An Overview of Gut Microbiome Studies in Inflammatory Bowel Disease

Siwei Tan *

Pharmacology, King's College London, London; Guy's Campus, Great Maze Pond, London SE1 1UL, United Kingdom

* Corresponding Author Email: Siwei.tan@kcl.ac.uk

Abstract. Inflammatory Bowel Disease (IBD) is a complex disorder marked by ongoing inflammation in the gastrointestinal tract. Its intricate connection with the gut's microbial makeup is a significant aspect of its pathology. This detailed investigation delves into the interaction between IBD and gut microbiota, underscoring the crucial role of microbial imbalance in the development of this condition. A thorough comparative examination of the gut microbiota in individuals with and without IBD reveals notable differences. Special attention is given to Short-Chain Fatty Acids (SCFAs) for their influence on intestinal barrier function and immune regulation. The study also assesses the efficacy of microbial intervention strategies like probiotics, prebiotics, Fecal Microbiota Transplantation (FMT), and butyrate supplementation. These findings illuminate the potential of microbiome-focused treatments in reshaping gut flora, pointing to a new direction in IBD management. The paper concludes by proposing a holistic treatment approach that integrates dietary changes with novel therapeutic methods. This research significantly advances our understanding of the gut microbiome's function in IBD, offering novel insights and avenues for more effective management and treatment strategies.

Keywords: Gut microbiome; IBD; Dybiosys; Ulcerative Colitis (UC) and Crohn's Disease (CD); Short-chain fatty acids (SCFAs).

1. Introduction

Inflammatory Bowel Disease (IBD), which includes Crohn's Disease (CD) and Ulcerative Colitis (UC), is defined by persistent inflammation within the gastrointestinal system. This condition greatly affects patients' well-being, presenting with symptoms like stomach pain, frequent diarrhea, and persistent tiredness. These symptoms disrupt daily activities, and work productivity, and can lead to social isolation and psychological distress. Such multifaceted impacts highlight the necessity for comprehensive care that simultaneously addresses both physical and mental health aspects.

The primary endpoints of IBD treatment have traditionally centered on clinical remission and response. However, evolving treatment strategies now incorporate biomarkers and mucosal healing, indicative of a more profound understanding of the disease's extensive implications.

The burden of IBD is increasing globally, with significant variations in levels and trends across different countries and regions. In 2019, approximately 4.9 million IBD cases were recorded worldwide, with the highest prevalence in China (911,405 cases) and the USA (762,890 cases). The global evolution of IBD can be characterized into four stages: the Emergence Stage, evident in sporadic cases in developing countries; the Acceleration in Incidence Stage, observed in newly industrialized countries with rapid case increases; the Compounding Prevalence Stage, common in Western countries where incidence stabilizes but prevalence grows; and the Prevalence Equilibrium Stage, a projected future phase where prevalence is expected to stabilize [1].

The pathogenesis of IBD is multifaceted, involving genetic predisposition, environmental factors, immune dysregulation, and notable changes in the gut microbiome. The gut microbiome is the predominant microbiota in humans, and is essential in the regulation of immune response, cellular growth, and differentiation, thus significantly influencing intestinal diseases [2-4].Recent pharmaceutical research has increasingly focused on gut microbes due to their diversity, abundance, and complex functionality. These microbes are instrumental in developing various digestive diseases,

including IBD. The imbalance in the gut microbiome, known as dysbiosis, is a common feature in IBD, believed to substantially affect both the development and severity of the disease [3].

The purpose of this research is to explore the intricate association between the gut microbiome and IBD, assess how changes in the microbiome influence disease progression, and evaluate current and emerging microbiome-targeted therapies for effective IBD management and treatment.

2. Gut Microbiome in IBD Patients and Healthy Individuals

The gut microbiome of healthy individuals is a complex and dynamic ecosystem crucial to overall health. It comprises a diverse and balanced array of bacteria, fungi, and viruses. It comprises diverse bacteria, fungi, and viruses, with about 100 trillion bacteria playing crucial roles in nutrient metabolism, immune system support, and pathogen defense [5].The predominant bacterial groups in a healthy gut include Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. A combination of genetic factors, cultural background, environmental interactions, dietary habits, and lifestyle choices determines the composition of the gut microbiota [3].

In contrast, those suffering from IBD display marked changes in their gut microbial communities. Such changes commonly manifest as a decrease in advantageous bacterial groups including Christensenellaceae, Coriobacteriaceae, and Faecalibacterium prausnitzii. In CD, there's often a surge in bacteria that can potentially be harmful, like Actinomyces, Veillonella, and Escherichia coli. UC patients generally show lower levels of Eubacterium rectale and, with occasional increases in E. Col [3].These alterations lead to gut microbiota in IBD patients tends to be less varied and more imbalanced when compared with healthy individuals.

A comprehensive meta-analysis involving IBD patient groups across five nations has provided insights into these alterations. At higher phylogenetic levels, the gut microbiota of both healthy subjects and those with IBD display striking similarities. However, deeper analysis reveals significant disease-specific changes at the order level or lower within the taxonomic structure. Notably, these variations are prominent in metabolic processes, including the biosynthesis and metabolism of amino acids and glycans, which differ markedly between CD and UC [3].

Subsequent studies have pinpointed clear distinctions in the gut microbiota of patients with CD compared to those with UC. While microbial orders like Bacteroidales and Clostridiales are consistently present across studies, a more in-depth species-level analysis has identified 195 Operational Taxonomic Units (OTUs) with significant differences between CD and UC. [3] Notably, species within the genus Clostridium, linked to two different families, are indicative of either CD or UC. Additionally, species such as Ruminococcus lactaris are more prevalent in CD than in UC. This detailed differentiation in gut microbial composition between CD and UC patients has significant implications for diagnosis and targeted treatment strategies [5].

Contrasts in the gut microbiomes of individuals with IBD compared to those without the condition are underscored by changes in alpha and beta diversity. IBD patients often exhibit reduced alpha diversity, suggesting a less diverse gut microbiota that could impact pathogen defense and overall health. Beta diversity also shows notable differences, reflecting the disease's impact on the gut environment. Approximately 80% of studies assessing microbiota from the colonic lining in subjects with IBD versus healthy individuals have reported inconsistent results, underscoring the complexity of the gut microbiome in IBD [3].

3. Role of Gut Microbiota and Metabolic Dysregulation in IBD Pathogenesis

IBD’s pathogenesis is significantly influenced by the interaction between the gut microbiota and the host's immune system. Central to this interaction are microbial metabolites, particularly Short-Chain Fatty Acids (SCFAs) like butyrate, propionate, and acetate. Originating from the fermentation of dietary fibers, SCFAs are crucial for preserving the integrity of the gut barrier and regulating

immune cell activities. These fatty acids are instrumental in maintaining immune tolerance and minimizing inflammatory responses [6].

Patients with IBD often exhibit altered metabolic pathways, notably those involving bile acids and tryptophan metabolites. These alterations significantly impact the gut microbiota's makeup and ensuing immune reactions. For instance, metabolites of tryptophan are recognized for their role in activating the aryl hydrocarbon receptor (AhR), which is essential for mucosal immunity and controlling inflammation [7].Furthermore, the increased gut permeability often associated with IBD leads to elevated levels of lipopolysaccharides (LPS) from Gram-negative bacteria, which exacerbate inflammatory processes [6].This dysregulation in gut microbiota-derived metabolites is a common feature in various immune-related inflammatory disorders, highlighting their crucial role in immune homeostasis and disease pathogenesis. This dysregulation in gut microbiota-derived metabolites is a common feature in various immune-related inflammatory disorders, highlighting their crucial role in immune homeostasis and disease pathogenesis [7].

Microbial dysbiosis is the primary driver of inflammation in IBD, which includes conditions such as CD and UC. This dysbiosis typically leads to a reduction in beneficial metabolites, such as SCFAs, while increasing the presence of pro-inflammatory compounds [7]. In UC, the dysbiosis manifests as a decrease in beneficial bacteria like Eubacterium rectale and Akkermansia. This is sometimes accompanied by an increase in harmful bacteria such as E. coli, disrupting mucosal and immune homeostasis. Conversely, CD is often characterized by a reduced abundance of Firmicutes bacteria, which are crucial for producing butyrate, an anti-inflammatory SCFA. The resulting decrease in butyrate production exacerbates the inflammatory processes in CD [5,6]. This imbalance in microbial composition and metabolites contributes to the chronic inflammation characteristic of IBD [5,6]. The complex interplay between microbial metabolites and the immune system in IBD offers new insights into potential therapeutic approaches, indicating that focusing on the gut microbiome and its metabolites may improve IBD management [5].

Studies have identified a correlation between IBD and notable alterations in the gut microbiota and metabolomic profiles. Metabolomic and metagenomic profiles correlate with markers of gut inflammation, such as fecal calprotectin levels [6]. Specific metabolites, including sphingolipids and bile acids, show differential abundance in IBD patients [7].These changes result in depletions of certain compounds like triacylglycerols and tetrapyrroles, exacerbating chronic inflammation in IBD and impacting crucial metabolic functions, including the production of SCFAs [5]. The deviation from the microbial diversity and composition observed in healthy individuals highlights the significance of microbial imbalance in the development of IBD.

4. Microbial Therapies in IBD

Changes in bacterial and other microbial populations have a profound effect on the structure and function of IBD. Conventional treatments, such as corticosteroids, immunomodulators, and biological therapies, are effective for inducing remission. However, numerous alternative strategies specifically target the microbiome to alleviate dysbiosis and inflammation. These strategies are divided into established methods, like the use of probiotics, and prebiotics, along with newer practices like Fecal Microbiota Transplantation (FMT) and Butyrate replacement. Additionally, dietary interventions are part of this evolving landscape, representing innovative concepts in microbiome-targeted therapies for IBD management [8].

4.1. Probiotics

Probiotics, which are beneficial live microorganisms given in proper amounts, can provide health advantages to the individual. They are pivotal in managing IBD by possibly restoring equilibrium within the gut's microbial community, shifting from pro-inflammatory to anti-inflammatory states [8].Probiotics like Lactobacillus and Bifidobacterium species modulate the gut environment by

enhancing mucosal barrier integrity and modulating immune responses, which are key factors in reducing inflammation in IBD.

A clinical trial evaluated the Probio-Tec AB-25 product, containinig Lactobacillus LA-5 and Bifidobacterium lactis BB-12, in treating UC over 52 weeks. Although it did not significantly maintain remission in UC patients ($p = 0.01$), it improved immune and inflammatory parameters, aligning with other studies showing probiotics' immunomodulatory effects. For example, Lactobacillus casei Shirota and Lactobacillus delbrueckii have shown anti-inflammatory effects. Additionally, S. boulardii combined with mesalazine induced remission in active UC, suggesting its therapeutic potential. However, S. boulardii did not significantly affect CD treatment outcomes ($p = 0.07$), indicating that probiotics may be more beneficial for UC than CD [9].

4.2. Prebiotics

Prebiotics are indigestible dietary components that specifically encourage the growth and activity of beneficial colonic bacteria, beneficially impacting the host. They are a primary energy source for gut microbiota and can favorably modify its composition. Prebiotics mainly consist of substances like fructo-oligosaccharide (FOS), insulin, and galacto-oligosaccharide (GOS). Their primary function is to selectively promote the proliferation of specific intestinal bacteria and enhance the production of SCFAs within the gut [8]. Emerging research has also highlighted the potential of tea flower polysaccharides to modulate the gut microbiome, providing a new direction in this field [10]. Notably, prebiotics, by increasing SCFAs, particularly butyrate, by prebiotics is instrumental in reinforcing the integrity of the intestinal barrier and in steering immune reactions, which are essential aspects of IBD treatment.

A study on tea flower polysaccharides (TFPS) revealed significant differences in gut microbiota between healthy individuals and those with IBD. TFPS fermentation significantly changed the gut microbiota, increasing metabolites (SCFAs) in both healthy individuals (4.54 ± 0.43 mM) and CD patients (5.21 ± 0.51 mM). In healthy individuals, TFPS promoted the growth of beneficial bacteria like Collinsella, Dialister, Klebsiella, Megasphaera, Lactobacillus, and Bifidobacterium, while decreasing potentially harmful bacteria such as Prevotella and various Clostridium species. Conversely, in CD patients, TFPS led to a roughly 40% increase in Escherichia/Shigella, along with Collinsella, Bifidobacterium, Enterococcus, and Lactobacillus. It also reduced the abundance of Enterobacter, Streptococcus, and other less favorable microbes. These findings indicate that TFPS positively affects the gut environment in both healthy and Crohn's disease conditions, but it may exacerbate inflammation rather than offer therapeutic benefits in CD [10].

4.3. Fecal Microbiota Transplantation (FMT)

Fecal Microbiota Transplantation (FMT) is a therapeutic process that transfers stool from a screened donor into the gastrointestinal system of a recipient. This technique focuses on restoring a healthy balance of microbiota in individuals whose gut flora is often disrupted by antibiotics. Currently under investigation for treating IBD, FMT is hypothesized to correct dysbiosis, an imbalance in gut microbiota that is believed to contribute to IBD's development. Transplanting fecal matter from healthy donors may reduce inflammation and alleviate IBD symptoms [11]. The success of FMT may depend on the microbial diversity of the donor and the existing gut environment of the recipient, which can vary significantly among individuals.

A thorough review was undertaken to evaluate the effectiveness of FMT for treating UC in adult patients. This review included a total of four studies, involving 277 participants, predominantly suffering from mild to moderate UC. The findings revealed that 37% of participants undergoing FMT achieved clinical remission at the end of 8 weeks, a figure noticeably higher than the 18% remission rate observed in the control group (RR 2.03, 95% CI, 1.07 to 3.86). Significantly, no relapses were reported in the FMT group at the 8-week checkpoint. In terms of severe adverse events, both the FMT and control groups demonstrated similar occurrences, with 7% of the FMT group and 5% of the control group experiencing such events (RR 1.40, 95% CI 0.55 to 3.58). General adverse events were

common in both groups, occurring in 78% of the FMT group and 75% of the control group (RR 1.03, 95% CI 0.81 to 1.31) [12].

Another meta-analysis and review focused on the efficacy and safety of FMT as a treatment for IBD across pediatric and adult demographics. In this expanded analysis of 596 patients, where 459 underwent FMT, clinical remission was achieved in 26%, affirming FMT's effectiveness and safety for IBD sufferers across age groups. The clinical remission rates were estimated at 21% for UC (95% CI: 8%-37%) and 30% for CD (95% CI: 11%-52%), acknowledging variability in both conditions. In the control group, 10% of pediatric UC patients (95% CI: 0%-43%), 26% of adult UC patients (95% CI: 10%-48%), 45% of pediatric CD patients (95% CI: 24%-66%), and 22% of adult CD patients (95% CI: 3%-52%) reached clinical remission. Meta-analysis shows that patients with moderate to severe IBD have a more significant clinical remission after receiving FMT treatment compared to those with mild to moderate conditions (P=0.037). In UC and CD, the delivery method does not impact the efficacy of FMT. Present data suggests the remission rates for UC are higher with frozen stool FMT than with fresh stool, while no notable difference was observed for CD. The choice of optimal donor stool for FMT is still under research. Moreover, meta-analysis of Randomized Controlled Trials (RCTs) indicates a notably higher clinical remission rate in the FMT-treated group compared to placebo (28% vs 9% for UC, P=0.0003) [13].

4.4. Butyrate Replacement Therapy

Butyrate replacement therapy applied to patients with IBD involves administering butyrate, a type of the SCFAs. This therapy aims to reinstate normal levels of butyrate in the colon either through direct use of butyrate or by employing agents that boost its production in the gut such as specific dietary fibers or probiotics. Various methods including dietary supplements and enemas are utilized for this administration. Research indicates that SCFAs may play a critical role in reducing inflammation and maintaining the integrity of the epithelial barrier, as observed in IBD mouse models. The efficacy of butyrate can depend on the mode of administration and the unique gut environment of the individual. Oral supplements may not always effectively deliver adequate concentrations to the colon suggesting that enemas or other direct delivery methods might be more efficacious.

Changes in gut microbiota and SCFA levels significantly influence IBD's development and progression. A meta-analysis has pointed out variations in SCFA levels among individuals with IBD, accentuating their significant role in the disease's pathogenesis. Specifically, in CD patients, the standardized mean differences (SMDs) for acetate, butyrate, and valerate are −1.43 (95% CI −2.81 to −0.04), −0.77 (95% CI −1.39 to −0.14), and −0.75 (95% CI −1.47 to −0.02) respectively. SCFAs, particularly butyrate, are known to alleviate inflammation and support the epithelial barrier in IBD, advocating their inclusion in disease management [14].

SCFAs play roles beyond direct application. They are involved in regulating immune functions and stabilizing the intestinal barrier. SCFAs can suppress intestinal inflammation by inhibiting toll-like receptor signaling. A fiber-rich diet that increases SCFA levels in the gut has been effective in reducing such inflammation, suggesting that dietary strategies promoting SCFA production could be beneficial in both preventing and treating IBD. Additionally, SCFAs are linked to a reduction in SCFA-producing microorganisms in IBD patients, indicating a possible role in the disease's progression [14].

Butyrate supplementation therapy utilizes butyrate's anti-inflammatory characteristics and its beneficial impact on the intestinal lining. It aims to improve symptoms, heal the gut, and potentially influence the progression of gut-related diseases. The effectiveness and optimal delivery method of this therapy are subjects of ongoing research. Currently, it is recommended as a complementary treatment, under the guidance of healthcare professionals [14].

4.5. Dietary Interventions

Nutritional choices play a critical role in the control of IBD by influencing the gut microbiota and the immune system. Selecting the right foods is crucial for the effective management of IBD. Foods

high in fat, lactose, and certain fibers can trigger IBD symptoms. Conversely, low-fiber diets may increase CD risk due to alterations in the gut microbiota in susceptible individuals [15].

Promoting gut health through diet is a key aspect of IBD management. Eating a diet abundant in prebiotics, such as fruits, vegetables, and whole grains, is advantageous. These non-digestible food components encourage the proliferation of good bacteria in the colon, leading to well-balanced gut microbiota and lessened inflammation. For example, the side chains of pectin in prebiotics enhance prebiotic effects and can downregulate inflammatory cytokines such as IL-6.Additionally, it's important to consider individual dietary tolerances and preferences, as IBD patients often have unique dietary needs and sensitivities. Personalized dietary plans, developed in collaboration with dietitians and healthcare professionals, can optimize gut health and overall well-being in IBD patients.

Diets with anti-inflammatory properties, like the Mediterranean diet, are beneficial for IBD patients. This diet, rich in omega-3 fatty acids, antioxidants, and fiber, boosts microbiota diversity. It particularly increases the presence of Faecalibacterium prausnitzii, a bacterium known for its anti-inflammatory effects[15].

IBD often results in malabsorption and nutritional deficiencies. Therefore, tailoring diets to ensure sufficient nutrient intake is vital. While some studies indicate that antibiotics can maintain remission in UC patients, their long-term use may not always be advantageous. This underscores the need for personalized diet plans, developed in collaboration with healthcare professionals, as individual responses to dietary interventions in IBD vary greatly.

5. Conclusion

This systematic review has explored the complex relationship between the gut microbiome and IBD, highlighting the pivotal role that microbial imbalances play in the origin of the disease and the potential for treatments focused on the microbiome. In IBD, the gut microbiome undergoes marked alterations characterized by reduced diversity and imbalances in bacterial families leading to a pro-inflammatory profile. CD often shows an increase in harmful bacteria like Actinomyces, Veillonella, and Escherichia coli, whereas UC is marked by lower levels of beneficial microbes like Eubacterium rectale and Akkermansia. This dysbiosis significantly influences IBD progression by altering the gut environment.

Short-chain fatty Acids (SCFAs), such as butyrate, propionate, and acetate, are crucial in preserving the integrity of the gut barrier and in the regulation of immune functions. The role of these SCFAs in reducing inflammation and fostering immune tolerance highlights the gut microbiome's essential contribution to maintaining immune equilibrium. Additionally, the altered metabolism of bile acids and tryptophan metabolites in IBD patients affects microbial composition and immune responses, further exacerbating symptoms.

Identifying the gut microbiome as a key focus for intervention in the treatment of IBD has given rise to a variety of therapeutic strategies. Probiotics and prebiotics aimed at rebalancing the gut flora have demonstrated efficacy in modulating immune and inflammatory responses. Fecal Microbiota Transplantation (FMT) represents an innovative approach with particular effectiveness in UC. Butyrate replacement therapy capitalizes on SCFAs' anti-inflammatory properties.

Dietary interventions are crucial in managing IBD. Customizing diets to reduce symptom flare-ups, promote gut health, and address nutritional deficiencies is crucial. An anti-inflammatory diet, such as the Mediterranean diet, which is abundant in omega-3 fatty acids and antioxidants, serves as a beneficial model for dietary management in individuals with IBD.

Future research should focus on investigating the gut microbiome's role in IBD to develop more effective and personalized treatments. A deeper understanding of the microbiome's impact on IBD will enhance management strategies for this increasingly prevalent condition, improving patient outcomes and quality of life. This includes expanding clinical trials on microbiome-targeted therapies and exploring genetic and environmental factors contributing to microbial dysbiosis in IBD.

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