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Review article

Gut microbiota and its importance in the management of inflammatory bowel disease: A promising pathway to better health

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ABSTRACT

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract. The gut microbiota plays a crucial role in the development and progression of IBD. In IBD patients, the composition of the gut microbiota is significantly different from that of healthy individuals. Dysbiosis, an imbalance of beneficial and harmful bacteria, is a hallmark of IBD. The development of microbiota-targeted treatments requires a comprehensive understanding of the gut microbiota composition, its interaction with the host immune system, and its role in the pathogenesis of IBD. This review discusses the prospects for microbiome-based therapies in IBD. Pre- and probiotics, as well as faecal microbiota transplant (FMT), are examples of microbiome-targeted treatments. These approaches are predicated on the idea that reestablishing a healthy gut microbiome might reduce mucosal inflammation. The fundamental components of commensal gut bacteria's metabolism are known as prebiotics. Probiotics are supplements that artificially introduce gut microorganisms that are believed to have positive effects on the surrounding microenvironment and may even help with IBD symptom relief. FMT is a more direct way of introducing bacteria than probiotics, yet the same bacteria are present in the bodies of healthy people at larger concentrations. Current evidence suggests that microbiome-targeted therapeutics may have some benefit for IBD. With advancements in technology and research, microbiota-targeted treatments have the potential to revolutionize the management of IBD and improve clinical outcomes for patients.

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1. Introduction

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the gastrointestinal tract that includes two subtypes: Crohn's disease (CD) and ulcerative colitis (UC) [1]. The incidence of IBD is increasing rapidly, and its pathogenesis is influenced by multiple factors, including genetic susceptibility, immune dysfunction, and gut microbiota [2]. The gut microbiota refers to the complex community of microorganisms that reside in the human gastrointestinal tract, including bacteria, viruses, protozoa, and fungi. The composition and diversity of the gut microbiota play a crucial role in the development and progression of IBD [3, 4].

The gut microbiota consists primarily of bacteria, with over 1,000 species residing in the gastrointestinal tract. These bacteria have important functions in host homeostasis, including nutrient metabolism, immune regulation, and defense against pathogens [5]. In IBD patients, the gut microbiota composition differs significantly from that of healthy individuals [6]. Dysbiosis, characterized by an imbalance between beneficial and harmful bacteria, is a hallmark of IBD [7, 8]. Specific bacteria, such as *Bacteroides fragilis*, *Ruminococcus torques*, and *Ruminococcus gnavus*, have been found to be enriched in IBD patients. The excessive increase in the prevalence of mucolytic bacteria, specifically Ruminococcus gnavus, could potentially contribute to the development of inflammatory bowel disease (IBD) by providing nourishment for non-mucolytic bacteria that are associated with the mucosa. This could explain the overall increase in the number of bacteria associated with the mucosa in individuals with IBD. These alterations usually involve a decrease in bacterial diversity and an over-representation of pro-inflammatory bacterial species, such as *Escherichia coli* and *Fusobacterium*. These changes can perpetuate inflammation in the GI tract, leading to increased intestinal permeability and immune dysregulation [9]. A vital aspect of the gut microbiota's role in our lives is the breakdown of complex carbohydrates found in plant-based foods. These substances cannot be digested by human enzymes alone. Our microbial allies break these carbohydrates down into short-chain fatty acids (SCFAs), which nourish the cells lining our gut and contribute to reducing inflammation throughout the body [10, 11]. Perhaps one of the most compelling aspects of the gut microbiota is its impact on our immune system. The gut is home to approximately 70% of our immune cells, underscoring its importance as a nexus for human health. The microbes that inhabit our intestines interact with these immune cells and help train them to recognize harmful pathogens while coexisting peacefully with beneficial microbes. By fostering diversity within our microbial cityscape, we can cultivate resiliency against potential invaders like harmful bacteria or viruses. One surprising connection between the gut microbiota and overall health lies in its influence on mental well-being. Scientists have discovered a link, commonly called the gut-brainaxis, between the bacteria residing in our intestines and various neurochemicals regulating mood, anxiety, and stress responses [12].

Understanding the role of the gut microbiota in the pathogenesis of IBD is crucial for developing personalized approaches to treat this complex disease. This review aims to explore the composition and diversity of the gut microbiota in IBD, the interaction between the microbiota and the intestinal epithelial barrier, the role of microbiota-derived metabolites in IBD, the interaction between immune cells and the microbiota, and the microbiota-targeted treatment options for IBD.

2. Microbiota Composition and IBD

Microbiota composition has been a topic of interest in recent years, as research has shown that the microorganisms living in and on the human body can significantly impact health. The composition and diversity of the gut microbiota play a crucial role in the development of IBD. In IBD patients, the gut microbiota is characterized by dysbiosis, which refers to an imbalance between beneficial and harmful bacteria. Dysbiosis in IBD patients is more pronounced than in healthy individuals [13, 14]. The dysbiosis of the gut microbiota in IBD patients can lead to a breakdown in the intestinal barrier, which can result in the translocation of bacteria and their products into the bloodstream. This can trigger an immune response, leading to chronic inflammation and tissue damage. Studies have shown that the levels of beneficial bacteria, such as *Bifidobacterium longum*, *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis*, are significantly reduced in IBD patients compared to healthy controls. Harmful bacteria, such as *Bacteroides fragilis*, are more abundant in IBD patients [15, 16].

The abundance and composition of specific bacterial species vary between CD and UC patients. For example, *Ruminococcus torques* and *Ruminococcus* are enriched in both CD and UC patients at the onset of the disease [9]. *Actinomyces* spp., *Veillonella* spp., and *Escherichia coli* increase in CD patients, while *Eubacterium rectum* and *Akkermansia muciniphila* decrease. *Eubacterium rectum* is enriched in UC patients, while *Akkermansia muciniphila* is decreased [17, 18]. These differences in bacterial composition between CD and UC patients may contribute to the different clinical manifestations and treatment responses observed in these subtypes of IBD (Table 1).

Adherent-invasive *Escherichia coli* (AIEC) linked with CD have the ability to enter epithelial cells and undergo replication within macrophages, potentially leading to the development of chronic experimental colitis [27, 28]. *Klebsiella pneumoniae*, a member of the Enterobacteriaceae family, was isolated from a patient diagnosed with Crohn's disease. This particular strain of *K. pneumoniae* has been found to produce experimental colitis and elicit a significantly heightened Th1 immune response when compared to other control strains and species [29].

Table 1: Abundance of Gut microbiota and their metabolites in IBD subtypes relative to healthy people

IBD subtypes	Gut microbiota or metabolite	Abundance compared with healthy people	References
UC	*Bifidobacterium longum*	Low	[19]
UC & CD	*Eubacterium rectale*	Low	[19]
UC & CD	*Faecalibacterium prausnitzii*	Low	[19]
UC & CD	*Roseburia intestinalis*	Low	[19]
UC & CD	*Bacteroides fragilis*	High	[19]
UC & CD	*Ruminococcus torques*	High	[9]
UC & CD	*Ruminococcus*	High	[9]
UC & CD	*Clostridium hathewayi*	High	[9]
UC & CD	*Clostridium bolteae*	High	[9]
UC & CD	*Ruminococcus gnavus*	High	[9]
CD	*Christensenellaceae*	Low	[17]
CD	*Coriobacteriaceae*	Low	[17]
CD	*Clostridium leptum*	Low	[17]
CD	*Actinomyces*	High	[17]
CD	*Veillonella*	High	[17]
UC & CD	*Escherichia coli*	High	[17]
UC	*Eubacterium rectum*	Low	[17]
UC	*Akkermansia muciniphila*	Low	[17]
UC & CD	*Intestinibacter*	High	[20]
CD	*Coprococcus*	Low	[20]
UC & CD	*Blastocystis*	Low	[21]
UC & CD	*Sphingolipids*	High	[22]
UC & CD	Bile acid	High	[23]
UC & CD	Triacylglycerol	Low	[22]
UC & CD	Tetrapyrrole	Low	[22]
UC & CD	SCFAs	Low	[24]
UC & CD	Tryptophan	High	[25]
UC & CD	N-acyl ethanol amin	High	[26]

The strains of *Fusobacterium varium* derived from patients with UC exhibit a greater propensity to penetrate epithelial cells when compared to strains obtained from healthy individuals. Moreover, these UC-derived strains have been found to induce experimental colitis [30]. On the other hand, certain species of *Clostridium* have been suggested as potential anti-inflammatory microorganisms. Clostridia represent a significant proportion of intestinal microorganisms, constituting more than 60% of bacteria linked with the mucosa [31]. Certain resident species of Clostridium have the ability to generate SCFAs and elicit the development of colonic regulatory T cells (Tregs), as well as IL-10-producing B cells and macrophages, hence protecting against experimental colitis [32, 33].

Genetic factors also play a role in shaping the gut microbiota composition in IBD patients. Certain genes, such as Caspase recruitment domain family member 9 (CARD9), Nucleotide binding oligomerization domain containing 2 (NOD2), Autophagy related 16 like 1 (ATG16L), Immunity related GTPase M (IRGM), and Fucosyltransferase 2 (FUT2), have been found to be associated with alterations in the gut microbiota composition [19]. The genetic variants affecting the immune system can influence the gut microbiota and contribute to the pathogenesis of IBD [34]. The interplay between genetic susceptibility, environmental factors, and the gut microbiota is complex and requires further investigation to fully understand its role in IBD.

3. Microbiota Interact with the Intestinal Epithelial Barrier in IBD

The intestinal epithelial barrier plays a crucial role in maintaining gut homeostasis and preventing the invasion of harmful microorganisms. Dysbiosis of the gut microbiota can disrupt the integrity of the intestinal epithelial barrier, leading to increased permeability and inflammation [35]. The dysregulated immune response in IBD patients can further exacerbate the damage to the intestinal epithelial barrier [36]. Growing evidence suggests that glycosylation of intestinal epithelial cells results in an increase in the expression of truncated O-glycans and a change in the expression of terminal glycan structures. Changes in glycan composition can disrupt the mucosal

layer and immunity, thereby contributing to the development of IBD [37]. The destruction of tight junction proteins causes damage to the intestinal mechanical barriers.

The interaction between the gut microbiota and the intestinal epithelial barrier is a complex process involving various factors. One of the mechanisms by which the gut microbiota interacts with the intestinal epithelial barrier is through the production of metabolites. SCFAs, such as butyric acid, propionic acid, and acetate, are important metabolites produced by the gut microbiota during the fermentation of carbohydrates and indigestible oligosaccharides [10]. SCFAs provide energy for the intestinal epithelium and have anti-inflammatory effects by regulating immune cells. Beneficial bacteria in the gut microbiota, such as *Faecalibacterium prausnitzii*, produce butyrate, which plays a protective role in IBD by inhibiting the IL-6/signal transducer and activator of transcription 3 (STAT3)/IL-17 pathway and promoting the function of regulatory T cells [38].

The gut microbiota can also produce antimicrobial peptides and bacteriocins, which help to maintain the balance between beneficial and harmful bacteria in the intestine. For example, some strains of *Lactobacillus* produce lactobacillin, which inhibits the growth of pathogenic bacteria such as *Listeria monocytogenes* [39]. *Lactobacillus acidophilus* nisin A has potent antimicrobial action against *Bacillus cereus, Staphylococcus aureus*, and *Salmonella enterica*. Therefore, it has been suggested that bacteriocins and commensal bacteria residing in the gut can establish a defensive barrier against pathogenic bacteria. By inhibiting the growth of pathogenic microorganisms and modulating the intestinal microbiota, these bacteriocins contribute to the enhancement of the immune response of the host [40].

The gut microbiota can also influence the production and secretion of immunoglobulin A (IgA), the most common antibody subtype in the intestine. IgA-coated bacteria from IBD patients can invade the mucus layer and exacerbate intestinal inflammation [41]. Breastfeeding, which contains specific components of IgA, has been shown to reduce the incidence of newborn enterocolitis [42].

In addition to metabolites and immune responses, the gut microbiota can directly interact with the intestinal epithelial cells. Some pathogenic bacteria, such as AIEC, can penetrate the mucus layer and adhere to intestinal epithelial cells, leading to inflammation and damage to the intestinal barrier [43]. Other bacteria, such as *K. pneumoniae*, can invade intestinal epithelial cells and interact with immune cells, promoting the release of inflammatory cytokines and contributing to intestinal inflammation [44]. The gut microbiota dysbiosis can also induce mitochondrial dysfunction in intestinal epithelial cells, leading to inflammation and metabolic imbalance [45].

4. Microbiota-Derived Metabolites in IBD

The gut microbiota produces a wide range of metabolites that can influence the development and progression of IBD. One of the most well-studied groups of metabolites is SCFAs, which are produced by the fermentation of dietary fibers by the gut microbiota. SCFAs, such as butyrate, propionate, and acetate, have been shown to have anti-inflammatory effects and promote intestinal homeostasis [46]. Butyrate, in particular, has been found to inhibit the IL-6/STAT3/IL-17 pathway and promote the function of regulatory T cells, thereby reducing inflammation in the intestine [38].

Bacteriocin serves as a significant antibacterial agent. The bacteria that produce bacteriocins exhibit inhibitory or competitive effects on bacteria belonging to the same species or closely related species. The secretion of enterotoxin by Enterotoxigenic *E. coli* (ETEC) has been found to increase the permeability of the intestinal epithelium, leading to the inhibition of ascorbic acid uptake through the NF-κB pathway [47].

Bile acids, which are produced by the liver and modified by the gut microbiota, also play a role in the development of IBD. The gut microbiota can modify bile acids and influence host immune responses. Bile acids can activate immune cells and regulate the balance between pro-inflammatory and anti-inflammatory responses [48]. Alterations in bile acid metabolism have been observed in IBD patients, and targeting bile acid metabolism may be a potential therapeutic strategy [49].

The gut microbiota can metabolize Tryptophan, an essential amino acid, to produce biologically active compounds. Tryptophan metabolites have been shown to have immunomodulatory effects and can regulate inflammatory responses in the gut [50]. Changes in tryptophan metabolism have been observed in IBD patients and may contribute to the pathogenesis of the disease [25].

Other metabolites produced by the gut microbiota, such as N-acylethanolamine and indole, have also been implicated in the development of IBD [26]. These metabolites can modulate immune responses and intestinal homeostasis, and targeting their production may be a potential therapeutic strategy for IBD [51].

5. Interaction Between Immune Cells and the Microbiota in IBD

The gut microbiota plays a crucial role in shaping the immune response in the intestine. Patients with IBD often have stronger immune responses, characterized by increased antibody and T-cell reactions to microbial antigens [52-54]. The beginning of IBD involves the participation of a diverse array of immune cells and inflammatory factors. Inoue *et al.* (2005) have suggested that the interaction between T-cell differentiation subgroups and the gut microbiota could potentially influence the development of IBD [55]. The protective mechanism initiated by Th cells, known as the inflammatory response, protects the host from harmful microorganisms. However, it is worth noting that the over-activation of Th cells has

been associated with the initiation and progression of intestinal inflammation [56].

Dysbiosis of the gut microbiota can disrupt the balance between pro-inflammatory and anti-inflammatory immune cells, leading to chronic inflammation in IBD. Th17 cells, a subset of T helper cells that produce the cytokine IL-17, have been implicated in the pathogenesis of IBD. Th17 cells can promote inflammation and tissue damage in the intestine. IL-17 and IL-22, two of the cytokines released by Th17 cells, are crucial in mediating immunological damage and autoimmune disorders. When acute colitis develops, IL-22 is thought to serve a protective role, but in chronic colitis, IL-22 is discovered to interact with IL17A to mediate pathogenicity. The gut microbiota can induce the differentiation of naive T cells into Th17 cells through the production of specific metabolites and the activation of immune pathways. The activation of macrophages to create IL-6 and Transforming growth factor-β (TGF-β) is initiated by necrotic intestinal mucosal cells. Necrotic intestinal mucosal cells trigger IL-6 and TGF-β production by macrophages via STAT3 and RORγt, leading to Th17 cell development. Low doses of TGF-β and IL-6 can induce Th17 differentiation in T cells. High amounts of TGF-β can reduce Th 17 cell production and increase Treg cell production. SFB causes Th17 cells to release IL-17 and IL-22 and inflame the gut. The *Clostridium* spp. produced Tregs. IBD-related genes Atg16L1 and NOD2 induced Tregs in *B. fragilis*. *B. thetaiotaomicron* mimics gut microbiota and induces T-regs to impact IBD immunity. *K. pneumoniae* increase Th1 cell induction to cause inflammation (figure 1). This activation occurs through the involvement of a Signal transducer and activator of transcription 3 (STAT3) and Retinoid related orphan receptors γ (RORγt). Consequently, the production of IL-6 and TGF-β by macrophages leads to the development of Th17 cells [57-59].

On the other hand, the gut microbiota can also promote the development of regulatory T cells (Tregs), which have anti-inflammatory properties and help to maintain immune homeostasis in the intestine. Specific bacteria in the gut microbiota, such as *Clostridium* spp. and *Bacteroides fragilis*, have been shown to induce the production of Tregs and regulate immune responses [60, 61]. The balance between Th17 cells and Tregs is critical for maintaining intestinal homeostasis, and dysregulation of this balance is associated with the development of IBD [62].

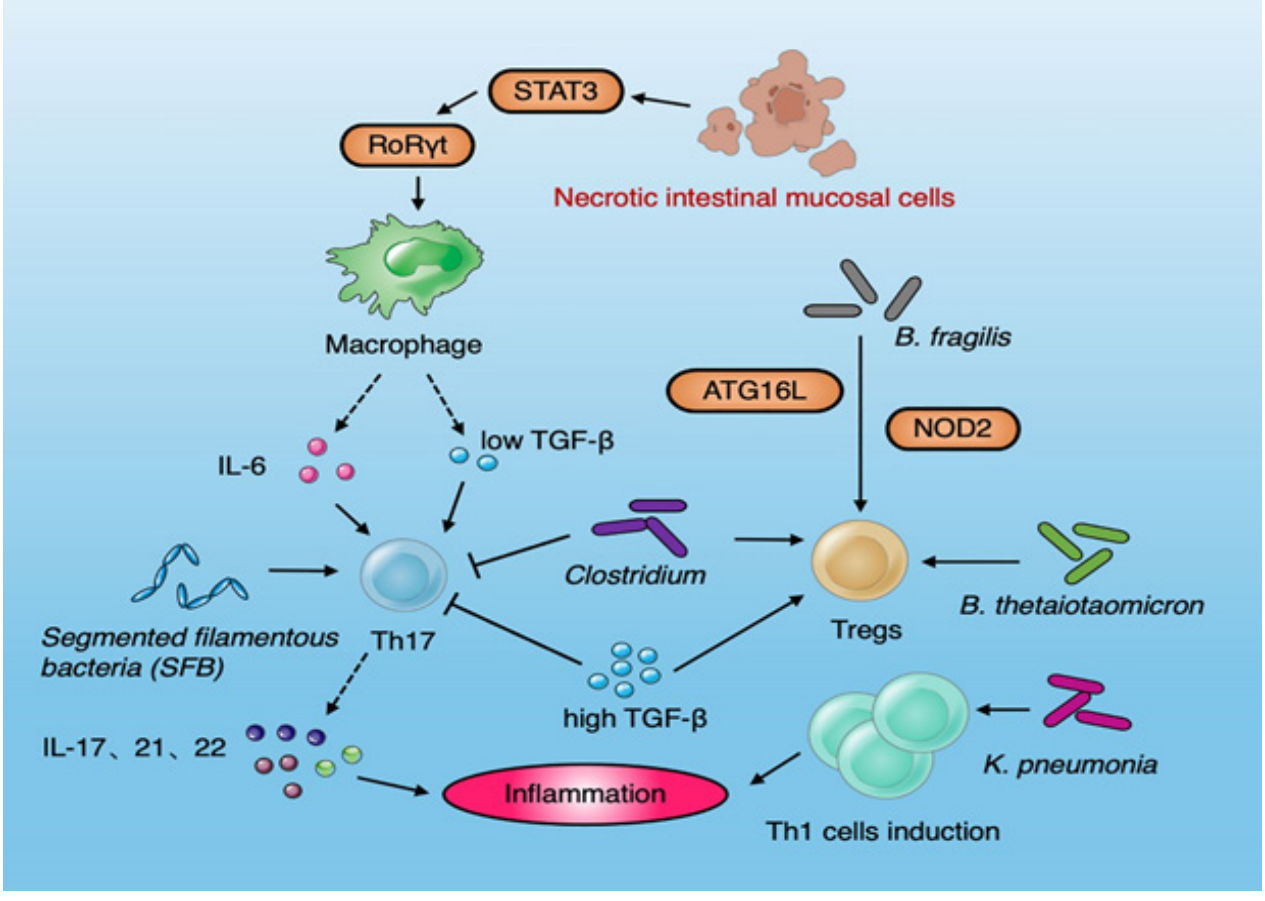

Figure 1: Model of immune cell-microbiota interaction in IBD [63].

The interaction between immune cells and the gut microbiota is complex and multifaceted. The gut microbiota can directly interact with immune cells by producing microbial antigens and activating immune receptors. These interactions can modulate immune responses and contribute to the development and progression of IBD.

6. Microbiota-Targeted Treatment in IBD

Given the important role of the gut microbiota in the pathogenesis of IBD, microbiota-targeted treatment strategies have emerged as potential therapeutic options. Probiotics, which are live microorganisms that confer health benefits to the host, have been studied for their potential in IBD treatment. Probiotics, such as *E. coli Nissle* 1917, have been shown to be beneficial in maintaining remission in UC patients [64]. FMT, which involves the transfer of fecal microbiota from a healthy donor to a patient, has also shown promising results in treating IBD [65]. FMT can restore the gut microbiota composition and improve clinical outcomes in IBD patients. Other microbiota-targeted treatments, such as the use of antibiotics, diet modification, and novel biological agents, are also being explored for their potential in IBD treatment [66-68].

Developing microbiota-targeted treatments require a comprehensive understanding of the gut microbiota composition and its role in IBD. Advances in sequencing technologies and bioinformatics have enabled researchers to characterize the composition and functional potential of the gut microbiota in IBD patients. This knowledge can help guide the development of personalized treatment strategies that target the specific dysbiosis observed in individual patients [65, 69].

7. Future Directions

Future research in the field of gut microbiota and IBD should focus on several key areas. First, there is a need for further research to elucidate the complex interactions between the gut microbiota and the host immune system. The mechanisms by which the gut microbiota modulates immune responses and contributes to the development and progression of IBD are still not fully understood. Second, developing personalized treatment strategies targeting the specific dysbiosis observed in individual patients is a promising direction for future research. The use of advanced sequencing technologies and bioinformatics tools can help identify microbial biomarkers that can predict treatment responses and guide therapeutic interventions. Third, the development of novel microbiota-targeted therapies, such as engineered probiotics and microbial metabolites, holds great potential for the treatment of IBD. These therapies can be designed to specifically modulate the gut microbiota and restore microbial homeostasis in IBD patients. Lastly, large-scale clinical trials and international collaborations are needed to validate the efficacy and safety of microbiota-targeted treatments in IBD. These studies should include long-term follow-up and comprehensive evaluation of clinical outcomes, microbiota composition, and immune responses.

In conclusion, the gut microbiota plays a crucial role in developing and treating IBD. Dysbiosis of the gut microbiota is a hallmark of IBD, and restoring microbial homeostasis is a promising therapeutic strategy. The development of microbiota-targeted treatments requires a comprehensive understanding of the gut microbiota composition, its interaction with the host immune system, and its role in the pathogenesis of IBD. Future research should focus on unraveling the complex mechanisms underlying gut microbiota-host interaction and developing personalized treatment strategies based on microbial biomarkers. With advancements in technology and research, microbiota-targeted treatments have the potential to revolutionize the management of IBD and improve clinical outcomes for patients.

Authors' contributions

ZR, LH, HH Study Conception and desgin: ZR, HH; Data Collection and/or Processing: ZR, LH; Statistical Analysis and/or Data Interpretation: LH; Literature Review: ZR, LH, HH; Manuscript drafting and Critical Review: ZR, HH: All authors read and approved the final version of manuscript.

Conflict of Interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

Ethical declarations

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