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| RESEARCH ARTICLE

The Impact of the Interaction between Intestinal Flora and Intestinal Wall Immune Microenvironment on Ulcerative Colitis

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| ABSTRACT
Ulcerative colitis (UC) is a chronic, non-specific inflammatory disease of the intestine with an unknown etiology. The primary clinical manifestations include recurrent abdominal pain, diarrhea, mucus and purulent discharge, bloody stools, and tenesmus. Experts generally agree that the onset of this disease is primarily associated with factors such as intestinal flora, dietary composition, genetics, immunity, infections, and systemic inflammation. The intestinal flora constitutes the largest microecological system within the human body, consisting of a vast array of microorganisms that interact dynamically with the immune cells located in the intestinal wall. This interaction is crucial for maintaining a balance with the intestinal mucosa. The intestinal flora plays a significant role in the development of the immune system, sustaining normal immune function, and cooperatively countering the invasion of pathogenic bacteria. Alterations in the composition of the intestinal flora can influence the equilibrium between intestinal tolerance and immunity. Research has demonstrated that the disease process in UC patients is closely linked to disturbances in the structure of the intestinal bacterial flora, and symptoms can be significantly alleviated following the transplantation of normal flora. Therefore,Modulating the structure of the intestinal microbiota may serve as an effective strategy for treating ulcerative colitis (UC). This article examines the relationship between intestinal flora and intestinal wall immunity in the context of UC, while also exploring novel approaches for its treatment.

| KEYWORDS
Intestinal flora; intestinal microorganisms; intestinal wall immune microenvironment; chronic ulcerative colitis.

| ARTICLE INFORMATION
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1. Introduction

1.1 Overview of Intestinal Flora

1.1.1 The Composition of the Gut Microbiome

Human microorganisms are extensively distributed, with approximately 1014 colonies residing on both the internal and external surfaces of the human body, including the gastrointestinal tract, conjunctiva, skin, and oral cavity [Savage, 1977],This microbial community far exceeds all other microbial populations associated with body surfaces and is responsible for a number of functions, including cellular processes and reproduction, outnumbering human cells by a factor of ten [Bäckhed, 2005].The intestinal flora, in particular, is highly diverse, comprising bacteria, fungi, protists, archaea, and viruses, and accounts for 60% of the dry mass of stool [Katdare, 2010].

The intestinal microbiota consists of more than 35,000 species distributed in more than 50 different phyla [Robles-Alonso, 2013].Most of them are anaerobic bacteria (99%), but there is a high density of aerobic microorganisms in the cecum [Gomaa, 2020]. Additionally, bacterial diversity and abundance vary significantly from the distal esophagus to the rectum. In the distal esophagus, duodenum, and jejunum, Streptococcus is the dominant bacterial genus. Helicobacter pylori (Helicobacter) is the dominant genus present in the stomach and determines the entire microbial structure of the gastric flora [Justesen, 1984].The

large intestine is composed of more than 70% of the microorganisms in the body. The intestinal flora usually discussed in disease states mainly refers to the cecum and colon flora. In addition to longitudinal differences, there are also axial differences from the intestinal lumen to the intestinal mucosal surface. The dominant bacteria in the intestinal lumen are Bacteroides, Bifidobacterium, Streptococcus, Enterobacteriacae, Enterococcus, Clostridium, Lactobacillus and Ruminococcus, while Clostridium, Lactobacillus, Enterococcus, Akkermansia are the intestinal mucosa and mucus layer The dominant bacteria are found in the mucus layer and epithelial crypts of the small intestine [Andersson, 2008].

1.2 Function of Intestinal Flora

The relationship between intestinal flora and human health is closely linked. Healthy gut flora largely determines the overall health of the host. The human intestinal flora is established at birth, and researchers call it a "microbial organ": it has a quorum sensing effect and can regulate the host's remote organs; affects the consumption, storage and redistribution of the body's energy; and mediates related physiological functions. key material changes [Pan, 2022].

1.2.1 The Role of Intestinal Flora in Metabolism

The daily intake of dietary water and cereals by the human body is the most important raw material for intestinal flora metabolism and affects the structure and composition of intestinal flora.The intestinal flora can use the residues in the diet,digestive tract secretions, and dead and shed epithelial cells to carry out biosynthesis and metabolism.On the one hand, it synthesizes essential nutrients for the human body [Jeffery, 2013],and on the other hand, it promotes the decomposition and excretion of harmful metabolites from the body, maintain the health of the body [Yano, 2015]. In addition the intestinal flora can also play an immune defense role by adjusting the ratio of probiotics and pathogenic bacteria, using the intestinal mucosal barrier to resist the invasion of exogenous pathogenic bacteria [Sommer, 2013],and can regulate the secretion of intestinal mucosal cytokines to promote the immune system. Mature, induce the formation of immune tolerance, and maintain the stability of immune responses [Francino, 2014].

The intestinal microbiota mainly digests dietary fiber, protein and peptides through fermentation and anaerobic degradation, provides energy through metabolism, and maintains intestinal health [Acheson, 2004].The main by-products formed by various microbial fermentation reactions are gases, such as H_2, CO_2, methane and short chain fatty acids (SCFAs). SCFAs regulate many metabolic pathways in the gut and liver, adipose tissue, muscle and brain, contributing to many physiological effects including regulation of energy homeostasis, sugar/lipid metabolism, inflammation and even immunity and cancer [Vitali, 2023]. In addition to their well-known effects and mechanisms, some short-chain fatty acids may also serve different functions than previously thought. For example, butyrate has been repeatedly described as an important source of energy for colon cell proliferation and maintenance of the intestinal barrier. However, recent evidence suggests that butyrate also strongly affects the microbial environment by communicating with colon cells. The gradual decrease in oxygen content in the luminal portion of the intestine and its concentration in the epithelial cells is a key requirement for anaerobic bacteria to remain in close proximity to the epithelial cells, and facultative anaerobes such as Enterobacteriaceae have been shown to increase intestinal inflammation risk [Litvak, 2019]. In addition to propionic and butyric acids, the effects of succinic acid are also being studied. Succinate is an intermediate in the tricarboxylic acid cycle and is considered a substrate for mitochondrial oxidative phosphorylation, but is also a bacterial metabolite [Fernández-Veledo, 2019].Gut bacteria can also synthesize amino acids and provide them to the host. However, the final consequences of amino acid synthesis and degradation remain largely to be determined, implicating the role of the gut microbiota in managing systemic nitrogen metabolism.

1.2.2 The Role of Intestinal Flora in Body Immunity

Intestinal flora not only promotes the metabolic process of the human body, but also exerts a series of physiological effects on the host, such as immune system development, resistance to pathogens, host intestinal epithelial cell development and maintenance of tissue homeostasis. Effector and regulatory T cells, gut-associated lymphoid tissue (GALT), immunoglobulin (Immunoglobulin A, IgA)-producing B cells, Group 3 innate lymphoid cells, macrophages in the lamina propria and dendritic cells are components and major cell types of the immune system involved in immunomodulatory processes [Jiao, 2020].

Pattern recognition receptors (PRRs) are part of the host's innate immune system and can sense commensal and pathogenic microorganisms. PRRs are receptors that recognize conserved pathogen-associated molecular patterns (PAMPs) from viral, bacterial, fungal or parasitic components [Chu, 2013]. Endotoxin (Lipopolysaccharide, LPS) found on the cell membrane of Gram-negative bacteria is a potent activator of inflammatory response, and even a small amount of LPS released into the circulation is enough to cause an inflammatory response. LPS and other PAMPs exert their activity by activating PRRs, which sense microorganisms and infectious agents and signal defense responses.

Toll-like receptors (TLRs) are widely distributed in immune cells, including macrophages, natural killer cells, mast cells, dendritic cells, neutrophils, basophils and eosinophils cells, but also found in other body cells such as intestinal epithelial cells [Chu, 2013].

Their activation induces activation of antigen-presenting cells, thereby linking innate and adaptive immune responses and stimulating signaling cascades as an attempt to defend against microbial invaders or repair damaged tissue. Although this inflammatory response is necessary for the elimination of infection, overactivation of TLRs can lead to disruption of immune homeostasis, and the sustained production of chemokines and proinflammatory cytokines can increase the risk of inflammatory diseases and autoimmune diseases [Pan, 2022]. A large number of studies have shown that metabolic by-products such as SCFAs produced by symbiotic bacteria regulate the immune response of GALTs through epigenetic mechanisms, playing a role in host defense and maintaining immune tolerance to symbionts [Jiao, 2020].

2 Intestinal Wall Immune Microenvironment

The immune microenvironment of the intestinal wall refers to the complex interactions between various immune cells, molecules and microorganisms present in the intestine. This microenvironment plays an important role in maintaining intestinal health and defending against pathogen invasion. The immune microenvironment of the intestinal wall is a dynamic and complex system, and its components interact to maintain intestinal health and prevent inflammation and disease. Understanding this microenvironment has important implications for the development of new therapeutic strategies and interventions.

2.1 The Composition of Immune Cells

There are a variety of immune cells in the intestine, including T cells, B cells, macrophages, dendritic cells, and eosinophils.Together, these cells participate in immune responses and maintaining intestinal homeostasis.

2.2 Gut-associated Lymphoid Tissue

Gut-associated lymphoid tissue (GALT) includes lymph nodes and Peyer's patches in the intestine. These structures are an important part of the intestinal immune system and are responsible for recognizing and responding to antigens entering the intestine.

2.3 Barrier Function

The intestinal epithelial cells and mucus layer form a physical barrier to prevent the invasion of pathogens and harmful substances. Immune cells monitor the integrity of these barriers and mount an immune response when needed.

2.4 The Role of the Microbiome

Intestinal flora interact with the host immune system to promote immune tolerance, prevent excessive inflammatory responses, and effectively balance intestinal health.

2.5 Cytokines and Signaling Molecules

Immune cells regulate immune responses and communication between cells by secreting signaling molecules such as cytokines and chemokines, promoting inflammation or inhibiting immune responses in response to different pathogens and environmental changes.

3 The Impact of the Interaction between Intestinal Flora and Intestinal Wall Immune Microenvironment on Ulcerative Colitis

3.1 Imbalance of Flora

UC patients often show reduced diversity of intestinal flora, reduced number of probiotics, and increased number of harmful bacteria [Mayer, 2019]. This imbalance may lead to an increased inflammatory response. On the one hand, the imbalance of intestinal flora leads to an increase in the number of pathogenic bacteria, which destroy the normal intestinal mucosal barrier through invasiveness and toxins, increasing the permeability of the intestinal mucosa [Pickard, 2017]; on the other hand, imbalance of intestinal flora can cause The expression and release of inflammatory factors increase, the normal immune balance of the intestine is disrupted, and abnormal immune responses are activated, leading to intestinal mucosa and tissue damage [Li, 2017]. Recently, the relevant team summarized the research progress of traditional Chinese medicine in the treatment of ulcerative colitis and explored the mechanism of traditional Chinese medicine in regulating intestinal flora and repairing damaged intestinal barrier, providing a theoretical basis for future research to clarify the traditional Chinese medicine treatment mechanism of intestinal flora. New ideas for clinical treatment of ulcerative colitis [Wang, 2024]. In 2022, a team discovered that while exploring the therapeutic effect and mechanism of probiotic Lactobacillus plantarum HNU082 (Lp082) on UC, they found that Lp082 played a protective role in a mouse model of DSS-induced colitis. Probiotic Lp082 can protect the intestinal mucosal barrier, reduce inflammatory response and regulate microbial imbalance [Wu, 2022].

3.2 Short Chain Fatty Acids

Short-Chain Fatty Acids (SCFAs) are metabolites produced by intestinal microorganisms fermenting dietary fiber, mainly including acetic acid, propionic acid, and butyric acid. They play an important role in maintaining intestinal health and overall metabolism.

Short-chain fatty acids (such as butyrate) produced by intestinal microbial metabolism have anti-inflammatory effects, promote the repair of intestinal epithelial cells, and enhance intestinal barrier function. Butyric acid has significant anti-inflammatory properties, which can inhibit the release of inflammatory mediators, help regulate immune responses, and reduce the risk of intestinal inflammation. Short-chain fatty acids help maintain the balance of the intestinal microbiota by inhibiting the growth of harmful bacteria and promoting the reproduction of good bacteria. Studies have found that levels of these beneficial metabolites tend to be reduced in UC patients. In 2023, relevant teams have demonstrated that Herba Origani can protect mice from DSS-induced ulcers by reshaping intestinal flora to regulate bile acid and SCFA metabolism, which is enough to show that Herba Origani is expected to be used to treat inflammatory bowel disease [Yu, 2023].

A related team studied the traditional Chinese medicine Pulsatilla Decoction (PD) for the treatment of ulcerative colitis and found that PD has a good therapeutic effect on UC mice. The pharmacological mechanism may be to maintain the homeostasis and diversity of intestinal flora, increase the content of SCFA, and repair the colon mucosal barrier. Thereby achieving the effect of improving UC [Niu, 2023].

3.3 Intestinal Barrier Function

Gut flora affects local and systemic immune responses by regulating the activity of T cells and B cells. In UC, an exaggerated immune response leads to intestinal wall damage and inflammation.

Healthy intestinal flora helps maintain the integrity of the intestinal epithelium and prevents the invasion of pathogens and toxins. Imbalance of bacterial flora may lead to impairment of intestinal barrier function, thereby aggravating the condition of UC [Sommer, 2017]. The team has demonstrated that IL-22 expression is controlled by the aryl hydrocarbon receptor (AhR) while studying the beneficial effects of interleukin 22 (IL-22) on innate lymphocytes (ILC3) on the intestinal barrier. In an in vivo experimental study, this study demonstrated that baicalein improves colitis by improving the intestinal epithelial barrier through the AhR/IL-22 pathway in (ILC3s), thus providing a potential treatment for UC [Li, 2022].

3.5 Therapeutic Potential

Studies have shown that adjusting the intestinal flora (such as using probiotics, prebiotics or fecal transplants) may be beneficial to UC patients, helping to restore a normal immune microenvironment and reduce symptoms [Moayyedi, 2015]. In a study of modulating intestinal microbiota through fecal microbiota transplantation (FMT), it was found that experimental colitis in mice was alleviated. This study aimed to demonstrate the ameliorative effect of FMT in a DSS-induced UC model and elucidate its effect in mice. Relative mechanisms in the model. The results showed that FMT intervention reduced the disease activity index (DAI) level of experimental animals and increased the body weight, colon weight and colon length of experimental animals. It also alleviated histopathological changes and reduced key cytokine expression and oxidative status in the colon. Downregulation of gene expression levels related to the NF-κB signaling pathway was also observed. This suggests that FMT intervention may be suitable for UC control [Zhang, 2020].

In summary, the interaction between intestinal flora and the immune microenvironment of the intestinal wall plays an important role in the pathogenesis of ulcerative colitis. Understanding these mechanisms may provide clues for the development of new treatments.

4. Summary and Outlook

Intestinal microorganisms, the host, and the environment are interdependent and restrictive, maintaining the stability of the biological environment in the host's intestine. Once the stability is broken, diseases will easily occur [Zhang, 2016]. The relationship between intestinal flora, intestinal mucosal immunity and ulcerative colitis is also interdependent and mutually restrictive. Due to the influence of infectious diseases, drugs, diet, stress and other environmental factors, the intestinal flora in the human body is disordered, the beneficial flora in the intestines are reduced, and harmful pathogenic bacteria take the opportunity to attack and cause chaos. T cells in the body cannot identify the quality of cells and attack the body's own cells at the same time, causing an autoimmune reaction and thereby releasing inflammatory factors [Chen, 2017], which can lead to the occurrence of ulcerative colitis. The continuous release of inflammatory factors will destroy the intestinal mucosa, damage intestinal epithelial cells, and lead to further disorder of intestinal flora, forming a vicious cycle. Personalized microbial therapy: By analyzing the characteristics of the patient's intestinal flora, a personalized probiotic or prebiotic therapy can be developed to restore a healthy flora balance and reduce the inflammatory response.

The interaction between intestinal flora and the immune microenvironment of the intestinal wall plays an important role in the pathogenesis of ulcerative colitis (UC). Future research and treatment directions may tend to be in the following aspects:

4.1 Targeted Immunomodulation

Study how the immune response is influenced by modulating gut microbiota. Whether specific bacteria or their metabolites can be exploited to promote immune tolerance and reduce attack on the intestinal tissue itself.

4.2 Intestinal Barrier Repair

Explore strategies to improve intestinal epithelial cell function to enhance barrier function and prevent the invasion of pathogens and toxins, thereby reducing inflammation.

4.3 Monitoring the Gut Microbiome

Develop new technical means to monitor changes in intestinal flora in real time to help clinicians evaluate disease progression and efficacy, so as to better formulate treatment plans.

4.4 Nutritional Intervention

Study the effects of dietary ingredients on intestinal flora and immune microenvironment, and promote plant-based diets or fiber-rich diets to promote the growth of beneficial bacteria and improve symptoms.

4.5 Multi-omics Integrated Research

Combining genomics, transcriptomics, metabolomics and other technologies to comprehensively understand the dynamic changes of intestinal flora and immune microenvironment, providing a theoretical basis for the development of new treatments.

Future research will deepen our understanding of the interaction between intestinal flora and the immune microenvironment of the intestinal wall and promote the development of precise treatment and prevention strategies for ulcerative colitis.

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