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Review Article

Gut Microbiota Coordinates with the Host Immunity against Bacterial Infections

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Abstract

The coexistence of mammals and gut microbiota is essential for the host health. In this context, microbial metabolites play a critical role. This review describes the intricate interplay between the gut microbiota and the host immune system, in order to provide further insights into alternative therapies, based on the host metabolism modulation, to counteract bacterial infections.

Keywords: Gut Microbial Metabolites; Host Immunity; Pathogens; Immunometabolism

Introduction

Human body is a complex ecosystem of human and microbial cells. Each person carries trillions of symbiotic microbes (bacteria, virus, fungi, archaea and protozoa) [1], which collectively constitute the microbiota [2]. This community is extremely variable among individuals [3] and this variability starts in utero (vertical or maternal transmission) and continues during and post-partum [4,5]. Natural or caesarean delivery, as well as microbe colonization in the first days of life (horizontal transmission), are critical for the establishment and development of mature microbiota.

Microbiota, especially gut microbiota, is often considered as an independent organ and a second genome, providing the host with 100-fold more genes [6,7]. These genes are involved in processing indigestible dietary polysaccharides and producing primary metabolites [8,9].

The interaction between microbial and human metabolites is particularly relevant in the context of the immune system regulation [10]. This crosstalk is indispensable for energy metabolism and inflammatory response [8,11], highlighting the essential role of microbiota in human health [12].

Given the importance of microbiota, it is not surprising that its dysregulation (dysbiosis) - due to environmental factors such as diet and drug consumption - can affect the host homeostasis promoting serious diseases (Obesity, Malnutrition, Chronic Inflammatory Diseases and Cancer) [13]. In addition, dysbiosis of gut microbiota has also been correlated with an imbalanced immune regulation against self and non-self-bacteria.

The host has developed mechanisms of tolerance and resistance that enable symbiotic bacteria to support the immune system without causing tissue damage. However, in specific scenarios, such as opportunistic invasion by commensal bacteria into non-native tissues, this delicate equilibrium can be disrupted, leading to systemic infections [10,14].

Infectious diseases are - at the moment - one of the most important challenges for the global public health. The inappropriate use of antibiotics in humans and animals have significantly contributed to this concern, generating Drug-Resistant Pathogens (DRPs) [15]. It is estimated that in 2050, DRPs will cause more than 10 million of deaths every year, surpassing cancer in the list of the major causes of death [16]. In this perspective, novel

therapeutical interventions are imperative.

Developing strategies targeting metabolic pathways of the host immune cells, through modulation of microbial metabolites, could represent a promising approach.

This review aims at providing a lesson on the reciprocal dynamics between the gut microbiota and the host immune system, elucidating the role of microbial metabolites in fostering host immune cells, in an attempt to exploit these knowledges to improve human health and control infectious diseases.

Host-Microbiota Co-Evolution: Immune Tolerance

The mammalian immune system has evolved to protect the host from pathogens, while nurturing tolerance towards beneficial symbiotic microbes. This intricate process, named immune tolerance, relies on the difficult interplay between innate and adaptive immune responses, which coordinate their activities against pathogens, while preserving self-components [17].

Mucosae are the primary site for innate and adaptive immune regulation. They coordinate the host immune defense through a pool of lymphoid tissues and cells, which collectively constitute the Mucosa-Associated Lymphoid Tissue (MALT) [18].

The Gut-Associated Lymphoid Tissue (GALT) is the largest reservoir of mucosa-associated immune cells, including B and T cells, macrophages, plasma cells and Dendritic Cells (DCs) [19]. These cells serve to set up a barrier against harmful antigens and mount a fine-tuned immune response, which protects the host without altering the gut microbial ecosystem [20].

To initiate the mucosal immune response, GALT utilizes specialized non-immune cells named Microfold (M) cells, which represent 10% of Follicle-Associated Epithelial (FAE) cells found in Peyer's Patches (PPs), vermiform appendix and Isolated Lymphoid Follicles (ILFs) [21,22]. M cells play an essential role in transporting gut lumen antigens to intestinal Dendritic Cells (DCs), through transcytosis, phagocytosis or forming pores in inter-epithelial tight junctions [23]. Microbial transcytosis has been proven to stimulate Lipopolysaccharide (LPS)-mediated IL-1 release - and consequently - proliferation of T and B lymphocytes and IgA production [20,24]. IgA antibodies are critical in mounting an effective mucosal immune response against pathogens [25]. Further, they also limit mucosal penetration by commensal microorganisms, ensuring a tolerogenic response [25,26].

Similar to pathogenic bacteria, commensal microbes are recognized by innate immune receptors [27]. However, unlike their pathogenic counterparts, commensal microorganisms do not provoke an inflammatory response [26]. In opposition, they stimulate the release of anti-inflammatory mediators such as IL-10 and TGF-β1, which help preserve the integrity of the intestinal epithelial cell barrier and maintain a stable intestinal microbial community, contributing to overall gut health [27]. Growing evidences also demonstrate the role of RORγt+ FoxP3+ peripherally derived T regulatory cells (pTregs) in tolerogenic response due to IL-10 production [28], suggesting IL-10 as a critical immunoregulator mediator (Figure 1). Lack of IL-10, in fact, has been documented to increase the risk for chronic enterocolitis [29].

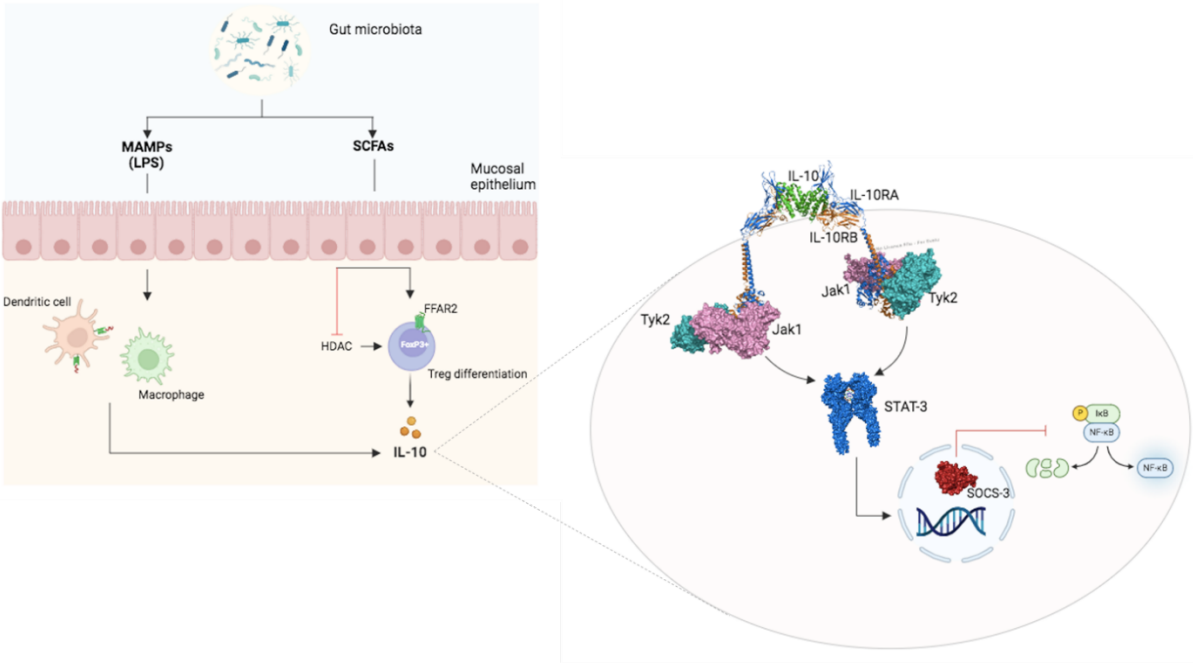

Figure 1: The role of IL-10 in immune tolerance and bacterial infection resistance. Commensal microbiota stimulates Lipopolysaccharide- (LPS) or Short Chain Fatty Acid- (SCFAs) mediated IL-10 production in the intestinal lamina propria. IL-10 is primarily produced by dendritic cells, macrophages and FoxP3+ T regulatory cells (Tregs). Upon release, IL-10 initiates cellular response by interacting with the heterotetrametric IL-10 Receptor (IL-10R) complex, which is characterized by two IL-10RA and IL-10RB subunits. The interaction between IL-10 and IL-10RA triggers a signalling cascade involving Jak1, Tyrosine kinase 2 (Tyk2) and the activator of transcription 3 (STAT-3). In detail, following IL-10 binding, both Jak1 and Tyk2 are phosphorylated, thus stimulating STAT3 recruitment and phosphorylation and allowing its translocation into the nucleus. Here, STAT-3 induces the SOCS-3 (suppressor of cytokine signalling 3), which, in turn, inhibits the NF-kB nuclear transcription and the pro-inflammatory gene expression [30].

In conclusion, whereas gut microbiota stimulates the immune system and induces immunogenic responses to harmful antigens, immune system inhibits unnecessary inflammatory response against innocuous gut microorganisms, suggesting a reciprocal balance between gut microbiota and immune system, which is critical for maintaining the host health.

Gut Microbe Metabolites: A Linking Point Between Microbiota and The Host Immune System

For a long time, it was believed that the immune system operates alone in identifying and eliminating harmful pathogens. This conclusion has been largely surpassed by current understanding of microbiota functions. Studies have demonstrated that germ-free animals exhibit underdeveloped immune systems characterized by absence of Th17 cells, reduced populations of αβ and γδ intraepithelial lymphocytes, and diminished levels of IgA antibodies [31,32]. This compromises the immune system and increases the susceptibility to infectious diseases, reducing life expectancy [31]. Interestingly, transplantation of mice microbiota into germ-free mice was found to restore immune functions. It provides microbial species which increase the expression of T cell markers genes (Cd4, Cd8a and Foxp3); CD8a+ intestinal lymphocytes and induce Th17 cells [33], thus enhancing the immune surveillance against pathogens.

To date, the precise mechanisms used by symbiotic microbes to influence the host physiology are still unclear. However, the emerging interest in high throughput technologies, such as metabolomics, has facilitated the acquisition of detailed information on how gut microbiota shape the host immune system for host defense.

The sophisticated relationship between gut microbiota and the host immune system depends on microbial metabolites. Gut microbes can generate metabolites through different approaches: i) de novo synthesis; ii) digestion of dietary components (Short Chain Fatty Acids and indole derivatives) and iii) biochemical modification of host metabolites (secondary bile acids) [11,34]. Collectively, these metabolites represent approximately 10%

of blood mammalian metabolites and together with the host metabolites contribute to the establishment of an immunological barrier against infections.

Short Chain fatty Acids

Short-chain fatty acids (SCFAs; acetate, propionate and butyrate) protects the host from pathogens, participating to the intestinal energy metabolism. They are produced by gut microbes through fermentation of dietary nondigestible fibres [11,35]. Thus, the diet can affect SCFAs production. High-Fat Diets (HFDs) decrease SCFAs production, compared to high-carbohydrate or high-protein diets (HCDs and HPDs, respectively) [36,37]. In particular, HPDs lead to production of Branched-Chain Fatty Acids (BCFAs; isovalerate, isobutyrate and 2-methylbutyrate) through fermentation of proteins rich in Branched-Chain Amino Acids (BCAAs). In addition, fluctuations of the gut microbe composition due to age-related changes also affect the levels of SCFAs [38]. In the early stage of life, *Bifidobacteria* prevail and increase acetate, lactate ad formate (two minors SCFAs) production, resulting from Human Milk Oligosaccharides (HMO) fermentation [39]. Upon breastfeeding interruption, *Firmicutes* prevail and increase propionate production, resulting from sugar fermentation [38]. Finally, in the late stage of life, there is an increase in *Proteobacteria* and a decrease in *Firmicutes* and *Bacteroides*, which, in turn, results in reduction of butyrate and propionate production [38].

SCFAs exert their immunomodulatory function against pathogens through different mechanisms. They can affect the signalling transduction pathway of immune cells by: i) activating specific extracellular G-protein coupled receptors, including free fatty acid receptor 2 and 3 (FFAR2 or GPR43 and FFAR3 or GPR41, respectively) and hydroxycarboxylic acid receptor 2 (HCA2, GPR109A); ii) inhibiting histone deacetylases (HDACs) and iii) promoting the activity of the histone acetyltransferase (HAT) enzymes [37].

By sensing FFAR2 on dendritic cells and neutrophils, SCFAs can switch B-cells into plasma cells and stimulate neutrophil recruitment to the inflammatory site, thus increasing antibody and inflammatory responses against pathogens [40]. Acetate has been found to facilitate the immune response against *Citrobacter rodentium* by recruiting neutrophils and Th17 cells and increasing the expression of IL6, CXCL1 and CXCL2 genes, as well as the production of IgA and IgG [40,41]. Of note, recent studies have demonstrated that the activation of Formyl peptide receptors by pro-inflammatory ligands strongly potentiates the acetate FFAR2-mediated effects, increasing chemotaxis and ROS production, for a successful antimicrobial response. However, excessive and prolonged ROS production due to neutrophil priming may exacerbate inflammatory response, leading to tissue damage [42]. In such condition, acetate can interfere to mitigate the inflammatory response by inducing regulatory T cell (Treg) accumulation in a FFAR2-dependent manner [43]. In addition, butyrate and propionate have also been found to suppress the inflammatory response by directly inhibiting histone deacetylase and encouraging Treg cell differentiation and IL-10 release (Figure 1) [43,44]. Overall, these findings indicate the key regulatory role of SCFAs in mounting a defensive response against pathogens and, concurrently, ensuring a balance between pro- and anti-inflammatory responses.

Indole derivatives

Indole (In) and indole derivatives (InDs) provide competitive advantages to gut microbes, supporting the host catabolism of tryptophan [46]. As an essential amino acid, changes in diet influence tryptophan abundance and, consequently, InD production. In addition, similar to SCFAs, gut microbe composition also affects InD production.

Clostridia are the major tryptophan-metabolizing microbial strains, involved in producing indole (In), indole-3-acetic acid (IAA), 3-indole acrylic acid (IA), Indole-3-Propionic Acid (IPA) and tryptamine (Roager & Licht, 2018). *Clostridium* colonization typically begins during childhood, specifically during the transition from breastfeeding to solid food intake, emphasizing the crucial role of diet in host homeostasis and infection susceptibility [46,47].

In Ds have been shown to inhibit the growth of different pathogens, including *Salmonella enterica*, *Staphylococcus aureus*, *Lactobacillus plantarum* and *Penicillium* strains [46]. Recent studies have also demonstrated that In- and InD-producing bacteria protect the host from *Cryptosporidium* infections 48]. This protective effect has been mainly attributed to the capacity of In in reverting the host mitochondrial reprogramming induced by *Cryptosporidium* to grow and replicate within the host [48]. In addition, the beneficial effects of In can also be attributed to the activation of the Aryl Hydrocarbon Receptor (AhRs) signalling pathway [49].

AhR belongs to the Periodic Circadian Protein (PER)-AHR Nuclear Translocator (ARNT)-Single-Minded Protein (SIM) superfamily of transcription factors, which can recognize exogenous and endogenous ligands, including In and InDs, and modulate both innate and adaptive immunity.

According to the ligand and the cytokine context, AhR signalling pathway can stimulate Th17, Foxp3+ Treg or type 1 regulatory T (Tr1) cell differentiation [50]. Th17 differentiation is mediated by IL-6, TGF-β1or IL-21 cytokines and together with IL-23 or IL-1β-activated RORγt+ Innate Lymphoid Cells (ILC) stimulate IL-22 release [49,51], inducing production of antimicrobial peptides and pro-inflammatory molecules involved

in host defense against pathogens. Recent studies revealed the essential role of IL-22 in conferring protection against *Helicobacter pylori* infection in immunized animals, likely due to the expression of the antimicrobial peptide RegIIIβ (regenerating islet-derived protein IIIβ) [52]. Tr1 differentiation instead, is mediated by IL-27 and enhanced by IL-10, IL-21 and CD39, while Foxp3+ Treg differentiation is initiated by TGF-β1 [50]. Furthermore, AhR activation in dendritic cells also participates to T cell polarization, favouring T_{reg} differentiation [49]. Both Tr1 and Foxp3+ Treg cells exert immunosuppressive functions [53,54].

Together, these findings suggest the pleiotropic role of InDs in mounting an effective immune response against pathogens, establishing their importance in host-microbe interactions and immune regulation.

Secondary Bile Acids

Gut microbial communities significantly influence the composition and dynamics of the bile acid pool [55,56]. *Firmicutes*, *Bacteroides* and *Actinobacteria* express hydrolase genes that catabolize approximately 5% of taurine or glycine-conjugated bile acids into taurine or glycine and primary bile acids (PBAs) [56,57]. The obtained amino acids are used for energy production, while PBAs undergo further biotransformation by gut microbes to produce secondary bile acids [SBAs; e.g., deoxycholic acid (DCA), lithocholate (LCA) and Urodeoxycholic Acid (UDCA)] (Figure 2) [58].

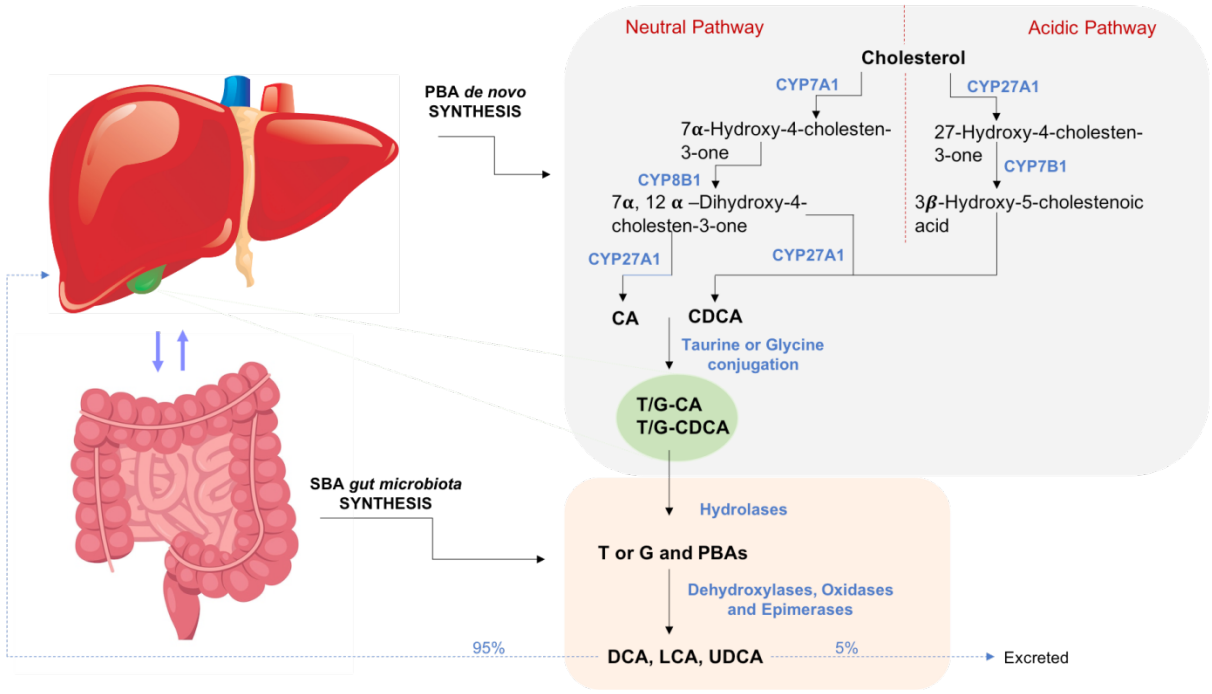

Figure 2: Primary Bile Acids (PBAs) biotransformation by gut microbes. Cholesterol is converted into PBAs [cholic acid (CA) and chenodeoxycholic acid (CDCA)] in the liver by the neutral or acidic pathway. Both CA and CDCA are successively conjugated with taurine or glycine to form bile salts, which are finally converted into secondary bile acids [SBAs; deoxycholic acid (DCA), Lithocholic Acid (LCA) and urodeoxycholic acid (UDCA)] by gut microbiota.

As ligands of the farnesoid-X-receptor (FXR), SBAs play critical roles in regulating immune responses. They have been shown to exert anti-inflammatory effects by suppressing inflammation through different mechanisms. SBAs inhibit the NF-kB-mediated pathway of TLR4 in macrophages, limiting the release of IL-6, TNF-α and IL-1β cytokines [59]. Additionally, they induce epigenetic changes and influence the transcription of innate immune genes [60]. Notably, SBAs have also been documented to inhibit Th17 cell differentiation, while stimulating the differentiation of FOXP3+ regulatory T (Treg) cells [61]. The capacity of SBAs to modulate both innate and adaptive immune responses, make these molecules effective in providing protection against opportunistic pathogens [62].

Recently, Burgess et al. demonstrated that the symbiotic *Clostridium scindens* protects the host from *Entamoeba histolytica* colonization and attributed this result to an increase in DCA production [63]. They showed that DCA administration stimulates granulocyte-monocyte progenitor expansion *in vivo* via epigenetic modifications, including H3K27me3 decrease and H3K4me3 increase [63]. Furthermore, DCA, combined with LCA, was found to protect the host against *Clostridium difficile* infections. This result was attributed to their ability of inhibiting pathogen growth, spore germination and toxin production [64].

In conclusion, these findings give reason for suggesting gut microbiota-metabolized bile acids as additional elements helpful in addressing the modern challenge of bacterial infections.

Gut Microbiota Dysbiosis and Host Resistance to Pathogens

For several years, it was thought that genetic variation in the host was the key determinant for microbial diversity. Recent evidences clearly confuted this hypothesis, suggesting environmental factors as main players involved in shaping microbial composition [65]. Investigations on monozygotic (MZ) and dizygotic (DZ) twins revealed that, even though MZ twins share a higher degree of similarity in microbiome composition compared to DZ twins [66,67], when living apart, MZ paired-twins change their microbiome profile [68].

Lifestyle and most notably diet, strongly influence gut microbial ecosystem by altering the relative abundance of some of the most important bacterial taxa, including *Bacteroides*, *Prevotella* and *Bifidobacteroides* [65,69]. These changes compromise the physiological balance between host and gut microbiota, leading to dysbiosis, key factor for the occurrence of inflammatory and metabolic diseases [70,71]. In addition, dysbiosis may also predispose to infectious diseases [72]. Malnutrition is the major contributor to bacterial infections. It is widely recognized that under- or overnutrition strongly imbalance density and ratio of gut dominant bacterial taxa, which reflect an impaired production of bioactive metabolites [73]. In other words, dysbiosis associated with the nutritional status strongly influences the host resistance to infections.

Dietary pattern and dysbiosis

In humans, both long-term and short-term dietary changes (LTDCs and STDCs, respectively) significantly influence microbial composition [8].

David LA, et al. [69] proved that STDCs promptly influence both structure and activities of gut microbial communities, with noticeable changes occurring as early as day 1 after the diet modification. They observed that animal-based diet (ADt) increases fat and protein intake while reducing fiber intake compared to plant-based diet (PDt). Interestingly, ADt was found to diminish the similarity in gut microbiome composition between the analyzed samples. Specifically, ADt depleted bacteria belonging to the genus *Prevotella*, which contribute to carbohydrate degradation and Short-Chain Fatty Acid (SCFA) production, and enriched bacteria exhibiting Bile Salt Hydrolase (BSH) activity [74]. Consequently, ADt may predispose to enteric diseases by enlarging the population of pathogenic *Enterobacteriaceae* and increasing the production of secondary bile acids.

Growing evidences suggest that BSH and its derivatives, including DCA and LCA, although proposed as potential therapeutical targets for infectious and metabolic diseases (as previously specified), may also participate to colorectal cancer development and progression via activation of the Wnt/Beta-catenin signalling pathway, induction of M2 macrophage polarization and infiltration of Tregs in the tumor microenvironment [75,76]. In addition, alterations in gut microbiota-mediated bile acid signalling associated with consumption of a high-fat diet have also been correlated with obesity [77].

Mice fed a high-fat diet and prone to obesity showed decreased abundance of *Clostridium scindens* and *Clostridium hylemonae* and, accordingly, decreased levels of the non-12-OH bile acids [ursodeoxycholate (UDCA), chenodeoxycholate (CDCA) and lithocholate (LCA)], which modulate the anorexogenic GLP-1 hormone [77,78] involved in insulin release and appetite control [79,80]. Similarly, reduction of SCFA levels due to high fat diet also impairs the insulin sensitivity and increase body weight and fat mass [81,82]. In this regard, emerging studies on mice and humans have demonstrated that fecal microbiota transplantation (FMT) from lean donors to obese acceptors can restore microbial metabolite dysregulation and improve insulin sensitivity, controlling both mass fat and body weight [83,84]. However, appropriate diet regimen is required. Thus, taken together these findings clearly indicate that gut microbiota rapidly

responds to dietary changes and that gut microbiota manipulation through probiotic supplementation or FMT, by reconstituting a balanced gut microbiota, could represent a valid approach to reduce dysbiosis and the related bacterial infection susceptibility due to malnutrition or dietary pattern modifications.

Conclusion

Gut microbiota plays a critical role in regulating the host homeostasis by providing beneficial metabolites, which communicate with the host immune cells. Notably, gut microbiota influences the host immunometabolism, through SCFAs production, bile acid detoxification and tryptophan metabolism [12].

The extensive plasticity of gut microbiota could compromise the intracellular metabolism of host immune cells, leading to pathological events, including bacterial infections. Understanding how structural and functional perturbations in gut microbiota facilitate pathogen colonization is a critical aspect for developing valid strategies for disease control.

It is widely recognized that gut microbiota composition strongly reflects the individual dietary choices [81]. This finding paves the way to dietary interventions as an alternative therapy to modulate the host resistance to bacterial infections. Personalized dietary approaches emerge as promising strategies to regulate host-microbiota metabolism and favor microbial species producing helpful metabolites.

In conclusion, modulation of gut microbiota pathways might aid the host immune system in inhibiting pathogen colonization, representing a potential therapeutical intervention against bacterial infections. Nevertheless, further studies enrolling larger sample size are needed to deeper investigate the intricate relationship gut microbiota-host immunometabolism and explore the way to modulate microbiome metabolism for host benefit.

Conflict of interest

The authors declare no conflict of interest.

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