Inflammatory bowel disease treatment: Mechanisms to clinical translation (Review)

SIQI TANG[1-3*], GUOYOU GOU[1-3*], YOUJIA LIU[1], FANG WANG[1], FEIHONG SHU[2], YA DENG[2], TING ZHANG[2], JINGYU XU[2] and RUI XIE[1,3]

[1]Department of Endoscopy and Digestive System, Guizhou Provincial People's Hospital, Guiyang, Guizhou 550002, P.R. China; [2]Collaborative Innovation Center for Tissue Repair and Regenerative Medicine, Zunyi Medical University, Zunyi, Guizhou 563006, P.R. China; [3]Guizhou Provincial Key Laboratory for Digestive System Diseases, The Affiliated Hospital of Guizhou Medical University, Guiyang, Guizhou 550002, P.R. China

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Abstract. Inflammatory bowel disease (IBD) is a group of chronic, relapsing and systemic inflammatory disorders primarily affecting the gastrointestinal tract, including Crohn's disease, ulcerative colitis and rarer distinct subtypes such as indeterminate colitis. IBD has shown a marked shift in global epidemiology, with increasing incidence in newly industrialized regions across Africa, Asia and Latin America. The pathogenesis of IBD reflects a complex interplay between genetic susceptibility, mucosal immune dysregulation, intestinal barrier dysfunction, microbial dysbiosis and environmental exposures. Clinically, conventional therapy, including 5-aminosalicylic acid, corticosteroids and conventional immunosuppressants, is limited by incomplete efficacy and safety concerns. Alternative therapeutic strategies included biological agents (anti-tumor necrosis factor α, anti-integrin, anti-IL-12/23 and anti-tumor necrosis factor-like ligand 1A), small-molecule inhibitors (JAK inhibitors, tyrosine kinase 2 inhibitors, sphingosine-1-phosphate receptor modulators and NLRP3 inhibitors), microbiome-based interventions (fecal microbiota transplantation, probiotics and engineered microbes) and regenerative approaches (mesenchymal stem cells and intestinal organoids). The present review aimed to summarize mechanistic insights and clinical evidence for established and emerging therapies and discusses current challenges and future directions for individualized, disease-modifying treatment of IBD.

Correspondence to: Professor Jingyu Xu, Collaborative Innovation Center for Tissue Repair and Regenerative Medicine, Zunyi Medical University, 1 Campus Road, Zunyi, Guizhou 563006, P.R. China
E-mail: xujingyu_gzzy@126.com

Professor Rui Xie, Department of Endoscopy and Digestive System, Guizhou Provincial People's Hospital, 395 Jinzhu East Road, Guiyang, Guizhou 550002, P.R. China
E-mail: xr19841029@aliyun.com

*Contributed equally

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Contents

1. Introduction

Inflammatory bowel disease (IBD) is a group of chronic, non-specific inflammatory disorders affecting the gastrointestinal tract. The primary clinical manifestations include diarrhea, abdominal pain, hematochezia, tenesmus/urgency, as well as systemic symptoms such as fever, weight loss and fatigue (1). The two primary types are Crohn's disease (CD) and ulcerative colitis (UC). A subset of patients (10-15%) displays overlapping features and is classified as indeterminate colitis (IC); over time, more than half of these patients are reclassified as UC or CD, with a small percentage (4-5%) remaining diagnosed with IC (2). IBD incidence and prevalence are increasing in newly industrialized regions, including Asia (urban IBD incidence surged up to 30-fold over 30 years) (3), Latin America (2-4-fold growth in disease prevalence) (4) and parts of Africa (urban incidence doubled within 15 years) (5), reflecting environmental and lifestyle transitions associated with urbanization (6).

The pathogenesis remains incompletely understood but involves genetics, immune dysregulation, epithelial barrier defect, microbiome alterations and environmental exposures. Recent mechanistic studies have suggested new precision

targets and highlight the need for multidimensional, individualized treatment strategies (7,8).

The therapeutic objectives for IBD are to induce and maintain remission, promote mucosal healing, improve quality of life and prevent complications. Conventional treatments include amino salicylates, glucocorticoids and immunosuppressants, however, issues such as inefficacy and adverse reactions are common (9). As research into IBD advances, novel therapeutic approaches, including biological agents, small-molecule targeted therapies and microbiome therapy, may emerge, thereby providing an expanded array of treatment options for patients with IBD (10) (Fig. 1).

The present article aims to review the epidemiological characteristics, pathogenesis, conventional treatments and advancements in therapeutic strategies for IBD, with a focus on the mechanisms, clinical efficacy and safety profiles of novel therapeutic approaches.

2. Epidemiology and economic burden

The distribution of IBD has evolved from being concentrated in high-income Western countries to a global disease; the four-stage epidemiological model, encompassing emergence, acceleration in incidence, compounding prevalence and prevalence equilibrium, captures the regional differences associated with industrialization (11).

In China, for example, the incidence of IBD increased from 1.45 in 1990 to 3.62/100,000 population in 2019 (12); age-standardized epidemiological data up to 2021 confirmed this continuous upward trend, with the age-standardized incidence rate reaching 4.75/100,000 population (13), transforming IBD from a rare disease into a common disorder.

Beyond its global epidemiological shift, IBD imposes a burden on global healthcare systems and economies. Patients typically require long-term treatment, encompassing medication, hospitalization, surgery and regular monitoring, with associated direct costs. Beyond this, indirect costs, including reduced productivity, absenteeism and early retirement, amplify the societal impact of the disease (14).

3. Pathogenesis and risk factors

Genetic factors. IBD is characterized by substantial genetic susceptibility, with a positive family history representing the strongest known risk factor for disease development. Notably, offspring of two affected parents carry the highest lifetime risk (>30%), while the age-adjusted IBD risk is ~5% for siblings and 10% for offspring of a single affected individual. Familial aggregation is more pronounced in CD than in UC: Relatives of patients with CD face a higher overall IBD risk, and monozygotic twin concordance rates are higher for CD compared with UC (15). Beyond risk stratification, familial IBD cases exhibit distinct phenotypic features relative to sporadic counterparts. Familial cases present with earlier disease onset [UC, 33, interquartile range (IQR), 25-44] vs. 37 years (IQR, 27-49); CD, 27 (IQR, 21-35) vs. 29 years (IQR, 22-40)] and a higher prevalence of extraintestinal manifestations (UC, 17.2 vs. 14.0%; CD, 30.1 vs. 23.6%). For familial CD, additional phenotypic differences include a higher proportion of ileocolic involvement (42.7 vs. 51.8%), penetrating disease behavior (21.0 vs. 17.6%) and perianal disease (32.0 vs. 27.1%). These phenotypic disparities are independent of the degree of kinship between affected individuals (16).

Beyond familial aggregation, sex differences in IBD genetics and clinical phenotypes have gained increasing attention (17-20). A large-scale sex-stratified genetic association meta-analysis of IBD, including 34,579 patients and 39,125 controls, focused on sexual dimorphism in the genetic mechanisms of the disease, filling the research gap of traditional combined male-female analysis models (17). The aforementioned study revealed sex-associated differences in IBD clinical features, such as lesion location and perianal complications in CD and lesion extent in UC, and identified three genome-wide significant sex-specific genetic loci (chr 9q22, capping protein regulator and myosin 1 linker 1 and ubiquitin associated and SH3 domain containing A (UBASH3A)), sex-specific association patterns at several known IBD loci and three associations between the X chromosome and IBD (including a newly identified CD susceptibility locus in the Xp22 region). These findings not only deepen the understanding of sexual dimorphism in IBD biology, but also provide the foundation for the subsequent construction of sex-specific IBD polygenic risk score systems and precise assessment of disease risk across sexes (17).

To decipher the regulatory mechanisms underlying IBD pathogenesis and clinical heterogeneity, Bohar *et al* (21) analyzed genotype data from 2,636 patients with IBD using the genomics analysis pipeline integrative single nucleotide polymorphism (iSNP). The aforementioned study revealed the core mechanism of patient-specific regulatory network reprogramming in IBD: SNPs) in non-coding regions mediate the deviation of upstream signaling pathways toward disease-associated directions by altering transcription factor binding sites, thereby affecting key pathological processes such as pro-inflammatory immune responses and epithelial barrier function. Furthermore, the aforementioned study identified SNP-regulated transcription factors specific to or shared by UC and CD, stratifying patients into four subgroups via distinct regulatory network patterns. Those findings not only provide a mechanistic explanation for the clinical heterogeneity of IBD, but also establish a theoretical basis for the development of individualized treatment strategies (21).

Genome-wide association studies have identified >200 genetic susceptibility loci associated with IBD (22,23). These loci primarily involve pathways associated with innate and adaptive immune responses, epithelial barrier function, autophagy and microbial responses (24,25). Among these, nucleotide-binding oligomerization domain-containing protein 2 (NOD2), the first identified CD-susceptible gene, serves a pivotal role in bacterial recognition and innate immune regulation (26). As a cytoplasmic pattern recognition receptor, NOD2 activates downstream signaling by recognizing muramyl dipeptide (MDP), a derivative of bacterial peptidoglycan, thereby negatively regulating toll-like receptor (TLR)-mediated inflammatory responses. However, CD-associated NOD2 mutations impair this regulatory effect, leading to abnormally enhanced intestinal inflammatory responses to commensal flora (27). Pre-stimulation with NOD2 ligands induces the expression of the inhibitory factor interferon regulatory factor 4 (IRF4) (28), which maintains

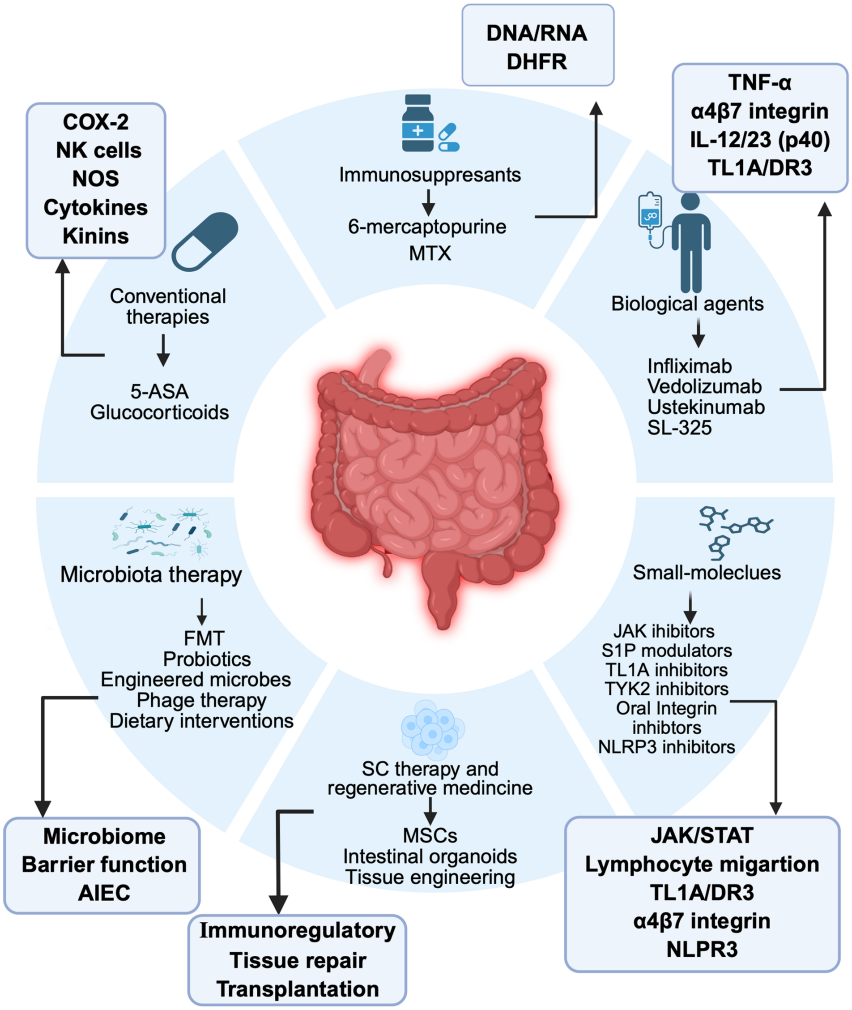

Figure 1. Schematic overview of current and emerging therapeutic strategies for inflammatory bowel disease. Interventions targeting the gastrointestinal tract included conventional drugs (5-ASA, glucocorticoids), immunosuppressants (6-mercaptopurine, MTX), biological agents (infliximab, vedolizumab, ustekinumab), small-molecules (JAK inhibitors, S1P modulators, NLRP3 inhibitors), microbiota therapies (FMT, probiotics, engineered microbes) and SC/regenerative medicine (MSCs, intestinal organoids), associated with modulation of cytokines (TNF-α, IL-12/23), immune cell trafficking (α4β7 integrin) and microbial barrier function. ASA, Acetylsalicylic acid; MTX, methotrexate; S1P, phingosine-1-phosphate; FMT, fecal microbiota transplantation; MSC, mesenchymal stem cells; DHFR, dihydrofolate reductase; TL1A, tumor necrosis factor-like ligand 1A; DR, death receptor; TYK, tyrosine kinase; AIEC, adherent-invasive *Escherichia coli*; COX, cyclooxygenase; NK, natural killer; NOS, nitric oxide synthase.

intestinal homeostasis by blocking TLR inflammatory pathways (29). Additionally, MDP injection in normal mice induces IRF4 production and prevents experimental colitis, providing a potential direction for CD treatment targeting the NOD2 pathway (30,31). Notably, previous research combined artificial intelligence (AI) with molecular biology techniques to identify the association between NOD2 and CD: The balance between intestinal inflammatory (anti-pathogen) and non-inflammatory macrophages (tissue repair) is key for intestinal homeostasis; binding of a specific region of the NOD2 protein to girdin protein maintains this balance by inhibiting excessive inflammation, eliminating harmful microorganisms and promoting tissue repair (27). Common NOD2 gene mutations in CD lead to the deletion of the girdin-binding region, which results in an imbalance between the two types of macrophage and triggers chronic intestinal inflammation (27,32,33). In mice, girdin deficiency exacerbates intestinal dysbiosis, inflammation and sepsis risk, providing theoretical support for the development of CD treatment strategies targeting the restoration of the NOD2-girdin interaction (34).

In parallel with the exploration of single-gene and locus-specific mechanisms, recent research has developed polygenic risk scores (PRSs) to quantify cumulative genetic susceptibility to IBD (35,36). PRS is associated with the risk of developing IBD and exhibit interactions with lifestyle factors (37). A previous study based on data from 51,772 individuals in the UK Biobank explored the complementary roles of plasma protein-based risk scores (PRORS) and PRS in predicting IBD onset (35). While traditional PRS is suitable for long-term IBD risk assessment, it has inherent limitations, including limited predictive power and inability to indicate the timing of disease onset (38). By contrast, PRORS based on plasma proteome offers time-sensitive advantages, enabling accurate prediction of short-term disease risk by reflecting current physiological and inflammatory states (35). The combined use of PRORS and PRS improves the predictive performance for IBD onset (including CD and UC), with PRORS showing superior predictive performance in individuals with high PRS (35). Longitudinal analyses further confirm that both scores can stably exert predictive value at

different time points after blood sampling (35,39). The aforementioned study provided a multi-omics integration approach for the early identification, stratified management and precise intervention of patients with high-risk IBD, bridging the gap between genetic susceptibility and clinical translatability (35).

Immune dysregulation. The key pathophysiological features of IBD are dysregulation of immune responses and mucosal inflammatory reactions. In healthy individuals, the intestinal immune system maintains tolerance towards the gut microbiota. In patients with IBD, however, this balance between the immune system and gut microorganisms is disrupted, leading to excessive and persistent inflammatory responses (40).

The balance between T helper (Th)17 cells and regulatory T cells (Tregs) is crucial in the pathogenesis of IBD. Th17 cells secrete pro-inflammatory cytokines such as IL-17, IL-21 and IL-22, thereby driving inflammatory responses; conversely, Tregs exert anti-inflammatory and immunosuppressive functions via the secretion of IL-10 and TGF-β (41). In patients with IBD, the Th17/Treg balance shifts towards Th17 dominance, leading to persistent intestinal inflammation (42). Tumor necrosis factor (TNF) serves a key role in the pathogenesis and progression of IBD. TNF interacts key core inflammatory signaling pathways in macrophages and T cells, including NF-κB and the MAPK pathway. These pathways promote the release of other pro-inflammatory cytokines such as IL-1, IL-6, IL-12 and IL-23, thereby exacerbating the inflammatory response (43).

Macrophages are key for maintaining intestinal homeostasis, yet in IBD they promote inflammation. During inflammatory states, excessive activation of the CCL2-CCR2 axis leads to an influx of lymphocyte antigen 6 complex, locus C^+ monocytes into the gut, where they differentiate into pro-inflammatory macrophages. Pro-inflammatory macrophages secrete IL-23 to activate Th17 cells, forming an IL-17-IL-6 positive feedback loop. Overactivation of NADPH oxidase in macrophages generates reactive oxygen species (ROS), disrupting epithelial tight junctions (such as zonula occludens-1 and occludin) (44). ROS also activate the NF-κB and MAPK pathways, inducing macrophages to secrete increased levels of TNF-α and IL-1β, thereby establishing a cycle between ROS and pro-inflammatory factors (43).

Intestinal barrier and microbiome. Impaired intestinal barrier function is a key factor in the development and progression of IBD. The intestinal barrier comprises epithelial cells, tight junctions and a mucus layer, preventing microorganisms and antigens within the gut from entering the submucosal layer (45). Patients with IBD exhibit compromised intestinal barrier integrity, leading to increased intestinal permeability and bacterial and antigen translocation, thereby triggering abnormal immune responses (46).

Patients with IBD exhibit severe dysbiosis in the composition and function of their gut microbiota, characterized by decreased microbial diversity, diminished levels of beneficial bacteria such as *Clostridium difficile* and increased presence of potentially pathogenic microorganisms (47). The association between IBD-associated genes [autophagy related 16 like 1 (ATG16L1) and NOD2) and *Bacteroides fragilis*, a human gut commensal bacterium, involves the secretion of outer membrane vesicles (OMVs) that deliver immunomodulatory molecules (capsular polysaccharide A) to immune cells. OMVs require both ATG16L1 and NOD2 to activate the non-canonical autophagy pathway in dendritic cells, thereby conferring protective effects against colitis (48). Microbiome dysbiosis not only contributes to the pathogenesis of IBD, but may also influence treatment outcomes (49).

Environmental and lifestyle factors. Environmental factors serve a pivotal role in the pathogenesis of IBD. The typical Western diet, characterized by low fiber and high sugar, animal protein and fat content, is associated with an increased risk of IBD (50). High-sodium diets are associated with the onset of IBD. Previous research suggests that the increased salinity of the intestinal environment induced by high-sodium diet may represent an upstream pathogenic factor in IBD (51). High-salt diet exacerbates the inflammatory pathology of colitis in IL-10-deficient mouse models (52,53). Furthermore, a high-salt diet stimulates Th17 responses in the mouse gut, suppresses regulatory T cell function and exacerbates 2,4,6-trinitrobenzenesulfonic acid-induced colitis (54). These dietary patterns may influence the onset of IBD by altering gut microbiota composition, disrupting the intestinal barrier and promoting inflammatory responses (55) (Fig. 2).

Other environmental factors include antibiotics (particularly when used during childhood), non-steroidal anti-inflammatory drugs, smoking and stress (56). Certain factors exert differing effects on CD and UC. For example, smoking constitutes a risk factor for CD, whereas it may exert a protective effect against UC by reinforcing intestinal mucus barrier and restraining mucosal inflammatory cascades (57,58). Smoke-induced G protein-coupled receptor 15 (GPR15) signaling augments intestinal Treg formation; these immunosuppressive cells secrete IL-10 and TGF-β to dampen superficial colonic inflammatory lesions (59). Although smoking causes other serious health problems, this may reflect differences in the pathological mechanisms of the two diseases.

4. Conventional therapeutic strategies and limitations

5-Aminosalicylic acids (5-ASAs). 5-ASA (mesalazine, sulfasalazine, olsalazine and balsalazide) is the first-line treatment for mild-to-moderate UC, although its efficacy in CD is relatively limited (60). The mechanism of action primarily involves inhibiting natural killer cell activity, suppressing the cyclooxygenase and lipoxygenase pathways of arachidonic acid metabolism, thereby decreasing prostaglandin and leukotriene levels, inhibiting the activation of various inflammatory cells and protecting the intestinal mucosa (61). Common adverse reactions include diarrhea, headache, nausea, rash and thrombocytopenia. These adverse reactions are typically mild and may be alleviated by decreasing the dosage. 5-ASA formulations that employ specialized delivery systems designed for specific intestinal segments, resulting in fewer adverse reactions (62).

Certain bacterial species acetylate 5-ASA into the inactive N-acetyl-5-ASA (63-66). Previous research has further identified 12 microbial 5-ASA acetyltransferase genes. These genes encode drug-inactivating enzymes, including sulfotransferases

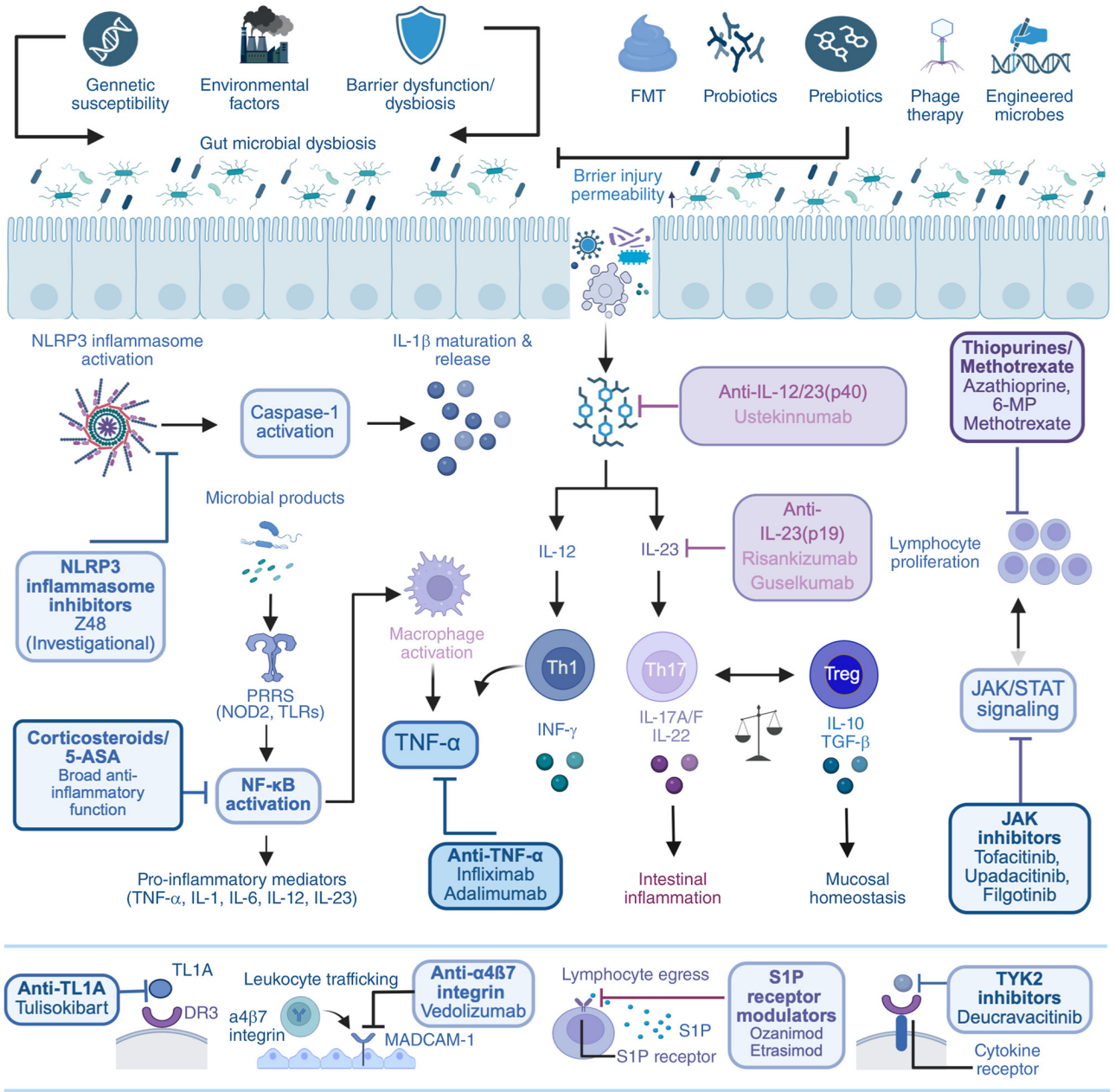

Figure 2. Inflammatory bowel disease pathogenic pathways and targeted therapeutic interventions. Genetic susceptibility, environmental triggers and gut microbial dysbiosis induce intestinal barrier dysfunction. Microbial products activate PRRs (NOD2, TLRs) and NLRP3 inflammasome, triggering NF-κB cascade, macrophage activation and secretion of pro-inflammatory cytokines (TNF-α, IL-1β, IL-12, IL-23). The imbalance of pro-inflammatory Th1/Th17 cells and anti-inflammatory Tregs drives persistent intestinal inflammation. Therapies targeting key nodes of the inflammatory cascade include conventional anti-inflammatory agents (5-ASA, corticosteroids), immunomodulators (thiopurines, methotrexate), biological agents (anti-TNF-α, anti-integrin α4β7, anti-IL-12/23 p40/p19, anti-TL1A), small-molecule inhibitors (JAK, TYK2, S1P receptor, NLRP3) and microbiota-regulating strategies (FMT, probiotics, prebiotics, phage and engineered microbes). PRR, pattern recognition receptor; TLR, toll-like receptor; Th, T helper; Treg, regulatory T cell; ASA, acetylsalicylic acid; TL1A, tumor necrosis factor-like ligand 1A; TYK, tyrosine kinase; S1P, sphingosine-1-phosphate; FMT, fecal microbiota transplantation; MP, mercaptopurine; DR, death receptor.

and acyl-CoA N-acetyltransferases (67). Concurrently, four acyltransferase genes (C7H1G6, R5CY66, R6CZ24 and T5S060) are associated with 5-ASA treatment failure, which is characterized by the requirement for subsequent corticosteroid therapy (67).

Corticosteroids. Glucocorticoids are effective agents for inducing remission in moderate-to-severe IBD, exerting anti-inflammatory effects by downregulating multiple cytokines and kinins and their receptors, adhesion molecules, nitric oxide synthase and cyclooxygenase-2 (68). Glucocorticoids influence the expression of ~20% of human genes and lack tissue or organ specificity, resulting in adverse reactions that are widespread and complex (69).

In the gastrointestinal tract, the primary adverse effects of glucocorticoids are the exacerbation of peptic ulcers and the induction of gastrointestinal hemorrhage. Furthermore, they may cause acute pancreatitis (70). Long-term use of glucocorticoids may induce systemic adverse reactions, such as central obesity, hyperlipidemia, insulin resistance and

hepatic dysfunction. To mitigate systemic side effects, locally acting corticosteroids (budesonide) have been developed. Budesonide exhibits a high first-pass metabolism rate and low systemic bioavailability, resulting in fewer systemic adverse reactions (71). However, budesonide is less effective than conventional corticosteroids and is primarily used for inducing remission in mild-to-moderate IBD (72).

Previous research indicates that ~20% of patients with IBD exhibit resistance to glucocorticoids (73); ~20% of patients with CD show no response to glucocorticoids, whilst 36% exhibit steroid dependence (74). Among patients with UC, ~30% exhibit resistance to glucocorticoids (75).

Immunosuppressants. Thiopurine drugs (azathioprine and 6-mercaptopurine) are key medications for the maintenance treatment of IBD, particularly for patients who are corticosteroid-dependent or -resistant (76). These drugs are metabolized through a series of reactions into the active metabolite 6-thio-guanosine nucleotide, which inhibits DNA and RNA synthesis, thereby suppressing lymphocyte proliferation and immune responses (77). Thiopurine drugs also induce adverse effects. A Dutch cohort study involving 363 patients receiving thiopurine therapy over an 8-year follow-up period revealed that 32% patients experienced hepatotoxicity, 19% developed gastrointestinal effects, 12% exhibited bone marrow suppression, 11% presented with pancreatitis, 11% developed fever, 9% experienced general malaise and 8% suffered from joint pain (78).

Methotrexate (MTX) is a dihydrofolate reductase inhibitor that exerts therapeutic effects by inhibiting cell proliferation and modulating immune function (79). MTX is primarily used for maintenance therapy in CD, particularly in patients who are intolerant or unresponsive to thiopurine-based medications (80). Its principal adverse reactions include bone marrow suppression, hepatotoxicity and pulmonary fibrosis (81).

Biological therapy

Anti-TNF-α. Monoclonal antibodies targeting TNF-α (infliximab and adalimumab) are used in IBD management (82), decreasing inflammation, promoting mucosal healing and decreasing the need for surgery (83). TNF-α serves a key role in intestinal inflammation during IBD, promoting the production of pro-inflammatory cytokines, increasing intestinal permeability, activating immune cells and facilitating inflammatory cell migration (84). Mechanistically, anti-TNF-α neutralizes soluble and transmembrane TNF-α, decreases NF-κB activation (85) and diminishes downstream cytokine cascades (IL-1β, IL-6 and IL-12/23) (86). However, such drugs also present limitations, including infusion reactions, increased risk of opportunistic infection (such as tuberculosis recurrence) and secondary non-response (87), with the latter typically attributable to the generation of drug-specific antibodies or alterations in pharmacokinetics (88).

Combined use of immunosuppressants (such as thiopurine drugs) decreases the rate of antidrug antibody production against anti-TNF biological agents (including infliximab, adalimumab, golimumab and certolizumab pegol) (89,90), thereby increasing drug concentration and enhancing therapeutic efficacy (91). However, this combination therapy may also increase the risk of adverse reactions, such as enhanced susceptibility to infection and lymphoma, necessitating its cautious use (92).

Anti-integrin α4β7 therapy. Vedolizumab is a humanized monoclonal antibody targeting α4β7 integrin, exerting selective immunosuppression by inhibiting lymphocyte homing to the intestinal mucosa (93). α4β7 integrin serves a key role in the trafficking of gut-specific lymphocytes. It binds the intestinal mucosal addressin cell adhesion molecule-1 (MAdCAM-1), thereby mediating lymphocyte migration into intestinal tissue (94).

The advantage of vedolizumab is its gut selectivity, with weaker systemic immunosuppressive effects, thereby presenting a lower risk of opportunistic infection (95). Furthermore, with the advent of subcutaneous injection formulations, convenience has been enhanced, leading to improved patient compliance (93). Common adverse reactions include headache, joint pain, nausea and fever, with a low incidence of serious infection (96).

However, vedolizumab exhibits a relatively slow onset of action, with clinical response rates at week 14 of 32% in patients with UC and 30% in patients with CD (97). This is not ideal for critically ill patients requiring rapid induction of remission, typically necessitating combination with other fast-acting medications such as cyclosporine (98), glucocorticoids and JAK inhibitors (99).

Anti-IL-12/23 (p40) therapy. Ustekinumab is a monoclonal antibody targeting the p40 subunit common to IL-12 and IL-23, indicated for the treatment of moderate-to-severe CD and UC (100). IL-12 and IL-23 serve key roles in immune-mediated inflammatory disease, with IL-12 promoting Th1 cell differentiation and IL-23 facilitating Th17 cell activation and maintenance (101).

Ustekinumab inhibits IL-12- and IL-23-mediated signaling and cytokine cascades by blocking the binding of IL-12 and IL-23 to the IL-12Rβ1 receptor protein on target cell surfaces (102). Previous clinical trials have demonstrated that ustekinumab exhibits notable therapeutic efficacy in both CD and UC (103-105). Furthermore, this medication delivers demonstrable clinical benefits in patients who fail to respond to treatment with TNF-α antagonists (106,107). A previous meta-analysis indicated that, among patients who failed anti-TNF-α therapy, ustekinumab demonstrates a significantly higher steroid-free remission rate at 52 weeks (46%) compared with vedolizumab (27%), alongside superior treatment persistence [odds ratio (OR)=2.37] (108). Indirect comparative studies have confirmed that ustekinumab demonstrates superior clinical response rates (OR=1.87) and biochemical parameter improvements during the maintenance phase compared with vedolizumab (109,110).

Previous research has revealed that gut microbiota may influence the efficacy of ustekinumab (111). *Faecalibacterium prausnitzii* within the gut inhibits the EGR1-IL12RB1 signaling axis of Th17 cells in patients with CD by biosynthesizing L-ornithine (10). This blocks the pro-inflammatory IL-23/tyrosine kinase 2/STAT3 pathway, reducing the release of pro-inflammatory factors such as IL-17A (10,111). This enhances the anti-inflammatory effect of ustekinumab (10). For patients with UC, decreased levels of short-chain fatty

acids (SCFAs) are associated with increased Th17 cell activity. Interventions involving butyrate (which can be produced by *F. prausnitzii*) or dietary fiber to increase SCFA levels may serve as important adjunctive strategies for optimizing ustekinumab therapy in UC (112).

Following the introduction of ustekinumab, selective inhibitors directed against the p19 subunit of IL-23, including risankizumab and guselkumab, have been developed (113). These agents offer a more targeted approach by exclusively blocking the IL-23 pathway while preserving IL-12-dependent function (114) and have demonstrated superior efficacy over ustekinumab in certain head-to-head trials (115,116).

Anti-TNF-like ligand 1A (TL1A)/death receptor 3 (DR3) strategies. SL-325 is a potential DR3 antagonist antibody, with TL1A as its ligand, currently under development for the treatment of IBD and other inflammatory immune-mediated disorder (117). SL-325 is a fully Fc-muted humanized immunoglobulin G monoclonal antibody that has demonstrated high-affinity binding to human DR3 and effective inhibition of TL1A binding in a preclinical study (117). It exhibits favorable safety profiles and potent, durable efficacy in non-human primates (117). The US Food and Drug Administration has approved SL-325 for investigational new drug application (118). The completed Phase I study reported encouraging clinical data and Phase II testing in Crohn's disease patients is ongoing (119).

DR3 is key for maintaining intestinal mucosal immune homeostasis. Its abnormal activation drives the activation of pro-inflammatory effector cells (such as Th1 and Th2 cells and type 1 innate lymphoid cell (ILC1)] and triggers a cytokine storm. It also induces an imbalance in Treg subsets, manifested by a decrease in functional $CD25^+$ $Foxp3^+$ Tregs and an increase in defective $CD25^-$ $Foxp3^+$ Tregs, while simultaneously depleting protective ILC3. By blocking DR3, the transmission of these pro-inflammatory signaling pathways is precisely inhibited, restoring Treg functional homeostasis and re-establishing the intestinal barrier repair function of ILC3. At the molecular regulatory level, this demonstrates the feasibility of targeting DR3 blockade as a therapeutic approach for IBD (120).

5. Small-molecule agents

JAK inhibitors. JAK inhibitors (tofacitinib, upadacitinib and filgotinib) block JAK-STAT signaling downstream of multiple cytokine receptors (including IL-2, IL-4, IL-6, IL-7 and IL-12/23), producing broad immunomodulation (121).

Tofacitinib is an effective, selective, orally administered JAK inhibitor employed for the treatment of acute, severe UC (122). Tofacitinib exhibits a favorable safety profile, with the most common adverse reactions being infection and parasitic infestation. The majority of adverse events are mild or moderate in severity, and overall tolerability is good during long-term treatment (with a maximum follow-up of 114 months) (123).

Tofacitinib shows significant efficacy in treating acute severe UC. Among these patients, tofacitinib is predominantly used as second-line therapy following steroid treatment failure (122), or as third-line therapy following failure of infliximab, cyclosporine or similar treatments, yielding colonic resection-free survival rates of 85, 86 and 69% at 30, 90 and 180 days, respectively. The proportion of patients continuing tofacitinib during follow-up ranges from 68 to 91%, with clinical remission rates of 35-69% and endoscopic remission rates of 55% (124). JAK inhibitors, as oral small-molecule drugs, offer a novel therapeutic avenue for IBD treatment, particularly in refractory cases, by leveraging precision targeting, convenience, efficacy and favorable safety profile (125).

Sphingosine-1-phosphate (S1P) receptor modulators. S1P receptor modulators (such as etrasimod and ozelamod) bind S1P receptors on lymphocyte surfaces, functionally inhibiting lymphocyte migration out of lymphoid tissue. This decreases the number of pathogenic lymphocytes in peripheral blood and prevents their recruitment to sites of intestinal inflammation, while exerting relatively minor effects on overall immune system function (126).

In a Phase II clinical trial, etrasimod demonstrated a higher clinical remission rate in patients with moderate-to-severe active UC following 12 weeks of daily 2 mg oral treatment compared with the placebo group (27 vs. 7%). At week 52, the clinical remission rate in the etrasimod group remained significantly higher than that in the placebo group (34 vs. 7%). As a once-daily oral agent, etrasimod serves as an effective induction and maintenance therapy for UC. The most common adverse reactions include headache, abnormal liver function, UC exacerbation, coronavirus disease 2019 infection, dizziness, fever, arthralgia, abdominal pain and nausea (127).

Additionally, a Phase III clinical trial on ozelamod enrolled 1,012 patients with moderate-to-severe active UC. Following 10 weeks of once-daily oral administration of 0.92 mg drug, the clinical remission rate in the ozelamod group was significantly higher than that in the placebo group (18 vs. 6%). At week 52, the clinical remission rate in the ozeamod group remained higher than that in the placebo group (37.0 vs. 18.5%) (126). S1P receptor modulators demonstrate potential in the treatment of UC, particularly for patients unresponsive to first-line therapy.

TL1A inhibitors. TL1A is a member of the TNF superfamily that enhances interferon-g production by T cells in peripheral and mucosal $CCR9^+$ T cell populations. During chronic intestinal inflammation in IBD, TL1A and its receptor DR3 are upregulated (128). Among patients with CD, the incidence of intestinal fibrosis and strictures caused by chronic inflammation is high (129). TL1A/DR3 signaling may also be involved in the pro-fibrotic pathway (130,131). Chronic inflammation induces lamina propria immune cells to secrete TL1A, which binds DR3 highly expressed on intestinal fibroblasts. This activates NF-κB and MAPK cascades to upregulate TGF-β and connective tissue growth factor, driving fibroblast-myofibroblast transformation and excessive deposition of collagen (132). TL1A/DR3 sustains Th1/Th17 inflammatory responses to form an inflammation-fibrosis cycle, ultimately triggering intestinal stricture, a notable complication of CD (133).

Anti-TL1A antibodies (such as afimkibart and tulisokibart) may inhibit both inflammatory pathways and fibrotic processes by blocking the binding of TL1A to its receptor DR3. In a

Phase II trial on tulisokibart for moderate-to-severe UC, a 12-week treatment regimen (1,000 mg intravenous infusion on day 1, followed by 500 mg on weeks 2, 6 and 10) demonstrated a significantly higher remission rate in moderate-to-severe UC compared with placebo (26 vs. 1%). The response rate in the TL1A-associated gene-positive subgroup reached 32%, markedly exceeding that of the placebo group (11%) (134). Additionally, the results of a Phase IIb trial for afimkibart were also favorable. During the 12-week induction phase, patients received subcutaneous injections of 50, 150 or 450 mg every 4 weeks, followed by a 40-week maintenance phase with the same dosage. The response rates were 26, 23 and 24%, respectively, all notably higher than that in the placebo group. Adverse reaction rates were comparable with those observed in the placebo group (135). Anti-TL1A antibody simultaneously ameliorates both inflammation and fibrosis in IBD, exhibiting high clinical remission rates, precise targeting and favorable safety profiles. It represents a key emerging therapeutic approaches in IBD treatment.

TYK2 inhibitors. TYK2 is a member of the JAK family, primarily mediating the signaling of IL-12, IL-23 and type I interferon (136). Selective TYK2 inhibitors (such as deucravacitinib) achieve selective inhibition through allosteric mechanisms, theoretically avoiding inhibition of JAK1/2/3 and improving safety (137). Deucravacitinib has been approved for the treatment of psoriasis and has also demonstrated potential in Phase II studies for IBD (138,139). The incidence of adverse reactions in patients treated with deucravacitinib is 70.1%, compared with 47.6% in the placebo group. The most common adverse reactions are rash, acne and worsening of UC (139). TYK2 inhibitors remain in the early stages of development for the treatment of IBD and require further exploration.

Oral integrin inhibitors. Oral integrin inhibitors (such as MORF-057 and orbofiban) suppress α4β7 integrin on lymphocyte surfaces via small-molecule oral drugs, preventing its binding to MAdCAM-1 and inhibiting lymphocyte homing to intestinal tissues (140). A Phase II study demonstrated that treatment with 100 mg MORF-057 twice daily for 12 weeks resulted in 22.7% of patients with UC achieving Robarts histopathology index remission and 25.7% achieving clinical remission. During the 52-week treatment period, 51.4% of patients experienced adverse reactions (140). However, oral anti-integrin agents exhibit low bioavailability and notable concentration fluctuations, with orbofiban bioavailability being <10% (141). Oral anti-integrin agents for IBD treatment lack sufficient data and require further research, but they still hold exploratory potential.

NLRP3 inflammasome modulation. NLRP3 undergoes a series of reactions upon exposure to pathogens (such as bacteria or viruses) or injury-associated molecules (such as uric acid crystals or ROS), promoting the maturation and release of the pro-inflammatory cytokines IL-1β and IL-18, thereby triggering inflammation (142). The NLRP3 inflammasome signaling pathway may regulate immune mechanisms in pediatric IBD by upregulating the expression of caspase-1 and IL-1β, and its expression is associated with disease severity (143). NLRP3 serves a key role in the pathogenesis of IBD, but whether it exerts a protective or pro-inflammatory effect remains controversial and may be associated with disease stage, genetic background and differences in gut microbiota composition (144). Z48 (an effective and specific NLRP3 inhibitor obtained from docking-based virtual screening and structure-activity association study) exhibits notable therapeutic efficacy in a dextran sulfate sodium-induced UC mouse model (145). However, certain studies also support the role of NLRP3 in suppressing inflammation during the pathological process of IBD (146,147). In NLRP3 knockout mice, IL-18 levels in colonic tissue decrease by 40%, while neutrophil infiltration increases (147). NLRP3 exhibits dual roles in IBD pathogenesis, and its mechanisms warrant further investigation, however, it offers a highly promising therapeutic avenue for IBD treatment.

6. Microbial therapy and gut microbiota modulation

Fecal microbiota transplantation (FMT). FMT involves transplanting the gut microbial community from a healthy donor into a patient to restore disrupted intestinal microbiome (148). Its key mechanisms include competitive exclusion of pathogenic bacteria, restoration of microbial diversity and promotion of mucosal barrier repair (149).

A previous study involving 85 patients with active UC across three Australian tertiary hospitals randomized participants to receive either multi-donor FMT from 3-7 donors or placebo. The results demonstrated significantly higher clinical remission rates at week 8 in the FMT group compared with placebo (27 vs. 8%), with sustained improvements in microbial diversity (148). Remitters exhibited gut microbiota compositions more closely resembling donors, and *C. difficile* abundance was negatively associated with remission. The study provided the first evidence confirming the efficacy of high-dose FMT for UC (148). Donor-derived transplants demonstrate superior efficacy compared with autologous transplants. A previous randomized clinical trial revealed that anaerobically prepared donor FMT (32% remission rate) more readily achieves steroid-free remission within 8 weeks in patients with mild-to-moderate UC than autologous transplantation (9% remission rate) (150).

For patients with CD, a meta-analysis incorporating 12 studies (228 patients with CD) indicated that FMT induces a clinical remission rate of 57% (95% confidence interval, 49-64%), with a notably higher remission rate in the antibiotic pretreated group (68%, 95% CI, 53-80% vs. 43%, 95% CI 29-58%). Microbiological analysis reveals increased microbial diversity and restored *Bacteroidetes phylum* abundance in remitters. However, long-term remission rates require further data (151).

Combining FMT with other therapy may yield improved treatment outcomes (152,153). For example, in patients with UC who fail vedolizumab therapy, certain individuals achieved favorable results after receiving FMT in combination with vedolizumab (154). The combination of FMT with anti-TNF-α drugs also significantly increases the clinical response rate (155). It is evident that FMT, when combined with other IBD treatment regimens, holds promise for enhancing patient outcomes and demonstrates potential for clinical application.

Probiotics, prebiotics and symbiotics. Specific probiotic strains, such as *Escherichia coli* Nissle 1917, demonstrate efficacy comparable with that of low-dose mesalazine in maintaining remission in UC. Their mechanism of action involves enhancing tight junctions in the intestinal epithelium, inhibiting pathogen colonization and modulating local immune responses (156). Prebiotics (such as fructooligosaccharides and inulin) selectively promote the growth of beneficial bacteria (such as *Bifidobacterium* and *Lactobacillus*). Their fermentation products, SCFAs, serve a crucial role in anti-inflammatory effects and maintaining intestinal barrier integrity (157). Symbiotics (a combination preparation of probiotics and prebiotics) may produce synergistic effects, but the current strength of clinical evidence still requires further support from large-scale randomized controlled trials (158).

Engineered microbes and phage therapy. Synthetic biology has revolutionized microbial therapeutics by successfully engineering the probiotic *E. coli* strain Nissle 1917. This transformation created an intelligent microbial system capable of precisely identifying and eliminating *Pseudomonas aeruginosa* intestinal infection, demonstrating promising efficacy in animal models (159-161). Target-AID base editing system targeting *Lactobacillus* species, when applied to genetically engineered *Lactobacillus plantarum*, decreases the production of imidazole propionate, a compound associated with type 2 diabetes, through impaired glucose tolerance and disrupted insulin signaling (160). Furthermore, by applying clustered regularly interspaced short palindromic repeats-CRISPR-associated protein 9 (CRISPR-Cas9) to *Lactobacillus acidophilus*, it may be endowed with additional functions (enhanced gut-colonization fitness, improved auto-aggregation phenotype, enhanced environmental stress tolerance), revealing its potential in future therapeutic applications (162). In addition, a phage cocktail therapy (comprising three potent phages) can specifically target and eliminate pathogens such as adherent-invasive *E. coli* associated with IBD without disrupting the commensal microbiota (163). This approach also offers a strategy for precisely regulating the gut microbiome.

Dietary interventions. Diet is one of the most direct means of regulating the structure and function of the gut microbiota. Exclusive enteral nutrition is the first-line therapy for inducing remission in pediatric CD, with mechanisms of action including providing complete nutrition, decreasing dietary antigen exposure, improving intestinal permeability and indirectly altering the composition of the microbiota (164). Other dietary approaches such as CD elimination, specific carbohydrate and low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (used to alleviate irritable bowel syndrome-like symptoms) diets have also demonstrated potential in certain patients with CD and UC (165-167). However, dietary interventions exhibit notable individual variability in response, necessitating personalized plans developed by nutritionists.

7. Stem cell (SC) therapy and regenerative medicine

Mesenchymal SCs (MSCs). MSCs exert immunoregulatory and reparative actions through secretion of paracrine mediators (prostaglandin E2, indoleamine 2,3-dioxygenase (IDO) and tumor necrosis factor-α-stimulated gene-6 (TSG-6)), suppression of effector T cells and macrophages, induction of Treg differentiation and promotion of epithelial proliferation and angiogenesis (168). Local injection of allogeneic MSCs (such as darvadstrocel/Cx601) achieves fistula closure in perianal CD in Phase III trials (169,170). Phase II clinical trials investigating the intravenous infusion of MSCs for the treatment of IBD are underway and preliminary results indicate a favorable safety profile (171).

Intestinal organoids and tissue engineering. Autologous intestinal organoids self-organize into miniature organs with crypt-villus architecture during three-dimensional *in vitro* culture, preserving the pathophysiological characteristics of the original tissue (172). These organoid models are used for high-throughput drug screening, investigating the pathogenesis of IBD and evaluating individual patient responses to drugs, thereby aiding in the selection of treatment regimens for patients (173). Additionally, endoscopic organoid transplantation may serve as a viable treatment option for refractory IBD (174). A three-dimensional bioengineering model has successfully replicated the core pathological features of IBD *in vitro*, enabling dynamic simulation of disease progression and may become the standard for future IBD research (175). The future directions involve integrating organoids with biomaterial scaffolds to construct engineered intestinal tissue suitable for transplantation, offering hope for patients with IBD exhibiting short bowel syndrome (176).

8. Therapeutic selection according to patient clinical profiles

Management of IBD requires individualized therapeutic stratification guided by disease subtype, severity, previous treatment outcome and safety considerations (177,178). The therapeutic goal is mucosal healing, which can be pursued through step-wise application of conventional agents including 5-ASA, biological agents and oral small-molecule drugs, alongside microbial-targeted and SC-based modalities (101,179). Multi-omics biomarkers provide additional support for personalized clinical decision-making (180). The present study aimed to summarize guideline-consistent therapeutic recommendations for typical IBD clinical presentations, differentiating established standard-of-care therapy from investigational experimental intervention.

UC

Mild UC. Oral combined with topical 5-ASA is first-line for both induction and maintenance. Systemic corticosteroids are not recommended for routine use (181).

Moderate UC. Oral 5-ASA remains the first-line for low-risk patients; biological agents (anti-TNF agents, vedolizumab, ustekinumab) are recommended as first-line treatment for patients with high-risk features or 5-ASA-refractory disease (181).

Severe UC. Systemic corticosteroids combined with biological agents are the mainstay of induction therapy. Thiopurines or long-term biological agents are used for maintenance to prevent relapse (181).

Acute severe UC. Intravenous corticosteroids are first-line rescue therapy. For steroid-refractory cases, intravenous infliximab or cyclosporine is recommended as second-line rescue therapy to avoid emergency colectomy (181).

CD

Mild luminal CD. Budesonide (for ileal/right colonic involvement) is preferred for induction; thiopurines are used for steroid-sparing maintenance. 5-ASA is not recommended as first-line due to limited efficacy (182).

Moderate-to-severe luminal CD. Anti-TNF agents, ustekinumab and anti-IL-23 p19 antibodies (such as risankizumab) are recommended as first-line biological options for induction and long-term maintenance. Vedolizumab is preferentially indicated for patients at elevated risk of systemic infection, owing to its gut-restricted immunosuppressive profile. Concomitant use of thiopurines or MTX with biological agents can reduce anti-drug antibody formation and improve sustained response rates (89,182).

Perianal fistulizing CD. Consistent with European Crohn's and Colitis Organization (ECCO) surgical and medical guidelines, anti-TNF agents (infliximab, adalimumab) are the gold-standard first-line therapy for complex perianal fistulas, combined with thiopurines or MTX to decrease postoperative recurrence of fistulae (182). Short-term ciprofloxacin or metronidazole are used as adjuvant antibiotics to control local abscess and infection, yet antibiotics alone cannot achieve permanent fistula closure (182). For patients with anti-TNF secondary failure, ustekinumab is a feasible alternative, while vedolizumab is only a conditional option due to insufficient high-grade evidence for fistula healing (182,183).

Treatment-defined subgroups

Corticosteroid-dependent/-refractory IBD. Thiopurines or MTX achieve steroid-free remission; biological agents are escalated if immunomodulator monotherapy fails (181,184-186).

Patients with prior anti-TNF therapeutic failure. Patients in this subgroup should switch to biological agents with different mechanisms (anti-IL-12/23, anti-integrin); oral small-molecule JAK/S1P inhibitors are rescue choices for multi-biological refractory IBD (181,185,187).

Patients requiring gut-selective immunosuppression. Vedolizumab is prioritized owing to its intestine-restricted action and low systemic infection risk; topical 5-ASA is preferred for distal intestinal lesions (47,181).

Patients with high systemic infection risk and contraindications to broad immunosuppressants. Gut-targeted topical preparations and selective gut-limited small molecules are used preferentially; long-term systemic corticosteroids and high-dose non-selective immunomodulators are avoided (47,181).

Distinction between mature clinical regimens and investigational therapies. The aforementioned regimens are guideline-endorsed standard clinical treatments. Although local injection of allogeneic adipose-derived MSCs (darvadstrocel) for perianal fistula has demonstrated efficacy in a positive phase III trial (188), a subsequent confirmatory phase III trial did not meet its primary endpoints (189); evidence supporting luminal mucosal regeneration is still scarce (189). Collectively, these cell-based therapeutic approaches are not universally recommended for routine IBD clinical practice, despite partial regulatory approval for perianal fistula indications.

9. Precision medicine and future prospects

The treatment of patients with IBD is shifting from broad-spectrum immunosuppression toward personalized therapy targeting precision-guided, mucosal healing and disease-modifying approaches. The characteristics of therapeutic strategies and their primary mechanisms are shown in Table I.

In biomarker applications, pharmacokinetic studies on anti-TNF agents (such as infliximab) have demonstrated that real-time monitoring of anti-drug antibody levels and drug concentrations in patients elevates the 52-week composite disease control rate to 55.3%, notably outperforming conventional empirical dosing regimens (190,191). In multi-omics research, further insights into the molecular heterogeneity of IBD have demonstrated butyrate levels in fecal metabolomics serve as a predictive indicator for response to vedolizumab therapy, while changes in the abundance of *F. prausnitzii* within the gut microbiota are associated with the efficacy of anti-IL-23 therapy (10). Additionally, the association between short-chain acyl-CoA dehydrogenase gene variants and serum butyrate metabolism suggests metabolic intervention may serve as a target for precision treatment in IBD (192).

The next phase of IBD diagnosis and treatment may rely on integration of core next-generation technologies (193). In the diagnosis of IBD, deep learning based on magnetic resonance imaging has demonstrated the ability to distinguish between perianal fistula-in-ano CD and crypt-glandular fistula (194). Convolutional neural networks (MobileNetV2 and ResNet50) were used to construct diagnostic models. Both models significantly outperformed specialist radiologists, exhibiting greater robustness across diverse patient cohorts with varying demographic characteristics and fistula features (194). Additionally, previous research has identified IRF1, guanylate-binding protein 5 and PARP9 as potential genes associated with the pathogenesis of IBD through machine learning (ML) (195). In IBD treatment, transcriptomics and ML have achieved preliminary success. For example, ML models built on patient baseline gene expression profiles predict clinical response to upadacitinib with 89% accuracy, providing technical support for pre-treatment drug selection (196). ML has potential in the diagnosis and treatment of IBD. With the development of additional ML models and continuous improvements in algorithmic capabilities, the diagnosis and treatment of IBD may become more efficient and precise.

Despite these promising advances, the widespread clinical implementation of AI in IBD faces practical barriers. The majority of current diagnostic and predictive models are trained on single-center retrospective cohorts with non-standardized imaging and omics workflows, and large-scale prospective multi-center validation remains scarce, limiting real-world generalizability (197,198). From a health system perspective, high upfront infrastructural costs and a lack of established reimbursement pathways restrict equitable access, particularly

Table I. Therapeutic strategies for inflammatory bowel disease.

Therapy	Representative treatment	Mechanism	Advantages	Limitations	Current status	(Refs.)
Traditional drugs	Mesalazine	Local anti-inflammatory	Good safety, suitable for mild cases	Limited efficacy	In clinical use	(65,66)
Glucocorticoid	Glucocorticoids	Systemic anti-inflammatory effect	Applicable for acute/severe cases	Extensive and unclear side effects	In clinical use	(68,73)
Immunosuppressants	Azathioprine	Inhibits DNA/RNA synthesis	Suppresses lymphocyte proliferation and immune response	Multiple side effects (myelosuppression, hepatotoxicity, gastrointestinal intolerance, increased infection risk)	In clinical use	(77,78)
Biological agents	Infliximab, vedolizumab, ustekinumab	Neutralizes relevant antigens	Strong efficacy, most already in clinical use	Infusion reaction, secondary loss of response	Approved	(82,93,100)
JAK inhibitors	Tofacitinib	Inhibits JAK/STAT pathway	Oral convenience, rapid onset	Infection, thromboembolic risk	Approved	(121,123)
S1P modulators	Ozanimod	Inhibits lymphocyte migration	Oral convenience, intestinal selectivity	Bradycardia risk	Approved	(126,127)
TL1A inhibitors	Afimikabart	Blocks TL1A/DR3 signaling	Simultaneously inhibits inflammation and fibrosis	Limited long-term safety data	Phase III clinical trial	(134,135)
TYK2 inhibitors	Deucravacitinib	Selectively inhibits JAK/STAT signaling pathway	Avoids inhibition of JAK1/2/3, fewer side-effects vs. pan-JAK inhibitors	Requires more research support	Phase II clinical trial	(139)
Oral integrin inhibitors	MORF-057	Anti-integrin effect	High oral convenience, good safety	Efficacy inferior to biological agents	Phase II clinical trial	(140,141)
NLRP3 inhibitors	Z48	Anti-NLRP3 effect	NLRP3-inhibitory activity	Pre-clinical stage; human efficacy and safety remain unknow	Preclinical research	(147)
Microbiota therapy	FMT, probiotics, engineered microbes	Regulates microbiota, enhances intestinal barrier integrity	High safety	Large inter-individual variability in efficacy	Phase II clinical trial	(112,149, 151,157)
SC therapy	MSCs, intestinal organoids, tissue engineering	Immunomodulation, tissue repair, transplantation	Targets key pathogenic drivers	High cost, technical complexity	Phase II clinical trial	(168,169, 172,174)

S1P, sphingosine-1-phosphate; TL1A, tumor necrosis factor-like ligand 1A; DR, death receptor; TYK, tyrosine kinase; FMT, fecal microbiota transplantation; MSC, mesenchymal stem cell.

in resource-constrained settings (199). Additionally, the opacity of deep learning systems, alongside unresolved regulatory and data governance frameworks, undermines clinician trust and slows institutional adoption (198,200). Targeted efforts to address these challenges are key to realize the clinical value of AI in IBD care.

In summary, the complexity of IBD necessitates multi-dimensional and personalized treatment strategies. Future success depends on deeper insights into the molecular networks, leveraging biomarkers and multi-omics (genomics, metagenomics, proteomics and metabolomics) to optimize therapeutic approaches, and fostering multidisciplinary collaboration to translate research into clinical practice to alter disease progression, restore healthy intestinal structure and function and enhance long-term quality of life for patients with IBD.

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Authors' contributions

GG wrote the manuscript. FS, YD, GG and YL performed the literature review. ST, JX and TZ conceived the study and edited the manuscript. FW constructed figures and performed the literature review. RX edited the manuscript. Data authentication is not applicable. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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