

Cytokine-Driven Immune Mechanisms and Emerging Therapeutics in Inflammatory Bowel Disease

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ABSTRACT

Inflammatory Bowel Disease (IBD), comprising Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic relapsing-remitting inflammatory disorder of the gastrointestinal tract. Its pathogenesis involves complex interactions among genetic susceptibility, environmental factors, intestinal microbiota dysbiosis, and dysregulated immune responses. An imbalance between pro-inflammatory and anti-inflammatory cytokines contributes to persistent mucosal inflammation, tissue injury, and disease progression. This review aims to summarize cytokine-driven immune mechanisms underlying CD and UC and to evaluate emerging therapeutic strategies targeting key immune pathways involved in IBD pathogenesis. A comprehensive review of current literature was conducted focusing on cytokine profiles, immune cell interactions, and the clinical outcomes of biologic and small-molecule therapies used in IBD management. Relevant studies investigating cytokine signaling pathways, therapeutic targets, and treatment efficacy were critically analyzed. Major pro-inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNF- α), Interleukin (IL)-6, IL-17, and IL-23, play central roles in activating pathogenic T-cell responses and sustaining intestinal inflammation. Conversely, regulatory cytokines such as IL-10 and Transforming Growth Factor-beta (TGF- β) are essential for maintaining immune tolerance and promoting mucosal healing. Biologic agents targeting TNF- α and the IL-12/23 signaling axis have significantly improved clinical outcomes; however, therapeutic limitations include primary non-response, secondary loss of response, and treatment-related adverse effects. Novel therapeutic approaches, particularly Janus Kinase (JAK) inhibitors and other small-molecule agents, offer promising alternatives for patients with inadequate responses to conventional biologics. Enhanced understanding of cytokine-regulated immune pathways has facilitated the development of targeted therapies for IBD. Continued research is essential to optimize personalized treatment strategies, achieve sustained remission, and minimize disease- and treatment-related complications.

Keywords: Biologics, Chronic inflammation, Cytokines, IL-17, IL-23, Immune dysregulation, Inflammatory bowel disease, JAK Inhibitors, Molecular therapeutics, TNF- α .

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INTRODUCTION

IBD immune response to intestinal microbiota, leading to chronic and recurrent gastrointestinal inflammation. Two types of idiopathic intestinal illness, ulcerative colitis, and CD, differ in the location and degree of colon wall involvement. Immunological interaction between enteric antigens and the enteral mucosa that is dysregulated causes immune-mediated inflammation (Hsu *et al.*, 2017). Anti-TNF- α therapies have significantly advanced research into the role of cytokines in IBD pathogenesis and



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treatment (Leppkes and Neurath, 2020). IBD's pathophysiology and etiology, but environmental variables and genes are believed to play a part in the disease's development (Ye *et al.*, 2015). Studies that found elevated cytokine levels in IBD patient peripheral and mucosal samples as well as in IBD mouse models (Fiocchi, 2012). Consequently, targeting cytokine signaling pathways represents a promising therapeutic strategy for IBD management. Targeting immune mediators in IBD is shown in Figure 1 (Melmed and Targan, 2010).

Intestinal homeostasis is maintained by a variety of mechanisms, including immunological modulation, cell migration, autophagy, adaptive immunity, innate mucosal defense, metabolic processes linked to cellular homeostasis, and epithelial barrier function (Cohen *et al.*, 2019; Liu and Stappenbeck, 2016; Mehta *et al.*, 2017). Epithelial barrier lets microbes through, the innate immune system releases extracellular mediators that attract in other cells, including adaptive immune cells. This stimulates the right tolerogenic, inflammatory, and restitutive responses. Mutations in NOD2, the first gene linked to Crohn's disease, are responsible for around one-third of all cases (Kucharzik *et al.*, 2006; Ran and Shen, 2009). *Gram-positive* and *Gram-negative* bacteria's cell walls include peptidoglycan that contains MDP, a mildly bioactive component that NOD2 recognizes. NOD2 attaches to its ligand, alters its conformation, and then binds to the adaptor protein Receptor-Interacting serine/threonine-Protein kinase 2 (RIP2's) caspase recruitment domain. RIP2 ultimately polyubiquitinates the main scaffolding protein of NF- κ B, the main regulator of NF- κ B, I κ B. This activation of NF- κ B leads to the subsequent production of proinflammatory cytokines such as IL-12. In addition, the MAPK signaling pathway could be triggered (Strober *et al.*, 2008; Strober and Watanabe, 2011; Yamamoto and Ma, 2009). NOD2 interacts with ATG16L1 upon bacterial identification to act as molecular scaffolds for the nucleation of the autophagy machinery (Magalhaes *et al.*, 2011). Mice with precisely deleted ATG16L1 T cells have spontaneous intestinal inflammation, characterized by a reduction in Foxp3 + Treg cell numbers and abnormal Th2 responses to dietary and microbial antigens (Kabat *et al.*, 2016). GWAS has identified several SNPs in the IL-23R gene that are closely associated with Crohn's disease and ulcerative colitis (Balzola *et al.*, 2011; Duerr *et al.*, 2006). The etiology of IBD is aberrant immune responses to the intestinal microbiota by the host (Zuo and Ng, 2018). Antibiotics, exogenous enzymes, fecal microbiota transplantation, probiotics, prebiotics, nutrition, and other environmental factors can all have an impact on the gut microbiota (Richard and Sokol, 2019). Health, illness, and intestinal homeostasis and function are all impacted by this gut microbiota (Saleh and Elson, 2011). Microorganisms of many different kinds have PAMPs, and PRRs including TLRs, NLRs, C-type lectin receptors, and RIG-like receptors may be used to identify bacteria (Nell *et al.*, 2010). The immune response in inflammatory bowel disease and immune

activation and barrier dysfunction in IBD breakdown is depicted in Figure 2 (Guan, 2019).

The balance of pro and anti-inflammatory cytokines in the colonic mucosa maintains proper gut homeostasis. A cytokine profile change that promotes increased production of pro-inflammatory cytokines may lead to IBDs (Casini-Raggi *et al.*, 1995; Xavier and Podolsky, 2007). Th1 cytokines, including IL-12, IFN- γ , and TNF- α , are the key things that cause inflammation (Saleh *et al.*, 2024). Because of this, some sometimes call CD a model for T-helper (Th) 1-mediated diseases. Even though there isn't a clear link between UC and IL-4, another definitive Th2 cytokine, UC is typically thought of as a Th2-type disease since the intestines make more of the Th2-associated cytokines IL-5 and IL-13. Pro-inflammatory cytokines such IL-1 α , IL-1 β , IL-2, -6, -8, -12, -17, -23, IFN, or TNF- α are involved in the start and progression of UC and CD in IBD (Alsharawneh *et al.*, 2025). Anti-inflammatory cytokines also affect the pathophysiology of IBD by stopping the production of pro-inflammatory cytokines including IL-4, -10, and maybe IL-13 (Fuss *et al.*, 1996).

MATERIALS AND METHODS

A comprehensive literature search was conducted using the electronic databases Medline, Embase, ScienceDirect, and Scopus. Articles published in English between 2010 and 2025 were considered. The search employed combinations of the keywords: "Inflammatory bowel disease," "cytokines," "chronic inflammation," "TNF- α ," "IL-17," "IL-23," "immune dysregulation," "molecular therapeutics," "biologics," and "JAK inhibitors." Additional relevant information was obtained from textbooks, review articles, and reference lists of selected publications. Studies were included if they focused on the role of cytokines in IBD pathogenesis, immune signaling pathways, or cytokine-targeted therapeutic strategies in preclinical or clinical settings. Publications unrelated to IBD, non-English articles, conference abstracts without full text, duplicate studies, and reports lacking sufficient scientific evidence were excluded. The retrieved literature was screened for relevance, scientific quality, and contribution to the objectives of this review.

Pro-inflammatory cytokines in Crohn's disease and ulcerative colitis

IL-1

The interaction between this pleiotropic proinflammatory cytokine and its natural inhibitor, IL-18-binding protein (IL-18BP), may play a role in the development of IBD (Leach *et al.*, 2008). There has been evidence of a localized increase in IL-18 expression in chronic CD lesions compared to uninvolved regions or normal controls (Pizarro *et al.*, 1999).

IL-6

IL-6 signaling via STAT3 exerts a substantial impact on the pathophysiology of ulcerative colitis and the progression of colorectal cancers linked to it (Kishimoto *et al.*, 1995; Li *et al.*, 2010). Lamina propria macrophages and CD4+ T cells produce higher IL-6 in people with experimental colitis and IBD. IL 6 binds to the soluble IL 6R (sIL 6R) and then binds to the gp130 surface protein, which is also known as IL 6R subunit- β . This activates the target cells in the intestines. IL-6 may have pro-inflammatory effects via activating different types of cells, such T cells and APCs. The IL 6-sIL 6R complex selectively promotes the production of pro-inflammatory cytokines by mucosal T cells while suppressing their programmed cell death (apoptosis) (Atreya *et al.*, 2000).

IL-12

Patients with ulcerative colitis have higher mucosal levels of IL-12 expression, which is associated with disease activity. Naïve CD4+ T cells are stimulated to become Th17 cells by IL-23 (Nielsen *et al.*, 2003). Because IL-23 receptor (IL-23R) polymorphisms are widely distributed throughout many immune cells, they may be harmful in ulcerative colitis (Saifan *et al.*, 2025). IL-23R is expressed by NK cells, NKT cells, CD4+ T cells, and CD8+ T cells (Maul and Zeitz, 2012). The newly found IL-35 is mostly produced by the Tregs (Collison *et al.*, 2007). DCs and macrophages in Crohn's disease released more IL 12 than those in ulcerative colitis, suggesting that activated APCs may promote the growth and activation of TH1 cells (Monteleone *et al.*, 1997; Ng *et al.*, 2011). Crohn's disease patients also have high levels of IL 23 produced by these cells (Liu *et al.*, 2011). This cytokine both maintains local TH17 cell responses and inhibits the activity of regulatory T (Treg) cells (Villarino *et al.*, 2008). Numerous investigations have shown that IL 27 has pro-inflammatory effects when persistent intestinal inflammation is present (Hanson *et al.*, 2014). Nevertheless, in models of colitis, some research has shown that IL-27 either has no impact or has an anti-inflammatory effect (Troy *et al.*, 2009).

IL-13

IL-13 has been identified as a key effector cytokine in ulcerative colitis, which has historically been thought of as a Th2-mediated disease (Fuss *et al.*, 2004). Numerous studies have examined the functional significance of IL-13 produced from NKT cells in UC. Colonic epithelial cells were shown to have both IL-13 receptors, according to IL-4Ra and IL-13Ra2, UC can have functional IL-13 signaling. It has also been shown that IL-13 impairs tight junction integrity, promotes epithelial cell death, and decreases restitution velocity, all of which have a detrimental effect on the function of the epithelial barrier (Heller *et al.*, 2005).

IBD pathophysiology and cytokines

GWASs have shown the presence of genes-producing T Helper (TH) proteins as well as cytokine and chemokine receptor signaling in certain IBD risk regions (Alzaareer *et al.*, 2024).

Cell responses include IL-12R, IL-23R, CCR6, CCL2, CCL13, and STAT1-STAT3-STAT4. Another study found that IBD risk loci include genes that generate cytokines, including IL-2, IL-21, IFN γ , IL-10, and IL-27. This implies that the pathogenesis of the disease may include these cytokines (Almagharbeh and Al-Motlaq, 2021). The initial clinical use of infliximab, a neutralizing antibody specific for TNF- α , in Crohn's disease patients was a significant breakthrough, despite the disappointing results of treating patients with anti-inflammatory cytokines (e.g., IFN β , IL-10, and IL-11) (Herrlinger *et al.*, 2006; Musch *et al.*, 2005; Tilg *et al.*, 2002; van Dullemen *et al.*, 1995). The effect of cytokine families in IBD is given in Table 1.

TNF biology and signaling pathways

The intracellular transcription factor NF- κ B may be activated by TNF- α attachment to its receptors, TNFR1 and TNFR2, leading to a variety of pro-inflammatory consequences in colitis. Additionally, TNFR1 signaling may stimulate the proteins RIPK1 and caspase 3 to cause cell death. Some of the pleiotropic pro-inflammatory effects of TNF- α signaling colitis include macrophage and effector T cell activation, necroptosis-induced Paneth cell death, matrix metalloproteinases generated by myofibroblasts, increased angiogenesis, and direct damage to IECs through MLCK activation. IL-6 has several roles in the gastrointestinal system, including immune response modulation against environmental microorganisms, intestinal epithelial integrity preservation, and mucosal barrier function (Holtmann *et al.*, 2002; Meijer *et al.*, 2007).

Role in chronic inflammation and tissue damage

In IBD, identifying an inflammatory response depends critically on the ratio of the primary pro- and anti-inflammatory cytokines (Dolcet *et al.*, 2005; Garbers *et al.*, 2012). The creation and maintenance of intestinal inflammation and cell signaling have been shown to rely on this cytokine-cell network (Bradham and McClay, 2006). TNF- α , IL-1, IL-6, IL-17, IL-22, and IL-23 are among the inflammatory cytokines that may induce intestinal inflammation when their levels are increased (Mihara *et al.*, 2012). All cytokines, although in dramatically varied quantities, are generated by the inflammatory mucosa, making the distinction between cytokine subgroups mostly arbitrary (Rabiei *et al.*, 2025). TNF- α and IL-6 are likely nonpolarized proinflammatory cytokines that are the primary mediators of tissue damage (Fujino *et al.*, 2003).

Current Cytokine-Targeted Therapies in IBD

Many components of the immune response are influenced by the signaling molecules called cytokines, which are essential to the immunological response (Almagharbeh, 2024). As a result of the correlation between cytokine dysregulation and several inflammatory and autoimmune disorders, targeted therapies have been developed (Korta *et al.*, 2023).

Biologics (TNF- α , IL-12/23 inhibitors)

TNF- α Signaling and Therapeutic Targeting in IBD

TNF- α is crucial for the inflammatory response. By preventing inflammation, the inhibitors infliximab and adalimumab may be used to treat autoimmune diseases and reduce their symptoms (Desmet *et al.*, 2014).

Mechanisms and Clinical Applications of IL-12/23 Inhibitors

Primarily, IL-12 stimulates naïve T cells to develop into Th1 cells, which in turn triggers the production of IFN- γ and macrophage activation (Alqaraleh *et al.*, 2025). Through controlling Th17 cell growth and maintenance, the cytokine IL-17, which depends on IL-23, regulates the responses to inflammation and autoimmune (Subih *et al.*, 2025).

Efficacy and challenges

Cytokine-directed therapies, including monoclonal antibodies against TNF- α , IL-12, IL-23, and others, have completely changed how IBD is treated (Sultan and Jessri, 2023). But they have challenges ahead of them. Primary non-response is reported in around 20-30% of patients, as the treatment response may be influenced by genetic or epigenetic variables, and not all IBD cases are caused by the targeted cytokines (Ashour *et al.*, 2024). Biologic therapy like anti-TNF- α medications and JAK inhibitors, the immunosuppressive activity of these treatments raises the risk of infections, particularly causing reactivated TB and opportunistic fungal infections. Biologics are also very difficult to get because of their high price and scarcity, especially in low-income

communities. Another major drawback is the cost of biologics (Saleh *et al.*, 2025). In addition, these agents frequently do not provide a benefit in the treatment of extraintestinal manifestations of IBD, including arthritis or uveitis, which require additional therapies that carry a higher risk of adverse effects and drug-drug interactions. Its use is restrained by negative events, inclusive of infusion reactions, systemic allergic reactions, and long-term period risks along with cancer (Kamel *et al.*, 2025). As cytokine inhibitors provide symptomatic control but are sometimes unable to achieve complete mucosal healing or to alter disease progression, exposing patients to complications like strictures or fistulas (Moldoveanu *et al.*, 2015). Resistance mechanisms, including compensatory activation of alternative inflammatory pathways, exemplify the challenge of targeting specific cytokines (Alsharawneh *et al.*, 2024). However, the practical application of these medicines is fraught with more challenges, including the requirement for active monitoring and specialized care, as well as keeping patients compliant (Yacoub *et al.*, 2025). Future investigations are designed to address such matters by focusing on bespoke medicine, contemporary modalities, biomarker identification, and supplementary delivery systems, aiming to increase the potency, save the adverse effects, and further the control of medicines aimed at cytokines (Yi *et al.*, 2024).

Emerging Therapeutic Targets

The hallmark of IBD, a chronic gastrointestinal disorder, is ongoing inflammation. Environmental, immunological, and genetic variables interact intricately to produce it. CD and UC are both manifestations of IBD (Molinelli *et al.*, 2015).

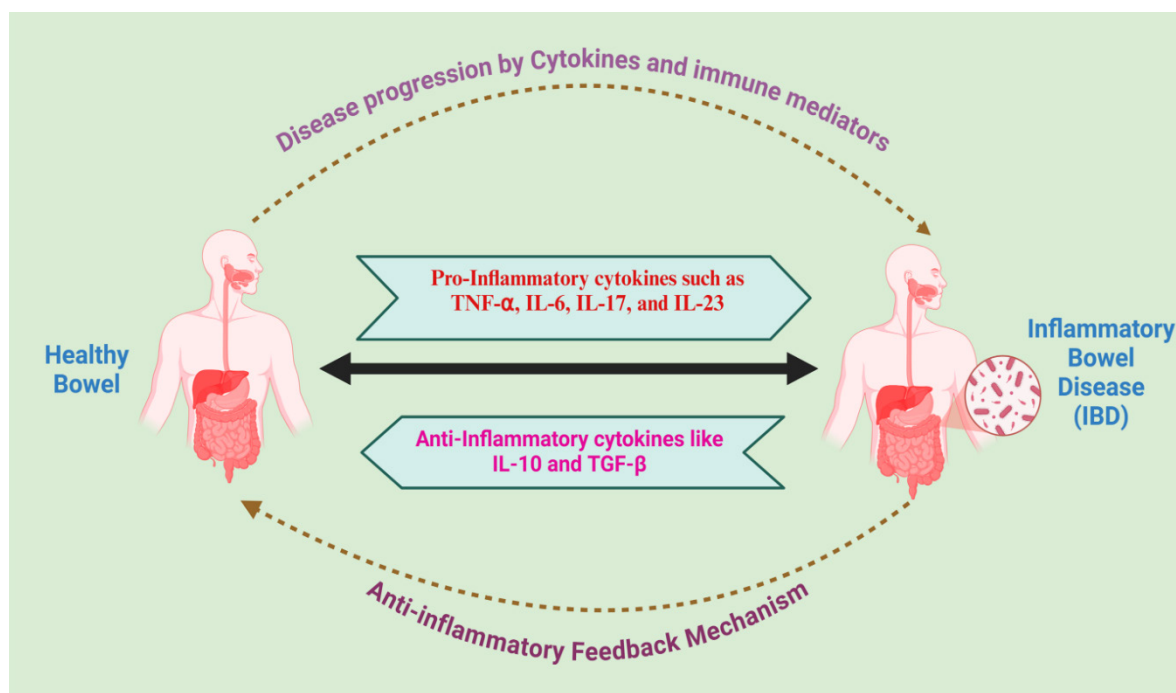


Figure 1: Targeting immune mediators in IBD.

Table 1: Effect of cytokine families in IBD.

Cytokine Family	Subgroups	Source of Production	Key Mechanism in IBD	Impact on IBD
TNF	TNF- α , TNF- β	Macrophages, T cells, dendritic cells	Activates NF- κ B signaling, promotes leukocyte recruitment and epithelial injury	Generates pro-inflammatory cytokines and angiogenesis, induces cachexia, aids T-cell resistance to apoptosis, and causes epithelial cell death.
Interferons (IFN)	IFN- α , IFN- β , IFN- ω , IFN- γ	T cells, NK cells, plasmacytoid dendritic cells	Enhances antigen presentation, macrophage activation, and epithelial immune responses	Encourages epithelial renewal and IL-10 production, increases antigen processing, activates macrophages, and may induce epithelial cell death.
Colony-Stimulating Factors	G-CSF, GM-CSF, M-CSF	Macrophages, endothelial cells, fibroblasts	Stimulates differentiation and survival of granulocytes and macrophages	Encourages myeloid cell growth and maturation, influencing intestinal immune defense and inflammation.
Interleukins	IL-1, IL-18, IL-33, IL-36, IL-38, IL-4, IL-6, IL-10, IL-11, IL-13, IL-22, IL-9	T helper cells, macrophages, dendritic cells, epithelial cells	Regulates Th1/Th2/Th17 responses, epithelial barrier function, and immune tolerance	Exhibits pro-inflammatory, anti-inflammatory, and pleiotropic effects; modulates mucosal inflammation, tissue repair, and immune homeostasis.
Chemokines	CXCL8 (IL-8), CCL2, CCL20, CXCL10	Epithelial cells, macrophages, fibroblasts	Recruits neutrophils, monocytes, and lymphocytes to inflamed mucosa	Amplifies leukocyte trafficking and sustains chronic intestinal inflammation.
Transforming Growth Factors	TGF- β 1, TGF- β 2, TGF- β 3	Regulatory T cells, epithelial cells, fibroblasts	Controls immune tolerance and tissue remodeling	Promotes mucosal healing and fibrosis; dysregulation contributes to chronic inflammation and strictures.

JAK Inhibitors

These drugs utilize an inhibition of the JAK enzyme which ultimately limits STAT protein phosphorylation and activation, thus decreasing inflammatory gene transcription. JAK inhibitors are particularly beneficial for this affliction due to their ability to target multiple cytokines simultaneously (Subih *et al.*, 2024). The mechanistic role of JAK inhibitors in Crohn's disease, and inhibitors of JAK in Crohn's disease is depicted in Figure 3 (Sandborn *et al.*, 2008). Mechanism of action IL-23, JAK inhibitors, Integrin α 4 β 7 (LPAM-1), Sphingosine-1-Phosphate (S1P) Modulators, TL1A (TNFSF15), Microbiome Modulation, TLR agonists, Stem cell therapies are given in Table 2.

Cytokine Networks as Key Therapeutic Targets

Divergent cytokines have similar but opposing functions in the pathogenesis of inflammatory disease and cytokine networks mediate both of these processes (Aldarawsheh *et al.*, 2024). As a result of its role in amplifying inflammatory reactions and recruiting immune cells, TNF- α has traditionally been

viewed as a target. Two of the first anti-TNF- α biologics to alter the treatment of IBD, psoriasis, and RA were infliximab and adalimumab (Al-Akash *et al.*, 2024). However, there remain significant problems such as infection risk, loss of efficacy, and resistance development. Although they are not without risk of infections and liver dysfunction, such therapies targeting IL-6 (e.g., tocilizumab) would be uniquely beneficial in both rheumatoid arthritis and the CRS. Similarly, Anakinra and Canakinumab development aimed to inhibit IL-1 β , an inflammatory amplifier, which has both humanized the treatment of gout and autoinflammatory syndromes. However, the effect of these treatments on complicated disorders is not so great, and they can be taken only at regular intervals (Balzola *et al.*, 2012). The IL-23/IL-12 pathway, which regulates T-helper cell responses, is a major contributor to chronic inflammation. IL-23 inhibitors, such as Ustekinumab and Guselkumab, have a slow onset of action and it is challenging to pinpoint who will respond to treatment, despite their broad anti-inflammatory effects in IBD and psoriasis. Secukinumab and Ixekizumab are IL-17 pathway inhibitors that are relevant to Th17-mediated

inflammation. TGF- β is a complex and promising therapeutic target that modulates immunological tolerance while inducing fibrosis. Indirect modulation of IFN- γ (critical for macrophage activation) is achieved using JAK inhibitors. These inhibitors are effective in cytokine-driven tumorigenesis, but they threaten antimicrobial immunity (Alsaraireh *et al.*, 2024). GM-CSF is one of the mediators involved and also activates neutrophils and macrophages to help with inflammation (Alfanash *et al.*, 2025). There is limited long-term safety information available about similar agents; however, inhibitors, like mavrilimumab, are promising in RA and other conditions including cytokine storms associated with COVID-19 (Feagan *et al.*, 2017).

Translating Research to Clinical Practice

The discovery of novel treatments for IBD requires the application of cytokine research to clinical settings. Early trials have shown that clinical and endoscopic outcomes have improved significantly, which is encouraging. Recently, tofacitinib and other Janus Kinase (JAK) inhibitors have been introduced, acting on intracellular cytokine signaling pathways (Hendy *et al.*, 2025). It's an interesting new scientific observation. While injectable biologics fail people, they may benefit from a systemic option in the form of JAK inhibitors (Yadav *et al.*, 2026). However, they can cause thromboembolic events and other side effects,

requiring close monitoring during their use. These are not the only forthcoming data; studies of other target cytokines, such as IL-6 and IL-17, are being conducted. Given IL-17's protective role in the gut mucosa, IL-6 antagonists are promising candidates for dampening chronic inflammation while IL-17 antagonists have produced inconsistent outcomes in inflammatory bowel conditions (Higgins *et al.*, 2019). These include optimization of therapy through the use of biomarkers, and therapeutic medication monitoring. Those with refractory disease may also respond to step-up or combination treatment strategies. Precision medicine may one day revolutionize IBD treatment as well by customizing therapy to individuals' distinct cytokine profiles. Longitudinal studies will also need to be performed to understand how modulation of cytokine responses may affect disease course and patient outcomes over longer periods. Despite much progress, we still have a long way to go before these treatments are optimized, made safer, and rendered broadly available to patients around the world (Yeshe *et al.*, 2020).

DISCUSSION

Inflammatory Bowel Disease (IBD) is a complex, chronic immune-mediated disorder characterized by persistent intestinal inflammation resulting from interactions among genetic

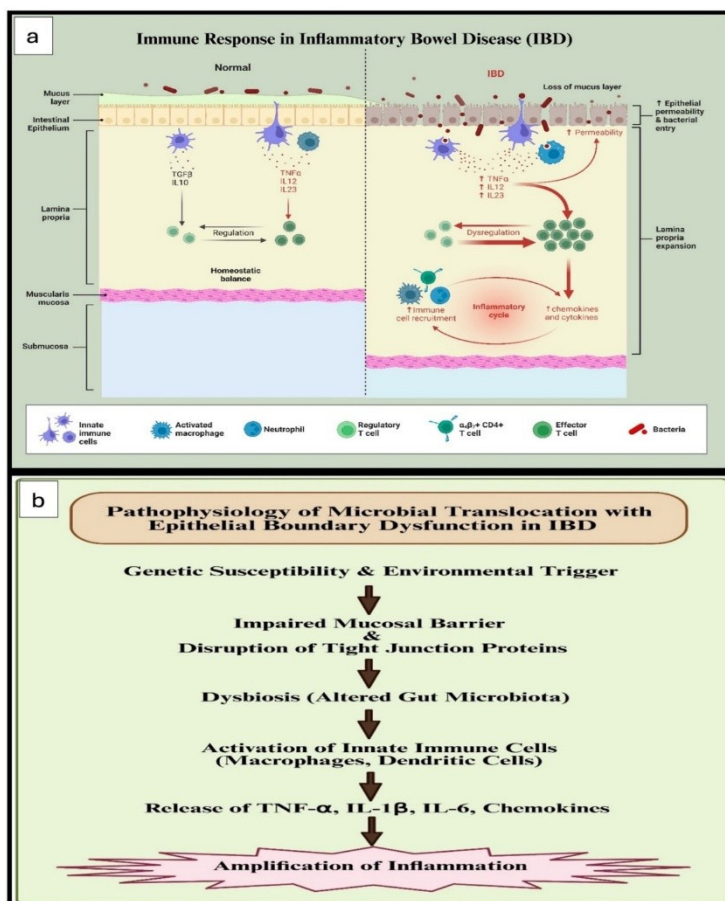


Figure 2: Immune Activation and Barrier Dysfunction.

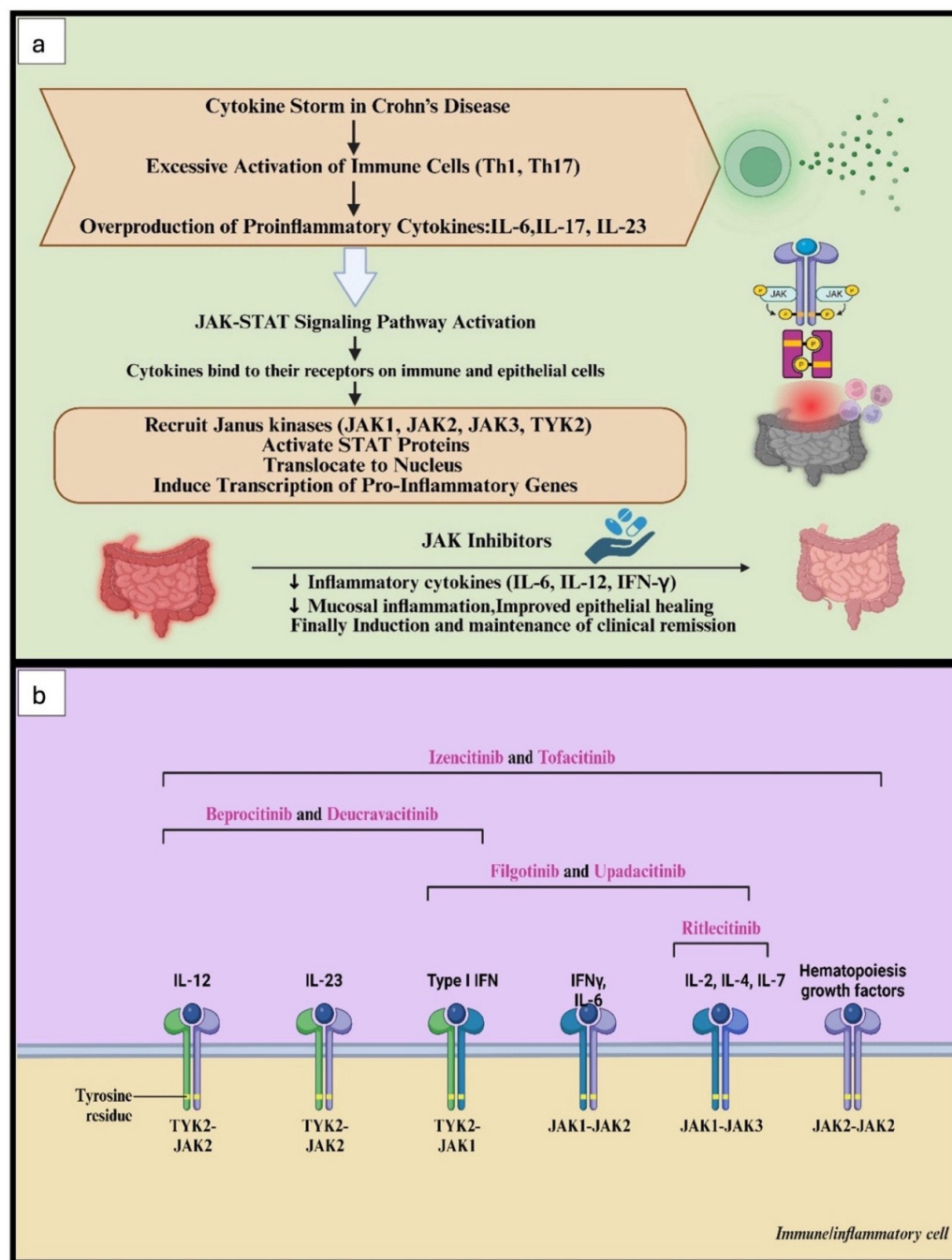


Figure 3: Mechanistic Role of JAK Inhibitors in Crohn's Disease.

susceptibility, environmental triggers, gut microbiota dysbiosis, and immune dysregulation. A growing body of evidence demonstrates that cytokines play a central role in orchestrating the inflammatory responses underlying both Crohn's Disease (CD) and Ulcerative Colitis (UC). Pro-inflammatory cytokines, including TNF- α , IL-6, IL-17, and IL-23, contribute to immune cell activation, epithelial barrier disruption, and sustained mucosal inflammation, whereas anti-inflammatory cytokines such as IL-10 and TGF- β are essential for maintaining immune homeostasis and limiting tissue damage. The clinical success of anti-TNF agents has validated cytokine-targeted therapy as an

effective strategy for IBD management. However, a substantial proportion of patients exhibit primary non-response or develop secondary loss of response over time, highlighting the heterogeneity of disease mechanisms and the need for alternative therapeutic approaches. The development of IL-12/23 and selective IL-23 inhibitors has expanded treatment options and demonstrated favorable efficacy and safety profiles in patients with moderate-to-severe disease. Similarly, JAK inhibitors have emerged as promising oral therapies by targeting multiple cytokines signaling pathways simultaneously. Despite these advances, challenges remain in optimizing treatment selection,

predicting therapeutic response, and minimizing adverse effects associated with long-term immunosuppression. Increasing evidence suggests that cytokine expression patterns, genetic markers, and microbiome signatures may serve as valuable biomarkers for personalized therapy. Furthermore, emerging strategies such as dual-target biologics, anti-fibrotic agents, stem cell therapies, and microbiome-based interventions may address unmet clinical needs and improve long-term outcomes. Overall, understanding the intricate cytokine networks involved in IBD pathogenesis has transformed therapeutic development and continues to drive innovation toward more precise, effective, and individualized treatment strategies for patients with IBD.

FUTURE PERSPECTIVES AND RESEARCH GAPS

Their prominent role in the mechanisms underlying immune-mediated signaling and inflammatory processes represents the most important explanation for the major contribution of cytokines to the pathogenesis of IBD, including CD and UC. Recent studies have highlighted the exciting potential of targeting cytokine networks in future inflammatory bowel disease therapeutics (Saad *et al.*, 2016). Inflammatory pathways in IBD involve cytokine signaling networks, particularly those mediated by IL-23 and TNF- α . These changes are also changing the landscape of therapy of IBD and pathways targeting pathways such as monoclonal antibodies against IL-23 and inhibitors of TNF- α . The findings of previous studies identify the novel cytokines and their receptors (IL-36 and IL-10) with a role in anti-inflammatory response which has been precisely adjusted by Antra-1 (Jansen *et al.*, 2022). Moreover, single-cell transcriptomic

and "omics" technologies are helping in decoding the complexity of this cytokine interaction and their potential involvement in the pathogenesis of IBD, thus paving the path for personalized therapeutics. There are also a variety of newer therapeutic alternatives that have been developed beyond the biologics at this point. Some of these options include JAK inhibitors, anti-integrin agents, and sphingosine-1-phosphate receptor modulators. Alternative pharmacological approaches for patients unresponsive to traditional medications (Bretto *et al.*, 2023; Das *et al.*, 2024; Pathak, Sharma, *et al.*, 2024; Sharma, Kaushik, *et al.*, 2024; Vebr *et al.*, 2023). Moreover, integrating biomarkers into treatment decisions could ensure that patients are targeted with therapies tailored to their cytokine profiles. Computational models and gene editing tools (e.g. CRISPR) for direct modulation of cytokine networks are currently being studied and developed (Chandra *et al.*, 2024; Halagali *et al.*, 2024; Pathak, Kaur, *et al.*, 2024; Ray *et al.*, 2024; Sharma, Kumar, *et al.*, 2024). Implementation of these approaches could transform the repair of immunological dysregulation in inflammatory bowel disease to curing agents other than symptom control. Recruiting and retention for clinical trials are frequently rate-limiting processes in the creation of novel treatments, and there are several difficulties with IBD clinical trial recruiting at the moment (Harris *et al.*, 2019). Thoroughly conducted Randomized Controlled Trials (RCTs) have propelled advancements. These include premarketing registrational studies that show the effectiveness and safety of new treatments as well as post marketing, extensive therapeutic strategy trials that have expanded the vision and aspirations for the possibility of disease modification and positively altering the otherwise debilitating

Table 2: Mechanism of action IL-23, JAK inhibitors, Integrin $\alpha 4\beta 7$ (LPAM-1), Sphingosine-1-Phosphate (S1P) Modulators, TL1A (TNFSF15), Microbiome Modulation, TLR Agonists, Stem Cell Therapies.

Sl. No.	Drug Target	Mechanism of Action	Illustrations	Positive aspects	Drawbacks
1.	IL-23 Inhibitors	The IL-23/Th17 inflammatory axis is disrupted when the p19 component of IL-23 is the focus.	Risankizumab, Guselkumab, Mirikizumab	Maximized cytokine manipulation with lower infection risk Validated efficacy in achieving remission and endoscopic improvement in individuals with moderate-to-severe inflammatory bowel disease.	Expensive not effective for all patients due to variability in their medical conditions.
2.	JAK inhibitors	They obstruct the JAK-STAT pathway by attaching to multiple pro-inflammatory cytokines. Diseases Introduce new drugs that target the Janus kinase (JAK) enzymes.	Tofacitinib, Upadacitinib, Filgotinib	Oral; broad-based cytokine inhibition	Issues with resistance, high cost, and long-term adverse events (infection, thromboembolism).

Sl. No.	Drug Target	Mechanism of Action	Illustrations	Positive aspects	Drawbacks
3.	Integrin $\alpha 4\beta 7$ (LPAM-1)	Stops lymphocytes from moving to the GIT by stopping the interaction between $\alpha 4\beta 7$ integrin and MAdCAM-1	Vedolizumab (approved); targeted anti-trafficking agents.	Fasting; Site-targeted GI intervention reduces systemic immunosuppression; beneficial in ulcerative colitis.	Limited efficacy in CD; late onset of response; identification of biomarkers to predict outcomes.
4.	Sphingosine-1-Phosphate (S1P) Modulators	Inhibits chemotaxis of lymphocytes out of the lymph nodes therefore reducing immune cell infiltration in the GI tract.	Ozanimod (approved); etrasimod (in phase 3 studies).	Oral dosing; reduces inflammation with little systemic immune suppression.	Potential cardiovascular and hepatic adverse effects; difficulties in monitoring and adherence.
5.	TL1A (TNFSF15)	Regulates T-helper cells and innate immunity by modulating TNFSF15 activity.	PF-06480605 and PRA023 (in studies).	Applicability to personalized therapy $\Leftrightarrow$ targets cytokine dysregulation inherent to IBD.	Data on longer-term efficacy are hard to come by; in addition, working out which patient subgroups are most likely to respond.
6.	Microbiome Modulation	Probiotics, prebiotics, or Fecal Microbiota Transplantation (FMT) restores gut microbiota equilibrium.	There are many experiments on fecal microbiota transplantation and genetically modified microbes being performed now	Targets the underlying cause of dysbiosis; has a non-invasive approach. Potential.	Strain in patient response; item and administration matter consistency; regulatory hurdles.
7.	Toll-like Receptor (TLR) Agonists	Essential for innate immune responses regulating the activation or inhibition of specific TLRs.	Cobitolimod is a TLR-9 agonist in phase 2 studies.	Localized therapy reduces systemic exposure; positive for ulcerative colitis.	Limited efficacy in Crohn's disease; formulations allow consistent output.
8.	Stem Cell Therapies	Contribute significantly to tissue regeneration and, via MSCs, regulate immunological responses.	CD patients with perianal fistulas, darvadstrocel is the best treatment.	Facilitates mucosal repair; potentially curative in fistulizing disease.	Higher costs; complex distribution mechanisms; lack of effectiveness.

and progressive natural history of IBD (Ma *et al.*, 2024). For patients with moderate to severe illness, the innovative IL-23 inhibitor Risankizumab-rzaa (Skyrizi) offers a fresh strategy.

The future of Inflammatory Bowel Disease (IBD) management is expected to be shaped by advances in precision medicine, biomarker-guided therapy, and the development of highly selective immunomodulatory agents. Although current biologics and small-molecule therapies have significantly improved disease outcomes, substantial challenges remain, including primary non-response, secondary loss of response, adverse effects, and high treatment costs. Future research should focus on identifying reliable molecular, genetic, microbiome,

and cytokine-based biomarkers that can predict therapeutic response and enable personalized treatment strategies. Emerging therapeutic approaches targeting novel cytokine pathways, including selective IL-23 inhibitors, dual cytokine blockade, and next-generation JAK inhibitors, hold promise for improving efficacy while minimizing systemic immunosuppression. Advances in multi-omics technologies, artificial intelligence, and machine learning may further enhance disease stratification and facilitate the identification of new therapeutic targets. In addition, growing evidence supports the role of the gut microbiome in IBD pathogenesis, encouraging the development of microbiome-based interventions such as engineered probiotics, fecal microbiota

transplantation, and microbial metabolite therapies. Future clinical trials should emphasize long-term safety, mucosal healing, prevention of fibrosis, and quality-of-life outcomes. Cytokine networks and immune-cell interactions will likely lead to innovative combination therapies and more effective disease-modifying treatments, ultimately improving long-term remission rates and reducing the global burden of IBD.

Despite significant advances in cytokine-targeted therapies for Inflammatory Bowel Disease (IBD), substantial gaps remain in understanding the complex interactions among cytokine networks, immune cells, host genetics, and the gut microbiome. Current treatments are limited by variable patient responses, secondary loss of efficacy, and treatment-associated adverse effects. Furthermore, reliable predictive biomarkers and personalized therapeutic strategies remain inadequately developed, necessitating further mechanistic and translational research.

Furthermore, heterogeneity in study design, patient populations, therapeutic interventions, and outcome assessment across clinical and preclinical studies may influence the comparability and generalizability of the findings. The absence of a systematic review methodology and quantitative meta-analysis may also limit the strength of the conclusions regarding cytokine-targeted therapies in inflammatory bowel disease.

CONCLUSION

IBD leads to a severe burden on society, which includes conditions such as CD and UC, where cytokine-mediated immune signaling is contributing more and more to our knowledge of their etiology. Targeting cytokine networks as a potential cornerstone to future therapeutic modalities in IBD by next-generation biologics was proposed in recent studies. There has been considerable knowledge gained in our understanding of cytokine biology since then, especially IL-23 and TNF- α , but also beyond these two pathways. Involved in inflammatory pathways related to IBD with potential for improved therapeutic targets. Because they control the process, management of IBD may need a different approach, which acknowledges the numerous genetic, microbiological, and environmental components that lead to the disease. It is unlikely that an already accepted approach to treatment would be effective in an individual case, highlighting the need for tailoring any therapy.

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ABBREVIATIONS

IBD: Inflammatory Bowel Disease; **CD:** Crohn's Disease; **UC:** Ulcerative Colitis; **JAK:** Janus Kinase; **NOD2:** Nucleotide-Binding Oligomerization Domain-Containing Protein 2; **RIP2:** Receptor-Interacting Serine/Threonine-Protein Kinase 2; **MAPK:** Mitogen-Activated Protein Kinase; **IL-23R:** Interleukin-23 Receptor; **GWAS:** Genome-Wide Association Study; **SNPs:** Single Nucleotide Polymorphisms; **PAMPs:** Pathogen-Associated Molecular Patterns; **PRRs:** Pattern Recognition Receptors; **TLRs:** Toll-Like Receptors; **IECs:** Intestinal Epithelial Cells; **MLCK:** Myosin Light Chain Kinase; **DR3:** Death Receptor 3; **STAT3:** Signal Transducer and Activator of Transcription 3; **sIL-6R:** Soluble Interleukin-6 Receptor; **TH:** T Helper Cell; **NF- κ B:** Nuclear Factor Kappa B; **TNF:** Tumor Necrosis Factor; **RCTs:** Randomized Controlled Trials; **APC:** Antigen-Presenting Cell; **CRS:** Cytokine Release Syndrome; **DC:** Dendritic Cell; **FMT:** Fecal Microbiota Transplantation; **GI:** Gastrointestinal; **MadCAM-1:** Mucosal Vascular Addressin Cell Adhesion Molecule-1; **MDP:** Muramyl Dipeptide; **MSCs:** Mesenchymal Stem Cells; **NK:** Natural Killer Cell; **NKT:** Natural Killer T Cell; **RA:** Rheumatoid Arthritis; **RIPK1:** Receptor-Interacting Serine/Threonine-Protein Kinase 1; **TGF- β :** Transforming Growth Factor-Beta; **Treg:** Regulatory T Cell.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

B.S., S.N.K., M.C., A.S., A.M., P.K., A.K., M.S., S.S., and H.S.: Contributed to the conceptualization of the review, literature collection and analysis, manuscript drafting, critical revision, and approval of the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

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