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Exploring the pathogenesis and treatment strategies of irritable bowel syndrome based on the gut microbiota microenvironment

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Abstract: Irritable bowel syndrome (IBS) is one of the common functional gastrointestinal disorders, which is characterized by long-term recurrent abdominal pain, abdominal distension, and change in stool shape, which has a great impact on patients' daily life and social and medical economy, etc. Western medicine believes that its pathogenesis is mainly related to the abnormal function of the brain-intestinal axis, visceral hypersensitivity, and abnormal gastrointestinal peristalsis, etc., but the latest research suggests that its occurrence may be closely related to the imbalance of the intestinal flora. However, recent studies suggest that the mechanism of its development may be closely related to the imbalance of intestinal flora. Intestinal flora, as a large number of bacteria in the human body, plays a key role in maintaining intestinal homeostasis, in which the decrease of beneficial bacteria and the increase of harmful bacteria can induce intestinal inflammation, damage the intestinal mucosal barrier, and affect the immune response to accelerate the progress of IBS. In recent years, the number of therapeutic strategies oriented to intestinal flora has been increasing, and their efficacy is becoming significant. Western medicine often adopts conventional drug symptomatic treatment, utilizes psychotherapy and diet therapy, and fecal bacteria transplantation to treat IBS, but its adverse effects are more frequent, limiting its clinical application. Chinese medicine classifies IBS as “abdominal pain” and “diarrhea”, the cause of which is internal injury of emotions and feelings, weakness of the spleen and stomach, and the mechanism of the disease is that the liver loses detachment and excretion, and the combination of deficiencies and realities often leads to lingering and unresolved disease. Traditional Chinese medicine (TCM) is often used to regulate intestinal microbial homeostasis, which has a significant therapeutic effect. However, the treatment of TCM lacks high-quality experimental data support and has not been widely used in clinical practice, and its identification and treatment need to be rationally explained by modern science and supported by sufficient evidence from clinical trials. Therefore, this article takes the intestinal flora as an entry point, reviews its specific occurrence mechanism and targeted therapeutic measures in IBS, and summarizes the therapeutic measures of Chinese medicine and Western medicine treatment, as well as their respective advantages and disadvantages, in order to provide progress for clinical treatment.

Irritable bowel syndrome (IBS) is a functional gastrointestinal disease characterized by abdominal pain or discomfort accompanied by changes in defecation habits and characteristics. The global incidence rate is 10%~15%, while in China it is as high as 1.4%~11.5% [1,2]. There is a gender difference in the incidence of this disease, with females being about 1.67 times higher than males, mainly females under the age of 50 [3]. With the acceleration of modern life rhythm and the change of eating habits, the incidence rate of IBS has increased year by year, and the lingering does not heal, which seriously affects the patients' sleep function, psychological status, social activities and work quality. IBS has significantly reduced the quality of life of patients, increased the incidence rate of psychological complications, increased the economic cost of treatment, and seriously increased the social and economic burden, which is an urgent clinical problem [4, 5]. According to the 2020 Chinese IBS Expert Consensus Opinion, IBS in China can be divided into four types: diarrhea type, undifferentiated type, mixed type, and constipation type. Diarrhea type is the most common in clinical practice [6,7]. At present, the pathogenesis of IBS is complex, including genetic factors, brain gut interaction disorders, intestinal infections and intestinal dynamics abnormalities, visceral hypersensitivity, etc. Intestinal microbiota disorders also play a key role in IBS [8]. At present, Western medicine treatment still focuses on symptomatic treatment and improving quality of life, lacking specific targeted treatment. Moreover, from long-term observation, there are disadvantages such as high recurrence rate and unstable efficacy. IBS is an advantageous disease in traditional Chinese medicine. Traditional Chinese medicine emphasizes the dialectical thinking of treating diseases and combining internal organs and meridians. By regulating the homeostasis of the intestinal environment, it significantly improves clinical efficacy and has broad application prospects [9]. Therefore, this article aims to elucidate the mechanism of IBS from the perspective of microbiota, and restoring the balance of intestinal microbiota through traditional Chinese and Western medicine treatment may provide a new treatment approach for clinical physicians to treat IBS.

1. Imbalance of gut microbiota induces IBS

The gut microbiota refers to the microbial community present in the human intestine. Under normal circumstances, a balanced gut microbiota can protect mucosal integrity, block pathogen invasion, regulate the immune system, and improve gastrointestinal function. The disruption of intestinal microbiota caused by the disruption of balance may trigger intestinal inflammation, damage mucosal integrity, hinder intestinal peristalsis, and induce IBS [10]. At present, the gut microbiota mainly includes Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria. The disruption of gut microbiota in IBS is mainly manifested by a decrease in the number of beneficial bacteria and an increase in harmful bacteria [11]. Research has shown that IBS after traumatic stress is characterized by an increase in aerobic microorganisms and a decrease in anaerobic microorganisms, while pressure stress leads to a significant increase in Proteobacteria. In addition, compared with the healthy control group, the gut microbiota of IBS patients showed an increase in Proteobacteria, Lactobacillaceae, and bacterial genera, while Clostridium, Fecal, and Bifidobacterium genera decreased [12, 13]. Research has shown that a decrease in lactobacilli secretion is associated with dysbiosis of the gut microbiota, which in turn triggers sustained intestinal inflammatory responses. And most IBS patients have sub-health psychological states such as depression and anxiety, which hinder gastrointestinal motility and affect the distribution of dominant bacterial populations [11, 14, 15]. IBS patients mainly exhibit a decrease in the abundance and diversity of the microbiota, and an imbalance in the normal gut microbiota can lead to the occurrence of IBS, which is associated with gastrointestinal motility, visceral hypersensitivity, intestinal inflammation, and psychological factors.

1.1 Intestinal flora and its metabolites affect intestinal peristalsis

The imbalanced gut microbiota affects biochemical processes in the gastrointestinal tract through various mechanisms, such as glycolysis and glucose metabolism, which in turn affects the excretion of metabolites such as short chain fatty acids, hydrogen, carbon dioxide, methane, and other organic acids to regulate the progression of IBS [16]. The large amount of undigested carbohydrates in the colon can promote water and electrolyte secretion, accelerate gastrointestinal motility, and lead to diarrhea. The excessive gas produced by metabolism directly stimulates the sensory nerve endings of the intestinal mucosa by dilating the intestinal wall, resulting in clinical symptoms such as abdominal distension and pain. Short chain fatty acids, as metabolic products of carbohydrates that are not fully digested by bacteria in the colon, can participate in intestinal immune responses, protect mucosal barriers, regulate electrolyte balance, and other functions [17]. Short chain fatty acids can enhance the expression of tryptophan hydroxylase 1 by acting on intestinal chromaffin cells, thereby increasing serotonin. When serotonin levels are too low, patients may experience symptoms such as irritability, anxiety, fatigue, and pain, which in turn hinder intestinal peristalsis. In addition, short chain fatty acids bind to G protein coupled receptors 41 and 43 on the surface of intestinal L cells, which can stimulate the secretion of gastrointestinal related hormones and neuropeptides by intestinal L cells, affecting neuroendocrine function and indirectly regulating gastrointestinal motility by acting on the intestinal nervous system, affecting the occurrence and development of IBS [18].

1.2 Imbalance of gut microbiota triggers inflammatory response and immune dysfunction

The normal colonization and balance of gut microbiota play a positive role in the development and activation of immune cells. Bifidobacterium genus activates lymphocytes, natural killer cells, and macrophages to release various immune active mediators such as interleukin-1 and interleukin-6 [19, 20]. After the imbalance of gut microbiota in IBS patients, it promotes an increase in intestinal mucosal permeability, allowing a large number of bacteria, endotoxins, and related inflammatory mediators to enter the bloodstream and activate the immune system. This significantly upregulates the number of CD3, CD25 cells, and lymphocytes, and then releases pro-inflammatory cytokines such as interleukin-1 β, 10, 6, tumor necrosis factor alpha, etc. in peripheral blood, causing the intestinal mucosa to remain in a chronic and persistent inflammatory state, which in turn triggers the occurrence of symptoms such as IBS abdominal pain and diarrhea [13]. Research has found that patients with IBS have significantly lower levels of Bifidobacterium, Lactobacillus, and Bacteroidetes compared to the healthy control group, while the number of Escherichia coli and Bacteroidetes is higher than the control group. In addition, the levels of cytokines 5-hydroxytryptamine (5-HT), interleukin-10 (IL-10), and interferon gamma (IFN - γ) in patients are significantly higher than those in the control group [21]. The increase in the number of anti-inflammatory factor IL-10 indicates that the intestine is in an inflammatory state at this time, which activates the intestinal immune response, damages the epithelial barrier function, induces intestinal motility disorders and visceral hypersensitivity reactions. In addition, an increase in IL-10 concentration is associated with the frequency and severity of pain [22]. IFN - γ is a pro-inflammatory cytokine, and the balance of IFN - γ/IL-10 is one of the factors that maintain the internal environment of the body. Breaking this balance can cause sustained immune activation and inflammatory response. 5-HT is a neurotransmitter, in which endotoxins in the feces of diarrhea predominant IBS can interact with pancreatic enzymes to stimulate mast cells to release prostaglandin E2 and secrete 5-HT, thereby participating in visceral hypersensitivity symptoms [23].

1.3 Dysbiosis of gut microbiota disrupts intestinal barrier function

In the normal intestinal barrier, epithelial cells maintain their integrity and play a protective role

due to tight connections between them. In IBS, downregulation of tight junction proteins such as occludin, bite protein, and band like occludin leads to decreased intestinal barrier function [24]. In addition, gut microbiota can regulate the expression of tight junction proteins, thereby affecting the protective function of the intestinal barrier. Under normal circumstances, the gut microbiota colonizes the mucus layer, and the proteases and protease inhibitors produced by disrupted gut microbiota can regulate the body's immune response. Specific microorganisms contribute to the increase or decrease of proteases, which may subsequently lead to damage and increased permeability of the intestinal barrier, causing bacterial products and metabolites to invade the epithelial barrier, leading to inflammatory reactions and promoting the progression of IBS [25, 26].

2. Targeted gut microbiota therapy for IBS

2.1 Western medicine treatment of IBS

At present, the drugs used to treat IBS mainly include antispasmodics, opioid receptor inhibitors, antibiotic preparations, 5-HT3 receptor antagonists, and other types. Its clinical efficacy is significant, but its adverse reactions limit its clinical use. Fecal microbiota transplantation has gradually become a research hotspot in recent years, and has been proven to have good clinical efficacy for IBS. It mainly involves oral and endoscopic methods to transplant healthy gut microbiota into patients, rebuild gut microbiota balance, and perform normal functions. Research has shown that fecal microbiota transplantation inhibits visceral hypersensitivity and mast cell activation in IBS rats by regulating the protein kinase activated receptor 2 and transient receptor potential vanillic acid receptor 1 pathways, thereby upregulating Firmicutes, Bacteroidetes, and Lactobacillus colonies, downregulating Spirobacteria, Proteobacteria, and Prevotella colonies to maintain gut microbiota balance and treat IBS [27]. Li Xuemei indicated that the combination of probiotics and trimethoprim can significantly treat diarrheal IBS by downregulating 5-HT, IL-8, and IFN - γ [28]. Zheng Anbin improved the gut microbiota by combining Bifidobacterium triple active capsules with Trimebutine Maleate dispersible tablets, thereby downregulating serum D-lactate, motilin, vasoactive intestinal peptide, and diamine oxidase to improve gastrointestinal function and treat IBS [29].

2.2 Traditional Chinese medicine treatment of IBS

IBS belongs to the categories of "constipation" and "abdominal pain" in traditional Chinese medicine. Traditional Chinese medicine believes that the occurrence of IBS is closely related to the imbalance of organs such as the liver, spleen, and stomach. The spleen is the foundation of postnatal development, and it mainly transports water and grains. The intestinal microbiota also needs nourishment from nutrients transported by the spleen. Weak temperament and inability to properly nourish the intestinal microbiota may be one of the causes of IBS [30]. If the temperament is strong, it will not be invaded by external pathogens, and traditional Chinese medicine can prevent and treat IBS by regulating the number of intestinal microbiota to maintain its steady state and maintain the normal function of spleen function. Research has shown that Chen Dan et al. used Xingnao Tiaoshen acupuncture to select acupoints such as Baihui, Shenting, Benshen, and Tianshu. They used 0.25 mm × 40mm filiform needles and left the needles for 30 minutes after obtaining qi, once every other day, with 10 times as one course of treatment. After 3 courses of treatment, it was observed that the symptoms of IBS abdominal pain and bloating could be significantly improved. By correcting the imbalance of intestinal microbiota in IBS patients, maintaining a normal intestinal microenvironment, and regulating the secretion of gastrointestinal hormones, IBS related symptoms could be alleviated, and inflammatory reactions could be reduced, thereby significantly improving the quality of life of patients [32]. The combination of floating needle therapy and medicinal moxibustion on the navel

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can also regulate the structure of intestinal microbiota and gastrointestinal hormones, effectively reduce visceral sensitivity, alleviate abdominal pain and bloating symptoms, and have good clinical efficacy [33]. In the study of traditional Chinese medicine monotherapy, Ni Honghui et al. found that Sheng Bai Zi Ren can improve intestinal microbiota, promote small intestinal peristalsis, and help treat IBS [34]. Ginseng polysaccharides significantly enhance the expression of tight junction proteins, strengthen the intestinal barrier, and inhibit the progression of IBS [35]. Rhubarb extract rhein, Huangqi extract Huangqi Gan, curcumin, etc. can effectively inhibit apoptosis of intestinal epithelial cells, upregulate tight junction protein expression, reduce bacterial and inflammatory invasion, and thus repair intestinal mucosal damage [36, 37]. In the study of traditional Chinese medicine formulas, Lichang Wan has shown significant therapeutic effects on IBS by improving the levels of Escherichia coli, Enterococcus, Bifidobacterium, and Lactobacillus [38]. The pain relieving formula regulates the expression of bone morphogenetic protein 2 and colony-stimulating factor 1 in colon tissue by modulating the gut microbiota, thereby alleviating symptoms in IBS rats [39]. Waitai Liuwu Huangqin Tang improves the clinical efficacy and quality of life of patients with diarrhea type IBS with mixed cold and heat syndrome by downregulating the Enterobacteriaceae family and increasing the ratio of Bifidobacterium to Escherichia coli, regulating the structure and abundance of intestinal microbiota [40].

In summary, acupuncture, moxibustion, traditional Chinese medicine, and fecal microbiota transplantation can all treat IBS by regulating the balance of gut microbiota. Among them, acupuncture regulates the nervous system through external stimulation to reduce the levels of inflammatory factors in the intestinal mucosa and lower visceral hypersensitivity. It also protects the intestinal mucosal barrier by regulating the expression of tight proteins or intervenes in the distribution of intestinal microbiota to treat IBS. Moxibustion plays a warming role in treating acupoints, promoting the smooth circulation of organs, meridians, qi and blood, and exerting therapeutic effects. Acupuncture moxibustion has the advantages of few side effects, precise therapeutic effects, and low cost, and is worthy of clinical promotion [41]. In addition, traditional Chinese medicine has the characteristics of multi molecule, multi-target, multi-level, and multi center treatment for IBS, which can significantly control the release of inflammatory factors, reduce inflammatory reactions, regulate the ratio of beneficial/harmful bacteria in the intestinal microbiota, reduce recurrence rates, and significantly improve symptoms [42]. However, the compatibility of traditional Chinese medicine formulas is relatively complex, and their specific mechanisms of action and mutual influence need further exploration. Fecal microbiota transplantation, as a new prevention and control strategy, has good development prospects.

3. Discussion

At present, IBS is a chronic and recurrent functional gastrointestinal disease, and its pathogenesis is not yet fully understood. But with the development of modern microbiology, gut microbiota disorder may be the main cause of IBS, which destroys the intestinal epithelial barrier through the secretion of related proteases and inflammatory cytokines, mediates immune regulatory responses, and leads to intestinal inflammation induced IBS [43]. IBS persists and seriously affects the quality of life of patients. Therefore, it is urgent to explore more effective treatment measures, and targeted treatment measures for gut microbiota have opened up new paths. Among them, traditional Chinese medicine or Chinese herbal compound therapy is a commonly used method for treating IBS, although it can also improve the gut microbiota microbiota to a certain extent to alleviate intestinal inflammation, reduce visceral hypersensitivity, repair the intestinal mucosal barrier, and enhance intestinal peristalsis. However, after discontinuation, it is highly prone to recurrence and lacks extensive clinical trial support and guidelines, which limits its large-scale clinical use. Future research

may focus more on clinical trials for the treatment of IBS, in order to confirm its effectiveness and use modern pharmacology to provide a more scientific explanation of the underlying mechanisms of traditional Chinese medicine in treating IBS [44-48]. Fecal microbiota transplantation, as one of the effective measures for the treatment of IBS, can be achieved by increasing the abundance of bacterial genera and gut microbiota. Firmicutes can regulate intestinal structure, Proteobacteria is involved in metabolic disorders and intestinal inflammation, and Bacteroidetes can cause visceral hypersensitivity and promote intestinal permeability, leading to worsening diarrhea and abdominal pain. The gut microbiota structure of IBS patients is significantly imbalanced, and fecal microbiota transplantation can increase the abundance of gut microbiota in patients and play a role. However, there are many factors that affect fecal microbiota transplantation, including the method of supply, fresh or frozen feces, placebo type, IBS subtypes and their specific doses, and microbial activity level. Therefore, in clinical trials, the determination of relevant indicators and the design of specific experimental protocols should be rigorously designed to ensure their safety and effectiveness. Moxibustion has definite therapeutic effects and obvious advantages in treating IBS. Its side effects are small and cost-effective, and the recurrence rate of patients is low, which can significantly improve their quality of life. However, its clinical sample size is small, the research time is short, and there is a lack of follow-up, making it impossible to observe long-term efficacy. In future clinical studies, the sample size can be appropriately expanded, the efficacy evaluation and prognostic indicator system can be improved, and its clinical conclusions can be more scientific. In summary, based on the latest literature progress, this article reviews the specific mechanisms and treatment strategies of IBS based on gut microbiota, and provides prospects in combination with the author's own clinical work, in order to provide some reference for this research field.

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