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Mucosal Healing Research Advances of Inflammatory Bowel Disease

Changming Zhang[1,2], Dong Ming[1], Gang Ji[2,*]

[1]Shanxi University of Traditionnal Chinese Medical, Xian'yang 712000, Shaanxi, China
[2]Department of Radiotherapy, Xijing Hospital, Air Force Military Medical University, Xi'an 710000, Shaanxi, China
[2]694227040@qq.com, [3]jigang@fmmu.edu.cn
**Correspondence Author*

Abstract: ***Inflammatory bowel disease (IBD) refers to a group of chronic intestinal diseases, including Crohn's disease (CD) and ulcerative colitis (UC). These diseases cause chronic inflammation of the intestinal mucosa and wall, leading to symptoms such as diarrhea, abdominal pain, constipation, fatigue, etc. Intestinal mucosal barrier can prevent microbial and other antigens enter the intestinal wall, maintain its healthy function. However, Immune system dysregulation, dysbiosis of the gut microbiome, and dysfunction of the intestinal epithelial barrier are key pathogenic mechanisms of IBD. The treatment of IBD remains an important medical challenge, the current treatment mainly by inhibiting immune activity, blocking certain inflammatory molecules. Although these methods can induce mucosal healing (MH), but infection and tumor adverse reactions associated with immunosuppression still need to solve. Therefore, researchers are exploring new treatments, to promote the healing of the intestinal mucosa and maintain intestinal health. This review summarizes the traditional treatment of IBD and the application of new technologies such as hydrogels, organoids, probiotics and prebiotics, which aim to safely and effectively promote mucosal barrier healing and restore intestinal function and balance.***

Keywords: Inflammatory bowel disease, Mucosal healing, Hydrogel, Organs, Probiotics and prebiotics**.**

1. Introduction

Inflammatory bowel disease (IBD) is a chronic autoimmune disease characterized by inflammation of the intestines. The most common types of IBD are ulcerative colitis (UC) and Crohn's disease (CD) [1]. Common symptoms of IBD include diarrhea, abdominal pain, weight loss, and malnutrition, and if the disease is severe, it may also lead to fistulas, abscesses, and intestinal obstruction [2]. The population most commonly affected by IBD is usually under the age of 30, the chronic and persistent inflammatory state associated with IBD significantly affects the patients' quality of life and increases their risk of developing colorectal cancer, and the IBD treatment is still an important medical challenge [3]. The pathogenesis of IBD involves a variety of factors, including immune system disorders, intestinal microbiota disorders and intestinal epithelial barrier dysfunction. Aiming at these factors, promoting mucosal healing (MH) is one of the key means to treat IBD [3, 4].

Traditionally, the primary method of assessing MH has been endoscopy. In CD, with inflammatory lesions, presence or absence of ulcer and narrow area to determine whether to MH [5]. In UC abnormalities such as erythema, friability, ulcers, and erosions, as well as the presence of vascular patterns and spontaneous bleeding, are considered in determining MH [5].

MH can also be defined histologically, more in-depth than endoscopy, and recent studies of some imaging assessments and newer markers such as fecal calprotectin can also identify MH [6, 7]. The intestinal barrier and MH are closely related, it is the body's internal and external environment on the border of a barrier, it can make the nutrition and the liquid is absorbed through the intestinal epithelium (IEC), and prevent harmful material such as toxins and bacteria into the body [8, 9]. IEC can through the bridge, attach to connect (AJ) and tight junction (TJ) three adhesion complexes forming complex protein - protein network to maintain its selective barrier function [8, 9]. These compounds in cells and is connected to the cytoskeleton of protein interactions [10, 11].

The intestinal epithelium is armed with immune functions, using antimicrobial peptides and protective mucus layers to effectively combat pathogens. Secretory cells such as goblet cells and Paneth cells can prevent damage to the epithelial barrier by secreting mucus and antimicrobial proteins, which provide a barrier against bacteria, fungi, and other antigens in the intestinal lumen [12]. Immune cells added to the physics of IEC and function barrier, the secretion of cytokines involved in intestinal stem cells (ISC) regulation [13, 14]. Intestinal mucosal damage causes an upregulation of immune cells and the release of various cytokines, these cytokines induced by specific cell signaling pathways interact with different components of complex to coordinate transportation so as to promote the intestinal MH [5].

The interaction between the host microbiota and their metabolites with the intestinal epithelial cells is one of the key factors in maintaining intestinal homeostasis [15]. They are also key proponents of restoring the integrity of the IEB after injury [16, 17]. Some pathogenic microorganisms can affect MH by destroying the adhesion complex in IEB [18, 19]. However, metabolites produced by the gut microbiota can regulate the mucosal immune system, host-microbe communication, and gut homeostasis [20, 21]. Microbial metabolites, such as short-chain fatty acids (SCFAs), regulate the expression of intestinal epithelial cell ZO-1 by activating the AMPK pathway, thereby enhancing epithelial cell TJ and protecting the integrity of the epithelial mucosal barrier [22, 23].

At present the treatment of IBD is mainly to control the symptoms of the disease is given priority to, and not completely solve the mucosal epithelium repair, barrier steady-state [24]. This paper reviews the conventional therapy and new treatment strategies to strengthen the intestinal

barrier function.

1.1 Traditional Therapy

At present for the treatment of IBD mainly to reduce chronic inflammation and relieve symptoms as the goal, for example, the sugar cortical hormone drugs, the amino acid drugs and some immunosuppressants, but they didn't really to promote the expected results, and the overall process of MH [25].

Budesonide is one of the main drugs used to control severe intestinal inflammation by inhibiting inflammation [26]. Studies have shown that in two randomized, double-blind, placebo-controlled trials, in over 200 mild-to-moderate IBD patients treated with budesonide MMX 9 mg, colonoscopy showed a significantly higher rate of intestinal MH compared to placebo after 8 weeks of treatment [27]. However, long-term application of budesonide can also cause adverse reactions such as headache, nausea, abdominal pain, nasopharyngitis, and bloating [28].

Amino acid drugs can by adjusting the key proteins of mucous membrane barrier E - calcium mucin and beta serial protein membrane positioning way interfere with cell adhesion and restore AJ in order to have promote the MH [29, 30]. However, these amino acid drugs long-term use can cause such as infertility, hemolytic anemia, photosensitive and many side effects such as disease of grow in quantity of granulocyte [28].

Immune regulator is also indirectly promoting the role of MH. Studies have shown that the use of azathioprine alone to MH in 16.5% of cases, and antibody therapy joint of 43.9%, when using mercaptopurine 16 weeks after treatment, patients with remission of MH incidence was 47.1% [28, 31-33]. But at the same time the immune regulator may cause many risks, such as bone marrow suppression, liver damage and symptoms such as gastrointestinal intolerance [34-36].

1.2 Monoclonal Antibody Therapy

Monoclonal antibodies are relatively new drugs used in the treatment of IBD. They include tumor necrosis factor-α inhibitors, adalimumab, infliximab, ustekinumab, certolizumab pegol, and vedolizumab. These biologic agents have shown significant clinical efficacy and are currently widely used as first-line treatments for IBD. They can promote MH and achieve the goal of treating IBD [37].

Ustekinumab is a kind of total anthropogenic immunoglobulin monoclonal antibody, can block IL - 40 and IL - 12 p23 subunits [38]. Li group treated by 2630 such as IBD, to assess their histology disease activity, histologic improvement (defined as less than 5% in the crypt of neutrophil infiltration in the composite, no fossae damage, erosion, ulceration or granulation tissue) and at the end of the induction period and maintenance period of the association between clinical end points. When a more stringent definition of histological improvement was used, ustekinumab was found to have the effect of promoting the rate of MH under tissue endoscopy [39].

Vedolizumab can be and T lymphocytes in alpha beta 4 7 integrin union, interference with intestinal mucous membrane of endothelial cells on the adhesion of cell adhesion molecule 1 vascular interaction, has proven to be a safe and effective drug [40, 41]. In a study, patients with moderate to severe IBD were included and received vedolizumab treatment for 52 weeks. The results showed that these patients had significant mucosal healing observed during endoscopy [42]. Laurent and others through the system evaluation and meta-analysis, infliximab, compare single resistance in adult moderate to severe CD or UC patient's efficacy and safety of infliximab, the study found that infliximab treatment in patients achieved clinical response, clinical remission, or MH in both CD and UC [43]. Although, monoclonal antibody therapy has improved the health status of patients with IBD in recent years, the occurrence of non-response or loss of response is quite high. It can also lead to adverse reactions such as infection, fever, cough, respiratory distress, hypotension, and even heart failure. Even in patients who respond well to treatment, the disease is not completely eradicated [28, 44].

1.3 Other Treatment

Janus kinases (JAKs) are a group of tyrosine kinases, including JAK1, JAK2, and JAK3, which can interact with some cytokines related to IBD and are also new drugs used to treat IBD [45, 46].

Tofacitinib is a non-selective JAK inhibitor that can be used in patients with moderate to severe IBD, and it is also one of the new drugs that can be used clinically [46]. In an experiment, 593 IBD patients were given either 5mg or 10mg of tofacitinib daily. After 24 weeks, patients receiving daily 5mg treatment achieved MH of 43.9%, while patients receiving daily 10mg treatment achieved MH of 46.2% [47].

The sphingosine-1-phosphate (S1P) receptor family is composed of a variety of widely expressed receptors (S1P1-S1P5), which is closely related to many systems. It can also affect intestinal MH through part of the signaling pathway IBD [48, 49].

Ozanimod is also a type of S1P receptor family, and it is a new oral medication commonly used to treat UC [50]. The TOUCHSTONE study conducted a randomized, double-blind, placebo-controlled phase II trial, recruiting 197 patients to receive Ozanimod treatment. After 8 weeks of treatment with 0.5mg per day, the MH of the patients reached 32%. After 32 weeks of treatment with 1mg per day, the MH of the patients reached 33% [47, 51].

Overall, while current treatment approaches provide evidence for achieving MH in IBD, most rely on simple immune suppression to reduce inflammation and associated damage. The complete restoration of intestinal epithelial disruption is a multifactorial process that remains challenging, and the long-term efficacy and safety of these therapies are still unclear, with some patients developing resistance or intolerance [52, 53]. Therefore, there is a need for a deeper understanding of the inflammatory and intestinal mucosal repair processes in IBD to develop new therapeutic approaches that can actively promote intestinal mucosal repair.

2. Hydrogels

Hydrogels are a class of biomaterials based on biopolymers such as chitosan and hyaluronic acid. They are multifunctional and biocompatible materials that can exhibit antimicrobial and anti-inflammatory properties. They have been increasingly explored for local treatment in UC [54-56]. Hyaluronic acid (HA) is a kind of sulfating sugar glycosaminoglycans (GAG). It is a biological polymer that can be produced by the human body and can be involved in various inflammatory reactions [57]. Due to the good physical and chemical properties of HA, such as biocompatibility and biodegradability, it has been used as a dressing for various diseases such as electrospinning membranes, nanoparticle hydrogels, etc. Among them, there are new developments in IBD [58, 59]. High molecular weight HA has anti-inflammatory effects and can control the recruitment of inflammatory cells, while low molecular weight HA has pro-inflammatory effects and can promote angiogenesis and tissue remodeling during the wound healing process [60, 61]. A recent study found that in mice UC model HA with TNF stimulate the secretion of gene - 6 product (TSG - 6) interaction and to promote the intestinal MH [62]. Li and colleagues used HA has the ability to aggregate drugs in inflamed colonic epithelium. Studies have shown that it not only has anti-inflammatory effects, but also regulates the gut microbiota, thereby assisting in the recovery of the intestinal epithelial barrier [63]. The high molecular weight sodium HA composed of HA functionalized polymer nanoparticles can be formulated into a rectal suspension, which provides a thick, viscous biophysical barrier on the epithelial surface. The HA-functionalized particles preferentially accumulate in the inflamed colonic epithelium and interact/penetrate with epithelial cells. It has also been shown to promote the up-regulation of TJ family proteins claudin4 (Cldn2) and occluding, thereby strengthening the epithelial barrier and accelerating gut MH [64].

At the same time, hydrogels can also be used as carriers for drug delivery. Due to their highly porous morphology, hydrogels can be used as carriers to accurately transport drugs to the wound of IBD to promote MH [65, 66]. Manisha et al. achieved effective colon-specific delivery by using a hydrogel loaded with budesonide, and observed a significant repair effect on the colonic epithelium [67]. Andreea team by making a hyaluronic acid gel will dexamethasone delivery directly to the inflamed tissue, thereby reducing systemic exposure [68]. The hydrogel, with a negative charge, can interact with positively charged proteins selectively accumulated at the inflammatory site, further promoting the MH [69, 70].

3. Organoid Culture Engraftment

Sato and Levers described three-dimensional cultures of intestinal stem cells (ISCs) as "organoids" in 2009 [71]. ISCs are located at the base of intestinal crypts and play an essential role in maintaining the balance of the body and rapid turnover of the intestinal epithelium, which is closely related to the MH [72, 73]. Organoids generated from induced pluripotent stem cells or ISCs of patients with IBD preserve the genetic and transcriptomic profiles and have the ability to perform some of the functions related to the organ they are derived from [74, 75].

Recently, significant progress has been made in obtaining human intestinal organoids derived from ISC development. A study found that injecting organoids into the anus of mice led to the repair of epithelial damage caused by dextran sulfate sodium. The injected organoids can attach to the site of intestinal injury in mice and assist in the reconstruction of the intestinal epithelium from donor sources, thereby promoting intestinal repair and healing [76]. This approach can significantly shorten the time for intestinal repair and reduce the risk of intestinal inflammation and other related diseases, thus promoting intestinal homeostasis [76]. In a study, researchers enveloped the intestinal-like organ with matrix gel and cultured it with some cytokines in order to simulate the in vivo ecological microenvironment of ISCS [77]. This enables personalized medicine for IBD.

Meanwhile, the molecular mechanisms of some drugs can be studied through intestinal organoids, providing more accurate and effective treatment options for clinical applications. This promotes a large change in the quality of life of the patient. For example, the group led by Vineeta used intestinal organoids to establish a mouse model lacking TNF-α and IL-10 in the intestine to investigate the different molecular interactions between drugs such as sulfasalazine and mesalazine with the intestinal epithelium. They discovered that sulfasalazine and mesalazine protect the intestinal mucosal barrier by increasing E-cadherin and affecting Desmoglein-2 expression, thereby promoting intestinal homeostasis [30]. In order to investigate the mechanism of intestinal inflammation, researchers led by Pan added multiple inflammatory cytokines to organoid cultures of the intestine [78]. Further studies revealed that exposure to these cytokines downregulated the levels of TJ proteins and AJ proteins. In addition, it promotes the phosphorylation of some intestinal epithelial barrier proteins, ultimately leading to damage to the intestinal epithelial mucosa. However, prednisone can inhibit the signaling pathways of these cytokines, thereby promoting intestinal MH [78].

Organoid technology can also simulate the intestinal environment to provide a suitable environment for gut microbiota and promote the restoration of the gut microbiome. In a recent study, microfluidic devices were utilized to control fluid flow at microliter scales, improving the cellular microenvironment [79]. By simulating the intestinal environment, setting up two channels allows for the cultivation of gut microbiota using both the top and bottom sides. This enables the microbiota to simultaneously receive nutrients from two directions, promoting their even distribution in the culture medium to prevent overgrowth. Additionally, it allows for the supplementation of fresh culture medium and removal of dead cells [79, 80]. It can effectively improve the host - microflora balance, enhance epithelial barrier, regulating local and systemic immune responses, and promote the MH [81].

4. Probiotics and Prebiotics

Probiotics are beneficial microbes, known to many positive influences on human health, to improve the intestinal ulcer healing of skin wound healing and infection, research shows that application of probiotics on intestinal MH also shows promising results [82]. Among various probiotics,

Lactobacillus acidophilus is one of the most extensively studied beneficial bacteria with its positive effects [83]. Lactobacillus acidophilus is an important genus that is widely present in the intestinal tract of breastfed infants and is closely related to intestinal barrier function in infants [84, 85]. By administering Bifidobacterium orally to mice with IBD, Niu's team found that Bifidobacterium can promote the expression of TJ proteins, down-regulate the levels of cytokines, and regulate the diversity of intestinal microbiota to promote intestinal MH [86].

In addition, LP082 can promote gut MH in mice with UC by improving the gut microbiota and modulating inflammation and disease pathways [87]. Lactobacillus can decrease the secretion of inflammatory cytokines caused by inflammation, reduce the severity of intestinal inflammation, and thus play a protective role in maintaining the intestinal epithelial barrier [88]. It also activates specific signal pathways, leading to the differentiation of Paneth cells and an increase in the expression of antimicrobial peptides. These actions work together to inhibit the growth and colonization of harmful bacteria, ultimately promoting gut MH [88].

Prebiotics are a type of non-digestible food ingredient that can be utilized by intestinal microbiota, aiding in the maintenance and promotion of gut health. They promote the growth of microbial communities and play a positive role in wound healing [89]. Especially the inulin and low poly galactose these two kinds of oligosaccharides, they can be the breakdown and absorption of intestinal probiotics, promote the beneficial bacteria growth and reproduction, and most promote MH [90]. Julia team conducted a study, such as long term by giving mice fed inulin and sodium butyrate, found that this kind of food can improve IBD in mice inflammation symptoms. Further research found that inulin and sodium butyrate can induce intestinal produce antibacterial peptide, thus reducing obesity caused by intestinal barrier dysfunction. These findings suggest that inulin and sodium butyrate can improve intestinal health and increase production of antimicrobial peptides for repair of the intestinal epithelium [91]. Similarly, after supplementing with fermented products containing inulin, it promotes the expression of claudin-3 and ZO-1, increases the richness of gut microbiota, thus improving the intestinal barrier function and homeostasis [92].

5. Conclusion

In recent years, the incidence of IBD has been gradually increasing. These chronic diseases have long-term negative effects on patients' health and often lead to a worsening of the condition. Currently, the treatment of IBD mainly relies on immunosuppressive agents and biologics, primarily aimed at reducing inflammation. However, these medications have broad immunosuppressive effects and may lead to adverse events such as infections and tumors. Nowadays, the treatment of IBD not only aims to alleviate symptoms but also hopes to help damaged tissues heal and regenerate. MH has become one of the important therapeutic targets for treating IBD patients. Hydrogels, organoids, probiotics, and prebiotics each have different advantages and prospects for promoting mucosal healing in IBD. Therefore, in future research and treatment of IBD, efforts will be made to determine which methods have higher prospects and evaluate their potential risks and associated issues.

Ethics Declarations

Ethics approval and consent to participate
Not applicable.

Consent for Publication

Not applicable.

Data Availability

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Competing Interests

The authors declare that they have no competing interests.

Author Contributions

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