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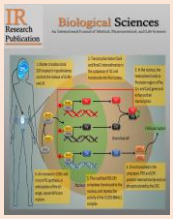

Interplay of Microbiome and Ulcerative Colitis

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ABSTRACT

The gut microbiome plays a crucial role in the pathogenesis of ulcerative colitis (UC), a chronic inflammatory bowel disease. Dysbiosis, characterized by reduced microbial diversity and shifts in bacterial populations, is commonly observed in UC patients. Key microbial species such as Firmicutes, Bacteroidetes, and Proteobacteria are implicated in disease development, influencing immune responses and intestinal barrier integrity. This review explores the complex interplay between the microbiome and UC, focusing on mechanisms such as immune modulation, barrier disruption, and the production of metabolites like short-chain fatty acids. Microbiome-targeted therapies, including probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary interventions, show promise in restoring microbial balance and alleviating UC symptoms. Additionally, emerging microbiome-modulating drugs provide new therapeutic avenues. Despite these advancements, challenges remain, including the heterogeneity of UC, the need for personalized treatments, and the causal relationship between microbiome changes and UC. Future research should focus on longitudinal studies, personalized therapies, and the application of advanced technologies like metagenomics to deepen our understanding of the microbiome's role in UC. Long-term clinical trials will be essential for determining the safety and efficacy of microbiome-based treatments. This review highlights the potential of the microbiome as a therapeutic target and underscores the need for continued research to improve UC management.

Introduction

Ulcerative colitis (UC) is a chronic condition that causes inflammation and ulcers in the lining of the colon. It is one of the main types of inflammatory bowel disease (IBD) and is characterized by symptoms like abdominal pain, diarrhea, and bloody stools. UC tends to be a lifelong condition, with periods of flare-ups followed by remission. The exact cause of UC remains unclear, but it is thought to involve a combination of genetic factors, immune system dysfunction, and environmental triggers (1). Over time, persistent inflammation can lead to complications such as colorectal cancer, making effective management crucial.

One of the most important factors in the development of UC is the gut microbiome- the community of microorganisms, including bacteria,

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fungi, and viruses, that live in the digestive tract. In a healthy gut, these microbes play an essential role in digesting food, producing vitamins, protecting against harmful bacteria, and helping to regulate immune responses (Human Microbiome Project Consortium, 2012) (1). However, when this microbial community is disrupted, a condition known as dysbiosis, it can contribute to the development of diseases like UC (2).

In UC patients, the gut microbiome often shows reduced diversity, meaning there are fewer types of beneficial bacteria. This imbalance allows harmful microbes to thrive, which can lead to an overactive immune response that damages the gut lining and causes inflammation (3). Additionally, certain bacteria and microbial metabolites can directly influence the immune system, exacerbating the inflammatory process in UC (4).

The relationship between the microbiome and UC is complex and still not fully understood. While dysbiosis may contribute to the disease, it is also possible that the immune system's response to microbial changes plays a role in initiating and sustaining the inflammation seen in UC (5). Recent research suggests that restoring a healthy microbial balance might be a potential therapeutic strategy for managing UC. Treatments such as probiotics, fecal microbiota transplantation (FMT), and dietary interventions are currently being studied as ways to help rebalance the microbiome and reduce inflammation (4).

This review will explore the role of the gut microbiome in UC, discussing how microbial imbalances contribute to the disease and how targeting the microbiome might offer new avenues for treatment. By examining the latest research, we aim to provide a clearer understanding of how the microbiome influences UC and how this knowledge might lead to better therapies in the future.

The Gut Microbiome: Composition and Function

The human gut microbiome is a complex and dynamic ecosystem composed of trillions of microorganisms, including bacteria, fungi, viruses, and archaea. These microbes are predominantly bacteria, with Firmicutes and Bacteroidetes being the most abundant phyla in a healthy adult gut (1). The composition of the microbiome varies between individuals but is generally stable over time in healthy individuals, reflecting a balanced and diverse microbial community. This diversity is critical for the maintenance of intestinal health, as it allows for the efficient breakdown of complex dietary components, the regulation of immune responses, and the prevention of infections (6). Reduced microbial diversity has been linked to various diseases, including inflammatory bowel diseases (IBD) like ulcerative colitis (UC) (2), indicating that a healthy, diverse microbiome is essential for proper gut function.

Microbial Diversity

In healthy individuals, the gut microbiota is diverse and includes a wide range of bacterial species that interact in a symbiotic relationship. These bacteria help maintain intestinal homeostasis by performing a variety of beneficial functions. For example, Bacteroides species are involved in the breakdown of complex carbohydrates, while Firmicutes contribute to the fermentation of fiber to produce short-chain fatty acids (SCFAs), which are important for gut health and immune regulation (7). The relative abundance of different microbial groups is thought to be shaped by factors such as diet, genetics, and environmental exposures (8). A stable and diverse microbiome contributes to the resilience of the gut, allowing it to adapt to dietary and environmental changes without triggering harmful immune responses.

Functions of the Microbiome

The gut microbiome performs several key functions that are vital for human health:

Immune Modulation: The microbiome plays a crucial role in shaping the host's immune system. It educates the immune cells to distinguish between harmful pathogens and harmless antigens, promoting tolerance to beneficial microbes while triggering an immune response to harmful ones. This is achieved through the production of microbial metabolites such as SCFAs, which influence immune cell activity and inflammation (9). Dysbiosis, or microbial imbalance, can lead to immune system dysfunction and is associated with conditions like UC, where the immune system attacks the body's own tissues in response to microbial signals (10).

Digestion and Metabolism: The gut microbiome aids in the breakdown of complex carbohydrates and fibers that the human body cannot digest on its own. In the process, the microbiota produces SCFAs, including acetate, propionate, and butyrate, which are important energy sources for colon cells and help maintain the integrity of the intestinal barrier (11). These SCFAs also have anti-inflammatory properties and may reduce the severity of UC by promoting regulatory T cells that dampen excessive immune responses (12).

Protection Against Pathogens: The gut microbiome also acts as a protective barrier against

pathogens. By occupying ecological niches in the gut and competing for resources, beneficial microbes prevent harmful microorganisms from colonizing the gut lining. Furthermore, the microbiome can enhance the gut's physical barrier by promoting the production of mucus and strengthening tight junctions between epithelial cells, which prevents pathogen infiltration (13). In UC, the breakdown of this protective barrier due to dysbiosis can lead to increased intestinal permeability and inflammation.

Factors Influencing the Microbiome

Several factors can influence the composition and diversity of the gut microbiome, including:

Diet: Diet is one of the most significant factors shaping the microbiome. A diet rich in fiber, for example, promotes the growth of beneficial bacteria that produce SCFAs, while a diet high in fat and animal protein can reduce microbial diversity and increase the abundance of harmful microbes (8). Dietary interventions, such as the Mediterranean diet or a high-fiber diet, have been shown to positively affect the microbiome and may reduce the risk of diseases like UC (14).

Antibiotics: Antibiotics, particularly broad-spectrum ones, can significantly alter the gut microbiome by reducing microbial diversity and allowing the overgrowth of opportunistic pathogens such as Clostridium difficile (15). Antibiotic use has been linked to an increased risk of developing IBD, and patients who have been treated with antibiotics early in life may be more susceptible to UC later on (16).

Genetics: Genetics also play a role in shaping the microbiome, although it is less significant than environmental factors like diet and antibiotics. Studies have shown that individuals with genetic susceptibility to UC may harbor a microbiome that is more prone to dysbiosis, possibly due to a combination of host genetic factors and immune system dysfunction (17).

Environmental Factors: Other environmental factors, such as stress, pollution, and infections, can influence the microbiome's composition. Studies have found that individuals living in urban areas with high levels of pollution tend to have a less diverse microbiome compared to those living in rural areas (18). Additionally, infections and inflammation in the gut can lead to shifts in microbial populations that may perpetuate or worsen UC symptoms (19).

Alterations in the Microbiome in Ulcerative Colitis

Ulcerative colitis (UC) is a chronic inflammatory condition of the colon that is associated with significant changes in the gut microbiome. In healthy individuals, the microbiome plays a crucial role in maintaining intestinal homeostasis, but in UC patients, this balance is often disrupted. The phenomenon of microbial imbalance in UC is referred to as dysbiosis, which is characterized by a reduction in microbial diversity and changes in the relative abundance of certain bacterial species. These alterations in the microbiome are thought to contribute to the pathogenesis and progression of UC.

Dysbiosis in UC

Studies have consistently shown that UC patients exhibit dysbiosis, which is associated with a decrease in microbial diversity. This reduction in diversity can lead to an overrepresentation of pathogenic bacteria and a depletion of beneficial microbes. For example, UC patients often have lower levels of Firmicutes and Bacteroidetes and an increase in Proteobacteria, which are considered to be pro-inflammatory (20). A lack of beneficial bacteria such as Faecalibacterium prausnitzii, a known producer of anti-inflammatory short-chain fatty acids (SCFAs), has been commonly observed in UC patients (21). This dysbiotic state not only disturbs the balance of the gut microbiota but also impairs the microbiome's ability to regulate inflammation and protect the gut from harmful pathogens.

Research has also shown that the diversity of gut microbes is more significantly reduced in UC patients with active disease compared to those in remission, suggesting that dysbiosis might play a role in the severity and recurrence of the disease (22). The loss of microbial diversity in UC may therefore contribute to a persistent inflammatory environment, making it harder for the gut to heal and regulate immune responses effectively.

Specific Bacterial Species and UC

Several specific microbial species have been implicated in the pathogenesis of UC. The most prominent among them are members of the Firmicutes, Bacteroidetes, and Proteobacteria phyla.

Firmicutes: These bacteria are normally abundant in a healthy gut and are known for their ability to produce SCFAs such as butyrate, which help maintain intestinal barrier function and regulate inflammation. However, UC patients tend to have a reduced abundance of Firmicutes species like Faecalibacterium prausnitzii, which is known for its

anti-inflammatory properties (21). The loss of these beneficial bacteria may lead to a reduced capacity to suppress inflammation, contributing to the chronic inflammation seen in UC.

Bacteroidetes: Bacteroidetes are another dominant group of bacteria in the gut microbiota. In UC patients, the abundance of Bacteroidetes is often decreased, which further disturbs the balance of the microbiome. These bacteria are involved in the fermentation of complex carbohydrates and the production of beneficial metabolites such as SCFAs. A decrease in Bacteroidetes could therefore impair gut health and exacerbate inflammation (20).

Proteobacteria: In contrast, Proteobacteria are often more abundant in UC patients and are considered to be pro-inflammatory. These bacteria, which include species like Escherichia coli, have been linked to an increased risk of inflammation and infection in the gut (23). An overrepresentation of Proteobacteria is thought to contribute to the inflammatory processes that characterize UC, as these bacteria can produce toxins and activate immune responses that exacerbate gut inflammation.

Impact of Dysbiosis on Immune Function

Dysbiosis in UC can have profound effects on the immune system and its ability to regulate inflammation. The gut microbiome interacts with the immune system to maintain homeostasis, and an imbalance in microbial populations can lead to dysregulated immune responses.

Inflammation: In UC, the immune system often becomes overactive, leading to chronic inflammation of the intestinal lining. Dysbiosis plays a critical role in this process by altering immune cell behavior. For example, certain pathogenic bacteria that overgrow in UC can stimulate pro-inflammatory immune cells such as T-helper 17 (Th17) cells, which are involved in the recruitment of inflammatory cytokines to the gut (24). The production of these inflammatory cytokines, such as IL-17 and TNF-α, drives the chronic inflammation characteristic of UC.

Epithelial Barrier Function: The microbiome also helps maintain the integrity of the gut's epithelial barrier. In a healthy gut, beneficial bacteria produce metabolites like SCFAs that strengthen tight junctions between epithelial cells, preventing harmful pathogens from entering the bloodstream. However, in UC, the dysbiotic microbiome disrupts the function of the epithelial barrier, leading to increased intestinal permeability, often referred to as "leaky gut." This loss of barrier function allows bacteria and toxins to penetrate the gut lining, triggering immune activation and inflammation (25).

In addition, microbial metabolites, such as SCFAs, can influence immune responses by interacting with immune cells. For example, butyrate, a major SCFA produced by Firmicutes, has been shown to promote regulatory T cell (Treg) activity, which is important for suppressing excessive immune responses and maintaining tolerance to the microbiota (26). The reduction of SCFA-producing bacteria in UC may, therefore, impair immune regulation and enhance inflammation. Thus, dysbiosis not only disturbs the balance of microbial populations but also disrupts immune functions that are essential for controlling inflammation and protecting the intestinal barrier.

Mechanisms Linking the Microbiome to UC Pathogenesis

The gut microbiome plays a central role in the development and progression of ulcerative colitis (UC). The disruption of microbial communities in UC patients is not just a consequence of the disease, but also a contributing factor to its pathogenesis. The gut microbiome influences several key processes that are directly linked to UC inflammation, including immune system modulation, intestinal barrier integrity, and the production of metabolites that affect the gut's inflammatory environment.

Immune System Modulation

The immune system is one of the main targets of microbiome disturbances in UC. A healthy microbiome plays an essential role in regulating both innate and adaptive immune responses. The interaction between the microbiota and immune cells is crucial for maintaining intestinal homeostasis. In UC, this relationship is disrupted, leading to excessive and chronic inflammation.

Innate Immunity: The gut microbiome influences innate immune responses by interacting with pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) on epithelial cells and immune cells. These receptors recognize microbial components like lipopolysaccharides and peptidoglycans, initiating immune signaling that promotes a balanced immune response. In UC, altered microbial compositions can lead to an overactivation of innate immune cells, such as macrophages and neutrophils, which contribute to the persistent inflammation in the intestinal lining.

Adaptive Immunity: The microbiome also impacts adaptive immunity, particularly the regulation of T cell responses. Beneficial microbes in a healthy gut

promote the development of regulatory T cells (Tregs), which help maintain immune tolerance and prevent excessive immune activation. However, in UC, the microbiome's dysbiotic state can impair Treg function and increase the activation of pro-inflammatory T-helper (Th) cells, such as Th17 cells, which are involved in driving chronic inflammation (27). This imbalance in immune responses is a key feature of UC pathogenesis, where the immune system attacks the intestinal tissues, leading to tissue damage and ulceration.

Intestinal Barrier Integrity

The intestinal barrier is crucial for maintaining gut homeostasis and preventing harmful pathogens from entering the bloodstream. The gut microbiome plays a vital role in preserving the integrity of this barrier by influencing the production of mucus and tight junction proteins that seal the spaces between epithelial cells. When the microbiome is disrupted in UC, the intestinal barrier becomes compromised, leading to increased intestinal permeability, often referred to as "leaky gut."

Microbial Influence on Epithelial Cells: Healthy microbiota help regulate epithelial cell function by promoting the expression of tight junction proteins, such as occludin and ZO-1, which maintain the intestinal barrier. Dysbiosis in UC can lead to a reduction in the abundance of beneficial bacteria that produce metabolites like short-chain fatty acids (SCFAs), which are important for strengthening tight junctions and preserving epithelial cell integrity (28). In the absence of these protective factors, epithelial cells become less able to maintain a functional barrier, allowing the passage of harmful bacteria and toxins into the bloodstream, which further activates immune responses and exacerbates inflammation.

Impaired Barrier Function in UC: Studies have shown that UC patients often have decreased levels of Faecalibacterium prausnitzii, a bacterium known to produce anti-inflammatory metabolites such as butyrate, which support the intestinal barrier. The loss of this beneficial microbe contributes to the disruption of the epithelial barrier and the increased permeability observed in UC patients (21). This increased permeability allows for the translocation of microbial products and pathogens, which can activate the immune system and sustain the chronic inflammation characteristic of UC.

Metabolites and Inflammatory Mediators

One of the major ways in which the microbiome affects UC pathogenesis is through the production of metabolites, particularly short-chain fatty acids (SCFAs) like acetate, propionate, and butyrate. These SCFAs are produced by the fermentation of dietary fibers by gut bacteria, and they have profound effects on gut health and immune function.

Short-Chain Fatty Acids (SCFAs): SCFAs are crucial for maintaining intestinal health. Butyrate, for example, is a primary energy source for colonic epithelial cells and plays a key role in maintaining the integrity of the intestinal barrier. Butyrate also has anti-inflammatory effects by inhibiting the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor that promotes the expression of pro-inflammatory cytokines. In UC, the decreased abundance of SCFA-producing bacteria leads to lower levels of butyrate, weakening the intestinal barrier and promoting inflammation.

Inflammatory Mediators: In addition to SCFAs, the microbiome also influences the production of various inflammatory mediators, including cytokines and chemokines. In UC, an imbalance in microbial populations can result in the overproduction of pro-inflammatory mediators like IL-1β, IL-6, and TNF-α, which contribute to the chronic inflammation observed in the disease. Microbial dysbiosis can also lead to the activation of inflammasomes, protein complexes involved in the production of interleukin-18 (IL-18) and IL-1β, which play a role in amplifying the inflammatory response (29). The altered microbial environment in UC thus drives a vicious cycle of inflammation, epithelial damage, and immune activation.

Microbiome as a Therapeutic Target in Ulcerative Colitis

Given the central role of the microbiome in the pathogenesis of ulcerative colitis (UC), targeting the microbiome has emerged as a promising therapeutic strategy. Various approaches, including probiotics, prebiotics, fecal microbiota transplantation (FMT), dietary interventions, and pharmacological treatments, aim to restore the balance of the gut microbiome and mitigate the inflammatory processes associated with UC. This section reviews the potential of these therapeutic strategies.

Probiotics and Prebiotics

Probiotics and prebiotics have garnered attention as potential therapies to restore microbial balance and improve UC symptoms.

Probiotics: Probiotics are live microorganisms that, when administered in adequate amounts, provide health benefits to the host. In UC, probiotics are thought to help restore the diversity and composition of the gut microbiota, particularly by increasing the abundance of beneficial bacteria like Lactobacillus and Bifidobacterium. Studies have shown that specific probiotic strains can help reduce UC symptoms by promoting intestinal barrier function, modulating immune responses, and inhibiting the growth of pathogenic bacteria (30). For example, Escherichia coli Nissle 1917, a strain of probiotic bacteria, has been found to be effective in maintaining remission in UC patients, demonstrating its potential as a therapeutic option (31).

Prebiotics: Prebiotics are dietary fibers that selectively stimulate the growth or activity of beneficial microbes in the gut. By promoting the growth of SCFA-producing bacteria, prebiotics help maintain gut health and reduce inflammation. In UC, prebiotics such as fructooligosaccharides (FOS) and inulin have been investigated for their ability to restore microbial diversity and improve intestinal barrier function (32). Prebiotic supplementation, combined with a high-fiber diet, may offer a complementary approach to probiotic therapy by nurturing beneficial gut bacteria and supporting long-term microbial balance.

Fecal Microbiota Transplantation (FMT)

Fecal microbiota transplantation (FMT) involves transferring fecal material from a healthy donor to a recipient in order to restore a healthy gut microbiome. The concept of FMT as a treatment for UC is based on the idea that restoring microbial diversity can reduce inflammation and promote mucosal healing in UC patients.

Mechanisms: FMT aims to restore a balanced microbial ecosystem in UC patients, thereby reversing dysbiosis and reducing disease activity. The transplant introduces a diverse array of microbes, which can help restore the abundance of beneficial bacteria, increase the production of SCFAs, and modulate immune responses. Studies have shown that FMT can significantly improve clinical outcomes in UC, with some patients achieving clinical remission following treatment (33). However, the success of FMT can vary depending on factors such as donor selection, the method of administration, and the patient's disease severity.

Outcomes and Evidence: Several studies have explored the efficacy of FMT in UC, with mixed results. While some trials have reported significant improvements in UC symptoms, others have shown limited benefits. For example, a large multicenter trial by Rossen et al. (2015)(34) demonstrated that FMT could induce remission in UC patients who had not responded to conventional treatments. However, the long-term benefits and optimal protocols for FMT in UC are still under investigation, and more controlled trials are needed to fully evaluate its efficacy and safety.

Dietary Interventions

Dietary interventions have a profound impact on the gut microbiome and can influence the outcome of UC. Certain diets can promote a favorable microbiome composition, reduce inflammation, and alleviate UC symptoms.

Low FODMAP Diet: The low fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAP) diet has been shown to improve gastrointestinal symptoms in various inflammatory bowel diseases, including UC. This diet restricts high-FODMAP foods that are poorly absorbed in the small intestine and fermented by gut bacteria, leading to a reduction in gas production and bloating. By reducing the load of fermentable carbohydrates, the low FODMAP diet may help restore microbial balance, reduce gut permeability, and alleviate symptoms like abdominal pain and diarrhea in UC patients (35).

Mediterranean Diet: The Mediterranean diet, rich in fruits, vegetables, whole grains, legumes, olive oil, and fish, has been associated with improved outcomes in UC. This diet supports gut health by promoting the growth of beneficial microbes such as Bifidobacterium and Faecalibacterium prausnitzii, which produce SCFAs and have anti-inflammatory effects. Studies have shown that the Mediterranean diet can modulate the gut microbiome, reduce inflammation, and improve the quality of life in UC patients (4). Dietary components like polyphenols from fruits and vegetables have anti-inflammatory properties, further supporting the potential of the Mediterranean diet as an adjunctive treatment for UC.

Pharmacological Approaches

Emerging pharmacological therapies aim to target the microbiome or its metabolites directly, providing a new avenue for UC treatment. These approaches include microbiome-modulating biologics and drugs designed to restore microbial balance and reduce inflammation.

Microbiome-Modulating Biologics: Several biologics that target the immune system have been

explored for their ability to indirectly modulate the microbiome. For example, vedolizumab, an integrin inhibitor used in UC, has been shown to influence gut microbial composition by altering immune cell trafficking to the gut (36). This biologic therapy, by reducing inflammation and promoting mucosal healing, may also help restore a more favorable microbiome. Other biologics targeting inflammatory cytokines, such as TNF-α inhibitors (e.g., infliximab), have shown promise in managing UC, and ongoing research is investigating their potential effects on the microbiome.

Microbial Metabolite-Based Drugs: Another area of interest is the development of drugs based on microbial metabolites. SCFAs, particularly butyrate, are known to have anti-inflammatory and barrier-strengthening effects. Researchers are exploring the therapeutic use of butyrate supplements or analogs to treat UC and other inflammatory bowel diseases (37). These metabolites may help modulate the immune system and protect the intestinal barrier, offering a novel strategy to target UC pathogenesis at the microbial level.

Challenges and Future Directions

While the microbiome holds significant promise as a therapeutic target in ulcerative colitis (UC), several challenges remain in fully understanding its role in the disease and translating this knowledge into effective treatments. Overcoming these obstacles requires addressing issues such as the heterogeneity of UC, leveraging new technological advancements, and filling critical gaps in current research.

Heterogeneity of UC

Ulcerative colitis is a highly heterogeneous disease, with variable clinical presentations, disease courses, and responses to treatment. This heterogeneity complicates the development of personalized treatments, as it remains challenging to identify specific microbiome signatures that correlate with disease severity or prognosis. UC patients exhibit different microbial profiles, and the diversity of the microbiome across individuals further complicates the search for universal microbial markers (38). As a result, the same therapeutic intervention, such as probiotic treatment, may have varying efficacy among UC patients due to differences in their baseline microbiome compositions (39).

The difficulty in defining a specific "UC-associated microbiome" adds to this complexity. While some studies identify particular microbial taxa associated with UC, these findings are often inconsistent. A tailored approach to microbiome-based therapies will require a deeper understanding of how individual microbial communities interact with host factors (e.g., genetic predisposition, immune status) and contribute to UC pathogenesis. Personalized microbiome modulation strategies that take into account these individual variations could offer more targeted and effective treatments.

Technological Advancements

The rapid advancement of genomic and transcriptomic technologies has revolutionized microbiome research and holds the key to furthering our understanding of its role in UC. High-throughput techniques such as metagenomics, which allows for the sequencing of microbial DNA, enable researchers to profile the entire microbiome, identifying a vast array of microorganisms and their functional potentials (40). These approaches have uncovered novel microbial species and pathways involved in UC that were previously unrecognized.

Additionally, single-cell RNA sequencing (scRNA-seq) is providing unprecedented insights into the interactions between microbial communities and the host. By examining gene expression at the single-cell level, researchers can now explore how immune cells in the gut respond to changes in the microbiome and how these responses contribute to inflammation and UC progression (41). This technology offers the potential to uncover the cellular mechanisms underlying UC and pinpoint microbial species or metabolites that drive disease pathology.

While these technologies offer exciting possibilities, their application to UC research is still in its early stages. The integration of metagenomic and transcriptomic data with clinical data will be critical for advancing personalized treatments and understanding the specific microbial factors involved in UC.

Unanswered Questions

Despite the progress made in microbiome research, several key questions remain unanswered, particularly regarding the causality between microbiome alterations and UC pathogenesis. It is still unclear whether dysbiosis in UC is a cause or consequence of inflammation. Longitudinal studies that track microbiome changes over time in individuals before and after the onset of UC are needed to establish causal relationships.

Additionally, the complexity of microbial-host interactions complicates our understanding of the precise mechanisms by which the microbiome contributes to UC. While microbial dysbiosis is well

documented in UC, the specific microbial species or communities that directly influence disease progression are not fully understood. The role of the microbiome in modulating the immune system, maintaining intestinal barrier integrity, and producing metabolites like short-chain fatty acids (SCFAs) is still an area of active investigation (42).

Moreover, much of the research on microbiome-based therapies for UC has been limited to short-term studies, leaving questions about the long-term safety and effectiveness of interventions like fecal microbiota transplantation (FMT) or probiotic treatment. More rigorous clinical trials with long follow-up periods are necessary to determine the sustainability of microbiome-modulating treatments and their potential side effects.

Finally, while the gut microbiome is a focal point in UC research, other microbial communities in the body (such as those in the oral cavity, skin, and lungs) may also contribute to disease pathogenesis and treatment outcomes. Expanding research to encompass these microbiomes could provide a more holistic understanding of UC and its systemic effects.

Future Directions

Future research in microbiome and UC will likely focus on several key areas:

Personalized Microbiome Therapies: As our understanding of the microbiome's role in UC deepens, personalized therapies based on an individual's microbiome profile may emerge. These therapies could include targeted probiotics, prebiotics, or FMT interventions designed to restore a specific microbial balance in the gut.

Longitudinal and Multi-Omic Studies: Large-scale, longitudinal studies integrating microbiome analysis with genomic, proteomic, and metabolomic data will be essential for understanding the complex relationship between the microbiome and UC. These studies will help establish causality and identify biomarkers for early diagnosis and treatment response.

Microbiome-Based Drug Development: New drugs that modulate the microbiome or its metabolites (such as SCFAs) are likely to emerge as important therapeutic options for UC. The development of microbiome-targeted biologics and small molecules offers exciting possibilities for more effective, microbiome-based treatments.

Conclusion

The review highlights the significant role of the microbiome in ulcerative colitis (UC). Dysbiosis, characterized by reduced microbial diversity and shifts in bacterial species like Firmicutes and Bacteroidetes, is linked to UC inflammation and intestinal barrier dysfunction. Microbial alterations influence immune responses and contribute to UC pathogenesis. Microbiome-based therapies, such as probiotics, prebiotics, fecal microbiota transplantation (FMT), and dietary interventions, show promise in restoring microbial balance and improving UC symptoms. These findings suggest that microbiome modulation could become a therapeutic approach for UC, with personalized treatments tailored to an individual's microbiome profile. FMT and dietary interventions may offer additional treatment options. Emerging microbiome-targeted biologics provide new possibilities for managing refractory UC. Future studies should focus on establishing the causal relationship between microbiome changes and UC through longitudinal research. Personalized microbiome therapies and more mechanistic studies are needed to identify specific microbial targets. Advanced technologies like metagenomics and single-cell RNA sequencing will continue to enhance our understanding. Long-term clinical trials are also crucial to assess the safety and efficacy of microbiome-based interventions.

Contribution of authors

Not Applicable

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Not Applicable

Conflict of interest

None

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