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Emerging strategy towards mucosal healing in inflammatory bowel disease: what the future holds?

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For decades, the therapeutic goal of conventional treatment among inflammatory bowel disease (IBD) patients is alleviating exacerbations in acute phase, maintaining remission, reducing recurrence, preventing complications, and increasing quality of life. However, the persistent mucosal/submucosal inflammation tends to cause irreversible changes in the intestinal structure, which can barely be redressed by conventional treatment. In the late 1990s, monoclonal biologics, mainly anti-TNF (tumor necrosis factor) drugs, were proven significantly helpful in inhibiting mucosal inflammation and improving prognosis in clinical trials. Meanwhile, mucosal healing (MH), as a key endoscopic and histological measurement closely associated with the severity of symptoms, has been proposed as primary outcome measures. With deeper comprehension of the mucosal microenvironment, stem cell niche, and underlying mucosal repair mechanisms, diverse potential strategies apart from monoclonal antibodies have been arising or undergoing clinical trials. Herein, we elucidate key steps or targets during the course of MH and review some promising treatment strategies capable of promoting MH in IBD.

KEYWORDS

inflammatory bowel disease, mucosal healing, intestinal mucosal barrier, emerging strategy, organoid

1 Introduction

Inflammatory bowel disease, a chronic and recurrent gastrointestinal disorder encompassing Crohn's disease (CD) and ulcerative colitis (UC), is characterized by non-specific inflammation of the intestinal mucosa (1). The vast majority of IBD patients experience cycles of recurrence and remission marked by abdominal pain, diarrhoea, fever, and tenesmus (2, 3). The natural history of IBD is highly

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individualized, which varies across disease stages, ranging from asymptomatic or mild disease to severe manifestations necessitating hospitalization, surgery, disability, or even mortality (4). Most patients with IBD can achieve long-term symptom control through pharmacological therapy alone (5). However, in most cases where drug therapy fails to adequately suppress intestinal inflammation or when complications such as obstruction, perforation, and bleeding arise, surgical interventions are often indispensable to remove the affected intestine (6, 7). In turn, intestinal resection significantly impacts patients' postoperative quality of life and may result in complications such as anastomotic leakage, bleeding, and short bowel syndrome, which could cause severe gastrointestinal damage or even systemic dysfunction (8). Though several treatment methods are available, unfortunately, IBD cannot be cured.

Various elements contribute to the pathophysiology of IBD (Figure 1). In the interplay of various intricate factors, a cascade of events occurs, resulting in modified microbial communities, aberrant expression of tight junction (TJ) proteins, and impairment to the mucus layer that facilitates the infiltration of luminal bacteria into the submucosa (9, 10), leading to mucosal inflammation and destruction. Subsequently, neutrophils are recruited to the site of infection, where phagocytose microorganisms and generate neutrophil extracellular traps (NETs) to immobilize pathogens (11). The demand for neutrophils during acute inflammation is met by rapid granulopoiesis in the bone marrow driven by the IL17-IL23A-CSF3

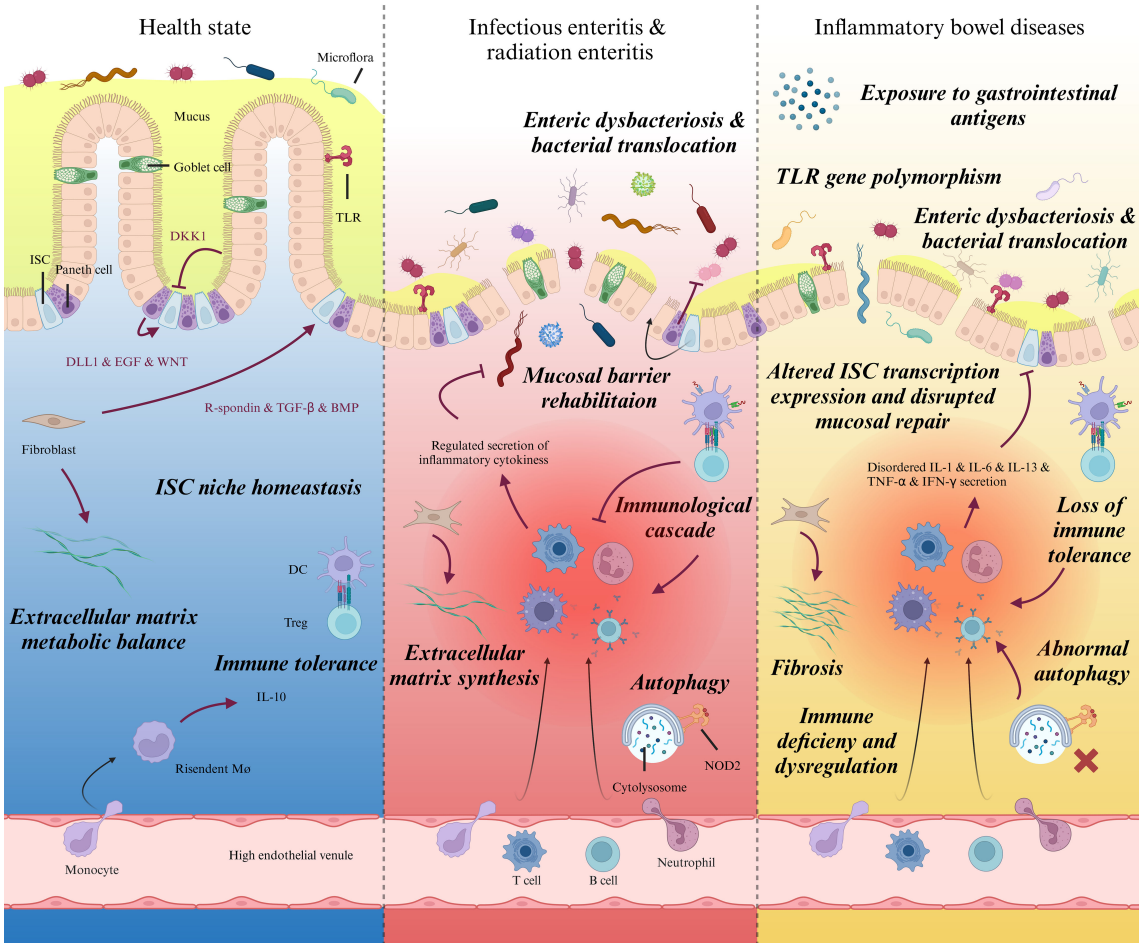

FIGURE 1
Intestinal pathophysiological characteristics during homeostasis, specific injury, and IBD. Schematic diagram showing prominent pathophysiological variations of intestinal mucosa and lamina propria in different states. Left: Gradients of biochemical signals secreted by neighboring Paneth cells, fibroblasts and enterocytes regulate the self-renewal and differentiation of ISCs synergistically. By programmed proliferation, differentiation, and migration towards top of the villi, ISC plays a significant role in intestinal barrier integrity and homeostasis. Middle: Epithelial cells are vulnerable to microorganism invasion or radiation damage, which usually bring about acute or subacute inflammation in lamina propria. The exposure to intestinal pathogens launches regulated immunoreaction. Upon receiving the activation from immune signal and physicochemical changes within the stem cell niche, ISCs exert stemness and produce terminally differentiated epithelial cells to replace injured ones and rehabilitate mucosal barrier. Right, Despite the vague etiology and different pathogenic site; IBD patients share common pathophysiological features, including immune dysregulation within lamina propria, enteric dysbacteriosis, fibrosis. Recently, much investigations have verified protracted post-transcriptional modification and damaged viability of ISCs as well as distinct differentiation pattern alongside the intestinal epithelium, which could be the potential immediate cause to delayed mucosal healing in IBD patients. ISC, Intestinal stem cell; DKK1, Dickkkopf-1; TLR, Toll-like receptor; EGF: Epidermal growth factor; TGF, Transforming growth factor; BMP, Bone morphogenetic protein; DC, Dendritic cell; Treg, Regulatory T cell; NOD2, Nucleotide-binding oligomerization domain 2.

axis (12). Monocytes and macrophages eliminate cellular debris generated by neutrophil activity, producing TNF, IL-6, IL-12, and IL-23 (2, 13). Subsequently, monocyte-macrophages act as antigen-presenting cells (APC) and participate in T helper cell differentiation into Th1, Th2, Th17, and other subtypes (14). B cell activation occurs in IBD, and the expansion of B cells has been shown to impede epithelial-stromal cell interactions (15). Further comprehension of the pathogenesis of IBD is pivotal in propelling research and development of targeted pharmaceuticals and novel therapeutic approaches, thereby facilitating the treatment and management of IBD while enhancing the quality of life for patients afflicted with this condition.

As the etiology of IBD remains elusive, the primary objective of treatment is to alleviate inflammation through various therapies including 5-aminosalicylic acid (5-ASA), antibiotics, corticosteroids, immunosuppressive agents and biological interventions (16). In the past, symptom assessment remains the cornerstone of clinical practice in the diagnosis and management of IBD, playing a pivotal role in evaluating disease severity, surgical candidacy, and treatment response (17). This underscores the importance of adopting a symptom-driven approach to managing symptoms such as abdominal pain, diarrhea, gastrointestinal bleeding, among others (17, 18). Ultimately, achieving clinical remission represents a key therapeutic goal for most IBD patients, which is accepted by patients and doctors. The utilization of standardized clinical scoring systems, such as the Truelove and Witts criteria, facilitated a more objective evaluation of the disease (19). The resolution of intestinal inflammation, repair of intestinal damage, and restoration of intestinal ecological balance should not be solely inferred from the relief of clinical symptoms (20). Currently, mucosal healing has emerged as a new long-term goal in IBD treatment and has garnered significant attention in recent years (21, 22).

2 Definition of Mucosal healing

A crucial characteristic of IBD is the impairment of the intestinal mucosal barrier (IMB) (23), which leads to the translocation of microorganisms and other antigens into the internal environment, resulting in uncontrolled immune activation (24). Current studies believe that the impairment of IMB may be the initial link in the development of IBD, whose severity is closely related to the symptoms (23). The foundation of mucosal healing is based on an undamaged barrier that limits the movement of bacteria and subsequent immune response activation (25). Definitions specific to mucosal healing often rely on endoscopic criteria such as the absence of ulcers with no fragility, blood, erosion or ulceration in CD and UC; or complete resolution of inflammatory and ulcerative lesions in both forms of IBD (25, 26). The evaluation criteria of mucosal healing are constantly changing, but Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) and Mayo score based on endoscopy is still one of the mainstream methods of mucosal healing diagnosis (27) (28). In fact, microscopic inflammation has been reported in up to 25% of patients with endoscopic mucosal healing (29). Additionally, the histological evaluation of mucosal healing is constantly evolving, and the histological definition and criteria of mucosal healing have evolved from "elimination of mucosal ulcer/erosion" to "absence of neutrophilic infiltration" (30). Therefore, the presence or absence of active inflammation has become a consensus in histological evaluation of mucosal healing. Currently, more than 30 different histological scoring systems have been created (31, 32), despite the fact that their utilization in clinical settings is still restricted. The Simplified Histologic Mucosal Healing Scheme (SHMHS) can identify active inflammation that may not be visible during endoscopy, and facilitate clinical application (33). Some scholars integrated endoscopy, histology, and other factors to avoid the potential inaccuracies of single index diagnosis. They focused on assessing neutrophil infiltration as a key determinant of disease progression and histological remission (34). In fact, the diagnosis of mucosal healing based on endoscopic techniques faces significant challenges in clinical practice (35, 36). For certain IBD patients, endoscopy is neither tolerable or necessary (37). Therefore, it is worth exploringto balance the advantages and disadvantages of endoscopy or expand the definition of mucosal healing further while avoiding invasive interventions. Some scholars have suggested that fecal calprotectin and other markers can serve as substitutes for serum or fecal markers (38–40). This approach would alleviate the discomfort experienced by IBD patients and reduce treatment costs (41). In the past few years, the application of artificial intelligence (AI) has mitigated operator errors in endoscopy or pathological interpretation and optimized diagnostic criteria for mucosal healing (42, 43). It is foreseeable that mucosal healing evaluation will need to evolve towards a multifactorial approach.

The process of mucosal healing involves a complex interplay between ISCs and signaling molecules throughout the course of regeneration. The regulation of ISC-driven differentiation into epithelial cells is mediated by BMP, Wnt, and Notch signalling pathways (44, 45). It is widely accepted that intestinal epithelial cells (IECs) located at the border of damaged mucosa, regulated by transforming growth factor-alpha/beta (TGF-α/β), trefoil factor and other signaling molecules (46–48), undergo redifferentiation, lose their columnar phenotype and acquire a migratory phenotype to migrate towards the defect site in order to form a primary barrier (49). Subsequently, regulated by nuclear factor-κb (NF-κB) and other factors (50), epithelial cells facilitates the stabilization and maturation of the nascent mucosal barrier. Ultimately, these newly formed undifferentiated epithelial cells undergo a process of differentiation, giving rise to a diverse array of mature intestinal epithelial cell types, encompassing Paneth cells, goblet cells, enteroendocrine cells, enterocytes and M cells, which give rise to the intestinal epithelial barriers (IEB).

3 The progress and dilemma of traditional therapies

When considering the possibility of incomplete healing of a patient's intestinal mucosa, how to repair the intestinal ecosystem becomes a crucial question. Currently available treatments, such as sucralfate, 5-ASA, antibiotics, corticosteroids, and immunosuppressive agents (51, 52), primary focus symptom alleviation and mitigating of chronic inflammation rather than mucosal healing and intestinal

ecological restoration as the end point of treatment. Although corticosteroids, methotrexate, and some immunosuppressive drugs promote healing of the intestinal mucosa to some extent in some studies (53, 54), they also lead to an increased risk of infection and cancer due to immunosuppression (55), so clinicians must balance the benefits with the risks.

Through continuous exploration of the complex mechanisms underlying IBD, treatment based on precise molecular targeting of inflammatory cascades has greatly advanced IBD therapy from clinical symptom relief to mucosal healing. Since the development and application of anti-TNF-α, a variety of monoclonal antibodies have been continuously developed and applied to enrich the precision targeted therapy for IBD.As first-line agents for the treatment of IBD, anti-TNF-α monoclonal antibodies such as infliximab and adalimumab have long been utilized to mitigate inflammation and promote mucosal healing (56). Anti-TNF-α therapy targets proinflammatory cytokines by obstructing soluble and membrane-bound TNF-α, inducing direct and indirect apoptosis of TNF-α-producing T cells and macrophages (57). Ultimately regulating intestinal inflammation, restoring the integrity of the IEB, and promoting mucosal healing. Several clinical studies have established a correlation between serum anti-TNF drug levels and mucosal healing in patients. For instance, Bella Ungar et al. (58) reported that maintaining a serum infliximab level of 6-10μg/mL can result in mucosal healing in 80% to 90% of adult IBD patients.

In certain patients, anti-TNF-α therapy may exhibit either non-response or withdrawal response, which could be attributed to specific network connections among IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells and stromal cells (59). For such individuals, treatment alternatives have shifted towards monoclonal antibodies that target other inflammatory factors. For example, the monoclonal antibody ustekinumab, which specifically targets IL-12/23p40, demonstrated a significant reduction in endoscopic range of motion among patients with IBD, thereby exhibiting its capacity to facilitate the restoration of mucosal integrity (60). Risankizumab, guselkumab, and mirikizumab are inhibitors of IL-23p19 that have demonstrated efficacy in clinical trials for symptom improvement, endoscopic findings enhancement, and histological remission (61–63). Additionally, the specific target of vedolizumab is the α4β7 integrin, which interacts with cell adhesion molecule 1 (MAdCAM-1). In a long-term study conducted on 374 individuals diagnosed with UC, vedolizumab treatment resulted in clinical remission and mucosal healing for more than half of the participants (64). In recent years, a plethora of novel oral small-molecule drugs have emerged, including the JAK inhibitors tofacitinib, filgotinib, and upadacitinib as well as the sphingosine-1-phosphate (S1P) receptor modulator ozanimod, which have been granted regulatory approval for treating IBD (65, 66). Limited clinical trials have unequivocally confirmed their potential to foster mucosal healing (66, 67). Currently, an array of monoclonal drugs are being actively developed with promising available clinical data (65–67).

Anti-tumor necrosis factor-alpha (TNF-α) drugs have ushered in a new era of IBD treatment (68). At present, the use of monoclonal antibodies as a treatment for IBD presents a novel therapeutic approach that yields favorable outcomes for the majority of patients (69, 70). Nevertheless, some individuals remain unable to achieve optimal results despite this intervention, and clinicians continue to grapple with issues related to antidrug antibody-mediated ineffectiveness and withdrawal reactions (55, 71, (72). Additionally, physiological inflammation serves as a self-protective mechanism of the body; however, excessive immune response inhibition may result in other risks such as infection. The intricate involvement of proteins and signaling pathways in IBD highlights the significance of individual differences and remains a significant field for further investigation (73, 74).

4 Novel and potential emerging therapies

In recent years, there has been continuous development of drugs for the treatment of IBD and significant progress in therapeutic strategies. However, current treatment methods such as 5-ASA, monoclonal antibodies, and other drugs have not yet achieved optimal results (51). For some patients, these treatments may even lead to serious complications. Most of the current treatment methods are based on the "immunity" strategy, and exploring approaches to mitigate immune suppression may present a novel concept, as immunity is indispensable for maintaining human health. While some of these methods may seem impractical for clinical implementation, others such as enteral nutrition (EN), faecal microbiota transplantation (FMT), and the utilization of certain growth factors have been partially integrated into clinical practice (75–77). These approaches demonstrate their potential in promoting mucosal healing without immunosuppression. These novel treatment methods have significantly advanced the development of intestinal mucosal healing and even hold the potential for curing IBD (Figure 2).

4.1 Dietary management and enteral nutrition

Dietary factors influence the occurrence and progression of IBD. Several epidemiological studies have confirmed the association between dietary macronutrient and micronutrient intake and the pathogenesis of IBD. For instance, adhering to a dietary pattern rich in fruits, vegetables, and fish has been shown to reduce the risk of developing UC by 50% among high school students (78). The role of diet in IBD is further supported by advancements in understanding genetic architecture and the gut microbiome's influence on immune dysregulation leading to gut inflammation. However, parenteral nutrition (PN) adversely affects intestinal growth, reducing mucosal mass, cell proliferation, and mucosal immune function, which undoubtedly worsens the condition of IBD. Diet can impact gut inflammation through various mechanisms including modulation of the microbiome, tight junctions, and mucosal barriers. Dietary interventions that alter a patient's microbiome composition during remission have demonstrated the potential for reversing many features associated with active diarrhea by affecting its metabolic

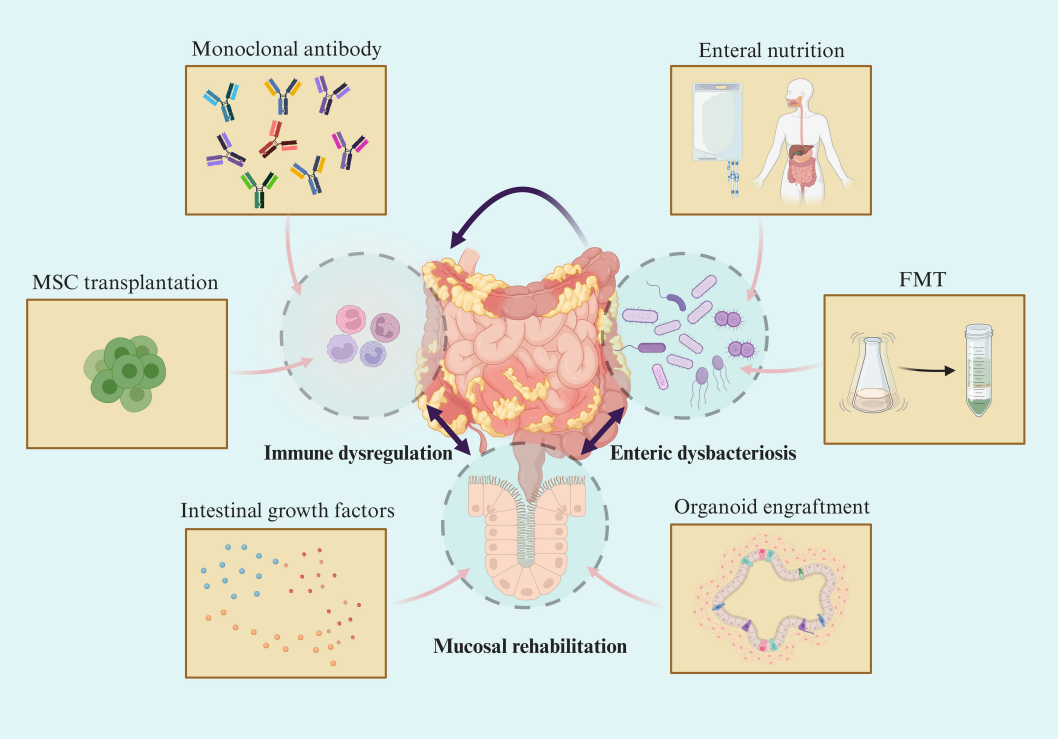

FIGURE 2
Novel therapeutic strategy towards mucosal healing in IBD. Symptoms in IBD patients are highly correlated with the degree of mucosal damage. Although emerging therapies target different intestinal components, they are beneficial to mucosal barrier rehabilitation and mucosal healing via intertwined pathophysiological changes in IBD.

function alongside its composition (79). A range of dietary approaches have been developed for patients with IBD, including Crohn's Disease Exclusion Diet, IBD Anti-Inflammatory Diet, Specific Carbohydrate Diet, and others (80–82). These diets commonly emphasize a high intake of fruits and vegetables, and lean meats, while excluding most dairy products, canned foods, tea, coffee, and alcohol. However, they exhibit variations in recommendations regarding certain foods such as yogurt, beans, and nuts. The aforementioned also implies the necessity for further research into the impact of alterations in individual dietary components on the human physique and the development of more suitable dietary patterns. Moreover, the intricacy involved in food handling, processing, and packaging exacerbates the heterogeneity observed in dietary intervention studies (83). Consequently, finding a solution to effectively achieve homogeneity comparison becomes an issue that demands resolution.

The efficacy of enteral nutrition treatment modalities has been partially demonstrated, with exclusive enteral nutrition (EEN) serving as a primary therapeutic approach for pediatric patients with CD, effectively alleviating clinical symptoms and promoting mucosal healing (84). Clinical studies have demonstrated that over 70% of children with CD treated with EEN achieved mucosal healing (85, 86). However, in adult patients, poor palatability often leads to low compliance with EEN, thereby diminishing its therapeutic efficacy (87). To assess the feasibility of using EEN in adult patients, Wall et al. (88) employed EEN alone or in combination with partial enteral nutrition for individuals suffering from active CD. The results showed clinical remission, reduced levels of serum CRP and FC, as well as increased serum insulin-like growth factor 1 (IGF-1) levels, suggesting a potential treatment for achieving mucosal healing. In another study conducted by Yang et al. (89), 47% of patients with complex active CD attained endoscopic mucosal healing following EEN treatment. Although not commonly used in UC patients, available evidence confirms the viability of synergistic corticosteroid therapy in cases of acute severe UC, significantly reducing CRP and FC levels (90). When attempting to elucidate the mechanism underlying mucosal healing induced by exclusive EEN, studies have observed a reduction in intestinal flora diversity, which appears contradictory to treatment expectations (91, 92). Alternative explanations encompass the modulation of inflammatory factors and hormones by EEN, including the secretion of serum IGF-1 and TGF-β1, as well as the promotion of mucosal healing (93). The future research directions should primarily focus on elucidating the underlying mechanisms by which EN enhances mucosal healing and its differential effects in patients with UC and CD. The forthcoming endeavors hold great promise in unraveling the intricate principles of enteral nutrition

through extensive multicenter randomized trials, a pursuit that carries immense significance. Furthermore, enhancing palatability of EEN may facilitate wider adoption among adult patients.

4.2 Organoid culture engraftment

Organoids, derived from stem cells through *in vitro* culture and self-assembly, represent three-dimensional (3D) cell cultures that possess both structural and functional specificity akin to the corresponding tissues (94). The organoids formed by ISCs *in vitro* usually form Bud-like organs composed of hyperplastic protruding cryptlike domains, closely resembling the structure of intestinal epithelium *in vivo* (95). In 2009, Clevers and Sato first reported a method for long-term culture of intestinal epithelium from purified stem cells (96). Intestinal organoids have made many breakthroughs in basic research and personalized treatment development for IBD with the mature application of stem cell *in vitro* 3D culture technology. Intestinal organoids are used for disease modelling and as preclinical tools in regenerative medicine through *in vivo* transplantation (97). Multiple studies have demonstrated the possibility of transplanting organoids of intestinal stem cells into damaged colons to lead to tissue regeneration and mucosal healing (98, 99). Back in 2012, a study presented a comprehensive account of epithelial organoid transplantation into the colon of a mouse model with inflammatory enteritis. In this experiment, organoids were administered via enema and exhibited effective adherence to the injured site, thereby facilitating epithelial restoration (100). Previous studies also demonstrated that intestinal organoids implanted into dextran sulfate sodium (DSS) -induced colitis models can accurately target donor cells to locate on the surface of colitis-induced ulcers and begin to rebuild and repair crypt structures (101). Consistent with these findings, the same mouse-derived intestinal organoids were injected anally by Watanabe and colleagues to facilitate colon repair in UC mice. These cultured organoids exhibited precise targeting within the damaged intestinal epithelium, as anticipated based on prior developmental investigations, these organoids retained their regional characteristics and exhibited functional enteric properties (102). The rapid development of endoscopic techniques for organoid infusion has now been shortened to 10 minutes (102). However, there remain numerous challenges to be addressed in organoid transplantation. It is yet to be determined whether the success of organoid cultures in non-IBD tissues can be replicated in IBD tissues, and whether autologous transplantation offers advantages over allogeneic transplantation. Additionally, evaluating the stability of cultured karyotypes is essential to understand the risk of tumorigenesis associated with these techniques (98). Furthermore, there is a need for improvement in the current protocols utilized for the isolation and cultivation of intestinal organoids. Studies have shown that intestinal organoids may not develop appropriately when derived from inflamed segments with damaged or lost epithelial layers (103). Nonetheless, the concept of cultivating new tissue *in vitro* and subsequently transplanting it into areas devoid of mucosa holds great promise for the future.

4.3 Mesenchymal stem cells transplantation

Mesenchymal stem cells (MSCs) are thought to be a versatile type of stem cells capable of differentiation, which can be derived from various sources, such as bone marrow, adipose tissue, umbilical cord and so on (104). MSCs have demonstrated the capacity to relocate towards areas affected by colitis-induced damage, where they possess the ability to differentiate into constituent cells of the intestinal epithelium or vascular endothelium. Alternatively, they can work together with intestinal epithelial stem cells in producing cytokines and promoting the healing process of the mucosal layer (105). MSCs mediate intestinal immune regulation through the secretion of prostaglandin E2 (PGE2), hepatocyte growth factor (HGF) and nitric oxide (NO) (106). Due to the presence of these soluble factors, MSCs exhibit immunomodulatory effects on various immune cell subsets. It has been documented that MSCs suppress Th1 and Th17 responses while promoting Th2 and Treg-mediated responses, thereby ameliorating colonic inflammation (107). Furthermore, MSCs supported intestinal barrier function by inducing the proliferation of IECs and up-regulating expression of TJ proteins, thereby ensuring intestinal barrier integrity (108). Hence, the transplantation of MSCs emerges as a promising therapeutic strategy for IBD due to their ability to secrete diverse bioactive molecules. Various clinical trials are currently underway to assess the safety and efficacy of MSCs in patients with IBD, and these findings have yielded positive outcomes in animal studies. Although the safety and short-term effectiveness of MSCs administration has been demonstrated, further validation is required to ascertain their long-term efficacy in transplantation. Prior research has shown that local injection of adipose-derived MSCs can effectively treat fistulas in CD (109, 110), and the recent meta-analysis encompassing seven trials investigating the efficacy of MSCs derived from bone marrow and umbilical cord in patients with UC demonstrated a certain level of efficacy (111). Despite some positive findings, the outcomes of systemic MSCs therapy in luminal CD patients thus far have been underwhelming. The results of various clinical trials have exhibited significant heterogeneity to date (112, 113), emphasizing the necessity for high-quality randomized controlled clinical trials and fundamental research.

In fact, less than 1% of intravenous MSCs can reach the damaged colon (114), and the method of MSCs transplantation is controversial. Despite the non-immunogenicity of allogeneic and autologous MSCs (115), stem cell transplantation may present certain drawbacks, including significant financial costs and the possibility of malignant transformation (112). Furthermore, the safety profile of systemic MSCs remains to be thoroughly investigated due to reports of exacerbated outcomes in patients with UC or CD, necessitating further exploration. Additionally, it is

imperative to address the optimal source, route of administration, and dosage of MSCs.

Some studies have turned their attention to exosomes secreted by mesenchymal stem cells (MSC-Exos) and have been used in various IBD models with promising results (116). Yang et al. (117) have significantly improved IBD symptoms by intraperitoneal injection of MSC-Exos. MSC-Exos can alleviate intestinal inflammation by increasing the expression of tumor necrosis factor-stimulating gene 6 (TSG-6) expression to repair the IMB and maintain immune balance (117). The utilization of MSCs for regenerating damaged mucosa holds great promise in expanding both the scope and efficacy of this therapeutic approach. A primary limitation of MSC-Exos therapy lies in its low yield, which presents a significant impediment to its clinical application. However, this challenge can be effectively overcome by embracing a 3D culture system as an alternative to the conventional 2D culture system (118).

The therapeutic approaches for MSCs can be complex and varied, incorporating autologous application, allogeneic MSCs, and cellular derivatives. These advancements hold immense potential in paving the path towards groundbreaking therapeutic strategies in IBD. Nevertheless, attaining this goal requires tackling fresh challenges by skillfully integrating cutting-edge methodologies and technologies while judiciously selecting ideal sources of MSCs to specifically target the multifaceted pathophysiological mechanisms involved in IBD.

4.4 Fecal microbiota transplantation (FMT)

Intestinal dysbiosis plays a pivotal role in the pathogenesis and progression of IBD, as well as in the persistence of complications that significantly impact patients' prognosis and overall quality of life (119). Research findings have indicated a notable decrease in the prevalence of advantageous microorganisms, including *Bifidobacterium*, *Lactobacillus* (Enterobacter), and *Firmicutes*, among IBD patients (120, 121). Conversely, the abundance of pathogenic intestinal bacteria, such as *Escherichia coli* or *Salmonella typhimurium*, is significantly increased, which facilitates the progression of chronic mucosal inflammation by disrupting the integrity of the IMB (122–124). FMT, also known as the transfer of healthy individuals' fecal microbiota to the intestinal tract of patients with IBD, presents a novel approach for treating IBD (76). The administration of FMT is commonly performed through nasogastric or nasojejunal tube, colonoscopy, enema, or oral capsule delivery routes (125). FMT can increase the diversity or abundance of the intestinal flora of the recipient. Specific microorganisms and microbial metabolites can regulate the wound repair of colonic epithelium after mucosal injury (126–128), thereby relieving clinical symptoms and promoting mucosal healing. Biao et al. (129), through repeated FMT combined with partial enteral nutrition, demonstrated improved clinical symptoms and enhanced mucosal healing in pediatric patients with active CD. However, severe IBD patients often experience adverse consequences due to compromised intestinal mucosal barrier function when undergoing FMT (130, 131). A systematic review of 129 studies on FMT across various medical conditions revealed an overall incidence rate of adverse events (ADE) at 19%, encompassing symptoms such as abdominal pain, diarrhea, fever, and other gastrointestinal disorders (132). In future research, greater attention should be devoted to aspects such as fecal donor selection, delivery system optimization, treatment duration determination, and standardization of emphasis in the field of fecal transplantation. The infection caused by Clostridium difficile (CDI) is a prevalent complication of IBD and is closely linked to the unfavorable prognosis of IBD. Recently, the Food and Drug Administration (FDA) has granted approval for rectal administration of Live-JSLM (REBYOTA) and oral delivery of Vowst, both microbiota-based products, for the treatment of CDI (133, 134). However, clinical trial evidence that excludes patients with IBD and uses clinical symptom relief as an effective indicator for treating CDI is still insufficient to apply these drugs to patients with IBD (135). Furthermore, considering the presence of potential adverse reactions associated with these drugs, it is imperative to meticulously evaluate both efficacy and safety aspects in forthcoming clinical trials.

Short-chain fatty acids (SCFAs), as crucial metabolites of the intestinal microbiota, primarily consist of acetate, propionate, and butyrate (122). They not only facilitate the proliferation and differentiation of colonic epithelial cells, maintaining intestinal mucosal epithelial barrier stability, but also regulate gut inflammatory response (135, 136), thereby potentially serving as treatments for FMT. *In vitro* and animal studies have demonstrated that butyrate possesses anti-inflammatory properties by inhibiting the production of pro-inflammatory cytokines and chemokines, thereby alleviating inflammation during IBD progression (122, 137). This discovery holds significant implications for IBD treatment, suggesting that supplementation of short-chain fatty acids could be a promising approach to promote intestinal mucosal healing. Both oral administration and enema delivery can be employed to administer short-chain fatty acids; however, enema administration circumvents challenges associated with intestinal absorption while ensuring direct drug delivery to the colon (138). Consequently, this may lead to divergent outcomes in patients with UC and CD. In colitis-induced mouse models, acetate supplementation plays a crucial role in the gut's response to injury and tissue repair (139). A preliminary study by Facchin et al. confirmed that sodium butyrate supplementation reduces inflammation in patients with IBD (140). Although there exists some preclinical evidence along with limited clinical data supporting potential therapeutic applications based on SCFAs therapies, further research is warranted to comprehensively elucidate their mechanisms of action, safety profiles, optimal dosage regimens, as well as long-term effects for treating IBD.

4.5 Extracellular matrix

The intestinal extracellular matrix (ECM) is a functional protein complex assembled in a specific grid structure composed of glycosaminoglycans (GAGs) (141, 142). Its major components include collagens, elastin, laminins and proteoglycan (143). In

addition to providing structural support for cells in tissues, the ECM also plays an active role in various cellular processes such as proliferation and migration (144). An increasing body of evidence demonstrates that in the process of mucosal healing, patients with IBD experience an augmented damage and repair mechanism of extracellular matrix due to enhanced protease activity and deposition of ECM degradation products, thereby disrupting the delicate equilibrium between ECM damage and repair (145, 146). Lindholm et al. (147) found that DSS caused direct damage to the intestinal basement membrane in an acute colitis rat model, and established a robust association between Collagen III remodeling and matrix regeneration during resolution of the injury. Meanwhile, the reconstruction of the mucosal layer *in vitro* was observed to be facilitated by fibronectin and Collagen IV, thereby enhancing the migration of intestinal epithelial crypt cells (148). The study conducted by Stronati et al. (149) revealed that dipotassium glycyrrhizate (DPG) effectively facilitated the process of mucosal healing through upregulation of the expression levels of ECM remodeling enzyme PLAUR and its ligand VTN. These collectively indicate that ECM remodelling is associated with the degree of intestinal mucosal healing. Therefore, the modulation of medical pathways that impact the ECM and its regenerative capacity following injury may hold promise as potential therapeutic interventions for IBD (150, 151). In the field of tissue engineering, hydrogel formulations based on ECM have demonstrated their reparative potential in specific tissues (152). Therefore, considering the use of ECM-derived hydrogels from the gut to promote healing of intestinal mucosal injuries alone appears to be a worthwhile consideration. However, due to the intricate composition of ECM and its associated pathophysiological processes that remain incompletely elucidated, in addition to the increasing integration of ECM as a carrier and other technologies in current studies (153), challenges arise when confirming the independent role of ECM in intestinal repair, necessitating further discussion.

4.6 Intestinal growth factors

TGF-β is a multifunctional cytokine synthesized by various cell types, which exerts pivotal regulatory effects on diverse cellular processes, immune responses, intestinal epithelial cell proliferation inhibition, and differentiation induction (154). In the context of intestinal immunity, TGF-β serves to suppress inflammatory responses elicited by luminal bacterial antigens and attenuate the production of pro-inflammatory cytokines (155, 156). The efficacy of TGF-β treatment in ameliorating methotrexate-induced intestinal mucositis in rats has been substantiated by studies, which revealed its ability to augment p-ERK and β-catenin-mediated intestinal cell proliferation while concurrently inhibiting apoptosis and preventing mucosal injury (157). Activation of the Smad pathway mediated by TGF-β can promote mucosal injury repair through enhanced epithelial revascularization while driving processes such as intestinal fibrosis, angiogenesis, and obstruction (158). High levels of Smad7 are intracellular inhibitors of TGF-β/Smad signaling (156). It has been reported that oral administration of Smad7 antisense oligonucleotide restores TGF-β signal transduction in the intestinal tract, thereby promoting clinical symptom resolution and endoscopic healing in patients with CD (159, 160). Despite these promising findings, a Phase 3 clinical trial yielded no clinical or endoscopic efficacy for Mongersen. However, the underlying reasons for this observed ineffectiveness remain uncertain, encompassing potential factors such as inadequate concentrations of the drug in colonic or ileal tissues, intended pharmacological mechanisms, or characteristics of the patient population (161). Although no definitive evidence exists, recent research suggests that variations in diastereoisomer content across different batches of mongersen used during the development program may contribute to disparate outcomes observed in clinical trials, thus explaining the failure of the Phase 3 trial (162). Further research and exploration are required to determine whether specific modifications in manufacturing schemes can effectively reduce diastereoisomer complexity. Moreover, the study revealed a significant association between long-term Smad7 deficiency and heightened progression of intestinal fibrosis (163). It is evident that additional experiments are warranted to further investigate the role of Smad7 in inflammatory responses related to IBD and reassess the efficacy and potential risks of mongersen as a therapeutic approach for IBD.

The Trefoil factor (TFF) family comprises three peptides, known as TFF1, TFF2, and TFF3, which are released by goblet cells located in the mucosa of the intestines (164). Among these peptides, TFF3 is predominantly synthesized by goblet cells in both the small and large intestine (165). Notably, TFF3 plays a crucial role in upholding the integrity of the IMB through its regulation of cytokine expression and immune cell migration (164), and PI3K/Akt signaling pathways are activated to enhance wound healing *in vitro* (166). An evident upregulation of serum TFF3 is observed in IBD patients and confirmed to be associated with disease activity, indicating its potential as a non-invasive marker (167). Studies have demonstrated that the utilization of TFFs facilitates the restoration of gastrointestinal mucosa, thereby presenting an innovative method for addressing the management of IBD. However, conflicting outcomes are frequently observed in DSS-induced colitis animal models due to variations in TFF forms, dosages, and routes of administration (168–170). In order to optimize the application of TFFs, a recombinant adenovirus vector was constructed to deliver the human intestinal trefoil factor (hITF) gene for improved healing of intestinal mucosal injury (171). The optimal dosing strategy and underlying signaling pathways of TFF3 remain unclear; however, TFF3 has demonstrated significant potential in both the diagnosis and management of IBD.

5 Conclusion

With the further development of the definition of mucosal healing, the requirements of mucosal healing are no longer limited to the repair of the intestinal barrier under endoscopy and the restoration of intestinal function but require the balance and homeostasis of the intestinal ecosystem in terms of omics and biology, that is the dynamic balance between the intestinal barrier

and intestinal flora. Because intestinal mucosal healing is closely related to the prognosis of IBD patients, and in the absence of means to promote mucosal healing, how to further improve the efficacy of current therapeutic measures and further develop new therapeutic modalities is a matter that needs to be considered at present and in the future. These new promising mucosal repair methods, including enteral nutrition, organoid transplantation, and intestinal microbiota transplantation, have been proposed, but the specific clinical practice remains a formidable challenge. Subsequent research will determine the viability of potentially promising pathways, while also weighing their impact against potential hazards and complexities like availability within biological systems, cell proliferation stimulation, and tumor formation.

Author contributions

MW: Writing – original draft. JS: Writing – review & editing. CY: Writing – review & editing. XZ: Writing – review & editing. GX: Writing – review & editing. ZX: Writing – review & editing, Writing – original draft. YM: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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