDN5	Forward	ACGGGAGGAGCGCTTTAC	https://doi.org/10.18632/aging.202836
	Reverse	GTTGGCGAACCAGCAGAG	

* Reference genes.

3.2. Consumption of *P. freudenreichii*-fermented milk attenuated the histological symptoms of DSS-induced colitis.

At a microscopic scale, the histopathological analysis revealed a length-wide destruction of the colonic epithelium, with considerable modification of the mucosal architecture, loss of crypts, cellular infiltration and thickening of the muscular layer, as a result of colitis induction (DSS), when compared to healthy control intestinal tissue (NC) (Fig. 2). As a result of this destruction, the histopathological score (Fig. 3A), based on the mucosal architecture, the presence and degree of cellular infiltration, the extent of muscle and the presence or absence of goblet cells, was increased in the DSS group from 2.04 + -0.85 in the control NC group to 6.68 + -3.37 in the DSS group. Accordingly, the depth of the crypts (Fig. 3B) and the number of goblet cells per crypt (Fig. 3C) were significantly reduced as a result of DSS treatment. None of the unfermented dairy products was able to reduce this score significantly, although results indicate a trend towards a reduced score, when compared to the DSS group. However, crypts depth and density of goblet cells remained low. Considering the *P. freudenreichii*-fermented dairy products, only the consumption of the fermented whole milk (DSS-WM129 group) significantly restored a low score, down to 2.2 + -1.41 (Fig. 2A and B). Furthermore, the crypt depth, which was dramatically reduced by DSS, was partially restored by the consumption of both fermented skim milk (DSS-SM129) and fermented whole milk (DSS-WM129) (Fig. 2C). The number of goblet cells, also drastically reduced in DSS-induced colitis group (9.05 + -1.08), was partially prevent by the two fermented products SM129 and WM129 (11.04 + -1.98 and 13.67 + -2.3, respectively), although only DSS-WM129 did not differ from the healthy control (14.22 + -3.29) (Fig. 2D).

3.3. Consumption of *P. freudenreichii*-fermented milk attenuated the pathological increase in intestinal permeability.

We further investigated the permeability of the gut by monitoring the passage of radiolabelled Diethylenetriamine Pentaacetic Acid (DTPA) from the gut content into the blood stream. Gut permeability was drastically increased as a result of DSS treatment (Fig. 2E). Indeed, the DTPA fraction monitored in the blood was 0.33%+-0.1 in control NC mice, while it was 0.74%+-0.18 in the DSS one. Consumption of unfermented sterile dairy products resulted in a trend towards reduced gut permeability, especially with whole milk, but this trend failed to reach

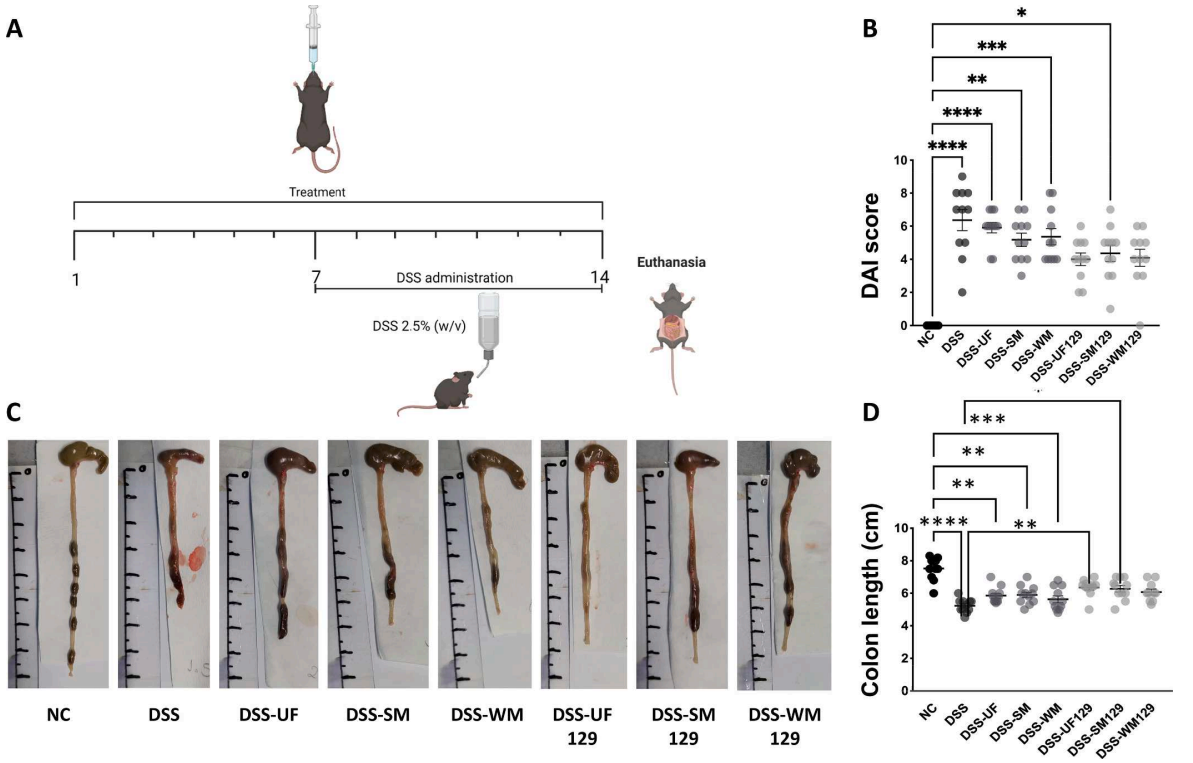

Fig. 1. *P. freudenreichii*-fermented milk alleviated DSS-induced experimental colitis in mice. (A) Design of the experimental protocol to investigate the effect of dairy matrices, fermented or not by *P. freudenreichii* CIRM-BIA129, in an experimental model of colitis in mice. Mice were gavaged during the 14 days of the experiment with 200 μL of sterile phosphate buffered saline (PBS), sterile milk ultrafiltrate (UF), sterile skim milk (SM), sterile whole milk (WM), or with 200 μL of *P. freudenreichii* CIRM-BIA129 culture in milk ultrafiltrate (UF129), in skim milk (SM129), or in whole milk (WM129). Mice had access to sterilised drinking water for negative control mice (NC) or to 2.5 % DSS in drinking water. (B) Disease activity index (DAI) was determined according to the 3 main clinical symptoms of colitis: diarrhoea, rectal bleeding, and weight loss. (C) Representative examples of colon morphology. (D) Colon size. Data represent mean +/- SEM of 10 mice per group. Kruskal-Wallis test followed by Dunn's multiple comparisons test was performed. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$.

statistical significance. Consumption of *P. freudenreichii*-fermented dairy products however significantly prevented this increase in intestinal permeability (Fig. 2E) mitigating the permeability back to basal levels. In particular, the fermented whole milk reduced this DTPA fraction to 0.25%+-0.14.

3.4. Consumption of P. freudenreichii-fermented milk attenuate DSS-induced gene expression changes in the colon.

The impact of DSS treatment, of unfermented dairy products, and of *P. freudenreichii*-fermented dairy products was also assessed with respect to gene expression in colonic tissue. As expected, DSS-induced colitis drastically modulated the expression of genes coding for immunomodulatory and barrier related proteins. Indeed, the barrier related genes *ocln*, *cldn1* and *cldn5* were up to 11-fold less expressed in the DSS group than in the NC group (Fig. 4). Likewise, the expression of the inflammatory genes *tnf* and *il1b* increased 37 and 52 times in the DSS group, respectively (Fig. 5). The expression of *il6* was also highly induced by DSS, but changes were not statistically significant against the NC group. We also found that the expression of *pparγ*, coding for the peroxisome proliferator activated receptor gamma, was down-regulated by DSS, while the abundance of *nos2* coding for the nitric oxide synthase 2 was 80-fold higher in the DSS group than in the NC group. Interestingly, the consumption of fermented whole milk (DSS-WM-129) was able to prevent alterations of the expression of all these genes, except *tnf*. The other fermented preparations also appeared to exhibit similar effects, but in a lesser extent than DSS-WM-129. Moreover, while DSS-WM-129 prevented the effects of DSS on the expressions of *ocln*, *nos2* and *il1b*, their expressions in the DSS-WM group were similar to those in the DSS group, showing the impact of the fermentation. Altogether, these results showed that DSS treatment resulted in dramatic changes in the expressions of many colonic epithelium genes, changes that were prevented by *P. freudenreichii* fermented preparations, notably fermented whole milk.

4. Discussion

The food matrix containing the probiotic *P. freudenreichii* has been shown to play a determinant role in its probiotic effects. When consumed in a fermented dairy product such as a fermented milk or a cheese, *P. freudenreichii* reaches higher live populations in the gut, when compared to isolated bacteria (Hervé et al., 2007; Rabah, Ferret-Bernard, et al., 2018), and affords protection towards induced colitis (Plé et al., 2015). The structure of the food matrix, resulting from the network involving proteins, lipids, and minerals, clearly plays a protective role towards the probiotic and its key surface molecules involved in the modulatory effects. In the current research work, we sought the respective role of dairy proteins and of dairy fat in the anti-colitis effect of *P. freudenreichii* CIRM-BIA129, a strain known for its immunomodulatory potential. This work indicates that dairy fat plays a beneficial role in the *in vivo* monitored anti-inflammatory effect of *P. freudenreichii*-fermented milk, giving new evidence for the need to consider the impact of the food delivery vehicle on the efficacy of probioticsfurther arguing

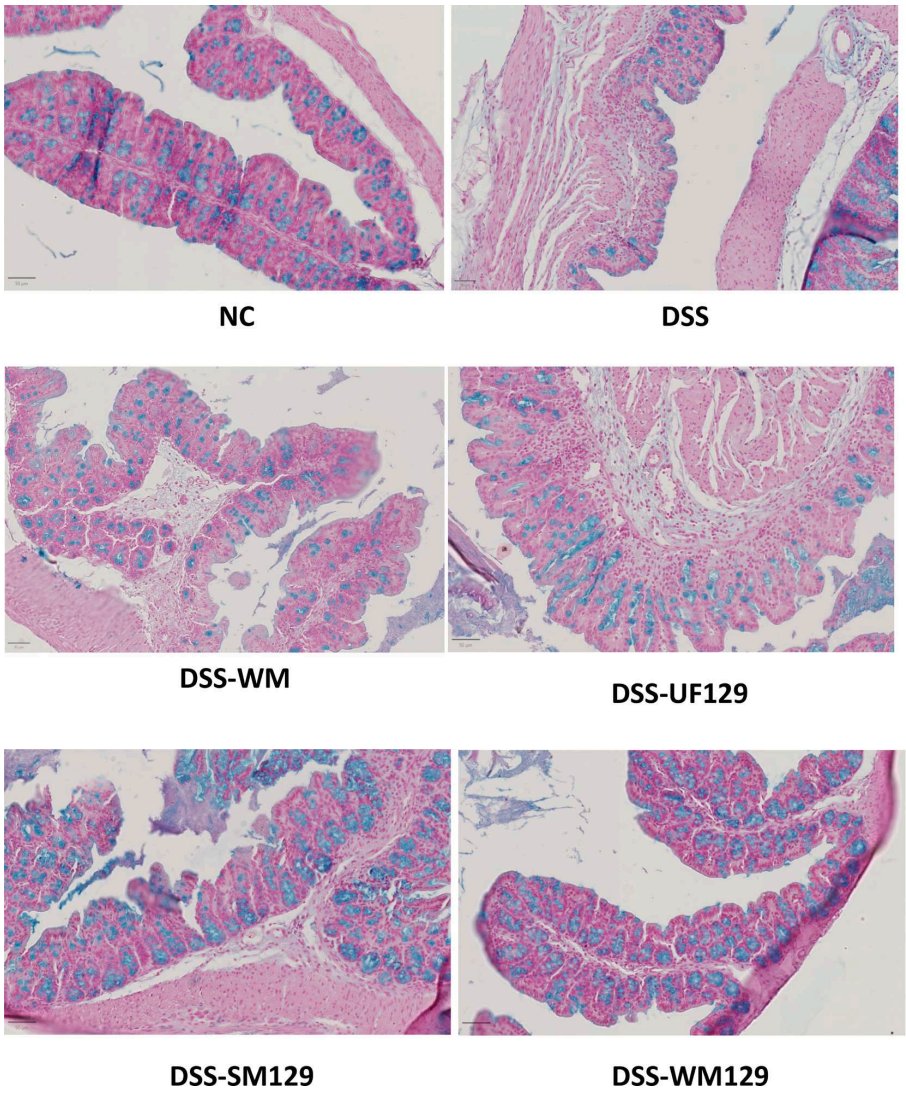

Fig. 2. *P. freudenreichii*-fermented milk alleviated DSS-induced colon histological damages. Representative images of Hematein Phloxin Safran (HPS) and Alcian Blue stained colon tissues (magnification 200 x) illustrate damages caused by DSS, when compared to control animals (NC). Damages were lower in mice consuming *P. freudenreichii*-fermented whole milk (DSS-WM129). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for a focus on how to improve the effectiveness (Lê et al., 2022).

Several strains of *P. freudenreichii* were already described as modulators of inflammation and of chemically induced colitis in mice models. A first study reported a promising protective effect of propionibacteria cultures in mice with TNBS-induced colitis (Foligné et al., 2010). In the same model, cheese containing *P. freudenreichii*, either as a sole bacterium (Plé et al., 2015), or in conjunction with selected immunomodulatory strains of the dairy starters *S. thermophilus* and *L. delbrueckii*, also afforded protection towards TNBS-induced colitis (Plé et al., 2016). Such a cheese furthermore protected mice from DSS-induced colitis (Rabah, 2020). In these studies, consumption of *P. freudenreichii* limited colon shortening and thickening, reduced disease activity index, histopathological score, colonic myeloperoxidase (MPO) activity, as well as pathological increase of gut permeability. In the research work presented here, consumption of milk fermented by *P. freudenreichii* CIRM-BIA129 was further shown to exert a preventive effect towards colitis induced by DSS. As a macroscopic indication, the shortening of the colon length was prevented by this consumption, whatever the food matrix. However, the disease activity index, which is increased during colitis, was reduced by the consumption of *P. freudenreichii*-fermented milk, yet not of fermented ultrafiltrate, which consists in the aqueous phase of milk, devoid of fat and of proteins. Furthermore, as a microscopic indication, the histopathological score was reduced as a result of fermented whole milk consumption, while the other fermented products failed to do so. Hence, the food matrix components, including dairy fat, play a role in the protective effect of *P. freudenreichii*-fermented products.

In our study, consumption of *P. freudenreichii*-fermented milk

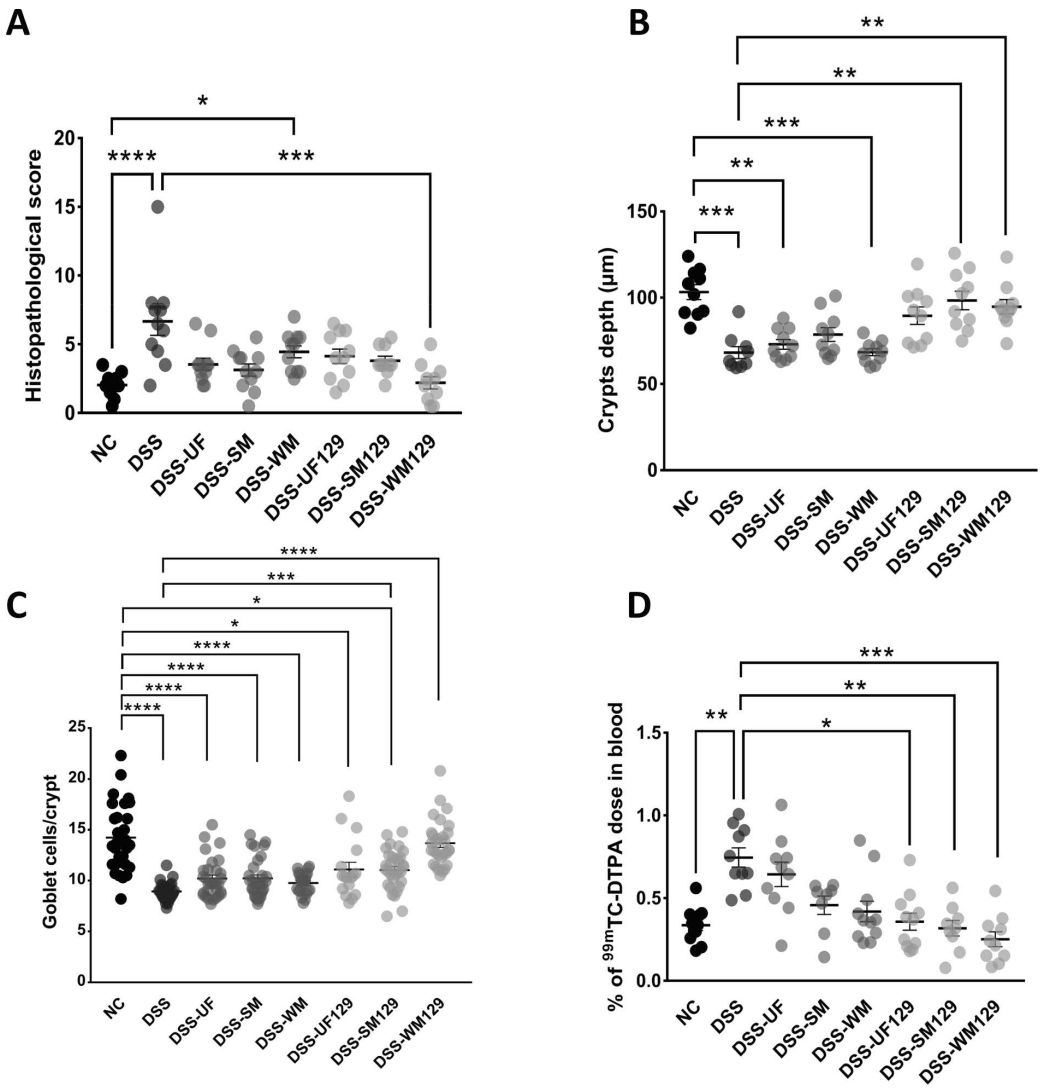

Fig. 3. *P. freudenreichii*-fermented milk alleviated DSS-induced colon histopathological injury and increased permeability. (A) Histological score were evaluated by quantifying the destruction of mucosal architecture, cellular infiltration, muscle thickening and loss of goblet cells. (B) The depth of colon crypts was measured for 50 crypts per animal. The mean value was used for comparison between groups. (C) Goblet cells were measured as the ratio goblet cells/crypt, 50 crypts per animal. The average was used for comparison between groups. (D) On the last day, mice were gavaged with a solution of radiolabelled 99mTc-DTPA. After 4 h, the animals were anesthetized and radioactivity determined in the blood. Data represent mean +/- SEM of 10 mice per group. Kruskal-Wallis test followed by Dunn's multiple comparisons test was performed. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$.

prevented the pathological increase of gut permeability upon colitis induction by DSS. Indeed, passage of the radiolabelled DTPA to the blood stream, which was drastically increased by DSS-induced colitis, was limited by the consumption of all the *P. freudenreichii*-fermented products. As key actors of gut integrity, intestinal epithelial cells, under the mucus layer, are tightly bound by tight junctions (TJ). TJ proteins, including ZO-1, occludin and claudin, are main actors of the integrity of the gut epithelial barrier and play a crucial role in intestinal homeostasis and tightness. Indeed, reduced expression of TJ proteins coincides with permeability increase in a leaky gut and has been described in animal models of colitis (Camilleri, 2019). We thus investigated the expression of genes encoding TJ proteins. Indeed, expression of the genes encoding occluding, claudin-5 and claudin-1 were repressed in DSS-treated mice in the present work, which is in line with the observed increased gut permeability. By contrast, consumption of *P. freudenreichii*-fermented whole milk restored expression of genes encoding TJ proteins. This is consistent with the concomitant restoration of intestinal integrity as shown by DTPA monitoring. Damages of the intestinal epithelial TJ result in abnormal increase of gut permeability. Pro-inflammatory metabolites of the gut microbiota, including lipopolysaccharide, in turn translocate through the intestinal barrier and elicit an inflammatory response. This last in turn exacerbates gut barrier defects in a vicious circle. Identifying food components able to restore gut barrier integrity thus constitutes a major quest. Protection of the gut barrier integrity, in the context of DSS-induced colitis, was already reported for probiotic bacteria such as *Limosilactobacillus reuteri* (H. L. (Lee et al., 2022);

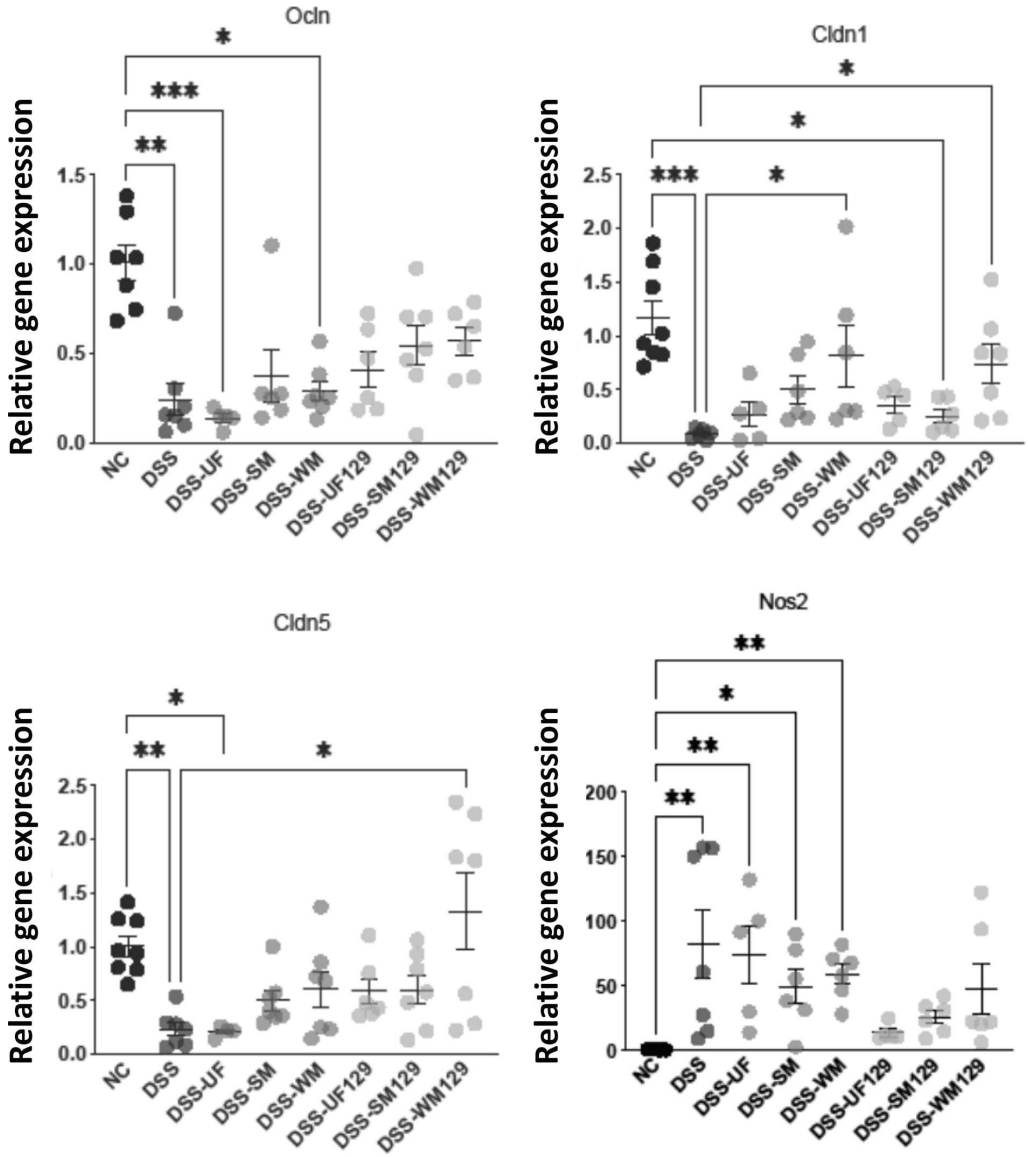

Fig. 4. *P. freudenreichii*-fermented milk modulated expression of key genes in the colon. The expression of key genes was monitored in colon extracts. Data are presented for genes Ocln, Cldn1, Cld5, Nos2, Il1b, Il6, Tnf and Pparg. Relative expression was determined using Actb, Gapdh and Tuba as reference normalisation genes. Kruskal-Wallis test followed by Dunn's multiple comparisons test was performed. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$.

Lacticaseibacillus casei (Zakostelska et al., 2011); *Limosilactobacillus fermentum* (Kaur et al., 2022); *Bifidobacterium breve* (Niu et al., 2022); *B. bifidum* (Shang et al., 2022) and *B. longum* (Y. (Chen et al., 2021). In these reports, the probiotic bacteria were also shown to restore the expression of tight junction protein genes. Such an effect was evidenced here as a result of *P. freudenreichii*-fermented products. Moreover, we show here that milk components, and in particular dairy fat, potentiate this protective effect. Indeed, the amount of propionibacteria was the same, i.e. 10^9 CFU $g.L^{-1}$, so that the differential effect of fermented products cannot be attributed to differential population of propionibacteria.

In the different animal studies dealing with probiotics and cited above, restoration of the gut barrier integrity was intimately linked to the ability of the probiotic bacterium to modulate inflammation. The inflammatory response includes the induction of the production of pro-inflammatory cytokines, which in turn contribute to the progression of colitis. Several probiotic bacteria, including dairy starters, were reported to mitigate the inflammatory response by preventing such inductions (Illikoud et al., 2022) and by repressing the TLR4-NF-κB pathway (Y. (Chen et al., 2021). In our study, DSS upregulated the pro-inflammatory cytokine IL-1β, indicating the induction of gut inflammation. IL-1β is a key factor in the pathogenesis of colitis and its upregulation is associated with ulcerative colitis (Bergemalm et al., 2021). Such induction exacerbates gut inflammation through the dysregulation

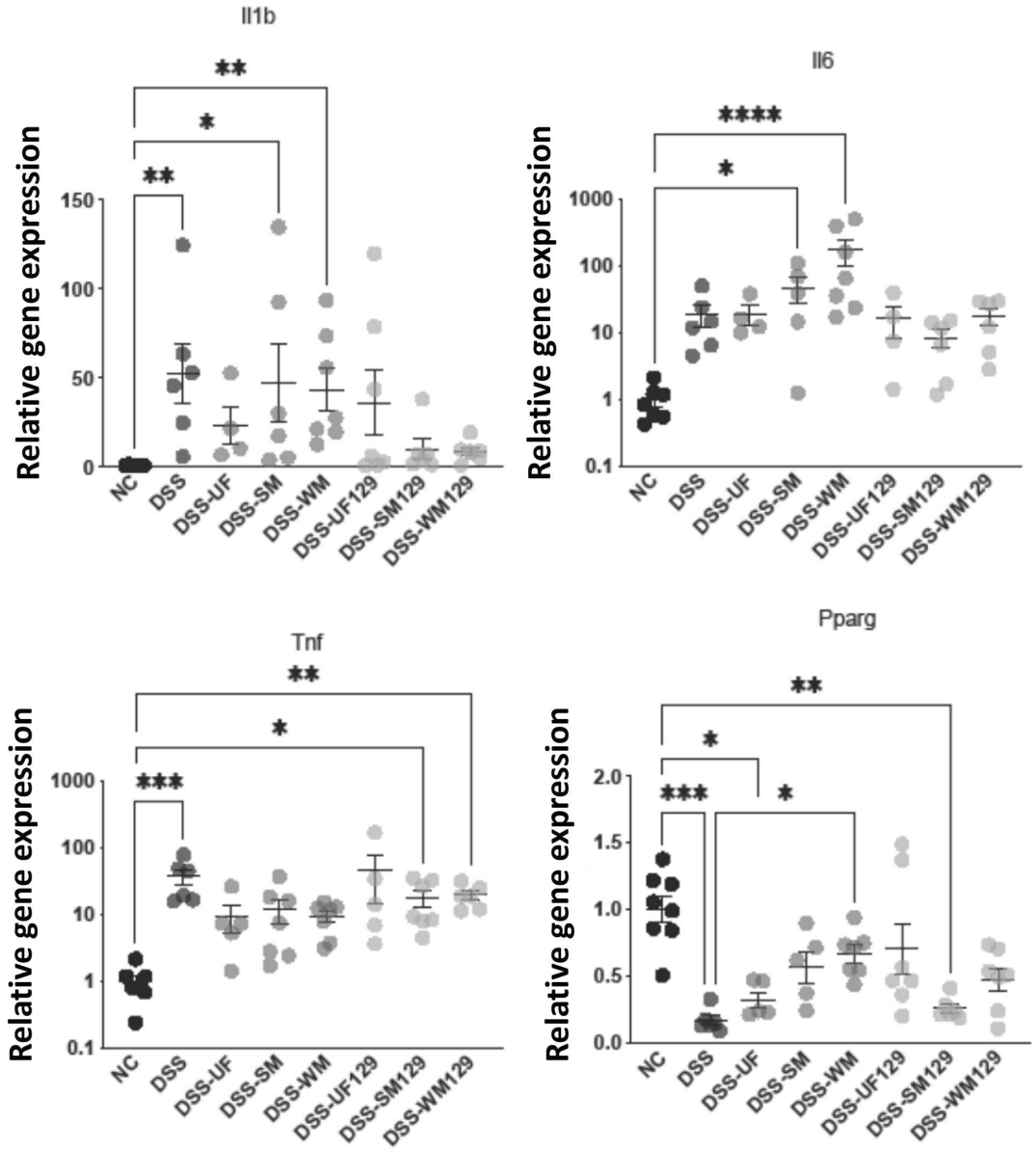

Fig. 5. ***P. freudenreichii*-fermented milk modulated expression of key genes related to inflammation in the colon.** The expression of key genes was monitored in colon extracts. Data are presented for genes Ocln, Cldn1, Cld5, Nos2, Il1b, Il6, Tnf and Pparg. Relative expression was determined using Actb, Gapdh and Tuba as reference normalisation genes. Kruskal-Wallis test followed by Dunn's multiple comparisons test was performed. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ and **** $p < 0.0001$.

of macrophage polarization. However, consumption of *P. freudenreichii*-fermented milk prevented this IL-1β induction, in line with previous probiotic studies. Immunomodulation was accordingly reported in *P. freudenreichii*, including an ability to induce IL-10 production in human immune cells (PBMC), and to prevent induction of pro-inflammatory cytokines *in vivo* in the context of colitis (Foligné et al., 2010) (Plé et al., 2015). Our study further demonstrates that an appropriate food delivery vehicle is necessary for this potential to give rise to protection against colitis. Indeed, protection was significant here only when *P. freudenreichii* was provided within a fermented milk, yet not in a UF culture. Accordingly, fermented whole milk afforded protection, while unfermented whole milk failed to do so.

Altogether, our results indicate that milk constituents, including dairy proteins and fat, potentiate the anti-colitis effects of the probiotic *P. freudenreichii*. Interestingly, consumption of unfermented whole milk also restored a gut permeability similar to that of healthy control mice, while being less anti-inflammatory than the fermented whole milk. In line with this, a previous report evidenced that the probiotic *L. casei* BL23, when provided within a fermented milk, alleviated symptoms of colitis in mice, while it failed to do so when provided in a nutrient-free buffer (~~B.~~ (Lee et al., 2015). This raises the question of the potentiating effect of milk constituents in fermented milk anti-colitis effects.

Interestingly, milk phospholipids were shown to alleviate DSS-induced colitis and to prevent goblet cell depletion (Wang et al., 2019). The protective effect of milk polar lipids was then shown to be more pronounced if mice received a western high-fat diet (Garcia et al., 2022). Milk fat globule membranes (MFGM) were shown to maintain the gut mucosal barrier, to inhibit oxidative stress and to attenuate colitis and hepatic injury in DSS-treated mice (Wu et al., 2022). Milk extracellular vesicles (mEVs) are bioactive constituents of milk and play a role in maintaining intestinal health. Their consumption alleviates the symptoms of DSS-induced acute colitis and limits the induction of pro-inflammatory cytokines (Du, Wang, et al., 2022). Furthermore, two subsets of mEVs contribute differently to colitis healing, one by modulating innate immunity and the other by decreasing inflammation (Benmoussa et al., 2019). This protective effect of mEVs was further shown to involve modulation of intestinal gene expression and of the gut microbiota in favour of bifidobacteria (Du, Wang, et al., 2022). Exosomes deriving from both bovine and human milk were further shown to mitigate DSS-induced colitis, to reduce expression of pro-inflammatory cytokines and to provide miRNAs involved in gene expression regulation (Reif et al., 2020). Milk fat globule-EGF factor 8 (MFG-E8) is known to play a role in maintaining the integrity of the gut mucosa. Accordingly, administration of this protein alleviates colitis and promotes mucosal repair (Chogle et al., 2011). Feeding mice with casein was further shown to facilitate recovery from DSS-induced colitis (Yu et al., 2021). Dietary intervention revealed that consumption of milk proteins limited the colon shortening and the IL-1β levels, while increasing the gut concentration of bifidobacteria, in DSS-induced colitis (Ma et al., 2021). Indeed, several probiotics revealed an anti-colitis effect when provided within a fermented milk, an effect which may be stronger than when the probiotic is consumed without a food matrix (~~B.~~ (Lee et al., 2015). As a possible explanation, immunomodulation often relies on key surface proteins or glycoproteins acting as MAMPs (microbial associated molecular pattern) and such MAMPS are susceptible to proteolysis during digestion. The dairy matrix protects such molecules from proteolysis, which may enhance their probability to interact with the host immune response. Concerning *P. freudenreichii*, its anti-colitis effect was accordingly particularly strong, in a previous study, when using Emmental cheese as food matrix delivery vehicle, with a significant effect on macroscopic, histological and immunological markers (Rabah, 2020). This cheese, as a Swiss-type (pressed cooked) cheese, is particularly rich in dairy proteins and lipids. Thus, different dairy matrices, with different structures, may potentiate the effects of probiotic bacteria. A special attention should thus be paid to protein and lipid constituent of the food matrix, when developing innovative fermented functional foods.

5. Conclusion

As a conclusion, this work demonstrates the key role of milk, including milk fat, in potentiating the anti-colitis potential of *P. freudenreichii*. This opens new perspectives for the development of fermented functional foods, which should consider the presence of the different components of milk, as well as the food structure, in addition to bacterial fermentation.

Ethics statement

The Ethics Committee on Animal Experimentation of the Universidade Federal de Minas Gerais (CEUA-UFMG, Brazil) approved all experimental procedures realized in this work by the protocol no. 148/2020.

CRediT authorship contribution statement

Marine Mantel: Investigation. **Tales da Silva:** Investigation. **Rafael Gloria:** Investigation. **Danièle Vassaux:** Investigation. **Kátia Duarte Vital:** . **Valbert Nascimento Cardoso:** . **Simone Odília Antunes Fernandes:** Investigation. **Éric Guédon:** Data curation. **Yves Le Loir:** Supervision. **Ana Maria Caetano Faria:** . **Malvyne Rolli-Derkinderen:** Supervision. **Vasco Azevedo:** Supervision. **Gwénaël Jan:** Conceptualization, Formal analysis, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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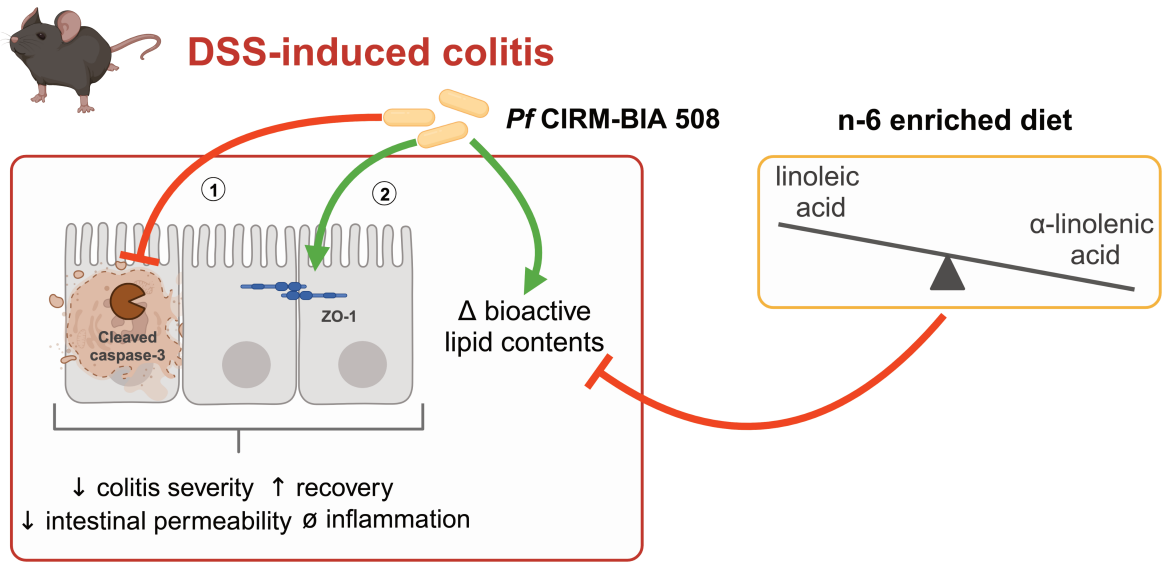
Article 3

n-6 diet counteracts the probiotic effect of dairy propionic bacteria *Propionibacterium freudenreichii* CIRM-BIA 508 on gut bioactive lipids and colitis.



3. ARTICLE 3 : OPTIMISER LES BIENFAITS DE *P. FREUDENREICHII* CIRM-BIA 508 : L'IMPACT DE L'ALIMENTATION SUR CE PROBIOTIQUE PROMETTEUR

Les deux derniers articles s'intéressaient à la souche *P.freudenreichii* CIRM-BIA129. Ils ont permis de mettre en avant les effets renforçateurs de barrière de la bactérie dans un modèle de colite et poser la question de l'impact de la matrice laitière sur l'effet du probiotique, avec les lipides du lait comme potentialisateur des effets anti-colite. L'alimentation apparaît comme un régulateur puissant des fonctions de la BEI, et est fortement impliquée dans le développement des MICI. C'est le cas d'une alimentation riche en oméga 3 ou oméga 6. En effet, certains métabolites dérivés des oméga 6 sont bénéfiques pour la fortification de la BEI (Pochard et al. 2021; Coquenlorge et al. 2016). Cependant, les patients atteints de MICI présentent une altération du métabolisme des oméga 6, avec des défauts des enzymes de synthèse et une diminution de certains métabolites, notamment impliqués dans la régulation des fonctions de la BEI (Sadler et al. 2016; Pochard et al. 2016). La synthèse de ces dérivés peut faire intervenir des bactéries, suggérant que le microbiote intestinal peut intervenir dans le métabolisme lipidique (Moens de Hase et al. 2023). De plus, *P.freudenreichii* est lipolytique, et impacte le microbiote intestinal en plus de ses effets immunomodulateurs, faisant de cette bactérie un bon candidat pour l'utilisation combinée avec des régimes lipidiques dans le cadre de traitements potentiels.

Dans ce contexte, le but de ce travail est dans un premier temps d'identifier une nouvelle souche de *P.freudenreichii* avec des effets encore plus puissants. Les effets immunomodulateurs de *P.freudenreichii* ont été corrélés à ses effets anti-colite. En partant de postulat, nous avons criblé 33 souches de *P.freudenreichii* sur leurs propriétés immunomodulatrices, en supposant que la souche la plus immunomodulatrice serait également la plus renforçatrice de la BEI. La souche identifiée a été testée dans un modèle de colite aigüe au DSS, et également dans un modèle de rémission. Enfin, dans le but d'optimiser les effets de prévention de colite de *P.freudenreichii*, le probiotique a été combiné avec un régime riche en oméga 6, en supposant que du fait de sa capacité lipolytique et son impact sur le microbiote intestinal, *P.freudenreichii* pourrait favoriser le métabolisme lipidique.

Ce travail identifie *P.freudenreichii* CIRM-BIA 508, une nouvelle souche faiblement immunomodulatrice, comme un puissant renforçateur de la BEI. *P.freudenreichii* CIRM-BIA 508 renforce la BEI *via* 1) une inhibition de l'apoptose et 2) une modulation de ZO-1, et la promotion de la réparation en améliorant la rémission. De façon inattendue, le régime enrichi en oméga-6 inhibe les effets bénéfiques de *P.freudenreichii* sur la prévention de la colite et la rémission. Le régime enrichi en oméga-6 modifie l'impact bénéfique de *P.freudenreichii* CIRM-BIA 508 sur le métabolisme lipidique du côlon. Ce travail de recherche souligne l'importance de prendre en compte le statut nutritionnel du patient lors de la prise de probiotique, et suggère une alimentation avec un ratio oméga-6 / oméga-3 plus faible afin de maximiser les effets bénéfiques de la bactérie dans un contexte de colite.

Cet article est en préparation.

n-6 diet counteracts the probiotic effect of dairy propionic bacteria *Propionibacterium freudenreichii* CIRM-BIA 508 on gut bioactive lipid metabolism and colitis.

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What is already known on this topic

Propionibacterium freudenreichii is a beneficial probiotic presenting anti-inflammatory properties and able to reinforce the mucosa.

Previous findings reported that n-3 or n-6 polyunsaturated fatty acid (PUFA)-enriched diet enriched diet could be linked to IBD development.

Linoleic and linolenic acid-derived metabolites regulate the intestinal barrier.

What this study adds

P. freudenreichii CIRM-BIA strains can prevent inflammation-induced intestinal epithelial damages, in a strain-dependent manner but independently of their immunomodulatory properties.

The strain *P. freudenreichii* CIRM-BIA508 reinforces the intestinal epithelial barrier (IEB) first through the inhibition of apoptosis and secondly via/by the modulation of ZO-1 protein and the promotion of repair mechanisms.

n-6 PUFA-enriched diet counteracts the protective effects of *P. freudenreichii* CIRM-BIA508 against colitis and its ability to favor IEB repair.

n-6 PUFA-enriched diet and *P. freudenreichii* CIRM-BIA508 differentially alter the metabolism of linoleic and linoleic acid-derived metabolites in the colon.

How this study might affect research, practice or policy

Our findings underlie *P. freudenreichii* as a therapeutic approach to protect against colitis through IEB strengthening.

n-6 enriched diet alters the protective effects of *P. freudenreichii* CIRM-BIA508 on linoleic and linolenic acid metabolism of the colon.

Balanced intake of n-6/n-3 PUFA might help to increase probiotic efficacy to maintain intestinal health in the context of modern stresses that promote chronic inflammatory diseases.

FOOTNOTES

Contributors Conceptualisation: GJ, YLL, MN and MRD; Design and Methodology: GJ and MRD; Investigation: MM, TD, AB and NC; Formal analysis: MM and MRD; Writing: MM, JM, GJ and MRD; Funding acquisition, YLL, MN, GJ and MRD; Supervision, GJ and MRD. Authors have approved the final draft of the manuscript.

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Competing interests None declared

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ABSTRACT

Background:

Accumulating evidence indicates that the intestinal epithelial barrier (IEB) defects play a central role in the pathogenesis of inflammatory bowel disease (IBD). Among the strategies of IEB reinforcement there is a growing interest for probiotic but also specific diet such as lipid-enriched diet. Specifically, the propionic bacteria *Propionibacterium freudenreichii (P. freudenreichii*) has immunomodulatory properties that could depends on fat intake, and n-6 polyunsaturated fatty acid (PUFA) derivatives can strengthen the IEB.

Objective:

To screen *P. freudenreichii* strains for their IEB strengthening properties and to investigate the potential of *P. freudenreichii* and n-6 PUFA interplay to protect against colitis development in mice.

Results:

We have identified that the *P. freudenreichii* CIRM-BIA508 strain prevents inflammation-induced increase of IEB permeabilities as well as inflammation-induced healing defect on Caco-2 cells. *In vivo*, this strain also decreases the score of DSS-induced colitis severity and promotes recovery. It inhibits the cleaved-caspase 3 expression and holds the expression of the tight junction (TJ) proteins zonula occludens-1 (ZO-1). Finally, n-6 enriched diet, that alone reduces colitis, can counteract the protective effects of *P. freudenreichii* CIRM-BIA508 and even fosters inflammation through the modification of the PUFA derivative production in the mouse colon.

Conclusion:

The strain *P. freudenreichii* CIRM-BIA508 owns beneficial properties on IEB repair and promote the recovery from colitis in a highly n-6/n-3 PUFA ratio dependent manner. N-6 PUFA enriched diet counteracts the *P. freudenreichii* CIRM-BIA508 modification of PUFA derivatives bioavailability in the colon, supporting the notion that the interplay of lipid diet and probiotic should be tightly controlled to maximize probiotic properties upon intestinal health.

Keywords: Inflammatory bowel disease, dairy propionic bacteria, intestinal epithelial barrier, poly-unsaturated fatty acids.

INTRODUCTION

The inflammatory bowel diseases (IBD) that encompass both ulcerative colitis (UC) and Crohn's disease (CD) are complex chronic inflammatory disorders. The incidence of these diseases varies between different countries but overall has increased greatly in recent years, and IBD is now a major public health problem that affects approximately 3.6 million people in the United States and Europe (Ananthakrishnan et al. 2018).

IBD pathogenesis remains unclear, but combine dietary, lifestyle and environmental factors to genetic predispositions (Ananthakrishnan 2015). It is sustained by immune disorders, a decreased diversity of the gut microbiota and alterations of the intestinal epithelial barrier (IEB). This is the few that we know, and the control of the inflammation constitutes the base of the main actual (anti-TNF-α, -β4 integrin antibodies) and in development (anti-IL12, -IL23, -IL17, -MADCAM, -CCR9 antibodies) therapeutics (Plevy et Targan 2011). Despite an optimized use of immunosuppressive drugs and the new biologic agents, preventing disease outcome remains a challenge and the need for intestinal resection in CD and UC has remained stable. Primary and secondary failure to respond to approved therapies, and in some cases inability to provide a surgical solution, represents unmet needs in the treatment of IBD. In addition, when effective, the therapeutic approaches directed against pro-inflammatory effector cytokines (anti-TNF-α, -IL12, -IL23), bear the risk to blunt physiological immune responses and are therefore sometimes complicated by increased infection risk. The treatments, which have to be given life-long, are unsatisfying and neglect to consider another active player of IBD development as target of therapy: the intestinal epithelial barrier.

An increase in intestinal permeability occurs in asymptomatic first-degree relatives of CD patients (Munkholm et al. 1994) and precedes the onset and relapse of CD (Wyatt et al. 1993). This increase also occurs in segments of the gut that are not involved by the disease (Joossens et al. 2010; Plevy et Targan 2011), and, if the barrier disruption is not enough to induce the disease, reducing barrier permeability prevents the development of inflammation in a genetic model of CD (Arrieta et al. 2009). In addition to permeability defects, mucosal healing is altered and efficient mucosal healing is a marker of the good evolution of the pathology and correlates with better clinical outcomes among which less relapse frequency, less surgery and shorter hospital stay for the patients (Schett et Neurath 2018; Kato, Yoshida, et Hiraoka 2019; Na et al. 2019). Therefore, approaches aimed at reinforcing or re-establishing IEB functions could be of interest both in the prevention of relapses, and in the treatment of IBD, along with the current therapeutics.

Better that pharmacological approaches (Arrieta et al. 2009) probiotics and diet are emerging as powerful regulators of IEB functions (Lê et al. 2022). The gut microbiota, in healthy conditions, helps maintain the physiological integrity of tight junction proteins, and thus of the impermeability of the intestinal barrier (Paradis et al. 2021). *Akkermansia muciniphila* strengthens tight junction (Chelakkot et al. 2018; W. Wu et al. 2017), *Faecalibacterium prausnitzii* favors the proliferation of gut epithelial cells and enhances the synthesis of tight junction proteins (Xu et al. 2021), and *Bifidobacteria* maintain intestinal microvilli integrity (Ruiz et al. 2017). In the same manner, numerous types of diet or diet components are involved in IBD or colitis intensification or relief. N-3 or n-6 polyunsaturated fatty acids (PUFA)-enriched diets are among the most investigated nutrients for their potential association to IBD. These diets have a renewed interest especially because they regulate

and/or are regulated by key elements of digestive homeostasis: lipids and microbiota (T. Wu et al. 2022; Pujo et al. 2021; Schreiner et al. 2020). N-6 PUFA-enriched diet protects from intestinal injury induced by ischaemia/reperfusion (Gobbetti et al. 2015) and n-6 PUFA-derived metabolites can alleviate colitis and inhibit intestinal epithelial permeability and apoptosis (Pochard et al. 2021).

In this context, the *Propionibacterium freudenreichii (P. freudenreichii),* is of particular interest. This actinobacterium found in Swiss-type cheese, which holds a Generally Recognized as Safe (GRAS) status in the United States, as well as a Qualified Presumption of Safety (QPS) status in Europe, has immunomodulatory properties and could protect the IEB. *P. freudenreichii* induces the IL-10 cytokine production in human peripheral ***blood*** mononuclear cells to mitigate the severity of TNBS-induced colitis (Foligné et al. 2010). More recently, *P. freudenreichii* was shown to reduce the gut permeability induced by the cancer chemotherapy drug 5-fluorouracyl (do Carmo et al. 2019), suggesting that *P. freudenreichii* could exert a protective effect towards the gut epithelial barrier.

As *P. freudenreichii* properties are highly strain-specific (Foligné et al. 2013) and depends on the presence of dairy fat (Mantel et al. 2023), we looked for strains that could protect the intestinal epithelial barrier from damages induced by inflammation and investigated whether *P. freudenreichii* could thereby inhibit mice colitis with or without n-6 PUFA enriched diet.

METHODS

Growth of dairy propionibacteria

The 33 strains of *Propionibacterium freudenreichii* CIRM-BIA (*P. freudenreichii* CIRM-BIA, **Table S1**), were initially isolated from a Swiss-type cheese. They were provided by the CNIEL (Centre National Interprofessionel de l'Economie Laitière) and maintained by the CIRM-BIA microbiological resource center (Centre International de Ressources Microbiennes, Bactéries d'Intérêt Alimentaire, Rennes, France). Starting from a frozen stock, precultures were grown in liquid Yeast Extract Lactate (YEL) medium containing 0.1M sodium DL-lactate (Sigma Aldrich, Saint Louis, USA) and 10 g/L yeast extract as described (Malik, Reinbold, et Vedamuthu 1968). *P. freudenreichii* CIRM-BIA were then grown at 30°C under micro-aerophilic conditions for 60 hours in milk ultra-filtrate (MUF) supplemented with 5 g/L casein peptone (casein peptone plus, Organotechnie, La Courneuve, France), 0.1M sodium DL-lactate filter-sterilized using a 0.2 µm NalgeneTop filter (Thermoscientific).

PBMCs stimulation

Peripheral blood mononuclear cells (PBMCs) were purchased from Stemcell Technologies (Vancouver, BC, Canada), they were isolated from blood of a single healthy donor. The reference bacterial strains were prepared as previously described (Foligne et al., 2007). Propionibacteria were harvested from fermented milk ultrafiltrate (MUF) by centrifugation (12,000xg, 5 min, 4°C), washed twice with phosphate buffer salt (PBS), and resuspended in PBS containing 20% glycerol. Human PBMCs were washed in RPMI 1640 medium (Roswell Park Memorial Institute medium, Stemcell technologies, Vancouver, BC, Canada) and adjusted to $1x10^6$ cells/mL in RPMI 1640 supplemented with 2 mM L-glutamine, 100 U/mL penicillin, 100 µg/mL streptomycin and 10% fetal calf serum (PAN-Biotech GmbH, Aidenbach, Germany). PBMCs were seeded in 24-well tissue culture plates (Corning, NY, US) and stimulated with the bacterial suspensions, MOI (10:1). Two controls were included: *B. longum* Bb536 as a positive IL-10-inducing control and *Lactococcus lactis* (MG1363) as a positive IL-12-inducing control. After 24 h of coculture at 37°C and 5% CO2, culture supernatants were collected and clarified by centrifugation (800xg, 8 min, 20°C). The supernatant was collected and transferred to 96-well plated containing 5 µL/well of protease inhibitor (Sigma-Fast). The plates were stored at -20°C until ELISA assays.

Cytokines quantifications

Levels of IL-10 and IL-12 present in the PBMC supernatants were measured in 96 well plates (Nunc Immuno MaxiSorp, Thermo Electron LED) using commercially available ELISA kits (BD Bioscienced, Pont de Claix, France) in accordance with the manufacturer's instructions. Absorbances were read at 450 nm using microplate spectrophotometer system (Bio teck instruments, Inc, Winooski, USA). Quantified data presented is the total concentration (pg/mL) of a given cytokine produced. All quantifications were performed in triplicate.

Caco-2 cell culture

The human intestinal epithelail cell (IEC) line Caco-2 was obtained from the American Type Culture Collection (Manassas, VA) and cultured in Dulbecco modified Eagle medium containing 4.5 g/L glucose (Gibco, Life Technologies, Carlsbad, CA) supplemented with 10% heat-inactivated fetal calf serum, 2 mmol/L glutamine, 100 IU/mL penicillin, and 100 µg/mL streptomycin. For treatments, trans-epithelial electrical resistance (TEER) and permeability experiments, 116.071 cells/cm^2 were seeded onto Transwell Permeable Supports (Costar, REF 3460) and grown for 21 days.

Caco-2 treatments, TEER, permeability and healing measurement *In vitro*

To determine the effect of *Propionibacteria* or inflammation on intestinal epithelium, the TEER was measured before and after treatments with an epithelial voltohmmeter (EVOM; World Precision Instruments, Inc, Sarasota, FL). Caco-2 cells were incubated for 24 hours with either *P. freudenreichii* CIRM-BIA129 or *P. freudenreichii* CIRM-BIA508 or *P. freudenreichii* CIRM-BIA1472 or *P. freudenreichii* CIRM-BIA1477 or *P. freudenreichii* CIRM-BIA1495 or *P. freudenreichii* CIRM-BIA1496 (MOI 1:100), in DMEM medium (0% FBS, 1% P/S) in the apical compartment. After 24 hours, an inflammatory stimulation was induced with a cytomix containing 50 ng/mL of TNF-α (human TNF-α, 50µg, 130-094-017, Milteny Biotec) and 500 ng/mL of IFN-ɣ (human IFN-g1b, 1000µg, 130-096-486, Milteny Biotec) in 0% FBS in the apical compartment as well as in 10% FBS in the basolateral compartment, for 6 days with a renewal on day 3. To determine the effect of these treatments on permeability, 50 µL of the apical medium was replaced by 50 µL of 1 mg/mL of 0,4kDa sulfonic acid-FITC, 6 mg/mL of dextran 4 kDa -TRITC and 3 mg/mL of 44kDa HRP (Peroxidase from horseradish, P8250, Sigma-Aldrich). The fluorescence level of basolateral aliquots (150 µL) was measured every 30 minutes for a period of 180 minutes using a fluorimeter (BioTek Synergy H1, microplate reader). Paracellular permeability was determined by averaging the slope change in fluorescence intensity over time by a linear regression fit model. To assess transcellular permeability to HRP (Peroxidase from horseradish, P8250, Sigma-Aldrich), an enzymatic activity assay with (TMB Substrate Reagent Set, 555214, BD Biosciences) was performed. For wound healing experiments, Caco-2 cells were stimulated for 24 hours with *P. freudenreichii* CIRM-BIA508 (MOI 1:100), in DMEM medium (0% FBS, 1% P/S) in the apical compartment. After 24 hours, an inflammatory stimulation was induced with a cytomix containing 50 ng/mL of tumor necrosis factor-alpha (TNF-α) (human TNF-α, 50µg, 130-094-017, Milteny Biotec) and 500 ng/mL of interferon-gamma (IFN-ɣ) (human IFN-g1b, 1000µg, 130-096-486, Milteny Biotec) in 0% FBS in the apical compartment as well as in 10% FBS in the basolateral compartment, for 6 days with a renewal on day 3. On day 4, a wound was created using a pipette tip and wound healing closure as well as TEER were followed every day until cell fixation with 4% PAF at day 3.

n-6 PUFA enriched diet

Three-week-old C57Bl/6NRj male mice from Janvier Labs (Le Genest St Isle, France) were housed in a ventilated cage system under a 12-h light-dark cycle and *ad libitum* access to food and drinking water. Mice were randomly assigned to one of the two isocaloric diets containing 5% of fat (w/w) for 8 weeks. A control (SAFE U8958 Version 367), and an n-6 enriched diet (SAFE U8958 Version 368) were provided. Control diet contained grape seed oil,

and n-6 enriched diet soybean oil. The full composition of the diet is given in Figure 7 and Sup. Figure 2. Pellets were stored at -20°C and changed twice a week to avoid oxidative degradation of lipids. Mice were weighted once a week and after 8 weeks, they were randomly divided into 8 groups of 4 animals to receive *P. freudenreichii* CIRM-BIA508 and/or DSS as described below.

DSS-induced colitis and recovery, *in vivo* DAI and permeability assessment

Eight-week-old C57Bl/6NRj male mice from Janvier Labs (Le Genest St Isle, France) were housed in a ventilated cage system under a 12-h light-dark cycle and ad libitum access to food (SAFE A04) and drinking water. They were randomly divided into 4 groups of 5 animals: MUF (milk ultrafiltrate), 508 (MUF fermented with *P. freudenreichii* CIRM-BIA508 stran), DSS (dextran sodium sulfate), and 508DSS (MUF fermented with *P. freudenreichii* CIRM-BIA508 strain and DSS). Mice were gavaged either with 200 µL of MUF (MUF and DSS groups) or 200µL of 508 at 1.10^8 CFU (508 and 508DSS groups) for 11 days. The last 4 days, colitis was induced by 4% (w/v) of Dextran Sulfate Sodium (DSS, colitis grade 36,000-50,000, MP Biomedicals) in drinking water renewed every day for the groups DSS and 508DSS. To observe the recovery, at day 11, DSS was replace by drinking water for 11 additional days. The Disease Activity Index (DAI) was determined as indicated in **Table 1**, according to the 3 main clinical symptoms of colitis: diarrhea, rectal bleeding, and weight loss, following a scoring previously described (Cooper et al. 1993).

Animals were weighted daily and at day 11 or day 13, mice received (5 µl/g of mouse) a solution comprising 30 mg/ml carmine red (cochineal carmine, Prolabo #22259), 10 mg/ml fluorescein-5,6-sulfonic acid (FSA, fluorescein-5-(and-6)-sulfonic acid, trisodium, F1130, In vitrogen), 100mg/mL Dextran TRITC (TRITC-dextran 4 kDa, TdB Labs), and 10 mg/ml horseradish peroxidase (HRP; Peroxidase from horseradish, P8250, Sigma-Aldrich) resuspended in 0.5% carboxymethylcellulose in PBS (Sigma-Aldrich) *via* gavage, and then placed in individual cages. Four hours after gavage, blood was collected from the tail vein and permeability was evaluated in 5 µL of plasma. Paracellular permeabilities were evaluated *via* titration of FSA and TRITC-dextran fluorescence intensity measured at 487 nm and 520 nm, respectively, using an automatic microplate reader (BioTek Synergy H1, microplate reader). Mice were killed at the end of the protocol by cervical dislocation. Colonic tissues were collected and snap frozen for further gene and protein expression analysis or were also fixed for 24 hours in 4% paraformaldehyde for histopathological analysis. This procedure was repeated 3 times independently. The entire protocol was submitted and approved by the ethic committee.

Histopathological score

After fixations, distal colons were dehydrated and embedded in paraffin. Sections of 5 µm were stained with haematoxylin–phloxine–saffron (HPS) or Alcian Blue (MicroPICell platform, Nantes, France) for histopathological analysis. Images were taken using a slide scanner (Nanozoomer; Hamamatsu). As previously described, distal colonic tissue damage was evaluated by two investigators in a blinded manner through the calculation of a micro disease activity index (mDAI) which reflects the destruction of mucosal architecture, the cellular infiltration, muscle thickening and goblet cells depletion (Pochard et al. 2021). The scoring for the destruction of mucosal

architecture was as follows: 0-3 (0: none, 1: 1/3 basal, 2: 2/3 basal, and 3: loss of crypt and epithelium). The extent of cellular infiltration was rated on a scale of 0-3 (0: none, 1: infiltrate around crypt basis, 2: extensive infiltration reaching the muscularis mucosae, and 3: infiltration of the submucosa). The degree of muscle thickening was also ranging from 0 to 3, when the thickening was none, mild, moderate, or extensive thickening, respectively. The loss of goblet cell depletion was scored as 0 (normal presence) or 1 (massive depletion). A multiplication factor of 1–4 was applied for each measured criteria, depending on the extent of affected area (25, 50, 75, or 100%) of the considered sample.

Immunohistochemistry analysis

Paraffin was removed from the slides using successive baths of xylene, ethanol and distilled water. After washing the slides in PBS, antigen retrieval was performed *via* incubation at 95°C for 10 min in Dako antigen retrival buffer (5169984, 500mM, Dako). After three rinses with PBS, tissue sections were blocked with Dako Blocking Buffer (X0909, Dako) for 1 hour at room temperature (RT). Distal colon sections were then incubated with primary antibodies (**Table S2**) in Dako diluent (S0809, Dako), over-night at 4°C. After washing in PBS, sections were stained with Cy5-conjugated secondary antibodies (**Table S2**) for 2 hours at RT. Coverslips were mounted using ProLong Gold Antifade Mountant (P36930, Invitrogen). Images were acquired with an Axio Observer (Zeiss).

Immunocytochemistry analysis.

Caco-2 cell transwell filters were fixed in 4% paraformaldehyde (PAF) in PBS for 30 minutes. The size of IEC was determined using ZO-1 immunostaining. Briefly, fixed filters were first permeabilized with 0.5% Triton in PBS and then blocked using a solution of 0.5% Triton in PBS containing 10% horse serum (HS). Cells were incubated with primary antibody (**Table S2**) in 0.5% Triton-PBS 10% HS overnight at 4°C. After washing in PBS, cells were stained with Cy5-conjugated secondary antibodies (Table S1) for 1 hour at RT. Filters were mounted using ProLong Gold Antifade Mountant (P36930, Invitrogen). Images were acquired with an Axio Observer (Zeiss).

Lipocalin-2 enzyme-linked immunosorbent assay faecal quantification

The faeces of each mouse were resuspended in a solution of PBS-Tween 20 0.1% protease inhibitor cocktail (1/2 tablet for 25 ml solution, cOmplete; Roche) to reach 100 mg faeces/ml. Lcn-2 was measured in the faecal solution using an enzyme-linked immunosorbent assay (ELISA) kit (Mouse Lcn-2/NGAL DuoSet ELISA; Bio-Techne), according to the manufacturer's protocol.

mRNA and protein extractions

Proximal colons from mice were lysed in RA1 buffer (Macherey-Nagel) with the Precellys 24 tissue homogenizer (Bertin Technologies, Montigny-le-Bretonneux, France), and total RNA and protein extraction was performed with a Nucleospin RNAII kit according to the manufacturer's recommendations. For Caco-2 filters, cells were lysed in ice-cold RIPA Lysis buffer (20-188, Merk) complete with protease inhibitor (66373700, Merk), a phosphatase inhibitor cocktail (P0044, Sigma) and sodium orthovanadate (S6508, Sigma).

Quantitative real-time PCR analysis

One microgram of purified mRNA was denaturated and processed for reverse transcription using Superscript III reverse transcriptase (Life Technologies). qPCR amplifications were performed using FastSYBR Green Master Mix kit (Applied Biosystems, Foster City, CA, USA) and run on a StepOnePlus system (Life Technologies). The primers used are listed in **TABLE S3**. Ribosomal protein S6 (RPS6) transcript was used as a reference. The relative expression of the gene of interest was measured by the $2^{\Delta\Delta Ct}$ method.

Enzyme-linked immunosorbent assay for colon cytokine quantification

Proteins from proximal colons were extracted as described above and resuspended in NETF lysis buffer complete with protease inhibitor (66373700, Merk), phosphatase inhibitor cocktail (P0044, Sigma) and sodium orthovanadate (S6508, Sigma). Suspensions were sonicated, and cytokines concentrations measured using an ELISA kit (ELISA MAX™ Deluxe Set Mouse IFN-ɣ, Biolegend, 430804).

Western Blot

For proximal colon, proteins were resuspended in 1:1 protein solving buffer and tris(2-carboxyethyl) phosphine-reducing agent (PSB-TCEP, Macherey-Nagel), sonicated and denatured for 5 min at 95°C. For Caco-2 filters, cells were washed with ice-cold PBS and lysed in ice-cold RIPA buffer complete with protease inhibitor (Roche) and serine-threonine phosphatase inhibitor (Sigma-Aldrich) cocktails and completed with NuPAGE™ LDS Sample Buffer 4X (NP0008, Invitrogen) and NuPAGE™ Sample reducing agent 10X (NP0009, Invitrogen), sonicated and denatured for 10 min at 70°C. Fifteen microgram of proteins were separated using NuPAGE™ 4-12% Bis-Tris or NuPAGE™ 3-8% Tris-Acetate gels (Life Technologies) and transferred to nitrocellulose membranes (Life Technologies). After blocking with Tris-buffered saline/0.1% Tween-20/5% nonfat dry milk for 30 minutes, blots were incubated overnight at 4°C with the primary antibodies (**Table S1**) diluted in Tris-buffered saline/5% nonfat dry milk.

Immunoblots were probed with HRP-conjugated anti-rabbit (Life technologies, 1:5000) or anti-mouse secondary antibodies (Sigma, 1:5000) and visualized by chemiluminescence (Clarity Western ECL Substrate, 170-5061, BioRad or Femto Maximum Sensitivity Substrate, 34095, Thermofisher) using a ChemiDoc MP Imaging System (Bio-Rad). Western Blot data are expressed as relative values to ß-actine and normalized to the control mean.

Polyunsaturated fatty acid metabolite profiling.

PUFA metabolites were also quantified in mouse proximal colons on day 11 via mass-spectrometry after lipid extraction, as previously described (Le Faouder et al. 2013). After the addition of 500 µL of PBS and 5 µL of deuterated internal standard (IS) mixture (5-HETEd8, LxA4d4, and LtB4d4), the colons were crushed by lysing MatrixA tubes in Precellys (Bertin Biotechnologies). Following two crush cycles (6.5 ms to 1.30 s), 10 µL of suspension was withdrawn for protein quantification and 0.3 mL of cold methanol (MeOH) was added. The samples were centrifuged at 1,016 x g for 15 min (4°C) and the resulting supernatants were subjected to a solide-

phase lipid extraction using an HLB plate (OASIS HLB 30 mg, 96-well plate; Waters, Saint-Quentin-en-Yevelines, France). Briefly, the plates were conditioned with 500 µL MeOH and 500 µL H2O/MeOH (90:10, v/v). The samples were loaded at a flow rate of approximately 1 drop per 2 s, and after complete loading, the columns were washed with 500 µL H2O/MeOH (90:10, v/v). The phases were thereafter dried under aspiration, and the lipids were eluted with 750 µL of MeOH. The solvent was evaporated under N_2, and the samples were resuspended in 140 µL of MeOH and transferred into a vial (Macherey-Nagel, Hoerdt, France). Finally, 140 µL of MeOH was evaporated and each sample was resuspended in 10 µL of MeOH for liquid chromatography-tandem mass spectrometry (LC-MS/MS) analysis. MetaboAnalyst web interface was used for data analysis. The data were first scaled using an auto-scaling method to obtain mean-centered values divided by the standard deviation of each variable. A heatmap was generated with hierarchical clustering of group averages and metabolites, using the average clustering algorithm and the Euclidean distance measure of the scaled data.

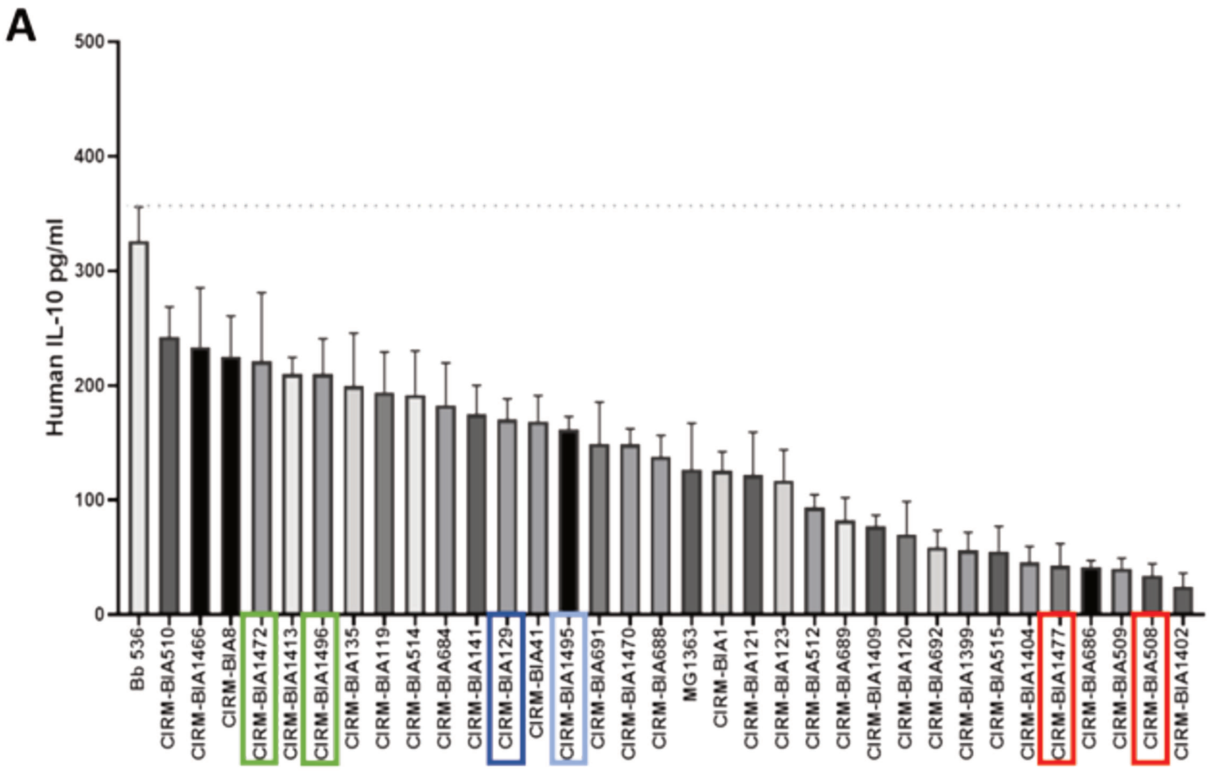
Statistical analysis

Results were expressed as mean +/- SEM. Outliers were excluded using Grubbs' tests. Statistical significance was analysed by an ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test, with a single pooled variance or a Kruskal-Wallis test, followed by a Dunn's multiple comparisons test (GraphPad Prism 9). Differences between experimental groups were considered significant at *p<=0.05, ** p<=0.01, *** p<=0.001.

RESULTS

P. freudenreichii strains have variable immunomodulatory properties.

The anti-colitis properties of *P. freudenreichii* (*P. freudenreichii)* are associated with its anti-inflammatory properties, particularly its ability to induce the interleukin-10 (IL-10) production by human Peripheral blood mononuclear cells (PBMCs) (Foligné et al. 2010). To screen the bacteria for their ability to induce IL-10 production and not IL-12, PBMCs were stimulated with 33 strains of *P. freudenreichii* CIRM-BIA. The strains were compared to two positive controls: *B. longum* Bb536 as a positive IL-10-inducer and *Lactococcus lactis* (MG1363) as a positive IL-12-inducer, and to the gold standard strain, *P. freudenreichii* CIRM-BIA129, which is framed in dark blue (Figure 1A, B). All the tested strains induced IL-10 production, but at highly variable levels (Figure 1A). Except the strain CIRM BIA691 and 119, the strains tested did not induce IL-12 production (Figure 1B). We selected five strains that did not induce IL-12 production but which have different potential to induce IL-10 production: two strains inducing a high level of IL-10 production (*P. freudenreichii* CIRM-BIA1472 and 1496) framed in green, the CRIME BIA 1495 (framed in light blue) inducing IL-10 levels comparable to the gold standard strain *P. freudenreichii* CIRM-BIA129 (framed in drak blue), and two strains that induce a low level of IL-10, the *P. freudenreichii* CIRM-BIA1477 and *P. freudenreichii* CIRM-BIA508 (framed in red) (Figure 1A). These strains were further tested to determine if their anti-inflammatory properties correlate with IEB strengthening properties that are the maintain of permeability and healing.



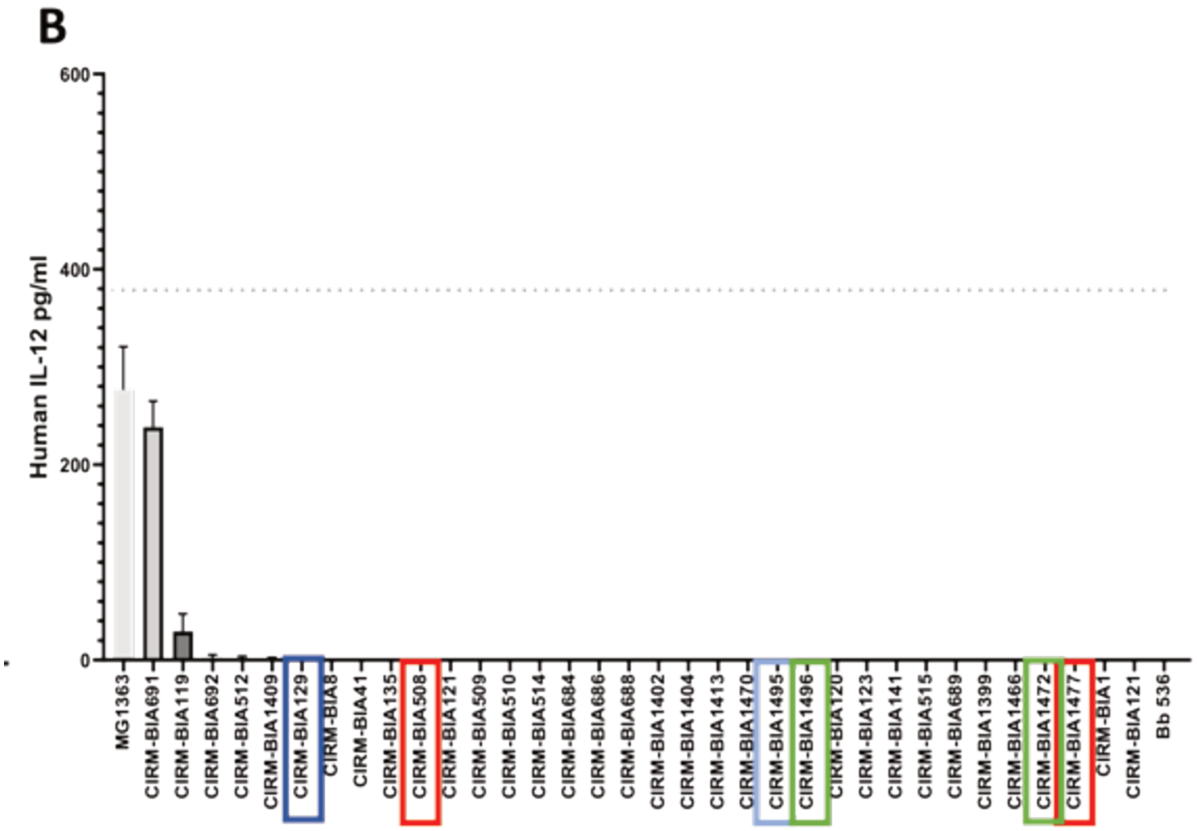


Figure 1

Figure 1. *Pf* CIRM-BIA strains have variable immunomodulatory properties. Production of cytokines by human peripheral blood mononuclear cells (PBMCs) in response to 33 different strains of *P. freudenreichii* or reference bacteria *Bifidobacterium longum* (BB536) and *Lactococcus lactis* (MG1363). (A) IL-10 and (B) IL-12 were assessed by ELISA in the supernatants collected from 24 hours cultures human PBMCs stimulated with the bacteria. *Pf* CIRM-BIA129 is the gold standard strain framed in dark blue. *Pf* CIRM-BIA1472, *Pf* CIRM-BIA1496, framed in green, *Pf* CIRM-BIA1495 framed in light blue and *Pf* CIRM-BIA508 and Pf CIRM-BIA1477 framed in red, were selected for their immunomodulatory properties. Data are expressed in pg/mL as mean +/- SEM (n=3).

P. freudenreichii strains 129, 508 and 1477 protect against inflammation-induced IEB breakdown.

The model of IEB disruption used consisted in Caco-2 cells cultured for 21 days on transwells and stimulated with TNF-α and IFN-γ for 6 days. These cells were treated with *P. freudenreichii* strains one day before the inflammation (Figure 2A). The three strains *P. freudenreichii* CIRM-BIA129, 508 and 1477 prevented the inflammation-induced decrease in TEER (Figure 2B) and increase in sulfonic acid permeability (Figure 2C). Only the *P. freudenreichii* CIRM-BIA508 and 1477 prevented the inflammation-induced increase in dextran permeability (Figure 2D), while only the *P. freudenreichii* CIRM-BIA508 inhibited the inflammation-induced increase in permeability (Figure 2E). The three other strains *P. freudenreichii* CIRM-BIA1472, 1495 and 1496, did not protect against the inflammation-induced decrease in TEER and increase in permeability, and rather worsened them (Supplemental Figure 1). These findings show that *P. freudenreichii* CIRM-BIA strains can counteract inflammation-induced IEB damages, but in a strain-dependent manner and independently of their immunomodulatory properties. *P. freudenreichii* CIRM-BIA508 demonstrated the strongest capacity in inhibiting inflammation-induced IEB paracellular as well as transcellular permeability. We therefore further tested this strain to foster IEB healing.

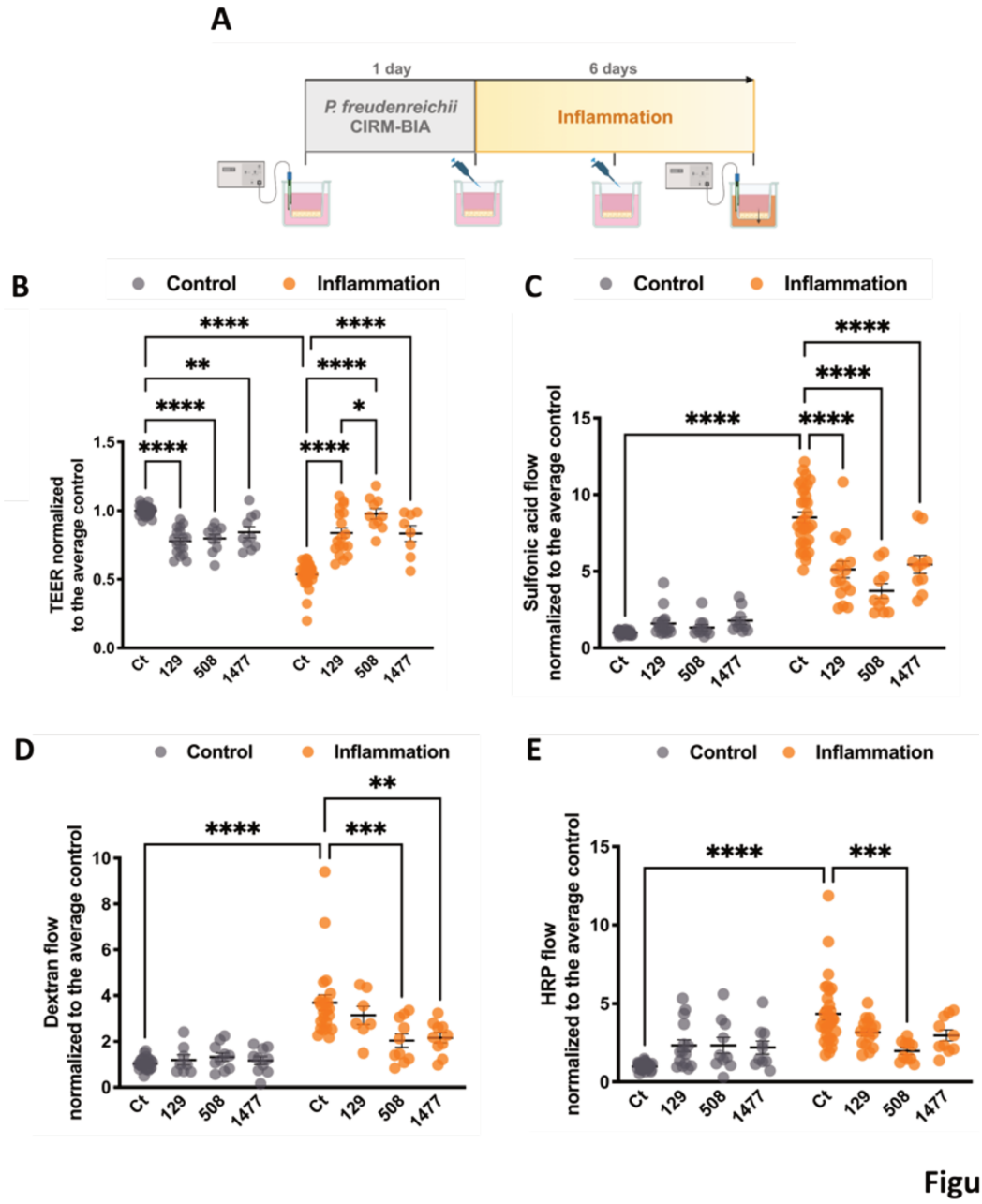


Figure 2

Figure 2. *Pf* CIRM-BIA protects against inflammation-induced IEB breakdown in a strain-dependent manner. (A) Caco-2 cells were grown on transwell for 21 days, and then left untreated or pre-treated with Propionibacteria (MOI 100:1) for 24 hours. They were removed and treated with an inflammatory cytomix containing TNF-α or IFN-ɣ for 6 days, with a renewal at day 3. (B) Trans-epithelial electrical resistances (TEER), (C) Sulfonic acid-FITC diffusion, (D) Dextran-TRITC diffusion and (C) HRP diffusion were measured at the end of the experiment. Data are normalized to control mean. Values are expressed as means +/- SEM. An ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test was performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

P. freudenreichii CIRM-BIA 508 improves healing through stimulating epithelial spreading.

To investigate if *P. freudenreichii* CIRM-BIA508 can directly improves epithelial restitution, we used the *in vitro* model of Caco-2 monolayer subjected to inflammation with or without pre-treatment with *P. freudenreichii* CIRM-BIA508. On day 4, a wound was operated, and the healing process was analysed at day 7 (Figure 3A). The wound was closed in all inflammatory conditions with or without *P. freudenreichii* CIRM-BIA508 at day 7 (Figure 3B, 3C). Nevertheless, the TEER was significantly reduced by inflammation, and *P. freudenreichii* CIRM-BIA508 prevented this decline (Figure 3D). The analysis of ZO-1 immunostaining allowed the evaluation of the epithelial cell surface and the localization of ZO-1 on tight-junctions at the plasma membrane. In control conditions, the healed area was well paved with spread cells, but in inflammatory conditions, the plasma membrane was very tortuous, the ZO-1 staining was irregular (Figure 3E) and the cell surface tended to be smaller (Figure 3F). *P. freudenreichii* CIRM-BIA508 treatment smoothed the cell border and significantly improved the cell surface area under inflammation (Figure 3E, 3F). In summary, these data showed that the inflammation-compromised healing process was improved by *P. freudenreichii* CIRM-BIA508. This strain demonstrated a high capacity in counteracting the effects of inflammation on the IEB. We therefore assess its potency to reduce colitis *in vivo*.

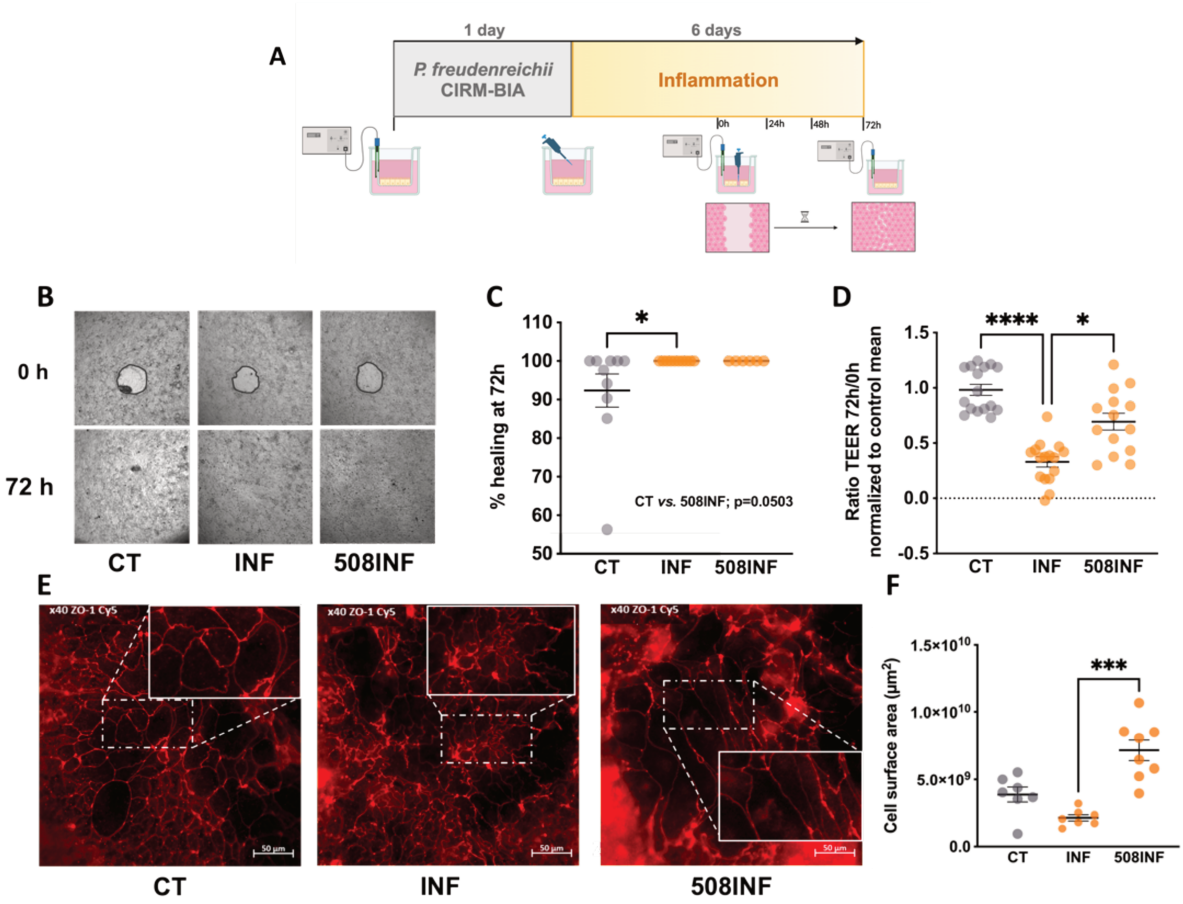


Figure 3

Figure 3. Functional impact of *Pf* CIRM-BIA508 stimulates on IEB healing *in vitro*. (A) Caco-2 cells were grown on transwell for 21 days, and then left untreated or pre-treated with *Pf* CIRM-BIA508 (MOI 100:1) for 24 hours. They were then removed and treated with an inflammatory cytomix containing TNF-α or IFN-ɣ was added for 6 days, with a renewal at day 3. On day 4, a hole was formed and healing as well as trans-epithelial electrical resistance (TEER) were followed. (B) Representative pictures of epithelial healing of Caco-2 monolayers taken immediately after creating the breach and again 72 hours later, within the three groups: control (CT) and inflammation (INF and 508INF). (C) Epithelial healing was measured as a percentage of restitution between 0 and 72 hours. (D) TEER ratio between 72h and after creating the breach normalized to control mean. (E) Representative immunostaining of ZO-1 on day 7. Left, control condition, middle, inflammation condition and right Caco-2 cell pre-treated with *Pf* CIRM-BIA508 and challenged with inflammation (508INF). (F) Epithelial spreading was evaluated through the measure of cell area delimited by ZO-1 staining. N=1-4. Ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test and Kruskal-Wallis test, followed by a Dunn's multiple comparisons test were performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

P.freudenreichii CIRM-BIA 508 mitigates colitis and promotes recovery *in vivo.*

For *in vivo* assessment of *P. freudenreichii* CIRM-BIA508 ability to reduce colitis, 8–10-weeks-old male were supplemented, or not, with the *P. freudenreichii* CIRM-BIA508 for 7 days before the addition of 4% DSS in the drinking water for 4 additional days. At day 11, DSS was removed from drinking water to allow the recovery (Figure 4A). Mice that received DSS in their drinking water experienced a significant weight loss after 2 days of recovery (day 13) (Figure 4B). A similar trend was observed with mice treated with *P. freudenreichii* CIRM-BIA508 (508DSS). All the DSS mice were dead by day 15 while 50% of the 508DSS mice survived by day 16, and the survival ones begun to gain weight (Figure 4B et 4C). At day 11, the disease activity index (DAI, reflecting weight loss, stool consistency and rectal bleeding) increased by DSS was prevented by *P. freudenreichii* CIRM-BIA508 supplementation (Figure 4D). At day 11, *P. freudenreichii* CIRM-BIA508 (508DSS) did not avoid the increase in paracellular permeability caused by the DSS (Figure 4E). The histopathological score (mDAI), reflecting the remodeling of the distal colon (cellular infiltration, muscle thickening, epithelial destruction, and goblet cell loss), was significantly increased only in the DSS group but not in the 508DSS group (Figure 4F and 4G). Under basal conditions, *P. freudenreichii* CIRM-BIA508 (508) supplementation had no impact on the measured parameters (Figure 4D—G). At the beginning of the recovery, at day 13 (2days post DSS removal), both DSS groups (DSS and 508DSS) exhibited a significant increase in DAI (Figure 4H). However, neither the paracellular permeability nor the colon remodeling (mDAI) were significantly increased within the 508DSS group, in opposition to the DSS group (Figure 4I-K). Overall, these findings emphasize the role of *P. freudenreichii* CIRM-BIA508 in protecting mice from colitis and facilitating recovery.

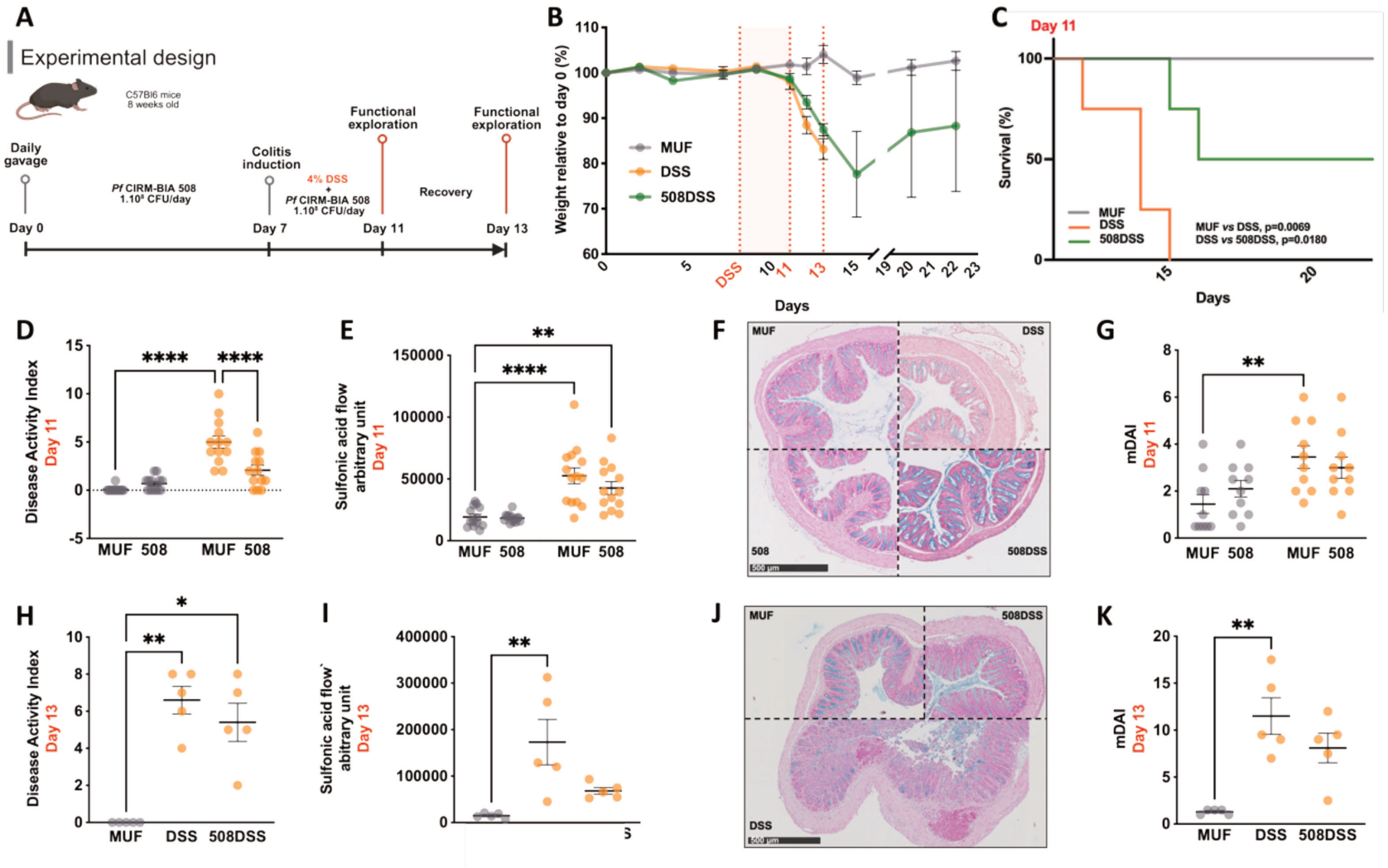

A
Experimental design
C57Bl6 mice
8 weeks old
Daily gavage
Pf CIRM-BIA 508 1.10⁸ CFU/day
Colitis induction
4% DSS + Pf CIRM-BIA 508 1.10⁸ CFU/day
Functional exploration
Recovery
Functional exploration
Day 0
Day 7
Day 11
Day 13
B
Weight relative to day 0 (%)
MUF
DSS
508DSS
Days
C
Day 11
Survival (%)
MUF
DSS
508DSS
MUF vs DSS, p=0.0069
DSS vs 508DSS, p=0.0180
Days
D
Disease Activity Index Day 11
MUF 508 MUF 508
E
Sulfonic acid flow arbitrary unit Day 11
MUF 508 MUF 508
F
MUF
DSS
508
508DSS
G
mDAI Day 11
MUF 508 MUF 508
H
Disease Activity Index Day 13
MUF DSS 508DSS
I
Sulfonic acid flow arbitrary unit Day 13
J
MUF
508DSS
DSS
K
mDAI Day 13
MUF DSS 508DSS

Figure 4

Figure 4. *Pf* CIRM-BIA508 mitigates colitis and promotes recovery *in vivo*. (A) Eight-week-old C57BL6 mice were gavaged during 11 days with milk ultra-filtrate (MUF) without or with 1.10^8 CFU of *Pf* CIRM-BIA508 (508). At day 7, 4% DSS was added to drinking water or not for 4 days. At day 11, DSS was removed from drinking water for 2 days. On days 11 and 13, permeabilities were measured, mice sacrificed, and the tissues collected. (B) Weight curves of the animals, where the weight was normalized as per the weight on the first day (day 0). (C) Survival curves, after day 11, of control mice without colitis (grey), of mice receiving DSS (orange), and of mice receiving DSS and *Pf* (green). (D) Disease activity index (DAI) of the 4 groups: control (MUF) or *Pf* CIRM-BIA508 (508) in control conditions (grey) or with DSS (DSS or 508DSS in orange) at day 11. (E) Paracellular permeability evaluated by measurement of sulfonic acid in animal plasma of the same groups, 4 hours after mice gavage. (F) Representative images of Alcyan Blue staining of the distal colon. (G) Histological scores (mDAI) quantifying the destruction of mucosal architecture, cellular infiltration, muscle thickening and loss of goblet cells at day 11, for the same 4 groups. Data represent mean +/- SEM of 14 mice per group. Ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test was performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001. (H) DAI of the 3 groups: control (MUF), DSS colitis (DSS) or DSS colitis with *Pf* (508DSS) at day 13. (I) Paracellular permeability evaluated by measurement of sulfonic acid in animal plasma 4 hours after mice gavage at day 13, for the same 3 groups. (J) Representative images of Alcyan Blue staining of the distal colon. (K) Histological scores (mDAI) quantifying the destruction of mucosal architecture, cellular infiltration, muscle thickening and loss of goblet cells at day 13, for the same 3 groups. Data represent mean +/- SEM of 5 mice per group. Kruskal-Wallis test, followed by a Dunn's multiple comparisons test was performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

P. freudenreichii CIRM-BIA 508 fails to reduce local colon inflammation.

To assess more specifically the inflammation observed in these conditions, the concentrations of faecal lipocalin-2, a biomarker of intestinal inflammation, and colon mRNA level of cytokines were measured at day 11 (Figure 5A-D) and 13 (Figure 5E-H). At day 11, faecal lipocalin was increased in the DSS group and supplementation with *P. freudenreichii* CIRM-BIA508 significantly reduced it (Figure 5A). The administration of DSS significantly increased *il1ß* mRNA expression, while reducing *il10* mRNA expression, and having no effect in *tnfα* at day 11 (Figure 5B—D). These changes were not prevented by *P. freudenreichii* CIRM-BIA508 supplementation (Figure 5B—D). At day 13, the faecal lipocalin-2 was increased only in the DSS group (Figure 5E). Both DSS groups (DSS and 508DSS) displayed a significant rise in *il1ß* mRNA expression. Only mice that received *P. freudenreichii* CIRM-BIA508 (508DSS) exhibited an increase in *tnfα* mRNA expression compared to the control group. There were no differences between groups concerning *il10* mRNA expression (Figure 5F). Overall, these data suggest that *P. freudenreichii* CIRM-BIA508 mitigates the severity of DSS-induced colitis without changing cytokine mRNA expression, but, limiting neutrophil presence.

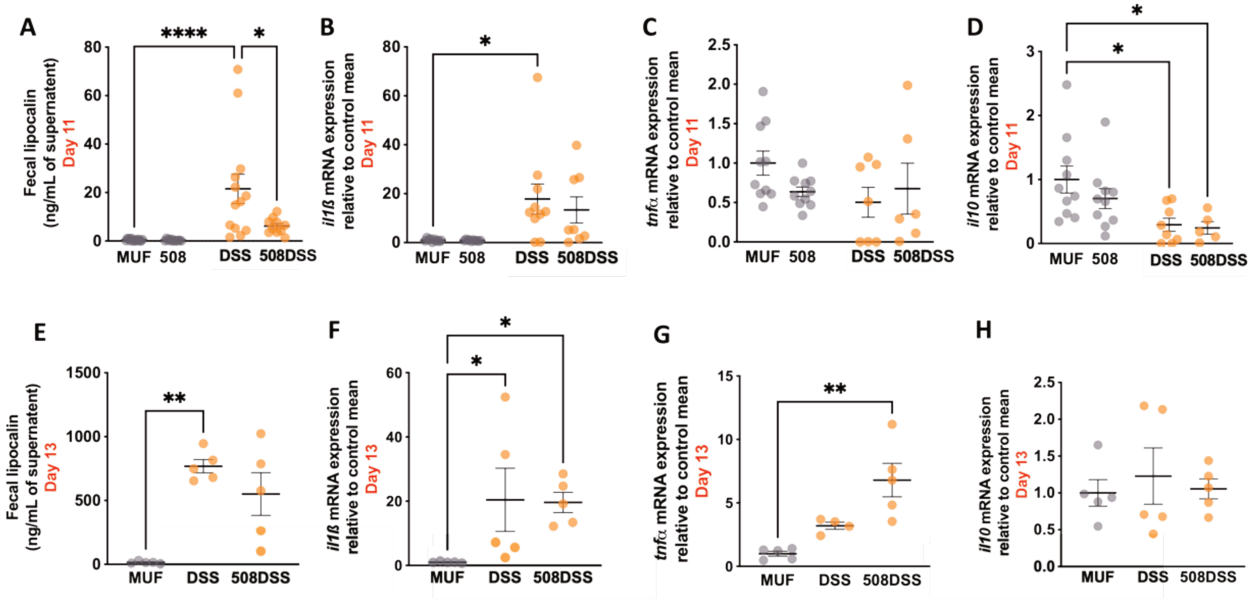


Figure 5

Figure 5. *Pf* CIRM-BIA508 fails to reduce local colon inflammation. (A) Fecal lipocalin contents were measured at day 11. mRNA expression of (B) *il-1ß*, (C) *tnf-α* and (D) *il-10* measured at day 11 in the proximal colon of the four groups: control groups (MUF and 508) and DSS groups (DSS and 508DSS). (E) Fecal lipocalin contents were measured at day 13. mRNA expression of (F) *il-1ß*, (G) *tnf-α* and (H) *il-10* measured at day 13 in the proximal colon of the control group (MUF) or DSS groups (DSS and 508DSS). Relative expression was determined using Rps6 as reference. Both protein and mRNA expressions were normalized to control mean. Ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test and Kruskal-Wallis test, followed by a Dunn's multiple comparisons test were performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

P. freudenreichii CIRM-BIA 508 prevents apoptosis and maintains ZO-1 expression.

To identify the molecular mechanisms regulated by *P. freudenreichii* CIRM-BIA508 to control IEB function, the expressions of tight-junction protein ZO-1 and cleaved caspase-3 (CC3) marker of apoptosis, were assessed in the proximal colon of mice at days 11 (Figure 6A-C) and 13 (Figure 6D-F). At day 11, western-blot analyses revealed that *P. freudenreichii* CIRM-BIA508 supplementation did not change ZO-1 expression under DSS-induced colitis (Figure 6A, 6B). Nevertheless, *P. freudenreichii* CIRM-BIA508 (508DSS) reduced the expression of CC3 expression under-DSS condition (Figure 6A, 6C). Regarding day 13, DSS led to a significant reduction in ZO-1 expression that was inhibited by *P. freudenreichii* CIRM-BIA508 supplementation (Figure 6D, 6E). At this time, no significant difference in CC3 expression was observed between the three groups (Figure 6D, 6F). Immunohistochemistry analyses showed discontinuous ZO-1 labeling on the plasma membrane of enterocytes in the DSS group at day 13. This effect was absent in the presence of *P. freudenreichii* CIRM-BIA508 supplementation (Figure 6G). Taking together, these findings support the idea that *P. freudenreichii* CIRM-BIA508 reinforces IEB through first the inhibition of apoptosis and second the modulation of TJ proteins and promotion of IEB repair.

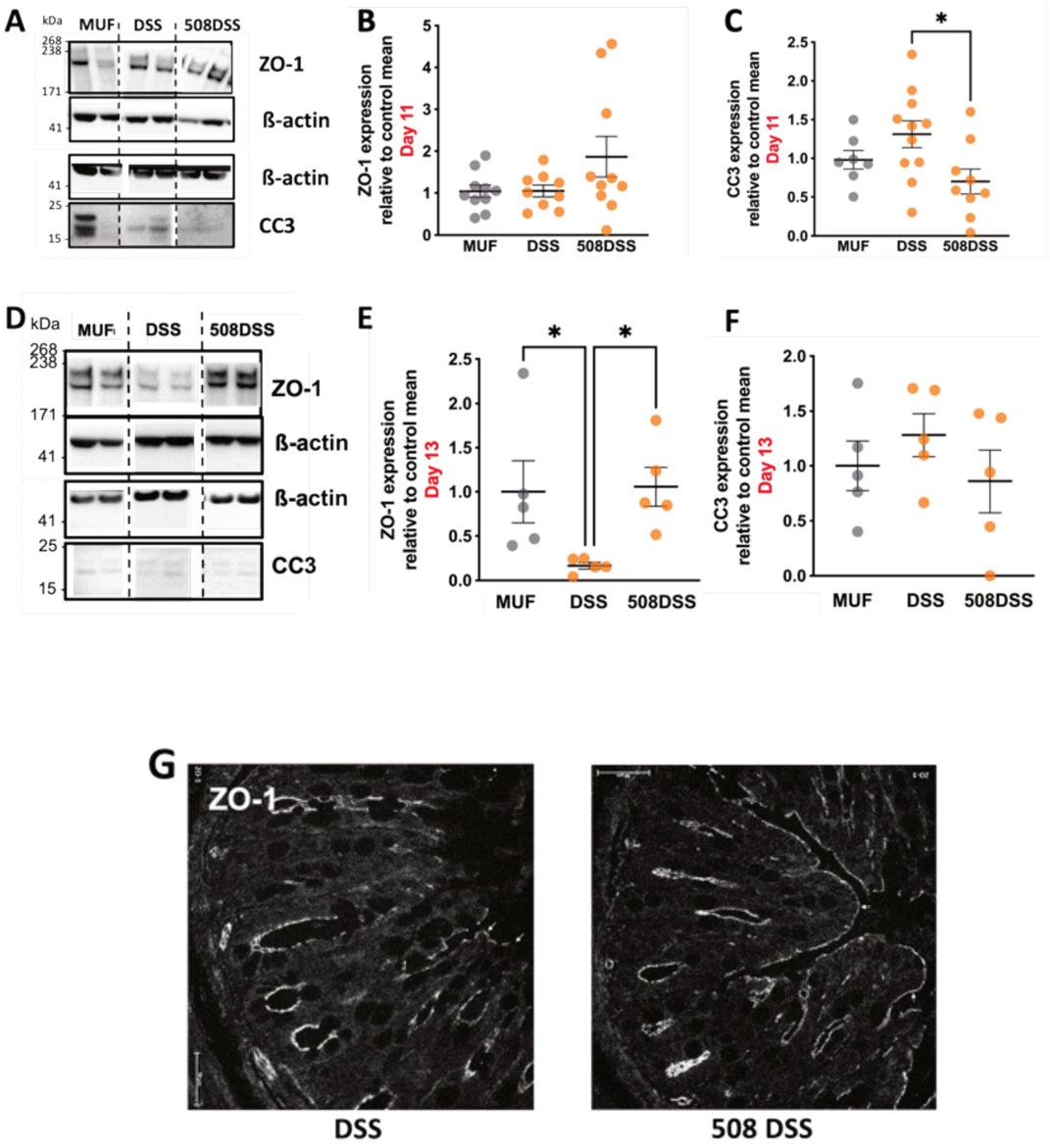


Figure 6

Figure 6. *Pf* CIRM-BIA508 inhibits apoptosis and promotes ZO-1 expression (A) Representative Western blot analysis of ZO-1, cleaved-caspase 3 (CC3) and ß-actin in the proximal colon of the three groups: control groups (MUF) and DSS groups (DSS and 508DSS) at day 11. (B) Quantification of ZO-1, and (C) cleaved caspase 3 (CC3) expression normalized to β-actin and relative to control mean. (D) Representative Western blot analysis of ZO-1, cleaved-caspase 3 and ß-actin in the proximal colon of the three groups: control group (MUF) and DSS groups (DSS and 508DSS) at day 13. (E) Quantification of ZO-1, and (F) cleaved caspase 3 expression normalized to β-actin and relative to control mean. (G) Representative immunostaining of ZO-1 in the distal colons of both DSS groups (DSS on top and 508DSS below) at day 13. Ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test and Kruskal-Wallis test, followed by a Dunn's multiple comparisons test were performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

n-6 PUFA enriched diet inhibits the *P. freudenreichii* CIRM-BIA 508 protection upon colitis.

n-6 PUFA metabolites can alleviate colitis and reduce intestinal epithelial permeability and apoptosis (Pochard et al. 2021) and n-6 PUFA-enriched diet protects from intestinal injury induced by ischaemia/reperfusion (Gobbetti et al. 2015). Hence, we next examined whether a n-6 enriched diet can ameliorate *P. freudenreichii* CIRM-BIA508 protective properties in a colitis model. Both control and n-6 PUFA-enriched synthetic diets presented similar nutritional values (Supplemental Fig2) but the n-6/n-3 ratio was increased in n-6 diet (Figure 7A and Supplemental Fig2). Diets were given for 8 weeks before *P. freudenreichii* CIRM-BIA508 supplementation and DSS treatment (Figure 7B).

All mice under the control diet survived DSS treatment when supplemented with *P. freudenreichii* CIRM-BIA508 (Figure 7C). In contrast, under n-6 PUFA-enriched diet, 50% of the mice supplemented with *P. freudenreichii* CIRM-BIA508 supplementation died within 3 days after DSS removal, whereas n-6 PUFA-enriched diet protected them from DSS (Figure 7D). Consistently, the DSS-induced increase of DAI was prevented in the 508DSS group fed with control diet (Figure 7E). However, the mice supplemented with *P. freudenreichii* CIRM-BIA508 and fed with n-6 diet showed an increased DAI under DSS although the n-6 diet alone had no effect on the DAI under DSS (Figure 7F). At day 11, the permeabilities were increased in the DSS group with or without *P. freudenreichii* CIRM-BIA508 but also with or without n-6 PUFA enriched diet (Supple Fig 3A-D). By investigating further gut inflammation, we observed that the faecal lipocalin content was significantly increased by DSS only in mice with n-6 PUFA enriched diet, that *Pf* CIRM-BIA508 supplementation did not reduced its levels (Figure 7G and H). In contrast, the DSS-induced *il1ß* and *tnfα* mRNA expressions, were inhibited by *P. freudenreichii* CIRM-BIA508 in control diet, but only significantly increased in the 508DSS group for animals with n-6 enriched diet (Figure 7I—L). These data confirm the protective role of *P. freudenreichii* CIRM-BIA508, show a partial protection with n-6 PUFA enriched diet, but restricts it to animals fed with diet poor in n-6.

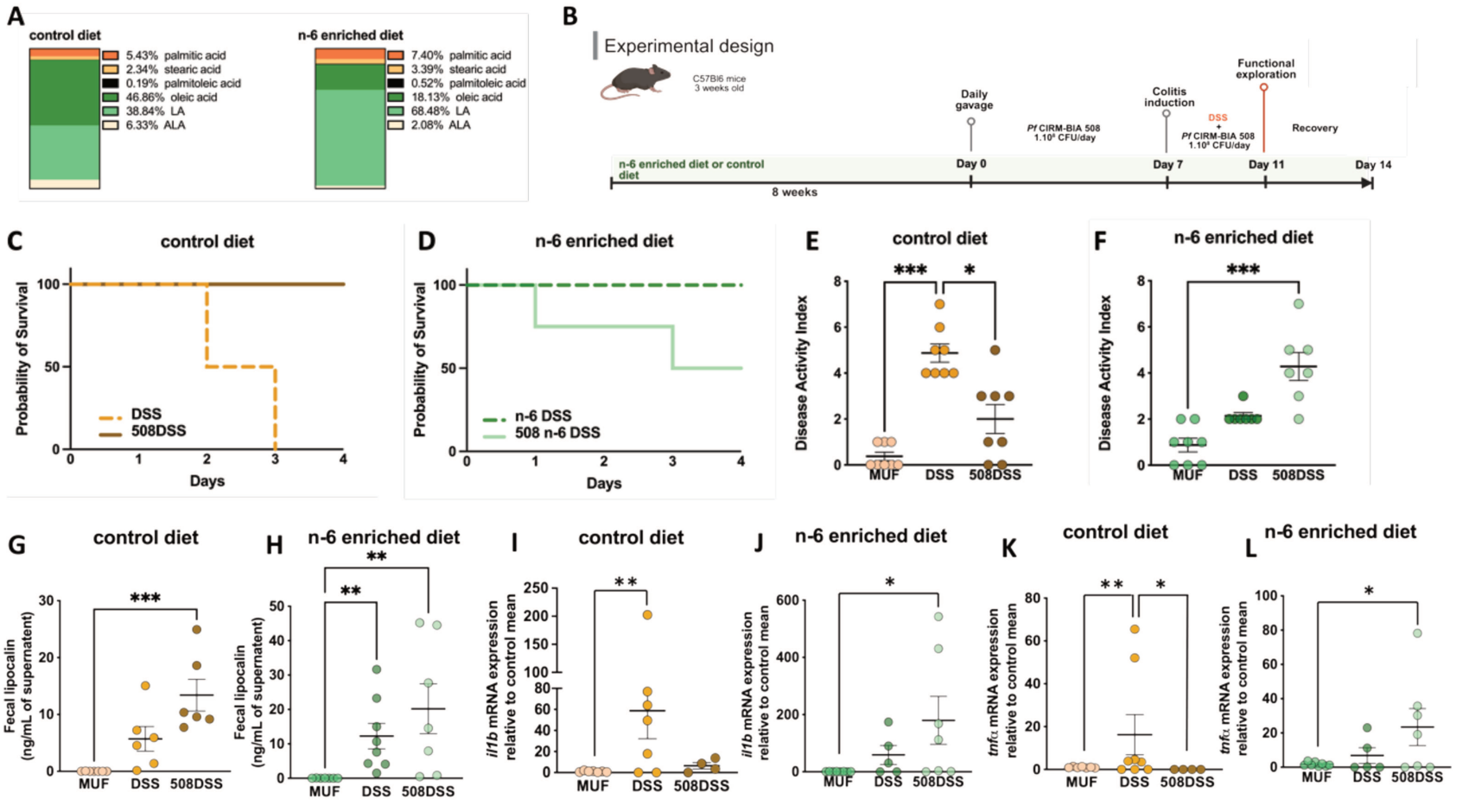
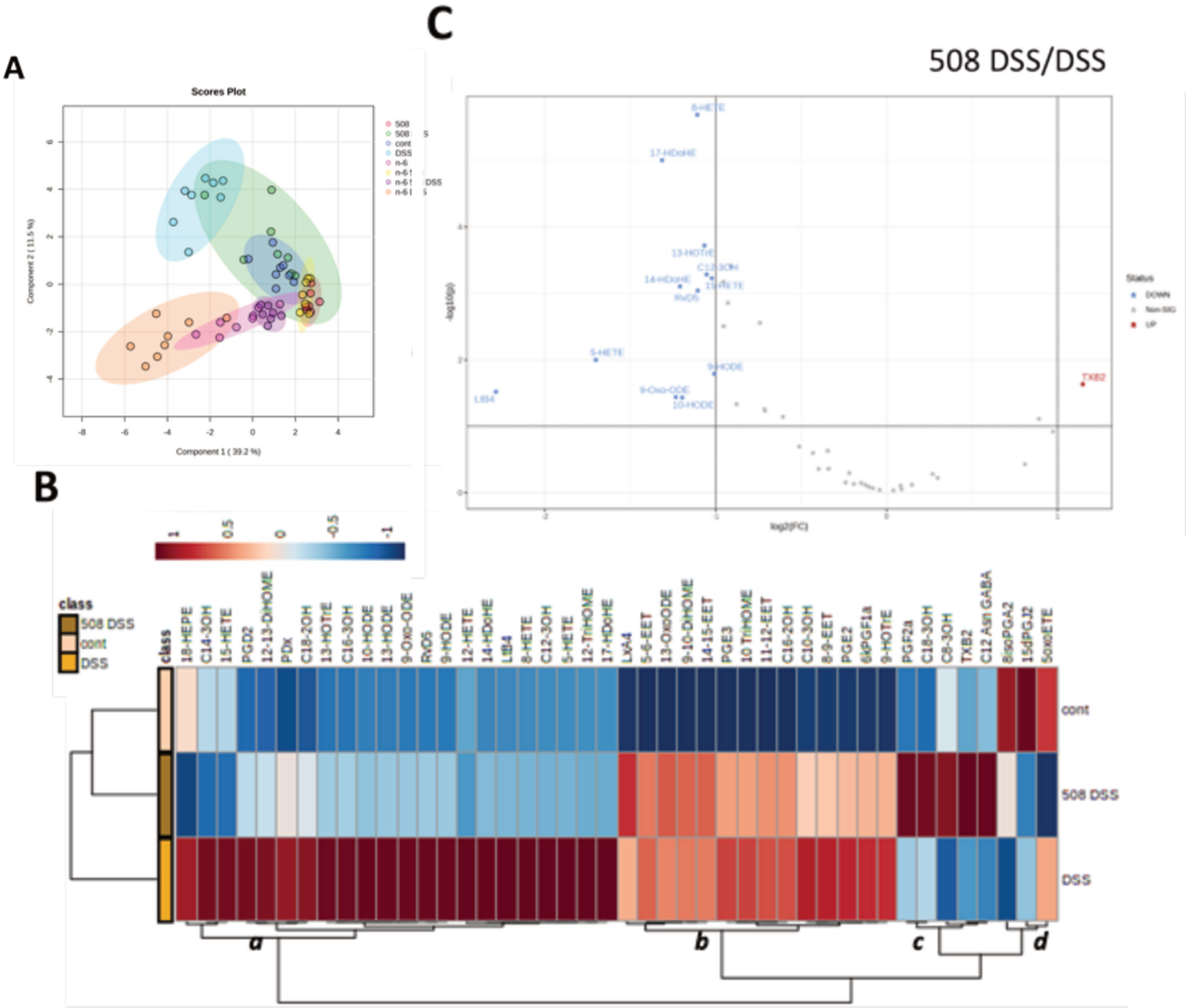

A
control diet
5.43% palmitic acid
2.34% stearic acid
0.19% palmitoleic acid
46.86% oleic acid
38.84% LA
6.33% ALA
n-6 enriched diet
7.40% palmitic acid
3.39% stearic acid
0.52% palmitoleic acid
18.13% oleic acid
68.48% LA
2.08% ALA
B
Experimental design
C57Bl6 mice
3 weeks old
Daily gavage
Pf CIRM-BIA 508 1.10⁸ CFU/day
Colitis induction
DSS + Pf CIRM-BIA 508 1.10⁸ CFU/day
Functional exploration
Recovery
n-6 enriched diet or control diet
8 weeks
Day 0
Day 7
Day 11
Day 14
C
control diet
Probability of Survival
DSS
508DSS
Days
D
n-6 enriched diet
Probability of Survival
n-6 DSS
508 n-6 DSS
Days
E
control diet
Disease Activity Index
MUF
DSS
508DSS
F
n-6 enriched diet
Disease Activity Index
G
control diet
Fecal lipocalin (ng/mL of supernatent)
H
n-6 enriched diet
Fecal lipocalin (ng/mL of supernatent)
I
control diet
il1b mRNA expression relative to control mean
J
n-6 enriched diet
il1b mRNA expression relative to control mean
K
control diet
tnfα mRNA expression relative to control mean
L
n-6 enriched diet
tnfα mRNA expression relative to control mean

Figure 7

Figure 7. n-6 enriched diet inhibits the *P. freudenreichii* CIRM-BIA 508 protection towards colitis (A) Fatty acids plots of the control diet (left) and of n-6 enriched diet (right). (B) Three-week-old C57BL6 mice were fed with control diet or n-6 enriched diet for 8 weeks. Then, mice were gavaged during 11 days with milk ultra-filtrate (MUF) without or with 1.10^8 CFU of *Pf* CIRM-BIA508 (508). At day 7, 3% or 4% DSS was added to drinking water or not for 4 days. At day 11, DSS was removed from drinking water for 3 days. On day 11, permeabilities were measured, mice sacrificed, and the tissues collected. Survival curves of mice fed with (C) the control diet or (D) the n-6 enriched diet under 4% DSS. (E) Disease activity index (DAI) of the 3 groups: control (MUF), DSS or 508DSS at day 11 under control diet or (F) under n-6 enriched diet. Fecal lipocalin contents were measured at day 11 under (G) control diet or (H) n-6 enriched diet. mRNA expression of (I) *il-1β* under control diet or (J) n-6 enriched diet and (K) *tnf-α* under control diet or (L) n-6 enriched diet. Relative expression was determined using Rps6 as reference. mRNA expressions were normalized to control mean. Ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test and Kruskal-Wallis test, followed by a Dunn's multiple comparisons test were performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

n-6 PUFA-enriched diet switches the bioactive lipid profile of the colon.

The impacts of n-6 diet on intestinal bioactive lipids play a central role in controlling intestinal inflammation and its downstream consequences. To further decipher the worsening effect of n-6 diet with *P. freudenreichii* CIRM-BIA508 supplementation on host metabolism, we quantified the linoleic and linolenic acid-derived metabolites in the colon of the different group of animals. Use of LC/MS-MS identification and quantification followed by sparse PLS Discriminant Analysis (sPLS-DA) revealed that mice groups have overlapping but also clear treatment-based lipid clustering (Figure8A and suppl fig 4) indicating that all DSS, *P. freudenreichii* CIRM-BIA508 and n-6 diet markedly shifted colon bioactive lipid contents. This clear alteration is observed on a heatmap representing a majority of metabolites (clusters a, b and d) with opposite production between the control and the DSS group, and the impact of *P. freudenreichii* CIRM-BIA508 (508DSS) that tends to bring closer to control half of them (the cluster a) (suppl fig 4A and B). Twelves of them had a concentration significantly reduced, and 1 significantly increased in the 508DSS group compared to the DSS group (Figure 8C). Use of orthogonal PLS-DA to observe the impact of n-6 enriched diet revealed another switch of metabolites between the n-6 508DSS and the 508DSS groups (Figure 8D). Again, the concentration of twelves metabolite was significantly reduced between n6 508DSS and the 508DSS groups (Figure 8E). Thus, n-6 diet changed the metabolism of lipid induced by *P. freudenreichii* CIRM-BIA508.


A
Scores Plot
Component 1 (39.2 %)
Component 2 (11.5 %)
C
508 DSS/DSS
-log10(p)
log2(FC)
Status
DOWN
UP
8-HETE
17-HDoHE
13-HOTrE
14-HDoHE
RvD5
5-HETE
9-HODE
9-Oxo-ODE
10-HODE
LTB4
TXB2
B
class
508 DSS
cont
DSS
18-HEPE
C14-3OH
15-HETE
PGD2
12-13-DiHOME
PDx
C18-2OH
13-HOTrE
C16-3OH
10-HODE
13-HODE
9-Oxo-ODE
RvD5
9-HODE
12-HETE
14-HDoHE
LTB4
8-HETE
C12-3OH
5-HETE
12-TriHOME
17-HDoHE
LxA4
5-6-EET
13-OxoODE
9-10-DiHOME
14-15-EET
PGE3
10 TriHOME
11-12-EET
C16-2OH
C10-3OH
8-9-EET
PGE2
6kPGF1a
9-HOTrE
PGF2a
C18-3OH
C8-3OH
TXB2
C12 Asn GABA
8isoPGA2
15dPGJ2
5oxoETE
a
b
c
d

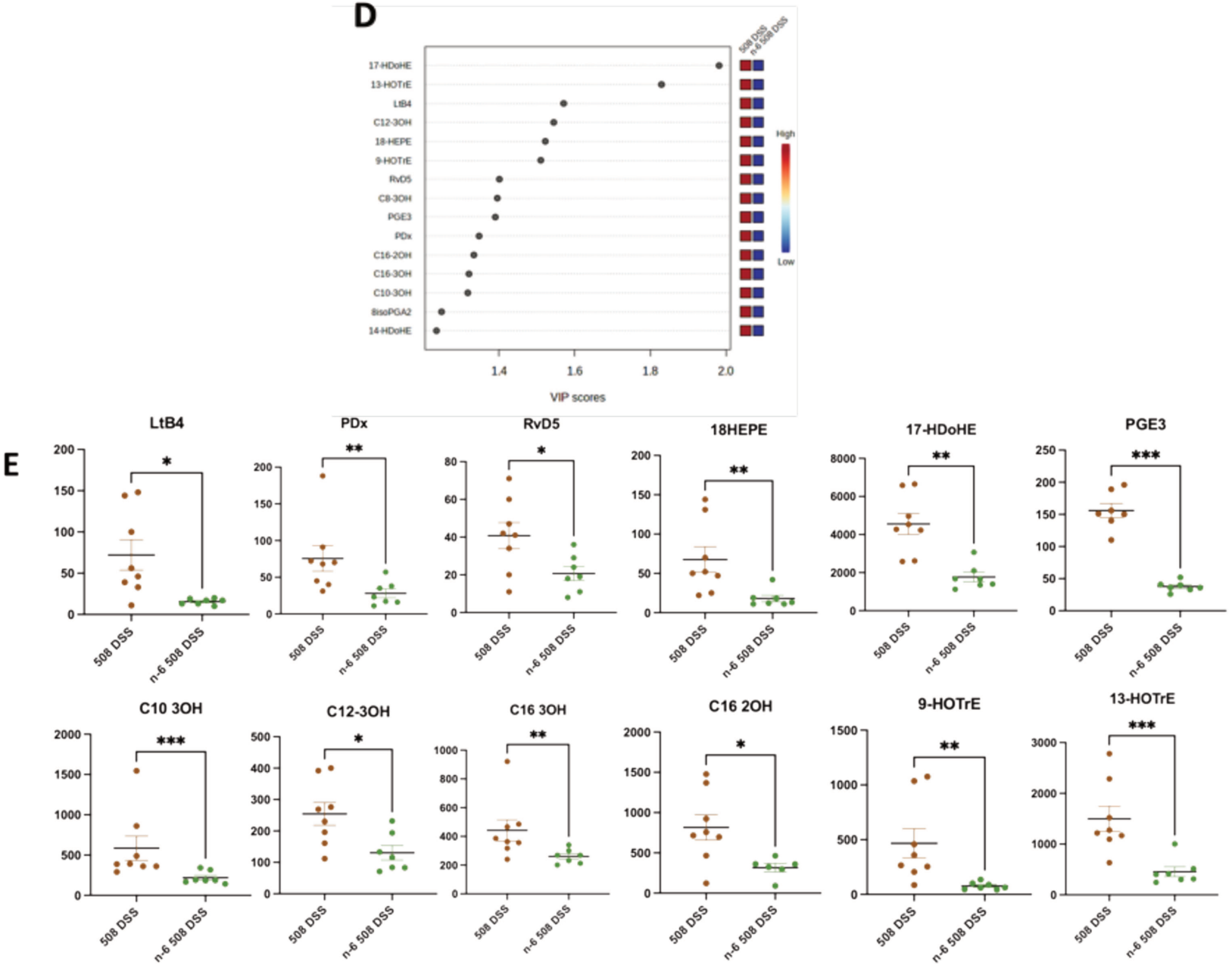

D
17-HDoHE
13-HOTrE
LtB4
C12-3OH
18-HEPE
9-HOTrE
RvD5
C8-3OH
PGE3
PDx
C16-2OH
C16-3OH
C10-3OH
8isoPGA2
14-HDoHE
1.4
1.6
1.8
2.0
VIP scores
508 DSS
n-6 508 DSS
High
Low
E
LtB4
PDx
RvD5
18HEPE
17-HDoHE
PGE3
C10 3OH
C12-3OH
C16 3OH
C16 2OH
9-HOTrE
13-HOTrE
508 DSS
n-6 508 DSS

Figure 8

Figure 8. n-6 enriched diet switchs the bioactive lipid profile of the colon (A) sparse Principal Components Analysis (sPCA) of proximal colon bioactive lipids contents of the 8 groups: the four groups fed with the control diet under control conditions (control (cont) or 508), or DSS (DSS or 508DSS) and the four other groups fed with n-6 enriched diet under control conditions (n-6 or n-6 508) or DSS (n-6 DSS or n-6 508DSS). (B) Heatmap showing the 44 lipid mediators in the proximal colons of the 3 groups: control group and DSS groups (DSS and 508DSS) fed with control diet. The color gradient indicates the fold-change, with red and blue colors indicating up- and down-regulation, respectively. (C) Volcano plot displaying the differential regulation of bioactive lipids contents in the proximal colon between 508DSS and DSS groups when using the control diet. In this plot, red and blue colors represent significant up- and down-regulation, respectively. (D) Variable Importance in Projection (VIP) score plot of the bioactive lipids that differed in 508DSS *vs*. n-6 508DSS. (E) Analysis of the concentrations of lipid mediators: Leukotriene B4 (LtB4), protectin Dx (PDx), resolving D5 (RvD5), 18-hydroxyeicosapentaenoic acid (18-HEPE), 17-hydroxydocosahexaenoic acid (17-HDoHE), prostaglandin E3 (PGE3), 3-hydroxydecanoic acid (C10-3OH), 3-hydroxydodecanoic acid (C12-3OH), 3-hydroxypalmitate (C16-3OH), 2-hydroxypalmitate (C16-2OH), 9-hydroxyoctadecatrienoic acid (9-HOTrE), 13-hydroxyoctadecatrienoic acid (13-HOTrE).

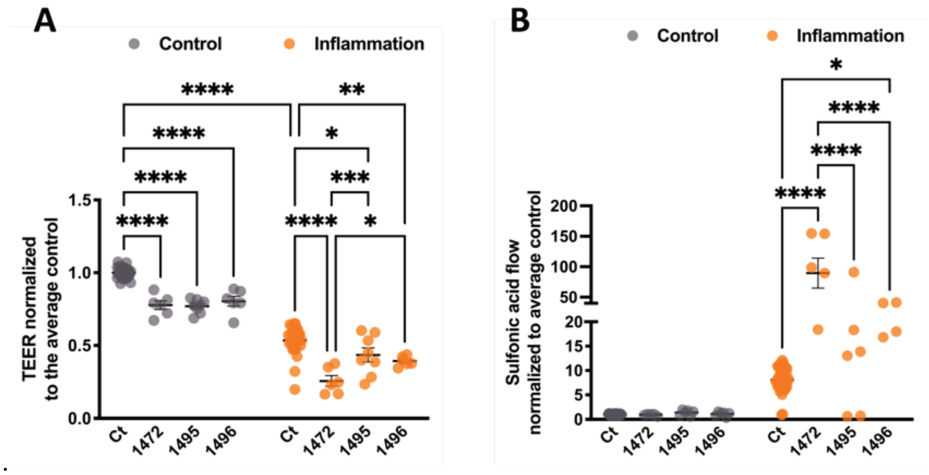
DISCUSSION

The intestinal epithelial barrier stands as a pivotal target for effective IBD therapies (Chang et al. 2017), and among the strategies to strengthen the IEB, the presence of beneficial bacteria in the diet has gained increasing interest. Indeed, beneficial gut bacteria were shown to enhance gut epithelial barrier. As an example, *Akkermansia muciniphila* enhances the expression of tight junction protein 1 (Tjp1) and occludin (Ocln) genes (Chelakkot et al. 2018; W. Wu et al. 2017). Accordingly, the presence of this bacterium in the microbiota is strongly correlated with reduced low-grade inflammation in animals and in humans (Cani et al. 2022). *Faecalibacterium prausnitzii* favors the proliferation of gut epithelial cells and enhances the synthesis of tight junction proteins (Xu et al. 2021). Bifidobacteria were shown to maintain intestinal microvilli integrity and to promote the production of anti-inflammatory cytokines (Ruiz et al. 2017). We have shown that *P. freudenreichii* CIRM-BIA508 can not only inhibit the increase in permeability induced by inflammation *in vitro*, but also counteract the failure observed on trans-epithelial resistance after healing in inflammatory conditions. *In vivo* we noticed the two steps process operated by *P. freudenreichii*, that first consists in limiting epithelial apoptosis through cleaved-caspase 3 limitation, and second in maintaining ZO-1 expression to control epithelial permeability. These effects are strong enough to promote recovery from colitis, that is quite unusual for a probiotic and must be further studied to consider its use in the induction of remission in IBD patients.

But our work also demonstrates the limitation of *P. freudenreichii* CIRM-BIA508 use, and the necessity to pair it with n-3 enriched diet. In the past decades, the intake of n-6 (omega-6) fatty acid increased, and the n-3 (omega-3) fatty acid decreased, resulting in a large increase in the n-6/n-3 ratio from 1:1 during evolution to 20:1 today or even higher. This change in the composition of fatty acids parallels a significant increase in the prevalence of overweight and obesity (Simopoulos et al., 2016) and most importantly is linked to an increased systemic inflammation. In the gut, the production of some n-6 proinflammatory PUFA derivatives is increased in the lower GI tract of IBD patients compared with control subjects (Shannon, Stenson, et Holtzman 1993; Ligumsky et al. 1981) or in inflamed mucosa relative to non-inflamed mucosa (Lauritsen et al. 1988; Le Loupp et al. 2015; Hawkey, Karmeli, et Rachmilewitz 1983; Zifroni et al. 1983) and correlates with inflammation severity (Masoodi et al. 2013). These findings support the idea of the imbalance between the n-6 and n-3 derivatives as pathologic contributing factors, however, a paradox places concerning the effects of n-6 PUFAs on the intestine, where they are not as armful as we might have thought. Several n-6 derivatives have homeostatic functions (Das et al., 2016; Dennis et Norris 2015) participate in anti-inflammatory processes (Ajuebor, Singh, et Wallace 2000; Li et al. 2017) and are associated with inflammation resolution (Gobbetti et al. 2015; Gilroy et al. 2003; Rajakariar et al. 2007; Vong et al. 2010). We recently reported that the 15-hydroxyeicosatetraenoic acid (15-HETE) (Pochard et al. 2016), the prostacyclin (PGI_2) (Pochard et al. 2021) and prostaglandin (PG) 11β-$PGF_{2\alpha}$ (Coquenlorge et al. 2016), can regulate IEB permeability and healing. They are down-regulated in CD (Pochard et al. 2016; Coquenlorge et al. 2016; Pochard et al. 2021) suggesting a pro-resolutive and pro-homeostatic function in IBD. We have observed that eight weeks of n-6 enriched diet does not induces overweight and protect from colitis induced by DSS as observed by the decreased disease activity index and the survival in mice receiving n-6 and

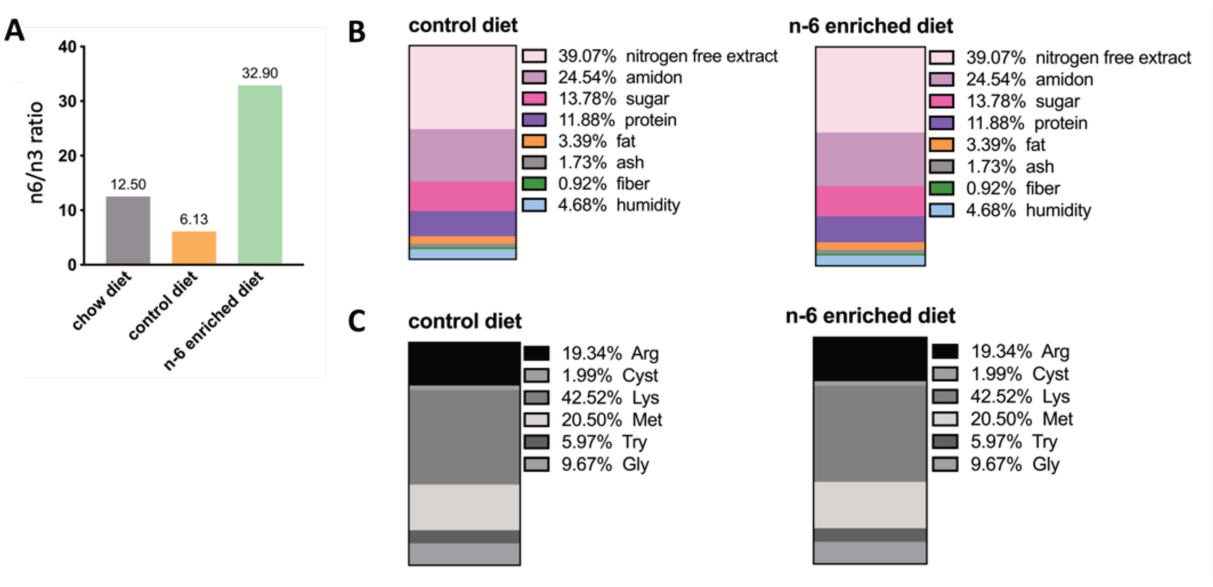
DSS. Consistently, the intestinal inflammation quantified by lipocaline-2 fecal content, *il-1b* and *tnf-a* mRNA expression in colon was not significantly increased in the n-6 DSS compared to the DSS groups. In contrast, in case of *P. freudenreichii* CIRM-BIA508 supplementation, these inflammatory markers were increased in groups receiving n-6 enriched diet (supple fig 3), and the association of n-6 diet to *P. freudenreichii* CIRM-BIA508 supplementation markedly worsened the colitis induced by DSS in mice. But in addition to n6/n-3 ratio unbalance, our work supports the notion that unbalance between metabolites is decisive for colitis evolution. Indeed, we could assume that in control diet condition, *P. freudenreichii* CIRM-BIA508 inhibits a cluster of metabolites that mediate inflammation (cluster a, mainly LOX-dependent metabolites) but also maintains at high concentration or induce metabolites that will help inflammation resolution and/or intestinal protection (cluster b and c). They include in particular two metabolites produced by the probiotic *Escherichia coli* strain Nissle 1917: the C12AsnGABA, a lipopeptide with analgesic properties (Pérez-Berezo et al. 2017), and the 3-hydroxyoctadecaenoic acid (C18-3OH) that presents anti-inflammatory properties and decreases colitis induced by DSS (Pujo et al. 2021). More interestingly, they encompass the PGE_3, the C10-3OH, the C16-3OH and the 9HoTrE, that were associated with anti-inflammatory effects observed in mice fed with prebiotic fructooligosaccharides and/or C18-3OH, and that are all four downregulated in mice fed with n-6 diet in addition to *P. freudenreichii* CIRM-BIA508. These animals have also a decreased in leucotriene B4 (LtB4), protectin DX (PDx) or resolving D5 (RVD5) that regulate immune cell infiltration to limit inflammation (McHugh et al., 2020; Moens de Hase et al. 2023). We lack of data concerning the functions regulated by monohydroxy PUFA (9- or 13-HOTrE) or PUFA metabolites, hydroxylated on the second or the third carbon, but their synthesis could involve bacteria (Moens de Hase et al. 2023) suggesting that changes in gut microbiota could have also driven these lipidomic changes. *P. freudenreichii,* in addition to lipolytic and immunomodulatory properties, can survive in the GI tract, increasing the caecal concentration of propionate and butyrate (Lan et al. 2007) and stimulating the growth of bifidobacterial (Uchida, Mogami, et Matsueda 2007). High linoleic acid (n-6) consumption has already been linked to colitis susceptibility, through microbial and host-initiated pathways involving alterations in the balance of bioactive metabolite of n-6/n-3 PUFAs (Deol et al. 2023). This was the case for, gut bacteria, including members of the Oscillibacter and Desulfovibrio genera, that may disrupt gut barrier integrity in the context of high-fat diet (Malesza et al. 2021). Gut dysbiosis, by favoring disrupting bacteria in the expense of protective ones, leads to modifications of the gut barrier functionality and to translocation of gut microorganisms, and/or of their products, into the systemic circulation (Ghosh et al. 2013). We can suppose that *P. freudenreichii* interplay with metabolite of n-6 enriched diet in the same manner.

Increased number of studies analyze probiotic impact in diverse pathophysiological contexts, and numerous are disappointing or present slight effects, while they could have been more powerful with an appropriate diet. This work, in addition to describing the IEB strengthening and pro-recovery potential of *P. freudenreichii*, demonstrates that lipid content can erase probiotic efficacy, and should therefore be tightly control to maximize probiotic properties upon intestinal health.



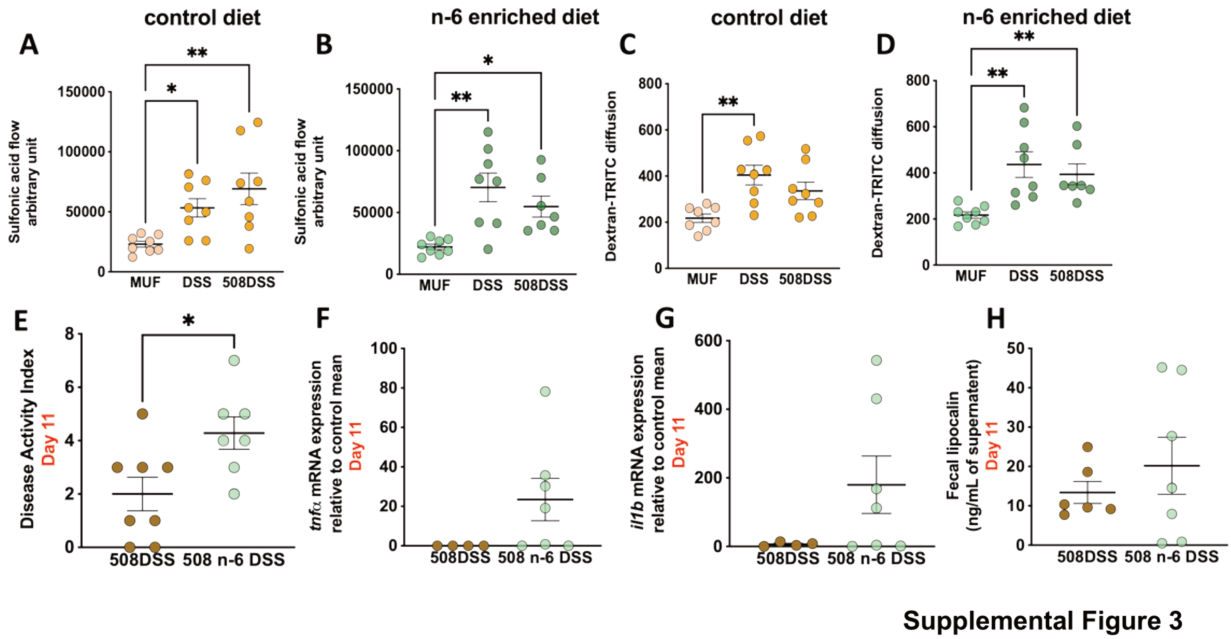
Supplemental Figure 1

Supplemental Figure 1. The highly immunomodulatory *Pf* CIRM-BIA strains did not protect against inflammation-induced IEB breakdown. Caco-2 cells were grown on transwell for 21 days, were left untreated or pre-treated with Propionibacteria (MOI 100:1) for 24 hours before removal and treatment with an inflammatory cytomix containing TNF-α or IFN-ɣ was added for 6 days, with a renewal at day 3. (A) Trans-epithelial electrical resistances (TEER), (B) Sulfonic acid-FITC diffusion were measured at the end of the experiment. Data are normalized to control mean. Values are expressed as means +/- SEM. An ordinary two-way ANOVA, followed by a Tukey's multiple comparisons test was performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.



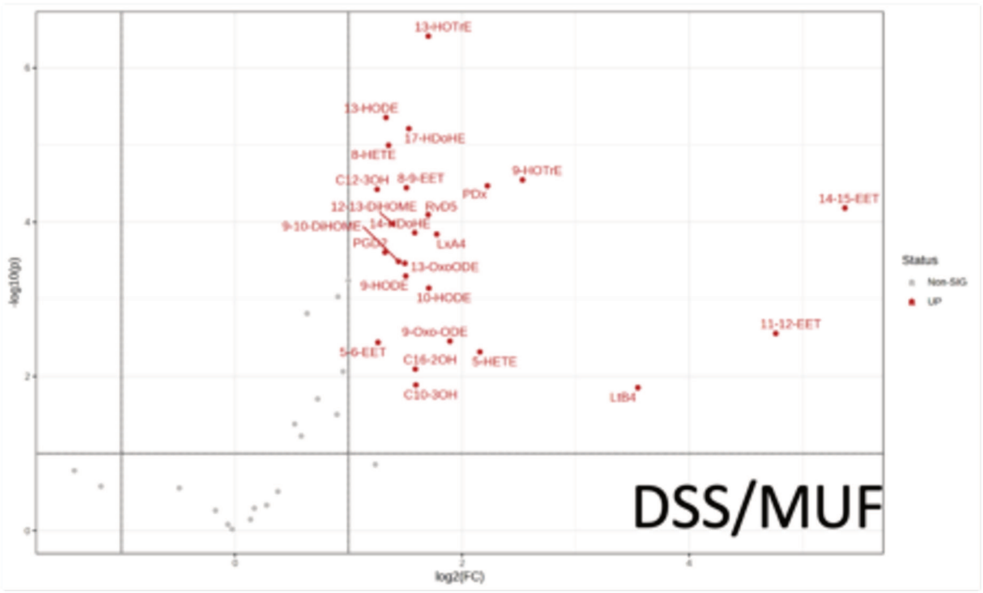
Supplemental Figure 2

Supplemental Figure 2. Control and n-6 diet compositions. (A) omega6 / omega 3 ratio of the three diet: chow diet, control diet and n-6 enriched diet. (B) Nutritional composition in percentage of the control diet and the n-6 enriched diet. (C) Amino acids composition in percentage of the control diet and the n-6 enriched diet.



Supplemental Figure 3. N-6 enriched diet and *Pf* CIRM-BIA508 supplementation impact on permeabilities and inflammation. (A) Three-week-old C57BL6 mice were fed with control diet or n-6 enriched diet for 8 weeks. Then, mice were gavaged during 11 days with milk ultra-filtrate (MUF) without or with 1.10^8 CFU of *Pf* CIRM-BIA508 (508). At day 7, 3% DSS was added to drinking water or not for 4 days. On day 11, permeabilities were measured, mice sacrificed, and the tissues collected. (A) Paracellular permeability evaluated by measurement of sulfonic acid in animal plasma 4 hours after mice gavage of the 3 groups: control (MUF), DSS or 508DSS at day 11 under control diet or (B) n-6 enriched diet. Paracellular permeability evaluated by measurement of dextran in animal plasma 4 hours after mice gavage of the 3 groups control (MUF), DSS or 508DSS at day 11 under (C) control diet or (D) n-6 enriched diet. (E) Disease activity index (DAI) between the 2 groups: 508DSS and 508 n-6 DSS. mRNA expression of (F) *tnf-α* (G) *il-1ß* between the 2 groups: 508DSS and 508 n-6 DSS. Relative expression was determined using Rps6 as reference. mRNA expressions were normalized to control mean. Fecal lipocalin contents were measured at day 11 between the 2 groups: 508DSS and 508 n-6 DSS**.** Data represent mean +/- SEM of 4 mice per group. Kruskal-Wallis test, followed by a Dunn's multiple comparisons test was performed. *p<0.05, **p<0.01, ***p<0.001 and ****p<0.0001.

A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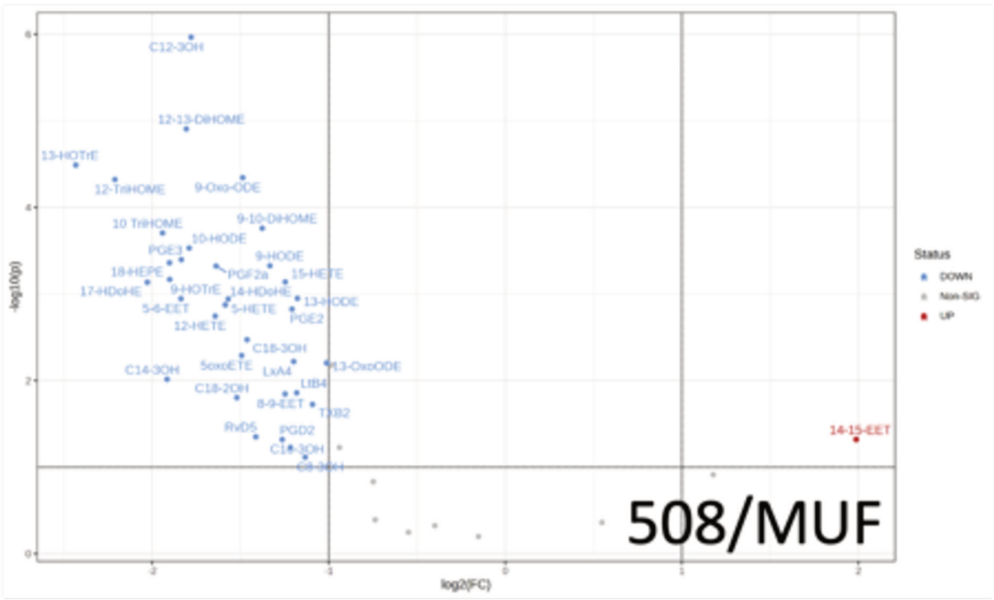
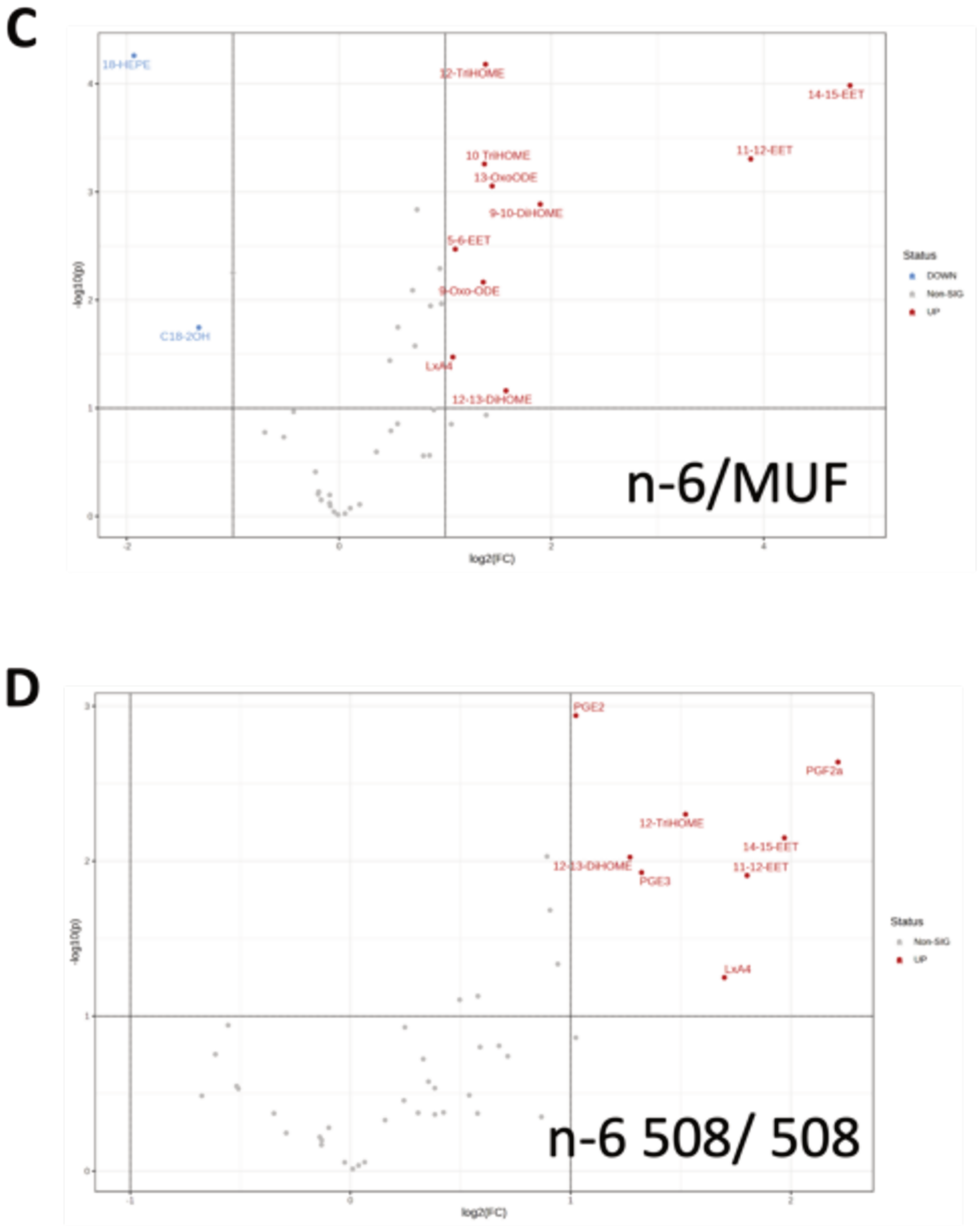
13-HODE
17-HDoHE
8-HETE
9-HOTrE
C12-3OH
8-9-EET
PDx
14-15-EET
12-13-DiHOME
RvD5
9-10-DiHOME
14-HDoHE
PGD2
LxA4
13-OxoODE
9-HODE
10-HODE
11-12-EET
9-Oxo-ODE
5-6-EET
C16-2OH
5-HETE
C10-3OH
LtB4
DSS/MUF
-log10(p)
log2(FC)
Status
Non-SIG
UP

B


C12-3OH
12-13-DiHOME
13-HOTrE
12-TriHOME
9-Oxo-ODE
9-10-DiHOME
10 TriHOME
10-HODE
PGE3
9-HODE
18-HEPE
PGF2a
15-HETE
17-HDoHE
9-HOTrE
14-HDoHE
13-HODE
5-6-EET
5-HETE
PGE2
12-HETE
C18-3OH
C14-3OH
5oxoETE
LxA4
13-OxoODE
C18-2OH
LtB4
8-9-EET
TXB2
RvD5
PGD2
C16-3OH
14-15-EET
508/MUF
-log10(p)
log2(FC)
Status
DOWN
Non-SIG
UP



Supplemental Figure 4

Supplemental Figure 4. N-3 and n-6 PUFA metabolites concentration under DSS, *Pf* CIRM-BIA508 supplementation or n-6 enriched diet. (A) Volcano plot displaying the differential regulation of bioactive lipids contents in the proximal colon between DSS and MUF when using the control diet. In this plot, red and blue colors represent significant up- and down-regulation, respectively. (B) Volcano plot displaying the differential regulation of bioactive lipids contents in the proximal colon between 508 and MUF when using the control diet. In this plot, red and blue colors represent significant up- and down-regulation, respectively. (C) Volcano plot displaying the differential regulation of bioactive lipids contents in the proximal colon between n-6 and MUF when using the control diet. In this plot, red and blue colors represent significant up- and down-regulation, respectively. (D) Volcano plot displaying the differential regulation of bioactive lipids contents in the proximal colon between n-6 508 and 508 when using the control diet. In this plot, red and blue colors represent significant up- and down-regulation, respectively.

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DISCUSSION

Si ce travail a augmenté nos connaissances sur les propriétés et modes d'action de *Propionibacterium freudenreichii*, il adresse également différentes questions qui font l'objet de cette discussion.

Propionibacterium freudenreichii est une bactérie reconnue pour ses propriétés immunomodulatrices et son impact significatif sur le microbiote intestinal. Dans ce travail, nous avons non seulement confirmé les effets immunomodulateurs de *P. freudenreichii in vitro*, mais nous avons également révélé que cette bactérie possède des effets directs sur la BEI, tant *in vitro* qu'*in vivo*. De manière novatrice, notre étude a identifié une nouvelle souche, *P. freudenreichii* CIRM-BIA 508, qui favorise la rémission *in vivo* en inhibant l'apoptose et en restaurant les protéines impliquées dans la perméabilité intestinale. Si les propriétés anti-inflammatoires de *P. freudenreichii in vitro* étaient corrélées à ses effets anti-colite *in vivo* (Foligne et al. 2007), nous avons au contraire montré que ses effets renforçateurs de BEI étaient associés à une plus grande efficacité *in vivo* dans la rémission de la colite. Ceci suggère que traiter l'inflammation ou la BEI serait efficace, mais serait-il possible de cibler les deux en même temps ? Devons-nous l'envisager avec différentes souches de *P. freudenreichii* ou avec des modes d'action ou produits dérivés de *P. freudenreichii* ?

Un second élément de notre recherche est le changement d'efficacité de *P. freudenreichii* selon la matrice laitière ou le contenu en AGPI de l'alimentation. Nous avons identifié les lipides du lait comme le composant clé favorisant les effets protecteurs de la bactérie, et nous avons montré qu'un régime enrichi en oméga 6 inhibe les effets protecteurs de *P. freudenreichii* CIRM-BIA 508 dans la rémission. Cela soulève des questions cruciales quant à l'utilisation des probiotiques en fonction du régime alimentaire de l'individu, ou à la définition d'un régime qui optimiserait les propriétés des probiotiques.

Enfin, *P. freudenreichii* montre un potentiel considérable non seulement dans la prévention et/ou le traitement des MICI, mais plus généralement pour renforcer la BEI. Faut-il alors envisager son utilisation pour traiter d'autres pathologies intestinales, des symptômes digestifs de pathologies extra-digestives, ou même d'autres pathologies de l'axe intestin-cerveau ?

1. UTILISATION DES PROBIOTIQUES DANS LES MICI

1.1. LES PROBIOTIQUES DANS LES MICI

L'utilisation des probiotiques dans les MICI n'a pas encore été intégrée de manière systématique dans les pratiques médicales courantes, et il faut encore travailler à montrer leur efficacité, mais également leur acceptabilité et tolérance. En effet, les gastroentérologues sont peu enclins à proposer des bactéries à des patients qui souffrent de diarrhées, ballonnements, gaz et douleurs intestinales. Cette position est appuyée par le manque d'efficacité des probiotiques actuels, et les effets indésirables décrits par les patients. L'efficacité du mélange de probiotique VSL#3 et de *E. Coli* Nissle 1917 n'est pas supérieure à celle des 5-ASA. De plus, les

patients atteints de MC et recevant *E. Coli* Nissle 1917 ont décrit des gaz, douleurs et ballonnements qui les ont poussés à arrêter le traitement. Enfin, une récente étude a démontré que l'utilisation de probiotiques en vente libre compromettait l'efficacité de l'immunothérapie par inhibiteur de point de contrôle (Spencer et al. 2021; Jensen et al. 2023), et rappelle que nous connaissons encore très peu les conséquences de l'introduction de ces organismes vivants dans notre tube digestif.

Néanmoins, les résultats expérimentaux actuels montrant des effets protecteurs s'accumulent et incitent à envisager et à développer cette approche. Des données *in vitro* et *in vivo* montrent différents organes cibles des probiotiques, et suggèrent différents mécanismes d'action des probiotiques *via* leurs protéines de surface et/ou la production de médiateurs solubles diffusibles. Tout d'abord, ils renforcent la BEI en diminuant la perméabilité *via* une restructuration des protéines de jonction serrées et une diminution de l'apoptose épithéliale. Les probiotiques améliorent les défenses de l'hôte en stimulant la production de mucus. De plus, ils modulent le microbiote intestinal en produisant des PAM permettant d'empêcher la croissance de pathobiontes et d'augmenter les symbiontes. Enfin, ils présentent des propriétés immunomodulatrices en agissant, notamment, sur les cellules immunitaires (**Figure 35**). Le probiotique idéal aurait un effet « microbiote physiologique augmenté », c'est-à-dire une augmentation de l'effet de barrière, de la modulation du système immunitaire, de la dégradation des fibres, de la fermentation produisant des acides gras à courte chaîne, de la transformation des acides biliaires conjugués et primaires en acides biliaires secondaires et épimères comme l'acide ursodésoxycholique, de la synthèse de vitamines B et K, ou de la bioconversion de polyphénols.

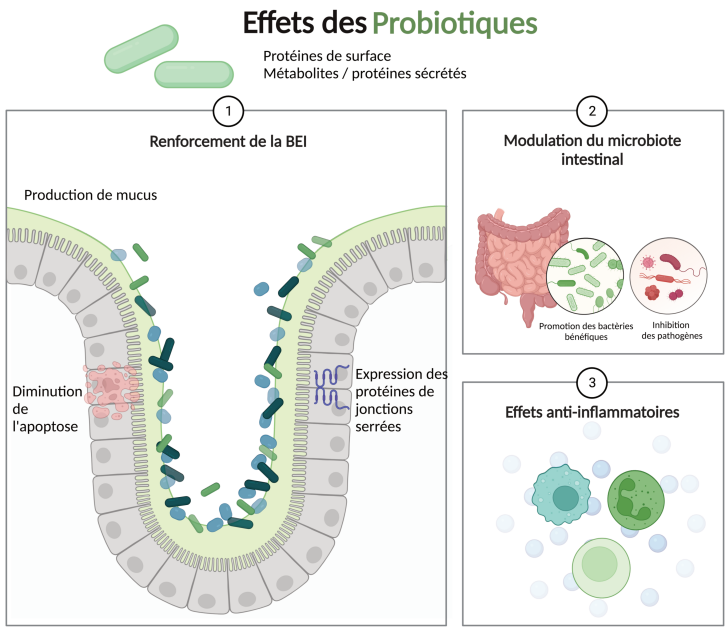

Figure 35. Schéma bilan des modes d'action des probiotiques. Les probiotiques *via* des protéines de surface, protéines et/ou métabolites sécrétés 1) renforcent la BEI en induisant la production de mucus, en inhibant l'apoptose, en restaurant l'expression des protéines de jonctions serrées 2) modulent le MI en favorisant l'expansion des bactéries bénéfiques au détriment des pathogènes 3) présentent des effets anti-inflammatoires.

En clinique, certains probiotiques se sont révélés efficace pour induire et/ou maintenir la rémission dans la RCH. Parmi eux, **VSL#3**, qui est un mélange de 4 souches de *Lactobacillus*, 3 souches de *Bifidobacterium* et une souche de *S. thermophilus*, se distingue comme la combinaison de souche la plus efficace dans les essais cliniques dans la prévention de la pochite. D'autres probiotiques, tels que *S. boulardii* montrent des résultats convaincants dans le maintien de la rémission des patients Crohn. Si *E. Coli* Nissle 1917 est recommandée dans la prévention de la rechute de la RCH, d'autres essais cliniques sont nécessaires pour fournir des preuves suffisantes de son efficacité potentielle ou de celle de LGG dans l'induction ou la rémission des MICI. *Faecalibacterium prausnitzii*, est la bactérie commensale qui aurait le plus de potentiel pour traiter les patients atteints de MC. Les sujets chez lesquels son taux est le plus bas ont un plus haut risque de récidive postopératoire de la MC et un plus haut risque de rechute après arrêt des anti-TNF. *Faecalibacterium prausnitzii*, a des effets immunomodulateurs et renforçateurs de BEI *in vitro* et *in vivo,* mais actuellement aucun essai clinique n'est publié concernant sa potentielle utilisation chez des patients atteints de MC. Il existe d'ailleurs un manque notable d'études cliniques portant sur la MC par rapport à la RCH. La maladie de Crohn affecte l'ensemble du tractus gastro-intestinal, ce qui se traduit par des communautés microbiennes différentes en fonction de sa localisation (McCallum et Tropini 2023; Jensen et al. 2023), et il apparaît plus complexe de proposer une prise en charge unique. Il est donc impératif de mieux comprendre les mécanismes d'action des bactéries afin de choisir le type de probiotique approprié, et il pourrait être judicieux d'adapter le probiotique au profil du patient en fonction de son microbiome, c'est-à-dire en tenant compte des fonctions bactériennes spécifiques.

1.2. *P. FREUDENREICHII* DANS LES MICI

Dans notre étude, nous avons mis en lumière les effets de *P. freudenreichii* sur la BEI, avec des effets différents en fonction de la souche considérée. Compte tenu de ses effets immunomodulateurs et sur le MI, cette bactérie se positionne comme un candidat potentiel pour la prévention et/ou le traitement des MICI.

1.2.1. COMBINAISON DE SOUCHES

Notre étude souligne une remarquable **variabilité** au sein des souches de l'espèce *Propionibacterium freudenreichii*. En effet, ses propriétés immunomodulatrices ou ses propriétés de renforcement de la BEI sont portées par des souches distinctes, qui ont d'ailleurs différents mécanismes d'action. Nous avons mis en évidence que la souche anti-inflammatoire *P. freudenreichii* CIRM-BIA 129 prévient des dommages causés à la BEI par l'inflammation, que ce soit *in vitro* ou *in vivo* en maintenant l'expression d'une protéine de jonction serrée, à savoir ZO-1. Cette souche n'est pourtant pas efficace dans l'induction ou l'accélération de la rémission. A l'inverse, nous avons identifié une nouvelle souche, *P. freudenreichii* CIRM-BIA 508, qui présente des caractéristiques différentes de la souche *P. freudenreichii* CIRM-BIA 129 sur la BEI. Tout d'abord, *P. freudenreichii* CIRM-BIA 508 ne prévient pas de l'augmentation de perméabilité induite par le DSS *in vivo,* contrairement à *P. freudenreichii* CIRM-BIA 129. En effet, *P. freudenreichii* CIRM-BIA 508 n'agit pas sur ZO-1 au pic de l'inflammation, mais prévient de l'augmentation de l'apoptose observée à ce moment. De plus, *P. freudenreichii* CIRM-BIA 508 induits et accélère la rémission. La bactérie favorise la survie des souris, la réparation, et diminue la perméabilité

intestinale *in vivo* en maintenant l'expression de ZO-1 et en favorisant la réparation. Ainsi, cette souche a un effet en deux temps sur la BEI : 1) l'inhibition de l'apoptose 2) le remodelage des protéines de jonction serrées.

Nous faisons donc face à deux souches de *P. freudenreichii* CIRM-BIA avec des **propriétés distinctes**. En raison de ces différences, il est envisageable que ces deux souches se complètent mutuellement et pourraient être testées conjointement dans le modèle de colite induite par le DSS, en observant à la fois le pic de l'inflammation et la phase de rémission. Une hypothèse serait que ces deux souches agissent de manière **complémentaire** sur la BEI. La souche 129 maintient l'expression de ZO-1, tandis que la souche 508 favorise la réparation et réduit l'apoptose (Figure 36). Par conséquent, en renforçant la BEI de manière complémentaire, ces deux souches pourraient potentialiser leur efficacité dans la promotion de la rémission et la réduction de la sévérité de la colite. La figure 36 propose un protocole expérimental pour infirmer ou confirmer cette hypothèse, et, de la même manière que le cocktail de souches probiotiques VSL#3 est le plus efficace à l'heure actuelle dans l'induction et le maintien de la rémission de patients RCH, envisager un cocktail de souches de *P. freudenreichii* pour traiter la colite.

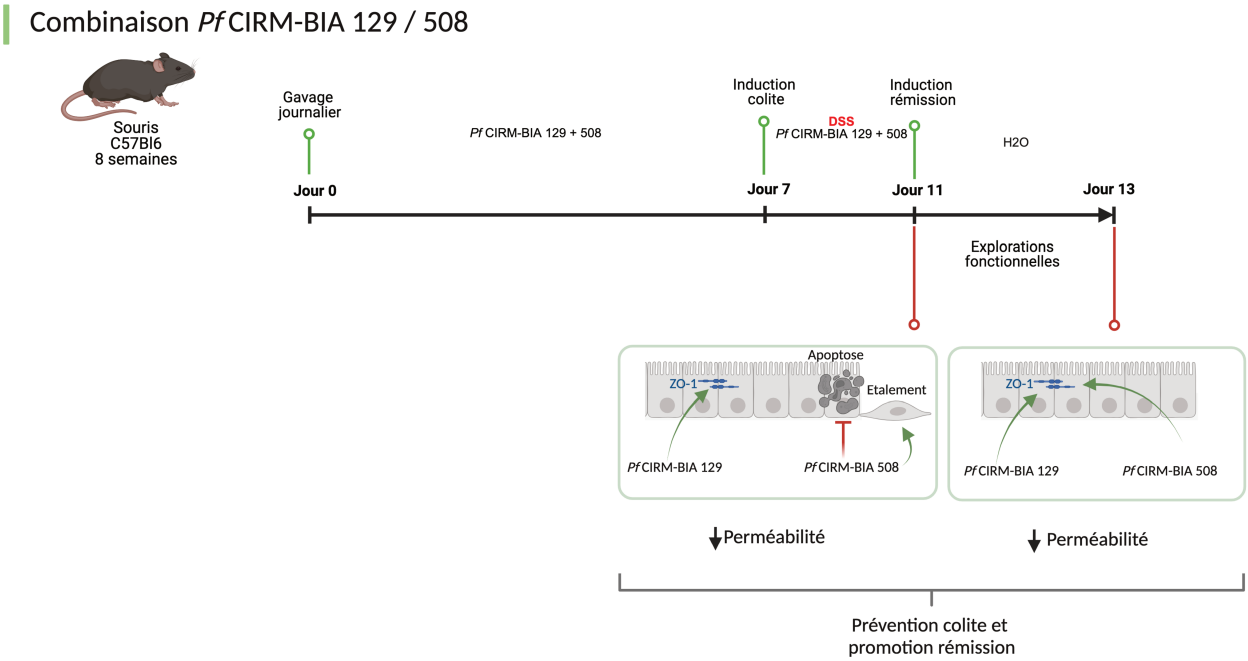

Figure 36. Combinaison de *P. freudenreichii* CIRM-BIA 129 et 508 dans un modèle de colite. Une hypothèse est la combinaison des deux souches de Pf CIRM-BIA : 129 et 508 dans un modèle de colite et de rémission. La souche 129 restaure à la fin de la colite l'expression de ZO-1, en parallèle la 508 inhibe l'apoptose et favorise l'étalement contribuant à diminuer la perméabilité. Au jour 13 les deux souches restaurent l'expression de ZO-1. La combinaison des deux souches permettrait des effets plus efficaces sur la prévention de la colite et la promotion de la rémission.

1.2.2. LES VESICULES EXTRACELLULAIRES : POSTBIOTIQUES ?

Des études cliniques informent sur l'augmentation du risque de développer des effets secondaires indésirables, tels que des symptômes gastro-intestinaux, des douleurs abdominales, lors de la prise de probiotique chez des patients atteints de MICI (Dore et al. 2019). L'utilisation de **postbiotique** permettrait **d'éviter** les éventuels **effets secondaires** associés à la consommation de bactéries vivantes.

Notre étude apporte de nouvelles connaissances sur les propriétés des **vésicules extracellulaires** de *P. freudenreichii* CIRM-BIA 129. Précédemment, l'équipe de microbiologie du laboratoire STLO a mis en avant les effets anti-inflammatoires des VEs de la souche 129 *in vitro* (Rodovalho et al. 2020). Nos résultats démontrent que les VEs dérivées de la souche 129, qui contiennent la protéine SlpB, préviennent l'augmentation de perméabilité paracellulaire induite par l'inflammation *in vitro*. La prochaine étape consistera à tester ces VEs *in vivo* dans le but de prévenir la sévérité de la colite en renforçant la BEI et en atténuant l'inflammation. Des données récentes évoquent l'utilisation de VEs issues de souches probiotiques dans des modèles de colite. Par exemple, l'administration de VEs dérivées de *L. plantarum* Q7 à des souris ayant une colite induite au DSS entraîne une baisse de l'expression génique de plusieurs cytokines pro-inflammatoires, telle que l'*il-6*, l'*il1b*, l'*il-2* et le *tnf-a*, tout en augmentant la diversité du microbiote intestinal de ces souris (Hao et al. 2021). Une autre étude démontre l'efficacité de VEs dérivées de *Clostridium butyricum* dans la réduction du développement de colite induite au DSS chez la souris. Ces VEs non seulement préviennent de l'expansion de pathogène de type *E. coli* ainsi que *S. flexneri*, mais elles modulent également le métabolisme du tryptophane (Ma et al. 2023). Ces données sont encourageantes quant à l'utilisation des VEs de *P. freudenreichii* CIRM-BIA 129 *in vivo*. Cependant, il reste encore à déterminer dans quelle mesure les VEs sont résistantes aux agressions du tractus GI. Quelques études suggèrent que la bicouche lipidique des VEs les protège contre les variations de température et la lyophilisation, mais aucune étude n'a encore exploré leur résistance aux environnements à faible pH (Alves et al. 2016). De plus, le choix approprié de la matrice fournissant les VEs est essentiel, car il influe sur la quantité, la taille et le contenu des VEs. Dans le cas des VEs dérivées de *P. freudenreichii* CIRM-BIA 129, il a été observé qu'elles sont plus abondantes et de taille plus réduite lorsque les propionibactéries sont cultivées dans du perméat d'ultra-filtration de lait par rapport à celles obtenues après croissance dans un milieu de laboratoire YEL classique. De plus, la protéine SlpB est plus abondante dans cette matrice (Rodovalho et al. 2023). Enfin, il reste à élucider les mécanismes d'action des VEs de *P. freudenreichii* CIRM-BIA 129 dans le renforcement de la BEI : sont-elles internalisées par les cellules ? traversent-elles la BEI ? Sur quelles voies moléculaires exercent-elles leur action, et est-ce qu'elles permettent uniquement d'apporter la protéine SlpB, ou d'autres acteurs entrent-ils en jeu ?

2. L'IMPACT DE LA NUTRITION DANS L'INTERACTION BACTERIE/HOTE.

2.1. L'IMPACT DE LA MATRICE VECTEUR DE PROBIOTIQUE

Les probiotiques sont généralement consommés sous forme de micro-organismes lyophilisés encapsulés ou en comprimés, mais le développement **d'alimentation fonctionnelle fermentée** permettrait de protéger le probiotique ou d'augmenter et développer ses propriétés probiotiques.

En effet, le choix de la matrice, notamment la matrice laitière, utilisée en tant que vecteur de probiotique, n'est pas anodin. Tout d'abord, la matrice module la **survie** du probiotique dans le tractus gastro-intestinal. En effet, le fromage fermenté par *P. freudenreichii* favorise la viabilité de la bactérie, et protège la protéine SlpB de la protéolyse dans un système de digestion gastro-intestinal *in vitro,* par rapport à une culture liquide. D'autre part, une étude clinique a comparé une mixture de probiotique contenant *P. freudenreichii* soit en capsules, dans du fromage ou dans un yaourt chez des individus sains. Le yaourt augmente la quantité et l'activité métabolique de *Pf* dans les selles (Saxelin et al. 2010; Hervé et al. 2007). *In vivo*, la quantité de *P. freudenreichii* dans les selles de porcelets sains gavés avec *P. freudenreichii* n'est pas modifiée mais les propriétés immunomodulatrices de la bactérie sont modulées. En effet, la matrice fromagère favorise les populations de Treg et de Th2 de PBMCs et des MLNCs (pour « mesenteric lymphe node cells ») provenant de porcelets gavés avec un fromage contenant *P. freudenreichii,* par rapport à une culture liquide de *P. freudenreichii* (Rabah et al. 2018). D'autre part, la matrice permet d'apporter des **substrats** impactant les métabolites produits par la bactérie et par conséquent ces effets. Par exemple, le lait contient de l'acide linoléique qui est converti par *P. freudenreichii* en acide linoléique conjugué, en particulier l'acide ruménique connu pour ses propriétés anti-oxydantes et anti-colite (Bergamo et al. 2017). Enfin, la matrice peut jouer un **rôle en elle-même**. Concernant la matrice laitière, les protéines du lait ont des propriétés anti-inflammatoires, telles que les caséines du lait qui*, in vitro*, inhibent la voie NFkB et des MAP kinases activées par un traitement au LPS (**Figure 37**).

Figure 37. Optimisation des effets bénéfiques de probiotique par la matrice. La matrice laitière, en tant que vectrice de probiotique, protège la bactérie contre les agressions provenant du tractus GI, et permet l'apport de substrats. Par conséquent, les effets du probiotique sont optimisés avec 1) un effet direct de la matrice 2) une augmentation de la survie du probiotique 3) une augmentation de l'activité du probiotique.

Dans notre étude, lorsqu'on compare les effets anti-colite de *P. freudenreichii* CIRM-BIA 129 en fonction de la composition de la matrice laitière, le lait entier améliore les effets bénéfiques de *P. freudenreichii,* suggérant un rôle des lipides du lait dans les effets anti-colite. Nos données identifient quel type de composé présent dans la matrice laitière est responsable de l'amélioration des effets du probiotique. Cependant, il reste à déterminer comment les lipides médient ces effets : est-ce qu'ils jouent sur la survie du probiotique ? Son activité ? Une activité directe sur l'hôte en synergie avec la bactérie ?

2.2. L'IMPACT DE LA NUTRITION SUR L'HOTE

Notre étude a mis en évidence une perte des effets protecteurs de la souche *P. freudenreichii* CIRM-BIA 508 lorsqu'elle était combinée avec un régime enrichi en oméga-6 (n-6). Après 8 semaines de régime enrichi en oméga 6 (ratio oméga3/oméga6 de 32,9 contre 6,13 pour le régime contrôle), la souche *P. freudenreichii* CIRM-BIA 508 ne permettait plus de diminuer le score de sévérité de la colite ainsi que l'expression génique de cytokines pro-inflammatoires telles que l'*il1ß* et le *tnfa* ou la présence de dérivés des AGPI dans le côlon. Ces résultats interrogent sur l'impact que peut avoir la **nutrition de l'hôte** sur **l'efficacité** du **probiotique**, à quel point peut-elle moduler l'activité, la survie du probiotique dans le tractus gastro-intestinal ? Est-ce que cette modulation par l'alimentation est directe ou indirecte ? Est-ce la réponse de l'hôte qui est modifiée ?

Le nombre important d'études pré-cliniques sur l'efficacité des probiotiques qui ne sont pas reproduites en clinique, ainsi que les grandes variations entre les différentes études chez l'Homme questionnent sur le rôle important des facteurs environnementaux, en particulier **l'alimentation** sur **l'efficacité** des **probiotiques**. En effet, quelques récentes études appuient ces propos. Tout d'abord, l'alimentation modifie le **microbiote**

intestinal de l'hôte de façon rapide et reproductible (David et al. 2014). En modulant le microbiome, l'alimentation influe sur l'efficacité du probiotique, en particulier si le probiotique a peu d'effet sur le microbiote intestinal. Par exemple, *L. helveticus* R0052 présente des effets différents sur l'anxiété de souris en fonction du régime, à savoir un régime riche en fibres ou un régime occidentalisé : WD (WD pour « Western Diet »). Le régime WD induit des changements du microbiote intestinal, de l'expression de cytokines et augmente l'anxiété des souris. Le probiotique diminue le comportement anxieux des souris avec un régime classique mais échoue sous le régime WD (Ohland et al. 2013). Une autre étude s'intéressant à comprendre pourquoi seuls certains individus sains présentent une amélioration du métabolisme du glucose après une consommation de trois jours de pain à base de grains d'orge, identifie un motif distinct au niveau du microbiote intestinal des deux groupes : répondeurs et non répondeurs. Le groupe répondeur dispose d'une augmentation du ratio *Prevotella*/*Bacteroides*. La supplémentation de *Prevotella copri* chez des souris ayant un régime classique améliore le métabolisme du glucose. Cependant, les effets sont perdus avec une alimentation riche en gras ou pauvre en fibres, soulignant l'importance des fibres alimentaires pour la colonisation de l'intestin par *Prevotella* afin de médier ses effets bénéfiques sur le métabolisme du glucose (Kovatcheva-Datchary et al. 2015). Cependant, ces études comparent des régimes alimentaires avec un apport énergétique différent. Une équipe Québécoise démontre qu'à apport énergétique équivalent, les effets de deux souches de LAB, *L. reuteri* et *L. paracasei*, sont différents en fonction du régime alimentaire. Trois types d'alimentations ont été testés : une alimentation pauvre en gras (LFD pour « low-fat diet »), une riche en gras (HFD pour « high fat diet ») et une autre mimant l'alimentation des fast-food (FFMD pour fast food mimicking diet) qui favorise le développement de NAFLD (pour « non alcoholic fatty acid liver disease ») et NASH (pour « stéato-hépatite non alcoolique »). Pendant 12 semaines, les souris ont reçu l'un de ces 3 régimes, et ont été gavées ou non avec *L. reuteri* ou *L. paracasei.* De façon intéressante, les deux probiotiques ont des effets opposés en fonction du régime alimentaire. *L. reuteri* DSM 32910 atténue les effets néfastes de la FFMD à savoir une augmentation de la résistance à l'insuline, le développement de NAFLD, des changements de composition du MI, alors que cette souche échoue à réduire les effets néfastes causés par la HFD chez les souris. C'est le contraire concernant la souche *L. paracasei* DSM 32851 (Larsen et al. 2023). Ces données appuient la nécessité de tenir compte de la spécificité d'efficacité des probiotiques en fonction de la souche probiotique. De plus, elles démontrent clairement l'influence de l'alimentation sur l'efficacité du probiotique. D'autre part, l'alimentation module la **survie** du probiotique. *In vitro*, le type de nutriment utilisé favorise la croissance de certains probiotiques. *In vivo*, dans un modèle de colite induite au TNBS, un régime WD favorise la survie de *L. plantarum* WCFS1. De façon intéressante, bien que le régime WD exacerbe l'inflammation, *L. plantarum* WCFS1 est plus efficace pour contrer l'inflammation induite par la colite sous le régime WD que le régime contrôle (Tachon, Lee, et Marco 2014).

Ces études vont dans le même sens que nos données avec la souche *Pf* CIRM-BIA 508 qui présente des effets différents en fonction du régime alimentaire. Cependant, il nous reste à identifier quel élément du régime perturbe l'activité du probiotique. En effet, bien que nos deux régimes aient la même valeur énergétique, la différence entre le régime contrôle et celui enrichit en oméga 6 ne se limite pas uniquement à une différence du ratio oméga 3 / oméga 6, la proportion d'autres acides gras est également modifiée. C'est le cas de l'acide oléique

qui représente 47% des acides gras dans le régime contrôle et 18% dans le régime enrichit en oméga 6. L'acide oléique est le composant majeur de l'huile d'olive. L'huile d'olive faisant partie du régime méditerranéen, est connue pour ses effets bénéfiques pour la santé. En effet, elle présente des effets anti-oxydants, anti-inflammatoires, prévient le développement de plusieurs pathologies telles que l'obésité, le diabète, les maladies cardiovasculaires et neurodégénératives. De plus, elle modifie la composition du microbiote intestinal (Isaakidis et al. 2023). De façon intéressante, l'acide oléique favorise la survie *in vitro* du probiotique LGG dans un milieu acide (pH 2,2) qui simule l'acidité gastrique (Corcoran et al. 2007).

En résumé, l'alimentation module l'activité des probiotiques *via,* notamment, une action **directe** sur la **survie** de la bactérie dans le tractus gastro-intestinal ou **indirect** en modulant le **microbiote intestinal** de l'hôte en faveur ou en défaveur des effets du probiotique. De façon intéressante, le microbiote intestinal de l'hôte exerce lui-même une influence sur l'impact de la nutrition. En effet, certaines bactéries du MI synthétisent des métabolites intermédiaires dérivés des AGPI retrouvés dans l'alimentation. C'est le cas de *L. salivarius* et *L. gasseri* qui produisent à partir de l'acide linoléique de l'acide 10-hydroxy-*cis*-12-octadecenoic (HYA), conférant à l'hôte une résistance aux effets néfastes d'un régime alimentaire de type HFD. En cas d'excès d'acide linoléique, ces bactéries favorisent la production de HYA plutôt que la production d'eicosanoïdes, impliqués dans les processus inflammatoires (Miyamoto et al. 2019; 2015). Dans l'ensemble, ces données soulignent l'importance de prendre en compte la spécificité de la souche du probiotique ainsi que l'alimentation de l'individu. De plus, il est primordial d'identifier quels paramètres impactent la sensibilité de réponse de l'hôte au probiotique.

Enfin, si notre étude met en évidence un impact de la composition en lipides sur l'efficacité du probiotique *P. freudenreichii*, elle nous a permis d'observer une différence de sensibilité au DSS et de réponse au *Pf* CIRM-BIA508 selon des régimes alimentaires définis comme « contrôles » : le régime standard (STD) de l'animalerie (« chow diet » dans l'article) et le régime contrôle (CT) vis-à-vis du régime enrichi en oméga 6. Les effets de *Pf* étaient plus puissants avec le régime STD, en particulier en ce qui concerne la lipocaline fécale, un marqueur de l'inflammation intestinale. Le probiotique inhibe l'augmentation de la lipocaline fécale en condition DSS avec le régime STD, cependant il échoue à la réduire avec le régime CT. Encore plus marquant, les souris nourries avec le régime CT sont plus sensibles au DSS. Avec une concentration de DSS inférieure (3%), le score de sévérité de la colite est plus important que celui avec le DSS 4% soumis au régime STD. Les différences entre ces deux régimes sont nombreuses avec un ratio oméga-3 / oméga-6 supérieur dans le régime STD par rapport au régime CT, mais aussi des différences au niveau de la composition en sucre, fibres, et en acides aminés.

3. L'UTILISATION DE *P. FREUDENREICHII* DANS D'AUTRES PATHOLOGIES ?

Nombreuses sont les pathologies qui présentent, comme les MICI, une barrière perméable, une dysbiose du MI ainsi que de l'inflammation digestive. En effet, une BEI hyper-perméable associée à de l'inflammation a été décrite dans d'autres pathologies allant de l'obésité, au diabète de type II, à l'allergie et même aux pathologies neurodégénératives.

3.1. *P. FREUDENREICHII* : UTILISATION DANS D'AUTRES PATHOLOGIES

Un modèle génétique de souris obèse ainsi qu'un modèle d'hyperglycémie présentent des altérations de la BEI avec une diminution de l'expression de ZO-1 et de E-cadhérine, une augmentation de perméabilité intestinale *in vivo* ainsi qu'une augmentation de susceptibilité aux infections (Thaiss et al. 2018). L'obésité est également caractérisée par une inflammation de bas grade ainsi qu'une dysbiose du MI. De plus, certains probiotiques tel que *L. acidophilus* ont des effets anti-obésité en diminuant le poids de souris ayant reçu un régime riche en gras. Ce probiotique permet également de reverser la dysbiose induite par un tel régime, et également de renforcer la BEI en diminuant la perméabilité *in vivo via* le maintien de l'expression de l'occludine (Kang et al. 2022). En étude clinique, la supplémentation *d'Akkermansia muciniphila* pendant 3 mois chez 32 volontaires obèses, ou en surpoids ayant une résistance à l'insuline, permet de réduire la masse grasse, le cholestérol plasmatique et des marqueurs de l'inflammation chez les patients (Depommier et al. 2019).

En considérant les effets de *P. freudenreichii* sur le microbiote intestinal, ses propriétés immunomodulatrices ainsi que sa capacité à renforcer la BEI, l'utilisation de cette bactérie dans d'autres pathologies est envisageable. Par ailleurs, une souche de *P. freudenreichii* a d'ores et déjà été testée dans un modèle de souris obèse induit par un régime riche en gras. La consommation de *P. freudenreichii* par ces souris réduit le poids des souris sans qu'il y ait de modifications de leur apport alimentaire et énergétique, suggérant un impact de *Pf* sur le métabolisme glucidique ou lipidique. En effet, *Pf* diminue l'accumulation de lipides dans le foie, toxique pour l'organe, en inhibant l'expression de gènes impliqués dans l'adipogenèse et la lipogenèse et en favorisant ceux impliqués dans la lipolyse. De fait, en modulant le métabolisme lipidique des souris soumises à un régime riche en gras, *Pf* prévient des désordres associés à l'obésité tels qu'une hyperlipidémie, et les maladies du foie gras non alcoolique (NAFLD) (An, Park, et Lim 2021). *Pf* a également des effets bénéfiques sur le développement des allergies. La supplémentation d'une mixture de probiotique contenant *Pf* chez des femmes enceintes ainsi que leur nouveau-né pendant 6 mois après la naissance montre que les probiotiques préviennent du développement d'allergies et d'eczéma chez les nourrissons nés par césarienne (Kallio et al. 2019).

3.2. *P. FREUDENREICHII* DANS L'AXE MICROBIOTE INTESTIN CERVEAU

L'axe microbiote-intestin-cerveau forme un réseau de communication entre le MI, le SNE et le SNC *via* le nerf vague et la circulation sanguine. Le cerveau communique avec l'intestin en envoyant des messages neuronaux, endocrines et immuns. De la même façon, le microbiote intestinal produit des molécules telles que les AGCC, les SBA qui, *via* la circulation sanguine, influent sur le cerveau. Les CEE reçoivent des informations du microbiote intestinal et les transmettent avec leur neuropode au SNE ou au nerf vague qui informe le cerveau. Enfin, le microbiote peut communiquer avec le cerveau en agissant directement ou indirectement sur le SNE et le SI sous-jacent (Figure 38).

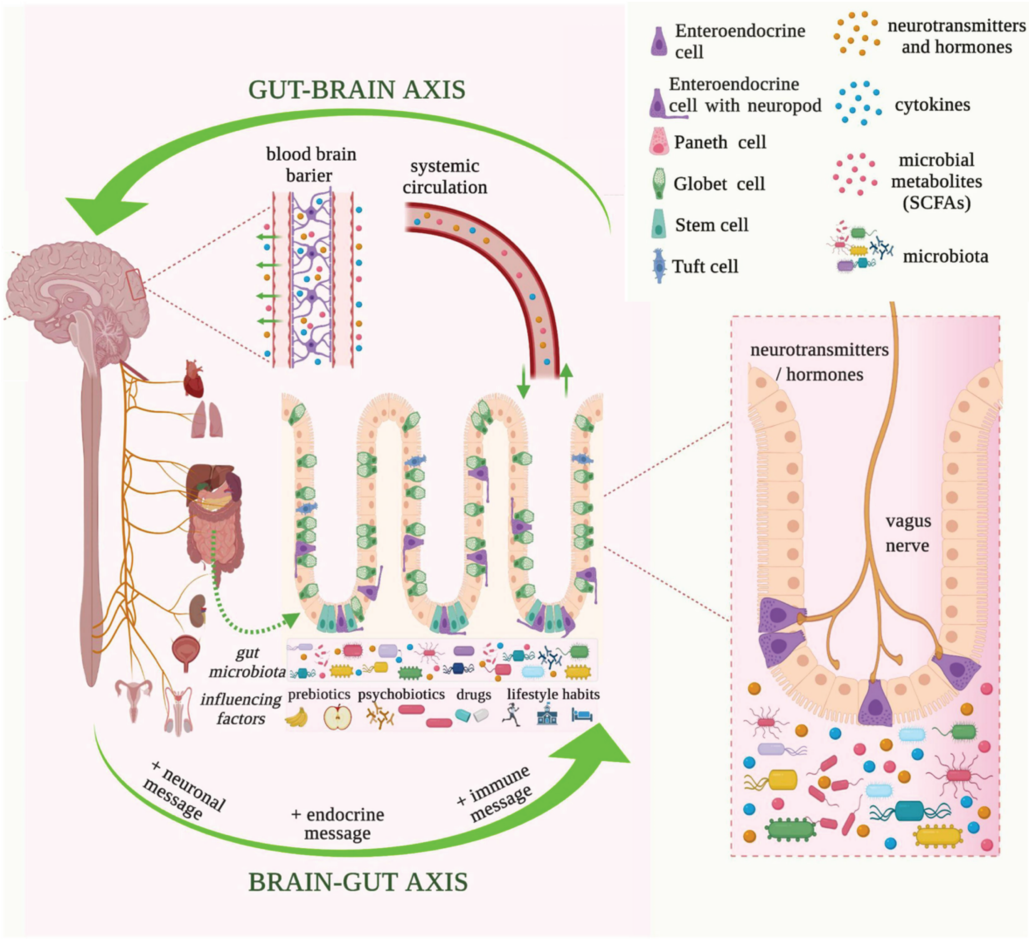

Figure 38. L'axe microbiote-intestin-cerveau (d'après Mitrea et al. 2022). L'axe microbiote-intestin-cerveau est bidirectionnel. Les messages transmis sont de types neuronaux, endocriniens et immunitaires. Des molécules bioactives GI (NT, hormones, cytokines, métabolites microbiens) sont produites sous l'influence de facteurs externes (probiotiques etc.) et parviennent au cerveau après avoir traversé la BHE. Les cellules entéro-endocrines avec des neuropodes, sont l'un des principaux acteurs de la communication bidirectionnelle cerveau-intestin.

L'altération de cet axe est impliquée dans de nombreuses pathologies neurologiques telles que la maladie d'Alzheimer, de Parkinson, les troubles du spectre autistique (TSA), la dépression, etc. Les patients atteints de ces pathologies souffrent fréquemment de troubles gastro-intestinaux associés à des altérations de la BEI ainsi

qu'une dysbiose du microbiote intestinal et une neuro-inflammation au niveau du SNE et du cerveau. De plus, la barrière hémato-encéphalique (BHE) est altérée, ce qui suggère un passage accru de molécules microbiennes, cytokines et cellules immunitaires dans le cerveau, alimentant la neuro-inflammation.

Il est tout à fait plausible d'émettre l'hypothèse que *Pf* pourrait influencer cet axe dans un contexte de neuro-inflammation, et nous avons voulu l'analyser dans notre modèle de colite induite au DSS. En effet, de la même manière que la dépression et l'anxiété soient particulièrement fréquentes chez les patients atteints de MICI, des comportements anxieux ont été observés dans des souris traitées au DSS. Nos études sur la souris ont permis de générer des données préliminaires indiquant que *Pf* CIRM-BIA 508 réduits l'expression de la GFAP, un marqueur de la réactivité gliale à l'inflammation, dans le côlon distal comme dans l'hippocampe des souris ayant une colite induite par le DSS, suggérant un effet anti-inflammatoire de *Pf* sur l'inflammation locale du SNE mais également centrale (Figure 39).

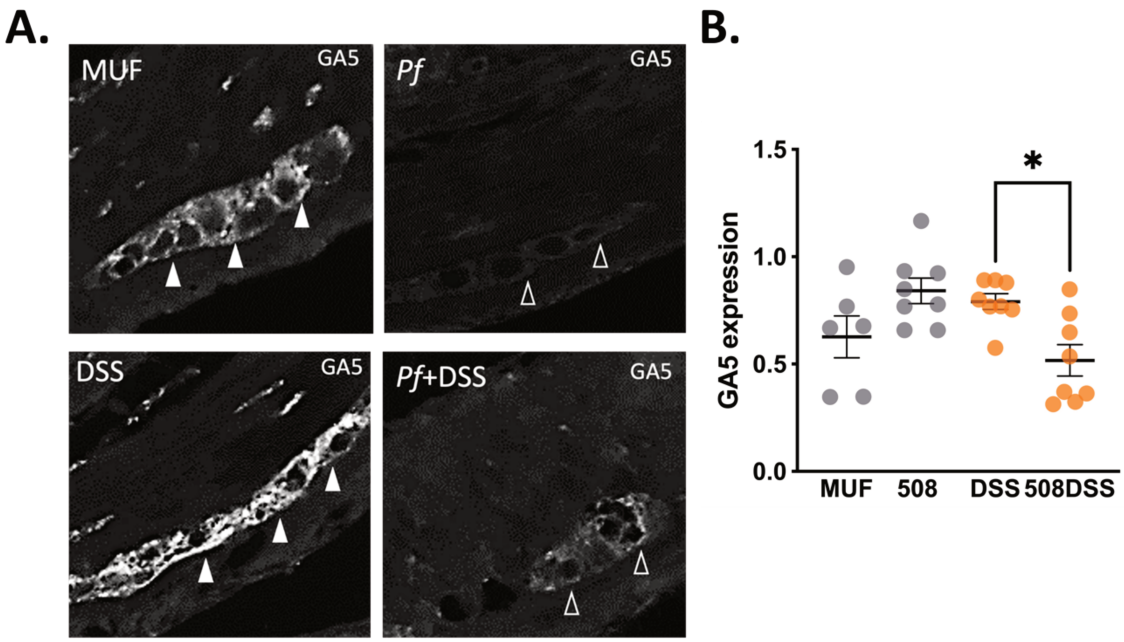

Figure 39. *P.freudenreichii* atténue l'inflammation induite par le DSS au niveau de la glie entérique (A) mais également hippocampique (B). L'expression de la GFAP a été révélée par immunohistochimie sur des côlons distaux (A) ou par western blot sur des lysats d'hippocampes de souris contrôle (MUF) ou DSS, gavées avec *Pf* CIRM-BIA508 (Pf ou 508) pendant 11 jours. N= 4-8.

D'autre part, nous avons montré que *P.freudenreichii* renforce la BEI, notamment *via* la production de VEs. Il serait intéressant d'explorer si ces VEs peuvent passer la BEI, comme c'est le cas pour d'autres souches bactériennes, et si elles ont la capacité d'influencer le SNE sous-jacent. De plus, les VEs de *Pf* pourraient, en regard de leurs effets sur la BEI, renforcer la BHE en supposant qu'elles puissent passer dans la circulation sanguine, ce qui pourrait potentiellement réduire l'inflammation au niveau du cerveau. En ce sens, il a été décrit que des VEs bactériennes étaient capable de traverser la BHE dans des modèles de stress et Alzheimer *in vivo* (**Figure 40**) (Kaisanlahti et al. 2023; Bleibel et al. 2023).

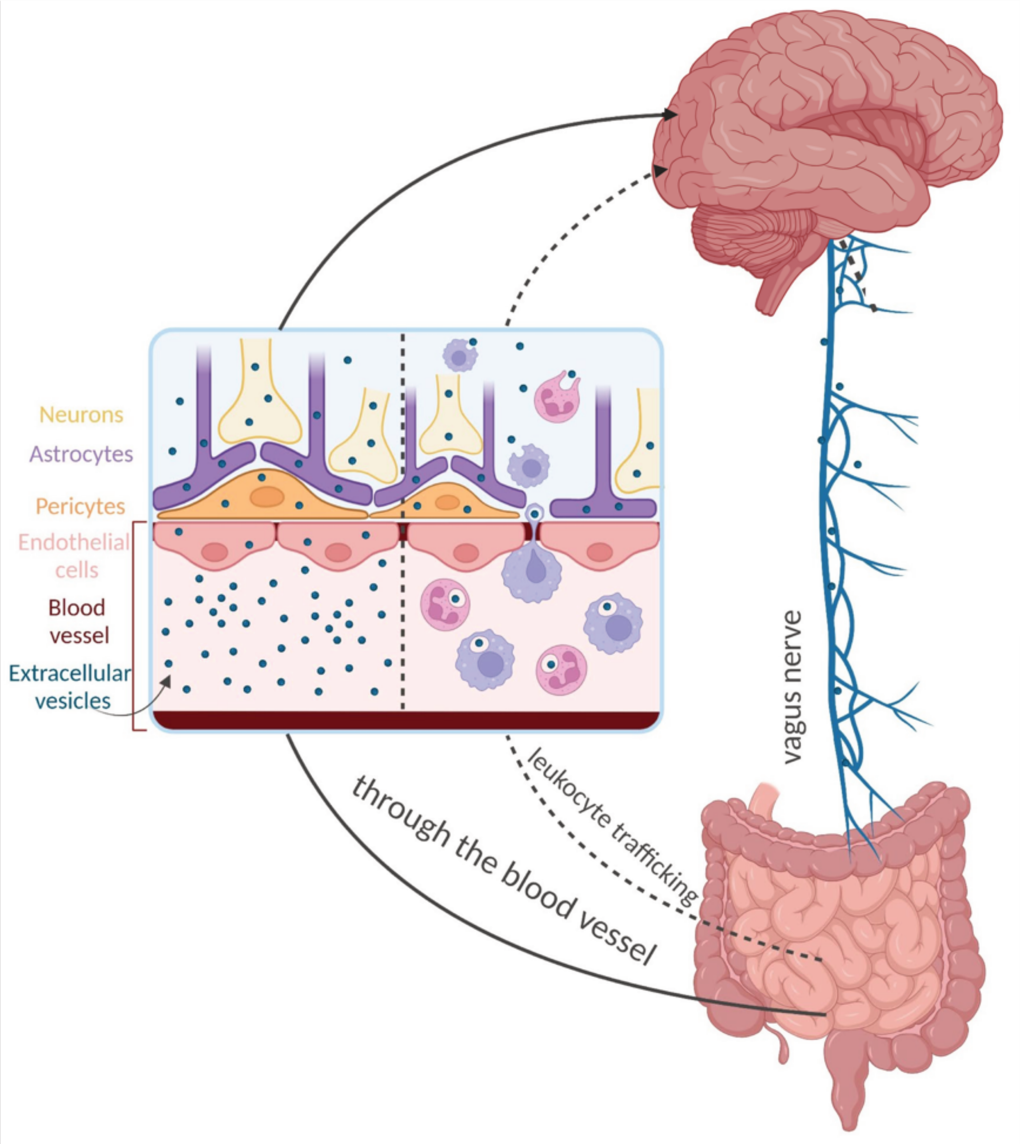

Figure 40. Moyen de passage de vésicules extracellulaires bactériennes au travers de la BHE (d'après Bleibel et al. 2023). Les VEs bactériennes peuvent traverser directement la BHE vers le cerveau. D'autres voies incluent le transport par le nerf vague ou encore par les leucocytes.

CONCLUSION GENERALE

L'objectif de ce travail de thèse était de développer de nouvelles stratégies thérapeutiques en ciblant la BEI, acteur négligé de la physiopathologie des MICI. Nos résultats montrent l'intérêt de l'utilisation de *Propionibacterium freudenreichii*, qui, dans un contexte intestinal inflammatoire, renforce la BEI et favorise la rémission. Si nos travaux confirment l'intérêt de l'utilisation de cette bactérie probiotique, ils soulignent aussi les limites de son utilisation, ou plutôt la complexité de la physiopathologie des MICI. Sortir du cercle vicieux impliquant dysbiose, inflammation et perméabilité, nécessite probablement une approche holistique, ou tout du moins l'association de biothérapies ciblées à des probiotiques à l'efficacité reconnue et à une nutrition personnalisée.

La description des effets protecteurs de *Propionibacterium freudenreichii* nous permet d'envisager des approches préventives ou thérapeutiques, mais elle questionne également sur l'étiologie des MICI qui reste difficile à établir. De nombreuses théories ont été proposées au cours du siècle dernier concernant la cause de la maladie de Crohn ou de la rectocolite hémorragique, de la rougeole, aux causes allergiques et nutritionnelles ou même aux microparticules du dentifrice, sans qu'aucune ne se soit révélée exacte. Néanmoins il est difficile de ne pas s'interroger en observant l'augmentation de l'incidence des MICI parallèlement à l'utilisation de réfrigérateur et la baisse de la fermentation comme processus de conservation, mais également à celle d'une alimentation plus riche en n-6. Ces éléments n'auraient-ils pas favorisé un déséquilibre sensibilisant le développement des MICI, déséquilibre que nous pourrions essayer de corriger avec une consommation de *Pf* et de n-3 ?

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Titre: Renforcement de la barrière épithéliale intestinale dans les maladies inflammatoires chroniques de l'intestin: une approche combinant nutrition lipidique et utilisation de bactéries propioniques probiotiques.

Mots clés: Bactérie propionique laitière, Maladies inflammatoires chronique de l'intestin, Perméabilité, Epithélium intestinal, Acides gras poly-insaturés.

Résumé: L'intégrité de la barrière épithéliale intestinale (BEI) est un paramètre physiologique crucial. Elle est compromise dans de nombreuses pathologies dont les maladies inflammatoires chroniques de l'intestin (MICI). Parmi les stratégies qui visent à la renforcer ou à la rétablir, un intérêt croissant est porté aux composés alimentaires, et en particulier aux probiotiques et aux lipides. Premièrement, la consommation de souches sélectionnées immunomodulatrices de la bactérie propionique laitière *Propionibacterium freudenreichii* (*Pf*) renforce les jonctions serrées de la BEI en augmentant l'expression de ZO-1. Deuxièmement, les produits du métabolisme des acides gras poly-insaturés oméga-6 (AGPI n-6) diminuent la perméabilité et augmentent les capacités de réparation de cette BEI.
Dans ce contexte ce projet a deux objectifs: Premièrement, il s'agira d'identifier les souches de *Pf* les plus compétentes pour protéger la BEI des dommages induits par l'inflammation *in vitro* et *in vivo*, et étudier leurs mécanismes d'action. Deuxièmement ce projet analysera l'effet additif, voire synergique, entre *Pf* et les AGPI n-6 sur la BEI.
En associant des analyses biochimiques à des explorations fonctionnelles *in vivo*, notre projet a pu identifier deux souches d'intérêt de *Pf*, la 129 et la 508, qui, par des mécanismes différents, renforcent la BEI et peuvent non seulement inhiber le développement de colite mais aussi favoriser sa rémission. Nous avons de plus mis en évidence que l'efficacité de ces souches dépend de la composition de la matrice qui la vectorise, et surtout est complètement inhibée par un régime riche en AGPI n-6.

Title: Reinforcement of the intestinal epithelial barrier in inflammatory bowel diseases: an approach combining lipid nutrition and the use of probiotic propionibacteria.

Keywords: Dairy propionibacteria, Inflammatory bowel disease, Permeability, Intestinal epithelium, Polyunsaturated fatty acids.

Abstract: The integrity of the intestinal epithelial barrier (IEB) is a crucial physiological parameter. It is compromised in numerous pathologies, including chronic inflammatory bowel disease (IBD). Firstly, consumption of selected immunomodulating strains of the dairy propionic bacterium Propionibacterium freudenreichii (Pf). strengthens the tight junctions of the EIB by increasing ZO-1 expression. Secondly, products of the metabolism of omega-6 polyunsaturated fatty acids (n-6 PUFAs) reduce permeability and increase the repair capacity of the IEB. In this context, this project has two objectives: Firstly, to identify the Pf strains that are most competent at protecting the IEB from inflammation-induced damage *in vitro* and *in vivo*, and to study their mechanisms of action.
Secondly, this project will analyse the additive, or even synergistic, effect of Pf and n-6 PUFAs on the IEB. By combining biochemical analyses with *in vivo* functional explorations, our project has identified two *Pf* strains of interest, 129 and 508, which, *via* different mechanisms, reinforce the IEB and can not only inhibit the development of colitis but also promote its remission. We have also shown that the efficacy of these strains depends on the composition of the matrix that vectors them, and, is completely inhibited by a diet rich in n-6 PUFAs.