

Gut microbiota-mucosal immunity crosstalk in the IBD microenvironment: Mechanistic insights into disease progression and intervention strategies

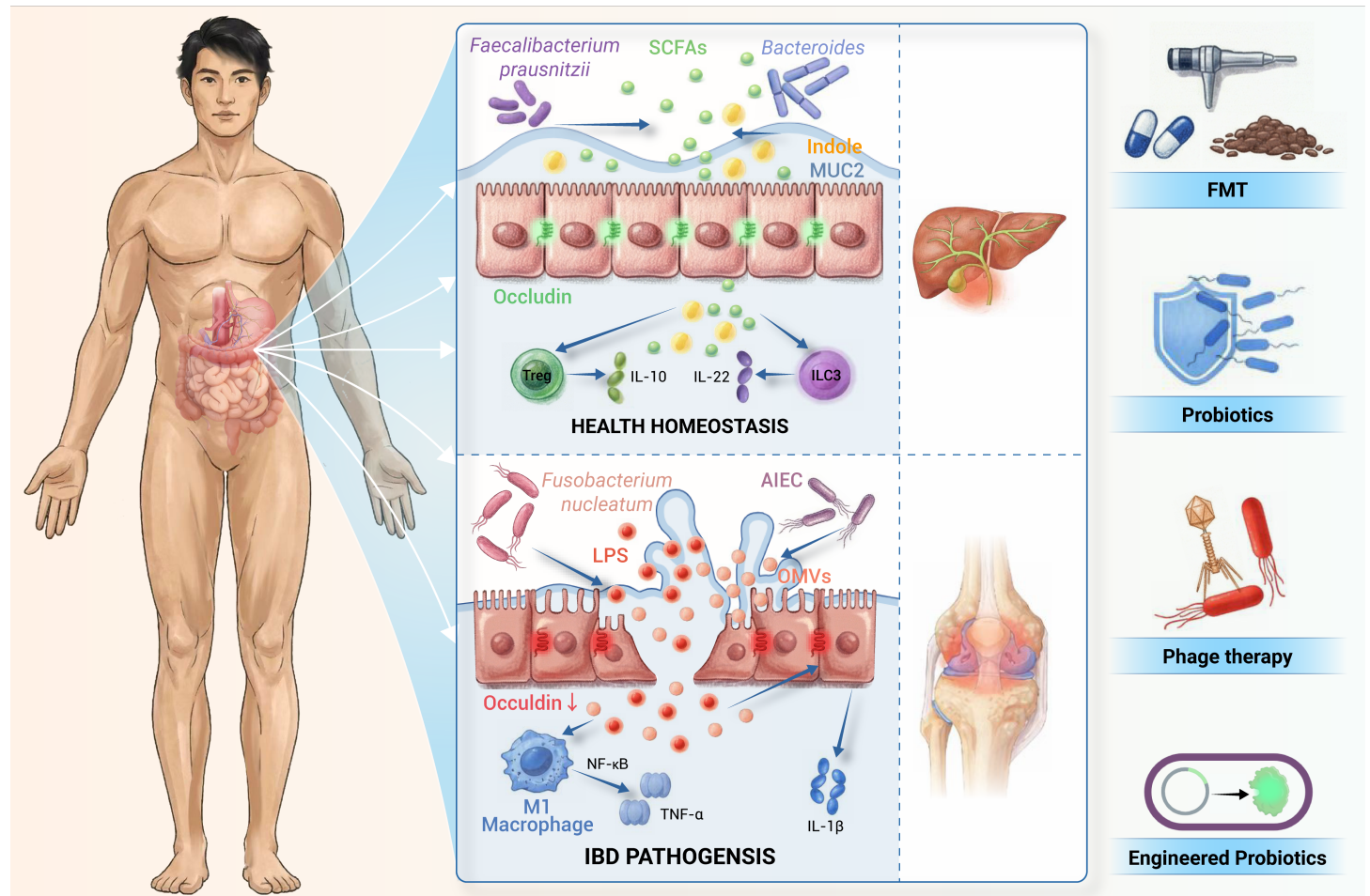
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GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Gut microbiota-immune crosstalk maintains homeostasis; disruption drives inflammatory bowel disease (IBD).
- Microbiota-immune interactions coordinate immune balance and contribute to IBD pathogenesis.
- Microbial components and metabolites reshape immune responses, promoting barrier damage.
- Microbiota-targeted strategies enable precision immunomodulation and improved disease control in IBD.

Gut microbiota-mucosal immunity crosstalk in the IBD microenvironment: Mechanistic insights into disease progression and intervention strategies

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The gut microbiota forms a highly dynamic and multilayered ecological system that plays a pivotal role in maintaining mucosal immune homeostasis. When the “microbiota-immune regulatory” axis is perturbed in genetically susceptible individuals, antigen recognition and effector responses at the mucosal surface may be reshaped, thereby driving the onset and persistent progression of IBD. This review highlights the distinct patterns of microbe-immune interactions under physiological and pathological conditions, with particular focus on the key immunoregulatory events at different disease stages. In the early phase of IBD, adhesive and invasive bacterial strains and microbial dysbiosis can disrupt epithelial barriers, trigger aberrant innate immune activation, and induce chronic local inflammation. As the disease advances, T-cell polarization, tissue remodeling, and extraintestinal manifestations collectively sustain the inflammatory network and promote systemic damage. We further summarize emerging microbiota-based immunotherapeutic strategies—such as fecal microbiota transplantation, probiotics/prebiotics, targeted manipulation of specific bacterial taxa, bacteriophage therapy, and engineered probiotics—and their potential value and remaining clinical challenges in IBD management. Future work should integrate gut microbiota-immune crosstalk to identify clinically actionable targets and validate their biological and therapeutic significance through well-designed prospective studies.

INTRODUCTION

The human gut microbiota is a highly complex symbiotic community residing along the intestinal mucosal surface. It is estimated that approximately 3×10^{13} microbial cells inhabit the adult gut, comprising diverse populations of bacteria, archaea, viruses, and fungi.¹ The microbiota exhibits marked spatial heterogeneity across different intestinal regions, with substantial variations in taxonomic composition, abundance, and metabolic capacity. For example, the small intestine harbors relatively fewer microbes, dominated by species specialized in rapid nutrient absorption and carbohydrate metabolism,² whereas the colon contains a dense and diverse microbial ecosystem that primarily ferments complex carbohydrates and produces short-chain fatty acids (SCFAs).³

This region-specific organization of microbial communities and functions not only shapes local digestion, absorption, and epithelial barrier integrity but also influences systemic immunity. Through metabolites, extracellular vesicles, and microbial signaling molecules, the gut microbiota orchestrates both innate and adaptive immune responses, thereby serving as a critical determinant of intestinal homeostasis and disease susceptibility.^{4–6} When this delicate balance is disrupted, microbial dysbiosis can impair immune regulation and drive the onset and progression of inflammatory bowel disease (IBD).⁷

The association between the gut microbiota and IBD has long been recognized, with early studies in the early 20th century first noting compositional differences in intestinal microorganisms between IBD patients and healthy individuals.⁸ With the advancement of molecular biology and high-through-

put sequencing technologies, substantial dysbiosis in the gut microbiome of IBD patients has been progressively elucidated. These alterations are characterized by reduced microbial diversity, a depletion of beneficial commensals, and an increased relative abundance of potentially pathogenic bacteria.^{9–10} In parallel, microbially derived metabolites such as SCFAs, tryptophan metabolites, and secondary bile acids have been shown to modulate host immunity, influence intestinal barrier integrity, and shape inflammatory signaling pathways.^{11–13}

In recent years, metagenomic and metabolomic studies have further uncovered the molecular mechanisms underlying host-microbiota interactions, including the regulation of T-cell polarization, modulation of innate immune cell activity, and promotion of mucosal barrier repair.^{14–15} These findings have provided new insights into the pathogenesis of IBD and established a scientific basis for microbiota-based therapeutic strategies such as probiotics, fecal microbiota transplantation, and metabolite-targeting interventions. With continued advances in high-throughput sequencing and metagenomics, systematic profiling of microbiota-immune crosstalk in IBD has become increasingly feasible. For instance, SCFAs have been demonstrated to regulate the Th17/Treg balance, thereby exerting a profound influence on intestinal inflammation.¹⁶ In murine models, transplantation of a healthy gut microbiota into dysbiotic mice has been shown to alleviate intestinal inflammation by enhancing regulatory T-cell (Treg) function and reducing pro-inflammatory ILC3 infiltration.¹⁷ In addition, the role of the gut microbiota in combination with biologics or immunomodulatory therapy has gradually been uncovered. Certain bacterial taxa can potentiate the therapeutic efficacy of anti-TNF- α or anti-IL-12/23 agents, offering promising avenues for precision immunomodulation in IBD.¹⁸

Despite significant advances in recent years, most existing reviews have primarily focused on mechanistic insights at a single level, such as microbial dysbiosis, dysfunction of immune cell populations, or alterations in specific inflammatory signaling pathways. However, a comprehensive synthesis of the bidirectional regulatory mechanisms between the gut microbiota and the immune system in IBD—particularly the metabolite-immune axis and its influence on disease progression and therapeutic response—remains lacking. Building upon previous studies, this review adopts a holistic perspective of the intestinal microenvironment to systematically integrate the dynamic interactions between the gut microbiota and mucosal immunity. Special emphasis is placed on the roles of microbial metabolites, immune signaling pathways, and inflammatory memory as key regulatory nodes in the progression of IBD. Furthermore, we discuss the potential applications of microbiome-targeted interventions in the precision treatment of IBD, and propose future research directions aimed at advancing our understanding of disease pathogenesis and therapeutic strategies. To facilitate comprehension of the conceptual framework presented in this review, we first outline the overall landscape of microbiota-immune interactions under both physiological homeostasis and pathological conditions of IBD.

MOLECULAR MECHANISMS AND SIGNALING REGULATION UNDERLYING INTERACTIONS BETWEEN THE GUT MICROBIOTA AND THE IMMUNE SYSTEM

The gut microbiota modulates immune cell activation, polarization, and downstream signaling through its structural components, metabolic products, and secreted factors. In the context of IBD, microbial dysbiosis often amplifies pro-inflammatory signaling, whereas certain commensal species contribute to immune tolerance and maintenance of epithelial barrier homeostasis. Conversely, the host immune system shapes microbial composition and spatial distribution via mechanisms such as pattern recognition receptors, cytokine signaling, and immune-cell recruitment. These bidirectional microbiota-immune interactions involve both cooperative and antagonistic dynamics. Despite increasing research efforts, many critical molecular details remain unresolved and warrant further systematic investigation.

Microbiota-derived mechanisms regulating immune responses

Structural components of microorganisms. Microbial structural components such as lipopolysaccharides (LPS), lipoteichoic acids, and flagellin can activate immune signaling pathways and shape the inflammatory microenvironment.¹⁹ In IBD, dysbiosis of the gut microbiota leads to elevated LPS levels, which subsequently upregulate NF- κ B signaling and drive the production of pro-inflammatory cytokines, thereby exacerbating mucosal inflammation.²⁰⁻²¹ Evidence from animal models further demonstrates that a reduction in LPS exposure suppresses the expression of inflammation-related cytokines in colitis, highlighting the central role of microbial structural components in amplifying intestinal inflammation.²²

Antigenic cross-reactivity of microbial surface proteins can also trigger aberrant immune activation. The flagellin of certain *Escherichia coli* strains shows structural similarity to intracellular epithelial proteins, leading to excessive activation of Th17 cells and increased IL-17 secretion—an event considered critical for amplifying local inflammation in patients with IBD.²³⁻²⁴ Another study showed that adhesins produced by adherent-invasive *E. coli* activate pro-inflammatory M1 macrophage polarization via the β -catenin pathway, inducing inflammatory mediator release and disrupting the intestinal barrier.²⁵ Conversely, surface polysaccharides derived from probiotics can promote macrophage polarization toward an anti-inflammatory M2 phenotype through PI3K/AKT signaling, thereby enhancing mucosal repair responses.²⁶

Microbial metabolites. The gut microbiota indirectly interacts with immune cells through the secretion of metabolic products, thereby influencing the onset and progression of IBD. Key microbial metabolites—including SCFAs, secondary bile acids, indole derivatives, and microbe-derived lipid signaling molecules—are capable of penetrating the mucosal barrier and exerting long-distance immunomodulatory effects by engaging host receptors or altering intracellular signaling pathways (e.g. Table 1). Among SCFAs, acetate can suppress histone deacetylase (HDAC) activity and enhance acetylation of Sox13 at lysine 30, thereby inhibiting IL-17A production in hepatic ILC3s and attenuating pro-inflammatory signaling. Meanwhile, acetate can activate neutrophils and Th17 cells via FFAR2, promoting a localized inflammatory microenvironment. This seemingly paradoxical bidirectional effect suggests that SCFA-mediated immune regulation cannot be simply categorized as anti-inflammatory or pro-inflammatory, but rather depends on specific immune cell subsets and microenvironmental contexts.

Butyrate primarily promotes M2 macrophage polarization and supports tissue repair by inducing autophagy and enhancing the secretion of CCL20.²⁹ Additionally, by modulating IL-12p19 expression in dendritic cells, it influences the Th17/Treg balance, highlighting the complexity of SCFAs in maintaining mucosal immune homeostasis and shaping the inflammatory microenvironment. Valerate and branched-chain SCFAs further expand this regulatory repertoire. Valerate enhances Foxp3 expression through HDAC inhibition, thereby facilitating Treg differentiation and suppressing inflammation. Isobutyrate acts through FFAR2/FFAR3 signaling to promote Treg differentiation and mildly modulate IL-22 production, contributing to epithelial barrier restoration. Isovalerate orchestrates neutrophil and macrophage chemotaxis and regulates inflammatory intensity, achieving dynamic local microenvironmental modulation.

Beyond their established role in lipid metabolism, bile acids also function as key immune regulators through nuclear receptors such as FXR, TGR5, and VDR, along with associated cytokine networks. 3β -hydroxydeoxycholic acid suppresses the immunostimulatory capacity of dendritic cells, induces Treg expansion, and alleviates inflammation. Isoallothiocholic acid inhibits Th17 differentiation and downregulates ROR γ t expression, reducing neutrophil infiltration and local inflammatory damage. Ursodeoxycholic acid contributes to gut-liver axis regulation by upregulating hepatic sinusoidal endothelial CXCL16 to promote CXCR6⁺ NKT cell accumulation. Other bile acids, including CDCA, deoxycholic acid, lithocholic acid, and UDCA, exert further immunomodulatory effects on macrophages, dendritic cells, and the Th17/Treg axis via FXR/TGR5 or VDR signaling. Importantly, these actions appear highly context-dependent, varying with local concentrations, immune status, and gut microbial composition.

Beyond SCFAs and bile acids, several other microbially derived metabolites modulate immune responses through distinct signaling pathways. For instance, shikimic acid activates macrophages by triggering ERK1/2, JNK, p38, and NF- κ B cascades, thereby promoting inflammatory reactions. Cyclic di-adenosine monophosphate stimulates STING-mediated type I interferon production, shaping interactions between natural killer cells and dendritic cells. Extracellular ATP enhances the activation of CD70⁺CD11c⁺ cells, inducing pro-inflammatory cytokines and facilitating Th17 differentiation and inflammatory expansion. TMAO drives macrophage M1 polarization, improving their phagocytic and antigen-presenting capacities. Indole-3-lactic acid (I3LA) increases IL-12 production by promoting IL12a-associated H3K27ac modification, thereby reinforcing anti-inflammatory cell responses. Collectively, these metabolites establish interconnected immunoregulatory networks across multiple immune cell types via specialized receptors and signaling mechanisms. In the context of IBD, they may either enhance host defense or, under dysregulated microenvironmental conditions, exacerbate inflammatory pathology.

Other microbe-derived mediators. Beyond metabolic products, the gut microbiota also influences host immunity through a variety of secreted molecular factors—including outer membrane vesicles (OMVs), effector proteins and toxins, microbial nucleic acids, and quorum-sensing molecules (QSMs)—all of which play crucial roles in immune dysregulation and epithelial barrier disruption in IBD. OMVs, nanoscale vesicles actively released by Gram-negative bacteria, contain diverse enzymes capable of traversing the epithelial barrier and being internalized by immune cells. These vesicles activate key inflammatory pathways such as NF- κ B and signal transducer and activator of transcription 3 (STAT3), thereby promoting the release of pro-inflammatory cytokines and amplifying mucosal immune responses.⁴⁷⁻⁴⁸

Recent studies have shown that OMVs derived from *Fusobacterium nucleatum* contain the outer membrane protein FomA and the adhesin FadA, which activate macrophages and dendritic cells through the TLR2/4-MyD88 signaling axis. This interaction increases the secretion of inflammatory mediators and exacerbates mucosal inflammation and barrier impairment.⁴⁹⁻⁵¹ In dextran sulfate sodium DSS-induced colitis models, these effects manifest as heightened epithelial damage and intestinal permeability.⁵² Similarly, OMVs from *Helicobacter pylori* carry CagA and VacA proteins that are recognized by macrophages, triggering robust production of IL-6, TNF- α , and IL-1 β while suppressing IL-10, leading to a pronounced pro-inflammatory microenvironment.⁵³ Moreover, disturbances in iron homeostasis can alter the abundance of VacA and LPS within OMVs, suggesting that micronutrient imbalance may modulate IBD pathogenesis by reshaping vesicular cargo composition.⁵⁴

Secreted proteins from intestinal bacteria also serve as key mediators that shape the crosstalk between the host immune system and the gut microbiota. Enterotoxigenic *Bacteroides fragilis* releases a toxin that cleaves epithelial tight junction proteins and disrupts barrier integrity.⁵⁵ It further activates the STAT3 and NF- κ B signaling pathways, driving IL-17A and IL-23 expression and establishing a typical Th17-dominated inflammatory loop.⁵⁶ Similarly, adhesion-related proteins secreted by Segmented Filamentous Bacteria directly bind to the epithelial surface, triggering serum amyloid A production, activating lamina propria dendritic cells, and promoting Th17 differentiation, thereby exacerbating intestinal inflammation.⁵⁷ In contrast, small peptides secreted by *Bifidobacterium* can inhibit dendritic cell maturation and mitigate inflammatory responses in IBD.⁵⁸

Table 1. Major microbiota-derived metabolites and their immunomodulatory interactions with host immune cells.

Microbial metabolites	Immune cell types	Mechanisms	Outcomes	References
SCFAs				
Acetate	Group 3 innate lymphoid cells (ILC3s)	Inhibits histone deacetylase activity; increases K30 acetylation of Sox13, leading to its reduced expression	Reduces IL-17A production in hepatic ILC3s	27
Acetate	Neutrophils	Enhances Th17 responses and promotes neutrophil chemotaxis via FFAR2-dependent signaling	Creates a pro-inflammatory microenvironment	28
Butyrate	Macrophages	Induces autophagy and CCL20 secretion; promotes M2 polarization	Enhances tissue repair	29
Valerate	Regulatory T cells (Tregs)	Inhibits HDAC activity; promotes Foxp3 expression	Increases Treg differentiation and suppresses inflammation	30
Valerate	Macrophages	Regulates M1/M2 polarization; suppresses IL-6 and TNF- α production	Alleviates intestinal inflammation and improves barrier function	31
Isobutyrate	Tregs	Activates FFAR2/FFAR3 signaling; enhances Treg differentiation; mildly modulates IL-22	Suppresses inflammation and enhances mucosal repair	32
Isovalerate	Neutrophils / Macrophages	Modulates chemotactic and inflammatory responses	Contributes to localized inflammation regulation	33
Butyrate derivatives	Dendritic cells / Macrophages	HDAC inhibition regulates Th17/Treg balance	Improves inflammatory microenvironment	34
Bile acids				
3 β -hydroxydeoxycholic acid	DCs	Attenuates DC immunostimulation and induces Treg expansion	Suppresses inflammation or promotes immune evasion	35
Lithocholic acid derivatives	Neutrophils	Inhibits Th17 differentiation and reduces ROR γ t expression	Limits neutrophil chemotaxis and alleviates inflammation	36
Nor-deoxycholic acid	NKT cells	Upregulates CXCL16 expression on hepatic sinusoidal endothelium, promoting CXCR6 ⁺ NKT accumulation	Suppresses gut–liver axis inflammation	37
Cholic acid	Macrophages	Activates FXR/TGR5 signaling; increases IL-10 while reducing IL-6/TNF- α	Anti-inflammatory effect	38
Deoxycholic acid	Neutrophils / Macrophages	FXR/TGR5-dependent inflammatory modulation	Context-dependent inflammatory outcome	39
Ursodeoxycholic acid	DCs / Th17 cells	VDR-mediated Th17 suppression and Treg enhancement	Improves mucosal immune homeostasis	40
Ursodeoxycholic acid	DCs / Macrophages	Inhibits NF- κ B signaling; promotes tolerogenic DC differentiation	Suppresses inflammation and enhances immune tolerance	41
Other metabolites				
Shikimic acid	Macrophages	Activates ERK1/2, JNK, p38 and NF- κ B pathways	Promotes macrophage activation and inflammation	42
Cyclic-di-AMP	Monocytes	Activates STING pathway to induce type I interferon	Regulates macrophage polarization and NK–DC crosstalk	43
ATP	Neutrophils	Activates CD70 ⁺ CD11c ⁺ APCs and induces IL-6, IL-23, TGF- β expression	Promotes Th17 differentiation and inflammation propagation	44
Trimethylamine N-oxide	Macrophages	Induces M1 polarization, enhances phagocytosis and antigen presentation	Modulates inflammatory and immune responses	45
Indole-3-lactic acid	Dendritic cells	Enhances IL12a enhancer H3K27ac modification, boosting IL-12 production	Activates CD8 ⁺ T-cell protective response	46

Under persistent inflammatory stress, gut microbes also release extracellular DNA (eDNA) and RNA fragments. eDNA can trigger Toll-like receptor activation in macrophages and dendritic cells, leading to the secretion of IL-6, TNF- α , and IL-1 β .⁵⁹ Meanwhile, microbial RNA is sensed by RIG-I and MDA5, initiating type I interferon responses and perturbing epithelial homeostasis.⁶⁰ Clinically, fecal eDNA levels are markedly elevated in patients with active IBD and are strongly associated with excessive neutrophil extracellular trap formation.⁶¹ Additionally, QSMs, such as N-acyl homoserine lactones (N-AHLs), regulate IL-22 and Reg3 γ expression via aryl hydrocarbon receptor signaling, facilitating epithelial repair and barrier restoration.⁶² However, pathological accumulation of N-AHLs during pathogenic bacterial overgrowth can induce oxidative stress and apoptosis in epithelial cells, aggravating mucosal injury.⁶³

Taken together, the gut microbiota regulates host immunity through multiple signals, including structural components, microbial metabolites, and secreted factors, thereby forming a multilayered regulatory network. These microbiota-derived molecules can modulate the activation, polarization, and functional responses of immune cells through PRRs and diverse intracellular signaling pathways, ultimately influencing intestinal mucosal barrier homeostasis and inflammatory responses. Under physiological conditions, this regulatory network contributes to the maintenance of immune tolerance and tissue homeostasis. However, in the context of microbial dysbiosis or alterations in the intestinal microenvironment, this network may shift toward a persistent inflammatory amplification loop, thereby promoting the initiation and progression of IBD.

Therefore, the intricate interplay among the gut microbiota, microbial

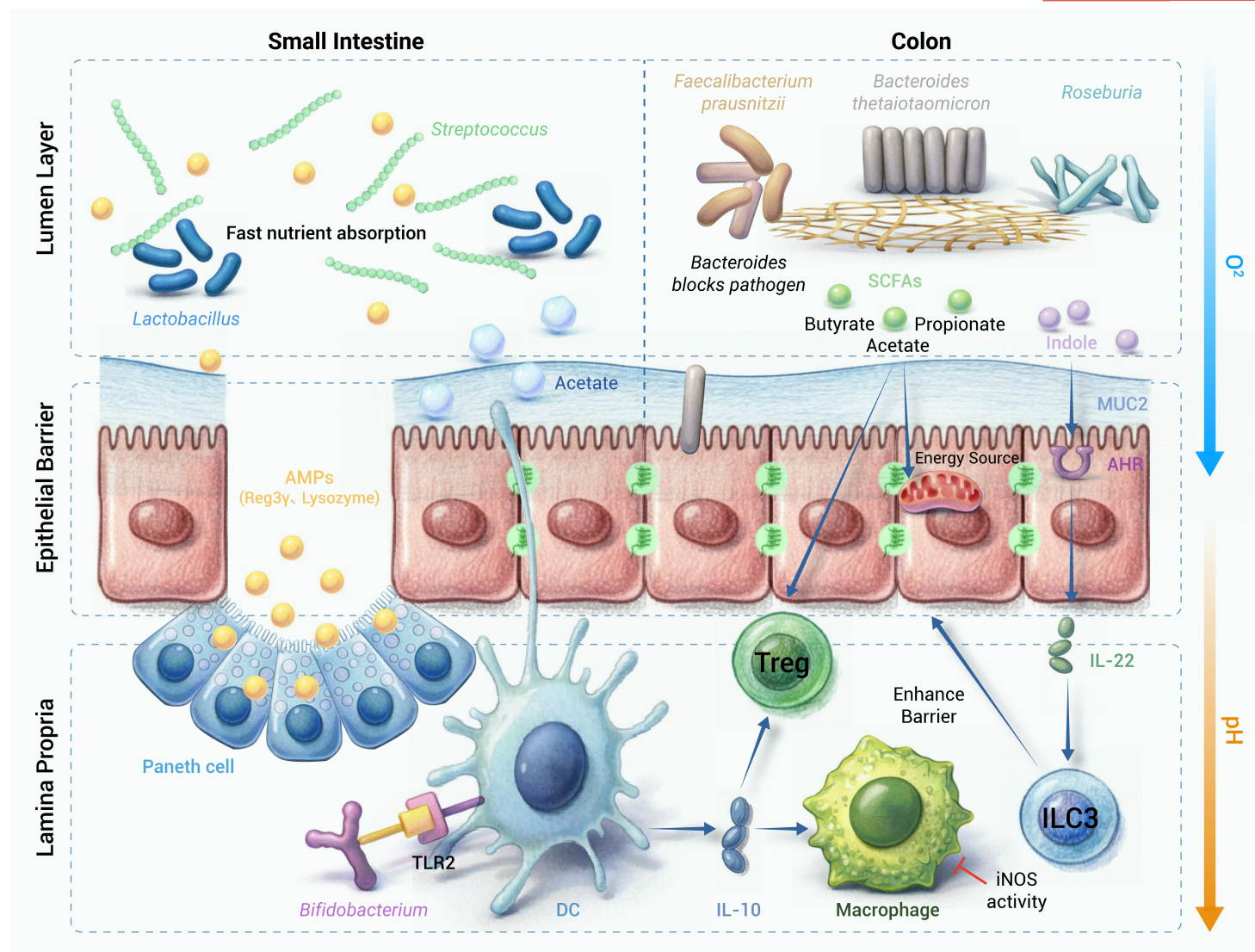


Figure 1. Region-specific interactions between gut microbiota and mucosal immunity in the small intestine and colon This schematic illustrates the spatial heterogeneity of gut microbiota-immune interactions along the small intestine and colon. In the small intestine, relatively low bacterial density, fast nutrient absorption, *Lactobacillus* and Paneth cell-derived antimicrobial peptides protect the epithelium. In the colon, anaerobic bacteria such as *Faecalibacterium prausnitzii*, *Bacteroides* and *Roseburia* produce SCFAs and tryptophan-derived indole, which fuel epithelial cells, enhance MUC2 and tight junctions, and promote IL-10+ Treg and IL-22^{hi} ILC3 responses via AHR signaling, thereby strengthening the barrier.

metabolites, and host immune signaling—conceptualized as the “microbiota-immune-metabolism axis” has emerged as a key mechanistic framework governing intestinal homeostasis and inflammatory responses in IBD. As illustrated in Figure 1, dysbiosis perpetuates a vicious cycle of IBD by activating innate immune pathways and compromising epithelial barrier function.

Genetic and epigenetic regulation of immunity and the gut microbiota

The host's genetic background fundamentally shapes immune responses to microbial signals within the gastrointestinal tract. Recent multi-omics studies indicate that susceptibility to IBD, disease activity, and therapeutic outcomes are tightly associated with polymorphisms in immune receptor genes and their epigenetic modifications.^{64–65} At the genetic level, variations in TLRs and NLRs are recognized as major determinants of host-microbiota interactions. For instance, TLR4 mutations are linked to heightened epithelial responsiveness to lipopolysaccharide in Crohn's disease, whereas reduced TLR9 expression weakens the induction of antimicrobial peptides and disrupts epithelial barrier homeostasis.^{66–68} Moreover, NOD2 variants diminish microbial peptidoglycan recognition, resulting in impaired intracellular pathogen clearance.⁶⁹

Epigenetic regulation further refines immune adaptability based on underlying genetic predisposition. Microbial metabolites such as short-chain fatty acids can inhibit histone deacetylases, promote acetylation of the FOXP3

promoter, facilitate regulatory T-cell differentiation, and suppress pro-inflammatory cytokine release.^{62–64} Concurrently, the tryptophan-derived metabolite indole-3-acetic acid activates the AhR-mediated DNA methyltransferase network, thereby limiting excessive IL-1β and IL-23 production in dendritic cells.⁸¹ Together, these findings highlight microbial metabolic cues as epigenetic “switches” capable of reshaping chromatin accessibility and immune phenotypes.

In addition, non-coding RNAs—particularly microRNAs (miRNAs)—play critical roles in orchestrating host-microbe and immune interactions. Signals from commensal microbiota can induce the expression of miR-146a and miR-155 via a MyD88-dependent pathway, thereby amplifying signaling through the TLR-NF-κB axis.⁷⁰ In patients with IBD, the upregulation of miR-21 and miR-31 is strongly associated with impaired intestinal barrier integrity and elevated pro-inflammatory cytokines, suggesting that miRNAs may act as key molecular intermediaries linking inflammatory responses to dysregulated microbial homeostasis.⁷¹

Of particular note, emerging evidence highlights metabolism-driven post-translational modifications as an additional critical layer governing host-microbe interactions. Lactylation has been identified as a metabolic-immune coupling signal that modulates the transcriptional activity of glycolytic enzymes and inflammatory mediators in macrophages.^{72–73} Together, genetic and epigenetic mechanisms shape the sensitivity and activation threshold of

immune recognition toward microbial cues. Future research integrating genomic, epigenomic, and metabolomic data will be essential to elucidate the multilayer regulatory networks that sustain immune homeostasis, thereby enabling refined disease stratification and the development of epigenetic-targeted therapeutic strategies for IBD.

Immune responses to the gut microbiota

The ability to discriminate between pathogens and the commensal gut microbiota is a fundamental property of the immune system. When recognizing resident commensal microorganisms, the immune system dampens its responses to establish immunological tolerance. In contrast, when pathogenic microbes are detected, rapid immune activation is triggered to eliminate harmful species and prevent potential damage. Macrophages contribute to dysbiosis by promoting inducible nitric oxide synthase (iNOS) expression through Stat1 signaling. To validate this mechanism, researchers administered a specific diet to LysM-Stat1 mice, in which macrophages are unable to respond to IFN- γ via Stat1. The results showed a significant increase in the relative abundance of Enterobacteriaceae in wild-type mice, whereas the abundance remained essentially unchanged in LysM-Stat1 mice, at approximately one-twelfth of that in their wild-type counterparts.⁷⁴

Pro-IL-1 β produced by mononuclear phagocytes remains unresponsive to commensals but can be converted into its active form in the intestine upon infection with pathogens such as Salmonella or Pseudomonas spp.⁷⁵ Subsequently, neutrophils are recruited and generate abundant ROS, helping to prevent microbial translocation and excessive overgrowth.⁷⁶ In infants whose adaptive immunity is still immature, TLR5-expressing brain-resident macrophages play a crucial role in protecting against pathogenic invasion.⁷⁷ In murine models of IBD, neutrophil depletion exacerbates intestinal inflammation, whereas antibiotic treatment or IL-17 neutralization attenuates inflammatory responses, underscoring the role of neutrophils in restraining inflammation-associated gut dysbiosis.⁷⁸

Owing to the complexity of causal relationships between the immune system and the gut microbiota—as well as technical challenges in accurately tracking microbial translocation. The precise mechanisms by which immune regulation shapes microbial composition and distribution have yet to be fully elucidated and warrant further investigation.

Gut microbiota and immune homeostasis

The bidirectional interaction between the gut microbiota and the immune system plays a pivotal role in maintaining—or disrupting—immune homeostasis. Mucosal-associated invariant T (MAIT) cells, a subset of innate-like lymphocytes, can be activated by antigens presented via major histocompatibility complex class I-related molecule 1 (MR1).⁷⁹ Observations in germ-free mice, in which both IgA secretion and MAIT cell development are markedly reduced, indicate that riboflavin biosynthesis-derived metabolites from the gut microbiota may promote MAIT cell generation and activation by inducing IgA production and enhancing MR1 expression, thereby supporting the integrity of the mucosal immune barrier.^{80–82} Additionally, MAIT cells sense microbial activity through the secretion of immunoregulatory cytokines, contributing to the fine-tuning of intestinal immune responses.⁸¹

Akkermansia-derived threonyl-tRNA synthetase (AmTARS) interacts with Toll-like receptor 2 (TLR2) to activate mitogen-activated protein kinase (MAPK) and PI3K/AKT signaling, which enhances the production of anti-inflammatory and central immunomodulatory mediators. Through this mechanism, AmTARS promotes the restoration of IL-10-producing macrophages and induces M2 polarization, thereby reinforcing immune surveillance and homeostatic regulation.⁸³ Conversely, the fimbrial adhesin H of adherent-invasive Escherichia coli modulates pro-inflammatory cytokine secretion and facilitates the recruitment of dendritic cells and macrophages, leading to immune dysregulation and microbiota-associated intestinal inflammation.^{84–85} Collectively, these findings suggest that targeted modulation of the gut microbiota to restore immune homeostasis may represent a promising strategy for alleviating intestinal inflammation.

Crosstalk of intrabacterial signaling pathways

The cooperative and competitive interactions within the gut microbiota are highly complex and remain incompletely understood. Gut microbes can acti-

vate the Wnt/ β -catenin signaling cascade through adhesin-mediated recognition of host target cells, thereby contributing to dysregulated apoptosis and the progression of inflammation. When the Helicobacter pylori outer membrane adhesin HopQ binds to its cognate epithelial adhesion molecules, the virulence factor CagA is translocated into host epithelial cells via the type IV secretion system (T4SS) and subsequently triggers the Wnt/ β -catenin pathway. This activation promotes the production of pro-inflammatory cytokines, aberrant cell proliferation, and tumorigenesis.^{86–88} Similarly, Salmonella enterica serovar Typhimurium delivers its effector AvrA into host cells through T4SS, thereby driving inflammatory responses.⁸⁹ In addition, Fusobacterium nucleatum activates Wnt/ β -catenin signaling through its Fusobacterium autotransporter protein adhesin, resulting in pro-inflammatory effects.⁹⁰

Furthermore, multiple factors within the gut microbiota modulate macrophage polarization and the resulting immune responses. Pro-inflammatory cytokines can shift naïve macrophages toward a classically activated M1 phenotype, whereas macrophage colony-stimulating factors promote alternative M2 polarization.^{91–93} Microbial species such as F. nucleatum, H. pylori, and Candida albicans have been shown to activate TNF- α production and drive macrophages toward an M1 phenotype.⁹⁴ In contrast, Akkermansia muciniphila, F. nucleatum, and Prevotella spp. can induce IL-10 production and facilitate M2 polarization.⁹⁵

Bacteroides species-derived acetate has been reported to promote M1 polarization and enhance cytotoxic CD8⁺ T-cell activity, markedly suppressing tumor cell proliferation in a murine hepatocellular carcinoma model.⁹⁶ Interestingly, the microbial metabolite butyrate can also promote M1 polarization and activate the NLRP3/Caspase-1 pathway, thereby sustaining inflammatory conditions.⁶⁴ Conversely, butyrate has been shown to upregulate H19 expression and induce M2 macrophage polarization, ultimately aggravating inflammatory progression.⁹⁷ These opposing effects may reflect context-dependent downstream signaling triggered by distinct microbial metabolites in different microenvironments. Notably, such binary classification is insufficient to capture the dynamic macrophage states observed in vivo, where phenotypic activation continuously shifts in response to environmental cues.⁹⁸

INTERACTIONS BETWEEN THE GUT MICROBIOTA AND THE IMMUNE SYSTEM UNDER PHYSIOLOGICAL CONDITIONS

The immune system and the gut microbiota engage in a highly coordinated bidirectional regulatory network. The intestinal microbiota not only functions as a critical microbial barrier but also modulates the differentiation and effector functions of immune cells through diverse metabolic and signaling pathways. Conversely, the host immune system maintains microbial homeostasis and promotes immune tolerance through mucosal barriers and selective immune surveillance. The dynamic equilibrium between these two components forms the fundamental basis for intestinal mucosal integrity and overall organismal health.

Gut microbiota and the establishment of the intestinal immune barrier

The interaction between the gut microbiota and the host immune system is fundamental to the establishment of intestinal immune defenses. A stable microbial community safeguards mucosal homeostasis by occupying ecological niches, competing for nutrients and adhesion sites, and thereby preventing the invasion of exogenous pathogens. Dominant commensal taxa, primarily members of the Firmicutes and Bacteroidetes phyla, form a natural ecological barrier against microbial disruption.^{99–100} In addition, several butyrate-producing bacteria secrete antimicrobial peptides (AMPs) that inhibit the colonization of pathogenic organisms.¹⁰¹ Together, these physical and biological barriers constitute the first line of defense against intestinal inflammation.

Microbial metabolites further play a pivotal role in maintaining the structural and functional integrity of the mucosal barrier. Among them, butyrate is one of the most critical. Beyond serving as a major energy source for epithelial cells, it enhances barrier integrity by epigenetically upregulating tight junction proteins such as occludin, claudins, and ZO-1.^{102–103} Butyrate also activates GPR41/43/109A receptors, suppresses the NF- κ B inflammatory cascade, and promotes the differentiation of Tregs, thereby restraining excessive immune responses.^{104–105} Under dysbiotic conditions, however,

potential pathobionts such as Enterobacteriaceae can expand rapidly, triggering TLR4-mediated inflammation and accelerating barrier damage.

In addition, tryptophan metabolism plays a pivotal role in maintaining mucosal barrier homeostasis. Microbiota-derived indole compounds activate the host aryl hydrocarbon receptor (AHR), which stimulates group 3 innate lymphoid cells (ILC3s) to produce IL-22, thereby enhancing mucin secretion and AMP expression and strengthening both the mucus layer and the physical barrier.¹⁰⁶⁻¹⁰⁷ Bile acid metabolites similarly modulate epithelial homeostasis and local inflammatory thresholds via FXR- and TGR5-mediated signaling.¹⁰⁸ Akkermansia muciniphila is known to promote mucus turnover; however, in dysbiotic mouse models, it paradoxically accelerates mucus thinning,¹⁰⁹ suggesting that its beneficial effects are highly dependent on the microenvironment. Germ-free mouse studies further demonstrate that the absence of commensal microbes leads to reduced tight junction proteins, a compromised mucus layer, and dysregulated ILC3 and Treg populations.¹¹⁰ Remarkably, short-term correction of these abnormalities can be achieved through administration of cytokine-expressing engineered bacteria.

The dynamic crosstalk between the immune system and the gut microbiota is not only essential for preserving homeostasis but also provides novel therapeutic entry points for IBD. Clinical studies have shown that fecal microbiota transplantation (FMT) restores the dominance of Firmicutes and Bacteroidetes, enhances the metabolic activity of butyrate-producing bacteria, upregulates tight junction proteins, decreases intestinal permeability, and alleviates symptoms in patients with IBD.¹¹¹ Meanwhile, targeting immune-mediated signaling pathways has also demonstrated the capacity to rebuild barrier integrity. For instance, probiotic formulations containing Faecalibacterium prausnitzii have been shown in animal models to promote AMP secretion, stabilize the mucus layer, and reduce IL-1 β and TNF- α levels, thereby mitigating DSS-induced acute colitis.¹¹²

Furthermore, therapeutic strategies aimed at metabolic pathways are emerging as a new frontier for precision treatment in IBD. Sodium butyrate supplementation, AHR agonists, and modulation of secondary bile acid metabolism have each been demonstrated to reinforce barrier architecture and lower inflammatory susceptibility.¹¹³⁻¹¹⁵ Elucidating the molecular mechanisms governing the microbiota-immune-barrier axis will not only refine our understanding of IBD pathophysiology but also accelerate the development of microbiota-based precision interventions.

Interactions between the immune system and gut microbiota in healthy individuals

Microbiota-driven regulation of immune system development. The gut microbiota plays a central role in the development and maintenance of the host immune system. Through the production of microbial metabolites and signaling molecules, the microbiota shapes immune cell differentiation, tissue localization, and effector functions, thereby exerting long-lasting influences on mucosal immune homeostasis. Accumulating evidence indicates that microbiota-derived AHR ligands activate downstream pathways that promote neutrophil recruitment to the mucosal surface and maintain epithelial barrier integrity. Moreover, microbial cues support the maturation and positioning of lymphoid tissue inducer (LTi) cells and ILC3s, contributing to the fine-tuned regulation of the Th17/Treg axis and mucosal immune balance.¹¹⁶⁻¹¹⁷

Emerging evidence further indicates that microbiota-derived metabolites and bile acid signaling contribute to the activation of ILC2s and eosinophils via receptors such as FXR and TGR5, thereby shaping the mucosal immune environment and enhancing host defense capacity.¹¹⁸⁻¹²⁰ In addition, ROR γ t-expressing cells within mesenteric lymph nodes (MLNs) function as antigen-presenting cells that facilitate the differentiation of Tregs, promoting local immune tolerance and restraining inflammatory responses.¹²¹

Studies in germ-free animals demonstrate that the absence of intestinal microbiota leads to impaired development of macrophages, dendritic cells, and lymphocytes, resulting in profound defects in immune function.¹²² However, it is equally important to recognize that commensal microorganisms are not universally beneficial. In the context of HIV infection, resident gut microbes have been shown to drive the expansion of CCR5⁺CD4⁺ T cells, increasing viral target cell availability and accelerating immune exhaustion.¹²³ Moreover, immune deficiency predisposes the host to opportunistic infections, which in turn exacerbate immune dysregulation.¹²⁴ Together, these

findings highlight the integral role of the gut microbiota in establishing and modulating immune plasticity through diverse metabolic and receptor-mediated pathways. While maintaining immune homeostasis under physiological conditions, the microbiota may conversely contribute to immune perturbation under specific pathological circumstances.

Immune selection of commensal microbiota and the establishment of immune tolerance. The host immune system possesses the capacity to distinguish pathogenic microbes from commensal residents, thereby initiating distinct immune responses. Among innate immune cells, neutrophils are the most abundant and serve as primary regulators of gut microbiota-immune homeostasis. They eliminate invading pathogens through phagocytosis, reactive oxygen species (ROS) production, and granule release, while also secreting chemokines and cytokines to orchestrate inflammatory responses.¹²⁵ Nevertheless, excessive neutrophil activation can inadvertently cause tissue injury.¹²⁶

Concurrently, the resident gut microbiota actively modulates immune signaling to sustain its stable colonization. Bifidobacterium breve, for instance, promotes the secretion of IL-10 and IL-27 by dendritic cells via the TLR2/MyD88 pathway, which subsequently induces IL-10-producing Tr1 cells and fosters the establishment of immune tolerance.¹²⁷⁻¹²⁸ Furthermore, immune effector molecules, including AMPs and members of the Regenerating islet-derived protein 3 (Reg3) family, play essential roles in maintaining spatial segregation between microbes and the lamina propria, thereby preventing unnecessary immune activation.¹²⁹

In addition, environmental factors such as nutrient gradients, oxygen partial pressure, and pH within the intestinal lumen generate heterogeneous ecological niches that determine the colonization advantages of different microorganisms.¹³⁰ The longitudinal gradients of oxygen tension and pH along the gut axis result in striking differences in microbial composition and immune interaction patterns between the small intestine and colon (as shown in Figure 2). Moreover, early-life events, long-term dietary habits, and antibiotic exposure exert persistent effects on microbial colonization and the establishment of immune tolerance.¹³¹ Within the gut microbial ecosystem, sex hormones exert particularly prominent selective regulatory effects. Estrogen can modulate epithelial barrier integrity and mucus secretion through estrogen receptor-mediated signaling, thereby indirectly shaping the microbial colonization landscape.¹³² Androgen-mediated enhancement of Toll-like receptor expression and antimicrobial peptide secretion in intestinal immune cells further imposes selective pressures on microbial community structure.¹³³

INTERPLAY BETWEEN THE IMMUNE SYSTEM AND GUT MICROBIOTA IN THE PATHOGENESIS OF IBD

The initiation and progression of IBD are driven by a dynamic imbalance between the host immune system and the gut microbiota. As the first line of mucosal defense, the immune system maintains microbial homeostasis by recognizing pathogen-associated molecular patterns (PAMPs). Once this equilibrium is disrupted, aberrant inflammatory signaling can be triggered, leading to epithelial barrier dysfunction and a self-amplifying immune response.

Emerging evidence suggests that, during the early stage of disease, dysbiosis may impair host homeostasis through immune evasion, compromised barrier integrity, and localized chronic inflammation. As the disease advances, this imbalance further facilitates regional inflammatory spread, stromal infiltration, and vascular translocation, ultimately establishing a persistent and systemic inflammatory network (e.g. Table 2). The development of IBD exhibits distinct temporal characteristics-transitioning from localized mucosal inflammation to widespread immune activation and relapsing disease activity (as illustrated in Figure 3).

Interaction between the immune system and gut microbiota in the initial stage of IBD

Promotion of immune evasion. Under normal physiological conditions, immune cells can recognize and eliminate cells expressing aberrant antigens, exerting strong surveillance pressure and preventing excessive inflammation.¹⁴⁴ Increasing evidence indicates that the gut microbiota contributes to this immunoregulatory process. Microbial dysbiosis can

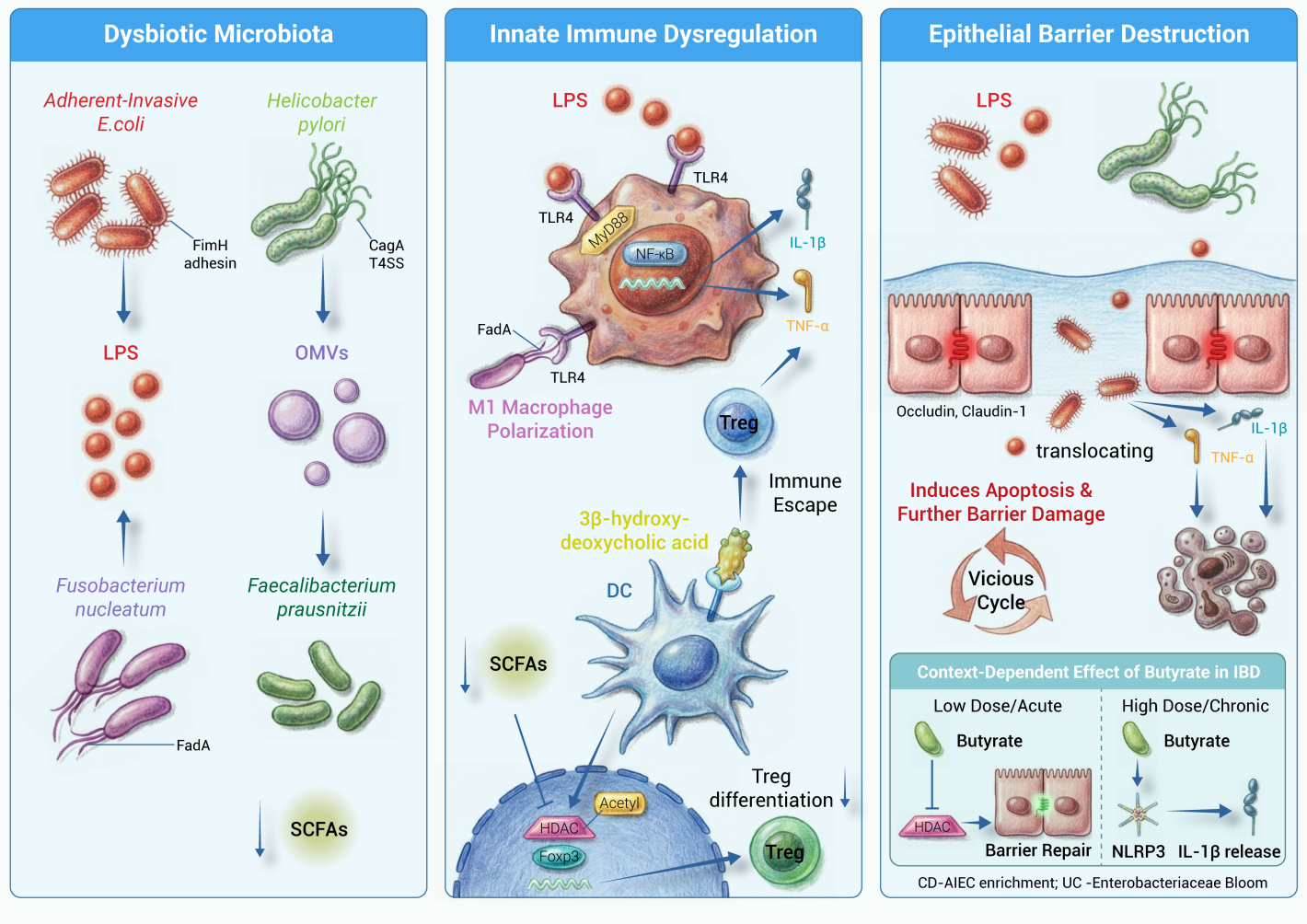


Figure 2. Microbiota dysbiosis-driven innate immune dysregulation and epithelial barrier destruction in IBD Dysbiotic taxa such as *adherent-invasive E. coli*, *Fusobacterium nucleatum*, and *Helicobacter pylori* release virulence factors including LPS, OMVs, FimH, and FadA that activate TLR4-MyD88-NF-κB signaling, promoting M1 macrophage polarization and elevated TNF-α/IL-1β production. Reduced SCFAs impair dendritic cell tolerance induction and Treg differentiation, facilitating immune escape. Meanwhile, epithelial tight junctions (occludin, claudin-1) are disrupted, enabling bacterial translocation and further barrier damage, forming a vicious inflammatory cycle. Butyrate exerts context-dependent effects in IBD, supporting barrier repair at low/acute levels while promoting NLRP3 activation and IL-1β release under chronic high-dose conditions.

suppress immune cell activity and promote the establishment of an immunosuppressive inflammatory microenvironment in local tissues.

Mechanistically, *Fusobacterium nucleatum* activates the TLR4/NF-κB/S100A9 signaling axis, driving M2 macrophage polarization and dampening anti-inflammatory responses.¹³⁵ *Klebsiella pneumoniae* represses IKK-NF-κB activity while activating the STAT6-KLF4-IL-10 pathway, thereby promoting M2 skewing and weakening macrophage-mediated inflammatory control.¹³⁶ Additionally, transforming growth factor-β (TGF-β) induces Foxp3 expression, leading to the expansion of immunosuppressive T cells that inhibit effector T-cell and dendritic-cell function through TRAF6-dependent mechanisms, ultimately facilitating inflammatory immune evasion.¹⁴⁵⁻¹⁴⁶

In the early phase of inflammation, TGF-β can also exert anti-inflammatory effects by enhancing cell-cycle arrest and apoptosis through the activation of ataxia-telangiectasia mutated (ATM) and p53 signaling.¹⁴⁷ However, whether modulation of dysbiosis-induced immune suppression can be therapeutically leveraged to restore anti-inflammatory immunity remains uncertain.

Several pathobionts, including *F. nucleatum* and *K. pneumoniae*, regulate cytokine production and recruit M2-like macrophages, thereby creating a microenvironment conducive to inflammation progression.¹³⁵⁻¹³⁶ Furthermore, the gut microbiota differentially regulates the transcriptional profiles of M1 and M2 macrophages.⁶⁰ Collectively, these findings imply that targeting gut microbiota composition to redirect macrophage polarization may represent a promising immunotherapeutic strategy for inflammatory bowel disease.

Impaired barrier integrity and disrupted interactions with the gut microbiota. Immune dysregulation within the gut microbiota compromises the

mucosal barrier, thereby promoting the onset and progression of intestinal inflammation. The expansion of certain microbial species may contribute to chronic, self-sustaining inflammatory responses. Specifically, *Candida albicans* triggers glycolysis and IL-7 secretion to stimulate group 3 innate lymphoid cells to produce IL-22, which aggravates inflammation, disrupts epithelial integrity, and exacerbates IBD pathology.^{148,137}

Diet- or genetically induced obesity-related shifts in gut microbial composition are characterized by an increased abundance of Gram-positive species, elevating levels of the bacterial metabolite deoxycholic acid (DCA). Under specific environmental conditions, DCA promotes a senescence-associated secretory phenotype (SASP) in hepatic stellate cells and enhances inflammatory signaling, ultimately contributing to DNA damage and IBD development in murine models.¹⁴⁹

16S rRNA profiling of intestinal mucosal tissue revealed enrichment of *Fusobacterium nucleatum* and depletion of *Streptococcus* species in patients with IBD relative to healthy controls, suggesting their potential value as microbial markers of disease activity and inflammatory progression.¹⁵⁰ Transcriptomic analyses further demonstrated that inflammation-associated signatures in IBD strongly correlate with an increased abundance of specific taxa, particularly *Streptococcus* and *Veillonella*.¹⁵¹ In vitro, these organisms activate major inflammatory pathways-including NF-κB and MAPK-to drive pro-inflammatory cytokine expression.¹⁵² Consistently, germ-free or antibiotic-treated mice exhibit attenuated inflammation in chemically induced colitis models.¹⁵³

Within the complex intestinal microenvironment of IBD, localized ecologi-

Table 2. Dysbiosis-associated microbial taxa and their immunological mechanisms contributing to IBD initiation and progression.

Microbial taxa	Target immune cells	Mechanisms	References
<i>Fusobacterium nucleatum</i>	Macrophages	Activates TLR4/NF- κ B/S100A9 signaling to drive M2 macrophage polarization and suppress anti-inflammatory responses, thereby exacerbating intestinal inflammation	134
<i>Klebsiella pneumoniae</i>	Macrophages	Inhibits IKK-NF- κ B but activates STAT6-KLF4-IL-10 signaling, inducing M2 polarization with reduced anti-inflammatory capacity and promoting IBD progression	135
<i>Peptostreptococcus anaerobius</i>	Macrophages	Enhances immunosuppressive macrophages and TAM expansion via TLR2/TLR4 pathways, impairing anti-inflammatory responses and worsening inflammation	136
<i>Candida albicans</i>	Macrophages	Enhances glycolysis and IL-7 production, driving ILC3-derived IL-22 secretion that disrupts epithelial barrier integrity and aggravates IBD	137
<i>Lactobacillus rhamnosus</i>	Dendritic cells	Promotes IL-12 production by DCs, enhances T-cell activation and Treg responses, contributing to immune homeostasis and alleviating intestinal inflammation	138
<i>Akkermansia muciniphila</i>	Dendritic cells	Activates DCs and promotes IL-12 secretion, thereby enhancing Treg responses and mitigating IBD inflammation	139
<i>Lactobacillus reuteri</i>	Regulatory T cells	Inosine-mediated enhancement of Treg suppressive capacity reduces excessive Th1/Th2 activation and alleviates inflammation	140
<i>Streptococcus mutans</i>	Dendritic cells	Activates TLR2/NF- κ B signaling in DCs, inducing IL-23 production and driving Th17 differentiation, thereby amplifying intestinal inflammation	141
<i>Clostridium perfringens</i>	T cells	Toxin-mediated activation of T cells promotes Th17 differentiation and exacerbates inflammation	142
<i>Clostridium perfringens</i>	Dendritic cells	Toxins activate DCs and induce Th17 polarization, reinforcing mucosal inflammatory responses	142
<i>Faecalibacterium prausnitzii</i>	Dendritic cells	SCFA secretion inhibits DC activation, promotes Treg differentiation, and reduces intestinal inflammation	143

cal niches selectively enrich microbial communities adapted to those specific sites. Dysbiosis destabilizes the mucosal barrier, activates local immune responses, and fuels a cascade of inflammation. This creates a detrimental feedback loop that amplifies epithelial barrier disruption and immune imbalance, accelerating IBD progression. Despite considerable advances, the precise mechanisms governing microbiota-immune interactions at the mucosal barrier remain incompletely understood, warranting deeper mechanistic investigations and the exploration of microbiota-targeted interventions as therapeutic strategies in IBD.

Exacerbation and sustained potential of chronic inflammation. While genetic alterations establish the molecular basis for inflammation, residual or subclinical inflammation during remission may further drive disease exacerbation. The intestinal microbiota can amplify inflammatory responses by infecting and activating immune cells-including macrophages, monocytes, neutrophils, and dendritic cells. These cells detect PAMPs or damage-associated molecular patterns (DAMPs) via TLRs on their membranes, leading to increased production of pro-inflammatory cytokines such as TNF- α and IL-1.¹⁵⁴⁻¹⁵⁵

Specifically, *Fusobacterium nucleatum*, *Peptostreptococcus anaerobius*, and *Enterococcus faecalis* activate TLR2/4 signaling through their adhesion proteins, resulting in NF- κ B activation and the upregulation of pro-inflammatory cytokines and adhesion molecules, which promote leukocyte recruitment to inflamed sites.^{134-135,143} Recruited neutrophils then release reactive oxygen species (ROS), causing DNA damage and genomic instability, which further intensify tissue injury and inflammatory amplification.¹⁵⁶ Additionally, bacterial metabolites may serve as pro-inflammatory mediators. In individuals consuming high-fat diets, *Clostridium* species generate increased levels of bile acids such as 3 β -hydroxy-deoxycholic acid, which has been implicated in exacerbating inflammation in IBD.⁷⁰

A substantial body of research has demonstrated that inflammatory cells and cytokines present within inflamed mucosa promote genomic alterations and immunosuppressive conditions. Evidence from IBD mouse models suggests that chronic inflammation and dysbiosis synergistically contribute to disease progression. Notably, sodium tungstate has been shown to restrict Enterobacteriaceae overgrowth, thereby suppressing intestinal inflammation and alleviating IBD-related symptoms.¹⁵⁷ Within such an immunosuppressive environment, enhancing host immune responses may aid in inflammation resolution. For example, microbial-derived stimulator of interferon genes (STING) agonists can induce type I interferon (IFN-I) production by monocytes and polarize M0 macrophages toward a pro-inflammatory M1 phenotype, thereby counteracting the immunosuppressive microenvironment.¹⁵⁸

Immune-microbiota interactions driving the translocation of inflammation in IBD

Mucosal barrier disruption and inflammatory propagation. Disruption of the mucosal barrier and the persistent outward expansion of inflammation represent core pathological features of IBD. As the local inflammatory response extends into the perimucosal stroma, inflammation progresses from a confined mucosal process to deeper tissue involvement-an "invasive" stage of disease exacerbation.¹⁵⁹ A key molecular event underlying this progression is EMT, in which intestinal epithelial cells shift from a polarized, tightly connected epithelial phenotype to a more migratory mesenchymal state.¹⁶⁰ Aberrant activation of EMT compromises the integrity of tight junctions, destabilizes the intestinal barrier, and facilitates disease advancement.

Evidence from Crohn's disease mucosal lesions has demonstrated classical EMT signatures, including reduced expression of E-cadherin and increased levels of vimentin in intestinal epithelial cells.¹⁶¹⁻¹⁶² Multicenter cohort studies employing immunohistochemistry, Western blotting, and single-cell transcriptomics in resected or biopsy specimens consistently show pronounced downregulation of the epithelial adhesion molecule E-cadherin, alongside upregulated mesenchymal markers such as vimentin and the EMT-inducing transcription factors Snail and Slug. These alterations are paralleled by decreased tight junction protein expression and reduced transepithelial electrical resistance (TEER), providing functional corroboration of barrier compromise. Notably, EMT activation correlates positively with both disease severity and chronicity.¹⁶³⁻¹⁶⁵

By promoting epithelial depolarization, loosening of cell-cell contacts, and increased mucosal permeability, EMT enables easier translocation of luminal microbes and their metabolites across the intestinal barrier. This breach stimulates lamina propria immune cells, including macrophages and dendritic cells, leading to amplified mucosal inflammation and further propagation of tissue damage.¹⁶⁶⁻¹⁶⁷

In this context, gut microbiota dysbiosis is not simply a downstream consequence of inflammation but also a pivotal driver of barrier disruption and chronic inflammatory persistence. Alterations in microbial composition, characterized by reduced mucosa-associated commensals and an overgrowth of opportunistic pathogens, can induce or reinforce epithelial-mesenchymal transition (EMT) through multiple pathways. Under dysbiotic conditions, bacterial structural components such as lipopolysaccharide and various metabolites may penetrate the impaired epithelium and activate intracellular NOD- and TLR-dependent signaling. This subsequently triggers EMT-related cascades including TGF- β /SMAD and β -catenin pathways, thereby exacerbating epithelial damage and sustaining inflammatory

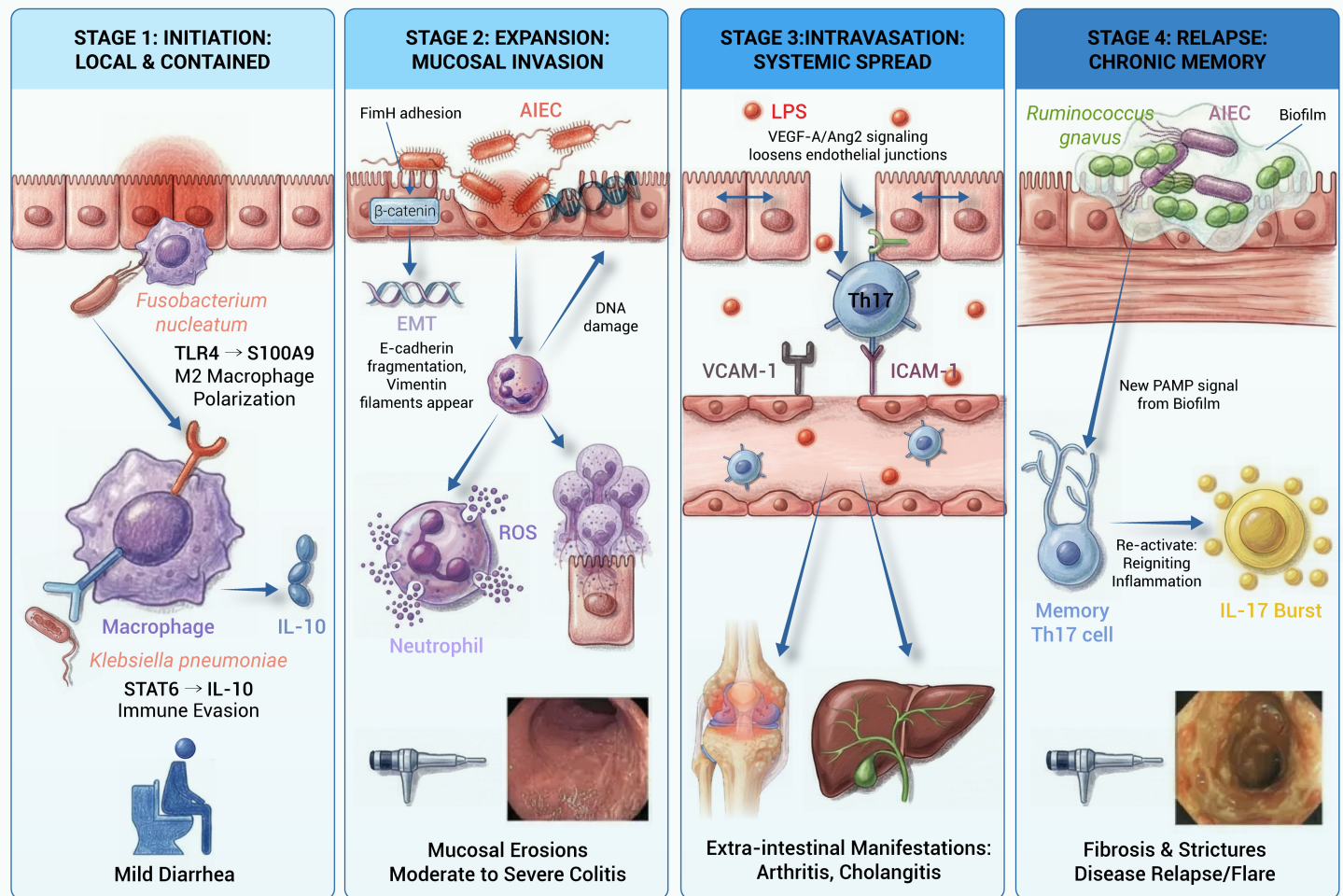


Figure 3. Sequential progression of inflammatory bowel disease from local initiation to systemic spread and chronic relapse This figure illustrates a four-stage model of IBD development. Stage 1 involves local inflammation with macrophage activation driven by dysbiotic bacteria such as *Fusobacterium nucleatum* and *Klebsiella pneumoniae*, resulting in mild diarrhea. Stage 2 is characterized by mucosal invasion, epithelial-mesenchymal transition (EMT), DNA damage, neutrophil infiltration, and mucosal erosions. Stage 3 features systemic dissemination with elevated LPS and Th17 recruitment through endothelial ICAM-1/VCAM-1 signaling, leading to extra-intestinal manifestations, including arthritis and cholangitis. Stage 4 reflects chronic relapse driven by biofilm-associated bacteria such as AIEC and *Ruminococcus gnavus*, which trigger IL-17 bursts and persistent memory Th17 activation, resulting in fibrosis, strictures, and recurrent disease flares.

responses.¹⁶⁸⁻¹⁶⁹ In parallel, macrophages and dendritic cells secrete pro-inflammatory mediators that further amplify EMT in epithelial cells, contributing to diminished mucosal repair capacity, increased permeability, and a perpetuated inflammatory microenvironment.¹⁷⁰⁻¹⁷¹

Beyond inflammation, EMT is tightly linked to fibrotic progression. In IBD, repetitive cycles of injury and repair allow epithelial or mesenchymal cells undergoing EMT to acquire migratory properties and enhanced extracellular matrix secretion, driving fibrosis and luminal narrowing in the submucosa and muscularis propria.¹⁷²⁻¹⁷³ Meanwhile, microbial components and metabolites act as catalytic factors in this process. For example, *Streptococcus* species and their products activate MyD88/NF-κB and TLR5 signaling to promote fibroblast activation, suggesting that fibrosis and barrier impairment may proceed independently even after inflammation is clinically controlled.^{135,141} Thus, chronic inflammation should not be viewed merely as transient mucosal damage but as a pathological state emerging from persistent disequilibrium across microbial, immune, and epithelial barrier networks.

Overall, chronic inflammation in IBD reflects a mutually reinforcing loop driven by microbiota-immune-barrier interplay. Dysbiosis compromises epithelial integrity, facilitating EMT activation and pro-inflammatory immune responses, which in turn perpetuate barrier dysfunction and inflammatory propagation. This mechanistic framework not only explains the relapsing and refractory nature of IBD but also highlights potential therapeutic intervention points. Targeting these critical nodes may offer new strategies to interrupt the chronic progression trajectory of the disease.

Endovascular transmigration-driven inflammatory spread. During the

chronic progression of IBD, the sustained disruption of intestinal epithelial integrity results in a highly permeable mucosal barrier. Under these conditions, luminal bacteria, their metabolites, and pro-inflammatory mediators readily traverse the epithelial layer, infiltrate the lamina propria, and further “transmigrate” into the vascular or lymphatic compartments. This process has emerged as a critical driver of systemic inflammatory dissemination and exacerbated mucosal injury in IBD.¹⁷⁴ Recent findings suggest that such “endovascular inflammatory transmigration” is tightly orchestrated by the microbiota-epithelium-immune axis and exhibits remarkable dynamic plasticity.

Several gut commensals can enhance the endothelial expression of adhesion molecules, thereby facilitating immune cell trafficking and translocation of microbial components across the vascular wall. For instance, adherent-invasive *Escherichia coli* activate host intracellular signaling pathways and induce marked upregulation of ICAM-1 and VCAM-1 on endothelial cells.¹⁷⁵⁻¹⁷⁶ These molecules promote the adhesion and transendothelial migration of monocytes and Th17 cells, intensifying both local and systemic inflammation. Similarly, Shigella-like strains and certain *Bacteroides* species disrupt the organization of endothelial tight junctions by altering JAM-A and Claudin-5 expression, consequently increasing vascular permeability.¹⁷⁷⁻¹⁷⁸

Microbial structural components synergize with immune cells to amplify this pathological process. Lipopolysaccharide (LPS) and flagellin potently activate dendritic cells, macrophages, and ILC3s, enhancing their production of pro-inflammatory cytokines.¹⁷⁹⁻¹⁸⁰ These inflammatory mediators expand mucosal damage and compromise endothelial stability via VEGF, Ang2/Tie2, and CXCL1/CXCR2 signaling pathways, collectively promoting the transvas-

Table 3. Ongoing and completed clinical trials targeting microbiota-based interventions for inflammatory bowel disease.

Type	NCT Number	Stage	Sample Size	Intervention Measures	Outcome Indicators
FNT	NCT03106844	II	50	Faecal bacterial transplantation	Number of Participants With FMT Failure
FNT	NCT03104036	II	61	Faecal bacterial transplantation	Clinical remission
FNT	NCT03078803	II	38	Faecal bacterial transplantation	Clinical and Endoscopic Remission
FNT	NCT01896635	II	81	Faecal bacterial transplantation	Composite Clinical remission & Endoscopic remission / response as measured by Mayo subscores
Probiotics	NCT03565939	II	119	Trichuris suis ova	Remission (Full Mayo)
Probiotics	NCT04969679	IV	131	E. coli Nissle 1917	Compare and evaluate the increase in IBDQ(Inflammatory bowel disease questionnaire) score between the Mutaflor group and the Placebo group
Probiotics	NCT07180186	II	70	Mesalamine and probiotics	Clinical Activity Index
Prebiotics	NCT03950336	II	33	Prebiotics	Change in small intestinal permeability over 6 weeks
Prebiotics	NCT03800277	II	122	Cranberry; Agaves	Change in metabolic endotoxemia: Measure concentration of LPS and Lipopolysaccharide Binding Protein in plasma
Prebiotics	NCT02865707	II	89	Synergy-1	Prevention of relapse
Antibiotics	NCT04479202	IV	76	Berberine	Changes in diarrhea frequency and Bristol Stool Scale
Antibiotics	NCT01772615	IV	100	Ciprofloxacin	Compare number of participants in remission

cular passage of inflammatory stimuli.¹⁸¹ In particular, VEGF-A and Ang2 act cooperatively to loosen endothelial junctions, allowing bacterial products to breach the vascular barrier and enter systemic circulation, triggering inflammatory responses in distal organs.¹⁸²

Immune cells themselves further amplify endovascular infiltration. M1-polarized macrophages and activated Th17 cells engage adhesion molecules through high integrin expression, accelerating the intravascular trafficking of inflammatory effectors.¹⁸³ Simultaneously, Th17-derived IL-17 and IL-22 activate NF- κ B signaling in endothelial cells, forming a self-reinforcing inflammatory loop.¹⁸⁴ Mechanistically, this resembles tumor intravasation, although the principal participants here are inflammatory leukocytes and microbial products rather than malignant cells.

Interestingly, microbial drivers of this process are not uniform. Enterococcus and Bacteroides strains are more prone to inducing endothelial activation and tight-junction disruption, whereas Lactobacillus and Bifidobacterium species have been shown in animal models to attenuate VEGF and ICAM-1 expression, exhibiting a protective role against vascular infiltration.¹⁸⁵⁻¹⁸⁶ Moreover, circulating microbial antigens and inflammatory cytokines can disseminate to joints, skin, biliary structures, and the lungs, precipitating extraintestinal manifestations such as reactive arthritis, erythema nodosum, and cholangitis.¹⁸⁷ These observations highlight that vascular infiltration represents a pivotal conduit linking intestinal pathology to systemic inflammation in IBD.

Despite growing mechanistic insights into the interactions among microbiota, vasculature, and immune networks, the temporal dynamics and receptor-ligand specificity shaping this process remain incompletely defined. Current evidence relies heavily on animal studies. Future investigations employing single-cell multi-omics and spatial transcriptomics are urgently needed to delineate the fine-scale regulatory architecture of inflammatory transmigration, ultimately enabling the development of systemic therapeutic strategies for IBD.

Formation of a pre-inflammatory Niche. Recent studies have increasingly recognized that IBD is not merely confined to chronic inflammation within the intestinal mucosa. Instead, dysbiosis and persistent immune activation in the gut can propagate systemic signals that reshape the immune microenvironment of distant organs¹⁸⁸, establishing a latent "pre-inflammatory niche." This primed condition renders extraintestinal sites such as joints, liver, and skin highly susceptible to inflammatory responses even before overt clinical manifestations emerge.¹⁸⁷

During the course of chronic intestinal inflammation, disrupted microbial homeostasis compromises the integrity of the mucosal barrier, leading to continuous exposure of PAMPs to the mucosal immune system. Adherent-

invasive Escherichia coli (AIEC) and Enterococcus spp. can penetrate the epithelial barrier, activating the TLR4/MyD88-dependent NF- κ B and IL-6/STAT3 pathways and triggering a substantial release of proinflammatory cytokines.¹⁷⁵ Some of these inflammatory mediators disseminate through the circulation, promoting endothelial activation and upregulation of adhesion molecules in distant tissues-facilitating the recruitment of monocytes and Th17 cells. Such covert immune activation is increasingly considered a key prerequisite for extraintestinal manifestations of IBD, including arthritis and primary sclerosing cholangitis.

Microbial metabolites serve as crucial modulators within this process. Disrupted homeostasis of SCFAs and altered secondary bile acid profiles influence immunological equilibrium in the liver and peripheral tissues via receptors such as GPR43, FXR, and TGR5. Expansion of Clostridium scindens has been shown to promote hepatic recruitment of NKT cells, accompanied by enhanced IL-13 and IL-4 expression, thereby escalating local immune activation.¹³⁴ In contrast, gut-derived metabolites such as indole-3-propionic acid can attenuate NF- κ B signaling and ROS production, demonstrating a protective role against systemic inflammatory propagation.⁸¹

Dysbiosis also drives hematopoietic skewing in the bone marrow, pushing the immune system into a state of "pre-activation." Chronic low-grade systemic exposure to LPS biases monocyte progenitors toward proinflammatory phenotypes, forming a readily mobilizable immune reservoir.¹⁸⁹ This primed immunologic background allows excessive and rapid responses upon secondary stimuli in peripheral tissues. Notably, depletion of Akkermansia muciniphila has been closely linked to these hematopoietic abnormalities, while its restoration can partially normalize immune cell composition,¹⁹⁰ underscoring a bidirectional regulatory relationship between the gut microbiota and host hematopoiesis.

At the tissue level, endothelial and stromal cells in distant organs are also influenced by gut-derived inflammatory cues. Increased expression of chemokines such as CCL2 and CXCL10 in the liver and synovium markedly lowers the threshold for inflammatory cell recruitment.¹⁹¹ Concurrent upregulation of adhesion molecules including ICAM-1 and VCAM-1 further facilitates immune cell adhesion and infiltration.¹⁹² Notably, this heightened inflammatory vulnerability is not incidental but rather reflects the cumulative consequences of chronic dysregulation along the gut-immune-metabolic axis.

Recolonization and reactivation of inflammatory cells. The relapsing nature of IBD highlights an inherent "memory-like" feature of the inflammatory microenvironment. Even during clinical remission, the intestinal mucosa retains immune-imprinted and metabolically primed cell populations, allowing external stimuli to rapidly trigger inflammatory reactivation. Recent single-

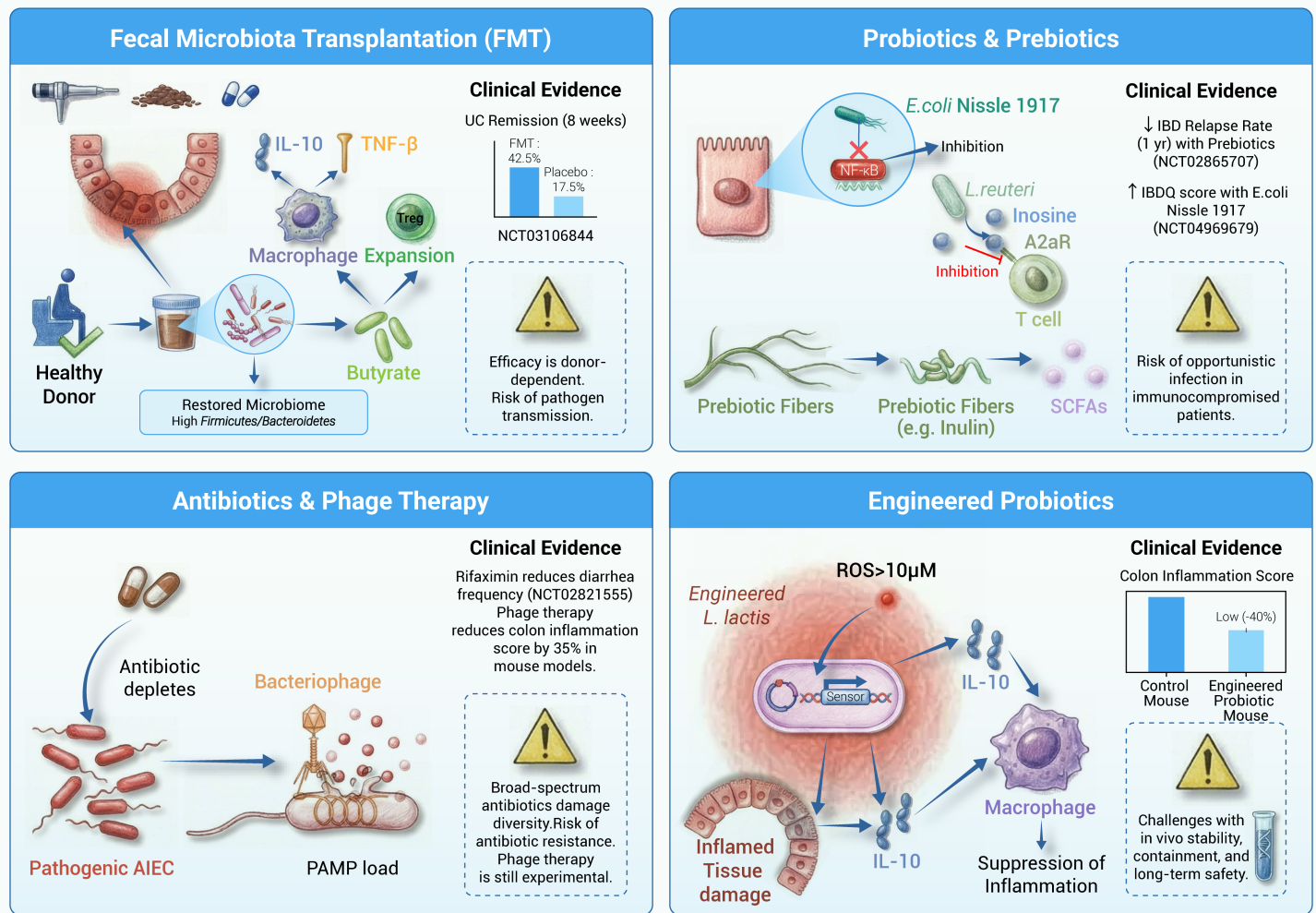


Figure 4. Microbiota-targeted therapeutic strategies and clinical evidence in IBD This figure summarizes four major microbiota-based interventions for IBD. FMT restores microbial composition and increases butyrate-producing species, expanding IL-10⁺ Treg responses, although efficacy is donor-dependent. Probiotics and prebiotics suppress NF-κB activation and promote SCFA production, with clinical trials showing reduced relapse risk. Antibiotics and bacteriophage therapy reduce pathogenic AIEC burden but carry risks of dysbiosis and antibiotic resistance. Engineered probiotics detect inflammatory signals such as ROS and deliver IL-10 to locally suppress inflammation, showing promising preclinical outcomes. Together, these strategies highlight evolving approaches for precision microbiome modulation.

cell studies have revealed a plastic symbiotic state between gut microbiota and immune cells that sustains a "latent inflammatory niche".¹⁹³ Reconstruction of this niche depends on microbiota-driven immune cell recolonization and functional reprogramming, forming a fundamental basis for chronic persistence and episodic flares in IBD.

In the remission phase, certain mucosa-associated or exopolysaccharide-producing bacteria, such as *Akkermansia muciniphila*, *Ruminococcus gnavus*, and adherent-invasive AIEC, can disrupt the mucus barrier and expose epithelial glycan receptors, promoting dendritic cell and monocyte-macrophage re-accumulation within the lamina propria.¹⁹⁴⁻¹⁹⁵ Under the influence of metabolic cues from SCFAs and secondary bile acids, these cells acquire a "quasi-inflammatory phenotype," lying between resting and fully activated states. Their metabolic profile is characterized by enhanced oxidative phosphorylation and fatty acid oxidation, conferring heightened sensitivity to TLR stimulation.¹⁹⁶ When exposed to renewed microbial signals such as LPS or flagellin, they rapidly activate the IL-1β/IL-23 axis, promote Th17 expansion, and initiate localized immune amplification.

Memory T cells in the mucosa also play a pivotal role in reigniting inflammation. Multiple studies report long-lived Th17 and Tc17 cells residing in mesenteric lymph nodes and the lamina propria of patients in remission, expressing high levels of CCR6 and integrin α4β7.¹⁹⁷⁻¹⁹⁸ Their homing behavior is regulated by microbiota-derived metabolites—particularly indole derivatives—which activate AhR signaling and IL-22 production, facilitating the re-entry of memory T cells into the epithelial compartment. Upon re-encounter with commensal antigens, these cells rapidly transition into effector states

and release IL-17, TNF-α, and GM-CSF, driving tissue injury and inflammatory relapse.

In parallel, the interaction between AIEC and epithelial NOD2 receptors is considered a molecular trigger for disease reactivation.¹⁹⁹⁻²⁰⁰ Under hypoxic and nitrate-rich conditions, AIEC rebuilds biofilm structures that activate epithelial NF-κB and induce IL-8 secretion, recruiting neutrophils and monocytes. Re-activated M1 macrophages subsequently produce ROS and IL-6, amplifying inflammatory cascades. Meanwhile, *R. gnavus*-derived adhesive polysaccharides promote IgA immune complex deposition, intensifying mucosal immune stimulation and epithelial stress responses.

Importantly, microbial influence on immune reactivation is bidirectional. *Bacteroides fragilis* polysaccharide A can induce Treg re-differentiation and suppress Th17 expansion via IL-10 production, thereby restoring immune tolerance.²⁰¹ Restorative colonization by *Lactobacillus* and *Bifidobacterium* species enhances tight junction integrity and raises the threshold for pro-inflammatory signaling.¹⁸⁵⁻¹⁸⁶ Thus, IBD relapse fundamentally reflects a dynamic disequilibrium among microbial composition, immune memory, and metabolic networks. From a systems-level perspective, the cyclical process of recurrent inflammation may be interpreted as a phenomenon of immune-microbiota resynchronization. Immune recolonization driven by fluctuations in the gut microbiota may maintain the intestinal immune system in a persistently "semi-activated" state. This concept not only helps explain the clinical observation that IBD frequently relapses after periods of remission, but also provides new perspectives for therapeutic intervention.

Microbiota-targeted strategies, such as FMT and probiotic-based thera-

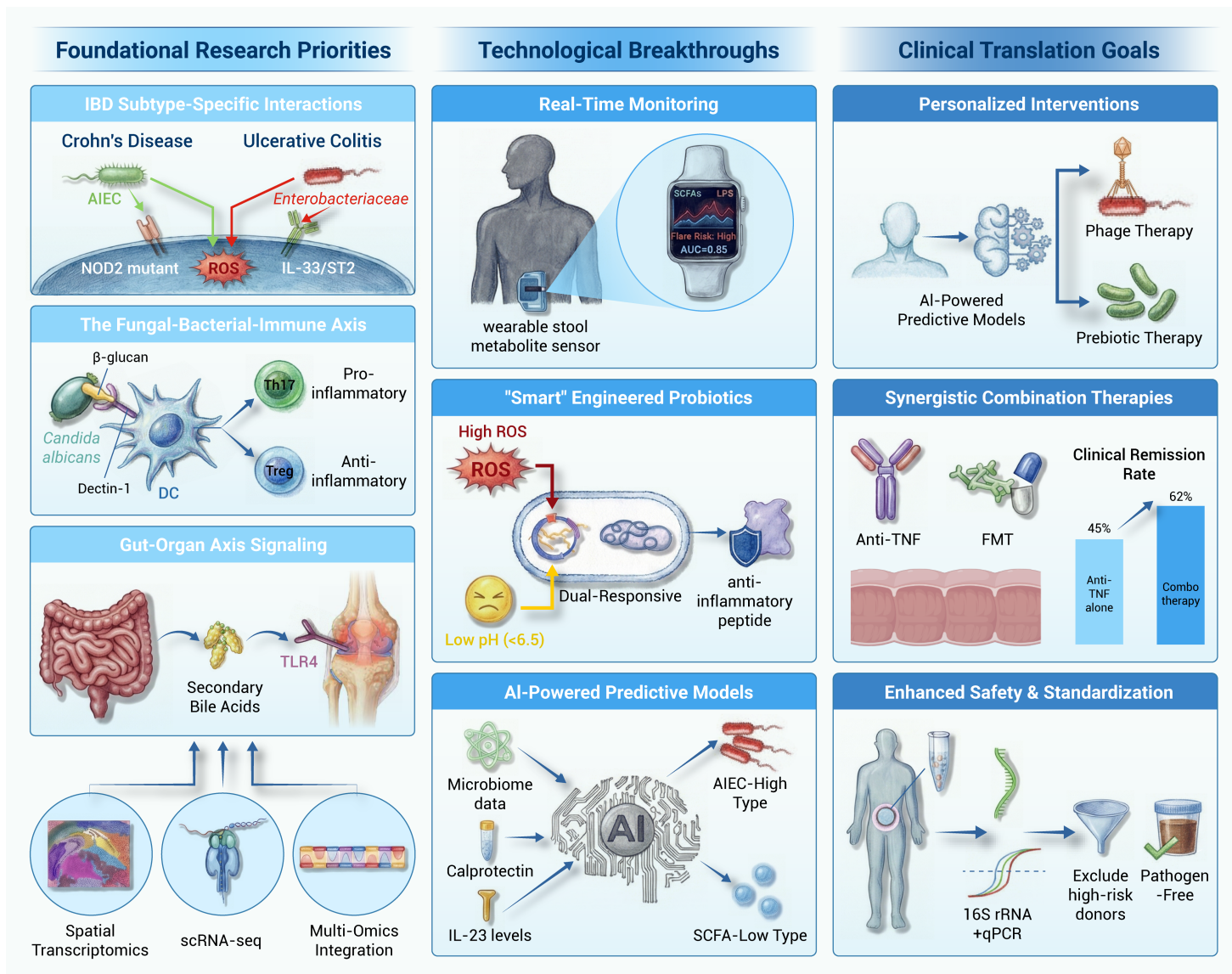


Figure 5. Future research priorities, technological innovations, and clinical translation goals for microbiota-immune regulatory strategies in IBD This figure summarizes the future directions of microbiota-based interventions in IBD, including: (i) foundational research priorities focusing on subtype-specific host-microbe interactions and cross-kingdom immune regulation; (ii) emerging technological breakthroughs such as real-time metabolite monitoring, dual-responsive engineered probiotics and multi-omics integration; and (iii) clinical translation goals emphasizing personalized therapy, synergistic combination strategies, and enhanced safety and standardization.

pies, have not yet been shown to directly eliminate pathogenic memory T cells. Nevertheless, these interventions may reduce persistent microbial antigenic stimulation by reshaping microbial community structure and metabolic environments, while restoring mucosal immune homeostasis, thereby limiting the reactivation of memory T cells. In addition, alterations in the gut microbiota may influence the maintenance of inflammatory memory by modulating the Th17/Treg balance and associated anti-inflammatory signaling pathways. As our understanding of microbiota-specific immune responses continues to deepen, future research may enable more precise modulation of this "memory effect" by targeting key microbial taxa, microbial antigens, or metabolic pathways, ultimately reducing the long-term risk of relapse in IBD.

Modulation of innate and adaptive immunity by the gut microbiota in IBD

During the chronic and relapsing inflammatory course of IBD, the interaction between the gut microbiota and the immune system is not a linear cause-effect relationship but rather a dynamically reshaped equilibrium. Accumulating evidence indicates that the microbiota does not passively revert to homeostasis during inflammation resolution; instead, it actively contributes to the reconstruction of immune architecture.

At the innate immune level, re-colonization by commensal communities

alters the activation thresholds of resident immune cells. For instance, polysaccharide A from *Bacteroides fragilis* can activate TLR2 signaling in dendritic cells to induce IL-10 production, thereby stabilizing peripheral Tregs.²⁰¹ In contrast, adhesive bacterial strains frequently detected in IBD can chronically stimulate the NLRP3 inflammasome, resulting in persistent IL-1 β and TNF- α release and preventing epithelial barrier repair.²⁰² This coexistence of "healing yet reactivation" is a defining pathological hallmark that underlies the difficulty of achieving durable remission in IBD.

At the level of adaptive immunity, shifts in microbiota-derived metabolites further remodel immune polarization. Reduced SCFAs weaken histone deacetylase inhibition and contribute to Th17/Treg imbalance, whereas the restoration of *Faecalibacterium prausnitzii* or *Roseburia* species can partially reverse this trend. Meanwhile, metabolites produced by lactic acid bacteria and *Akkermansia muciniphila* activate the AhR pathway to elevate IL-22 levels, promoting epithelial regeneration.

Notably, mucosal healing in the late phase of chronic inflammation often exhibits a pattern of "compensatory immune excess." In murine colitis models, conditional pathobionts such as *Enterococcus faecalis* expand during the recovery stage and stimulate residual M1 macrophages to secrete ROS and IL-6, leading to a mismatch between tissue regeneration and inflammation suppression.²⁰³ This localized immune reactivation embeds a

persistent “inflammatory memory,” where clinical remission does not necessarily translate into full restoration of immunological homeostasis.

Collectively, the microbiota-immune interaction network in IBD is not a simple dichotomy of pathogenicity versus protection. Rather, it represents a temporally sculpted, inflammation-driven dynamic system. Re-colonization patterns, metabolic redistribution, and immune repolarization together form the implicit logic of mucosal reconstruction. Future investigations should shift from single-pathway descriptions to multi-omics-based dynamic mapping to elucidate the true trajectory of microbiota-mediated immune rebalancing during inflammation resolution.

ADVANCES IN MICROBIOTA-BASED CLINICAL INTERVENTIONS AND IMMUNE MODULATION

The gut microbiota engages in highly intricate and dynamic interactions with the host immune system, and its dysbiosis is increasingly recognized as a major driver of chronic inflammation and immune dysregulation in IBD. Recent clinical research has shifted from mechanistic exploration toward therapeutic validation, with RCTs serving as the gold standard for assessing the efficacy and safety of microbiota-modulating strategies. Current intervention approaches include FMT, probiotics, prebiotics, antibiotics, and emerging modalities such as bacteriophage therapy and genetically engineered probiotics (e.g. Table 3). These interventions exhibit distinct yet complementary modes of action in reshaping immune responses, restoring mucosal barrier function, and alleviating intestinal inflammation, thereby establishing an integrated microbiota-immune therapeutic framework. Representative strategies and supporting clinical evidence are illustrated in Figure 4.

FMT: A systemic intervention to restore immune homeostasis

FMT currently represents the most clinically translatable strategy for microbiota reconstruction. Its core objective is to reestablish microecological balance and immune homeostasis in the host by transferring a complete, healthy intestinal microbial community from a donor. Multiple phase II randomized controlled trials have demonstrated that FMT significantly improves clinical remission rates in patients with IBD, and some studies have further reported concurrent endoscopic remission and mucosal healing (NCT03106844, NCT03078803). Recent evidence suggests that FMT restores SCFA-related metabolic pathways, inducing IL-10 and TGF- β secretion by dendritic cells and macrophages, thereby maintaining Treg homeostasis.²⁰⁴ Meanwhile, FMT attenuates excessive TLR4/NF- κ B activation, reduces pro-inflammatory cytokine release, and suppresses pathological Th17 differentiation.²⁰⁵

Preclinical studies have shown that FMT reestablishes IL-22 production by intestinal ILC3s, enhances the expression of epithelial tight junction proteins, and promotes the repair of barrier integrity.²⁰⁶ Single-cell transcriptomic analyses further reveal that FMT shifts intestinal CD8⁺ T cells from an inflammatory phenotype toward a reparative phenotype, highlighting the coupling between immune phenotypes and metabolic plasticity.^{207–208} Emerging findings indicate that metabolic rewiring induced by FMT shapes immune-signaling pathways, providing new therapeutic avenues for IBD management.²⁰⁹ Metabolomic profiling shows that increases in butyrate and secondary bile acids following FMT positively correlate with Treg activation, whereas aberrant accumulation of lactate and succinate is associated with excessive Th17 activation.^{16,210}

Despite its promise, FMT still faces substantial challenges in clinical application. Microbial discrepancies between donors, heterogeneous immune baselines of recipients, and varying routes of FMT administration contribute to inconsistent therapeutic outcomes. Moreover, long-term immune safety data remain insufficient, particularly regarding the risks of excessive immune tolerance or latent pathogen transmission.

Probiotic intervention: Long-term training of mucosal immunity

The primary role of probiotic intervention lies not merely in short-term modulation of the gut microbiota but in the long-term “training” of the host mucosal immune system. Phase II–IV clinical trials (NCT04969679) have demonstrated that specific probiotic strains, administered alone or in combination with mesalamine, achieve clinical remission rates comparable to stan-

dard therapies while maintaining excellent tolerability. Another clinical study (NCT07180186) indicated that probiotics, when combined with standard care, reduce clinical disease activity scores and drive intestinal CD4⁺ T cells toward an anti-inflammatory phenotype (IL-10⁺/FoxP3⁺). Mechanistically, probiotics enhance mucosal barrier function by promoting IL-10, IL-22, and secretory IgA production through pattern-recognition receptor signaling, thereby supporting epithelial repair and restoring tight junction integrity.²¹¹ Probiotics also regulate macrophage polarization, suppressing pro-inflammatory M1 responses while promoting the M2 reparative phenotype to maintain mucosal homeostasis.²¹²

In addition, certain strains reinforce oxidative phosphorylation, stabilize FoxP3 expression, and sustain metabolic homeostasis of regulatory T cells, thereby mitigating inflammation progression in UC animal models.²¹³ Recent studies further reveal the intricate immunoregulatory network of probiotics: *Lactobacillus rhamnosus* GG activates the epithelial STAT3-IL-22 axis, enhancing epithelial regeneration and local immune tolerance.²¹⁴ Multi-strain formulations have been shown to rebalance the Th17/Treg ratio and reduce disease relapse risk, underscoring their potential role in long-term maintenance therapy.²¹⁵

Prebiotics and antibiotic interventions: Microbial reset and immune reprogramming

Prebiotics and antibiotics represent two complementary strategies for modulating the gut microbiome in the clinical management of IBD. Prebiotics provide fermentable substrates that selectively stimulate the growth and metabolic activity of beneficial bacteria, thereby indirectly regulating host immune responses.²¹⁶ Phase II clinical trials have demonstrated that inulin, fructooligosaccharides, and cranberry polyphenols (NCT03950336, NCT03800277) improve intestinal permeability and reduce plasma LPS levels, ultimately alleviating chronic immune activation. Long-term prebiotic supplementation (NCT02865707) not only significantly lowers the recurrence rate of IBD but also elevates short-chain fatty acid (SCFA) production, enhances the anti-inflammatory capacity of regulatory T cells (Tregs), and promotes IL-10 secretion, collectively supporting mucosal immune homeostasis. Consistently, murine studies have shown that inulin enhances IL-22 secretion by type 3 innate lymphoid cells (ILC3s), upregulates tight junction proteins, and facilitates epithelial barrier repair.²¹⁷

Antibiotics primarily act by selectively eliminating pathogenic bacterial taxa, enabling microbiota resetting in IBD management. Short-term treatment with ciprofloxacin (NCT01772615) or berberine (NCT04479202) has been shown to alleviate diarrhea and reduce mucosal inflammation. Mechanistically, the reduction of specific pathobionts dampens TLR4/NF- κ B signaling and decreases pro-inflammatory cytokine release, thereby attenuating Th17-mediated mucosal inflammation. However, prolonged or broad-spectrum antibiotic use may disrupt microbial diversity, impair SCFA production and mucosal healing capacity,²¹⁸ and ultimately increase relapse risk.

Combined prebiotic-antibiotic interventions offer a promising approach for microbial and immune reprogramming in IBD. Recent clinical studies indicate that this strategy simultaneously supports the expansion of beneficial taxa, enhances Treg and ILC3 functions, and suppresses pathogen-associated inflammatory pathways, achieving synergistic therapeutic benefits.²¹⁹ Furthermore, SCFAs promoted by prebiotics can functionally complement pathogen depletion induced by antibiotics to optimize barrier integrity and immune tolerance, presenting a potential direction for personalized IBD therapy.

Phage therapy: Precision microbial modulation and immunoregulatory potential

Phage therapy, characterized by its high specificity in targeting pathogenic bacterial strains, provides a unique strategy for precision manipulation of the gut microbiota and is increasingly regarded as a promising breakthrough in the post-antibiotic era. Although large-scale RCTs are still lacking, exploratory studies have demonstrated that phages can markedly reduce the abundance of pro-inflammatory pathobionts such as adherent-invasive AIEC, thereby indirectly attenuating mucosal immune activation. The underlying mechanisms include the reduction of pathogen-associated molecular pattern (PAMP) signals and suppression of TLR4-dependent pathways, ultimately decreasing macrophage-derived IL-1 β and TNF- α production and restoring

intestinal homeostasis.²²⁰⁻²²¹

Moreover, phage-derived bacterial debris can act as an “immune noise modulator,” reshaping antigen-presenting environments in the gut epithelium and facilitating the establishment of immune tolerance. In murine models, phage administration significantly elevates IL-10 expression, expands Treg populations, and suppresses Th17-driven mucosal inflammation.²²² Further evidence suggests that phage-mediated interventions regulate local immune stability through the PD-L1 pathway, supporting the concept of concurrent microbiota and immune modulation.²²³⁻²²⁴ Collectively, these findings highlight that phage therapy not only enables precise ecological control but may also promote immune tolerance, offering a novel therapeutic avenue for IBD management.

Engineered probiotics: Targeted immune homeostasis and precision intervention

Engineered probiotics represent the evolution of microbiota-based therapy from broad ecological manipulation toward precise immune modulation. Through genetic engineering, these bacteria can be programmed to produce anti-inflammatory mediators—such as IL-10, TGF- β , or immunoregulatory peptides—specifically within inflamed intestinal niches, thereby promoting targeted restoration of immune homeostasis.²²⁵ Early experimental studies revealed that *Lactococcus lactis* engineered to express IL-10 significantly reduces colonic inflammation scores, inhibits NF- κ B activation, and increases Treg cell frequencies, ultimately improving mucosal tolerance.²²⁶

Recent advances have introduced “smart-response circuits,” enabling engineered strains to activate anti-inflammatory effector expression only upon detection of inflammation-associated cues such as nitrate or reactive oxygen species (ROS), thus minimizing systemic immunosuppression.²²⁷ In preclinical models, such bacteria can be combined with immune checkpoint inhibitors or anti-TNF agents, resulting in enhanced therapeutic efficacy and delayed resistance development.²²⁸ Additionally, engineered probiotics can modulate metabolic-immune signaling, achieving dual regulation of microbiota composition and host immune balance—for example, by strengthening Treg metabolic fitness through adenosine receptor pathways, suppressing pro-inflammatory Th17 responses, and aiding mucosal barrier repair.²²⁹

Notably, the therapeutic effects of microbial metabolites in IBD are often highly context-dependent. SCFAs, particularly butyrate, exert anti-inflammatory and barrier-protective functions under physiological conditions by promoting epithelial energy metabolism, enhancing the expression of tight junction proteins, and inducing the differentiation of regulatory T cells. However, under conditions of chronic inflammation, these metabolites may exert opposing effects by altering the metabolic state of immune cells or activating specific inflammatory signaling pathways. Therefore, future studies are needed to further define the optimal concentration ranges of key metabolites across different disease stages, microbial community structures, and host immune states, as well as to explore more controllable delivery strategies to improve the safety and therapeutic efficacy of microbiome-based interventions.

Overall, evidence from RCTs and emerging experimental studies highlights the bidirectional interplay between microbiota remodeling and immune regulation. Approaches such as FMT and probiotic therapies promote immune tolerance primarily through the restoration of ecological homeostasis. In contrast, prebiotics and antibiotics provide metabolic and ecological support for microbiota modulation, whereas bacteriophages and engineered bacteria represent promising future directions for precise immunomodulation. Future research should integrate multi-omics and single-cell technologies to systematically elucidate the dynamic feedback mechanisms between microbiota-based interventions and host immune networks. Particular attention should also be given to dose optimization and inter-individual variability, which will be critical for advancing personalized immuno-microbiota therapeutic strategies for IBD.

CONCLUSION AND FUTURE PERSPECTIVES

The gut microbiota modulates the development and function of the host mucosal immune system through bacterial components, metabolic products, and various signaling mediators. Conversely, the immune system selectively recognizes intestinal microorganisms to maintain immune tolerance or elimi-

nate pathogenic species. This bidirectional and dynamic interaction profoundly influences the onset of inflammatory bowel disease (IBD), the progression of chronic inflammation, and the risk of relapse. Although the potential of the gut microbiota in maintaining immune homeostasis and enhancing therapeutic responses in IBD has been increasingly recognized, clinical translation remains challenging.

To date, most findings have been derived from animal studies or small-scale clinical investigations. Once administered into the human gastrointestinal tract, exogenous microbial interventions such as fecal microbiota transplantation or probiotics inevitably interact with the complex resident microbial ecosystem, which may alter therapeutic outcomes. Therefore, the use of humanized mouse models that better recapitulate the characteristics of the human gut microbiota, together with rigorously designed, large-scale randomized controlled trials, will be essential for advancing this field.²³⁰ As illustrated in Figure 5, future research should focus on dissecting core mechanisms, refining microbial strain selection, and optimizing safety and precision in clinical applications.

Differences in study populations, methodological approaches, and statistical analyses continue to limit the reproducibility and generalizability of gut microbiota-based interventions in IBD. Rapid advances in bioinformatics have opened new avenues to address these challenges. In particular, machine learning algorithms can help identify key microbial taxa and metabolites, elucidate their immunoregulatory roles, and predict disease relapse or therapeutic responses. For example, microbiota-derived machine learning models have shown promising performance in predicting relapse risk in ulcerative colitis and evaluating response to FMT.²³¹

However, microbiota-targeted therapies still face safety concerns, including infection related to FMT, opportunistic infections induced by probiotic use in immunocompromised patients, and broad-spectrum antibiotic-driven dysbiosis,²³²⁻²³⁴ all of which restrict widespread clinical application. Emerging technologies may help overcome these barriers. Strategies such as enhanced donor screening and real-time pathogen surveillance, engineered probiotics, and bacteriophage-based precision therapy have the potential to enable personalized interventions while minimizing microbiota-associated adverse effects.

Future research should place greater emphasis on the dynamic regulatory mechanisms governing the interaction between the gut microbiota and the immune system, particularly the roles of inflammatory memory and long-term immune cell reprogramming in IBD relapse. With the rapid development of multi-omics technologies, the integration of metagenomics, metabolomics, and single-cell transcriptomics will enable deeper insights into the complex interaction networks between microorganisms and host immunity within the intestinal microenvironment. The application of these emerging technologies is also expected to accelerate the development of precision therapeutic strategies targeting the gut microbiome, including interventions directed at microbial metabolic pathways, engineered probiotics, and personalized FMT.

In addition, the gastrointestinal tract exhibits pronounced spatial heterogeneity in microbial composition and immune landscapes. For example, Crohn's disease frequently involves the terminal ileum, whereas ulcerative colitis is primarily confined to the colon and rectum. Consequently, future microbiome-based interventions may need to incorporate region-specific strategies, such as targeted delivery systems or localized microbial modulation, to achieve more precise therapeutic outcomes in IBD.

However, several key challenges remain for advancing this field. These include addressing the substantial heterogeneity between animal models and the human gut microbiome, establishing research frameworks capable of real-time monitoring of microbiota dynamics and immune responses, and developing strategies that effectively suppress inflammation while preserving intestinal immune tolerance. Furthermore, the standardization of experimental methodologies and data-analysis pipelines will be essential for improving the reproducibility and comparability of microbiome research. Addressing these challenges will provide a stronger theoretical foundation and facilitate the clinical translation of microbiota-based precision interventions for IBD.

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AUTHOR CONTRIBUTIONS

Tao Zhang, Zhetan Ren, and Feng Feng contributed equally to this work. Tao Zhang was primarily responsible for drafting the manuscript. Zhetan Ren mainly contributed to the preparation of figures. Feng Feng contributed to both manuscript writing and figure preparation. Ru Man, Longfei Shao, Hongkun Zhang, and Xiaozhen Cheng contributed to data collection, literature review, and provided support for the development of research ideas. Lei Gong, Jirun Peng, and Yongduo Yu, as corresponding authors, conceived and designed the overall research framework, supervised the research process, and revised the manuscript. All authors contributed to the manuscript and approved the final version.

DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.