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Review

Microbiome – Immune Crosstalk: From Gut to Systemic Immunity

D. Kumarasamyraja[1]*, Nivetha S R[2], M. Vimalraj[3]

[1,2,3] *PGP College of Pharmaceutical Science and Research Institute, Namakkal*

*Corresponding Author: Dr. D.Kumarasamyraja
Email: ksrajapharma83@gmail.com

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Abstract

The human gastrointestinal tract harbors a diverse and dynamic microbiome, comprising trillions of bacteria, viruses, fungi, and archaea that interact intricately with the host immune system. This bidirectional crosstalk is central to the maintenance of homeostasis and the prevention of chronic diseases. Over the past decade, advances in metagenomics, metabolomics, and immunology have unraveled the profound influence of gut microbiota-derived signals on both mucosal and systemic immunity. Short-chain fatty acids, microbial metabolites, and structural components such as lipopolysaccharides and peptidoglycans act as key mediators that calibrate the immune tone, influencing innate and adaptive responses. Dysbiosis, or disruption in microbial balance, has been implicated in inflammatory bowel disease, autoimmune disorders, metabolic syndromes, neuroinflammatory conditions, and cancer immunotherapy outcomes. This review provides a comprehensive analysis of the microbiome–immune crosstalk, tracing its molecular and cellular pathways, delineating its systemic reach beyond the gut, and highlighting its therapeutic potential. We explore recent findings on microbial modulation of T cells, dendritic cells, and macrophages, the role of microbial metabolites in epigenetic programming, and the emerging field of microbiota-targeted therapeutics. The manuscript concludes with future perspectives on precision microbiome engineering for immune modulation and translational challenges in clinical application.

Keywords: Microbiome; Gut–immune axis; Systemic immunity; Dysbiosis; Short-chain fatty acids; Immunomodulation.

1.0 INTRODUCTION

The gut microbiome has emerged as a pivotal regulator of human physiology, shaping not only metabolic and nutritional outcomes but also immune development and systemic health. It is now established that the human gut harbors approximately 10^{13}–10^{14} microbial cells, encoding a gene set at least 100 times larger

than the human genome [1]. This community influences nutrient assimilation, xenobiotic metabolism, and epithelial barrier integrity, but its most profound role arguably lies in the orchestration of immune functions. From the neonatal period, commensal microbes engage in a reciprocal relationship with the host immune system, ensuring the proper maturation of immune cells, tolerance to self and harmless antigens, and effective defense against pathogens [2]. The crosstalk between the microbiome and immune system occurs at multiple levels: through microbial-associated molecular patterns (MAMPs), metabolites such as short-chain fatty acids (SCFAs), and modulation of antigen- presenting cells that bridge innate and adaptive immunity. Importantly, this dialogue is not restricted to the intestinal mucosa but extends systemically, influencing immunity in distal tissues such as the lungs, skin, liver, and brain [3]. This has given rise to the concept of the "gut–immune axis," a unifying framework that links microbial ecology with host immunological balance.

This introduction sets the stage for a detailed review of how microbiota-derived signals orchestrate immune responses, how dysbiosis contributes to immunopathology, and how therapeutic interventions targeting microbiomes hold promise for systemic immune modulation.

1.1 The Human Gut Microbiome: Composition and Dynamics

The composition of the gut microbiome is dominated by the bacterial phyla Firmicutes and Bacteroidetes, with smaller contributions from Actinobacteria, Proteobacteria, and Verrucomicrobia [4]. Fungi (mycobiome), viruses (virome), and archaea add further complexity. This ecological community is shaped by diet, genetics, mode of birth, antibiotic exposure, geography, and lifestyle. In neonates, the gut microbiome is immature and highly dynamic, gradually stabilizing during early childhood to form a relatively resilient adult configuration [5]. The gut mucosa provides a niche wherein the microbiome interacts with epithelial and immune cells. The mucin layer, secreted antimicrobial peptides, and immunoglobulin A (IgA) shape microbial colonization patterns. In turn, microbial signals guide epithelial development and modulate tight junction integrity, establishing a barrier against pathogens while permitting nutrient absorption [6].

Importantly, the microbiome is not static. Dysbiosis, characterized by reduced diversity or altered abundance of keystone taxa such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, has been linked to multiple pathologies, including inflammatory bowel disease (IBD), obesity, diabetes, and autoimmunity [7]. This section emphasizes that understanding microbial composition and its dynamics is critical for unraveling how crosstalk occurs at both local and systemic levels.

1.2 Development of the Immune System and Microbial Signals

The immune system is uniquely shaped by microbial exposures during early life. Germ-free animal models demonstrate profound defects in lymphoid organ development, reduced T cell subsets, and impaired immunoglobulin production [8]. Colonization with defined commensals restores immune maturation, highlighting the nonredundant role of microbiota. Microbial components, including peptidoglycans, lipoteichoic acids, and flagellin, engage pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs) on epithelial and immune cells. These interactions drive dendritic cell (DC) maturation, macrophage polarization, and the differentiation of regulatory T cells (Tregs) or effector T helper (Th) subsets [9]. Moreover, specific microbes exert defined immunological imprints. For instance, segmented filamentous bacteria induce Th17 cell development, whereas *Clostridium* clusters IV and XIVa promote Treg differentiation through SCFA production [10]. Thus, microbial colonization is not only essential for immune development but also for shaping its functional polarity.

1.3 Mechanisms of Gut–Immune Crosstalk

Gut–immune crosstalk operates through multiple mechanisms that integrate microbial metabolites, structural components, and signaling pathways. Key mediators include SCFAs such as acetate, propionate, and butyrate, which act through G-protein coupled receptors (e.g., GPR41, GPR43) and histone deacetylase (HDAC) inhibition to modulate gene expression in immune cells [11]. Additionally, tryptophan metabolites, secondary bile acids, and polysaccharide A (from *Bacteroides fragilis*) regulate immune homeostasis. Polysaccharide A promotes Treg induction via DCs, while secondary bile acids influence innate lymphoid cell

(ILC) differentiation [12]. Microbial modulation of epithelial barrier function through tight junction proteins further controls antigen trafficking, influencing systemic immune activation. At the cellular level, intestinal DCs sample luminal microbes and migrate to mesenteric lymph nodes, where they prime naïve T cells. Cytokine milieus shaped by microbial metabolites influence whether these T cells differentiate into effector, regulatory, or memory subsets [13]. Together, these mechanisms establish the foundation for systemic immune effects.

1.4 Systemic Reach of Microbial Signals

The influence of the gut microbiome extends beyond the intestinal mucosa. Microbial metabolites can enter circulation and modulate distal immune responses. For example, SCFAs regulate hematopoiesis in the bone marrow and enhance anti-inflammatory macrophage differentiation [14]. Secondary bile acids influence liver immunity by shaping Kupffer cell polarization, while microbial-derived peptidoglycans reach systemic circulation to prime neutrophil responses [15]. Furthermore, the gut–lung axis demonstrates how dysbiosis can exacerbate respiratory diseases such as asthma, chronic obstructive pulmonary disease (COPD), and viral infections. Similarly, gut–brain axis studies reveal that microbial signals affect microglial maturation and neuroinflammation [16]. These systemic effects highlight that gut–immune crosstalk is not an isolated process but a central regulator of body-wide immune balance.

1.5 Dysbiosis and Immune Dysregulation

Dysbiosis, defined as a detrimental shift in microbiome structure, often precipitates immune dysregulation. In IBD, reduced SCFA-producing microbes impair Treg generation, fueling chronic inflammation [17]. In type 1 diabetes, altered microbial diversity contributes to the loss of peripheral tolerance and autoreactive T cell activation [18]. Likewise, obesity-associated dysbiosis promotes low-grade systemic inflammation via endotoxemia and altered bile acid signaling. Dysbiosis also impacts responses to cancer immunotherapy. Studies show that the abundance of *Akkermansia muciniphila* and *Bifidobacterium* species correlates with improved efficacy of immune checkpoint inhibitors, whereas antibiotic-induced dysbiosis diminishes therapeutic responses [19]. Collectively, these findings underscore the pathogenic consequences of disrupted microbiome–immune interactions, highlighting therapeutic opportunities for microbiome-targeted interventions.

2.0 Molecular Mediators of Microbiome–Immune Crosstalk

The bidirectional dialogue between the microbiome and immune system is orchestrated by a sophisticated network of molecular mediators that bridge microbial signals with host immunity. These mediators include microbial-associated molecular patterns (MAMPs), microbial metabolites, and host-derived mediators influenced by microbial activity. Recognition of MAMPs such as lipopolysaccharides (LPS), flagellin, lipoteichoic acid, and peptidoglycans occurs through pattern recognition receptors (PRRs) including Toll-like receptors (TLRs), NOD-like receptors (NLRs), and C-type lectin receptors (CLRs) [20]. Activation of PRRs initiates downstream signaling cascades that regulate cytokine production, dendritic cell (DC) activation, and macrophage polarization. Equally important are metabolites derived from microbial fermentation of dietary substrates. Short-chain fatty acids (SCFAs), tryptophan catabolites, polyamines, and secondary bile acids serve as signaling molecules with local and systemic immunomodulatory roles [21]. SCFAs, for instance, act through G-protein coupled receptors (GPR41, GPR43, GPR109A) and inhibit histone deacetylases, thereby influencing transcriptional programming of immune cells.

Additionally, the microbiome shapes the host metabolome by altering bile acid profiles, modulating levels of trimethylamine-N-oxide (TMAO), and regulating host-derived cytokines and hormones. Thus, molecular mediators form the biochemical foundation through which the gut microbiome exerts immunological Innate Immunity and Microbiome Interactions

Innate immunity constitutes the first line of defense and is profoundly influenced by the gut microbiome. Microbial signals educate innate immune cells including macrophages, dendritic cells, neutrophils, innate lymphoid cells (ILCs), and natural killer (NK) cells [22]. Macrophage function is shaped by microbial metabolites: SCFAs promote anti-inflammatory M2-like macrophages, while LPS exposure drives pro-

inflammatory M1 phenotypes. Similarly, DCs integrate microbial cues to balance tolerogenic and immunogenic presentations to T cells. Innate lymphoid cells (ILCs), particularly ILC3s, are central mediators of barrier immunity. Their production of interleukin-22 (IL-22) in response to microbial aryl hydrocarbon receptor (AhR) ligands enhances epithelial repair and antimicrobial peptide secretion [23]. Furthermore, NK cells are primed by microbial-derived cytokine signals, strengthening antiviral and antitumor immunity.

Importantly, innate immune training, also termed **trained immunity**, is increasingly recognized as a microbiome-driven phenomenon. Epigenetic and metabolic reprogramming of innate cells after exposure to microbial products confers enhanced secondary responses to subsequent challenges [24]. This mechanism may underlie the systemic benefits of a balanced microbiome in infectious disease resistance and vaccine responsiveness.

2.1 Adaptive Immunity and Microbiome Crosstalk

Adaptive immunity, characterized by antigen-specific memory, is equally reliant on microbial cues. The gut microbiome orchestrates the delicate balance between effector and regulatory T cell subsets. Segmented filamentous bacteria drive differentiation of Th17 cells, essential for mucosal defense but also implicated in autoimmunity when unchecked [25]. In contrast, *Clostridium* clusters IV and XIVa promote regulatory T cell (Treg) induction via butyrate-mediated epigenetic regulation of the Foxp3 locus [26]. B cells are also profoundly shaped by the microbiome. Intestinal IgA responses are calibrated by microbial antigens and metabolites, leading to polyreactive IgA that modulates microbial colonization and prevents pathogen adherence [27]. Germ-free mice show impaired germinal center reactions and reduced systemic IgG responses, demonstrating the essential role of microbial priming in humoral immunity. Additionally, the microbiome influences systemic T cell responses beyond the gut. Microbial metabolites condition circulating T cells and modulate immune checkpoint pathways, a phenomenon directly linked to cancer immunotherapy outcomes [28]. Collectively, adaptive immunity is tuned by the microbiome to balance tolerance, defense, and long-term immunological memory.

2.2 Epigenetic Reprogramming by Microbial Metabolites

An emerging paradigm in microbiome–immune crosstalk is the epigenetic reprogramming of immune cells by microbial metabolites. SCFAs such as butyrate and propionate inhibit histone deacetylases (HDACs), thereby promoting chromatin accessibility and enhancing expression of anti-inflammatory genes [29]. This epigenetic influence has been demonstrated in Tregs, where butyrate induces stable Foxp3 expression, conferring durable immunosuppression. Tryptophan metabolites, acting through AhR, regulate histone methylation patterns in DCs and T cells, shifting the immune response toward tolerance. Similarly, polyamines influence chromatin structure and impact transcriptional programs in macrophages and B cells [30].

Moreover, microbial regulation of host microRNAs has been implicated in shaping immune cell differentiation and inflammatory responses. For example, *Bacteroides fragilis*–derived polysaccharide A modulates DC microRNA expression, promoting Treg over Th17 balance [31]. These findings highlight how microbial signals extend beyond immediate receptor interactions to long-term epigenetic imprinting, with implications for chronic inflammation and autoimmunity.

2.3 Microbial Metabolites and Systemic Immunity

Microbial metabolites act as systemic mediators that extend the influence of the microbiome to distal organs. SCFAs regulate hematopoietic progenitor differentiation in the bone marrow, promoting generation of $Ly6c^-$ monocytes with anti-inflammatory potential [32]. They also enhance the cytotoxic activity of $CD8^+$ T cells and NK cells, amplifying antiviral and antitumor responses. Secondary bile acids, produced through microbial metabolism of primary bile acids, bind to host receptors such as farnesoid X receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5). These interactions modulate immune tone in the liver, influence Kupffer cell activity, and affect systemic metabolic inflammation [33]. Additionally, tryptophan-derived indole metabolites reach circulation and act through AhR in peripheral tissues, modulating skin and lung immunity. Microbiome-derived peptidoglycans also prime neutrophils systemically, enhancing microbial killing capacity [34].

This systemic immunomodulation underscores the microbiome's role as an endocrine-like organ, disseminating bioactive molecules with wide-ranging effects on host immunity.

3.0 Gut–Organ Axes and Systemic Immune Crosstalk

The systemic reach of the gut microbiome is now recognized as a defining feature of host–microbe interactions. While much of the foundational research has focused on local mucosal immunity, advances in metabolomics, gnotobiotic models, and human cohort studies have revealed that microbial signals travel far beyond the intestine, modulating immune responses in distant organs. This has given rise to the concept of gut–organ axes, encompassing the gut–lung, gut–brain, gut–skin, gut–liver, and gut–tumor immune axes [35]. Each axis illustrates how microbial metabolites, microbial-associated molecular patterns (MAMPs), and cytokine networks integrate with organ-specific immune niches to shape disease outcomes. Understanding these axes is essential for developing microbiome-targeted therapies for complex systemic disorders.

3.1 The Gut–Lung Axis

The gut–lung axis highlights how intestinal microbes influence pulmonary immunity and disease. Clinical and preclinical studies demonstrate that dysbiosis exacerbates asthma, chronic obstructive pulmonary disease (COPD), and viral respiratory infections, whereas restoration of microbial balance enhances resistance [36]. Mechanistically, SCFAs generated in the gut modulate alveolar macrophages, promoting anti-inflammatory phenotypes and enhancing their capacity to resolve inflammation. Circulating SCFAs also regulate dendritic cell precursors in the bone marrow, thereby shaping lung-resident immune populations [37]. Moreover, tryptophan metabolites acting through the aryl hydrocarbon receptor (AhR) in pulmonary epithelial cells upregulate barrier integrity and antiviral gene expression. In infectious diseases such as influenza and COVID-19, gut dysbiosis has been correlated with worse outcomes, marked by reduced abundance of *Faecalibacterium* and *Bifidobacterium* species. Restoration of these microbes has been associated with improved antiviral immunity and reduced cytokine storms [38]. These findings underscore the therapeutic relevance of microbiome modulation in respiratory health.

3.2 The Gut–Brain Axis

The gut–brain axis is perhaps the most widely studied gut–organ connection, linking microbiota-derived signals to neuroimmune interactions. The brain's immune system, composed largely of microglia and astrocytes, is highly sensitive to microbial metabolites. Germ-free mice exhibit defective microglial maturation, which can be restored upon colonization with complex microbiota or supplementation with SCFAs [39]. Microbial tryptophan catabolites generate indole derivatives and kynurenine pathway metabolites that act on AhR in microglia, regulating neuroinflammatory responses. Similarly, vagal nerve signaling provides a neuroimmune conduit for gut–microbiota interactions [40]. Dysbiosis has been linked to neurodegenerative diseases such as Alzheimer's and Parkinson's disease, as well as to psychiatric conditions including depression and autism spectrum disorders. From an immune perspective, systemic inflammation triggered by dysbiosis can cross the blood–brain barrier, leading to aberrant activation of microglia and astrocytes. Conversely, balanced microbiomes contribute to tolerance and resilience through the induction of Tregs and production of neuroprotective metabolites. Thus, microbiome–immune crosstalk serves as a bridge between gut physiology and brain health.

3.3 The Gut–Skin Axis

The gut–skin axis highlights how intestinal microbial communities shape cutaneous immunity and barrier integrity. SCFAs and bile acid metabolites travel through circulation to influence keratinocytes, Langerhans cells, and skin-resident T cells [41]. Dysbiosis has been strongly associated with inflammatory skin conditions such as atopic dermatitis, psoriasis, and acne. For example, butyrate supplementation has been shown to reduce skin inflammation by promoting Treg expansion and reducing IL-17 production. Furthermore, gut microbial regulation of bile acid metabolism impacts skin-resident immune responses, particularly through FXR and TGR5 signaling pathways [42]. Clinical studies indicate that probiotic interventions can improve eczema

severity in infants and modulate immune responses in psoriasis, underscoring the therapeutic promise of microbiome- targeted approaches for dermatological conditions. Importantly, skin health reflects systemic immune balance, making the gut microbiome a central player in cutaneous immune homeostasis.

3.4 The Gut–Liver Axis

The **gut–liver axis** is anatomically and physiologically unique, given the portal circulation that directly connects the intestine and liver. This axis is central to immune homeostasis in the liver, where Kupffer cells, hepatic stellate cells, and innate lymphoid cells interact with microbial metabolites and MAMPs [43]. Bacterial translocation across the gut barrier during dysbiosis introduces LPS and other microbial components into the liver, driving inflammation and fibrosis. Conversely, SCFAs and secondary bile acids can modulate Kupffer cell polarization and suppress excessive inflammation. Dysbiosis has been implicated in nonalcoholic fatty liver disease (NAFLD), alcoholic liver disease, and primary sclerosing cholangitis, all of which involve disrupted immune regulation [44]. Interestingly, bile acids themselves act as signaling molecules in a feedback loop. Microbial conversion of primary to secondary bile acids regulates FXR and TGR5 pathways, influencing not only metabolism but also innate and adaptive immunity within the liver. Thus, the gut–liver axis represents a prime example of how microbial crosstalk dictates organ-specific immunity.

3.5 The Gut–Tumor Immune Axis

The **gut–tumor immune axis** has attracted significant attention due to its impact on cancer immunotherapy. Tumor immunity is shaped by gut microbial composition, which influences systemic T cell priming, checkpoint receptor expression, and cytokine milieus [45]. Clinical studies in melanoma, lung, and renal cancer patients have shown that the presence of *Akkermansia muciniphila*, *Faecalibacterium prausnitzii*, and certain *Bifidobacterium* species correlates with improved responses to immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4) [46]. Antibiotic-induced dysbiosis, conversely, is associated with poor immunotherapy outcomes. Mechanistically, microbial metabolites enhance antigen presentation, promote effector $CD8^+$ T cell responses, and support the generation of memory T cells. Specific microbial taxa also regulate systemic levels of IL-12, IFN-γ, and other pro-inflammatory cytokines that enhance antitumor immunity [47]. This axis underscores the translational potential of microbiome engineering as an adjunct to immunotherapy. Approaches such as fecal microbiota transplantation (FMT), probiotics, and defined microbial consortia are being explored to enhance the efficacy of cancer immunotherapies by reprogramming host immunity through the gut–tumor immune axis.

4.0 Therapeutic Modulation of the Microbiome

Given the central role of the microbiome in systemic immunity, therapeutic strategies aimed at modifying microbial communities represent a rapidly expanding frontier in translational medicine. The primary goal of these interventions is to restore microbial balance, enhance beneficial taxa, suppress pathobionts, and recalibrate host immune responses. Current modalities include dietary interventions, probiotics, prebiotics, fecal microbiota transplantation (FMT), antibiotics, and next-generation engineered consortia [48]. Diet remains a fundamental modulator, with high-fiber diets enhancing SCFA production and microbial diversity, whereas high-fat and Western-style diets promote dysbiosis and systemic inflammation. Nutritional interventions thus provide a low- cost, scalable means to influence immune health. However, their effects may be gradual and variable, depending on baseline microbiome composition [49]. Beyond diet, direct microbial therapies are increasingly explored. While early approaches focused on probiotics and prebiotics, more recent work leverages microbiome-derived metabolites, live biotherapeutics, and synthetic microbial communities designed to confer defined immune benefits. These strategies signify a shift from broad ecological modulation to precision microbiome engineering.

4.1 Probiotics and Prebiotics

Probiotics are defined as live microorganisms that confer health benefits when administered in adequate amounts. Strains of *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* are among the most studied. These probiotics modulate immunity by enhancing IgA secretion, reducing pro-inflammatory cytokines, and supporting Treg expansion [50]. Clinical evidence supports their role in reducing antibiotic-associated

diarrhea, preventing necrotizing enterocolitis in infants, and modulating allergic and autoimmune responses. Prebiotics, typically non-digestible fibers such as inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS), selectively enrich beneficial taxa. Their fermentation produces SCFAs, which in turn modulate systemic immunity through HDAC inhibition and GPCR signaling. Combination therapies **synbiotics**, pairing probiotics with prebiotics offer synergistic benefits [51]. Despite promising outcomes, probiotics face limitations: strain-specific efficacy, transient colonization, and variable responses across individuals. Emerging research emphasizes the importance of personalized probiotic therapies guided by baseline microbiome profiling to optimize immune modulation.

4.2 Fecal Microbiota Transplantation (FMT)

FMT involves the transfer of processed fecal material from healthy donors into recipients to restore microbial diversity. It has achieved remarkable success in treating recurrent *Clostridioides difficile* infection, with cure rates exceeding 85% [52]. Beyond this indication, FMT is being explored in inflammatory bowel disease, metabolic syndrome, autoimmune conditions, and as an adjuvant in cancer immunotherapy. Mechanistically, FMT re-establishes ecological networks, restores SCFA production, and reduces pro-inflammatory pathobionts. Preclinical and clinical studies suggest that FMT can enhance responses to immune checkpoint inhibitors in melanoma by restoring beneficial taxa such as *Akkermansia muciniphila* [53]. However, safety concerns remain. Transmission of opportunistic pathogens, donor variability, and undefined long-term effects highlight the need for standardized protocols and screened donor banks. To overcome these challenges, capsule-based FMT and defined microbial consortia are under investigation, aiming to capture the therapeutic benefits while minimizing risks [54].

4.3 Next-Generation Microbiome Therapeutics

Next-generation microbiome therapeutics represent a paradigm shift toward precision and mechanistic interventions. These include live biotherapeutic products (LBPs), engineered microbial strains, and postbiotics (microbial metabolites, proteins, or cell components with immunomodulatory activity). For example, engineered strains of *E. coli Nissle 1917* have been modified to secrete anti-inflammatory molecules directly within the gut. Synthetic consortia designed to restore microbial diversity are being developed for conditions such as IBD and graft-versus-host disease [55]. Postbiotic therapies, such as butyrate analogues or defined secondary bile acids, bypass colonization barriers and deliver immune-modulating effects with greater control. Recent advances also highlight the potential of microbiome-based biomarkers to guide therapy. Predictive signatures of microbial composition are being developed to forecast vaccine responses, autoimmune risk, and cancer immunotherapy outcomes. As the field progresses, regulatory pathways for microbiome-based drugs are evolving, with increasing emphasis on quality control, safety, and reproducibility [56].

4.4 Future Perspectives

The future of microbiome–immune crosstalk research lies in precision medicine, where microbial interventions are tailored to individual host–microbiome profiles. Integration of multi-omics metagenomics, metabolomics, transcriptomics, and epigenomics will enable detailed mapping of microbiome–immune networks, paving the way for targeted therapies [57]. The development of microbiome–immune atlases at single-cell resolution will reveal context-specific interactions, such as how distinct microbes influence T cell subsets across different tissues. Moreover, advances in organoid and organ-on-chip models will allow mechanistic dissection of gut–immune crosstalk under controlled conditions. Another frontier is the intersection of the microbiome with emerging therapies. The efficacy of CAR-T cells, cancer vaccines, and biologic agents may be enhanced or hindered by microbial signals, making microbiome monitoring a critical component of immunotherapy pipelines [58]. Additionally, the microbiome's role in shaping responses to infectious diseases including pandemics such as COVID-19 will inform strategies for future epidemic preparedness. Ultimately, the field must also address challenges of equity and accessibility, ensuring that microbiome-based therapies are safe, scalable, and affordable across diverse populations.

Table 1. Representative Microbial Metabolites and Their Immunomodulatory Effects

Microbial Metabolite	Primary Source Microbes	Target Immune Cells/Pathways	Mechanism of Immunomodulation	Systemic Effect
Butyrate	*Clostridium* clusters IV, XIVa	Tregs, Macrophages, DCs	HDAC inhibition, Foxp3 activation, M2 polarization	Anti-inflammatory; promotes immune tolerance
Propionate	*Bacteroides*, *Veillonella* spp.	Neutrophils, DCs	GPCR (GPR43) activation, reduction of IL-6 and TNF-α	Regulation of systemic inflammation
Indole-3-aldehyde (I3A)	*Lactobacillus reuteri*	ILC3s, Epithelial cells	AhR activation, IL-22 induction	Mucosal defense, epithelial repair
Secondary bile acids (DCA, LCA)	*Clostridium scindens*, *Eubacterium* spp.	Tregs, Th17 cells	FXR/TGR5 signaling, inhibition of IL-17	Regulation of liver and intestinal inflammation
Polysaccharide A	*Bacteroides fragilis*	DCs, Tregs	TLR2-dependent DC modulation, IL-10 secretion	Induction of peripheral tolerance
Trimethylamine-N-oxide (TMAO)	*Enterobacteriaceae*	Macrophages, Endothelial cells	NF-κB activation, oxidative stress induction	Pro-atherogenic, inflammatory signaling
Polyamines (Spermidine, Putrescine)	*Bacteroides*, *Lactobacillus* spp.	B cells, Macrophages	Regulation of gene transcription, mitochondrial metabolism	Immune regulation, metabolic adaptation

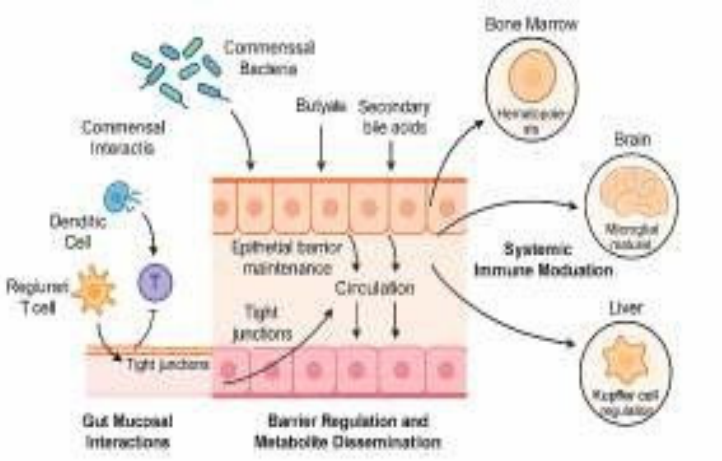

Figure 1. Mechanistic Overview of Microbiome–Immune Crosstalk from Gut to Systemic Immunity

4.5CONCLUSION

The gut microbiome stands as a central orchestrator of immune development, tolerance, and defense, extending its influence well beyond the intestine into systemic immunity. Through an intricate network of metabolites, molecular patterns, and cellular interactions, the microbiome shapes innate and adaptive immune responses across organs. Dysbiosis disrupts this equilibrium, contributing to autoimmune diseases, metabolic disorders, neuroinflammation, skin pathologies, liver disease, and cancer progression. Therapeutic interventions ranging from probiotics and prebiotics to fecal microbiota transplantation and next-generation engineered

therapeutics demonstrate immense promise in restoring microbial–immune balance. However, heterogeneity in responses, safety concerns, and regulatory complexities remain barriers to clinical translation. As the field advances, precision microbiome engineering, integrated multi-omics approaches, and personalized therapeutics will define the next era of microbiome research. By harnessing the full potential of microbiome–immune crosstalk, translational medicine may unlock novel avenues for preventing and treating a spectrum of immune-mediated diseases.

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