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Review article

THE ROLE OF THE GUT MICROBIOTA IN INFLAMMATORY BOWEL DISEASES

ULOGA CREVNE MIKROBIOTE U INFLAMATORNIM BOLESTIMA CREVA

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Abstract

The gut microbiota plays a crucial role in maintaining gastrointestinal balance and regulating immune system activity. Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are changes associated with significant alterations in both the composition and activity of the gut microbiota, a condition known as dysbiosis. Dysbiosis can lead to compromised mucosal barrier integrity, increased inflammation, and irregular immune system activity. Microbiota influences the development of IBD through altered short-chain fatty acid levels, lower microbial diversity, and an imbalance between protective and harmful bacterial populations. Current research continues to explore how interactions between the microbiota and immune cells contribute to the onset and persistence of inflammation. Therapies designed to adjust the gut microbiota, such as the use of probiotics, prebiotics, dietary modifications, and fecal microbiota transplantation, have shown encouraging results for symptom relief and longer remission in individuals with IBD. Enhanced knowledge of the complex microbiota role facilitates the development of tailored medical interventions and new treatment strategies for inflammatory bowel diseases.

Keywords:
microbiota, inflammatory bowel disease, dysbiosis, immune response, therapeutic modulation

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Sažetak

Mikrobiota creva igra ključnu ulogu u održavanju homeostaze gastrointestinalnog sistema i regulaciji imunološkog odgovora. Inflamatorne bolesti creva (IBC), Kronova bolest i ulcerozni kolitis povezani su sa značajnim promenama u sastavu i funkciji crevne mikrobiote – stanjem poznatim kao disbioza. Disbioza može doprineti narušenoj mukoznoj barijeri, pojačanoj inflamaciji i neadekvatnom imunološkom odgovoru. Mehanizmi putem kojih mikrobiota utiče na tok IBC obuhvataju promene u produkciji kratkolančanih masnih kiselina, smanjenu raznovrsnost mikrobiote, kao i narušavanje ravnoteže između protektivnih i patogenih bakterija. Interakcije između mikrobiote i ćelija imunog sistema, kao i njihova uloga u inicijaciji i održavanju inflamacije, predmet su intenzivnih istraživanja. Terapijski pristupi sa ciljem modulacije mikrobiote, poput upotrebe probiotika, prebiotika, dijetetskih intervencija i transplantacije fekalne mikrobiote (FMT), pokazuju potencijal u ublažavanju simptoma i produženju remisije kod pacijenata sa IBC. Razumevanje kompleksne uloge mikrobiote otvara mogućnosti za personalizovanu medicinu i razvoj novih strategija u terapiji IBC.

Ključne reči:
mikrobiota,
inflamatorne bolesti creva,
disbioza,
imunološki odgovor,
terapijska modulacija

Introduction

Inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), represents a group of chronic, recurring conditions that affect the gastrointestinal tract. The development of IBD is influenced by a multifaceted interaction between genetic predisposition, environmental triggers, immune system imbalance and alterations in the gut microbiota. Over the past two decades, accumulating research has highlighted the significant role of gut microbiota imbalance, known as dysbiosis, in the development and progression of IBD (1).

Changes in the gut microbiota associated with inflammatory bowel disease

Healthy gut ecosystems typically dominated by members of the phyla Firmicutes (e.g. *Faecalibacterium, Roseburia*), Bacteroidetes (e.g. *Bacteroides thetaiotaomicron*), Proteobacteria and Actinobacteria. Numerous studies on the human microbiome have revealed clear distinctions in gut microbial composition between individuals with IBD and healthy controls (2), leading to the conclusion that both the structure and variability of the gut microbiota play a crucial role in the pathogenesis of IBD (3,4). Decreased microbial diversity along with a reduction in beneficial Firmicutes and Bacteroidetes species and an increased abundance of Proteobacteria has been reported in IBD patients, particularly those with active disease (5). The shift in gut microbiota composition occurs during the initial phases of IBD. Microbiome composition fluctuations tend to be more significant in individuals with IBD than in healthy people (6). Compared to UC, CD is associated with a more pronounced disruption of the gut microbiota. (7,8). In comparison with healthy individuals, patients with both CD and UC show a notable reduction in beneficial bacterial species, including *Eubacterium rectale*, *Faecalibacterium prausnitzii*, and *Roseburia intestinalis*. These genera play a key role in producing short-chain fatty acids (SCFAs), which are known for their anti-inflammatory properties (9,10). Additionally, IBD patients' microbiota is characterized by reduced levels of and weakened adhesion of *Lactobacillus* species to epithelial cells (11). A significant reduction in the number of mucosa-associated *Bifidobacterium* has also been reported in patients with UC, while individuals with CD exhibit notably lower levels of specific *Bifidobacterium* species, including *B. bifidum*, *B. longum*, *B. adolescentis*, and *B. dentium* (10,11). At the same time, potentially harmful bacteria *Bacteroides fragilis* shows increased abundance and growth rates (12). Species such as *Ruminococcus torques* and *Ruminococcus gnavus* also become more prevalent during the onset of both CD and UC. *Ruminococcus gnavus*, a commensal bacterium typically found in healthy individuals, is present in notably higher amounts in patients with CD and has been shown to activate dendritic cells (DCs), leading to the production of pro-inflammatory cytokines (13). In individuals with CD, families such as *Christensenellaceae*, *Coriobacteriaceae*, and particularly *Clostridium leptum* are reduced, whereas *Actinomyces spp.*, *Veillonella spp.*, and *Escherichia coli* are elevated. In UC, there is typically a decrease in *Eubacterium rectale*, along with a decrease in *Akkermansia muciniphila* and an increased presence of *Escherichia coli* (14). A comparative study revealed that *Intestinibacter spp*. are more abundant in both CD and UC, whereas *Coprococcus spp.* are significantly reduced in CD patients (15).

Loss of beneficial microbes leads to reduced metabolic diversity and decreased production of health-promoting compounds, while overgrowth of pathobionts promotes inflammation, forms multispecies biofilms at the epithelial surface and impairs epithelial integrity. In addition, pathobionts can activate Toll-like receptor (TLR)-mediated pathways and produce pro-inflammatory metabolites.

Role of microbiota in intestinal barrier preservation in IBD

A healthy gut microbiota is important for maintaining the integrity and proper function of the intestinal

barrier (16). Impairment of the intestinal barrier resulting, at least in part, from alterations in gut microbiota composition (dysbiosis), includes disruption of the chemical, mechanical and immune barrier and is believed to play an important role in the pathophysiology of IBD (17, 18).

The chemical barrier of the intestine is mainly composed of a mucus layer rich in various substances and mucins (MUCs) produced by gastrointestinal tract cells. Additionally, antimicrobial agents produced by the gut microbiota contribute to this barrier. The peripheral mucus layer promotes the growth of gut microorganisms (19). Several beneficial bacteria including *Lactobacillus* and *Bifidobacterium* produce bacteriocins that can eliminate specific pathogenic microorganisms (20).

The mechanical barrier in the gut depends largely on maintaining a continuous layer of intestinal epithelial cells (IECs), along with the tight junction (TJ) complexes that connect them. It plays a crucial role in protecting the body against invading pathogens (21). Disruptions of the intestinal mechanical barrier, particularly increased apoptosis of IECs and the breakdown of TJs, have been widely documented in IBD. These defects allow luminal microbes and antigens to translocate through the epithelial barrier, triggering immune cell activation and chronic inflammation (22, 23). Alterations in glycan composition can compromise the integrity of the mucosal barrier and immune functions, thereby facilitating the onset of IBD (24). Beneficial microorganisms, including *Lactobacillus* and *Bifidobacterium*, play a pivotal role in modulating immune responses and maintaining intestinal health in IBD. They achieve this primarily through the production of short-chain fatty acids (SCFAs), which exert anti-inflammatory effects and support immune homeostasis (25). They help restore the intestinal barrier by modulating TJs and protecting IECs. Short-chain fatty acids have been demonstrated to enhance the expression of TJs proteins (claudin-1 and zonula occludens-1 (ZO-1)), while also facilitating the redistribution of occludin. Among SCFAs, butyrate acts as an important energy source for IECs, promoting their proliferation and reducing apoptosis (26, 27). *Bifidobacterium bifidum* enhances the intestinal epithelial TJs barrier by interacting with the apical surface of enterocytes via Toll-like receptor-2 (TLR-2). This interaction activates the p38 kinase pathway, improving barrier function without involving the NF-κB signaling pathway (28). However, levels of *Bifidobacteria*, particularly *B. bifidum*, are significantly reduced in patients with IBD (29). Also, IBD-related dysbiosis results in increased gut colonization with harmful, pathogenetic microorganisms which may contribute to the failure of the intestinal mechanical barrier through various mechanisms. Adherent-invasive *Escherichia coli* (AIEC), detected in microbiota of more than 50% CD patients, are capable of penetrating the mucus layer, attaching to intestinal epithelial cells, and colonizing the gastrointestinal mucosa (30, 31). Pathogenic microorganisms can disrupt the positioning and expression of TJ proteins, leading to their deterioration and activation of pro-inflammatory signaling pathways. An increase in pro-inflammatory cytokines may activate intracellular apoptotic signaling in IECs, triggering programmed cell death and compromising epithelial integrity, which results in intestinal barrier dysfunction (32). Soluble factors released by apoptotic IECs can be used by members of the *Enterobacteriaceae* family support their own proliferation and mucosal colonization. This is achieved by upregulating the *pflB* gene, which encodes pyruvate format-lyase, thereby contributing to the progression of IBD (33). *Klebsiella pneumoniae* is able to infiltrate IECs and interact with macrophages, prompting the release of pro-inflammatory cytokines such as interleukin 1β (IL-1β) and tumor necrosis factor (TNF) (34).

Some investigations suggest that dysbiosis impairs metabolic functions in IECs. For example, NLRX1 (nucleotide-binding oligomerization domain, leucine-rich repeat X1), a mitochondria-associated member of the NLR (nod-like receptor) family, shows promise as an anti-inflammatory factor in colitis. Nucleotide-binding oligomerization domain NLRX1 is essential for maintaining a balanced glutamine metabolism and proper barrier function. In patients with IBD, NLRX1 expression in IECs is reduced. This reduction leads to increased inflammation, impaired glutamine metabolism, weakened intestinal barrier function and increased intestinal permeability ("leaky gut") (35).

The intestinal immune barrier consists of a diverse population of immune cells located particularly in the lamina propria and within the intestinal epithelium (36). The gut microbiota plays an important role in the differentiation and activation of immune cells within the intestinal mucosa. In patients with IBD, compromised integrity of the intestinal epithelial barrier allows pathogens as well as opportunistic bacteria such as AIEC to reach the lamina propria and activate pattern recognition receptors (PRRs) on immune cells (37). Pathogen-associated molecular patterns (PAMPs) derived from harmful bacteria, such as lipopolysaccharide (LPS) and flagellin, primarily stimulate macrophages and DCs through PRRs including TLRs and NLRs, initiating pro-inflammatory immune responses (38, 39). Activation of these pathways leads to the secretion of interleukin-6 (IL-6) and interleukin-23 (IL-23) (40). These cytokines promote the differentiationof $CD4^+$ T cells into Th17-type cells (41).

Microbiota-derived metabolites in IBD

Impaired gut microbiota in patients with IBD results in altered modified synthesis of important metabolic compounds including SCFAs, tryptophan-derived molecules, and bile acids. Compared to healthy individuals, patients with IBD exhibit increased production of bile acids and sphingolipids, along with decreased levels of triacylglycerols and tetrapyrroles (42). The aforementioned changes play a role in weakening the epithelial barrier, disrupting immune regulation, and maintaining chronic inflammation in IBD (43).

Short-chain fatty acids contribute significantly to mucosal immune regulation by enhancing B-cell generation and facilitating both the development and expansion of

T regulatory (Tregs) cells. They may also influence the production of pro-inflammatory cytokines. Butyrate exerts immunoregulatory functions by increasing both the number and functional capacity of Tregs, while simultaneously suppressing the activity of neutrophils, macrophages, and dendritic cells. Decreased SCFA levels in patients with IBD have been linked to dysbiosis and increased infiltration of intestinal inflammatory cells (44). The detection of reduced levels of butyrate-producing species, accompanied by an increased abundance of *E. coli*, has been associated with lower concentrations of SCFAs in fecal samples. (45). They activate the NLRP3 inflammasome by signaling through GPR43 and GPR109A receptors, causing the release of potassium and calcium ions and contributing to epithelial healing in colitis by regulating IL-18 (46). The loss of SCFAs, frequently associated with antibiotic therapy, can promote the polarization of macrophages toward a proinflammatory M1 phenotype, which leads to elevated cytokine release and worsened intestinal inflammation (47).

The intestinal microbiota plays a major role in regulating bile acid concentrations, which in turn, affect the host immune functions (48). Bile acids have the ability to stimulate Tregs and effector T helper cells, particularly Th17 (49). Song and colleagues demonstrated that microbial bile acid transformation directly affects Treg cell populations in the animal model (50). This immunomodulatory effect of bile acids is linked to their interaction with receptors such as Farnesoid X Receptor (FXR). Patients with IBD often exhibit decreased bile salt hydrolase activity, causing an imbalance between primary and secondary bile acids (51).

Tryptophan is an essential aromatic amino acid that is metabolised through serotonin and kynurenine pathways in the host, while gut microbes mainly convert it into indole derivatives. Activation of the aryl hydrocarbon receptor (AhR) by microbial metabolites suppresses the secretion of pro-inflammatory cytokines (52,53). In a study involving 535 patients with IBD, alterations in tryptophan metabolism were associated with disease severity (54). Dietary tryptophan deficiency has been linked to worsened colitis in murine models (55).

Another relevant microbial metabolite in IBD is N-acylethanolamine, an endogenous signaling lipid whose levels are associated with microbial shifts, specifically increased abundance of *Proteus* and reduced *Bacteroides*. Modulating N-acylethanolamine could potentially restore gut microbial balance in IBD (56).

Overall, gut microbiota and their metabolites play a significant role in regulating the host immune system. Targeting these metabolites may offer a promising therapeutic strategy for the treatment of IBD.

Microbiota-targeted therapeutic strategies

Probiotic treatment in IBD

Probiotics are being increasingly investigated as a supportive treatment in IBD due to their potential to alleviate symptoms, reduce gut inflammation, and help restore microbial balance (57). According to the European Crohn's and Colitis Organization (ECCO) guidelines, the use of probiotics alongside anti-TNF therapy in IBD patients is generally considered safe. However, caution is advised when strains with beta-hemolytic activity are involved (58). There is a concern that probiotics may harbor antibiotic resistance genes that could transfer to pathogenic microbes, which could negatively impact therapeutic success (59).

Commonly used probiotics include species of *Bifidobacterium* and *Lactobacillus*, which have shown beneficial effects in managing IBD (60). Several *Lactobacillus* strains are known for their probiotic role and are often included in adjunctive therapies for IBD. They help reduce gut damage, support the intestinal barrier, and regulate immune system activity (61). Studies have shown that *Bifidobacterium bifidum* enhances the tight junctions of the intestinal mechanical barrier by activating TLR-2 (62), while *Lactobacillus rhamnosus* promotes mucus production and enhances the intestinal chemical barrier (63). In addition, *Lactobacillus casei* improves the intestinal immune barrier function and reduces the levels of pro-inflammatory cytokines including TNF-α and IL-12 (64). Members of the family *Bifidobacteriaceae* are associated with beneficial impact on gut health and their ability to reduce IBD symptoms (65). Numerous studies highlight the importance of *Bifidobacterium spp.* in keeping the intestinal barrier healthy and intact (66,67). A new class of probiotics, including *Faecalibacterium prausnitzii*, *Roseburia spp.*, and *Akkermansia muciniphila*, has been introduced as the "next-generation probiotics" for IBD (68). *F. prausnitzii*, member of the *Oscillospiraceae* family, is a major butyrate producer (69). Similarly, *Roseburia* species produce butyrate and have been associated with beneficial outcomes in IBD (70). *Roseburia intestinalis* supports recovery of gut microbiota by enhancing IL-22 expression and strengthening intestinal barrier integrity through increased levels of occludin, a key tight junction protein. Consequently, higher abundances of *Roseburia* are linked to reduced ulcerative colitis activity (71). Recent studies emphasize the potential role of probiotics in IBD management. Nevertheless, they are typically viewed as a supportive therapy, not a standalone treatment. The American Gastroenterological Association (AGA) Clinical Practice Guidelines recommend that probiotics should be used for adults and children with UC or CD only within clinical trials (72). The British Society of Gastroenterology acknowledges that probiotics may help UC patients, but does not recommend their routine use. Currently, evidence remains insufficient to support the effectiveness of probiotics in treating CD (73).

In order to enhance the reliability of existing evidence, future studies should emphasize rigorously designed, multicenter clinical trials with sufficiently large sample sizes.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) has emerged as a potential therapeutic option for individuals with IBD, drawing increasing interest due to its ability to reestablish microbial balance in the gut (74), FMT involves transferring stool from a healthy donor to a recipient's gut to help restore microbial balance and treat intestinal and systemic disorders. Current clinical guidelines support the use of FMT for the management of recurrent *Clostridioides difficile* infections, while its potential application is also being investigated for conditions such as IBD, IBS, and functional constipation (58, 75). Growing body of evidence confirms the clinical benefits of FMT in IBD patients by correcting dysbiosis, enhancing the abundance of beneficial microbial species, and reducing harmful ones (76-78). Brezina et al. and Fang et al. reported that FMT therapy achieved clinical remission rates comparable to, or even higher than conventional treatments such as 5-aminosalicylic acid (5-ASA) and corticosteroids (79,80). Although FMT is primarily used for managing UC, its effectiveness in CD remains to be confirmed through additional studies. According to the Rome consensus, FMT can be performed using either fresh or frozen donor stool. Frozen stool is generally preferred due to its safety profile and ease of storage (81). Nevertheless, it is still unclear whether fresh or frozen stool yields better outcomes in the treatment of IBD. A systematic review of 14 clinical trials reported comparable remission rates between fresh stool FMT (40.9%) and frozen stool FMT (32.2%), with no statistically significant difference observed (82). On the other hand, Cheng et al. observed a notably higher clinical remission rate with fresh stool compared to frozen (73% vs. 43%, $p < 0.05$) (83).

Challenges and Future Directions

Gut microbiota-derived metabolites, especially SCFAs, play a key role in mediating communication between the host and its microbiota (3,84,85). Understanding the complete range of microbiota-induced influences on host immune metabolism is still complex, as microbial metabolites may have differing effects depending on the surrounding microenvironment and the involved cell types. To address this complexity, modern approaches such as functional metagenomics, synthetic biology, and integrated bioinformatics are increasingly being applied. These technologies enable the exploration of microbial communities for novel bioactive compounds and gene clusters with potential relevance to IBD. Combining data-driven strategies with experimental systems holds great promise for the discovery of new microbial-derived therapeutic targets. Interestingly, even asymptomatic family members of patients with IBD may exhibit metabolic alterations similar to those seen in diagnosed individuals. These findings imply that it may be possible to identify individuals at risk before clinical manifestations develop. Moreover, detailed time-resolved profiling of the microbiome and metabolome may facilitate the discovery of dynamic biomarkers relevant to disease development, diagnostic processes, and treatment outcomes. The use of 16S rRNA sequencing and other advanced microbiological tools enables targeted manipulation of the gut microbiome, paving the way for personalized treatments. Comprehensive analysis of disease initiation and development is increasingly supported by multi-omics strategies, such as genomics, transcriptomics, proteomics, immunomics, and microbiomics (3). Alongside these advances, both traditional therapeutics and novel drug candidates are being optimized, with artificial intelligence (AI) algorithms expected to play a growing role in IBD diagnosis and treatment (86).

Conclusion

Recent findings have considerably advanced our understanding of the impact of gut microbiota on IBD. Important aspects involve dysbiosis characterized by a reduction in beneficial microorganisms and an increase in pathobionts, as well as the mechanistic role of microbial metabolites in immune modulation and maintenance of barrier integrity, and emerging microbiota-based therapeutic strategies, ranging from probiotics and FMT to engineered microbes and personalized dietary interventions. Biomarkers derived from microbiota and microbial function now offer promising tools for diagnosis, prognosis, and therapeutic guidance. Continued integration of longitudinal multi-omic data with controlled interventions will be essential to translating these insights into precision microbiome-based medicine in IBD.

Literature

1. Wang X, Peng J, Cai P, Xia Y, Yi C, Shang A et al. The emerging role of the gut microbiota and its application in inflammatory bowel disease. Biomed Pharmacother. 2024; 179:117302.
2. Haneishi Y, Furuya Y, Hasegawa M, Picarelli A, Rossi M. et Miyamoto J. Inflammatory Bowel Disease and Gut Microbiota. Int J Mol Sci 2023; 24(4):3817.
3. Lavelle A, Hoffmann TW, Pham HP, Langella P, Guedon E, Sokol H. Baseline Microbiota Composition Modulates Antibiotic-Mediated Effects on the Gut Microbiota and Host. Microbiome. 2019; 7(1):111.
4. Schirmer M, Garner A, Vlamakis H, Xavier RJ. Microbial genes and pathways in inflammatory bowel disease. Nat Rev Microbiol. 2019; 17(8):497-511.
5. Fu Q, Ma X, Li S, Shi M, Song T, Cui J. New insights into the interactions between the gut microbiota and the inflammatory response to ulcerative colitis in a mouse model of dextran sodium sulfate and possible mechanisms of action for treatment with PE&AFWE. Animal Model Exp Med. 2024; 7(2):83-97.
6. Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM, et al. Dynamics of the human gut microbiome in inflammatory bowel disease. Nat Microbiol. 2017; 2:17004.
7. Kriss M, Hazleton KZ, Nusbacher NM, Martin CG, Lozupone CA. Low diversity gut microbiota dysbiosis: drivers, functional implications and recovery. Curr Opin Microbiol. 2018; 44:34-40.
8. Yilmaz B, Spalinger MR, Biedermann L, Franc Y, Fournier N, Rossel JB, et al. The presence of genetic risk variants within PTPN2 and PTPN22 is associated with intestinal microbiota alterations in Swiss IBD cohort patients. PLoS One. 2018; 13(7):e0199664.

9. Nie K, Ma K, Luo W, Shen Z, Yang Z, Xiao M, et al. Roseburia intestinalis: A Beneficial Gut Organism From the Discoveries in Genus and Species. Front Cell Infect Microbiol. 2021; 11:757718.
10. Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Treuren WV, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014; 15(3):382-92.
11. Najafi S, Sotoodehnejadnematalahi F, Amiri MM, Pourshafie MR, Rohani M. Decreased mucosal adhesion of Lactobacillus species in patients with inflammatory bowel disease. Caspian J Intern Med. 2022; 13(4):713-20.
12. Vich Vila A, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z, et al. Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med. 2018; 10(472):eaap8914.
13. Crost EH, Coletto E, Bell A, Juge N. Ruminococcus gnavus: friend or foe for human health. FEMS Microbiol Rev. 2023; 47(2):fuad014.
14. Pittayanon R, Lau JT, Leontiadis GI, Tse F, Yuan Y, Surette M, et al. Differences in Gut Microbiota in Patients With vs Without Inflammatory Bowel Diseases: A Systematic Review. Gastroenterology. 2020; 158(4):930-46.
15. Forbes JD, Chen CY, Knox NC, Marrie RA, El-Gabalawy H, de Kievit T, et al. A comparative study of the gut microbiota in immune-mediated inflammatory diseases-does a common dysbiosis exist?. Microbiome. 2018; 6(1):221.
16. Wang X, Peng J, Cai P, Xia Y, Yi C, Shang A, et al. The emerging role of the gut microbiota and its application in inflammatory bowel disease. Biomed Pharmacother. 2024; 179:117302.
17. Qiu P, Ishimoto T, Fu L, Zhang J, Zhang Z, Liu Y. The Gut Microbiota in Inflammatory Bowel Disease. Front Cell Infect Microbiol. 2022; 12:733992.
18. Yue B, Luo X, Yu Z, Mani S, Wang Z, Dou W. Inflammatory Bowel Disease: A Potential Result from the Collusion between Gut Microbiota and Mucosal Immune System. Microorganisms. 2019; 7(10):440.
19. Ren Z, Guo C, Yu S, Zhu L, Wang Y, Hu H, et al. Progress in Mycotoxins Affecting Intestinal Mucosal Barrier Function. Int J Mol Sci. 2019; 20(11):2777.
20. Dobson A, Cotter PD, Ross RP, Hill C. Bacteriocin production: a probiotic trait?. Appl Environ Microbiol. 2012; 78(1):1-6.
21. Kurashima Y, Kiyono H. Mucosal Ecological Network of Epithelium and Immune Cells for Gut Homeostasis and Tissue Healing. Annu Rev Immunol. 2017; 35:119-47.
22. Coskun M. Intestinal epithelium in inflammatory bowel disease. Front Med (Lausanne). 2014; 1:24.
23. Llewellyn SR, Britton GJ, Contijoch EJ, Vennaro OH, Mortha A, Colombel JF, et al. Interactions Between Diet and the Intestinal Microbiota Alter Intestinal Permeability and Colitis Severity in Mice. Gastroenterology. 2018; 154(4):1037-46.
24. Kudelka MR, Stowell SR, Cummings RD, Neish AS. Intestinal epithelial glycosylation in homeostasis and gut microbiota interactions in IBD. Nat Rev Gastroenterol Hepatol. 2020; 17(10):597-617.
25. Roy S, Dhaneshwar S. Role of prebiotics, probiotics, and synbiotics in management of inflammatory bowel disease: Current perspectives. World J Gastroenterol. 2023; 29(14):2078-100.
26. Wang S, Dong Z, Wan X. Global, regional, and national burden of inflammatory bowel disease and its associated anemia, 1990 to 2019 and predictions to 2050: An analysis of the global burden of disease study 2019. Autoimmun Rev. 2024; 23(3):103498.
27. Tremaroli V, Bäckhed F. Functional interactions between the gut microbiota and host metabolism. Nature. 2012; 489(7415):242-9.
28. Al-Sadi R, Nighot P, Nighot M, Haque M, Rawat M, Ma TY. Lactobacillus acidophilus Induces a Strain-specific and Toll-Like Receptor 2-Dependent Enhancement of Intestinal Epithelial Tight Junction Barrier and Protection Against Intestinal Inflammation. Am J Pathol. 2021; 191(5):872-84.
29. Duranti S, Gaiani F, Mancabelli L, Milani C, Grandi A, Bolchi A, et al. Elucidating the gut microbiome of ulcerative colitis: bifidobacteria as novel microbial biomarkers. FEMS Microbiol Ecol. 2016; 92(12):fiw191.
30. Palmela C, Chevarin C, Xu Z, Torres J, Sevrin G, Hirten R, et al. Adherent-invasive Escherichia coli in inflammatory bowel disease. Gut. 2018; 67(3):574-87.
31. Shawki A, McCole DF. Mechanisms of Intestinal Epithelial Barrier Dysfunction by Adherent-Invasive Escherichia coli. Cell Mol Gastroenterol Hepatol. 2016; 3(1):41-50.
32. Jergens AE, Parvinroo S, Kopper J, Wannemuehler MJ. Rules of Engagement: Epithelial-Microbe Interactions and Inflammatory Bowel Disease. Front Med (Lausanne). 2021; 8:669913.
33. Anderson CJ, Medina CB, Barron BJ, Karvelyte L, Aaes TL, Lamberty I, et al. Microbes exploit death-induced nutrient release by gut epithelial cells. Nature. 2021; 596(7871):262-7.
34. Read E, Curtis MA, Neves JF. The role of oral bacteria in inflammatory bowel disease. Nat Rev Gastroenterol Hepatol. 2021; 18(10):731-42.
35. Leber A, Hontecillas R, Tubau-Juni N, Zoccoli-Rodriguez V, Abedi V, Bassaganya-Riera J. NLRX1 Modulates Immunometabolic Mechanisms Controlling the Host-Gut Microbiota Interactions during Inflammatory Bowel Disease. Front Immunol. 2018; 9:363.
36. Perez-Lopez A, Behnsen J, Nuccio SP, Raffatellu M. Mucosal immunity to pathogenic intestinal bacteria. Nat Rev Immunol. 2016; 16(3):135-148.
37. Tawfik A, Flanagan PK, Campbell BJ. Escherichia coli-host macrophage interactions in the pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2014; 20(27):8751-63.
38. Walsh D, McCarthy J, O'Driscoll C, Melgar S. Pattern recognition receptors--molecular orchestrators of inflammation in inflammatory bowel disease. Cytokine Growth Factor Rev. 2013; 24(2):91-104.
39. Stephens M, von der Weid PY. Lipopolysaccharides modulate intestinal epithelial permeability and inflammation in a species-specific manner. Gut Microbes. 2020; 11(3):421-32.
40. Xu YD, Cheng M, Shang PP, Yang YQ. Role of IL-6 in dendritic cell functions. J Leukoc Biol. 2022; 111(3):695-709.
41. Yan JB, Luo MM, Chen ZY, He BH. The Function and Role of the Th17/Treg Cell Balance in Inflammatory Bowel Disease. J Immunol Res. 2020; 2020:8813558.
42. Franzosa EA, Sirota-Madi A, Avila-Pacheco J, Fornelos N, Haiser HJ, Reinker S, et al. Gut microbiome structure and metabolic activity in inflammatory bowel disease. Nat Microbiol. 2019; 4(2):293-305.
43. Lee M, Chang EB. Inflammatory Bowel Diseases (IBD) and the Microbiome-Searching the Crime Scene for Clues. Gastroenterology. 2021; 160(2):524-37.
44. Gonçalves P, Araújo JR, Di Santo JP. A Cross-Talk Between Microbiota-Derived Short-Chain Fatty Acids and the Host Mucosal Immune System Regulates Intestinal Homeostasis and Inflammatory Bowel Disease. Inflamm Bowel Dis. 2018; 24(3):558-72.
45. Chattopadhyay I, Dhar R, Pethusamy K, et al. Exploring the Role of Gut Microbiome in Colon Cancer. Appl Biochem Biotechnol. 2021; 193(6):1780-99.
46. Macia L, Tan J, Vieira AT, Leach K, Stanley D, Luong S, et al. Metabolite-sensing receptors GPR43 and GPR109A facilitate dietary fibre-induced gut homeostasis through regulation of the inflammasome. Nat Commun. 2015; 6:6734.
47. Michaudel C, Sokol H. The Gut Microbiota at the Service of Immunometabolism. Cell Metab. 2020; 32(4):514-23.
48. Campbell C, McKenney PT, Konstantinovsky D, Isaeva OI, Schiaz M, Verter J, et al. Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells. Nature. 2020; 581(7809):475-9.
49. Hang S, Paik D, Yao L, Kim E, Trinath J, Lu J, et al. Bile acid metabolites control TH17 and Treg cell differentiation. Nature. 2019; 576(7785):143-8.
50. Song X, Sun X, Oh SF, Wu M, Zhang Y, Zheng W, et al. Microbial bile acid metabolites modulate gut RORγ+ regulatory T cell homeostasis. Nature. 2020; 577(7790):410-5.
51. Gadaleta RM, van Erpecum KJ, Oldenburg B, Willemsen ECL, Renooij W, Murzilli S, et al. Farnesoid X receptor activation inhibits inflammation and preserves the intestinal barrier in inflammatory bowel disease. Gut. 2011; 60(4):463-72.

52. Alexeev EE, Lanis JM, Kao DJ, Campbell EL, Kelly CJ, Battista KD, et al. Microbiota-Derived Indole Metabolites Promote Human and Murine Intestinal Homeostasis through Regulation of Interleukin-10 Receptor. Am J Pathol. 2018; 188(5):1183-94
53. Langan D, Perkins DJ, Vogel SN, Moudgil KD. Microbiota-Derived Metabolites, Indole-3-aldehyde and Indole-3-acetic Acid, Differentially Modulate Innate Cytokines and Stromal Remodeling Processes Associated with Autoimmune Arthritis. Int J Mol Sci. 2021; 22(4):2017.
54. Nikolaus S, Schulte B, Al-Massad N, Thieme F, Schulte DM, Bethge J, et al. Increased Tryptophan Metabolism Is Associated With Activity of Inflammatory Bowel Diseases. Gastroenterology. 2017; 153(6):1504-16.
55. Meisel M, Mayassi T, Fehlner-Peach H, Koval JC, O'Brien SL, Hinterleitner R, et al. Interleukin-15 promotes intestinal dysbiosis with butyrate deficiency associated with increased susceptibility to colitis. ISME J. 2017; 11(1):15-30.
56. Fornelos N, Franzosa EA, Bishai J, Annand JW, Oka A, Lloyd. Prince J, et al. Growth effects of N-acylethanolamines on gut bacteria reflect altered bacterial abundances in inflammatory bowel disease. Nat Microbiol. 2020; 5(3):486-97.
57. Martín R, Rios-Covian D, Huillet E, Auger S, Khazaal S, Bermúdez-Humarán LG, et al. Faecalibacterium: a bacterial genus with promising human health applications. FEMS Microbiol Rev. 2023; 47(4):fuad039.
58. Kucharzik T, Ellul P, Greuter T, Rahier JF, Verstockt B, Abreu C, et al. ECCO Guidelines on the Prevention, Diagnosis, and Management of Infections in Inflammatory Bowel Disease. J Crohns Colitis. 2021; 15(6):879-913.
59. Merenstein D, Pot B, Leyer G, Ouwehand AC, Preidis GA, Elkins CA, et al. Emerging issues in probiotic safety: 2023 perspectives. Gut Microbes. 2023; 15(1):2185034.
60. Jakubczyk D, Leszczyńska K, Górska S. The Effectiveness of Probiotics in the Treatment of Inflammatory Bowel Disease (IBD)-A Critical Review. Nutrients. 2020; 12(7):1973.
61. Li C, Peng K, Xiao S, Long Y, Yu Q. The role of Lactobacillus in inflammatory bowel disease: from actualities to prospects. Cell Death Discov. 2023; 9(1):361.
62. Al-Sadi R, Dharmaprakash V, Nighot P, et al. Bifidobacterium bifidum Enhances the Intestinal Epithelial Tight Junction Barrier and Protects against Intestinal Inflammation by Targeting the Toll-like Receptor-2 Pathway in an NF-κB-Independent Manner. Int J Mol Sci. 2021; 22(15):8070.
63. Martín R, Chamignon C, Mhedbi-Hajri N, Chain F, Derrien M, Escribano-Vázquez U, et al. The potential probiotic Lactobacillus rhamnosus CNCM I-3690 strain protects the intestinal barrier by stimulating both mucus production and cytoprotective response. Sci Rep. 2019; 9(1):5398.
64. Liu Y, Li Y, Yu X, Yu L, Tian F, Zhao J, et al. Physiological Characteristics of Lactobacillus casei Strains and Their Alleviation Effects against Inflammatory Bowel Disease. J Microbiol Biotechnol. 2021; 31(1):92-103.
65. O'Callaghan A, van Sinderen D. Bifidobacteria and Their Role as Members of the Human Gut Microbiota. Front Microbiol. 2016; 7:925.
66. Martín R, Laval L, Chain F, Miquel S, Natividad J, Cherbuy C, et al. Bifidobacterium animalis ssp. lactis CNCM-I2494 Restores Gut Barrier Permeability in Chronically Low-Grade Inflamed Mice. Front Microbiol. 2016; 7:608.
67. Hsieh CY, Osaka T, Moriyama E, Date Y, Kikuchi J, Tsuneda S. Strengthening of the intestinal epithelial tight junction by Bifidobacterium bifidum. Physiol Rep. 2015; 3(3):e12327.
68. Al-Fakhrany OM, Elekhnawy E. Next-generation probiotics: the upcoming biotherapeutics. Mol Biol Rep. 2024; 51(1):505.
69. Louis P, Flint HJ. Formation of propionate and butyrate by the human colonic microbiota. Environ Microbiol. 2017; 19(1):29-41.
70. Vacca M, Celano G, Calabrese FM, Portincasa P, Gobbetti M, De Angelis M. The Controversial Role of Human Gut Lachnospiraceae. Microorganisms. 2020; 8(4):573.
71. Machiels K, Joossens M, Sabino J, de Preter V, Arijs I, Eeckhaut V, et al. A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut. 2014; 63(8):1275-83.
72. Su GL, Ko CW, Bercik P, Falck-Ytter Y, Sultan S, Weizman AV, et al. AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. Gastroenterology. 2020; 159(2):697-705.
73. Lamb CA, Kennedy NA, Raine T, Hendy PA, Smith PJ, Limdi JK, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019; 68(Suppl 3):s1-s106.
74. Imdad A, Pandit NG, Zaman M, Minkoff NZ, Tanner-Smith EE, Gomez-Duarte OG, et al. Fecal transplantation for treatment of inflammatory bowel disease. Cochrane Database Syst Rev. 2023; 4(4):CD012774.
75. Cammarota G, Ianiro G, Tilg H, Rajilić-Stojanović M, Kump P, Satokari R, et al. European consensus conference on faecal microbiota transplantation in clinical practice. Gut. 2017; 66(4):569-80.
76. Ye Z, Eslick GD, Huang S, He X. Faecal microbiota transplantation for eradicating Helicobacter pylori infection: clinical practice and theoretical postulation. eGastroenterology. 2024; 2:e100099.
77. Pai N, Popov J, Hill L, Hartung E, Gryzwacz K, Moayyedi P, et al. Results of the First Pilot Randomized Controlled Trial of Fecal Microbiota Transplant In Pediatric Ulcerative Colitis: Lessons, Limitations, and Future Prospects. Gastroenterology. 2021; 161(2):388-93.
78. Huang C, Huang Z, Ding L, Fu Y, Fan J, Mei Q, et al. Fecal microbiota transplantation versus glucocorticoids for the induction of remission in mild to moderate ulcerative colitis. J Transl Med. 2022; 20(1):354.
79. Březina J, Bajer L, Wohl P, Ďuricová D, Hrabák P, Novotný A, et al. Fecal Microbial Transplantation versus Mesalamine Enema for Treatment of Active Left-Sided Ulcerative Colitis-Results of a Randomized Controlled Trial. J Clin Med. 2021; 10(13):2753.
80. Fang H, Fu L, Li X, Lu C, Su Y, Xiong K, et al. Long-term efficacy and safety of monotherapy with a single fresh fecal microbiota transplant for recurrent active ulcerative colitis: a prospective randomized pilot study. Microb Cell Fact. 2021; 20(1):18.
81. Lopetuso LR, Deleu S, Godny L, Petito V, Puca P, Facciotti F, et al. The first international Rome consensus conference on gut microbiota and faecal microbiota transplantation in inflammatory bowel disease. Gut. 2023; 72(9):1642-50.
82. Tan XY, Xie YJ, Liu XL, Li XY, Jia B. A Systematic Review and Meta-Analysis of Randomized Controlled Trials of Fecal Microbiota Transplantation for the Treatment of Inflammatory Bowel Disease. Evid Based Complement Alternat Med. 2022; 2022:8266793.
83. Cheng F, Huang Z, Wei W, Li Z. Fecal microbiota transplantation for Crohn's disease: a systematic review and meta-analysis. Tech Coloproctol. 2021; 25(5):495-504.
84. Nikolaus S, Schulte B, Al-Massad N, Thieme F, Schulte DM, Bethge J, et al. Increased Tryptophan Metabolism Is Associated With Activity of Inflammatory Bowel Diseases. Gastroenterology. 2017; 153(6):1504-16.
85. Osaka T, Moriyama E, Arai S, Date Y, Yagi J, Kikuchi J, et al. Meta-Analysis of Fecal Microbiota and Metabolites in Experimental Colitic Mice during the Inflammatory and Healing Phases. Nutrients. 2017; 9(12):1329.
86. Rodrigues RR, Shulzhenko N, Morgun A. Transkingdom Networks: A Systems Biology Approach to Identify Causal Members of Host-Microbiota Interactions. Methods Mol Biol. 2018; 1849:227-42.