International Journal of Colorectal Disease (2025) 40:130
https://doi.org/10.1007/s00384-025-04917-7

REVIEW

Role and mechanism of gut microbiota-host interactions in the pathogenesis of Crohn's disease

Yao Xu[1,2] · Runxiang Xie[3] · Yuqing Weng[2] · Yewei Fang[1] · Shuan Tao[1] · He Zhang[4] · Huimin Chen[1] · Axiang Han[1] · Qi Jiang[3] · Wei Liang[1]

Accepted: 8 May 2025

Abstract

Background Crohn's disease (CD) is a chronic, nonspecific inflammatory bowel disease with a poor prognosis. Despite its increasing incidence, curing CD remains challenging due to its complex etiology and unclear pathogenesis.

Methods A comprehensive PubMed and Web of Science search was conducted using the keywords Crohn's disease, gut microbiota, dysbiosis, pathogenesis and treatment, focusing on studies published between 2014 and 2024.

Results Recent studies have demonstrated a close relationship between gut microbiota dysbiosis and the development of CD. Although many dysbioses associated with CD have not yet been proven to be causal or consequential, it has been observed that the gut microbiota in CD patients exhibits reduced diversity, a decrease in beneficial bacteria, and an increase in pathogenic bacteria. These changes may lead to decreased intestinal barrier function, abnormal immune responses, and enhanced inflammatory reactions, which are related to the disease's activity, phenotype, drug treatment efficacy, and postoperative therapeutic outcomes. Therefore, further exploration of the microbiota-host interactions and the pathogenesis of CD, the identification of biomarkers, and the development of targeted strategies for modulating the gut microbiota could offer new avenues for the prevention and treatment of CD.

Conclusions This review highlights the pivotal role of gut microbiota dysbiosis in driving CD pathogenesis and its progression, while underscoring its potential as a therapeutic target through dietary modulation, microbial interventions, and integrative strategies to improve clinical management and prognostic outcomes.

Keywords Gut microbial dysbiosis · Crohn's disease · Gut microbiota · Pathogenesis · Treatment

Introduction

Crohn's disease (CD) is a non-specific chronic inflammatory bowel disease (IBD), primarily affecting the ileum and colon, though it may involve the entire digestive tract. It is characterized by discontinuous distribution, fully stratified granulomatous inflammation, and fistula formation [1, 2]. CD's incidence and prevalence are increasing globally, particularly in Asia and other developing countries like China [3, 4]. Its clinical manifestations are varied and can include abdominal pain, often nighttime diarrhea with blood and mucus, weight loss, fever, intestinal obstruction, perianal complications, anemia, and elevated inflammatory markers in lab tests [5, 6]. The disease course typically alternates between periods of recurrence and remission [5]. Despite medical advances, approximately 60–70% of CD patients undergo at least one surgical resection during their disease course, with 15% of cases attributed to medication non-response[7, 8]. These interventions carry a significant risk of postoperative recurrence and impose a considerable burden on patients' quality of life and socio-economic status [9]. The challenges in clinical diagnosis and treatment of CD are exacerbated by its unclear pathogenesis, complex clinical presentations, and significant inter-individual variability [4]. Consequently, unraveling the pathogenesis of CD, identifying

✉ Qi Jiang
Jiangqigua@163.com; fyyjiangqi@nbu.edu.cn

✉ Wei Liang
fyyliangwei@nbu.edu.cn; hslwys@163.com

[1] Department of Clinical Laboratory, The First Affiliated Hospital of Ningbo University, Ningbo, China

[2] Health Science Center, Ningbo University, Ningbo, China

[3] Department of Gastroenterology, The First Affiliated Hospital of Ningbo University, Ningbo, China

[4] Laboratory Medical School, Bengbu Medical University, Bengbu, China

Published online: 28 May 2025

biomarkers for early diagnosis and prognosis, and developing new effective treatments are of paramount importance.

The pathogenesis of CD is complex, primarily influenced by the interaction between genetic factors and gut microbiota, which impacts the immune response [10]. Over the past two decades, gut microbiota has emerged as a pivotal factor in CD pathogenesis. It consists of more than 100 trillion microorganisms, including bacteria, fungi, viruses, and archaea [11], with bacteria being the predominant group. In healthy individuals, approximately 160 key bacterial species colonize the gut, over 90% of which belong to the phyla Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteriota [11, 12]. Among these, Firmicutes and Bacteroidetes are the most prevalent in healthy adults [12]. Typically, there is a dynamic equilibrium between the gut microbiota and the host, which supports intestinal barrier integrity, immune homeostasis, and metabolic regulation [13]. However, this balance is disturbed in CD patients. Next-generation sequencing (NGS) technologies have unveiled alterations in the composition, abundance, and function of gut microbiota in CD, leading to a state known as gut microbial dysbiosis [14]. This dysbiosis not only compromises the host's defense against external pathogens but also significantly contributes to the onset and progression of CD by generating metabolites or triggering the production of pro-inflammatory cytokines by the host. Despite these insights, the exact mechanisms by which dysbiosis in the gut microbiota initiates CD remain elusive, and it is still debated whether dysbiosis is a cause or a consequence of the disease [15].

In recent years, advancements in high-throughput sequencing technology and bioinformatics analysis methods have enabled a deeper investigation into the correlation and mechanisms linking gut bacterial dysbiosis with disease progression, prognosis, and other aspects in patients with CD. Consequently, this review primarily focuses on bacterial components, aiming to elucidate the fundamental mechanisms and potential connections between gut bacterial dysbiosis and the onset and progression of CD. Additionally, it acknowledges that other components of the gut microbiota, including fungi, viruses, and archaea, also exhibit dysregulation in CD, indicating the complex interplay within the gut ecosystem. Lastly, the review highlights the latest developments in targeted gut microbiota interventions aimed at preventing and treating CD, demonstrating the potential for microbiome-based strategies to alleviate the condition.

Dysbiosis of the gut microbiota in patients with Crohn's disease

Evidence suggests that gut microbial dysbiosis plays a significant role in the development of CD. Numerous studies have recruited patients and utilized cohort analysis to identify differences in their gut microbiota compared to healthy control groups. While germ-free (GF) mice exhibit lower susceptibility to colitis, fecal microbiota transplantation (FMT) from CD patients into GF mice successfully recapitulates disease phenotypes, highlighting the pathogenic potential of CD-associated microbial configurations. Moreover, mouse models have shown that colonization by CD-related bacterial strains can induce intestinal inflammation in genetically susceptible mice [11, 16]. Lloyd Price et al. [17] conducted colon biopsy, blood, and fecal sample analysis on 132 patients with IBD, including CD patients and control group participants. They discovered that samples from IBD patients, particularly those with CD, exhibited lower α diversity. Notably, about one-third of CD patients displayed an increased abundance of mucosa-associated adherent bacteria [5]. While numerous studies have identified microbial species varying in abundance in CD patients, the presence, absence, or varying levels of many microbial species complicate the identification of common patterns. Phylogenetic analysis of species associations identified in metagenomic studies revealed that the phylum Proteobacteria is typically more abundant in CD, whereas Actinobacteria and Bacteroidetes tend to decrease. The phylum Firmicutes showed both increases and decreases in species numbers, especially among bacteria from the *Clostridium* clusters XIVa and IV [5, 18].

Bacteria

Gevers D. et al. [19] employed 16S rRNA sequencing and MaAsLin analysis to study the gut microbiome of CD patients, revealing significant alterations compared to a control group. They discovered an increased abundance of Enterobacteriaceae, Veillonellaceae, and Fusobacteriaceae in CD patients' gut microbiomes, while the levels of *Bacteroides*, *Roseburia*, and *Faecalibacterium* were notably lower. Notably, *Fusobacterium* has been identified as one of the most valuable biological diagnostic biomarkers for CD [20]. Further research indicates stark differences in the gut microbiome of IBD patients, including those with CD, compared to healthy individuals. These differences include a decreased abundance of *Bifidobacterium*, *Bacillus*, and *Faecalibacterium*, alongside an overall reduction in microbial diversity. While the abundance of most gut bacteria decreases in CD patients, the populations of *Ruminococcus*, *Shigella*, and *Escherichia* genera are on the rise [21].

Metagenomic sequencing of fecal samples from CD patients has shown a reduction in both the abundance and diversity of strains like *Faecalibacterium prausnitzii* (*F. prausnitzii*) and *Roseburia intestinalis* (*R. intestinalis*) [22], key species known for their beneficial roles in the gut. *F. prausnitzii* is one of the most abundant bacterial species in the intestine [23]. There is a significant correlation between the IBD genetic risk score and reduced *R. intestinalis* in healthy controls [24]. Additionally, a reduced abundance

of *Akkermansia muciniphila* (*A. muciniphila*) has been observed in CD patients [25], while familial CD cases show a decrease in *Parabacteroides* numbers [26]. A crucial aspect of CD pathogenesis is gut microbiota dysbiosis, transforming originally harmless or beneficial bacteria into opportunistic pathogens, leading to intestinal inflammation and damage. Various opportunistic pathogenic microorganisms found in CD patients include *Escherichia coli* (*E. coli*), *Ruminococcus gnavus* (*R. gnavus*), and *Bacteroides* [18, 27, 28]. The transition of gut microbiota from symbiosis to pathogenicity is evident, with an increase in *adhesive-invasive E. coli* (AIEC) observed in the mucosa of IBD patients [29]. Concurrently, an increase in *Escherichia-Shigella* and a decrease in short-chain fatty acids (SCFAs) producing bacteria are common in CD patients' microbial communities [30]. *Proteus*, especially *Proteus mirabilis*, is more prevalent and abundant in CD patients [31]. *Clostridioides difficile* also shows higher abundance in the CD group [32]. Research indicates *Pseudomonas* is more common in biopsy specimens from CD patients compared to non-IBD individuals [33]. *R. gnavus*, a gas-resistant specialized anaerobe, dominates the gut in about 25% of CD patients [18], yet its role in CD pathogenesis remains unclear [34]. *Bacteroides*, typically symbiotic, can also produce toxins or antibiotic-resistance genes, potentially increasing infection risk with other pathogenic bacteria [18]. The growth rate and abundance of *Bacteroides fragilis* (*B. fragilis*) are elevated in CD patients [18, 35]. Moreover, an increase in *Listeria monocytogenes* (LM) prevalence in IBD patients [36] is associated with a higher incidence rate of LM bacteremia [37]. Non-*Helicobacter pylori* species are also associated with IBD, particularly with the presence of *enterohepatic Helicobacter* species in CD [38]. *Enterohepatic Helicobacter*, including *Helicobacter hepaticus* and *Helicobacter bilis*, can induce IBD-like diseases in mice [39]. Multiple live bacteria have been isolated from the mesenteric adipose tissue (MAT) of CD patients, with *Clostridium innocuum* (*C. innocuum*) being the most prevalent [40]. Furthermore, *Atopobium parvulum* (*A. parvulum*), a hydrogen sulfide (H_2S) producing bacterium, is associated with colitis in genetically susceptible mice, and its elimination can mitigate the disease [41, 42].

Fungi

The increasing focus on the role of gut fungi in the pathogenesis of CD highlights a complex interplay within the gut microbiota that extends beyond bacteria. These fungi can influence the host's health either directly or indirectly by impacting the gut microbiota, including bacteriophages. Interestingly, research indicates that in CD patients' ileums, fungi populations increase at the bacteria's expense, suggesting a shift in microbial balance. This contrasts with patients with ulcerative colitis (UC) and those CD patients whose ileum is not affected, who instead display a reduction in fungal diversity [43]. Comparative studies between CD patients and healthy controls reveal a notable shift in fungal composition: an increase in the *Basidiomycota* to *Ascomycota* ratio, a decrease in *Saccharomyces cerevisiae* and *Malassezia sympodialis* (*M. sympodialis*), and an increase in *Candida albicans* [43]. Notably, *Malassezia restricta*, primarily found on human skin, is also enriched in the colon mucosa of CD patients, suggesting its involvement in CD pathogenesis [18, 44]. Similarly, *Candida tropicalis*, a pathogenic fungus identified in the intestines of mice, underscores the potential cross-species relevance of fungal pathogens in CD [45, 46]. However, the classification of *Debaryomyces hansenii* (*D. hansenii*) as a CD pathogen remains contentious, reflecting ongoing debates within the scientific community regarding its role [47].

Viruses

The exploration of viral groups in the context of CD is still in its infancy, with limited information available on their precise role. Viral communities within the gut can significantly impact the bacterial microbiome and its diversity, primarily because viruses often drive bacterial resistance mechanisms. One way they do this is by facilitating the horizontal transfer of genetic material among bacterial communities, potentially altering the balance of different microbial ecosystems. Notably, specific alterations in the viral composition of CD patients have been identified, such as the loss of "core bacteriophages" and an increase in the abundance of *Caudovirales bacteriophages* [48, 49]. Additionally, features associated with CD include the presence of infections by *Alteromonas macleodii* and Clostridiales, alongside an increased number of bacteriophages [50]. *Caudovirales* phage sequences have also been detected in the intestinal lavage and biopsy tissues of pediatric CD patients in Australia, indicating their relevance across different populations [51]. In mouse models of colitis, an increase in the abundance of *Caudovirales* virus phage families, including *Siphoviridae*, *Myoviridae*, and *Podoviridae*, has been observed in the intestines [52]. While the exact contribution of viral groups to CD pathogenesis remains to be fully elucidated, the available evidence suggests a potential role in promoting intestinal inflammation.

Archaea

Archaea are single-celled prokaryotic organisms that form a distinct domain known as Archaea [53]. Despite the burgeoning interest in the human gut microbiome, our understanding of gut archaea remains nascent, largely due to methodological approaches that have traditionally focused on symbiotic bacteria. *Methanogens*, methane-producing archaea, are the most prevalent archaea in the human intestine, constituting about 10% of the intestinal anaerobic bacterial population. *Methanobrevibacter smithii* (*M. smithii*) is

the most common methanogen found [54–56]. Notably, the occurrence of *M. smithii* in fecal samples from patients with IBD is significantly reduced compared to healthy controls [54]. Conversely, the presence of *Methanosphaera stadtmanae* is substantially higher in IBD patients, showing at least a threefold increase [57]. This emerging evidence suggests a complex relationship between archaea and CD, underscoring the need for further investigation into how archaea contribute to the pathogenesis and progression of CD, including their specific mechanisms of action. The predominant gut microbiota in patients with Crohn's disease includes bacteria, fungi, viruses, and archaea in Table 1.

Role of the gut microbiota in CD

Relationship between gut microbiota dysbiosis and intestinal mucosal barrier

The intestinal mucus layer is pivotal for maintaining a symbiotic relationship between the host and its gut microbiota, serving as both a spatial barrier and a selective filter that promotes crucial host-microbe interactions. Significant disparities between the gut mucosal microbiome and the fecal microbiome underscore its importance in the pathogenesis and diagnosis of CD [19]. A reduction in the abundance of Bacteroidetes and Firmicutes, key producers of SCFAs, may negatively affect intestinal health [22]. SCFAs, including acetate, propionate, and butyrate, are vital energy sources for colon mucosal cells and play roles in enhancing tight junction integrity and improving intestinal permeability [58, 59]. Certain strains, like *F. prausnitzii* and *R. intestinalis*, may mitigate inflammation by modulating the intestinal inflammatory response [60]. *A. muciniphila* enhances the intestinal barrier through interaction with toll-like receptor 2 (TLR2) via the Amuc_1100 protein [61]. AIEC can infiltrate intestinal mucosal epithelial cells, contributing to CD pathogenesis [18, 59, 62], potentially causing intestinal ulcers and disrupting the gut microbiota balance [22]. *R. gnavus* may accelerate disease progression by degrading the intestinal mucus layer [63]. Some strains of *B. fragilis*, particularly *enterotoxigenic Bacteroides fragilis* (ETBF), could increase mucosal permeability [64–66]. *Campylobacter concisus* (*C. concisus*), an adhesive and invasive bacterium, is linked with IBD [67–72]. Certain strains have acquired the zonula occludens toxin (Zot) gene from bacteriophages, possibly

Table 1 Altered gut microbiota in patients with Crohn's disease

	Increase	Decrease
Bacteria	*Shigella* spp. (P)	*Faecalibacterium prausnitzii* (F)
	Adherent-invasive *E. coli* (AIEC) (P)	*Roseburia hominis* (F)
	Proteus mirabilis (P)	Peptostreptococcaceae (F)
	Pseudomonas spp. (P)	Christensenellaceae (F)
	Helicobacter spp. (P)	*Clostridium* clusters XIVa and IV (F)
	Campylobacter concisus (P)	*Bacteroides* spp. (B)
	Clostridioides difficile (F)	Bifidobacterium (A)
	Ruminococcus gnavus (F)	*Akkermansia muciniphila* (V)
	Veillonellaceae (F)	*Clostridium innocuum* (F)
	Streptococcus spp. (F)	
	Listeria monocytogenes (F)	
	Fusobacterium spp. (F')	
	Bacteroides fragilis (B)	
	Atopobium parvulum (A)	
Fungi	*Candida albicans*	*Saccharomyces cerevisiae*
	Candida tropicalis	
	Clavispora lusitaniae	
	Malassezia restricta	
	Cyberlindnera jadinii	
	Kluyveromyces marxianus	
	Debaryomyces hansenii	
Virus	*Caudovirales* bacteriophages	
	Caudovirales phage	
Archaea	*Methanosphaera stadtmanae*	*Methanobrevibacter*

Abbreviations: *P*, Proteobacteria; *F*, Firmicutes; *F'*, Fusobacteria; *B*, Bacteroidetes; *A*, Actinobacteria; *V*, Verrucomicrobia

triggering IBD relapses by enhancing intestinal membrane permeability [73, 74]. The *Saccharomyces cerevisiae* CNCM I-3856 shows promise in reducing AIEC-induced ileocolitis in mice by blocking AIEC adhesion to intestinal cells and restoring barrier functionality [75, 76]. *D. hansenii* prompts macrophage release of interferon-β (IFN-β) and C–C motif chemokine ligand 5 (CCL5), impairing intestinal mucosal healing in colitis models [77].

Relationship between gut microbiota dysbiosis and immune response

In the lamina propria and epithelium, immune cells collaborate to respond to microbial stimuli. In CD, dysbiosis shifts the environment towards pro-inflammation, characterized by an increase in T helper cell 1 (Th1) and Th17 populations [5], and a noted dysfunction in intestinal regulatory T cells (Tregs) activity [5]. The interleukin-10 (IL-10) family plays a significant anti-inflammatory role in modulating intestinal inflammation. Certain species from *Clostridium* clusters IV, XIVa, and XVIII promote Tregs differentiation, contributing to immune tolerance [78, 79]. Butyrate, a SCFA, exerts anti-inflammatory effects by inhibiting IL-6, reducing tumor necrosis factor α (TNF-α) release induced by lipopolysaccharides (LPS) and blocking the TNF-α-activated nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inflammatory pathway [80]. SCFA-producing bacteria are crucial for regulating protective immunity and minimizing tissue inflammation [58, 59]. For instance, *F. prausnitzii* influences peripheral blood mononuclear cells (PBMCs) to lower IL-12 and IFN-γ production while increasing IL-10 secretion, showcasing anti-inflammatory capabilities. Furthermore, *F. prausnitzii*'s supernatant decreases IL-8 secretion by Caco-2 cells [81], and a specific 15 kDa protein produced by *F. prausnitzii* inhibits the NF-κB pathway, mitigating colitis in mice [59]. *R. intestinalis* also plays a role in reducing intestinal inflammation by boosting Tregs and anti-inflammatory cytokine expression [82]. *A. muciniphila* contributes to immune homeostasis, including IgG production and specific T cell responses [83]. Microbial-derived factors, like polysaccharides from *Helicobacter hepaticus* and *Bacteroides*, induce IL-10 production while inhibiting IL-1β generation [84]. Polysaccharide A (PSA) from Bacteroides fragilis directs $CD4^+$T cell development and Tregs' anti-inflammatory functions, relying on IL-10-producing $CD4^+$T cells for colitis protection [85, 86]. Furthermore, *B. fragilis*-produced sphingolipids regulate natural killer T (NKT) cell homeostasis in the intestine, preventing oxazolone-induced colitis [87]. *Bacteroides thetaiotaomicron* activates TLR on Paneth cells to regulate antimicrobial peptide expression, influencing innate immunity [88]. *C. innocuum*'s evolution has led to M2 macrophage recruitment, preventing further gut bacteria translocation [40].

AIEC can penetrate the lamina propria and be internalized by macrophages, where it replicates continuously and secretes high levels of TNF-α, contributing to intestinal inflammation [18, 59, 62]. Furthermore, AIEC also evades host immune responses by inhibiting the activation of signal transducer and activator of transcription 1 (STAT1) mediated by IFN-γ in intestinal epithelial cells (IECs), thereby preventing appropriate antibacterial responses [89]. Research from Clardy's lab indicates that *R. gnavus* can produce and release PSA1, which prompts dendritic cells (DCs) to express TNF-α via TLR4 activation. TNF-α is a key molecule involved in multiple signaling pathways during the development of IBD [90]. *R. gnavus* is associated with recurrent CD, poor response to anti-TNF-α treatments, and CD relapse post-surgery [18]. ETBF triggers localized colon STAT3 activation and a Th17 immune response [64–66]. The *B. fragilis* toxin (BFT) gene encodes oncotoxins that elevate IL-17 levels in the colon [66]. Previous research links colitis in IL-10 knockout mice inoculated with *Enterococcus faecalis* to gene expression changes observed in human IBD [91]. IL-1β is suggested to facilitate *Helicobacter hepaticus*-mediated colitis in mouse models of IBD by enhancing ILC activation and neutrophil recruitment [84]. *Helicobacter hepaticus* predominantly incites inflammatory Th17 cells in IL-10-deficient animals, leading to spontaneous colitis [92]. Additionally, gene silencing of IL-36 has been shown to alleviate *Citrobacter rodentium*–induced colitis in rodents [93]. *A. parvulum*'s pathogenic mechanism may involve H_2S-induced disulfide bond disruption in the mucus layer. Excessive H_2S has been linked to decreased mitochondrial detoxifying enzyme expression in the colonic tissues of CD patients, elevated inflammation-related gene expression in mice, and enhanced T-cell activation in vitro [63].

Recent research has illuminated the complex interaction between gut fungi and immune cells, highlighting its significance in gastrointestinal diseases. It is noted that a significant portion of patients, approximately 60–70%, possess antifungal antibodies in their serum, with anti-Saccharomyces cerevisiae antibody (ASCA) IgA being the most prevalent [5]. This is crucial because the depletion of the CX3XR1 gene in macrophages, observed in mouse models, correlates with a marked reduction in antifungal antibodies in patients with CD, potentially aggravating intestinal conditions following fungal colonization [94]. Moreover, studies, including one by Sokol, have demonstrated that brewing yeast significantly boosts the production of the anti-inflammatory cytokine IL-10, suggesting a protective role against inflammation [43]. Conversely, the latest findings reveal that *M. sympodialis* can trigger mast cells to increase the release of cysteine leukotriene and bolster the IgE response, contributing to pro-inflammatory effects [95]. Furthermore, *Malassezia restricta* has been shown to worsen colitis in mouse models by affecting the caspase-associated

recruitment domain 9 (CARD9) protein mechanism [18, 44]. *Candida albicans*, commonly found in the intestines of CD patients, is known to promote Th17 cell induction [96], further implicating fungal elements in the pathogenesis of IBD. Additionally, *Methanosphaera stadtmanae* is linked to antigen-specific IgG responses in IBD patients, emphasizing the diverse roles of fungal communities in immune responses [57]. These communities also engage with the immune system via the innate immune receptor Dectin-1, with studies showing that *Candida tropicalis* colonization in SPF mice leads to more severe colitis in Dectin-1-deficient mice compared to both non-colonized and colonized wild-type counterparts. This body of evidence underscores the intricate interactions between gut fungi and the immune system, revealing potential therapeutic targets for managing gastrointestinal diseases [45, 46].

Correlation between gut microbiota dysbiosis and laboratory inflammatory markers

To elucidate the potential involvement of gut bacteria in CD pathogenesis, various studies have examined the links between specific bacterial genera and key diagnostic markers. These markers often include elevated platelet counts, increased acute phase proteins—particularly C-reactive protein (CRP)—and the presence of anemia. One study highlights a positive correlation between CRP and WBC counts with the presence of *Escherichia-Shigella*, indicating this genus's possible role in elevating these inflammatory markers. Conversely, albumin (ALB) levels exhibit a negative correlation with *Veillonella*, *Escherichia-Shigella*, and *Atlantibacter* but show positive associations with *Roseburia* and *Lachnospira*, suggesting a complex interplay between these bacterial genera and systemic protein levels. Hemoglobin (Hb) levels, similarly, are positively associated with *Roseburia*, *Agathobacter*, and *Lachnospira*, further underscoring the intricate relationships between gut microbiota and host physiology [30]. Notably, variations in *Oscillospira* spp. Have been linked to changes in ESR and WBC counts, particularly in conditions involving stenosis [96]. Spearman correlation heatmap analyses reveal a significant negative correlation between *Roseburia* and fecal calprotectin (FC), as well as between *Faecalibacterium* and CRP, and *Dorea* and ESR, respectively. Conversely, a significant positive correlation exists between *Escherichia-Shigella* with CRP and between *Ruminococcus 2* with clinical symptoms, highlighting the diverse impacts of gut microbiota on inflammatory responses and CD symptoms [97]. Fecal biomarkers like FC are increasingly used for CD screening and activity assessment, with postoperative FC concentrations above 100 μg/g indicating a high sensitivity for predicting endoscopic recurrence [5]. However, the microbiome risk score, while associated with CD, does not show a correlation with FC levels, indicating the need for a multifaceted approach to understanding and utilizing these biomarkers in CD management [98]. The interplay between CD pro- and anti-inflammatory responses mediated by the gut microbiota is shown in Fig. 1.

The association between gut microbiota dysbiosis and the progression and prognosis of CD

Gut microbiota dysbiosis related to CD disease activity

Recent studies have delved into the gut microbiota's role in CD, uncovering distinct microbial patterns during different disease stages [99]. Notably, *Bacteroides* species have been found to predominate during periods of remission and intermediate stages of the disease. Furthermore, higher levels of *M. Smithii* have been observed during clinical remission compared to active phases [54]. An extensive prospective observational study of 259 CD patients revealed a correlation between microbial community characteristics and escalating symptom severity over time. Specifically, a deterioration in clinical symptoms was linked to a surge in pro-inflammatory bacteria, including Proteobacteria (such as *Klebsiella*, *Pseudomonas*, *Salmonella*, *Acinetobacter*, and *Hafni*) and Firmicutes (such as *Staphylococcus*, *Enterococcus*, and *Streptococcus*) [100]. Additionally, the presence of AIEC in the ileal mucosa has been associated with increased disease activity [101]. During moderate to severe CD episodes, an enhanced abundance and diversity of gut microbiota are observed, alongside a positive correlation between fungal manifestations and disease severity. This suggests that shifts in microbial composition may mirror fluctuations in CD activity [102, 103]. A systematic review has indicated that, compared to remission phases, the gut microbiome of patients with active CD exhibits a notable increase in Enterobacteriaceae, *Klebsiella*, Pseudomonadota, and *Fusobacterium*, while levels of *Bifidobacterium* and Clostridia significantly diminish [26, 104]. Additionally, it was found that in patients who had undergone small intestine resection and were not experiencing active disease, levels of *Parabacteroides* and *Clostridium* returned to normal [11].

Gut microbiota dysbiosis and disease phenotype prediction

The clinical phenotype of CD exhibits considerable complexity, with high heterogeneity in disease progression. Microbiome research has shed light on predicting disease progression and differentiating complex phenotypes. Initial studies indicate that mucosal-associated microbiota dysbiosis is linked to disease phenotypes [105]. Phylogenetic

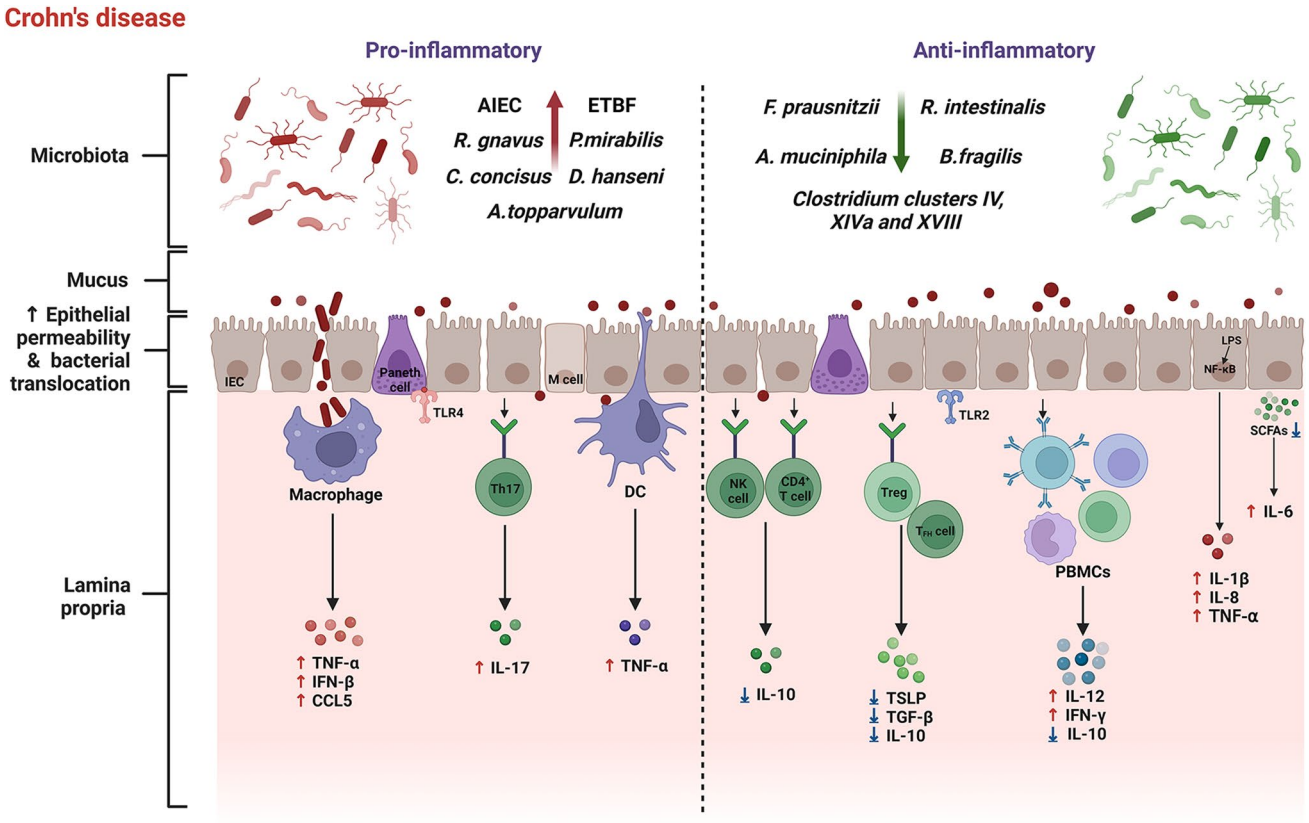

Fig. 1 Interplay between pro-inflammatory and anti-inflammatory responses in CD mediated by gut microbiota. Pathobionts, depicted on the left, can exacerbate CD by various mechanisms: increased epithelial permeability and bacterial translocation; interactions with immune cells leading to upregulation of pro-inflammatory cytokines such as TNF-α, IFN-β, and CCL5; and specific bacteria like AIEC and ETBF promoting inflammation via direct interaction with IECs, macrophages, and DCs. Conversely, the right side illustrates anti-inflammatory microbes that contribute to disease mitigation through the production of SCFAs and the downregulation of inflammatory cytokines, supporting the maintenance of a protective mucus layer and T_{reg} cell expansion, which can suppress excessive immune responses. Key anti-inflammatory species include *F. prausnitzii* and *R. intestinalis*. Red arrows represent the increased effect or presence of pathogenic actions, while green denotes regulatory or protective mechanisms. TNF, tumor necrosis factor; IFN, interferon; CCL5, C–C motif chemokine ligand 5; IECs, intestinal epithelial cells; DC, dendritic cell; SCFAs, short-chain fatty acids; T_{reg} cell, regulatory T cell

analyses reveal distinct species distributions in the gut microbiome among different IBD subtypes compared to controls. CD primarily affects the ileum (L1, 35%) and the ileocolon (L3, 64.7%). The prevalence of AIEC in the ileal mucosa of adult CD patients ranges between 21 and 63%, which is higher than in colon diseases [29]. Gut microbiota in colon CD patients differs from that in ileal CD, associated with reduced α diversity in ileal diseases [106]. Patients with ileal CD, particularly those undergoing surgical resection, show the most significant deviation from health [107]. Statistical analysis indicates that *Enterococcus faecalis* and unidentified Erysipelotrichaceae species levels are elevated in fecal samples when the disease is confined to the ileum, compared to the colon [108]. Furthermore, the fungal microbiota associated with colon mucosa is dominated by the phyla Basidiomycota and Ascomycota, whereas *Cystofilobasidiaceae* family and *Candida glabrata* species are overly represented [109]. Differences also exist in the mucosal-associated microbiota between narrowed and non-narrowed areas [96]. Therefore, assessing mucosal-associated microbiota could serve as a superior biomarker for CD over fecal microbiota.

Gut microbiota dysbiosis and evaluation of CD drug treatment efficacy

Numerous studies have established a close connection between the gut microbiota composition changes in CD patients and their response to biopharmaceutical therapy. A prospective study highlighted that IBD patients who achieved clinical remission early through anti-cytokine therapy, including anti-TNF-α and anti-IL-12/23, had significantly higher baseline microbial species richness [110]. This study also identified nine microorganisms at baseline

associated with early clinical remission in patients undergoing anti-TNF-α treatment, and three microorganisms correlated with the response to vedolizumab (VDZ). The microbiome of patients responding well to anti-TNF-α treatment gradually aligns with that of healthy individuals, marked by a reduction in Enterobacteriaceae (notably *E. coli*) and *Ruminococcus*, and an increase in Bacteroidetes and Firmicutes [111]. Moreover, other research has found that taxa such as *Bifidobacterium*, *Collinsella*, *Lachnospira*, *Roseburia*, and *Eggerthella* are linked to a positive response to anti-TNF-α treatment [11]. Treatment interventions based on Adalimumab (ADA) are associated with the restoration of a healthier microbial environment after six months, especially noticeable in the CD patient cohort. Patients treated with ADA exhibited a decrease in Proteobacteria and an increase in Lachnospiraceae, a pattern prevalent among those achieving successful treatment outcomes, suggesting a direct relationship between dysbiosis and treatment efficacy [112]. Retrospective analysis indicated that ADA significantly enhanced clinical remission and mucosal healing in patients with mild to moderate active CD, with notable microbiota changes serving as predictors of ADA effectiveness [113]. Furthermore, a study found a correlation between CD-related ecological dysbiosis, characterized by a decrease in Firmicutes, and the relapse time post-withdrawal from infliximab (IFX). The absence of certain bacterial communities or species, such as *F. prausnitzii*, could act as predictive markers for recurrence [114]. In the phase 2 CERTIFI study, OTUs in the fecal microbiota of CD patients treated with ustekinumab (UST), particularly *Faecalibacterium*, were associated with treatment-induced remission, suggesting potential biomarkers for post-treatment remission status [115]. Despite the limited evidence, it is also suggested that immunosuppressants may heighten the host's susceptibility to fungal infections [63].

Gut microbiota dysbiosis and postoperative treatment efficacy in CD

Mucosal healing stands as a primary objective in treating CD. The identification of six genera—*Faecalibacterium*, *Lachnospira*, *Paraprevotella*, *Dialister*, *Streptococcus*, and *Clostridium*—as predictive markers for mucosal healing signifies their potential role as biomarkers for healing in the small intestinal mucosa [116]. Notably, CD patients who achieve and maintain remission post-surgery exhibit gut microbiota compositions that closely resemble those of healthy control groups, marked by increased microbial abundance [117]. Furthermore, 16S rRNA sequencing has revealed significant shifts in the gut microbiome of CD patients who experience endoscopic disease relief one year after surgical intervention. Specifically, an uptick in *Alistipes* is observed, alongside a reduction in Actinobacteriota and *Bifidobacterium* [21]. These insights underscore the value of gut microbiota analysis in shaping treatment strategies for CD patients, particularly those considering surgical options.

The CD is notably characterized by its high postoperative recurrence rate, with up to 80% of patients requiring at least one surgical intervention, and approximately 70% facing endoscopic recurrence within a year following surgery [118]. Currently, there is a lack of an effective method for predicting or preventing such recurrences. Recent research has intensively examined the link between microbial imbalance and postoperative recurrence in CD, focusing primarily on the ileum's mucosa-associated microbiota (MAM). This focus is due to MAM's more accurate reflection of the gut microbiota's actual state, its superior predictive value for postoperative recurrence, and its stronger correlation with the clinical phenotype. Endoscopic recurrence is notably linked with significant alterations in MAM, particularly a reduction in microbial diversity [119]. During postoperative recurrence, there is an observed increase in potentially pathogenic bacteria (e.g., Bacteroidia, *Prevotella*, *Flavobacterium*, *Tepidimonas*, and *Escherichia-Shigella*), coupled with a decline in potentially beneficial bacteria (e.g., *Bifidobacterium*, *Lactobacillus*, *Faecalibacterium*, and *Butyricicoccus*) [120]. Moreover, a combined decrease in the relative abundance of *Proteus* and *Faecalibacterium* in postoperative ileal biopsies has been associated with a heightened risk of CD recurrence [31]. The significant microbiota differences between patients experiencing recurrent and first-time surgeries suggest that MAM patterns may play a role in triggering CD recurrences [120, 121]. Surgical interventions result in reduced diversity of mucosa-associated microbiota in CD patients, with variances observed among patients based on their clinical outcomes after 6 months [122]. A low level of *F. prausnitzii* is predictive of postoperative recurrence in ileal CD or recurrence after ceasing Infliximab treatment [11, 114]. AIEC colonization, marked by specific microbial community traits such as an increase in *R. gnavus*, underscores AIEC's involvement in early CD recurrence [123]. The disruption in the association network between Lachnospiraceae and Oscillospiraceae is linked with frequent CD recurrence and adverse reactions to TNF-α treatments [26]. Post-surgery, the gut microbiota in CD patients shows a reduction in *Parabacteroides* and Clostridiales and an increase in Enterobacteriales, leading to an almost inevitable recurrence if left untreated [26]. The presence of *Streptococcus* in preoperative fecal samples is associated with future recurrences [108]. Monitoring relapse-related bacteria could potentially aid in preventing postoperative CD recurrences, although no consistent

bacteria or metabolites have yet been identified as reliable predictors for such recurrences [124].

Recent studies have delved into the connection between the microbiota and postoperative complications following CD surgery. A pivotal prospective cohort study featured in The Lancet explored this relationship in 913 children with CD, who did not face complications within the first 90 days post-diagnosis. Through the collection and 16S rRNA sequencing of fecal samples from the ileum and rectum, researchers identified a significant association between certain genera, including *Campylobacter*, *Akkermansia*, *Collinsella*, and *Desulfovibrio*, with childhood CD. Additionally, *Ruminococcus* has been linked to stenosis complications, while *Veillonella* is associated with penetrating complications. Notably, in cases of penetrating CD, an increase in *Collinsella* bacteria is observed, with *Veillonella* levels particularly rising in the ileum [125]. At the genus level, a decrease in *Lactobacillus*, *Oscillospira*, *Subdoligranulum*, *Hydrogenophaga*, *Clostridium*, and *Allobaculum* is noted in narrowed intestinal segments [96]. *Oscillospira* sp. stands out for its negative correlation with intestinal fibrosis and the postoperative course, marking it as a potential biomarker for these conditions [96]. Surgical intervention is a common treatment pathway for 50–70% of CD patients, with surgical site infection (SSI) being a primary risk. The REMIND multicenter prospective cohort study has shown that ileal MAM could potentially forecast SSI following CD ileocolonectomy, offering a strategy to mitigate SSI risk. Furthermore, a retrospective analysis of 90 IBD patients revealed an association between the presence of *C. innocuum* bacteria and a lower incidence of abdominal abscesses in IBD patients, underscoring the potential of specific microbiota components in reducing post-surgical complications [126].

Targeting the gut microbiota for the prevention and treatment of CD

Dietary intervention

Diet significantly influences the composition and functionality of the gut microbiota, a critical factor in managing CD. Research, including the Adolescent Nutrition Study on Healthy Lifestyles in Europe and the Nurses' Health Study (NHS) and NHSII, highlights the link between dietary patterns and CD risk. These studies collectively suggest that a high intake of dietary fiber, particularly from cruciferous vegetables and cereals, correlates with a reduced incidence of CD [127, 128]. Specifically, a prospective study demonstrated that individuals in the highest quintile of long-term dietary fiber intake (median 24.3 g/day) experienced a 40% decrease in CD risk [127]. A 6-month study of CD patients revealed that high fiber intake (median 23.7 g/day) reduced flare risk by 42%, with no obstruction events reported even in stricturing disease subgroups. Notably, 30% of patients avoided fiber due to intolerance concerns, yet these individuals faced 40% higher flare rates [129]. This protective effect of dietary fiber against CD may be attributed to the gut microbiota's ability to metabolize fiber into SCFAs, which promote mucosal immune tolerance [130]. Importantly, CD patients with prior surgery or strictures tolerated high-fiber diets without complications, challenging conventional recommendations for fiber restriction [129]. Therapeutic diets play a pivotal role in both inducing and maintaining CD remission. Exclusive enteral nutrition (EEN) stands out as an effective method for reducing inflammation and modulating gut microbiota composition [131], showing equivalent efficacy to corticosteroids in pediatric CD patients without the associated side effects [132–134], making it particularly beneficial for this group [135]. Moreover, the CD Therapeutic Dietary Intervention (CD-TDI) presents a novel dietary strategy that induces clinical and biomarker remission in active CD patients [136]. Dietary interventions can also align the gut microbiota of patients consuming a non-diversified diet (NDD) more closely with those on a diversified diet (DD) [137]. Additionally, adopting a plant-based or low-inflammatory diet can enhance microbial characteristics and mitigate disease symptoms [138]. These findings underscore the critical role of diet in mitigating CD microbiota dysbiosis and fostering a balanced microbial community. Therefore, when devising nutritional guidelines for CD patients, it is essential to consider the comprehensive impact of diet on symptoms, microbiota composition, and the long-term prognosis.

Probiotics, prebiotics, synbiotics, and postbiotics

Probiotics, defined as live microorganisms that confer health benefits on the host when ingested in adequate amounts, present a potential strategy for modulating the gut microbiota in CD patients [139]. This approach involves either curbing the growth of harmful bacteria or fostering the recovery of beneficial ones through probiotic supplementation. Despite the promise, the efficacy of currently available probiotics in managing CD is limited, offering only temporary improvements in the gut environment without specificity for distinct CD patient groups [140]. A 2020 Cochrane systematic review analyzing two randomized trials ($n = 46$) found no significant difference between probiotics and placebo in inducing remission (RR 1.06; 95% CI 0.65–1.71), with very low certainty evidence due to small sample sizes and methodological limitations

[141]. Nonetheless, recent advancements have spotlighted more targeted probiotic formulations like the Visbiome (derived from the original VSL#3 composition), which combines specific anti-inflammatory bacterial strains shown to modulate mucosal immunity in preclinical models [142, 143]. Notably, even these next-generation formulations currently lack robust clinical validation in large-scale CD trials. This contrasts with the limited evidence for traditional probiotics highlighted in systematic reviews. Cutting-edge research has identified specific mechanisms through which probiotics can combat CD, including DL endopeptidases from *Lactobacillus salivarius* or mifamurtide, which target colonic inflammation and CD symptoms by revitalizing *NOD2* receptor functions [144]. Another promising probiotic category is butyrate-producing bacteria, like *F. prausnitzii* and *R. intestinalis*, known to significantly elevate butyrate levels in the colon. This increase enhances butyrate's presence in both the mucus layer and the lumen, contributing to colonic health [145]. Furthermore, experimental approaches, such as employing a thymidine restriction strategy to administer a recombinant *Lactococcus lactis* strain producing IL-10, have shown some efficacy, albeit leading to only modest disease activity improvement in a small cohort of CD patients [146]. In conclusion, while traditional probiotics may offer limited benefits for CD management, the exploration and development of novel probiotic strains and mechanisms hold considerable promise for future therapeutic interventions.

Prebiotics are dietary fibers and non-digestible food ingredients selectively utilized by host microorganisms, conferring health benefits [147]. They modulate the gut microbiome's composition and metabolism through fermentation by symbiotic intestinal microorganisms [140, 148, 149], thereby enhancing the host's health. Among various types, oligofructose-enriched inulin (OF-IN), derived naturally from foods like chicory roots and onions, is the most extensively studied prebiotic [140, 147]. Despite the potential benefits, a placebo-controlled study involving 120 active CD patients supplemented with 15 g/day of fructo-oligosaccharides (FOS) did not demonstrate clinical improvement [150]. Nonetheless, other studies have shown promising results, indicating that an increased microbial shift towards *Bifidobacterium longum* correlates with improved disease activity in CD patients, particularly those who are inactive or have mild to moderate disease activity after consuming 10 g of OF-IN daily. Additionally, OF-IN consumption has been associated with elevated levels of fecal butyrate and acetaldehyde, suggesting its beneficial effects on the gut environment and potentially on CD management [151, 152].

Synbiotics refer to the strategic combination of prebiotics and probiotics that interact synergistically to enhance gastrointestinal health. Probiotics promote the growth of beneficial gut microbiota, while prebiotics serve as nourishment for these beneficial bacteria, together effectively inhibiting the proliferation of pathogenic bacteria. This synergistic interaction enhances the intestinal barrier's integrity, contributing to overall gut health. In a focused placebo-controlled randomized trial involving 35 patients with active CD, administering a synbiotic consisting of Synergy 1 and *B. longum* resulted in notable improvements in histological samples after 3 months and 6 months. This intervention led to significant clinical symptom relief in patients with active CD, underscoring the potential of synbiotics as an effective therapeutic strategy for managing CD [153].

Metabiotics, also known as postbiotics, are bioactive compounds produced by the metabolic activity of probiotics. These substances include a wide range of beneficial products, such as enzymes, peptides, organic acids, and polysaccharides. The American Gastroenterological Association has acknowledged the potential of probiotics, and by extension metabiotics, in treating functional symptoms of IBD [154]. Research has shown that the oral administration of live *Clostridium* perfringens or its supernatant, which contains a variety of metabiotics, can significantly ameliorate the severity of trinitrobenzene sulfonic acid (TNBS)-induced colitis. This effect is attributed in part to the secretion of metabiotics capable of inhibiting the activation of NF-κB and the production of IL-8, both of which are crucial in the inflammatory response [81]. Moreover, *A. muciniphila*, or specifically its outer membrane protein Amuc_1100, represents another fascinating example of metabiotic action. This intervention has been found to mitigate colitis symptoms, leading to a reduction in the infiltration of macrophages and $CD8^+$ cytotoxic T lymphocytes (CTL) in the colon [155]. Such findings highlight the promising therapeutic potential of metabiotics in managing inflammatory conditions like IBD by modulating immune responses and intestinal inflammation.

FMT

FMT represents a groundbreaking and effective approach to modulating the gut microbiota in CD patients. This procedure involves the transplantation of fecal matter from healthy donors into the gastrointestinal tract of CD patients, aiming to reestablish a normal microbial community structure and functionality. Initially celebrated for its significant efficacy in treating *Clostridioides difficile* infection (CDI), FMT is now being investigated as a potential therapeutic strategy for CD. Notably, a randomized, single-blind, placebo-controlled trial investigating the impact of FMT on patients with colon or ileal CD did not reveal a significant difference in the overall response rate when compared to autologous

fecal samples. However, a subgroup of patients showing a higher colonization ability of donor microbiota demonstrated a greater likelihood of maintaining remission [156]. Moreover, another randomized controlled trial focusing on ileum CD patients reported a reduction in disease severity index, as assessed by endoscopy, 6 weeks post-FMT [157]. Further compelling evidence comes from a case report of a CD colitis patient who, after failing to respond to biologics, experienced clinical and endoscopic improvement following a single FMT [158]. Additionally, a pilot study involving patients with refractory CD utilized a midgut catheter for single FMT administration, showcasing the procedure's safety, feasibility, and preliminary efficacy [159]. While research into FMT's role in CD treatment remains at an early stage, the theoretical basis suggests that FMT could diminish pathogen levels by reinstating a balanced microbiota, enriched with beneficial bacteria and bacteriophages. This potential for microbial ecosystem restoration underscores FMT's promising horizon in CD management.

Traditional Chinese medicine

The healing benefits of Chinese traditional medicine, along with acupuncture and moxibustion, for CD have gained increasing recognition in recent years. Research by Xiaoye Liu and colleagues [160] highlights the efficacy of these treatments in managing gut microbiota and inflammatory responses in CD. For instance, the study on Bai Tou Weng Tang, a traditional Chinese herbal formula, compared to levofloxacin hydrochloride for treating *E. coli* infection in rats, revealed that Bai Tou Weng Tang not only restored *Bacteroidetes* spp. in the gut microbiota but also suppressed the release of IL-8 and ICAM-1, thereby protecting the intestinal barrier. Additionally, the combined use of Shen Ling Bai Zhu San and Si Shen Wan has been found to facilitate the recovery of the intestinal microbiota's structure and composition. This combination increases the production of SCFAs and reduces levels of inflammatory cells and cytokines, offering therapeutic relief for CD patients [161, 162]. While studies on acupuncture and moxibustion's impact on gut flora are limited, existing research indicates that these practices can effectively induce and maintain remission in active CD cases [163, 164]. Furthermore, when acupuncture and moxibustion are paired with probiotics, there is a significant regulation of intestinal flora imbalance. This synergistic approach enhances the concentration of probiotics in the gut, contributing to the maintenance of a balanced intestinal microecology. These findings underscore the potential of integrating Chinese traditional medicine, acupuncture, and moxibustion with modern probiotic therapy to offer a comprehensive and effective treatment strategy for CD, focusing on both symptom relief and the underlying microbial imbalances.

Conclusions

Significant progress has been made in understanding the gut microbiota, yet the intricate relationships among different microorganisms and their links to CD remain not fully elucidated. While numerous studies have established an association between pathogens and the onset and progression of CD, a comprehensive understanding of these relationships is still lacking. A deeper insight into the role of gut microbiota in CD pathogenesis, along with targeted monitoring and modulation at various stages, could offer innovative approaches for diagnosis and treatment. It is crucial to comprehend how microorganisms and their by-products influence the immune status of the host in both health and disease.

Targeting the microbiota in CD patients might emerge as a novel therapeutic strategy, despite some limitations in clinical data. Methods for modulating the gut microbiota encompass dietary interventions, probiotics, prebiotics, synbiotics, metabiotics, FMT, and TCM (Fig. 2). Specifically, FMT shows extensive potential as a therapy in CD, but its efficacy and safety necessitate further validation through rigorous, large-scale clinical trials. Microbial-derived therapies are in nascent stages; however, ongoing research and trials suggest that leveraging microbial pathways could lead to promising treatments for CD. The exploration of gut microbiota ushers in a fresh perspective and research avenue for understanding CD's clinical features and prognosis, offering new hope to patients. The recent advancements in CD microbiome research are encouraging, and we anticipate further studies to provide more profound insights, enhance therapeutic approaches, and improve treatment outcomes for this prevalent condition. Investigating the mechanisms of pathogen spread, promotion of symbiotic dysbiosis, immune evasion, and factors limiting clinical remission will enhance our understanding of inflammatory bowel disease pathophysiology. Accordingly, targeting pathogens may represent a pivotal focus for future therapeutic endeavors.

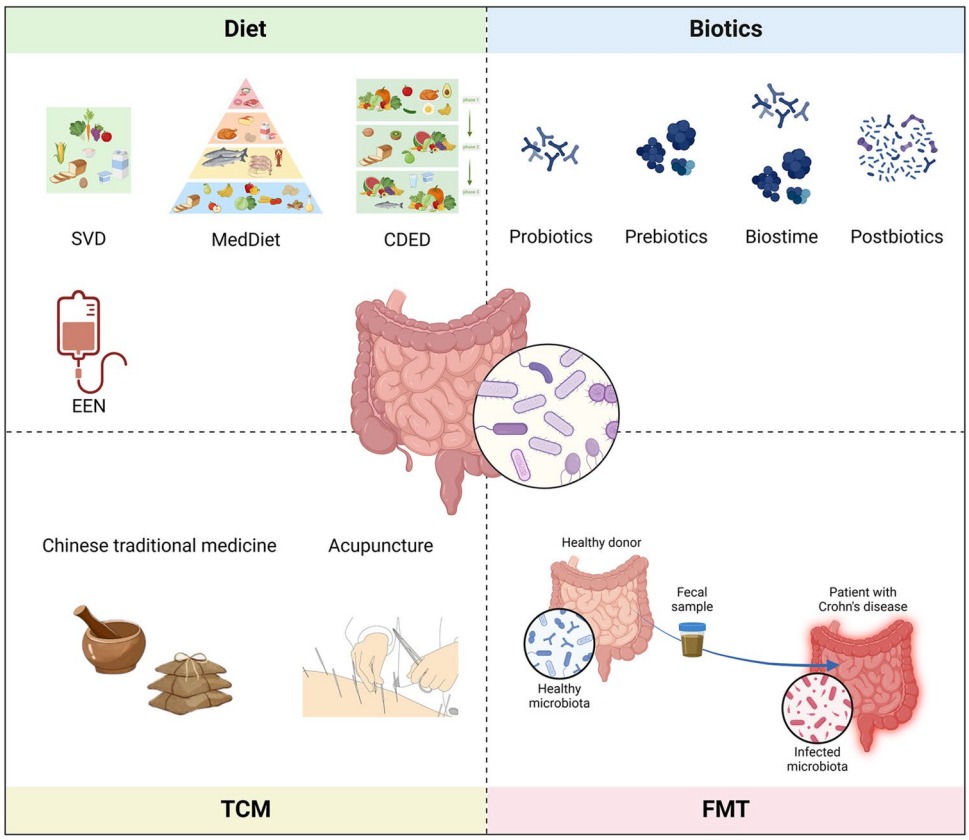

Fig. 2 Comprehensive strategies for microbiome-based therapeutic interventions in CD. This figure illustrates a four-pronged approach: (1) dietary modifications, including the SVD, MedDiet, CDED, and EEN, are shown as foundational measures to reshape the gut flora. (2) Biotics, such as probiotics, prebiotics, biostime, and postbiotics, aim to maintain and enhance beneficial microbiota. (3) TCM, represented by herbal remedies and acupuncture, is integrated to offer holistic modalities for managing gut health. (4) FMT is presented as a supplementary therapy, transferring fecal matter from a healthy donor to a CD patient to address dysbiosis. This diagram encapsulates the array of interventions designed to modulate the microbiota and counteract pathobionts, aiming to mitigate CD symptoms and facilitate clinical remission. SVD, semi-vegetarian diet; MedDiet, Mediterranean diet; CDED, Crohn's disease exclusion diet; EEN, exclusive enteral nutrition; TCM, traditional Chinese medicine; FMT, fecal microbiota transplantation

Author contribution Yao Xu and Runxiang Xie proposed the article idea, Yao Xu, Yuqing Weng, Yewei Fang, Shuan Tao, He Zhang, Huimin Chen, and Axiang Han performed the literature search and data analysis, and drafted the article.Runxiang Xie, Qi Jiang, and Wei Liang critically revised the work.

Funding This study was supported by the Project of key R&D program of the year 2022 of Ningbo Science and Technology Bureau (2022z2202022), the Key Project of Ningbo Municipal Science and Technology Bureau (2023j020), the Population Welfare Foundation Medical Innovation Project of China (SLB-6–20230912-351), the Medical Science and Technology Project of China (2022Y05), and the hospital-level project of the First Affiliated Hospital of Ningbo University (XGY2308).

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Siniagina MN, Markelova MI, Boulygina EA, Laikov AV, Khusnutdinova DR, Abdulkhakov SR et al (2021) Diversity and adaptations of escherichia coli strains: exploring the intestinal community in Crohn's disease patients and healthy individuals. Microorganisms 9(6):1299. https://doi.org/10.3390/microorganisms9061299
2. Nakase H, Uchino M, Shinzaki S, Matsuura M, Matsuoka K, Kobayashi T et al (2021) Evidence-based clinical practice guidelines for inflammatory bowel disease 2020. J Gastroenterol 56(6):489–526
3. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI et al (2017) Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet 390(10114):2769–2778
4. Roda G, Chien Ng S, Kotze PG, Argollo M, Panaccione R, Spinelli A et al (2020) Crohn's disease Nat Rev Dis Primers 6(1):22
5. Torres J, Mehandru S, Colombel JF, Peyrin-Biroulet L (2017) Crohn's disease. Lancet 389(10080):1741–1755
6. Baumgart DC, Le Berre C (2021) Newer biologic and small-molecule therapies for inflammatory bowel disease. N Engl J Med 385(14):1302–1315
7. 练磊, 吴小剑, 谢明颢, 兰平. 炎性肠病外科百年发展历程. 中华胃肠外科杂志. 2016;19(01):31–6.
8. Fiorino G, Bonifacio C, Peyrin-Biroulet L, Danese S (2016) Preventing collateral damage in Crohn's disease: the Lémann index. J Crohns Colitis 10(4):495–500
9. Packey CD, Sartor RB (2008) Interplay of commensal and pathogenic bacteria, genetic mutations, and immunoregulatory defects in the pathogenesis of inflammatory bowel diseases. J Intern Med 263(6):597–606
10. Zhang M, Sun K, Wu Y, Yang Y, Tso P, Wu Z (2017) Interactions between intestinal microbiota and host immune response in inflammatory bowel disease. Front Immunol 8:942
11. Glassner KL, Abraham BP, Quigley EMM (2020) The microbiome and inflammatory bowel disease. J Allergy Clin Immunol 145(1):16–27
12. Eckburg PB, Bik EM, Bernstein CN, Purdom E, Dethlefsen L, Sargent M et al (2005) Diversity of the human intestinal microbial flora. Science 308(5728):1635–1638
13. Petersen C, Round JL (2014) Defining dysbiosis and its influence on host immunity and disease. Cell Microbiol 16(7):1024–1033
14. Nishida A, Inoue R, Inatomi O, Bamba S, Naito Y, Andoh A (2018) Gut microbiota in the pathogenesis of inflammatory bowel disease. Clin J Gastroenterol 11(1):1–10
15. Halfvarson J, Brislawn CJ, Lamendella R, Vázquez-Baeza Y, Walters WA, Bramer LM et al (2017) Dynamics of the human gut microbiome in inflammatory bowel disease. Nat Microbiol 2:17004
16. Sartor RB (2004) Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 126(6):1620–1633
17. Lloyd-Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila-Pacheco J, Poon TW et al (2019) Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature 569(7758):655–662
18. Schirmer M, Garner A, Vlamakis H, Xavier RJ (2019) Microbial genes and pathways in inflammatory bowel disease. Nat Rev Microbiol 17(8):497–511
19. Gevers D, Kugathasan S, Denson LA, Vazquez-Baeza Y, Van Treuren W, Ren B et al (2014) The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe 15(3):382–392
20. Abdel-Rahman LIH, Morgan XC (2023) Searching for a consensus among inflammatory bowel disease studies: a systematic meta-analysis. Inflamm Bowel Dis 29(1):125–139
21. Strömbeck A, Lasson A, Strid H, Sundin J, Stotzer PO, Simrén M et al (2020) Fecal microbiota composition is linked to the postoperative disease course in patients with Crohn's disease. BMC Gastroenterol 20(1):130
22. Vila AV, Imhann F, Collij V, Jankipersadsing SA, Gurry T, Mujagic Z et al (2018) Gut microbiota composition and functional changes in inflammatory bowel disease and irritable bowel syndrome. Sci Transl Med 10(472):eaap8914. https://doi.org/10.1126/scitranslmed.aap8914
23. Lopez-Siles M, Duncan SH, Garcia-Gil LJ, Martinez-Medina M (2017) Faecalibacterium prausnitzii: from microbiology to diagnostics and prognostics. ISME J 11(4):841–852
24. Imhann F, Vich Vila A, Bonder MJ, Fu J, Gevers D, Visschedijk MC et al (2018) Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut 67(1):108–119
25. Png CW, Lindén SK, Gilshenan KS, Zoetendal EG, McSweeney CS, Sly LI et al (2010) Mucolytic bacteria with increased prevalence in IBD mucosa augment in vitro utilization of mucin by other bacteria. Am J Gastroenterol 105(11):2420–2428
26. Yilmaz B, Juillerat P, Oyas O, Ramon C, Bravo FD, Franc Y et al (2019) Microbial network disturbances in relapsing refractory Crohn's disease. Nat Med 25(2):323
27. Danilova NA, Abdulkhakov SR, Grigoryeva TV, Markelova MI, Vasilyev IY, Boulygina EA et al (2019) Markers of dysbiosis in patients with ulcerative colitis and Crohn's disease. Ter Arkh 91(4):17–24
28. Siniagina M, Markelova M, Laikov A, Boulygina E, Khusnutdinova D, Kharchenko A et al (2020) Cultivated Escherichia coli diversity in intestinal microbiota of Crohn's disease patients and healthy individuals: whole genome data. Data Brief 28:104948
29. Palmela C, Chevarin C, Xu ZL, Torres J, Sevrin G, Hirten R et al (2018) Adherent-invasive Escherichia coli in inflammatory bowel disease. Gut 67(3):574–587
30. Hu J, Cheng S, Yao J, Lin X, Li Y, Wang W et al (2022) Correlation between altered gut microbiota and elevated inflammation markers in patients with Crohn's disease. Front Immunol 13:947313
31. Zhang J, Hoedt EC, Liu Q, Berendsen E, Teh JJ, Hamilton A et al (2021) Elucidation of proteus mirabilis as a key bacterium in Crohn's disease inflammation. Gastroenterology 160(1):317–30.e11
32. Kang S, Denman SE, Morrison M, Yu Z, Dore J, Leclerc M et al (2010) Dysbiosis of fecal microbiota in Crohn's disease patients as revealed by a custom phylogenetic microarray. Inflamm Bowel Dis 16(12):2034–2042
33. Wagner J, Short K, Catto-Smith AG, Cameron DJ, Bishop RF, Kirkwood CD (2008) Identification and characterisation of Pseudomonas 16S ribosomal DNA from ileal biopsies of children with Crohn's disease. PLoS ONE 3(10):e3578
34. Hall AB, Yassour M, Sauk J, Garner A, Jiang XF, Arthur T et al (2017) A novel Ruminococcus gnavus clade enriched in inflammatory bowel disease patients. Genome Med 9(1):103. https://doi.org/10.1186/s13073-017-0490-5
35. Andoh A, Imaeda H, Aomatsu T, Inatomi O, Bamba S, Sasaki M et al (2011) Comparison of the fecal microbiota profiles between ulcerative colitis and Crohn's disease using terminal restriction fragment length polymorphism analysis. J Gastroenterol 46(4):479–486
36. Powell N, MacDonald TT (2017) Recent advances in gut immunology. Parasite Immunol 39(6). https://doi.org/10.1111/pim.12430

37. Miranda-Bautista J, Padilla-Suárez C, Bouza E, Muñoz P, Menchén L, Marín-Jiménez I (2014) Listeria monocytogenes infection in inflammatory bowel disease patients: case series and review of the literature. Eur J Gastroenterol Hepatol 26(11):1247–1252
38. Laharie D, Asencio C, Asselineau J, Bulois P, Bourreille A, Moreau J et al (2009) Association between entero-hepatic Helicobacter species and Crohn's disease: a prospective cross-sectional study. Aliment Pharmacol Ther 30(3):283–293
39. Chai JN, Peng Y, Rengarajan S, Solomon BD, Ai TL, Shen Z et al (2017) Helicobacter species are potent drivers of colonic T cell responses in homeostasis and inflammation. Sci Immunol. 2(13):eaal5068. https://doi.org/10.1126/sciimmunol.aal5068
40. Ha CWY, Martin A, Sepich-Poore GD, Shi B, Wang Y, Gouin K et al (2020) Translocation of viable gut microbiota to mesenteric adipose drives formation of creeping fat in humans. Cell 183(3):666–83.e17
41. Mottawea W, Chiang CK, Mühlbauer M, Starr AE, Butcher J, Abujamel T et al (2016) Altered intestinal microbiota-host mitochondria crosstalk in new onset Crohn's disease. Nat Commun 7:13419
42. Rowan F, Docherty NG, Murphy M, Murphy B, Calvin Coffey J, O'Connell PR (2010) Desulfovibrio bacterial species are increased in ulcerative colitis. Dis Colon Rectum 53(11):1530–1536
43. Sokol H, Leducq V, Aschard H, Pham HP, Jegou S, Landman C et al (2017) Fungal microbiota dysbiosis in IBD. Gut 66(6):1039–1048
44. Limon JJ, Tang J, Li DL, Wolf AJ, Michelsen KS, Funari V et al (2019) Malassezia is associated with Crohn's disease and exacerbates colitis in mouse models. Cell Host & Microbe 25(3):377
45. Iliev ID, Funari VA, Taylor KD, Nguyen Q, Reyes CN, Strom SP et al (2012) Interactions between commensal fungi and the C-type lectin receptor Dectin-1 influence colitis. Science 336(6086):1314–1317
46. Tang C, Kamiya T, Liu Y, Kadoki M, Kakuta S, Oshima K et al (2015) Inhibition of Dectin-1 signaling ameliorates colitis by inducing lactobacillus-mediated regulatory t cell expansion in the intestine. Cell Host Microbe 18(2):183–197
47. Olaisen M, Richard ML, Beisvåg V, Granlund AVB, Røyset ES, Rué O et al (2022) The ileal fungal microbiota is altered in Crohn's disease and is associated with the disease course. Front Med (Lausanne) 9:868812
48. Norman JM, Handley SA, Baldridge MT, Droit L, Liu CY, Keller BC et al (2015) Disease-specific alterations in the enteric virome in inflammatory bowel disease. Cell 160(3):447–460
49. Cadwell K, Patel KK, Maloney NS, Liu TC, Ng ACY, Storer CE et al (2010) Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell 141(7):1135-U64
50. Pérez-Brocal V, García-López R, Vázquez-Castellanos JF, Nos P, Beltrán B, Latorre A et al (2013) Study of the viral and microbial communities associated with Crohn's disease: a metagenomic approach. Clin Transl Gastroenterol 4(6):e36
51. Wagner J, Maksimovic J, Farries G, Sim WH, Bishop RF, Cameron DJ et al (2013) Bacteriophages in gut samples from pediatric Crohn's disease patients: metagenomic analysis using 454 pyrosequencing. Inflamm Bowel Dis 19(8):1598–608
52. Duerkop BA, Kleiner M, Paez-Espino D, Zhu W, Bushnell B, Hassell B et al (2018) Murine colitis reveals a disease-associated bacteriophage community. Nat Microbiol 3(9):1023–31
53. Baker BJ, De Anda V, Seitz KW, Dombrowski N, Santoro AE, Lloyd KG (2020) Diversity, ecology and evolution of Archaea. Nat Microbiol 5(7):887–900
54. Ghavami SB, Rostami E, Sephay AA, Shahrokh S, Balaii H, Aghdaei HA et al (2018) Alterations of the human gut Methanobrevibacter smithii as a biomarker for inflammatory bowel diseases. Microb Pathog 117:285–9
55. Chaudhary PP, Conway PL, Schlundt J (2018) Methanogens in humans: potentially beneficial or harmful for health. Appl Microbiol Biotechnol 102(7):3095–104
56. Khelaifia S, Caputo A, Andrieu C, Cadoret F, Armstrong N, Michelle C et al (2018) Genome sequence and description of Haloferax massiliense sp nov, a new halophilic archaeon isolated from the human gut. Extremophiles 22(3):485–98
57. Blais Lecours P, Marsolais D, Cormier Y, Berberi M, Haché C, Bourdages R et al (2014) Increased prevalence of Methanosphaera stadtmanae in inflammatory bowel diseases. PLoS ONE 9(2):e87734
58. Lee M, Chang EB (2021) Inflammatory bowel diseases (IBD) and the microbiome-searching the crime scene for clues. Gastroenterology 160(2):524–37
59. Liu S, Zhao W, Lan P, Mou X (2021) The microbiome in inflammatory bowel diseases: from pathogenesis to therapy. Protein Cell 12(5):331–45
60. Fujimoto T, Imaeda H, Takahashi K, Kasumi E, Bamba S, Fujiyama Y et al (2013) Decreased abundance of Faecalibacterium prausnitzii in the gut microbiota of Crohn's disease. J Gastroenterol Hepatol 28(4):613–9
61. Plovier H, Everard A, Druart C, Depommier C, Van Hul M, Geurts L et al (2017) A purified membrane protein from Akkermansia muciniphila or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nat Med 23(1):107–13
62. Ni J, Wu GD, Albenberg L, Tomov VT (2017) Gut microbiota and IBD: causation or correlation? Nat Rev Gastroenterol Hepatol 14(10):573–84
63. Gilliland A, Chan JJ, De Wolfe TJ, Yang H, Vallance BA (2024) Pathobionts in inflammatory bowel disease: origins, underlying mechanisms, and implications for clinical care. Gastroenterology 166(1):44–58
64. Wick EC, Rabizadeh S, Albesiano E, Wu X, Wu S, Chan J et al (2014) Stat3 activation in murine colitis induced by enterotoxigenic Bacteroides fragilis. Inflamm Bowel Dis 20(5):821–34
65. Chung L, Thiele Orberg E, Geis AL, Chan JL, Fu K, DeStefano Shields CE et al (2018) Bacteroides fragilis toxin coordinates a pro-carcinogenic inflammatory cascade via targeting of colonic epithelial cells. Cell Host Microbe 23(2):203–14.e5
66. Dejea CM, Fathi P, Craig JM, Boleij A, Taddese R, Geis AL et al (2018) Patients with familial adenomatous polyposis harbor colonic biofilms containing tumorigenic bacteria. Science 359(6375):592–7
67. Zhang L, Man SM, Day AS, Leach ST, Lemberg DA, Dutt S et al (2009) Detection and isolation of Campylobacter species other than C. jejuni from children with Crohn's disease. J Clin Microbiol 47(2):453
68. Man SM, Kaakoush NO, Leach ST, Nahidi L, Lu HK, Norman J et al (2010) Host attachment, invasion, and stimulation of proinflammatory cytokines by Campylobacter concisus and other non-Campylobacter jejuni Campylobacter species. J Infect Dis 202(12):1855–65
69. Mahendran V, Riordan SM, Grimm MC, Tran TA, Major J, Kaakoush NO et al (2011) Prevalence of Campylobacter species in adult Crohn's disease and the preferential colonization sites of Campylobacter species in the human intestine. PLoS ONE 6(9):e25417
70. Mukhopadhya I, Thomson JM, Hansen R, Berry SH, El-Omar EM, Hold GL (2011) Detection of Campylobacter concisus and other Campylobacter species in colonic biopsies from adults with ulcerative colitis. PLoS ONE 6(6):e21490

71. Kirk KF, Nielsen HL, Thorlacius-Ussing O, Nielsen H (2016) Optimized cultivation of Campylobacter concisus from gut mucosal biopsies in inflammatory bowel disease. Gut Pathog 8:27
72. Underwood AP, Kaakoush NO, Sodhi N, Merif J, Seah Lee W, Riordan SM et al (2016) Campylobacter concisus pathotypes are present at significant levels in patients with gastroenteritis. J Med Microbiol 65(3):219–26
73. Zhang L, Lee H, Grimm MC, Riordan SM, Day AS, Lemberg DA (2014) Campylobacter concisus and inflammatory bowel disease. World J Gastroenterol 20(5):1259–67
74. Mahendran V, Liu F, Riordan SM, Grimm MC, Tanaka MM, Zhang L (2016) Examination of the effects of Campylobacter concisus zonula occludens toxin on intestinal epithelial cells and macrophages. Gut Pathog 8:18
75. Sivignon A, de Vallée A, Barnich N, Denizot J, Darcha C, Pignède G et al (2015) Saccharomyces cerevisiae CNCM I-3856 prevents colitis induced by AIEC bacteria in the transgenic mouse model mimicking Crohn's disease. Inflamm Bowel Dis 21(2):276–86
76. Chiaro TR, Soto R, Zac Stephens W, Kubinak JL, Petersen C, Gogokhia L et al (2017) A member of the gut mycobiota modulates host purine metabolism exacerbating colitis in mice. Sci Transl Med 9(380):eaaf9044. https://doi.org/10.1126/scitranslmed.aaf9044
77. Jain U, Ver Heul AM, Xiong S, Gregory MH, Demers EG, Kern JT et al (2021) Debaryomyces is enriched in Crohn's disease intestinal tissue and impairs healing in mice. Science 371(6534):1154–9
78. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y et al (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331(6015):337–41
79. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H et al (2013) Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota. Nature 500(7461):232–6
80. Tedelind S, Westberg F, Kjerrulf M, Vidal A (2007) Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol 13(20):2826–32
81. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez-Humarán LG, Gratadoux JJ et al (2008) Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 105(43):16731–6
82. Shen Z, Zhu C, Quan Y, Yang J, Yuan W, Yang Z et al (2018) Insights into Roseburia intestinalis which alleviates experimental colitis pathology by inducing anti-inflammatory responses. J Gastroenterol Hepatol 33(10):1751–60
83. Ansaldo E, Slayden LC, Ching KL, Koch MA, Wolf NK, Plichta DR et al (2019) Akkermansia muciniphila induces intestinal adaptive immune responses during homeostasis. Science 364(6446):1179–84
84. Round JL, Mazmanian SK (2010) Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci U S A 107(27):12204–9
85. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL (2005) An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 122(1):107–18
86. Mazmanian SK, Round JL, Kasper DL (2008) A microbial symbiosis factor prevents intestinal inflammatory disease. Nature 453(7195):620–5
87. An D, Oh SF, Olszak T, Neves JF, Avci FY, Erturk-Hasdemir D et al (2014) Sphingolipids from a symbiotic microbe regulate homeostasis of host intestinal natural killer T cells. Cell 156(1–2):123–33
88. Kaser A, Zeissig S, Blumberg RS (2010) Inflammatory bowel disease. Annu Rev Immunol 28:573–621
89. Ossa JC, Ho NK, Wine E, Leung N, Gray-Owen SD, Sherman PM (2013) Adherent-invasive Escherichia coli blocks interferon-γ-induced signal transducer and activator of transcription (STAT)-1 in human intestinal epithelial cells. Cell Microbiol 15(3):446–57
90. Henke MT, Kenny DJ, Cassilly CD, Vlamakis H, Xavier RJ, Clardy J (2019) Ruminococcus gnavus, a member of the human gut microbiome associated with Crohn's disease, produces an inflammatory polysaccharide. Proc Natl Acad Sci U S A 116(26):12672–7
91. Barnett MP, McNabb WC, Cookson AL, Zhu S, Davy M, Knoch B et al (2010) Changes in colon gene expression associated with increased colon inflammation in interleukin-10 gene-deficient mice inoculated with Enterococcus species. BMC Immunol 11:39
92. Xu M, Pokrovskii M, Ding Y, Yi R, Au C, Harrison OJ et al (2018) c-MAF-dependent regulatory T cells mediate immunological tolerance to a gut pathobiont. Nature 554(7692):373–7
93. Russell SE, Horan RM, Stefanska AM, Carey A, Leon G, Aguilera M et al (2016) IL-36α expression is elevated in ulcerative colitis and promotes colonic inflammation. Mucosal Immunol 9(5):1193–204
94. Doron I, Mesko M, Li XV, Kusakabe T, Leonardi I, Shaw DG et al (2021) Mycobiota-induced IgA antibodies regulate fungal commensalism in the gut and are dysregulated in Crohn's disease. Nat Microbiol 6(12):1493–504
95. Selander C, Engblom C, Nilsson G, Scheynius A, Andersson CL (2009) TLR2/MyD88-dependent and -independent activation of mast cell IgE responses by the skin commensal yeast Malassezia sympodialis. J Immunol 182(7):4208–16
96. Zhan S, Liu C, Meng J, Mao R, Tu T, Lin J et al (2023) Mucosa-associated Oscillospira sp. is related to intestinal stricture and post-operative disease course in Crohn's disease. Microorganisms 11(3):794. https://doi.org/10.3390/microorganisms11030794
97. Ma X, Lu X, Zhang W, Yang L, Wang D, Xu J et al (2022) Gut microbiota in the early stage of Crohn's disease has unique characteristics. Gut Pathog 14(1):46
98. Raygoza Garay JA, Turpin W, Lee SH, Smith MI, Goethel A, Griffiths AM et al (2023) Gut microbiome composition is associated with future onset of Crohn's disease in healthy first-degree relatives. Gastroenterology 165(3):670–81
99. Schäffler H, Herlemann DPR, Alberts C, Kaschitzki A, Bodammer P, Bannert K et al (2016) Mucosa-attached bacterial community in Crohn's disease coheres with the clinical disease activity index. Environ Microbiol Rep 8(5):614–21
100. Buffet-Bataillon S, Bouguen G, Fleury F, Cattoir V, Le Cunff Y (2022) Gut microbiota analysis for prediction of clinical relapse in Crohn's disease. Sci Rep 12(1):19929
101. Galtier M, De Sordi L, Sivignon A, de Vallée A, Maura D, Neut C et al (2017) Bacteriophages targeting adherent invasive Escherichia coli strains as a promising new treatment for Crohn's disease. J Crohns Colitis 11(7):840–7
102. Kowalska-Duplaga K, Gosiewski T, Kapusta P, Sroka-Oleksiak A, Wędrychowicz A, Pieczarkowski S et al (2019) Differences in the intestinal microbiome of healthy children and patients with newly diagnosed Crohn's disease. Sci Rep 9(1):18880
103. Lewis JD, Chen EZ, Baldassano RN, Otley AR, Griffiths AM, Lee D et al (2015) Inflammation, antibiotics, and diet as environmental stressors of the gut microbiome in pediatric Crohn's disease. Cell Host Microbe 18(4):489–500
104. Aldars-García L, Chaparro M, Gisbert JP (2021) Systematic review: the gut microbiome and its potential clinical application in inflammatory bowel disease. Microorganisms. 9(5):977. https://doi.org/10.3390/microorganisms9050977

105. He C, Wang H, Liao WD, Peng C, Shu X, Zhu X et al (2019) Characteristics of mucosa-associated gut microbiota during treatment in Crohn's disease. World J Gastroenterol 25(18):2204–16
106. Cachanado M, Vila AV, Bonder MJ, Fu JY, Gevers D, Visschedijk MC et al (2018) Interplay of host genetics and gut microbiota underlying the onset and clinical presentation of inflammatory bowel disease. Gut 67(1):108–19
107. Santana PT, Rosas SLB, Ribeiro BE, Marinho Y, de Souza HSP (2022) Dysbiosis in inflammatory bowel disease: pathogenic role and potential therapeutic targets. Int J Mol Sci. 23(7):3464. https://doi.org/10.3390/ijms23073464
108. Pascal V, Pozuelo M, Borruel N, Casellas F, Campos D, Santiago A et al (2017) A microbial signature for Crohn's disease. Gut 66(5):813–22
109. Liguori G, Lamas B, Richard ML, Brandi G, da Costa G, Hoffmann TW et al (2016) Fungal dysbiosis in mucosa-associated microbiota of Crohn's disease patients. J Crohns Colitis 10(3):296–305
110. Lee JWJ, Plichta D, Hogstrom L, Borren NZ, Lau H, Gregory SM et al (2021) Multi-omics reveal microbial determinants impacting responses to biologic therapies in inflammatory bowel disease. Cell Host Microbe 29(8):1294–304.e4
111. Jones-Hall YL, Nakatsu CH (2016) The intersection of TNF. IBD and the microbiome Gut Microbes 7(1):58–62
112. Ribaldone DG, Caviglia GP, Abdulle A, Pellicano R, Ditto MC, Morino M et al (2019) Adalimumab therapy improves intestinal dysbiosis in Crohn's disease. J Clin Med. 8(10):1646. https://doi.org/10.3390/jcm8101646
113. Chen L, Lu Z, Kang D, Feng Z, Li G, Sun M et al (2022) Distinct alterations of fecal microbiota refer to the efficacy of adalimumab in Crohn's disease. Front Pharmacol 13:913720
114. Rajca S, Grondin V, Louis E, Vernier-Massouille G, Grimaud JC, Bouhnik Y et al (2014) Alterations in the intestinal microbiome (dysbiosis) as a predictor of relapse after infliximab withdrawal in Crohn's disease. Inflamm Bowel Dis 20(6):978–86
115. Doherty MK, Ding T, Koumpouras C, Telesco SE, Monast C, Das A et al (2018) Fecal microbiota signatures are associated with response to ustekinumab therapy among Crohn's disease patients. Mbio. 9(2):e02120-17. https://doi.org/10.1128/mBio.02120-17
116. Hattori S, Nakamura M, Yamamura T, Maeda K, Sawada T, Mizutani Y et al (2020) The microbiome can predict mucosal healing in small intestine in patients with Crohn's disease. J Gastroenterol 55(12):1138–49
117. Dey N, Soergel DA, Repo S, Brenner SE (2013) Association of gut microbiota with post-operative clinical course in Crohn's disease. BMC Gastroenterol 13:131
118. Di Sario A, Sassaroli P, Daretti L, Annulli G, Schiada L, Falcioni G et al (2017) Postoperative recurrence of Crohn's disease: pathophysiology, diagnosis and treatment. Curr Pharm Biotechnol 18(12):979–88
119. Sokol H, Brot L, Stefanescu C, Auzolle C, Barnich N, Buisson A et al (2020) Prominence of ileal mucosa-associated microbiota to predict postoperative endoscopic recurrence in Crohn's disease. Gut 69(3):462–72
120. Russo E, Giudici F, Ricci F, Scaringi S, Nannini G, Ficari F et al (2021) Diving into inflammation: a pilot study exploring the dynamics of the immune-microbiota axis in ileal tissue layers of patients with Crohn's disease. J Crohns Colitis 15(9):1500–16
121. Russo E, Cinci L, Di Gloria L, Baldi S, D'Ambrosio M, Nannini G et al (2022) Crohn's disease recurrence updates: first surgery vs surgical relapse patients display different profiles of ileal microbiota and systemic microbial-associated inflammatory factors. Front Immunol 13:886468
122. De Cruz P, Kang S, Wagner J, Buckley M, Sim WH, Prideaux L et al (2015) Association between specific mucosa-associated microbiota in Crohn's disease at the time of resection and subsequent disease recurrence: a pilot study. J Gastroenterol Hepatol 30(2):268–78
123. Buisson A, Sokol H, Hammoudi N, Nancey S, Treton X, Nachury M et al (2023) Role of adherent and invasive Escherichia coli in Crohn's disease: lessons from the postoperative recurrence model. Gut 72(1):39–48
124. Zhuang X, Tian Z, Feng R, Li M, Li T, Zhou G et al (2020) Fecal microbiota alterations associated with clinical and endoscopic response to infliximab therapy in Crohn's disease. Inflamm Bowel Dis 26(11):1636–47
125. Kugathasan S, Denson LA, Walters TD, Kim MO, Marigorta UM, Schirmer M et al (2017) Prediction of complicated disease course for children newly diagnosed with Crohn's disease: a multicentre inception cohort study. Lancet 389(10080):1710–8
126. Le PH, Chiu CT, Yeh PJ, Pan YB, Chiu CH (2022) Clostridium innocuum infection in hospitalised patients with inflammatory bowel disease. J Infect 84(3):337–42
127. Ananthakrishnan AN, Khalili H, Konijeti GG, Higuchi LM, De Silva P, Korzenik JR et al (2013) A prospective study of long-term intake of dietary fiber and risk of Crohn's disease and ulcerative colitis. Gastroenterology 145(5):970–7
128. Andersen V, Chan S, Luben R, Khaw KT, Olsen A, Tjonneland A et al (2018) Fibre intake and the development of inflammatory bowel disease: a European prospective multi-centre cohort study (EPIC-IBD). J Crohns Colitis 12(2):129–36
129. Brotherton CS, Martin CA, Long MD, Kappelman MD, Sandler RS (2016) Avoidance of fiber is associated with greater risk of Crohn's disease flare in a 6-month period. Clin Gastroenterol Hepatol 14(8):1130–6
130. Albenberg LG, Wu GD (2014) Diet and the Intestinal Microbiome: Associations, Functions, and Implications for Health and Disease. Gastroenterology 146(6):1564–72
131. Leach ST, Mitchell HM, Eng WR, Zhang L, Day AS (2008) Sustained modulation of intestinal bacteria by exclusive enteral nutrition used to treat children with Crohn's disease. Aliment Pharmacol Ther 28(6):724–33
132. Lee D, Albenberg L, Compher C, Baldassano R, Piccoli D, Lewis JD et al (2015) Diet in the pathogenesis and treatment of inflammatory bowel diseases. Gastroenterology 148(6):1087–106
133. Borrelli O, Cordischi L, Cirulli M, Paganelli M, Labalestra V, Uccini S et al (2006) Polymeric diet alone versus corticosteroids in the treatment of active pediatric Crohn's disease: a randomized controlled open-label trial. Clin Gastroenterol Hepatol 4(6):744–53
134. Grover Z, Muir R, Lewindon P (2014) Exclusive enteral nutrition induces early clinical, mucosal and transmural remission in paediatric Crohn's disease. J Gastroenterol 49(4):638–45
135. Mack DR, Benchimol EI, Critch J, de Bruyn J, Tse F, Moayyedi P et al (2019) Canadian association of gastroenterology clinical practice guideline for the medical management of pediatric luminal Crohn's disease. Gastroenterology 157(2):320–48
136. Raman M, Ma C, Taylor LM, Dieleman LA, Gkoutos GV, Vallance JK et al (2022) Crohn's disease therapeutic dietary intervention (CD-TDI): study protocol for a randomised controlled trial. BMJ Open Gastroenterol 9(1):e000841. https://doi.org/10.1136/bmjgast-2021-000841
137. Zhang Z, Taylor L, Shommu N, Ghosh S, Reimer R, Panaccione R et al (2020) A diversified dietary pattern is associated with a balanced gut microbial composition of Faecalibacterium and Escherichia/Shigella in patients with Crohn's disease in remission. J Crohns Colitis 14(11):1547–57
138. Rashed R, Valcheva R, Dieleman LA (2022) Manipulation of gut microbiota as a key target for Crohn's disease. Front Med (Lausanne) 9:887044

139. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, Pot B et al (2014) Expert consensus document. The international scientific association for probiotics and prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11(8):506–14
140. Lichtenstein L, Avni-Biron I, Ben-Bassat O (2016) Probiotics and prebiotics in Crohn's disease therapies. Best Pract Res Clin Gastroenterol 30(1):81–8
141. Limketkai BN, Akobeng AK, Gordon M, Adepoju AA (2020) Probiotics for induction of remission in Crohn's disease. Cochrane Database Syst Rev 7(7):Cd006634.
142. Fedorak RN, Feagan BG, Hotte N, Leddin D, Dieleman LA, Petrunia DM et al (2015) The probiotic VSL#3 has anti-inflammatory effects and could reduce endoscopic recurrence after surgery for Crohn's disease. Clin Gastroenterol Hepatol 13(5):928–35.e2
143. Sang LX (2021) Corrigendum to "Probiotic mixture VSL#3: an overview of basic and clinical studies in chronic diseases." World J Clin Cases 9(20):5752–3
144. Gao J, Zhao X, Hu S, Huang Z, Hu M, Jin S et al (2022) Gut microbial DL-endopeptidase alleviates Crohn's disease via the NOD2 pathway. Cell Host Microbe 30(10):1435–49.e9
145. Geirnaert A, Calatayud M, Grootaert C, Laukens D, Devriese S, Smagghe G et al (2017) Butyrate-producing bacteria supplemented in vitro to Crohn's disease patient microbiota increased butyrate production and enhanced intestinal epithelial barrier integrity. Sci Rep 7(1):11450
146. Braat H, Rottiers P, Hommes DW, Huyghebaert N, Remaut E, Remon JP et al (2006) A phase I trial with transgenic bacteria expressing interleukin-10 in Crohn's disease. Clin Gastroenterol Hepatol 4(6):754–9
147. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ et al (2017) Expert consensus document: the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14(8):491–502
148. Wasilewski A, Zielińska M, Storr M, Fichna J (2015) Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. Inflamm Bowel Dis 21(7):1674–82
149. Scaldaferri F, Gerardi V, Lopetuso LR, Del Zompo F, Mangiola F, Boškoski I et al (2013) Gut microbial flora, prebiotics, and probiotics in IBD: their current usage and utility. Biomed Res Int 2013:435268
150. Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL et al (2011) Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut 60(7):923–9
151. De Preter V, Joossens M, Ballet V, Shkedy Z, Rutgeerts P, Vermeire S et al (2013) Metabolic profiling of the impact of oligofructose-enriched inulin in Crohn's disease patients: a double-blinded randomized controlled trial. Clin Transl Gastroenterol 4(1):e30
152. Joossens M, De Preter V, Ballet V, Verbeke K, Rutgeerts P, Vermeire S (2012) Effect of oligofructose-enriched inulin (OF-IN) on bacterial composition and disease activity of patients with Crohn's disease: results from a double-blinded randomised controlled trial. Gut 61(6):958
153. Steed H, Macfarlane GT, Blackett KL, Bahrami B, Reynolds N, Walsh SV et al (2010) Clinical trial: the microbiological and immunological effects of synbiotic consumption - a randomized double-blind placebo-controlled study in active Crohn's disease. Aliment Pharmacol Ther 32(7):872–83
154. Colombel JF, Shin A, Gibson PR (2019) AGA Clinical practice update on functional gastrointestinal symptoms in patients with inflammatory bowel disease: expert review. Clin Gastroenterol Hepatol 17(3):380–90.e1
155. Wang L, Tang L, Feng Y, Zhao S, Han M, Zhang C et al (2020) A purified membrane protein from Akkermansia muciniphila or the pasteurised bacterium blunts colitis associated tumourigenesis by modulation of CD8(+) T cells in mice. Gut 69(11):1988–97
156. Sokol H, Landman C, Seksik P, Berard L, Montil M, Nion-Larmurier I et al (2020) Fecal microbiota transplantation to maintain remission in Crohn's disease: a pilot randomized controlled study. Microbiome 8(1):12
157. Mu C, Zhao Q, Zhao Q, Yang L, Pang X, Liu T et al (2023) Multi-omics in Crohn's disease: new insights from inside. Comput Struct Biotechnol J 21:3054–72
158. Bak SH, Choi HH, Lee J, Kim MH, Lee YH, Kim JS et al (2017) Fecal microbiota transplantation for refractory Crohn's disease. Intest Res 15(2):244–8
159. Cui B, Feng Q, Wang H, Wang M, Peng Z, Li P et al (2015) Fecal microbiota transplantation through mid-gut for refractory Crohn's disease: safety, feasibility, and efficacy trial results. J Gastroenterol Hepatol 30(1):51–8
160. Liu X, He S, Li Q, Mu X, Hu G, Dong H (2020) Comparison of the gut microbiota between pulsatilla decoction and levofloxacin hydrochloride therapy on Escherichia coli infection. Front Cell Infect Microbiol 10:319
161. Zhang Y, Tang K, Deng Y, Chen R, Liang S, Xie H et al (2018) Effects of shenling baizhu powder herbal formula on intestinal microbiota in high-fat diet-induced NAFLD rats. Biomed Pharmacother 102:1025–36
162. Chen F, Yin YT, Zhao HM, Wang HY, Zhong YB, Long J et al (2020) Sishen pill treatment of DSS-induced colitis via regulating interaction with inflammatory dendritic cells and gut microbiota. Front Physiol 11:801
163. Wang XM, Lu Y, Wu LY, Yu SG, Zhao BX, Hu HY et al (2012) Moxibustion inhibits interleukin-12 and tumor necrosis factor alpha and modulates intestinal flora in rat with ulcerative colitis. World J Gastroenterol 18(46):6819–28
164. Bao C, Wu L, Wang D, Chen L, Jin X, Shi Y et al (2022) Acupuncture improves the symptoms, intestinal microbiota, and inflammation of patients with mild to moderate Crohn's disease: a randomized controlled trial. EClinicalMedicine 45:101300