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MICRO REVIEW

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Molecular interactions between the intestinal microbiota and the host

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Abstract

The intestine is the most densely colonized region of the body, inhabited by a diverse community of microbes. The functional significance of the intestinal microbiota is not yet fully understood, but it is known that the microbiota is implicated in numerous physiological processes of the host, such as metabolism, nutrition, the immune system, and regulation of behavior and mood. This article reviews recent findings on how bacteria of the intestinal microbiota interact with the host.

Microbiota-microbiota and microbiota-host interactions are mediated by direct cell contact and by metabolites either produced by bacteria or produced by the host or the environment and metabolized by bacteria. Among them are short-chain fatty, including butyrate, propionate, and acetate. Other examples include polyamines, linoleic acid metabolites, tryptophan metabolites, trimethylamine-N-oxide, vitamins, and secondary bile acids. These metabolites are involved in regulating the cell cycle, neurobiological signaling, cholesterol and bile acid metabolism, immune responses, and responses to antioxidants. Understanding the host-microbiota pathways and their modulation will allow the identification of individualized therapeutic targets for many diseases. This overview helps to facilitate and promote further research in this field.

KEYWORDS
auto-immune disease, bile acids, gut permeability, immune system, inflammation, inflammatory bowel disease, microbe-associated molecular patterns, microbiome, short-chain fatty acids

1 | INTRODUCTION

The intestine is a habitat for a rich and diverse community of microbes and is the most densely colonized region of the body. The functional significance of the microbiota is not yet fully understood, though it is increasingly apparent that dysbiosis, a loss of balance in the complex relationship of microbial colonization in the intestine, is involved in various human diseases (Sekirov et al., 2010). The microbiota is implicated in many physiological host functions, including metabolic and nutritional processes (Degnan Patrick et al., 2014; Devillard et al., 2007), maturation and regulation of the immune system (Francino, 2014; Sekirov et al., 2010), and modulation of the brain and behavior (Hsiao et al., 2013; Sekirov et al., 2010). Microbiota-host and microbiota-microbiota interactions are mediated by direct cell contact and by metabolites either directly produced by bacteria or produced by the host or the environment and metabolized by bacteria (Agus et al., 2018). This article reviews recent findings on how bacteria of the intestinal microbiota interact with the host, including the molecular interactions.

2 | THE MICROBIOTA AND THE INTESTINAL MUCOSAL PERMEABILITY

The intestinal mucosa is made up of a mucus layer and an epithelial layer, it regulates the absorption of nutrients, electrolytes, and water from the lumen, and prevents the entry of pathogens and toxic substances into the bloodstream. The outer mucus layer is populated by commensal bacteria and contains secretory immunoglobulin A and antimicrobial peptides. In a healthy state, the inner mucus layer creates a physical barrier avoiding direct contact of bacteria with the epithelial layer. The epithelial layer consists of colonocytes or enterocytes, goblet cells, enteroendocrine cells, Paneth cells, tuft cells, and M cells which are connected by junctional complexes formed by transmembrane proteins (claudin, occludin, and tricullulin).

The interference of mucosal development, for example, through dysbiosis, can lead to intestinal permeability dysfunction and has been associated with a predisposition to immune diseases (Groschwitz & Hogan, 2009). To maintain the intestinal barrier, metabolites from numerous commensal bacteria, including *Akkermansia muciniphila* (Chelakkot et al., 2018; Everard et al., 2013; Plovier et al., 2017; Watson & Duckworth, 2010), *Bacteroides fragilis* (Hsiao et al., 2013), or *Bifidobacterium lactis* (Lindfors et al., 2008; Stratiki et al., 2007), influence the expression of tight junctions and the production of mucin (Table S1).

3 | THE MICROBIOTA AND THE IMMUNE SYSTEM

The microbiota plays a crucial role in the maturation of the immune system and the ability to differentiate between commensal and pathogenic bacteria, as well as tolerance and immunity to self and foreign antigens. Immune responses are initiated through the recognition of specific molecular structures by pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), and (NOD)-leucine-rich repeats-containing receptors (NLRs), found on innate immune or intestinal epithelial cells. TLRs detect ligands of bacterial, viral, and fungal origin, and NLRs ligands of bacterial origin. Microbe-associated molecular patterns (MAMPs), such as bacterial lipopolysaccharides (LPS), peptidoglycan, lipoteichoic acid (LTA), toxins, and flagellin, are ligands to PPRs. By sensing these MAMPs, the host PRRs initiate an intracellular signaling cascade culminating in changing the expression of various immune response genes, releasing interferons and cytokines.

The intestinal microbiota influences neutrophil migration and activity (Owaga et al., 2015), as well as T cell differentiation into different types of T helper cells (Th1, Th2, and Th17) or regulatory T (Treg) cells (Francino, 2014). Polysaccharide A produced by the commensal bacterium *B. fragilis* suppresses the production of interleukin (IL)-17 by Th17 cells and stimulates CD4+ T cells to differentiate into IL-10-producing Treg cells, which protects the intestine from inflammation (Table S1) (Mazmanian et al., 2005, 2008; Troy & Kasper, 2010). Treg cells are crucial for maintaining immune tolerance and preventing excessive inflammatory responses, their dysfunction can contribute to autoimmune disorders.

Bifidobacterium adolescentis increases the number of Th17 cells in the murine intestine (Tan et al., 2016). Th17 cells in the intestine help to mediate barrier defense and repair by producing IL-17 and IL-22. These cytokines increase the production of antimicrobial peptides and tight junction proteins by intestinal epithelial cells. IL-17 also promotes neutrophil recruitment. An increased Th17 response can be found in patients with inflammatory bowel disease (Table S1) (Kanai et al., 2012).

The proximity of intestinal epithelial cells with the intestinal microbiota is an important aspect of the crosstalk between the microbiota and the host immunity. Different subtypes of intestinal epithelial cells can directly influence the composition of the intestinal microbiota by releasing antimicrobial peptides, including regenerating gene family protein III c (RegIIIc), α-defensins, and angiogenins (Cash et al., 2006; Hooper et al., 2003). In mice, a decrease of α-defensin production by Paneth cells leads to a higher abundance of *Firmicutes* and a lower abundance of *Bacteroidetes*. These alternations in the microbiota have been associated with lower numbers of IL-17-producing T cells, which leads to a shift in the mucosa toward a proinflammatory state (Salzman et al., 2010).

In infants, the composition of the intestinal microbiota plays an important role in the development and regulation of the immune system. There is an early-life "critical window" during which the microbiota and the immune response develop concurrently. Altered bacterial colonization during this time of maturation of the immune system can result in defective immune tolerance, which can exacerbate autoimmune and inflammatory diseases (Sekirov et al., 2010).

4 | MICROBE-MICROBE INTERACTIONS

The microbiota is characterized by dynamic interactions between bacteria, forming complex metabolic networks. Microbe-microbe interactions mutually influence functional activities. Antagonistic interactions arise from competition for resources or space or the production of toxic metabolites. Agonistic interactions result from secreted metabolites utilized by other bacteria or environmental detoxification. *Bacteroidetes*, one of the most prevalent phyla in the intestinal microbiota of humans in developed countries, mostly has antagonistic interactions, while some bacteria of the phylum *Actinobacteria* and *Firmicutes* mainly have agonistic interactions (Venturelli et al., 2018).

Nutritional interactions can be categorized into nutrient competition, where bacteria compete for limited nutrients (Fischbach Michael & Sonnenburg, 2011), and syntrophic metabolism, where bacteria use molecules produced by other bacteria (Fischbach Michael & Sonnenburg, 2011).

An example of syntrophic metabolism can be shown when colonizing gnotobiotic mice with *Eubacterium rectale* and *B. thetaiotaomicron*. *E. rectale* up-regulates phosphoenolpyruvate carboxykinase in the presence of *B. thetaiotaomicron*, indicating a carbon dioxide

competition (Mahowald et al., 2009). The interaction of *E. rectale* and *B. thetaiotaomicron* results in lower propionate concentrations than *B. thetaiotaomicron* by itself and it is likely that *E. rectale* depletes carbon dioxide, stimulating *B. thetaiotaomicron* to produce acetate rather than propionate. This allows *E. rectale* to convert acetate to butyrate, thereby producing more adenosine triphosphate (ATP) (Table S1) (Fischbach Michael & Sonnenburg, 2011).

The ability of commensals and pathogens to expand in the intestine is also affected by mobility, adhesion, and biofilm formation. These behaviors are often regulated by a mechanism called quorum sensing (QS), cell-to-cell communication in which small chemical signals known as autoinducers (AIs) are synthesized in response to environmental changes, nutrient availability, and the threat of competing or pathogenic bacteria (Whiteley et al., 2017). AI signaling induces synchronized development of bacterial populations, allowing bacteria to regulate their gene expression (e.g., expression of virulence factors or biofilm formation) (Whiteley et al., 2017). Preliminary evidence shows how QS may affect the composition of the intestinal microbiota. For example, AI-2 produced by a variety of bacterial species, including *Bacteroides* (Antunes et al., 2005), *Ruminococcus* (Hsiao et al., 2014), *E. rectale*, and *Lactobacilli* (Lukás et al., 2008; Pereira et al., 2013; Tannock et al., 2005) may promote intestinal colonization by *Firmicutes* rather than *Bacteroidetes* (Table S1). Furthermore, AI-2 may mitigate infections by *Vibrio cholerae* (Antunes et al., 2005). Competence and sporulation factor (CSF) is a quorum-sensing molecule produced by *Bacillus subtilis*. It activates survival signal pathways, such as p38 MAP kinase and protein kinase B in intestinal epithelial cells. It also induces cytoprotective heat shock proteins that protect intestinal epithelial cells from oxidation-induced injury and loss of barrier function. Those effects may be involved in the development of Crohn's disease (Table S1) (Fujiya et al., 2007). The interference with QS in the microbiota could offer an opportunity to act on intestinal dysbiosis (Whiteley et al., 2017).

5 | BACTERIAL METABOLITES

5.1 | Short-chain fatty acids

SCFAs are end-products of nondigestible dietary fibers that underwent microbial fermentation. The main SCFAs generated by bacteria populating the large intestine are butyrate, acetate, and propionate. Bacteria producing butyrate include *Faecalibacterium prausnitzii* (Miquel et al., 2013; Sokol et al., 2008), *E. rectale* (Duncan et al., 2007; Prindiville et al., 2000; Rivière et al., 2015), and *Roseburia* (Duncan et al., 2007, 2008) (Table S1). *A. muciniphila* (Derrien et al., 2004; de Vos, 2017) can produce propionate and acetate during mucin fermentation and *Bifidobacterium longum* (Jiang & Savaiano, 1997; Nurmi et al., 2005) during lactate fermentation (Table S1). Growing evidence shows that SCFAs can modulate intestinal motility and may act as appetite regulators in mammals (Sleeth et al., 2010). SCFAs can circulate into various organs. In the brain, SCFAs can modulate tissue development and function (Macfabe, 2012). SCFAs also help maintain intestinal barrier function by regulating paracellular permeability in human epithelial cells (Suzuki et al., 2008).

5.1.1 | Butyrate

In the human intestinal microbiota, butyrate is mainly produced by Firmicutes, namely *F. prausnitzii* and *Clostridium leptum* from the *Ruminococcaceae* family and *E. rectale* and *Roseburia* spp. from the *Lachnospiraceae* family, respectively (Barcenilla et al., 2000; Louis & Flint, 2009). Furthermore, some bacteria produce butyrate from lactate and acetate, for example *Eubacterium hallii* and *Anaerostipes caccae* (Duncan et al., 2004).

For ex vivo colonocytes, butyrate serves as a source of energy via the tricarboxylic acid cycle, ATP production, and β-oxidation, and suppresses autophagy (Donohoe Dallas et al., 2011). Along with propionate, butyrate can induce intestinal gluconeogenesis. It can also directly activate gluconeogenic genes by increasing cyclic adenosine monophosphate (cAMP) (Chenard et al., 2020) (Figure 1). Furthermore, butyrate mediates a variety of anti-inflammatory effects on T cells, Treg cells, neutrophils, and macrophages by affecting migration, cytolytic activity, cytokine production, and gene expression (Chen & Vitetta, 2020).

In ruminants, butyrate production by *E. hallii* increases the transcription of mucin-related genes, contributing to goblet cell differentiation and mucus production (Table S1) (Ploger et al., 2012). Butyrate stimulates the mucin-2 expression by increasing the production of prostaglandin in subepithelial myofibroblasts near the intestinal epithelium and thereby supports the host's innate immune response against pathogens (Willemsen et al., 2003) (Figure 1). As a critical regulator of intestinal permeability, butyrate increases AMP-activated protein kinase activity (AMPK) in human epithelial cells (Peng et al., 2009), thereby inducing the assembly of tight junction complexes (Figure 1).

Impaired tight junction protein expression in germ-free mice leads to an increase in intestinal permeability and an impaired function of the blood–brain barrier (BBB) (Braniste et al., 2014). An increased BBB permeability results in greater concentrations of inflammatory molecules and immune cells in the brain tissue, commonly seen in patients suffering from neurological disorders such as multiple sclerosis and Alzheimer's disease (Bednarczyk & Lukasiuk, 2011).

Furthermore, an increase in intestinal butyrate, for example, produced by *C. tyrobutyricum* (Lee et al., 2016) or *E. hallii* activates anti-inflammatory and inhibits pro-inflammatory pathways. By inhibiting histone deacetylase in a butyrate-dependent way (Steliou et al., 2012), intestinal macrophages and dendritic cells in mice decrease their production of pro-inflammatory mediators such as IL-6, IL-12 (Figure 1), and reticuloendotheliosis viral oncogene homolog B (Relb) expression, supporting Treg differentiation (Arpaia et al., 2013). Butyrate induces transcription factor Forkhead-Box-Protein P3 (Foxp3) acetylation in Treg cells, which are essential for limiting inflammatory responses in the intestine (Arpaia et al., 2013).

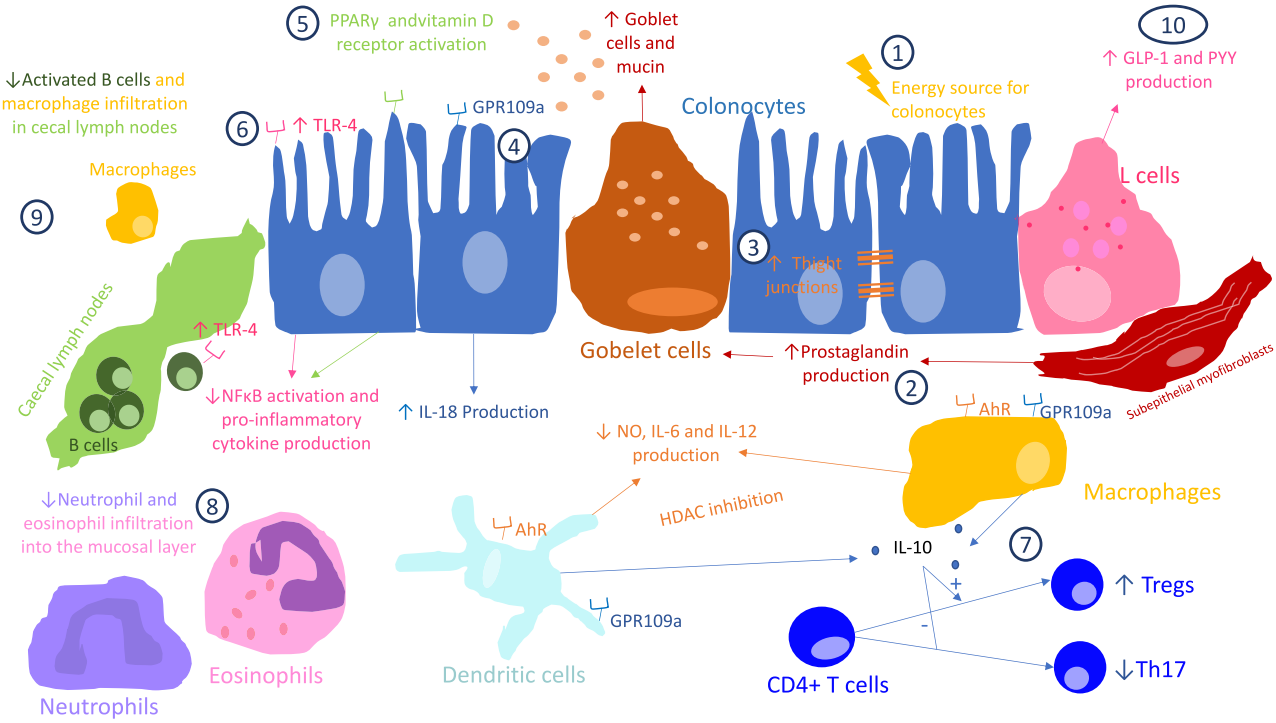

FIGURE 1 Butyrate action in the intestine. (1) Energy source for colonocytes. As a substrate, induction of gluconeogenesis and cAMP associated genes. (2) Induces prostaglandin production in subepithelial myofibroblasts, which increases the number of goblet cells and mucin production. (3) Increases AMPK activity which leads to augmented tight junction complexes assemblation. (4) Binds to GPR109a on colonocytes, inducing IL-18 production, which has an anti-inflammatory action in the colon. (5) Activates PPAR-γ and vitamin D receptors leading to the inhibition of NF-κB and reduction of pro-inflammatory chemokine production. (6) Downregulation of TLR-4 gene expression in B cells and colonocytes lead to the inhibition of NF-κB and reduction of pro-inflammatory chemokine production. (7) Binds on AhR on dendritic cells and macrophages leading to an enhanced IL-10 production (anti-inflammatory activity) and histone deacetylase inhibition (reduction of NO, IL-6 and IL-12 pro-inflammatory cytokines production). (8) Decreases the chemotaxis of neutrophils and eosinophils, preventing their infiltration into the mucosal layer. (9) Decreases the number of activated B cells in the cecal lymph nodes and macrophage migration into these nodes. (10) Induces the GLP-1 and PPY production in enteroendocrine L cells in the colon

Ultimately, this reduces the intestinal immune system's response allowing beneficial, butyrate-producing bacteria to establish themselves (Chang et al., 2014).

G-protein-coupled receptor (GPR) 109a is a receptor for butyrate in the intestine that suppresses inflammation. In colonic macrophages and dendritic cells, GPR109a signaling promotes anti-inflammatory properties by inducing the differentiation of Treg cells and IL-10-producing T cells. Furthermore, GPR109a mediates butyrate-dependent induction of IL-18 in colonocytes (Singh et al., 2014) (Figure 1). An additional anti-inflammatory effect is the downregulation of the TLR4 pathway, which is involved in the production of pro-inflammatory cytokines and the activation of nuclear factor kappa-light-chain-enhancer (NF-κB) in activated lymphoid cells and colonocytes in different animal models (Vaure & Liu, 2014) (Figure 1). Butyrate inhibits NF-κB by activating the peroxisome-proliferator-activated receptor γ (PPAR-γ) and the vitamin D receptor in vitro (Gaschott et al., 2001; Hamer et al., 2008) (Figure 1). Thus, tumor-necrosis-factor α (TNF-α) and LPS-dependent activation of NF-κB are suppressed (Schwab et al., 2007).

Finally, butyrate reduces the number of activated B cells in cecal lymph nodes, inhibits macrophage migration into these nodes, and prevents neutrophil and eosinophil infiltration to the mucosal layer, reducing intestinal mucosal inflammation (Vieira et al., 2012) (Figure 1).

The anti-inflammatory and intestine permeability controlling effects of butyrate may have a protective effect on colon diseases such as cancer (Scharlau et al., 2009) or inflammatory bowel disease (Miquel et al., 2013). There is evidence that *Firmicutes* producing butyrate, such as *F. prausnitzii*, are reduced in patients with inflammatory bowel disease (Table S1) (Miquel et al., 2013; Sokol et al., 2008).

5.1.2 | Propionate

Propionate is a SCFA mainly produced by *Bacteroidetes* (Louis & Flint, 2017). After transportation to the liver, it is either oxidized or used in the production of glucose. Propionate activates GPR41 (Xiong et al., 2004) and GPR43 (Hong et al., 2005). GPR41 can be found on adipocytes, where its activation through propionate stimulates leptin secretion in mice and in vitro (Xiong et al., 2004), on sympathetic neurons, where propionate reduces intracellular cAMP concentrations and promotes the extracellular signal-regulated kinase 1 and 2 phosphorylation, leading to diverse protein and transcription responses (Chenard et al., 2020) and on peripheral

neurons, where propionate increases glucose-6-phosphatase activity in the jejunum, inducing gluconeogenesis (Chenard et al., 2020). As a result of a rise in intestinal gluconeogenesis, glucose and insulin sensitivity are increased, helping to prevent type 2 diabetes (Chenard et al., 2020). In the intestinal tract of ruminants, propionate acts through different mechanisms on mucosal blood flow, acidic milieu, water and electrolyte absorption, and as an energy source for colonocytes (Ploger et al., 2012).

As shown in an in vitro experiment with human colon epithelial cells, propionate produced by *B. lactis* has anti-inflammatory activities by increasing the expression of cyclooxygenase-1 (COX-1) and decreasing the expression of COX-2 (Table S1) (Nurmi et al., 2005).

Propionic acid may be associated with anxiety. In rats, a higher concentration of propionic acid in the intestine has been associated with social behavior impairment (Shams et al., 2019).

5.1.3 | Acetate

Among commensal bacteria, *B. thetaiotaomicron* (Wrzosek et al., 2013), *B. longum* (Jiang & Savaiano, 1997), and *A. muciniphila* (Derrien et al., 2004; de Vos, 2017) produce acetate. In colonocytes or cancer cells, acetate is converted into acetyl-coenzyme A (CoA), which is an important intermediate between the glycolysis pathway and the Krebs cycle. Acetate is involved in the formation of sterols, hexosamines, and ketones. Histone acetylation by lysine acetyltransferases (KATs) and the acetyl-CoA-synthetase 2 (ACSS2) activity is important for signaling in peripheric tissues (Chenard et al., 2020).

Acetate can cause the parasympathetic nervous system to be over-activated. This leads to increased glucose-stimulated insulin secretion, increased ghrelin secretion, hyperphagia, obesity, and its related conditions, such as hypertriglyceridemia, nonalcoholic fatty liver disease (NAFLD), liver, and muscle insulin resistance (Perry et al., 2016).

Acetate metabolism plays a crucial role in a variety of cancers. ACSS2 converts acetate to acetyl-CoA in the cell, this conversion to acetyl-CoA is crucial for sustaining tumor growth. It has been shown that ACSS2 is expressed in several cancer types, including hepatocellular carcinoma, glioblastoma, breast cancer, and prostate cancer (Schug et al., 2016). In response to hypoxia and low nutrient availability, ACSS2 is upregulated, indicating its importance in the tumor microenvironment. Acetate may serve as a source of energy, a lipid converter, or a regulator of pH levels and gene transcription in tumors through histone acetylation modifications (Schug et al., 2016).

5.2 | Polyamines

Polyamines such as putrescine, spermidine, and spermine, which are synthesized by intestinal bacteria such as *Clostridia* (Matsumoto & Benno, 2007), are organic cations needed for cell growth, differentiation, and synthesis of deoxyribonucleic acid (DNA), ribonucleic acid (RNA), and proteins. Polyamines inhibit the production of inflammatory cytokines by macrophages (Zhang et al., 1997), regulate NF-κB activation, and intestinal permeability (Li et al., 2001). Polyamines are reactive oxygen species scavengers, acid tolerance factors, chemical chaperones, and regulators of the stress response (Rhee et al., 2007). Spermidine, synthesized by *B. lactis*, has been shown to have antimutagenic effects and is promising in decreasing colon mutagenesis or tumorigenesis in humans (Table S1) (Matsumoto & Benno, 2004; Matsumoto et al., 2011). Results from studies in rats suggest a connection between polyamine concentrations and aging (Das & Kanungo, 1982); intestinal polyamine concentrations are lower in elderly adults compared to younger adults (Matsumoto & Benno, 2007; Matsumoto et al., 2011).

6 | MODULATION OF DIETARY METABOLITES

6.1 | Vitamins

The intestinal microbiota modulates the bioavailability of vitamins from the diet. Vitamin K, a cofactor for regulating the coagulation cascade and immunity in mammals, is one such important example. Vitamin K is available as vitamin K1, dependent on food intake, and vitamin K2, which is produced when commensal bacteria such as *Enterobacter*, *Eubacterium lentum*, *Veillonella* or *Bacteroides* metabolize vitamin K1 (Table S1) (Biesalski, 2016; Blacher et al., 2017). Broad-spectrum antibiotics lead to significantly reduced vitamin K concentrations in human liver samples (Conly & Stein, 1994). Vitamin K2 may reduce the risk of coronary heart disease and osteoporosis (Beulens et al., 2013).

Many species of the human intestinal microbiota, including *Escherichia coli* and *B. thetaiotaomicron*, compete with the host for corrinoids (vitamin B12 being a well-known one) (Degnan Patrick et al., 2014). Acquiring corrinoids from the environment (from membranes of bacteria or epithelial cells) over de novo biosynthesis might pose a survival benefit (Seth & Taga, 2014). Corrinoids and corrinoid precursors can profoundly affect the metabolism of bacteria and the ability to occupy a particular niche. For example, the corrinoid-dependent enzyme ethanolamine ammonia-lyase is responsible for the ability of human pathogens, including *Listeria monocytogenes* and *Enterococcus faecalis* to utilize ethanolamine as a carbon and nitrogen source (Garsin, 2010; Tsoy et al., 2009) (Table S1).

6.2 | Linoleic acid metabolites

Several bacteria of the human intestinal microbiota, including *Roseburia*, *Bifidobacteria*, and *Butyriribrio fibrisolvens* (Table S1) actively metabolize linoleic acid to either vaccenic acid or hydroxyl-18:1 fatty acid, which are precursors to cis-9, trans-11-18:2 conjugated linoleic acid (CLA) (Devillard et al., 2007; Rosberg-Cody et al., 2004). Animal studies have shown that CLA inhibits colonocyte proliferation and inflammation (Bassaganya-Riera et al., 2004). The induction

of PPAR-γ and -δ (regulators of epithelial differentiation, lipid balance, and immune system functioning) through CLA may have beneficial effects in the treatment of IBD (Bassaganya-Riera et al., 2004) and maybe useful in tumor suppression (Rosberg-Cody et al., 2004; Sarraf et al., 1999). A CLA isomer was found to inhibit the growth of mammary, colon, colorectal, gastric, prostate, and hepatoma cells in vitro (Kelley et al., 2007).

6.3 | Tryptophan-derived metabolites

Tryptophan (Trp), an essential amino acid, enters the body through dietary sources. It can be metabolized by the intestinal microbiota to form aryl hydrocarbon receptor (AhR) ligands (Figure 2). AhR is expressed by different cells throughout the body and influences several host responses and pathways, including cell cycle, neurological signaling, immune responses, and responses to antioxidants, xenobiotics, and hormone-like estrogen (Agus et al., 2018) (Figure 2). AhR ligands modulate mucosal immune cells and the development, function, and production of metabolites. Tryptophanase, which converts Trp into indole, is expressed in *E. coli* (Agus et al., 2018; Alexeev et al., 2018), *Peptostreptococcus russellii* (Wlodarska et al., 2017), and *Lactobacilli* (Lamas et al., 2018). AhR activation by indole promotes intestinal homeostasis, among other mechanisms, the increased production of IL-22 (Table S1) (Agus et al., 2018; Alexeev et al., 2018; Lamas et al., 2018), which acts on intestinal epithelial cells, promoting proliferation and production of antimicrobial peptides (Lamas et al., 2018) (Figure 2). In addition, AhR ligands decrease the risk of colonization by intestinal pathogens. For example, indole-3-acetonitrile hinders the growth of *Candida albicans* biofilms and the attachment of *C. albicans* to intestinal epithelial cells in vitro (Oh et al., 2012).

The decreased expression of AhRs on immune cells (CD3+, CD4+, CD56+, CD25+) of IBD patients might be associated with the reduced production of these ligands by the microbiota observed in these patients (Lamas et al., 2018). Furthermore, AhR ligands invert inflammatory responses by reducing interferon (IFN)-γ expression and increasing IL-22 production (Monteleone et al., 2011). Targeting the IL-22 pathway may lead to the development of treatments for infections, chronic inflammation, and autoimmune diseases in the future.

Bifidobacterium infantis activates indoleamine 2,3-dioxygenase-1 (IDO-1), the rate-limiting enzyme of the metabolization of Trp to kynurenic acid, which is essential in immune responses as well as neurobiological functions. A possible anti-depressive effect of *B. infantis* has been shown in rats (Tian et al., 2019). The microbiota can also transform Trp into indole, which induces colonic L cells to produce GLP-1, possibly involved in the pathogenesis of metabolic syndrome (Chimerel et al., 2014) (Figure 2). Trp can be converted to tryptamine neurotransmitter by the tryptophan hydroxylase, *Lactobacillus bulgaricus*, *Clostridium sporogenes*, and *Ruminococcus gnavus* stimulate the activity of this enzyme (Table S1) (Williams Brianna et al., 2014). Tryptamine binds to trace amine-associated receptors (TAARs) in the brain, which increases the inhibitory response of cells to serotonin

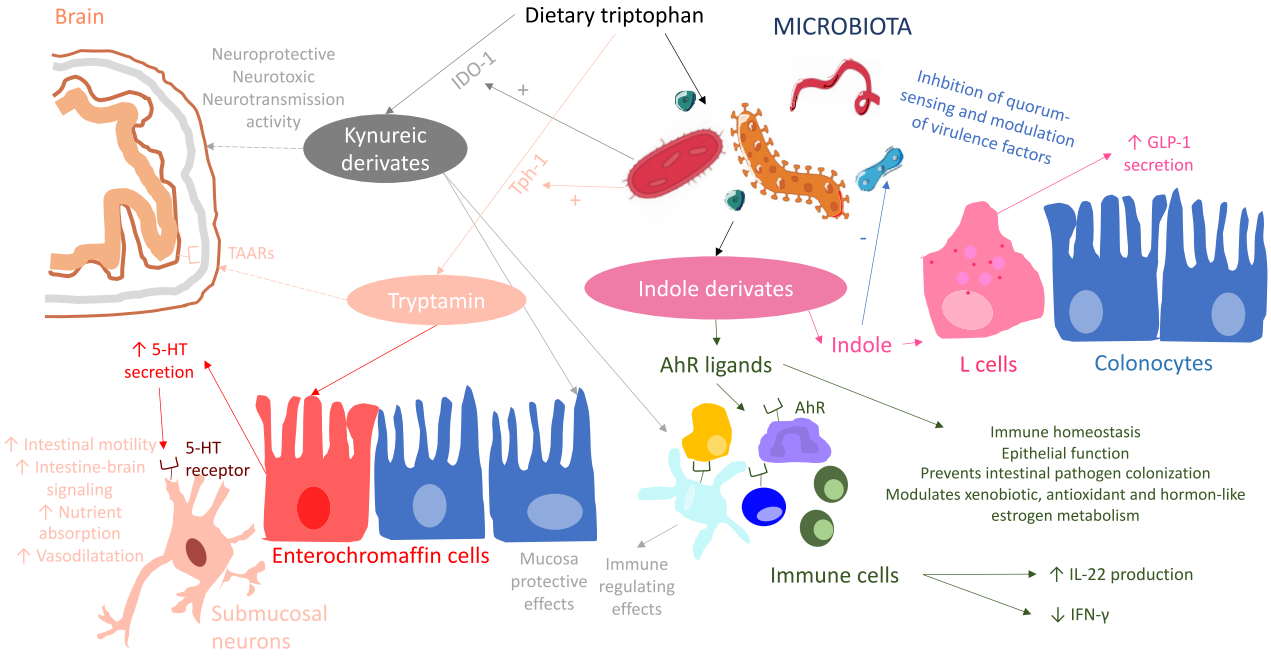

FIGURE 2 Tryptophan action in the intestine. In the intestine, the microbiota influences tryptophan metabolism by (1) conversion of tryptophan into indole derivates; several of these derivates are ligands to AhRs, which regulate immune homeostasis, epithelial function, and modulate xenobiotic, antioxidant and hormone-like estrogen metabolism—AhRs are also involved in prevention colonization by pathogens; (2) the kynurenine pathway in immune and epithelial cells via IDO-1 induction, which has neurotransmission activity. Kynurenic derivates can be neuroprotective or neurotoxic; (3) serotonin (5-HT) production in enterochromaffin cells via the induction of tryptophan hydroxylase 1 (Tph-1), leading to an increase in intestinal motility, intestine-brain signaling, nutrient absorption, and vasodilatation

(Williams Brianna et al., 2014). In mice, tryptamine also binds to the sigma-2 receptor, which may be involved in the development of cancer and Alzheimer's disease (Williams Brianna et al., 2014; Yang et al., 2020). In the intestinal tract, tryptamine stimulates the secretion of serotonin by enterochromaffin cells (Williams Brianna et al., 2014) (Figure 2). Fluctuations in intestinal serotonin concentrations are thought to modulate intestinal motility and may play a role in the pathophysiology of IBD (Williams Brianna et al., 2014). Given the importance of serotonin as a signaling molecule in the enteric nervous system, modulating serotonin receptors might be useful in the treatment of irritable bowel syndrome (IBS) (Williams Brianna et al., 2014).

6.4 | Trimethylamine-N-oxide

The metabolite trimethylamine-N-oxide (TMAO) is produced by bacteria, such as *Escherichia fergusonii*, *Proteus mirabilis*, and *Proteus penneri* by metabolizing dietary choline or L-carnitine, both of which are abundant in meat and high-fat diets (Blacher et al., 2017; Li et al., 2017; Wang et al., 2015). A high concentration of TMAO in mice results in enhanced atherosclerosis through altered cholesterol and bile acid metabolism, activation of inflammatory pathways, and increased foam cell formation and platelet hyperactivity (Duttaroy, 2021). In mice and humans, significantly higher fasting plasma TMAO concentrations are associated with adverse cardiovascular events, including myocardial infarction and stroke (Blacher et al., 2017; Wang et al., 2015). Measuring plasma TMAO may help predict short- and long-term risks of cardiovascular events helping in risk stratification among patients presenting with acute coronary syndrome (Li et al., 2017). However, even if TMAO has been associated with cardiovascular disease, controversy remains when studying specific cohorts of patients. No association between TMAO and an increased risk of cardiovascular disease or major adverse cardiovascular events was found in patients with end-stage renal disease (Kaysen et al., 2015) and patients with suspected coronary artery disease (Mueller et al., 2015).

7 | MODULATION OF HOST-DERIVED METABOLITES

7.1 | Bile acids

Bile acids are produced by hepatocytes, secreted into the intestine, and reabsorbed in large quantities in the ileum to be recycled by the liver. Primary bile salts solubilize dietary fats and fat-soluble nutrients to facilitate their absorption in the distal ileum. They also act as signal molecules between the liver and intestine to regulate lipid and glucose metabolism (Chiang, 2009). Approximately 5% of the primary bile acids escape reabsorption and are metabolized to secondary bile acids by bacteria in the large intestine, such as *Clostridia*, *Bacteroides*, *Bifidobacteria*, *Eubacteria*, *Escherichia*, and *Lactobacilli* (Table S1) (Fiorucci & Distrutti, 2015; Ridlon et al., 2006; Stellwag & Hylemon, 1976). The dehydroxylation of bile salts by *C. scindens* creates hydrophobic secondary bile acids which may be capable of inhibiting the growth and virulence of *C. difficile* (Table S1) (Buffie et al., 2015). In mice and humans, *Clostridium scindens* has been associated with resistance to infection with *C. difficile* in a bile acid-dependent manner (Buffie et al., 2015; Chiang, 2009), a reduction of secondary bile acids has been associated with several diseases, including recurrent *C. difficile* infections, IBD, metabolic syndrome, and gastrointestinal cancers (Blacher et al., 2017; Staley et al., 2017).

7.1.1 | Bile acid receptors

The microbiota-modulated secondary bile acids can bind to GPBAR1 (also known as TGR5) and the farnesoid X receptor (FXR) (Fiorucci & Distrutti, 2015). These are nuclear receptors mainly expressed within the intestine, the liver, and on immune cells (Fiorucci et al., 2018). Macrophages and dendritic cells express both GPBAR1 and FXR, while natural killer cells express FXR only (Blacher et al., 2017; Fiorucci et al., 2018). Activation of these receptors by bile acids causes macrophages to produce more IL-10 and less IL-6 and IFN-γ, dendritic cells to produce less TNF-α and IL-12, and natural killer cells to produce less osteopontin, a molecule involved in bone and immune processes (Fiorucci et al., 2018).

In the intestine, bile acid receptors are essential in the control of glucose and lipid metabolism. The activation of FXR or GPBAR1 in the colon decreases glucagon-like peptide (GLP-1) synthesis and secretion in colon enteroendocrine L cells. FXR also induces the release of fibroblast growth factor 15, a hormone that, inhibits bile acid synthesis (Mencarelli et al., 2013). Inhibition of intestinal FXR prevents, or opposes, high-fat diet-induced and genetic obesity, insulin resistance, and hepatic steatosis in mice (Li et al., 2013). Considering its role in glucose metabolism, FXR and GPBAR1 could be used as a pharmacological target for type 2 diabetes. In mice, hepatic FXR and GPBAR1 expression protect against hepatic steatosis and increased triglyceride and bile acid serum concentrations (Schmitt et al., 2015). FXR and GPBAR1 ligands may, therefore, offer a therapeutic option in treating nonalcoholic steatohepatitis (NASH) or NAFLD liver steatosis. Intestinal and hepatic FXR may exert opposing effects on steatosis (Fang et al., 2015).

The fact that bile acid receptor ligands play a role in regulating the liver and innate intestinal immunity, suggests that those ligands could maybe be used to treat clinical disorders related to metabolic and immune dysfunction. However, secondary bile acids have also been associated with a higher risk of colorectal cancer (Wirbel et al., 2019).

8 | CONCLUSION AND PERSPECTIVE

The human microbiota engages with the immune, endocrine, and nervous systems on multiple levels. Humanized mouse models with

the human microbiota enable to study the relationship between the microbiota and host physiology or pathology. However, using these models has limitations. First, the immune response differs between mice and humans, making it difficult to use the results for a human application. Second, studies in mice do not capture the genetic and environmental diversity of the human population, failing to include variables such as medication, smoking, and diet. Human microbiota research is becoming more and more prevalent. However, these experiments also have their limitations. The culture of microbiota is challenging for many bacteria and many microbiota studies focus on bacteria only, ignoring archaea, eukaryotes, and viruses. Furthermore, the microbiota compositions of fecal and mucosal samples differ, nevertheless most analyses are performed on fecal samples. Furthermore, the majority of studies are cross-sectional studies rather than long-term randomized controlled studies in large human cohorts (Ni et al., 2017).

Future research should analyze the role of microbiota as a marker of disease and progression. Is it possible to redesign the microbiota composition of patients according to their disease phenotype, genetics, and microbiota? Could microbiota-based interventions be used as preventative measures instead of treatments? Does dysbiosis results from inflammation or vice versa? Hopefully, prospective studies will provide the means to develop biomarkers that will help tailor healthcare strategies and identify new individualized preventive, screening, and treatment tools (Lazar et al., 2018).

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AUTHORS' CONTRIBUTIONS

Salomé Hertli drafted the initial manuscript and designed the figures. Petra Zimmermann critically revised the manuscript and both authors approved the final manuscript as submitted.

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SUPPORTING INFORMATION

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