



Guardians within: Cross-talk between the gut microbiome and host immune system

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Abstract

The gut microbiome, a complex ecosystem of trillions of microorganisms, plays a crucial role in immune system regulation and overall health. This review explores the intricate cross-talk between the gut microbiota and the host immune system, emphasizing how microbial communities shape immune cell differentiation, modulate inflammatory responses, and contribute to immune homeostasis. Key interactions between innate and adaptive immune cells – including macrophages, dendritic cells, natural killer cells, innate Lymphoid cells, T cells, and B cells – and gut microbiota-derived metabolites such as short-chain fatty acids are discussed. The role of commensal bacteria in neonatal immune system development, mucosal barrier integrity, and systemic immunity is highlighted, along with implications for autoimmune diseases, inflammatory conditions, and cancer immunotherapy. Recent advances in metagenomics, metabolomics, and single-cell sequencing have provided deeper insights into the microbiota-immune axis, opening new avenues for microbiome-based therapeutic strategies. Understanding these interactions paves the way for novel interventions targeting immune-mediated diseases and optimizing health through microbiome modulation.

Key Words: Gut microbiome; Immune system; Microbiota-immune axis; Dysbiosis; Inflammation

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Core Tip: This review highlights the critical interplay between the gut microbiome and the host immune system, focusing on how gut microbes and their metabolites, such as short-chain fatty acids, influence immune cell development, inflammatory regulation, and immune homeostasis. It emphasizes recent advances in metagenomics, metabolomics, and single-cell sequencing that have uncovered novel mechanisms of microbiota-driven immune modulation. The discussion also addresses the microbiome's role in early-life immune education and its implications for autoimmune diseases, inflammation, and cancer immunotherapy, offering insights into emerging microbiome-based therapeutic strategies.

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INTRODUCTION

The human microbial ecosystem comprises not only bacteria (microbiome) but also viruses (virome) and fungi (mycobiome), each playing distinct roles in regulating the immune system. The gut microbiome, dominated by bacterial communities, is pivotal in shaping host immunity through mechanisms such as metabolite production, regulation of epithelial integrity, and modulation of both innate and adaptive immune responses[1]. The virome, which includes bacteriophages and eukaryotic viruses, contributes to immune regulation by altering bacterial population dynamics and directly stimulating immune signaling pathways, particularly those involved in antiviral defenses[2]. The mycobiome, consisting of commensal fungal species, also influences immune responses by modulating mucosal immunity and participating in the balance between tolerance and inflammation at barrier sites[3]. Although the virome and mycobiome play supportive roles, current evidence emphasizes that the bacterial microbiome exerts the most significant and consistent impact on immune system development and disease modulation, making it the primary focus of immunological microbiome research. The gut microbiome, an intricate ecosystem of trillions of microorganisms residing in the gastrointestinal tract, plays a pivotal role in human health and disease. This microbial community, composed of bacteria, viruses, fungi, and archaea, is not merely a passive inhabitant but an active participant in various physiological processes. It influences digestion, synthesizes essential vitamins, and modulates metabolic activities, thereby contributing significantly to overall well-being[4]. Furthermore, disruptions in the gut microbiome – termed dysbiosis – have been linked to diverse conditions, including obesity, diabetes, inflammatory bowel disease (IBD) and neurodegenerative disorders[5]. Among its myriad functions, the gut microbiome is particularly notable for its role in shaping and regulating the host immune system. The immune system, a complex network of cells, tissues, and molecules, is tasked with protecting the body against pathogens while maintaining tolerance to self and non-harmful antigens. Immune homeostasis, the state of equilibrium between immune activation and suppression, is vital for preventing autoimmune diseases and chronic inflammation. The gut microbiome contributes to this balance by educating immune cells, modulating inflammatory responses, and maintaining the integrity of the intestinal barrier[6]. Emerging evidence underscores the bidirectional communication between the immune system and the gut microbiota, wherein microbial signals influence immune cell function, and, reciprocally, the immune system shapes the composition and activity of the gut microbiota[7].

The interplay between the gut microbiome and host immunity represents a frontier of biomedical research, with profound implications for understanding and treating human diseases. This review aims to explore recent findings that elucidate the mechanisms underlying the gut microbiome-host immunity interaction. We also aim to emphasize the role of the gut microbiome in maintaining immune balance and preventing immune dysregulation. Through this exploration, we hope to provide a comprehensive understanding of the “guardians within” and their pivotal role in maintaining homeostasis, fostering a deeper appreciation for the therapeutic potential of microbiome modulation.

COMPOSITION AND FUNCTION OF THE GUT MICROBIOME

The human gastrointestinal (GI) tract harbors a diverse and ever-evolving community of microorganisms, collectively known as the gut microbiome. This community includes bacteria, archaea, viruses, and fungi, which play essential roles in digestion, immune modulation, and overall health maintenance[8].

Overview of microbial diversity

The gut microbiome is predominantly composed of bacteria primarily composed of the *Firmicutes* and *Bacteroidetes* phyla, while *Actinobacteria*, *Proteobacteria*, and *Verrucomicrobia* are present in lesser abundances. Dominant genera include *Bacteroides*, *Prevotella*, *Ruminococcus*, and *Faecalibacterium*. The composition of these microbial communities varies along the GI tract, influenced by factors such as oxygen levels, pH and nutrient availability[8]. Multiple factors play a role in shaping the composition of the gut microbiota. Dietary patterns significantly impact microbiota composition. Fiber-rich diets support the proliferation of beneficial bacteria that generate short-chain fatty acids (SCFAs), whereas diets high in fat and sugar may contribute to microbial imbalance (dysbiosis), an imbalance associated with various diseases[9]. Host genetics

can shape the gut microbiome, affecting the abundance and diversity of microbial species. Genetic variations may influence the gut environment, thereby selecting for specific microbial communities[10]. Environmental factors, including geographic location, sanitation, and antibiotic exposure, contribute to microbiota composition. For instance, individuals in different regions exhibit distinct microbial profiles due to variations in diet, lifestyle, and healthcare practices[11].

Functional roles of the microbiome

The gut microbiome performs several critical functions. Indigestible dietary fibers are fermented by gut bacteria, leading to the formation of SCFAs such as acetate, propionate, and butyrate. These SCFAs provide energy to colonocytes, help regulate glucose and lipid metabolism, and possess anti-inflammatory properties. Additionally, certain gut microbes synthesize essential vitamins, including vitamin B and vitamin K, contributing to host nutritional status. The microbiome reinforces the intestinal barrier by stimulating mucus production and enhancing tight junction integrity, preventing pathogen translocation. Beneficial commensal bacteria help maintain homeostasis by competing with pathogens for nutrients and adhesion sites, producing antimicrobial compounds, and regulating the host immune response. Imbalances in the gut microbiome, referred to as dysbiosis, are associated with several conditions such as IBD, obesity, and metabolic disorders. Gaining insights into the factors that shape microbiota composition and function is essential for developing therapeutic approaches to restore microbial balance and support overall health. Apart from these, gut microbes play a crucial role in shaping host immunity by influencing both innate and adaptive immune responses. The gut microbiome acts as a critical modulator of immune system development, function, and homeostasis through several mechanisms. They contribute to the maturation of immune cells, such as T cells and B cells, during early life. Commensal bacteria play a crucial role in educating the immune system to differentiate between harmful pathogens and benign antigens[12]. The gut microbiota strengthens the intestinal epithelial barrier by promoting the production of mucus, antimicrobial peptides (AMPs), and tight junction proteins[13]. It stimulates the secretion of secretory immunoglobulin A (IgA), which plays a key role in mucosal defense[14]. Microbial components such as lipopolysaccharide (LPS) and peptidoglycans interact with pattern recognition receptors (PRRs) like toll-like receptors (TLRs) on immune cells, triggering inflammatory responses when needed[15]. The immune system's response to gut-associated bacteria can be just as potent as its reaction to pathogenic microbes, with variations observed across different bacterial phyla and strains. Myeloid cells engage specific innate receptors, such as TLR2 and TLR4, to detect bacterial taxa, showing distinct recognition patterns for *Bacteroidetes* and *Proteobacteria* that are indicative of their functional roles *in vivo*. These innate immune reactions can be replicated using combinations of up to eight TLR agonists. Moreover, the immunogenic characteristics of bacterial strains remain consistent over time[16]. SCFAs produced by gut bacteria (e.g., acetate, butyrate, propionate) modulate the function of macrophages and dendritic cells (DCs), promoting anti-inflammatory responses[17]. Gut microbes influence T cell differentiation, promoting the balance between regulatory T (Tregs) cells and pro-inflammatory T helper (Th) cells. Specific bacteria, such as *Bacteroides fragilis* (*B. fragilis*), have been shown to promote Treg differentiation, which helps maintain immune tolerance and prevent autoimmunity[18]. A well-balanced gut microbiome prevents chronic inflammation by regulating the production of pro-inflammatory and anti-inflammatory cytokines[19]. Dysbiosis (an imbalance in gut microbiota) can lead to immune dysregulation and has been linked to conditions such as IBD, allergies, and autoimmune disorders[20]. Commensal microbes prevent colonization by pathogens through competitive exclusion and production of antimicrobial substances[21]. The gut microbiota communicates with distant organs *via* microbial metabolites and immune signaling, impacting systemic immunity and even brain function (gut-brain axis)[22].

The detailed mechanism of modulation of innate and adaptive immune system by gut commensals are discussed in detail in the following sections.

ROLE OF GUT MICROBES IN SHAPING NEONATAL IMMUNE SYSTEM

The neonatal gut microbiota is established by the influence of various factors like delivery mode and feeding practices. Infants born through vaginal delivery acquire beneficial microbes from the mother's birth canal, whereas those delivered *via* cesarean section may experience altered microbial exposure, potentially affecting the transfer of essential bacterial strains. Similarly, breastfeeding supports the development of a diverse and beneficial microbiota, while formula feeding has been linked to reduced microbial diversity and a higher prevalence of pathogenic bacteria. Such imbalances in microbial composition have been associated with increased mucosal inflammation and a greater risk of conditions like necrotizing enterocolitis[23]. Although microbial colonization primarily occurs after birth, growing evidence suggests that the neonatal immune system may begin developing in utero. Microorganisms commonly found in the maternal gut and oral cavity have been detected in the placenta, umbilical cord, and amniotic fluid. However, the extent of bacterial presence in the fetal environment remains debated, with some studies suggesting minimal colonization of the fetal intestine. Additionally, recent research has identified key metabolites in the fetal gut, including amino acids, vitamins, and gut microbiota-derived bile acids, which may contribute to early immune system priming[24]. The hygiene hypothesis highlights the importance of early microbial exposure in establishing proper immune regulation. During fetal development, Tregs cells (Foxp3⁺ CD4⁺ Tregs) suppress immune responses against maternal antigens to prevent adverse reactions. After birth, commensal microbial antigens interact with PRRs, such as TLRs, on intestinal epithelial cells (IECs). This interaction plays a key role in modulating antimicrobial peptide production and promoting immune tolerance. Paneth cells further support gut immunity by releasing AMPs such as defensins, lysozyme and phospholipase-2 which selectively eliminate harmful pathogens while preserving beneficial microbes[25]. Among the beneficial microbes, *Bifidobacteria* play a pivotal role in immune system development by supporting T cell maturation and modulating immune responses. A deficiency in *Bifidobacteria* has been associated with reduced metabolism of human milk oligosaccharides and heightened

Th2/Th17 immune activation, which may increase the risk of allergic and inflammatory disorders. While formula feeding can temporarily lower *Bifidobacteria* abundance, breastfeeding helps restore and sustain its levels[26]. As infants transition from milk to solid foods, a process known as the 'weaning reaction'. During this phase, the gut microbiota undergoes substantial transformations, accompanied by a rise in bacterial and dietary metabolites, including SCFAs and retinoic acid, which influence immune function. Disruptions or delays in weaning can lead to long-term immune imbalances, increasing susceptibility to allergic inflammation and colitis. Furthermore, inadequate early microbial exposure can elevate immunoglobulin E (IgE) levels, contributing to hypersensitivity and conditions like asthma and IBDs.

The early colonization of mucosal surfaces plays a fundamental role in immune system maturation, with significant development occurring within the first few years of life. During this time, the gut microbiota undergoes dynamic changes before stabilizing around the age of three. This critical window not only shapes immune responses but also determines susceptibility to immune dysregulation. Neonates, with their immature immune systems, are particularly prone to infections, which remain a leading cause of infant mortality. In contrast, preterm infants often exhibit excessive inflammatory responses, increasing the risk of necrotizing enterocolitis[27]. Germ-free (GF) animal models have offered important insights into the relationship between microbiota and immune development. Research indicates that the absence of commensal microbes leads to impaired lymphoid tissue architecture and weakened immune function. In GF mice, intraepithelial lymphocytes (IELs) are significantly reduced, but microbial colonization can restore their numbers. Similarly, IgA, a key component of mucosal immunity, is markedly diminished in the absence of microbiota but increases upon exposure to commensal bacteria. Additionally, gestational exposure to maternal microbiota has been shown to promote the development of innate immune cells, including group 3 innate lymphoid cells (ILC3s) and mononuclear cells, in offspring[28]. Certain commensal bacteria also play distinct immunomodulatory roles. Th17 cell differentiation is promoted by *segmented filamentous bacteria* (SFB), which is crucial for immune regulation. Similarly, *B. fragilis* produces polysaccharides that help maintain immune balance by addressing T cell deficiencies and regulating Th1/Th2 responses. Additionally, gut microbiota influences the development of intestinal B cells and shape immunoglobulin repertoires, both of which are essential for immune homeostasis[29]. The neonatal gut microbiota plays a pivotal role in shaping long-term immune function and determining susceptibility to immune-related disorders. Early exposure to a diverse microbial community is crucial for developing an immunoregulatory network that prevents excessive immune reactions, such as mucosal IgE overproduction, which is linked to allergy development. TLR5, which detects bacterial flagellin, is essential in regulating gut microbiota composition during early life, thereby supporting long-term immune stability[30].

RELATIONSHIP BETWEEN THE INNATE IMMUNE CELLS AND GUT MICROBIOME

The gut microbiome plays a fundamental role in modulating host immune responses, particularly through interactions with innate immune cells. The mucosal immune system, which includes gut-associated lymphoid tissues (GALTs), innate lymphoid cells (ILCs), macrophages, DCs, and conventional natural killer (NK) cells, is essential in maintaining immune homeostasis. This section explores the roles of these immune components in the gut and their interactions with the microbiota.

GALT

GALT is a critical component of the mucosal immune system, serving as a primary site for immune surveillance and response. The major structures of GALT include Peyer's patches, crypt patches, isolated lymphoid follicles (ILFs), the appendix, and mesenteric lymph nodes (mLNs)[31]. The cellular composition of GALT houses several types of immune cells such as M cells (which transfer antigens), conventional lymphocytes including Th cells, cytotoxic T lymphocytes, Tregs cells, IgA-producing B cells, and phagocytes like DCs and macrophages which help mediate immune responses[31]. The development and function of GALT are influenced by the gut microbiota. GF animals exhibit impaired GALT development, with reduced crypt patches and ILFs. Studies have shown that gut microbial colonization is essential for the proper functionality of secondary lymphoid organs, particularly through interactions with lymphoid tissue inducer (LTi) cells, a subset of ILC3s[32]. Additionally, the gut microbiota plays a role in immune tolerance by influencing PRRs like TLRs and nucleotide-binding oligomerization domain (NOD) receptors[33]. PRRs recognize microbial-associated molecular patterns (MAMPs), facilitating the differentiation of immune cells and the production of AMPs[34]. GALTs serve as a vital interface between systemic immunity and local immune responses to gut microbiota. Their influence can extend to distant organs such as joints, skin, and even the central nervous system[35]. This connection is likely mediated through antigen-presenting cells (APCs) that migrate from the gut and circulate in the body, contributing to autoimmune susceptibility. Studies indicate that variations in pro-inflammatory cytokine production by GALTs, depending on the gut microbiota composition, may influence the predisposition to autoimmune diseases[36]. The role of PRRs in this process has been elucidated through studies on pathogen-associated molecular patterns (PAMPs) that gut bacteria produce. These PRRs, including TLRs and NOD receptors (NOD1/2), are crucial for the development and function of GALTs. In PRR-deficient mice, the development of ILFs in the colon and ileum is impaired, underscoring the importance of PRR-PAMP interactions in immune system development[37]. Additionally, the activation of PRRs in response to commensal bacteria aids in shaping GALTs' immune function, including the production of REGIIIb and REGIIIg (AMPs). In contrast, TLR pathway disruption can make the host more susceptible to infections, highlighting the critical role of PRR signaling in maintaining intestinal homeostasis and immunity. Microbial metabolites like SCFAs regulate immune responses in GALTs *via* epigenetic mechanisms, maintaining tolerance and defence, with imbalances potentially leading to inflammation such as colitis[38]. In conclusion, the gut microbiota plays a pivotal role in shaping the development of GALTs, priming them for immune responses, and ensuring tolerance toward commensals. The interactions between PRRs and

microbial components and the influence of microbial metabolites like SCFAs highlight the importance of the gut microbiota in immune system development and regulation. The early immune responses initiated in GALTs, especially within mLNs, are central to gut-driven immunity and may have crucial contribution in the onset of autoimmune diseases.

ILCs

ILCs are important elements of the innate immune system located in GALTs. Unlike T cells and B cells, ILCs do not possess antigen-specific receptors, hence, do not undergo antigen receptor gene rearrangement *via* recombinant activating genes for their development. Instead, ILCs express a range of surface receptors for activation, inhibition, and cytokines, which help them detect immune signals in the tissue microenvironment and guide their functional outcomes, such as promoting cytotoxicity or tolerance[39,40].

ILCs are classified based on their transcription factors and cytokine profiles. Group 1 ILCs, which are T-bet-dependent and similar to Th1 cells, primarily produce interferon- γ (IFN- γ). Group 2 ILCs, which resemble Th2 cells, depend on GATA3 and produce interleukins (ILs) (IL-13 and IL-5). ILC3s are ROR γ t-dependent like Th17 and Th22 cells and secrete IL-17 and IL-22[41,42]. Among the group 1 ILCs, there is a growing recognition of the distinction between cytotoxic NK cells and non-cytotoxic ILC1 cells[43]. ILCs are mostly located in non-lymphoid tissues like epithelial tissues (GI tract, skin, and respiratory tract) where they display considerable functional and transcriptomic diversity. It is hypothesized that local microbiota exposure may contribute to this diversity[44]. It is also evidenced by several studies that the lymphoid organs receive a microbiota-driven tonic signaling *via* metabolites or other molecules maintaining a state of immune readiness and homeostasis, essentially acting as a "baseline" signal to keep the immune system primed and responsive to potential threats[45].

Conventional NK cells: Conventional NK cells (cNK cells) are the sole cytotoxic ILCs, known for their property to differentiate between "self" cells and "non-self" cells *via* activating and inhibitory receptors[46]. These cells respond to signals indicating the presence of pathogens, tissue damage, or cancerous growth by circulating in blood stream and residing in different tissues like the gut. The activation of cNK cells depends on a balance between activating and inhibitory signals, along with interactions with cytokines, resulting in the release of cytotoxic molecules like perforin and granzyme. Additionally, cNK cells can engage in tumor necrosis factor (TNF)-related apoptosis-inducing ligand pathways and antibody-dependent cellular cytotoxicity[47]. Gut microbiota plays a vital role in the priming and education of cNK cells, particularly through dendritic cell activation by commensal bacteria, which influences the functional abilities of cNK cells[48].

Some gut bacteria produce metabolites that influence NK cell function. For example, butyrate (SCFA) secreted as a by-product of dietary fibre fermentation by gut microbiota, has anti-inflammatory effects on NK cells. When NK cells are cultured with butyrate, they display lower expression of activating receptors and a decrease in cytotoxic activity. This suggests that butyrate can limit NK cell effector functions, potentially maintaining immune homeostasis and preventing excessive inflammation[49]. Gut commensals and their products can directly influence NK cell activity through receptor-mediated signaling pathways. For example, microbial products such as LPS can induce sustained MYD88-dependent signaling, which in turn orchestrates the function of liver-resident NK cells. This interaction highlights the role of microbial components in shaping NK cell responses[50]. Gut commensals and their products can directly influence NK cell activity through receptor-mediated signaling pathways. For example, microbial products such as LPS can induce sustained MYD88-dependent signaling, which in turn orchestrates the function of liver-resident NK cells. This interaction highlights the role of microbial components in shaping NK cell responses[51].

Helper-like ILCs: ILC1, ILC2, and ILC3, including LTi cells, are helper-like ILCs that, unlike cNK cells, do not possess cytotoxic capabilities but perform critical immune functions. While their development appears independent of gut flora, the presence of gut microbiota influences their immune functions, such as cytokine production[52]. ILC3s are particularly important in the gut, where they secrete IL-22 to promote epithelial cell survival and enhance the production of AMPs, thus contributing to gut homeostasis[53,54]. Recent studies suggest that symbiotic bacteria may regulate the differentiation and function of ILC3s, affecting immune responses to pathogens and maintaining gut microbiota balance[55].

The interaction between ILC3s and commensal bacteria, especially through microbial metabolites like butyrate, is essential for maintaining gut immunity. Aryl hydrocarbon receptor (AhR) activation by these metabolites enhances ILC3 function, including IL-22 production, which is crucial for defense against infections. Moreover, ILC3s interact with CD4⁺ T cells to promote immune tolerance towards commensal bacteria, highlighting the significant role of gut microbiota in immune homeostasis. LTi cells, a subset of ILC3s, are involved in the formation of secondary lymphoid tissues in the gut. They interact with microbiota and stromal cells to promote the development of ILFs, which are essential for effective immune responses[56]. The development and function of other ILC subsets, such as ILC1 and ILC2, are also influenced by the gut microbiota, which affects their activation *via* cytokines produced by epithelial cells[57].

In conclusion, ILCs, especially ILC3s, are critical for maintaining gut immune function, balancing pathogen defense, and ensuring immune tolerance. Their interaction with gut microbiota is fundamental for their maturation and function, and disturbances in this relationship may contribute to autoimmune diseases.

Phagocytes: Macrophages and DCs

Phagocytes in the gut, including IECs, macrophages and DCs play key roles in maintaining intestinal homeostasis and regulating immune responses. These cells contribute significantly to immune tolerance toward commensal microbiota and pathogen recognition[58]. Gut macrophages, especially those located in the epithelium, lamina propria, and structures within GALTs (mLNs and Peyer's patches), are specialized for tissue residency. A notable subset of gut macrophages referred to as Tim-4⁺ macrophages, originate from circulating monocytes unlike macrophages in other organs, such as the liver or skin. Recent findings reveal that these subpopulation of gut macrophages (Tim-4⁺ CD4⁺) are main-

tained locally, while conventional macrophages (Tim-4-) are consistently replenished from peripheral sources[59]. The migration and development of these macrophages are guided by the chemokine receptor C-C motif chemokine receptor 2, with its expression being modulated by commensal bacteria. In the absence of gut microbiota, the chemotactic signal required for macrophage replenishment is disrupted, weakening the immune defense[60]. Furthermore, the gut microbiota can impact the production of peripheral myelocytes (including macrophages) by influencing both early hematopoiesis in the yolk sac and subsequent myeloid cell production in the bone marrow. The lack of gut microbiota significantly weakens the immune response, leading to increased vulnerability to infections due to diminished myeloid cell function[61].

DCs in the gut share similarities with macrophages, particularly in their distribution and phagocytic function. However, DCs stand out for their ability to process and present antigens to activate the adaptive immune system[62]. Gut DCs have two subsets: (1) CD103+ DCs; and (2) CD103- CD11b+ CX3CR1+ DCs. The presence of gut microbiota allows CD103+ DCs to migrate from the gut to mLNs, where they activate T cells to initiate immune response[63]. In contrast, CD103- DCs exhibit less migration potential and a diminished capacity to activate T cells, although they are involved in the phagocytosis of invasive pathogens[64]. In conditions of dysbiosis, such as during a *Salmonella* infection, CD103+ DCs are attracted to the epithelial layer, where they extend trans-epithelial dendrites to phagocytose and present antigens from pathogenic bacteria[65].

APCs, including DCs and macrophages, are vital for initiating adaptive immune response[66]. In the absence of gut microbiota, DCs in the mLNs of GF mice exhibit a reduced capacity to stimulate IL-17 and IFN- γ production in T cells, indicating that signals derived from the microbiota are crucial for initiating robust immune response[67]. Recent studies indicate that the presence of different bacterial strains influences APC activation, which in turn determines the outcome of immune responses, including the development of autoimmune diseases such as lupus[68]. Studies have shown that faecal transplantation alters the gut microbiota and shift immune responses, highlighting the connection between microbiota composition and autoimmune pathogenesis[69].

At the epigenetic level, SCFAs produced by the gut microbiota have been shown to modulate the function of phagocytes, including macrophages and DCs. SCFAs, such as acetate, butyrate, and propionate, influence immune responses through mechanisms that involve G-protein coupled receptor activation and histone deacetylase inhibition. In GF mice, DCs fail to produce essential pro-inflammatory cytokines like IL-6, TNF, and IFN- γ , due to the downregulation of H3K4-me3 modification, which impairs IRF3 and NF- κ B binding to promoter regions of these cytokines[70,71]. In addition, the lack of SCFAs in GF mice also disrupts macrophage polarization, preventing the induction of anti-inflammatory cytokines like IL-10 and leading to heightened inflammation.

Microbial metabolites, especially SCFAs, regulate the polarization of macrophages towards the M2 phenotype, which exerts anti-inflammatory effects, while inhibiting the M1 polarization that is associated with inflammation[72]. These SCFA-mediated effects also influence hematopoiesis, with studies showing that SCFAs enhance the production of immune cells such as macrophages and DCs from the bone marrow, further reinforcing the critical role of gut microbiota in immune system regulation[73]. In summary, gut microbiota-derived metabolites, have substantial roles in the epigenetic modulation of local immune cells and the overall immune homeostasis. These microbial signals are critical for maintaining a balanced immune response in the gut and preventing inflammation. Disruptions in the microbiota can lead to immune dysregulation and increase the risk of inflammatory diseases and autoimmunity. Thus, APCs act as essential links between the local immune system and systemic immunity, especially in the context of altered microbiota. A summary of the interaction of innate immune cells with beneficial gut commensals is given in **Figure 1**.

RELATIONSHIP BETWEEN THE ADAPTIVE IMMUNE CELLS AND THE GUT MICROBIOME

The interaction between the adaptive immune system and the gut microbiota is pivotal for maintaining immune homeostasis, preventing pathogenic infections, and ensuring mucosal integrity. The gut mucosal adaptive immune system primarily consists of IELs and lamina propria lymphocytes (LPLs)[74]. These immune cells play key roles in responding to microbial stimuli and regulating immune responses in the GI tract.

Gut mucosal lymphocytes (IELs and LPLs)

IELs are a unique subset of T cells expressing Helios transcription factor and act as the first line of defense against microbial invasion. Among them, $\gamma\delta$ T cells inhibit mucosal dissemination of bacteria by secreting antimicrobial proteins and pro-inflammatory cytokines[75]. These cells enhance CD4+ T cell responses by promoting mucosal IL-22 and calprotectin secretion, which are crucial for intestinal barrier integrity[76]. Several bacterial species and their metabolites, such as phosphatidylethanolamine and phosphatidylcholine from *Desulfovibrio* species, have been shown to promote $\gamma\delta$ T cell expansion[77]. According to some recent studies, $\gamma\delta$ T cell deficiencies result in augmented bacterial translocation and increased chances of pathogen entry. This is supported by clinical observations where acutely septic patients exhibit lower levels of circulating $\gamma\delta$ T cells[78] and reduced colonic $\gamma\delta$ T cells have been linked to IBD[79].

CD4+ and CD8+ T cells

The gut microbiota plays a pivotal role in shaping both CD4+ and CD8+ T cell responses, influencing their development and function. GF mice exhibit impaired adaptive immunity, which can be restored through microbial colonization, leading to the expansion of mucosal lymphocytes[80]. The activation of cytotoxic CD8+ T cells depends on antigen presentation by professional APCs and CD4+ T cell priming. These cells are crucial for clearing intracellular pathogens such as *Salmonella*, which can induce epigenetic modifications like histone methylation and acetylation to enhance T cell

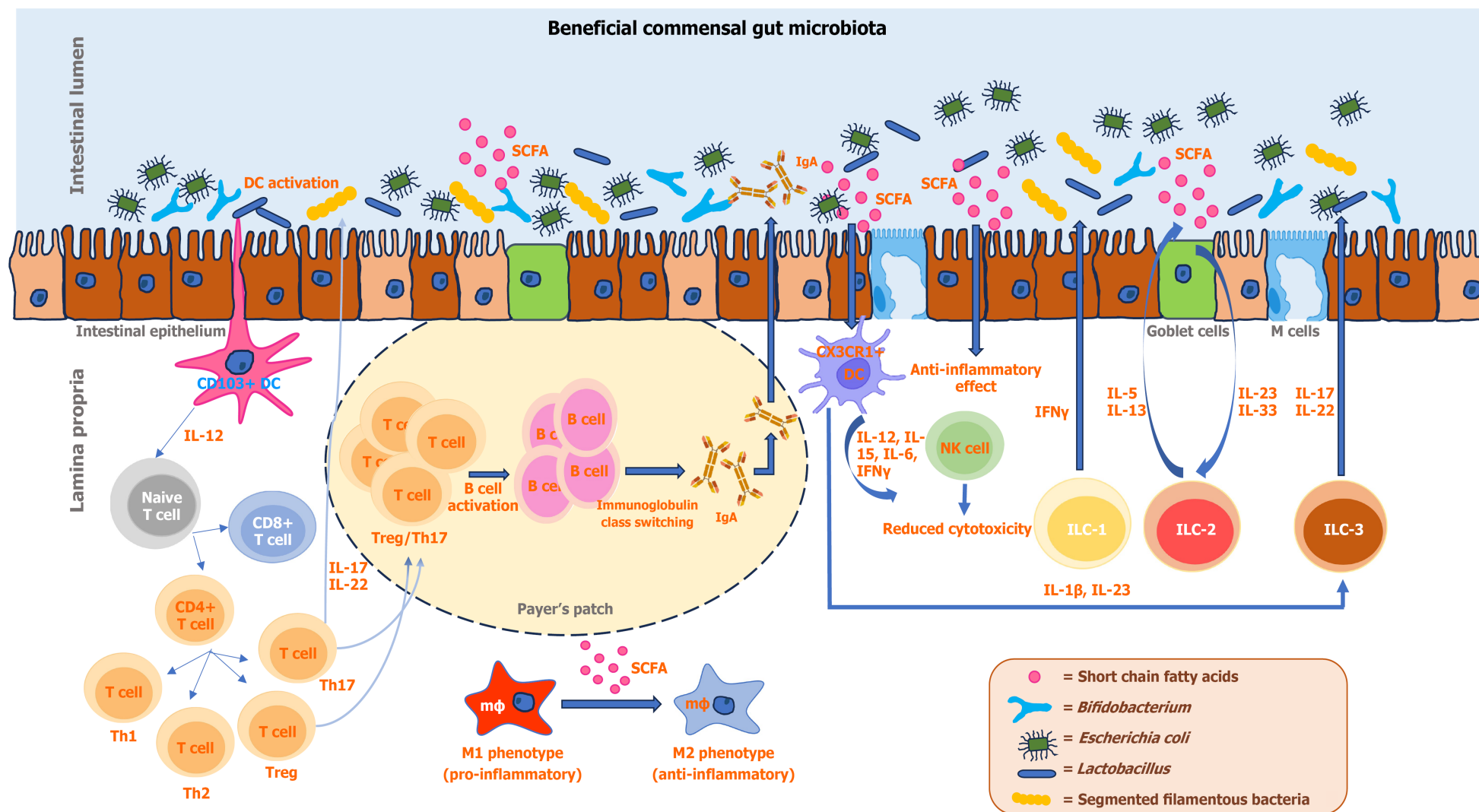


Figure 1 A simplified summary of the interaction of the beneficial gut commensals and gut resident immune cells. For simplicity, only some key members of the gut microbiota community have been mentioned here. DC: Dendritic cells; IFN- γ : Interferon- γ ; IgA: Immunoglobulin A; IL: Interleukin; ILC: Innate lymphoid cell; m ϕ : Macrophage; NK: Natural killer; SCFA: Short chain fatty acids; Treg: Regulatory T; Th: T helper.

response[81]. Additionally, tissue-resident memory CD8⁺ T cells provide long-term immunity against reinfection[82]. Commensal bacteria also contribute to CD8⁺ T cell differentiation, as demonstrated by a group of 11 bacterial strains collected from healthy human donors that promote IFN- γ -producing CD8⁺ T cells in the intestinal lamina propria. The differentiation of these cells relies on CD103⁺ DCs and major histocompatibility complex (MHC) class Ia antigen presentation [83]. Beyond local gut immunity, microbiota-derived metabolites such as mevalonate and dimethylglycine enhance systemic CD8⁺ T cell responses. SCFAs further facilitate the transformation of CD8⁺ T cells (antigen-activated) into memory cells by oxidative phosphorylation. These metabolites may circulate systemically, contributing to broader immune activation[84]. Additionally, *Staphylococcus epidermidis* in the skin influences CD8⁺ T cell responses by inducing IFN- γ and IL-17⁺ CD8⁺ T cells, which provide protection against pathogens like *Leishmania major* and *Candida albicans* while aiding tissue repair[85]. This induction is mediated by TLR2, Dectin-1 signaling, and antigen presentation via nonclassical MHC class I molecules on DCs[85]. Meanwhile, specific microbiota, such as *Lactobacillus reuteri* (*L. reuteri*), promote the differentiation of CD4⁺ CD8 $\alpha\alpha$ ⁺ IELs in the small intestine. This process is driven by *L. reuteri*'s metabolism of tryptophan into indole-3-lactic acid, which in turn activates the AhR together with transforming growth factor beta (TGF- β), suppressing the CD4 gene regulator ThPOK and upregulating transcription factors like RUNX3 and T-bet[86,87]. These specialized IELs contribute to immune tolerance, protecting against disorders such as food allergies and celiac disease, demonstrating the intricate interplay between microbiota and T cell-mediated immunity.

Th17 cell

Th17 cells play a pivotal role in gut immunity, contributing to both protective and inflammatory response[88]. While many Th17 responses are linked to inflammation, certain gut bacteria can induce non-inflammatory Th17 cells. For instance, *SFB* promote Th17 differentiation without triggering inflammation[89], whereas *Citrobacter species* induce pro-inflammatory Th17 responses[90]. GF mice lack Th17 cells, but colonization with commensals like *SFB* restores their presence[91].

Th17 differentiation is regulated by cytokines such as IL-6, and microbiota-dependent Th17 inflammation is brought about by α 2-6-sialyl ligands. Deficiency in α 2-6-sialyltransferase leads to excessive Th17 activity in the mucosa[92]. Additionally, *SFB* play a crucial role in shaping Th17 cells through host-microbe coevolution. These bacteria colonize the ileum, adhering to the intestinal epithelium without invading it, facilitated by mucolytic genes. *SFB* exhibit host specificity, meaning only native strains effectively attach to their host's epithelial surface. They promote Th17 differentiation by presenting bacterial antigens, which are internalized by IECs through microbial adhesion-triggered endocytosis. This process triggers IECs to produce serum amyloid A (SAA) proteins, leading to IL-1 β secretion and amplifying the immune response[93,94]. *SFB* also activate ILC3s to produce IL-22, further enhancing SAA expression and Th17 differentiation[95]. Peripheral Tregs cells (pTregs) help maintain immune balance by modulating Th17 activity. Beyond their immune role, Th17 cells support mucosal defense by promoting epithelial integrity and upregulating Nox1, α -defensins, and the polymeric immunoglobulin receptor, which facilitates IgA transport[96]. These mechanisms collectively strengthen host defense while preserving intestinal homeostasis.

Regulatory T cells

Regulatory T cells (Tregs cells) play a critical role in preserving immune tolerance and preventing autoimmunity within the gut[97]. Natural Tregs originate in the thymus to establish self-tolerance, whereas peripheral or inducible Tregs (pTregs) develop in response to microbiota and dietary antigens[98]. Microbiota-specific ROR γ t⁺ Tregs help regulate Th17 responses, ensuring intestinal immune balance. Several bacterial species, including *Helicobacter spp.* and *Akkermansia muciniphila* (*A. muciniphila*), promote Treg differentiation, while SCFAs such as propionate contribute to Treg induction and the regulation of the Th17/Treg balance[99,100]. Reduced SCFA levels have been linked to inflammatory diseases, highlighting their role in gut immune homeostasis. Microbial interactions play a crucial role in shaping pTregs, which express Foxp3, ROR γ t, and c-Maf but lack Helios and Neuropilin 1[101]. These cells modulate T cell responses and help sustain immune tolerance in the large intestine, primarily through and inducible T cell costimulator expression and CTLA4[101]. Certain *Clostridia* species, particularly clusters IV and XIVa, are key in inducing pTregs, offering immunological protection and counteracting Th17-driven inflammation. *Clostridium ramosum* is one such strain that promotes ROR γ t⁺ Tregs in the colon, while Treg responses is also enhanced by colonization of *Helicobacter hepaticus*, further demonstrating the microbiota's role in intestinal immune regulation[102]. The immunosuppressive function of pTregs is mediated by cytokines such as IL-35, IL-10, and TGF- β [103]. Additionally, a subset of colonic Tregs expressing GATA3 and the IL-33 receptor ST2 originates from the thymus and remains unaffected by microbial influence[104]. Collectively, these mechanisms highlight the intricate relationship between the microbiota and the host immune system in maintaining gut homeostasis.

T Follicular helper cells

T follicular helper (Tfh) cells are crucial for antigen-specific B cell and plasma cells differentiation, which are essential for producing immunoglobulins that help regulate microbiota composition and support microbial diversity[105]. Gut bacteria such as *A. muciniphila* and *SFB* play a key role in influencing Tfh cell differentiation, thereby enhancing IgA and IgG1-mediated microbiota regulation[106]. Colonization with *A. muciniphila* encourages the formation of Tfh cells (specific for microbial antigens) in mLN and Peyer's patches. Experiments showed that T cells from *A. muciniphila*-specific T cell receptor (TCR) transgenic mice could differentiate into various subsets, such as Th1 and Th17 cells, depending on the microbiota environment. In contrast, Tfh cell differentiation in Peyer's patches is promoted by *SFB* via IL-2 signaling in CD4⁺ T cells, independent of direct antigen recognition[107]. These findings suggest that different microbes employ distinct mechanisms to influence Tfh cell responses and shape gut immune interactions.

Th1 cell

Certain *Klebsiella* species, such as *Klebsiella aeromobilis* and *Klebsiella pneumoniae*, contribute to promoting Th1 cell responses in the gut through MyD88-mediated signaling and Batf3-dependent CD103+ CD11b- DCs, involving TLR activation and IL-18 signaling[108]. Th1 cells induced by *Klebsiella* often recognize specific bacterial antigens, like outer membrane protein X, though the precise mechanism by which these antigens are presented to lamina propria DCs remains unclear[109]. While *Klebsiella* can activate Th1 responses, it does not typically cause intestinal inflammation under normal conditions. Instead, it enhances the gut barrier by stimulating interferon-responsive genes in IECs. However, in situations of impaired immune regulation, such as in IL-10-deficient mice, Th1 cells specific for *Klebsiella* can trigger significant inflammation. Likewise, an *Escherichia coli* (*E. coli*) strain derived from a Crohn's disease patient when introduced in germ free mice, has been found to induce Th1 cells[110]. While both *E. coli* and *Klebsiella* are typically less abundant members of a healthy gut microbiome, they can proliferate and initiate Th1 responses when the microbial balance is disturbed.

The $\gamma\delta$ T cells

A less abundant class of circulating T cells, $\gamma\delta$ T cells, characterized by semi-invariant TCRs containing γ and δ chains, play significant role in several homeostatic functions, including immune surveillance, wound healing, thermogenesis, and central nervous system plasticity[111]. Though they are less in number in circulation, the tissue-resident IELs are mostly $\gamma\delta$ T cells, particularly in the gut and the skin[112]. The primary human $\gamma\delta$ T cell subsets, V δ 1+ and V γ 9V δ 2+, detect phospho-antigens and lipids. V γ 9V δ 2+ cells target microbial intermediates such as (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMB-PP), a precursor to isopentenyl pyrophosphate (IPP), produced by certain gram-negative bacteria and pathogens like *Clostridioides difficile* (*C. difficile*), *Mycobacterium tuberculosis* and *Listeria monocytogenes*[113]. Humans generate IPP through the mevalonate pathway since they do not produce HMB-PP. In orchestrating $\gamma\delta$ IEL cytokine production, behavior, and epigenetic processes, the microbiota plays significant role. For instance, colonization of *Salmonella typhimurium* by breaching the intestinal mucosal barrier leads to release of antimicrobial peptide RegIII γ by stimulating $\gamma\delta$ IEL, while colonization of non-invasive species like *Bacteroides thetaiotaomicron* and *SFB* doesn't have the same effect[114]. This process is mediated through a MyD88-dependent signalling pathway in epithelial cells, indicating that a unique signalling cascade is induced in $\gamma\delta$ IELs by invasive microbes[115].

Besides, $\gamma\delta$ T cells are the first to respond in infectious disease models, often producing IFN- γ and IL-17 cytokines. The gut microbiota influences $\gamma\delta$ IEL frequency, particularly IL-1R1+ IL-17+ $\gamma\delta$ T cells via VAV1 signaling, which may help protect against diseases[116]. The $\gamma\delta$ T cells has been shown to protect against *C. difficile* infection by producing IL-17A. The positioning and mobility of $\gamma\delta$ IELs within the intestinal epithelium are also microbiota-dependent. The $\gamma\delta$ IELs are located lower along the crypts in specific-pathogen-free mice vs GF mice, with microbiota-driven localization being crucial for effective surveillance. These patterns of mobilization also change during infections, partly due to epithelial cell MyD88 signalling in epithelial cells and metabolic shifts in $\gamma\delta$ IELs[117]. Additionally, the chromatin accessibility in both $\gamma\delta$ and $\alpha\beta$ T cells are affected by the microbiota, influencing various pathways and functional differences between mice with distinct microbiota composition[118].

Mucosal-associated invariant T cells

Another subtype of innate-like lymphocytes is mucosal-associated invariant T (MAIT) cells that express CD8 α , with a minor population lacking CD4 and CD8. These cells feature an invariant TCR- α chain paired with various V β chains, and they recognize MHC class Ib protein MR1 presented antigens[119]. MAIT cells detect microbial derivatives of vitamin B2 (riboflavin), such as ribityl-lumazines like 7-hydroxy-6-methyl-8-d-ribityllumazine and 5-(2-oxopropylideneamino)-6-d-ribitylaminouracil (5-OP-RU). These riboflavin derivatives are produced by the microbiota, and MAIT cell numbers are significantly reduced in GF animals[120]. Genes essential for the production of 5-OP-RU (*ribA*, *ribD*, *pyrP2*) are found in both skin and gut commensals. When GF mice are colonized with microbes such as *Proteus mirabilis* or *Enterococcus hirae*, which can produce these derivatives, the thymic MAIT cell numbers are restored to normal levels[121].

Tissue-resident MAIT cells require early exposure to MR1-bound antigens for proper development; without this exposure, their populations are permanently reduced. MAIT cells induced by the microbiota, particularly in the thymus and skin, often express ROR γ t and exhibit a type 17 effector phenotype[121]. MAIT cells that reside in skin secrete IL-17A in response to local commensals, promoting wound healing in an IL-18 and IL-1-dependent manner[122]. In addition, MAIT cells help protect against infections caused by pathogens such as *Mycobacterium*, *Klebsiella*, *Francisella*, and *Legionella* [123]. They also recognize viral infections via IL-18, IL-15, and type I interferons, enhancing the adaptive immune response. For instance, MAIT cells are essential for generating antigen-specific CD8+ T cells during adenovirus vector-based vaccinations[124]. As such, MAIT cells play a crucial role in bridging the innate and adaptive immune responses to infections and vaccines.

Invariant NK T cells

The invariant NK T (iNKT) cells recognize glycolipids from both host and microbial sources, presented by the MHC class Ib protein CD1d. These cells are characterized with an invariant α chain, along with a limited range of β chains, and cytokine synthesis upon activation. In mice, iNKT cells can be divided into subsets that resemble Th1, Th2, and Th17 cells, although these classifications are less defined in humans. While the factors influencing iNKT cell development, particularly in peripheral tissues, are not fully understood, interactions with the microbiota play a crucial role[125]. In GF mice, there is an increase in both the relative and absolute numbers of iNKT cells in the colonic lamina propria and lungs, driven by Cxcl16 hypermethylation and enhanced mucosal recruitment. Conventionalization of neonatal mice restores iNKT cell levels and provides protection against colitis and asthma models, but this does not occur in adults[126].

Monocolonizing neonatal mice with *B. fragilis* also restores iNKT cell numbers, though through a different mechanism. *B. fragilis* produces GSL-Bf717 (sphingolipid), which inhibits iNKT cell proliferation in the gut by competing with CD1d. However, other sphingolipids from *B. fragilis* feebly stimulate iNKT cell proliferation, suggesting that the gut sphingolipid profile plays a role in regulating iNKT cells[127]. The relationship between the microbiota and iNKT cells is bidirectional; mice which lack iNKT cells are more prone to overgrowth and translocation of invasive microbes in the small-intestinal.

It is evident from the above discussions that, T cells trained by the gut microbiota are essential for a healthy immune system. They help maintain a balanced gut environment by supporting antibody production, which controls harmful microbes while allowing beneficial bacteria to thrive. These T cells also strengthen the gut barrier, preventing infections and ensuring proper immune responses.

In addition to protecting against pathogens, gut-trained T cells play a role in long-term immunity. However, if their responses become too strong, they can contribute to inflammatory diseases like IBD. This highlights the importance of a well-regulated interaction between the microbiota and the immune system for overall health.

B cells

The intestinal microbes play a crucial role in regulating B cell development and function through both T cell-dependent and T cell-independent mechanisms[128]. In Peyer's patches and mLNs, commensal bacteria such as *B. fragilis* and *Clostridium species* stimulate APCs to activate CD4+ T cells. These T cells, particularly Tfh cells, provide signals like IL-21 and CD40 L that promote B cell class switching to IgA. This high-affinity, microbiota-specific IgA binds to beneficial microbes like *A. muciniphila* and *Bifidobacterium*, regulating their colonization and preventing pathogen overgrowth[129].

Some gut microbes can also influence B cell function independently of T cells. Bacteria such as *SFB* and *E. coli* interact with PRRs like TLRs on B cells, triggering IgA production through MyD88-dependent signaling[130]. Additionally, SCFAs from *Faecalibacterium prausnitzii* (*F. prausnitzii*) support B cell survival and antibody production. These mechanisms generate polyreactive, low-affinity IgA, which broadly shapes the gut microbiota while maintaining immune balance[131]. Together, these microbial interactions fine-tune B cell responses, ensuring intestinal homeostasis and effective defense against pathogens. Together, these gut microbes help fine-tune B cell responses, ensuring a stable gut environment while defending against harmful pathogens. A simplified summary of the innate-adaptive immune cells and beneficial gut microbiota crosstalk in maintaining a healthy gut microenvironment is presented in Figure 1.

Table 1 summarizes the key microbiota-immune interactions described in the previous sections. For each microbial taxon, the principal metabolite or MAMP it produces is listed, along with the host sensing mechanism or receptor involved, the primary target cell type, and the resulting immunological effect or outcome. A schematic summary of the different types of significant gut commensals and their interaction with both innate and adaptive immune cells is provided in Figure 2.

RECENT ADVANCES IN RESEARCH ON GUT MICROBIOTA AND IMMUNE SYSTEM INTERACTION

The gut microbiota, a complex and dynamic community of microorganisms residing in the GI tract, has emerged as a central player in modulating immune responses and maintaining systemic health. Recent advances in research have deepened our understanding of the intricate cross-talk between the gut microbiota and the immune system, revealing novel mechanisms and therapeutic opportunities. Below, we explore key findings and their implications across various domains of health and disease, supported by recent studies and references.

Gut microbiota and immune cell differentiation

The gut microbiota plays a pivotal role in shaping immune cell differentiation and function. One of the most exciting discoveries is the influence of specific gut bacteria on Tfh cells, which are critical for antibody production. For instance, *A. muciniphila*, a mucin-degrading bacterium, has been shown to stimulate the development of Tfh cells specific for microbial antigen in mLNs and Peyer's patches. This interaction enhances the production of IgA and IgG1 antibodies, which are essential for regulating the microbiota and maintaining gut homeostasis[132]. Such findings highlight the potential of targeting specific bacterial species to modulate immune responses and improve mucosal immunity.

Gut microbiota and cancer immunotherapy

The gut microbiota has also been implicated in cancer progression and treatment. Alterations in the gut microbiome can influence systemic immune responses, potentially affecting cancer development and the efficacy of immunotherapies. For example, certain gut bacteria, such as *Bifidobacterium* and *Faecalibacterium*, have been associated with enhanced responses to immune checkpoint inhibitors, a breakthrough in cancer treatment[133]. Conversely, dysbiosis may contribute to resistance to these therapies. This has led to the exploration of microbiome-based interventions, such as fecal microbiota transplantation (FMT) and probiotics, as adjuncts to cancer immunotherapy. These strategies aim to reshape the gut microbiome to boost anti-tumor immunity and improve patient outcomes.

Diet, microbiota, and immune health

Dietary intake is a major determinant of gut microbiota composition and function, with profound implications for immune health. A diet rich in fiber, polyphenols, and fermented foods promotes the growth of beneficial bacteria and the production of immunomodulatory metabolites. Conversely, a Western diet high in processed foods and saturated fats can lead to dysbiosis and immune dysregulation. Recent research emphasizes the need for an integrated mechanistic model to understand how diet, microbiota, and the immune system interact. Such insights are critical for developing personalized

Table 1 summarizes the key microbiota–immune interactions described in the manuscript

Microbiota	Metabolite/MAMP	Receptor/mechanism	Target cell	Effect/outcome
<i>Segmented filamentous bacteria</i>	Adhesion factors (MAMPs)	Microbial adhesion-triggered endocytosis uptake by IEC to SAA	IECs to Th17 cells	IEC-derived SAA drives IL-1 β to Th17 differentiation
<i>Citrobacter spp.</i>	Bacterial antigens	Antigen presentation by IEC/DC: Uptake and peptide presentation by IECs or dendritic cells	Th17 cells	Pro-inflammatory Th17 responses
<i>Clostridia</i> clusters IV and XIVa	SCFAs (butyrate, propionate)	GPR43/GPR109A activation HDAC inhibition	Peripheral (p) Tregs	ROR γ t+ pTreg induction and expansion
<i>Helicobacter spp./Helicobacter hepaticus</i>	Microbial antigens	Antigen presentation by DC	ROR γ t+ pTregs	Promotes pTreg differentiation
<i>Akkermansia muciniphila</i>	MAMPs (outermembrane components)	Antigen presentation cytokine cues	ROR γ t+ pTregs	Supports pTreg induction
<i>Faecalibacterium prausnitzii</i> and <i>Bacteroides fragilis</i>	SCFAs (butyrate, acetate)	GPR41/GPR43 activation HDAC inhibition	Macrophages and dendritic cells	M2 polarization; enhanced IL-10; epigenetic priming for IL-6, tumor necrosis factor production
<i>Bifidobacterium spp./Lactobacillus spp.</i>	Recolonization antigens	GALT colonization	GALT progenitors	Restores GALT development and T cell maturation

For each microbial taxon, the principal metabolite or microbe-associated molecular pattern (MAMP), it produces is listed, along with the host sensing mechanism or receptor involved, the primary target cell type, and the resulting immunological effect or outcome. DC: Dendritic cell; GALT: Gut-associated lymphoid tissue; GPR: G protein-coupled receptor; HDAC: Histone deacetylase inhibition; IEC: Intestinal epithelial cell; IL: Interleukin; MAMP: Microbe-associated molecular pattern; pTreg: Peripheral regulatory T cell (ROR γ t+); SAA: Serum amyloid A; SCFAs: Short-chain fatty acids; Th: T helper; Tregs: Regulatory T.

dietary interventions to prevent and treat chronic and infectious diseases.

Gut microbiota and intestinal barrier integrity

The gut microbiota plays a critical role in maintaining the integrity of the intestinal barrier, which prevents the translocation of harmful substances into systemic circulation. Dysbiosis can compromise this barrier, leading to a condition known as "leaky gut", which is associated with immune activation and the development of autoimmune disorders. For example, altered gut microbiota composition and function have been linked to the pathogenesis of conditions like multiple sclerosis, type 1 diabetes, and celiac disease[134]. Restoring gut barrier integrity through microbiome-targeted therapies, such as probiotics and postbiotics, may offer new avenues for managing autoimmune diseases.

Gut microbiota and neurological health

The gut-brain axis represents another fascinating area of research, highlighting the broader implications of microbiome-immune system interactions. Changes in the gut microbiota have been linked to neurological conditions such as anxiety, depression, and stroke. For instance, gut dysbiosis can trigger systemic inflammation, which may contribute to neuroinflammation and the progression of neurodegenerative diseases[135]. Additionally, gut microbiota-derived metabolites, including SCFAs and neurotransmitters, can influence brain function and behavior. These findings underscore the potential of microbiome-based interventions, such as psychobiotics, to improve mental health and neurological outcomes.

NOVEL TECHNIQUES AND TECHNOLOGIES TO EXPLORE GUT MICROBIOTA AND IMMUNE SYSTEM INTERACTION

Advances in metagenomics, metabolomics, and gnotobiotic models have significantly enhanced the study of gut microbiota and its interaction with the immune system.

Advances in metagenomics, metabolomics, and gnotobiotic models

The study of gut microbiota and its interaction with the immune system have been significantly advanced by high-throughput sequencing and omics technologies. Metagenomics, which involves the sequencing of microbial genomes directly from environmental samples, has revolutionized our ability to analyze the composition and functional potential of the gut microbiome. Shotgun metagenomics and 16S rRNA sequencing are widely used to profile microbial diversity and identify key taxa associated with immune regulation[136]. These approaches help in understanding how microbial communities influence immune responses, including the differentiation of T cells and the production of immunoglobulins [137].

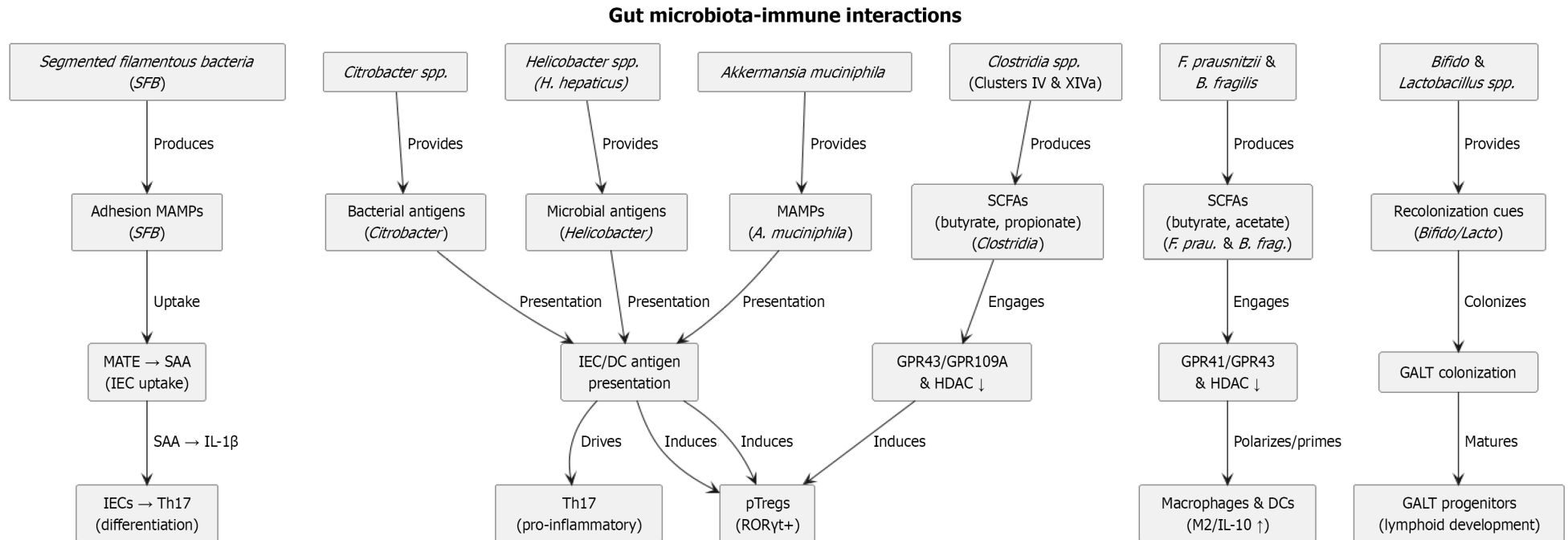


Figure 2 Schematic diagram depicts the gut microbiota-immune interactions. Each microbial taxon (left) produces a specific metabolite or microbial-associated molecular patterns (MAMPs) (next column) that is sensed by a defined host receptor or mechanism (center), leading to activation of intestinal epithelial or antigenpresenting cells and subsequent engagement of distinct immune cell subsets (right), which culminate in specific functional outcomes (far right). For example, *segmented filamentous bacteria* adhesion MAMPs are taken up *via* intestinal epithelial cells (IECs) microbial adhesion-triggered endocytosis transporters to induce serum amyloid A and Interleukin (IL)-1 β for T helper 17 (Th17) differentiation; *Citrobacter* antigens presented by IECs/dendritic cells (DCs) drive proinflammatory Th17 responses; *Clostridia*-derived short-chain fatty acids (SCFAs) (butyrate, propionate) engage G protein-coupled receptor (GPR) 43/GPR109A and inhibit histone deacetylases to expand RORyt+ peripheral Tregs; *Helicobacter* antigens presented by DCs promote pTreg differentiation; *Akkermansia muciniphila* MAMPs *via* antigen-presenting cell cues support pTreg maintenance; *Faecalibacterium prausnitzii* and *Bacteroides fragilis* SCFAs polarize macrophages/DCs toward IL-10 – producing M2 phenotypes through GPR41/GPR43 signaling and histone deacetylase inhibition; and *Bifidobacterium/Lactobacillus* recolonization cues drive gut-associated lymphoid tissue colonization and lymphoid tissue maturation. *B. fragilis*: *Bacteroides fragilis*; *Bifido/Lacto*: *Bifidobacterium/Lactobacillus*; DC: Dendritic cell; *F. prausnitzii*: *Faecalibacterium prausnitzii*; GALT: Gut-associated lymphoid tissue; HDAC: Histone deacetylase inhibition; IEC: Intestinal epithelial cell; IL: Interleukin; MAMP: Microbial-associated molecular pattern; SAA: Serum amyloid A; SFB: *Segmented filamentous bacteria*; Th: T helper.

Metabolomics, another crucial technique, enables the analysis of microbial-derived metabolites that modulate host immune functions. SCFAs such as butyrate, propionate, and acetate, produced by commensal bacteria like *F. prausnitzii* and *B. fragilis*, are known to influence Tregs cell differentiation and anti-inflammatory responses[138]. Metabolomic studies using mass spectrometry and nuclear magnetic resonance spectroscopy allow researchers to correlate specific microbial metabolites with immune-mediated diseases, such as IBD and allergies[139].

Gnotobiotic models, particularly GF and mono-colonized mice, provide a controlled system to study the causal relationships between microbiota and immune responses. GF mice, which do not have any microbiota, show underdeveloped GALTs and defective T cell maturation. Recolonization with specific bacterial strains, such as *Bifidobacterium* or *Lactobacillus*, restores immune function, demonstrating the essential role of microbiota in immune homeostasis. Addi-

tionally, humanized gnotobiotic mice, colonized with human-derived microbiota, serve as valuable models for studying host-microbiome interactions in disease pathogenesis.

Single-cell sequencing and its implications for microbiome research

Single-cell sequencing technologies have transformed microbiome research by enabling the detailed analysis of individual microbial and immune cells. Unlike bulk sequencing methods, single-cell RNA sequencing enables researchers to examine the diversity within immune cell populations and their reactions to signals derived from the microbiota[140]. This technology has been instrumental in identifying unique immune cell subsets, such as microbiota-responsive Th17 cells, which play a crucial role in mucosal immunity[141].

In microbiome research, single-cell genomics has facilitated the discovery of novel bacterial species that were previously uncultivable. Advances in microfluidics and droplet-based sequencing have enabled high-throughput single-cell analysis of gut microbes, revealing their metabolic functions and interactions with immune cells[142]. For instance, single-cell transcriptomic studies have shown how specific gut bacteria modulate dendritic cell maturation and cytokine production, influencing systemic immune responses[143].

Additionally, combining single-cell sequencing with spatial transcriptomics has offered valuable insights into the spatial arrangement of immune cells within the gut mucosa. This approach helps map microbiota-immune interactions at a tissue-specific level, improving our understanding of localized immune responses in conditions such as ulcerative colitis and Crohn's disease[144].

In conclusion, advances in metagenomics, metabolomics, gnotobiotic models, and single-cell sequencing have significantly enhanced our understanding of the gut microbiota's role in immune function. These cutting-edge techniques continue to provide valuable insights into host-microbiome interactions, paving the way for novel therapeutic strategies for immune-related diseases.

DISCUSSION

Recent research has considerably advanced our understanding of how the gut microbiota interacts with the host immune system to influence health outcomes. Nonetheless, important limitations persist, both in the current body of knowledge and in the tools available to study these interactions. Addressing these limitations is essential for translating microbiome-based insights into effective clinical applications. One of the most significant challenges in microbiome research is the high inter-individual variability of gut microbial communities. Factors such as genetic background, dietary patterns, geographic location, environmental exposures, medication use (including antibiotics and probiotics), and daily habits contribute to substantial differences across individuals[145]. This variability complicates the formulation of broadly effective microbiome-based therapies and reduces reproducibility in studies involving diverse populations. In addition, functional redundancy among microbial taxa means that multiple species can perform similar roles within the microbiota. This makes it difficult to assign specific immune-modulatory functions to individual microbes or to identify clear therapeutic targets[145]. Adding to this complexity is the spatial heterogeneity of microbial populations throughout the human body. Microbes are distributed across various mucosal surfaces and internal compartments, each with unique ecological characteristics[146]. Consequently, reliance on fecal samples alone may not accurately reflect the full diversity or function of host-associated microbial communities. Experimental models commonly used to study host-microbiota-immune interactions also present notable constraints. While GF and gnotobiotic mice allow for controlled microbial colonization studies, they do not fully mimic the diversity, dynamics, or immune development observed in human systems[147]. Moreover, differences in immune signaling and microbial colonization between species limit the direct applicability of these findings to humans[148]. Although organoid cultures have emerged as useful tools for studying epithelial interactions, they lack key immune components and the systemic complexity needed to capture full host-microbiota interactions[149]. To overcome these limitations, more physiologically relevant models, such as humanized mice colonized with human microbiota or gut-on-a-chip systems, must be further developed and validated.

A significant challenge in microbiome research lies in establishing causality, as most current studies are correlational, with outcomes often confounded by host genetics, environmental influences, and lifestyle factors. In addition, methodological inconsistencies – such as variations in sampling techniques, sequencing platforms, and data analysis – impede reproducibility across studies. While research predominantly focuses on bacterial communities, other microbiota components like viruses, fungi, and archaea remain underexplored, despite their potential roles in immune regulation. Nevertheless, rapid advances in multi-omics technologies – including metagenomics, metabolomics, transcriptomics, and single-cell sequencing – are enhancing our understanding of microbiota-host interactions. These tools support the development of personalized, precision-based interventions tailored to individual microbial and immune profiles. Emerging therapies such as probiotics, prebiotics, synbiotics, FMT, and engineered microbial consortia show promise in modulating immune responses and managing immune-related disorders. However, their clinical implementation is still constrained by the absence of standardized protocols, limited long-term safety data, and a lack of large-scale, well-controlled clinical trials across diverse populations.

CONCLUSION

The gut microbiome plays a central role in shaping immune homeostasis, balancing tolerance and defense to maintain

health. While significant progress has been made in elucidating the gut-immune axis, many questions remain. How specific microbes and metabolites influence distinct immune pathways, how dysbiosis drives immune-mediated diseases, and how host genetics and environment modulate these interactions are still not fully understood.

Future research must prioritize longitudinal studies, high-resolution omics, and integrative models to uncover causal mechanisms and actionable targets. The promise of microbiome-based therapies – such as precision probiotics, prebiotics, and microbiota transplants – depends on our ability to decode individual microbiome profiles and their functional outcomes. Personalized, microbiome-informed interventions could revolutionize the treatment of inflammatory, allergic, and autoimmune conditions.

Unlocking the full therapeutic potential of the gut microbiome will require interdisciplinary collaboration and a deeper mechanistic understanding. As we navigate this emerging frontier, the microbiome offers a transformative opportunity to redefine immune health and disease management.

FOOTNOTES

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