Review

Discovery Medicine 2026; 38(211): 2353–2365
https://doi.org/10.24976/Discov.Med.202638211.185

Microbiota-Immune Interaction Landscape of Treg/Th17 Dynamic Balance in Regulating Mucosal Immune Homeostasis: From Molecular Switches to Precision Intervention in Inflammatory Bowel Disease

Jing Wang[1,2], Mengwei Sun[3], Baoqing Zhang[4,*]

[1]The First Clinical Medical College, Shandong University of Traditional Chinese Medicine, 250355 Jinan, Shandong China
[2]Preventive Treatment of Disease Department, Qingdao Traditional Chinese Medicine Hospital (Qingdao Hiser Hospital Affiliated of Qingdao University), 266033 Qingdao, Shandong, China
[3]Preventive Treatment of Disease Department, Pingdu Traditional Chinese Medicine Hospital, 266700 Pingdu, Shandong, China
[4]Department of Pediatrics, Affiliated Hospital of Shandong University of Traditional Chinese Medicine, 250011 Jinan, Shandong, China
*Correspondence: 16600245720@163.com (Baoqing Zhang)
Submitted: 29 May 2026 Revised: 30 June 2026 Accepted: 13 July 2026 Published: 24 August 2026

Mucosal inflammatory disorders, including inflammatory bowel disease (IBD), have increased steadily in prevalence worldwide. These conditions follow a protracted clinical course with high complication rates and no curative therapies. The breakdown of intestinal mucosal immune homeostasis is central to their pathogenesis. Among the key regulatory pathways, the balance between regulatory T cells (Tregs) and T helper 17 (Th17) cells is a pivotal determinant of mucosal immune tolerance and the containment of excessive inflammatory responses. This review synthesizes current knowledge on the biological characteristics, differentiation regulatory networks, and functional crosstalk between Tregs and Th17 cells. We describe how the mutual antagonism between the lineage-specific transcription factors Forkhead box P3 (Foxp3) and retinoic acid-related orphan receptor gamma t (RORγt) acts as a core molecular switch governing this balance, while T cell receptor (TCR) signaling, the cytokine microenvironment, and epigenetic modifications form its upstream regulatory network. We further discuss the precise mechanisms by which commensal microbiota and their metabolites, intestinal epithelial barrier integrity, and regional heterogeneity of mucosal tissues modulate the Treg/Th17 balance, and we dissect how disruption of this balance drives IBD onset and progression. We also summarize Treg/Th17-related biomarkers for IBD diagnosis and disease monitoring and emerging therapeutic strategies targeting this balance. Finally, we outline priority research directions, emphasizing the translational potential of single-cell multi-omics and spatial transcriptomics for achieving tissue-specific precision regulation of Treg/Th17 balance in IBD.

Keywords: IBD; Treg/Th17 balance; mucosal immune homeostasis; gut microbiota; immune resilience

Introduction

The intestinal mucosa serves multiple essential functions, including nutrient absorption, commensal microbiota colonization, and pathogen defense. Maintenance of mucosal immune homeostasis is a cornerstone of systemic health [1]. The intestinal mucosal immune system must precisely eliminate invading pathogens while sustaining immune tolerance to food antigens and commensal microbiota. Disruption of this tolerogenic balance triggers persistent chronic inflammation, most notably manifesting as inflammatory bowel disease (IBD) [2].

IBD, comprising Crohn disease (CD) and ulcerative colitis (UC), is a group of chronic, non-specific inflammatory disorders of the gastrointestinal tract. Its global prevalence has risen steadily in recent decades, making it a major public health concern [3]. Current management relies on anti-inflammatory and immunosuppressive therapies, which provide symptomatic relief for some patients but are limited by insufficient response rates, high adverse event rates, and frequent relapse. These limitations stem from an incomplete understanding of the core pathological mechanisms underlying IBD [4].

Evidence indicated that functional imbalance of $CD4^+$ T cell subsets in the intestinal mucosa is a central pathological event driving IBD onset and progression [5]. Among these subsets, the regulatory T cells (Treg)/T helper 17 (Th17) axis, defined by the differentiation balance and functional crosstalk between Th17 and Treg cells, acts as the central regulatory hub governing mucosal immune homeostasis [6]. Th17 cells dominate pro-inflammatory immune responses and host defense against extracellular pathogens [7], whereas Treg cells are responsible for maintaining immune tolerance and suppressing excessive inflammation [8]. The two lineages are closely linked in their differentiation programs: they share upstream reg-

ulatory signals including transforming growth factor-beta (TGF-beta), while exerting direct antagonism via their master lineage transcription factors Forkhead box P3 (Foxp3) and retinoic acid-related orphan receptor gamma t (RORγt), endowing them with high plasticity in differentiation and function [9]. Within the intestinal mucosal microenvironment, multiple factors including commensal microbiota, epithelial barrier integrity, and cytokine networks coordinately regulate Treg/Th17 balance [10]; disruption of this balance triggers persistent intestinal mucosal inflammation and drives IBD progression [11,12].

Despite extensive research on Treg/Th17 balance in IBD, several key questions remain unresolved: the precise regulatory mechanisms underlying microbiota-immune cell crosstalk in the mucosal microenvironment, the tissue-specific functional characteristics of distinct cell subsets, and the bottlenecks limiting clinical translation of targeted interventions [13]. In this review, we systematically summarize the reciprocal regulatory mechanisms of Tregs and Th17 cells, the regulatory networks within the mucosal microenvironment, the pathological processes by which imbalance drives IBD, and the research advances in related diagnostic biomarkers and therapeutic strategies. We also analyze current challenges and future directions, with the aim of providing novel insights for mechanistic research and precision clinical management of IBD.

Biological Characteristics and Interactive Regulatory Mechanisms of Tregs and Th17 Cells

Tregs and Th17 cells are both derived from naïve $CD4^+$ T cells. They exhibit close lineage relationships during differentiation, while forming functional antagonism via core transcriptional regulation, and their dynamic balance constitutes the molecular basis for maintaining mucosal immune homeostasis.

Cell Phenotypic Characteristics and Mucosal Tissue Specificity

The differentiation and function of Th17 cells are dominated by the transcription factor RORγt (encoded by the *RORC* gene). These cells mainly secrete pro-inflammatory cytokines including interleukin (IL)-17A, IL-17F, IL-6, and tumor necrosis factor-α (TNF-α), and have a critical role in host defense against extracellular pathogens and the pathogenesis of autoimmune diseases [14]. Treg cells are specifically regulated by the transcription factor Foxp3 (encoded by the FOXP3 gene in humans and Foxp3 in mice). They exert immunosuppressive functions mainly via secretion of anti-inflammatory cytokines such as IL-10 and TGF-β and direct cell-cell contact, to maintain systemic immune tolerance [15].

In peripheral non-lymphoid tissues such as the intestinal mucosa, both Tregs and Th17 cells exhibit significant phenotypic and functional heterogeneity compared with their counterparts in circulating lymphoid tissues. Tissue-resident Tregs in the intestinal mucosa, in addition to their well-defined immunosuppressive functions, participate in the repair of mucosal barrier structure and maintenance of homeostasis via bidirectional crosstalk with intestinal epithelial cells (IECs) and commensal microbiota, representing a key cell subset for mucosal immune tolerance. Tissue-resident Th17 cells specific for intestinal commensal bacteria are not limited to exerting pro-inflammatory immune responses under homeostatic conditions, they can also mediate immunoregulatory effects and suppress excessive activation of effector T cells via upregulation of cellular musculoaponeurotic fibrosarcoma oncogene homolog (c-MAF) and IL-10 expression [16].

Recent seminal studies have revealed that Tregs and Th17 cells possess high lineage plasticity, and can undergo interconversion in specific microenvironments to form intermediate subsets with characteristics of both lineages, mainly including IL-17-secreting ($IL\text{-}17^+$) Tregs and IL-10-secreting ($IL\text{-}10^+$) Th17 cells. These intermediate subsets are abundant in the intestinal mucosa, and their abundance and functional status directly influence mucosal immune homeostasis. Under homeostatic conditions, $IL\text{-}10^+$ Th17 cells restrict excessive inflammatory responses, whereas in inflammatory microenvironments, the immunosuppressive function of $IL\text{-}17^+$ Tregs is significantly impaired, which in turn exacerbates local inflammation [17]. This finding breaks the traditional binary antagonistic view of Th17 and Treg cells, providing a novel perspective on the regulatory mechanisms of mucosal immune homeostasis.

Core Regulatory Network of Cell Differentiation

The lineage commitment of naïve $CD4^+$ T cells to Tregs or Th17 cells is collectively determined by a complex regulatory network consisting of TCR signaling, the cytokine microenvironment, and epigenetic modifications, among which the cytokine microenvironment is the key factor governing differentiation direction [18].

TGF-β is the core cytokine regulating the direction of Treg/Th17 differentiation. In the presence of low concentrations of TGF-β alone, it induces Foxp3 expression in naïve $CD4^+$ T cells and drives their differentiation into Tregs. In contrast, when TGF-β is present in combination with pro-inflammatory cytokines such as IL-6 and IL-1β, it inhibits Foxp3 expression, upregulates RORγt transcription, and drives the differentiation of naïve T cells into Th17 cells [19]. In addition, IL-23, an essential regulatory factor for maintaining the stability and pro-inflammatory function of Th17 cells, further upregulates the expression of RORγt and IL-17 via activation of the signal transducer and activator of transcription 3 (STAT3) pathway [20]. Conversely, IL-2 stabilizes Foxp3 expression and maintains the immunosuppressive function of Tregs via activation of the STAT5 pathway [21].

The strength and duration of TCR signaling activation also participate in regulating the differentiation direction of naïve $CD4^+$ T cells. High-intensity TCR signaling preferentially drives Th17 cell differentiation, whereas low-intensity, sustained TCR signaling is more conducive to the induction and stabilization of Tregs [22]. In the intestinal mucosa, continuous stimulation by antigens derived from commensal microbiota precisely regulates the local Treg/Th17 differentiation ratio via modulating TCR signal strength, thereby maintaining mucosal immune tolerance [23].

Epigenetic modifications precisely regulate the lineage stability and functional status of Treg/Th17 cells at the transcriptional level. Among them, itaconate inhibits Th17 cell differentiation by regulating chromatin accessibility to reduce the binding efficiency of RORγt to the Il17a promoter. α-synuclein drives Th17 cell differentiation and impairs the function and stability of Tregs via epigenetic regulation to promote RORC transcription [24,25]. Furthermore, targeted RORγt agonists/inhibitors can bidirectionally regulate Treg/Th17 differentiation via directly modulating the transcription of target genes, further validating the central hub role of RORγt in differentiation regulation.

Core Molecular Switch of Balance Regulation: Mutual Antagonism Between Foxp3 and RORγt

The core of the dynamic Treg/Th17 balance lies in the direct mutual antagonism between the two master lineage-specific transcription factors, Foxp3 and RORγt. The relative expression level and activity of these two factors directly determine the differentiation direction and functional phenotype of naïve $CD4^+$ T cells.

Foxp3 and RORγt can mutually inhibit each other's transcriptional activity via direct protein-protein interaction. Foxp3 binds to RORγt and blocks the transcriptional activation of its pro-inflammatory target genes, thereby inhibiting Th17 cell differentiation. Conversely, RORγt represses the transcriptional activity of Foxp3, impairing the immunosuppressive function of Tregs. The expression levels of the two factors show a significant negative correlation: in the inflamed intestinal mucosa of IBD patients, high RORγt expression coexists with low Foxp3 expression, directly driving excessive Th17 activation and Treg functional deficiency [11].

Numerous interventional studies have further confirmed the central role of this antagonistic mechanism. The RORγt inhibitor GSK805 markedly inhibits excessive proliferation of Th17 cells, reverses the reduction of Tregs in inflammatory microenvironments, and restores Treg/Th17 balance. Salidroside downregulates RORγt expression and upregulates Foxp3 levels via inhibiting the STAT3/hypoxia-inducible factor-1α (HIF-1α)/RORγt pathway, thereby correcting Treg/Th17 imbalance in models of aplastic anemia and colitis [12]. The identification of this core molecular switch provides key targets for interventional strategies targeting Treg/Th17 balance (Fig. 1).

Regulatory Mechanisms of Intestinal Mucosal Microenvironment on Treg/Th17 Balance

The intestinal mucosa constitutes a complex microenvironment formed by commensal microbiota, intestinal epithelial cells, immune cells, and cytokine networks. Within this microenvironment, microbiota-immune cell interactions, epithelial-immune cell crosstalk, and regional heterogeneity of mucosal tissues collectively and precisely govern the dynamic balance of local Treg and Th17 cells [26].

Microbiota-Immune Cell Crosstalk: Differential Regulation by Commensal and Pathogenic Bacteria

The gut microbiota is the dominant factor regulating mucosal Treg/Th17 balance. Commensal bacteria and their metabolites maintain Treg/Th17 balance via multiple pathways, whereas microbiota dysbiosis and pathogenic bacterial invasion disrupt this balance and drive the onset of mucosal inflammation (Fig. 2).

Short-chain fatty acids (SCFAs, mainly including acetate, propionate, and butyrate), the major metabolites of commensal bacteria, act as key mediators in the regulation of Treg/Th17 balance. SCFAs directly promote Foxp3 transcription, drive Treg differentiation and proliferation, and simultaneously inhibit RORγt expression and the pro-inflammatory function of Th17 cells via activating G protein-coupled receptors (GPR41, GPR43) or inhibiting histone deacetylases (HDACs). In addition, SCFAs indirectly suppress excessive Th17 activation by enhancing intestinal epithelial barrier function and reducing the translocation of microbial products [27,28].

Specific commensal genera exert differential regulatory effects on Treg/Th17 balance via distinct pathways. Enrichment of beneficial bacteria such as Lactobacillus, Bacteroides, and Akkermansia significantly increases SCFAs production and restores Treg/Th17 balance under inflammatory conditions. Strains of clusters IV and XIVa of the genus Clostridium enhance local immunosuppressive effects and inhibit the onset of intestinal inflammation via inducing the differentiation of $ROR\gamma t^+$ Tregs in the intestinal mucosa [29,30]. In contrast, pathogenic bacteria such as adherent-invasive Escherichia coli (AIEC) drive excessive Th17 activation and inhibit Treg function via disrupting the gut microbiota structure and activating the Toll-like receptor 4 (TLR4)-nuclear factor κB (NF-κB) pathway, ultimately exacerbating IBD progression [31].

Given the central role of microbiota dysbiosis in disrupting Treg/Th17 balance, remodeling the microbial ecosystem represents a logical therapeutic entry point. Furthermore, microbiota dysbiosis can also trigger disorders of bile acid metabolism, and secondary bile acids affect Treg/Th17 differentiation via regulating the farnesoid X

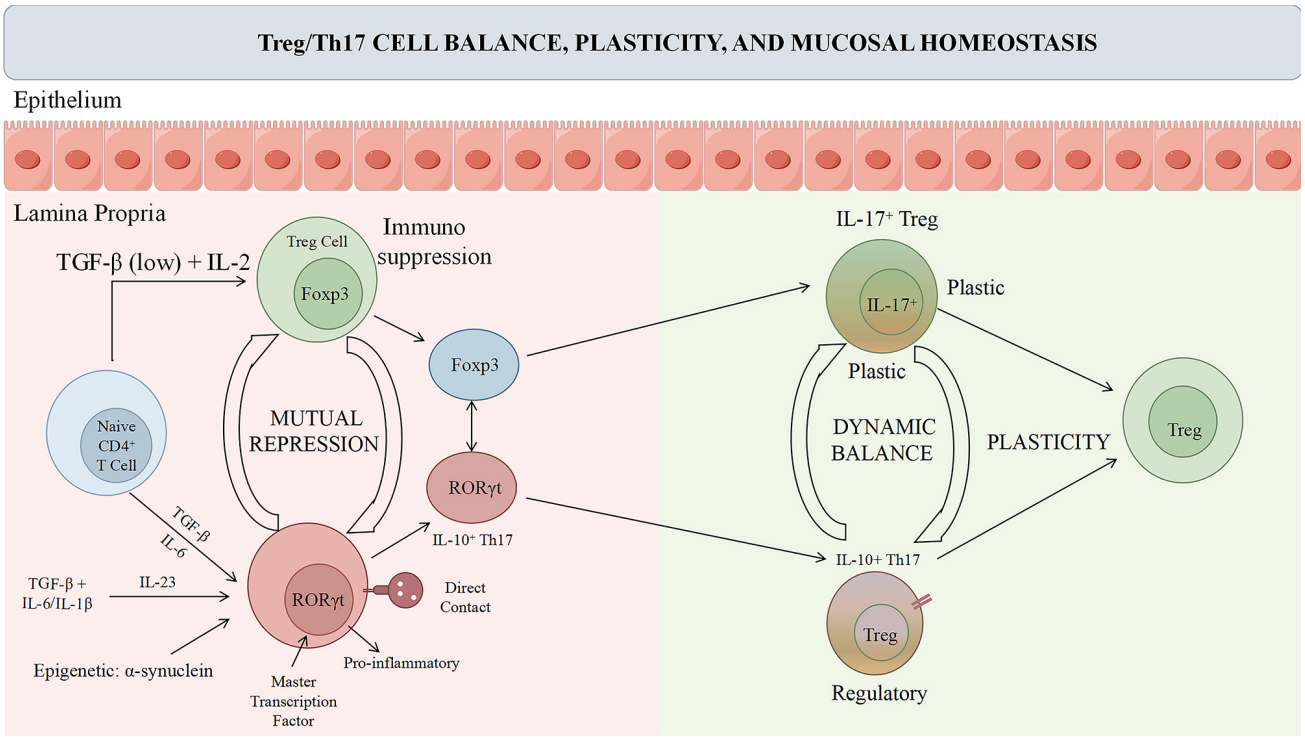

Fig. 1. Regulatory mechanisms of Treg/Th17 cell differentiation, plasticity, and mucosal homeostasis. Naïve $CD4^+$ T cells differentiate into Treg or Th17 lineages governed by specific cytokine milieus and transcriptional networks. Low-dose TGF-β combined with IL-2 induces Foxp3 expression, driving Treg differentiation for immunosuppression. Right: The combination of TGF-β with IL-6, IL-1beit, and IL-23 promotes RORγt-mediated Th17 differentiation, a process enhanced by α-synuclein via epigenetic regulation. The mutual repression between Foxp3 and RORγ serves as the core molecular switch determining the Treg/Th17 balance. In the mucosal microenvironment, both lineages exhibit high plasticity, interconverting into intermediate subsets such as IL-17^+ Tregs and regulatory IL-10^+ Th17 cells. The dynamic balance between these subsets is crucial for maintaining intestinal epithelial integrity and mucosal immune homeostasis. This figure was created using Adobe Photoshop 2022 (Adobe Inc., San Jose, CA, USA). Treg, regulatory T cell; Th17, T helper 17; TGF-β, transforming growth factor-beta; IL, interleukin; RORγt, retinoic acid-related orphan receptor gamma t; Foxp3, Forkhead box P3.

receptor (FXR) and Takeda G protein-coupled receptor 5 (TGR5) signaling, further disrupting mucosal immune homeostasis [32].

Recent technological advances in spatial transcriptomics and spatial multi-omics have provided unprecedented resolution to characterize microbiota-immune interactions *in situ*. A spatial host-microbiome profiling approach applied to pediatric ileal Crohn disease tissues demonstrated that bacterial abundance correlates with disease prognosis and endoscopic severity, with host transcriptional responses to bacteria varying across different tissue regions, providing spatial evidence for microbiota-driven Treg/Th17 dysregulation at the host-microbe interface [33].

Complementing these findings, cross-tissue multi-omics analyses combining spatial transcriptomics and single-cell RNA sequencing have systematically revealed how microbiota absence impacts organ morphology, immune homeostasis, and metabolism, demonstrating marked aberrations in B cells, myeloid cells, and T/NK cells across multiple organs, along with altered mucosal zonation [34]. These integrated approaches have further elucidated that the gut microbiota shapes intestinal epithelial functional zonation and modulates lipid dynamics, while influencing the development and differentiation of immune cells including intraepithelial gamma-delta T cells. Similarly, single-cell technologies have been instrumental in deciphering IBD pathogenesis by uncovering immune cell heterogeneity that bulk sequencing cannot resolve, with recent studies leveraging scRNA-seq to identify distinct immune cell plasticity in IBD and characterize the complex interplay between microbial signals and host immune responses [35]. Furthermore, investigations into colorectal cancer have demonstrated that spatial depletion of specific bacteria in tumor niches disrupts butyrate-HDAC signaling, leading to $CD8^+$ T-cell exhaustion via epigenetic reprogramming, underscoring how spatially defined microbiome-metabolic niches can drive T-cell dysfunction [36]. These spatially resolved multi-omics approaches are now being extended to integrate microbial metatranscriptomics with host transcriptomics, enabling simultaneous reconstruction of host

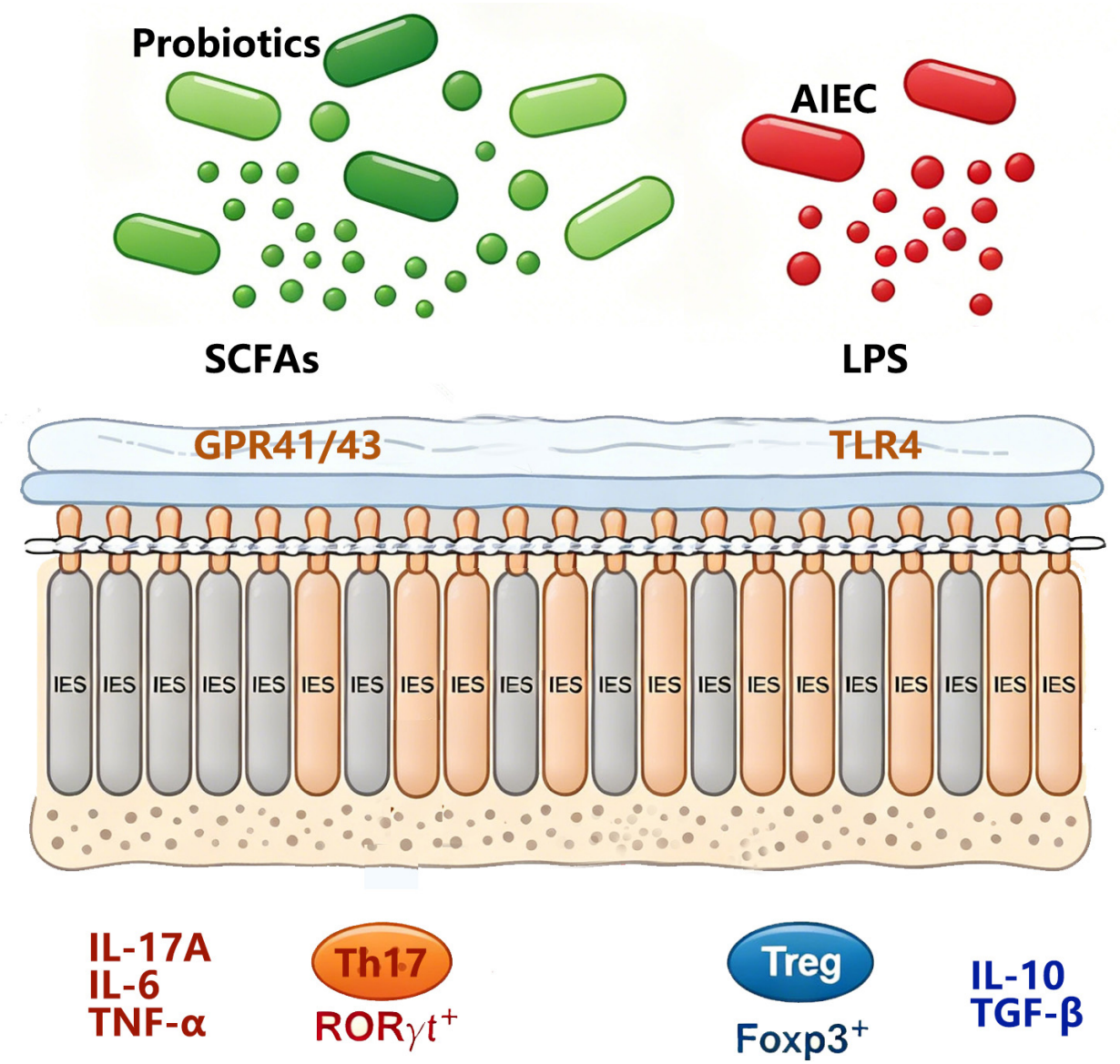

Fig. 2. The crosstalk among gut microbiota, intestinal epithelial cells and immune cells. The intestinal epithelial layer (middle) serves as a physical barrier and signal transducer: it receives microbial metabolites (SCFAs via GPR41/43) from the luminal microbiota (top) and transmits these signals to the lamina propria immune cells (bottom). In the lamina propria, the Treg/Th17 balance is governed by Foxp3–RORγt mutual antagonism. Disruption of this crosstalk creates a self-perpetuating inflammatory loop. This figure was created using Adobe Photoshop 2022 (Adobe Inc., San Jose, CA, USA).

transcriptional and microbiome compositional landscapes to deconvolute host-microbiome circuits and predict functional niches in IBD and CRC [37].

Therefore, based on the above findings indicating the relationship between gut microbiota and the development and progression of diseases, strategies to reshape the gut microbiota through probiotic supplementation and fecal microbiota transplantation (FMT) may effectively correct the Treg/Th17 imbalance in IBD. The underlying mechanism lies in restoring the microbial community structure and its metabolite profiles, with microbial metabolites such as short-chain fatty acids, tryptophan derivatives, and secondary bile acids acting as key signaling molecules that regulate Treg and Th17 differentiation through G protein-coupled receptors, nuclear receptors, and epigenetic modifications [38]. Notably, recent experimental evidence demonstrates that FMT treatment inhibits intestinal $CD4^+$ $ROR\gamma\text{-}t^+$ T cells and modulates immune responses via the JAK-STAT3 signaling pathway, with specific bacterial strains such as *Faecalibacterium prausnitzii* and *Bifidobacterium longum* playing pivotal roles in restoring immune homeostasis [39,40].

Epithelial-Immune Cell Crosstalk: Positive Feedback Regulation of Barrier Function and Immune Balance

The intestinal epithelial barrier serves as a structural physical barrier separating luminal contents from immune cells in the lamina propria, and its integrity is a prerequisite for maintaining Treg/Th17 balance. Bidirectional signaling between IECs and immune cells forms a positive feedback loop that mutually stabilizes barrier function and immune balance.

When the intestinal epithelial barrier is damaged, microbe-associated molecular patterns (MAMPs, such as lipopolysaccharide (LPS) and peptidoglycan) from the intestinal lumen translocate massively into the lamina propria. These MAMPs promote the secretion of pro-inflammatory cytokines such as IL-6 and IL-1β via activating the TLR4-NF-κB pathway and the NOD-like receptor pyrin domain-containing 3 (NLRP3) inflammasome, driving Th17 differentiation while inhibiting the immunosuppressive function of Tregs [41]. In turn, persistent inflammation caused by Treg/Th17 imbalance further aggravates intestinal epithelial barrier damage, forming a malignant positive feedback loop of "barrier damage-immune imbalance-inflammation exacerbation-further barrier disruption".

A direct bidirectional regulatory relationship exists between IECs and Treg/Th17 cells. Tregs promote the proliferation of IECs and the expression of tight junction proteins via secreting anti-inflammatory cytokines such as IL-10 and TGF-β, thereby strengthening barrier function. In contrast, alarmins such as IL-25 and IL-33 released by damaged IECs recruit and activate Th17 cells, exacerbating local inflammation and immune polarization bias [42].

In addition, mucosal-resident γδ T cells act as a bridge between the epithelial barrier and adaptive immunity. Upon microbial stimulation, they secrete IL-17 and simultaneously upregulate the expression of the inhibitory receptor programmed cell death protein 1 (PD-1). The PD-1-mediated negative feedback regulatory pathway inhibits excessive IL-17 release, thereby maintaining the balance between activation and inhibition of mucosal immunity under continuous microbial stimulation and preventing intestinal barrier damage and uncontrolled inflammation [43,44].

IECs serve a dual function as both a physical barrier and a signal transducer. Under homeostatic conditions, IECs receive IL-10 signals from Tregs and maintain tight junctions, forming a positive feedback loop that sustains epithelial integrity and immune tolerance. When the epithelial barrier is damaged, alarmins released by IECs and translocated MAMPs shift the local immune response toward a Th17-dominant state while suppressing Tregs. This transition from tolerance to inflammation represents a critical juncture at which mucosal inflammation may become self-perpetuating.

Regional Heterogeneity of Mucosal Tissues

Significant differences exist in the microenvironment of different mucosal sites (intestine, oral cavity, respiratory tract, etc.), and the regulatory mechanisms of Treg/Th17 balance also exhibit marked regional heterogeneity, among which the regulatory pattern in the intestinal mucosa is highly tissue-specific.

Within the intestinal mucosa, microbiota-derived SCFAs participate in the regulation of Treg/Th17 balance. Distinct intestinal segments exhibit marked differences in microbiota structure, SCFAs concentration, and antigen presentation mode, leading to site-specific differences in the distribution characteristics and regulatory mechanisms of Treg/Th17 cells. Among them, the colon has the highest abundance of microbiota and significantly higher SCFAs concentrations than the small intestine. Accordingly, the proportion of Tregs in the colon is much higher than that in the small intestine, and RORγt$^+$ Tregs are the dominant subset, mainly mediating immune tolerance to commensal microbiota. Tregs in the small intestinal epithelium exhibit a unique phenotype, with significantly downregulated CD25 expression, and their IL-2 dependence and response pattern are distinct from Tregs in other sites, constituting a unique immune regulatory pattern in the small intestine [45].

Gut microbiota dysbiosis can indirectly exacerbate periodontal inflammation via reducing the abundance of butyrate-producing bacteria and disrupting systemic Treg/Th17 balance. The upper respiratory tract mucosa mainly relies on the microbiota to regulate the function of γδ T cells and innate immune responses, thereby affecting Treg/Th17 balance to defend against pathogen invasion [46].

Thus, the distribution and function of Tregs and Th17 cells differ markedly across intestinal segments (e.g., colon vs. small intestine). This is not random but rather a precise adaptation to local microbial abundance and metabolite concentrations. In the high-SCFA environment of the colon, RORγt$^+$ Tregs are enriched to monitor commensal bacteria. In contrast, Tregs in the low-SCFA environment of the small intestine rely on distinct IL-2 signaling patterns. More importantly, the two cell types establish a functional buffer zone through intermediate states such as IL-17$^+$ Tregs and IL-10$^+$ Th17 cells, allowing flexible adjustment of immune intensity under homeostatic conditions rather than a binary switch. This region-specific plasticity model represents the core wisdom by which the mucosal system maintains long-term homeostasis.

Role of Treg/Th17 Imbalance in IBD Pathogenesis and Clinical Biomarkers

The Treg/Th17 imbalance in IBD involves a progressive pathological process that unfolds in three stages: initiation, amplification, and consolidation. A critical feature of this process is the transition from a state that can be restored

by normal regulatory mechanisms to one that becomes self-sustaining even after the initial trigger has been resolved.

Initiation of Imbalance: Microenvironmental Signals Shift From Synergy to Conflict

In healthy mucosa, signals such as TGF-β, IL-2, and SCFAs collectively maintain a low-level dynamic balance between Tregs and Th17 cells. The key event in the initiation phase of IBD is that dysbiosis and epithelial damage together create an signaling environment that simultaneously weakens Treg induction and drives Th17 differentiation: on one hand, reduced SCFAs and increased MAMPs weaken Treg induction and stability; on the other hand, pro-inflammatory signals such as IL-6, IL-1β, and IL-23 surge, potently driving Th17 differentiation. An even more decisive change is that factors such as IL-6 directly suppress Foxp3 expression, causing Tregs to lose their ability to maintain their function in an inflammatory environment. Thus, the starting point of imbalance is not simply the tipping of a scale toward one side, but rather the breach of the the tolerance threshold of Tregs to inflammatory signals—even if cell numbers have not yet changed dramatically, the foundation of systemic stability has already been undermined. In peripheral blood and inflamed intestinal mucosa of IBD patients, increased Th17 cell counts, upregulated RORγt and IL-17A expression, along with decreased Treg cell counts and downregulated Foxp3 expression, have indeed been observed [47].

Amplification of Imbalance: Three Interlocking Positive Feedback Loops Create System Locking

Once the initiation threshold is crossed, the imbalance automatically amplifies through the following three interlocking loops, no longer relying on the original triggering factors.

(1) Immune-immune loop: IL-17A secreted by Th17 cells activates epithelial and immune cells to produce more IL-6 and IL-1β, further suppressing Tregs and expanding Th17 cells [34].

(2) Immune-epithelial loop: Th17-derived IL-17 and TNF-α damage epithelial tight junctions, leading to massive MAMP translocation, which further enhances Th17 responses and weakens Tregs via the TLR4/NLRP3 pathway [48].

(3) Immune-microbiota loop: Th17-dominated inflammation remodels the microbial structure (reduced SCFA-producing bacteria, expansion of potentially pathogenic bacteria); the decline in SCFAs further weakens support for Tregs, while aberrant microbial antigens continuously sustain Th17 activation.

These three loops are nested within one another, transforming the imbalance from a pathological cascade into a self-sustaining feedback network. Once this stage is reached, even if the initial dysbiosis or epithelial damage is corrected, the inflammation can still self-sustain. This self-perpetuating nature is precisely the core reason why IBD presents as a chronic and relapsing condition. Functionally impaired Treg cells are unable to effectively suppress over-activated effector T cells or maintain immune tolerance to commensal microbiota, resulting in continuous amplification and failure of inflammation to resolve [49].

Consolidation of Imbalance: Tregs Undergo Pathological Reprogramming, not Merely Reduction

Previous studies have often emphasized the decline in Treg numbers, but a more critical change occurs within the residual Tregs themselves. In an inflammatory microenvironment rich in IL-6 and IL-23, Tregs undergo pathological reprogramming: some Tregs downregulate Foxp3, upregulate RORγt, and transform into ex-Tregs or IL-17^{+} Tregs. These transformed cells not only lose their immunosuppressive function but may even secrete IL-17, shifting from regulatory mechanisms that suppress inflammation to factors that promote inflammation [25]. Simultaneously, the ability of Tregs to secrete IL-10 and TGF-β is significantly reduced, and their capacity to promote epithelial proliferation and repair is consequently lost [47]. This means that the qualitative change in Tregs is far more pathologically significant than the quantitative change: simply supplementing Treg numbers without restoring their functional stability in the inflammatory environment will inevitably yield limited therapeutic effects [50]. The three-stage mechanism described above collectively explains why the common anti-inflammatory effect against disease relapse cycle observed clinically is difficult to break. It also suggests that any effective intervention strategy must simultaneously interrupt the positive feedback loops and restore Treg functional resilience, rather than merely aiming for normalization of cell ratios.

Treg/Th17 Axis-Related Biomarkers for IBD

Detection of Treg/Th17 axis-related indicators can provide clinically valuable biomarkers for the early diagnosis, disease assessment, therapeutic response monitoring, and prognosis prediction of IBD. Current related research mainly focuses on three directions: cell ratio, cytokine profiles, and combined microbiome-immune indicator analysis.

Clinical Value of Treg/Th17 Cell Ratio

The Treg/Th17 ratio in peripheral blood and intestinal mucosal tissues is the most intuitive indicator for evaluating the state of immune imbalance in IBD patients. Clinical studies have shown that the peripheral blood Th17/Treg ratio is significantly higher in IBD patients than in healthy controls, and the ratio is positively correlated with disease activity and inflammatory severity: the ratio is markedly higher in patients with active IBD than in those in remission, and significantly higher in patients with severe inflammation than in those with mild-to-moderate disease [51,52].

In intestinal mucosal tissues, the number of infiltrating Th17 cells is significantly increased and the proportion of Tregs is correspondingly reduced in inflamed sites, and the change in their ratio is closely correlated with the degree of mucosal inflammation and histological damage grade. After effective treatment, the Th17/Treg ratio of patients gradually returns to normal levels with disease remission, indicating that this indicator can be used for dynamic monitoring of clinical therapeutic response and prognosis assessment.

Diagnostic Significance of Characteristic Cytokine Profiles

The characteristic cytokine profiles of Th17 and Treg cells can more accurately reflect their functional status, providing a supplementary basis for disease assessment in IBD. Among them, Th17-related pro-inflammatory cytokines (IL-17A, IL-6, TNF-α) and Treg-related anti-inflammatory cytokines (IL-10, TGF-β) are the most representative detection indicators at present.

In the serum and lesioned intestinal mucosal tissues of IBD patients, the levels of pro-inflammatory cytokines such as IL-17A and IL-6 are significantly elevated, while the levels of anti-inflammatory cytokines such as IL-10 and TGF-β are markedly reduced, and their expression levels are closely correlated with disease activity. In experimental colitis mouse models, inflamed colonic tissues also exhibit a characteristic profile of high TNF-α and IL-17 expression accompanied by low TGF-β and IL-10 expression, after effective intervention, the above cytokine profile is significantly reversed, and intestinal inflammation is alleviated accordingly [15].

In addition, combined detection of cytokine profiles can also be used to predict patients' response to therapeutic regimens such as biological agents, providing a reference for the development of individualized clinical treatment strategies.

Combined Analysis Strategy of Microbiome and Immune Indicators

Single immune indicator or microbiome testing has limitations of insufficient diagnostic specificity, whereas combined analysis of gut microbiome biomarkers and Treg/Th17-related immune indicators can significantly improve the diagnostic accuracy of IBD, while providing guidance for individualized intervention.

Studies have shown that the abundance of SCFA-producing bacteria in the gut of IBD patients is positively correlated with the intestinal mucosal Treg/Th17 ratio, while the abundance of pathogenic bacteria is positively correlated with Th17 cell proportion and IL-17 levels. Combined analysis of microbiome indicators (such as gut microbiota structure and SCFAs concentration) with peripheral blood Treg/Th17 ratio and cytokine profiles can significantly improve the sensitivity and specificity of early IBD diagnosis, and can also be used to predict patients' response to microbiota-remodeling therapies [32,53].

This multi-dimensional combined analysis strategy can comprehensively dissect the pathophysiological state of IBD, and realize the whole-process guidance from precise diagnosis to targeted intervention, representing an important development direction for IBD precision medicine.

Therapeutic Strategies Targeting Treg/Th17 Balance in IBD

Targeted intervention of Treg/Th17 balance is an important research direction for IBD treatment. At present, a multi-dimensional therapeutic system has been formed, including biological agents, immune cell therapy, microbial interventions, and traditional Chinese medicine regulation, with some strategies having entered clinical application or clinical trial stages.

Biological Agent Therapy

Monoclonal antibodies targeting key cytokines of the Treg/Th17 axis are the most well-studied and widely used targeted therapeutic agents in current clinical IBD management. Their core mechanism of action is to block pro-inflammatory signal transduction, inhibit excessive Th17 activation, and subsequently restore the immunoregulatory function of Tregs.

Monoclonal antibodies targeting the IL-23 p19 subunit (such as guselkumab and risankizumab) block the IL-23/IL-23R signaling axis, inhibit Th17 cell differentiation and activation, reduce the release of pro-inflammatory cytokines such as IL-17, and simultaneously restore the immunosuppressive function of Tregs [54]. These agents have shown favorable efficacy and safety in clinical trials for moderate-to-severe UC and CD. The monoclonal antibody targeting the IL-6 receptor (IL-6R, tocilizumab) inhibits Th17 cell proliferation and promotes Treg functional restoration via antagonizing IL-6-mediated STAT3 signaling. In IBD treatment, it effectively corrects Treg/Th17 immune imbalance and alleviates intestinal inflammatory damage [55].

In addition, monoclonal antibodies targeting TNF-α (such as infliximab and adalimumab) downregulate the expression of pro-inflammatory cytokines such as IL-6 and IL-1β, indirectly modulate the Treg/Th17 ratio, and improve intestinal epithelial barrier function. They have now become first-line therapeutic agents for moderate-to-severe IBD [56].

Immune Cell Therapy

Engineered Treg adoptive cell transfer therapy is the core research direction of IBD cell therapy. Its core mechanism is to enhance the homing ability to inflammatory sites and immunosuppressive activity of Tregs via *in vitro* expansion of autologous Tregs, or construction of antigen-

specific chimeric antigen receptor Treg (CAR-Treg) cells, thereby restoring the local Treg/Th17 immune balance in the intestinal mucosa [57,58].

Preclinical studies have confirmed that CAR-Treg therapy can precisely target intestinal inflammatory foci, significantly inhibit inflammatory responses in the local mucosa, re-establish intestinal immune homeostasis, and reduce pathological damage to colonic tissues [57]. In addition, Th17 cell reprogramming technology can induce the conversion of pro-inflammatory Th17 cells into anti-inflammatory phenotypes such as IL-10$^+$ Th17 cells via epigenetic modification and transcription factor regulation. This strategy effectively restores intestinal immune balance while avoiding adverse reactions caused by systemic immunosuppression, representing a highly promising novel cell therapeutic strategy.

Microbial Intervention Strategies

Microbial intervention strategies based on the gut microbiota can precisely regulate Treg/Th17 balance from the upstream via reshaping the microbiota structure and modulating the microbiota metabolite profile, serving as an important adjuvant therapeutic modality in clinical IBD management. These strategies mainly include probiotic supplementation and FMT.

Probiotics (such as *Lactobacillus rhamnosus*, *Lactobacillus plantarum*, and *Lactobacillus reuteri*) inhibit the abnormal polarization of Th17 cells, promote the proliferation and functional activation of Tregs, repair the integrity of the intestinal epithelial barrier, and ultimately effectively alleviate intestinal inflammatory responses via increasing intestinal SCFAs production and inhibiting the activation of the TLR4-NF-κB signaling pathway and NLRP3 inflammasome. FMT comprehensively reshapes the gut microbiota structure of patients, restores the normal microbiota metabolite profile, and corrects Treg/Th17 imbalance via transplanting the complete fecal microbiota from healthy donors into the patient's intestine. It has shown certain efficacy in the clinical treatment of recurrent and refractory IBD at present [5,59].

Emerging Targeted Immunotherapies for Treg/Th17 Balance Restoration

Beyond the established biologic and small-molecule therapies discussed above, several emerging strategies have shown promise in directly restoring Treg/Th17 balance through pathway-specific mechanisms. Selective IL-23p19 inhibitors, including guselkumab and risankizumab, have demonstrated robust efficacy in moderate-to-severe ulcerative colitis and Crohn's disease by specifically blocking the IL-23/STAT3/RORγt axis that drives Th17 cell maintenance and pathogenicity while preserving Treg cell homeostasis [60,61,62]. The JAK1-selective inhibitor upadacitinib has shown rapid symptom improvement and mucosal healing in phase III ulcerative colitis trials, with its preferential suppression of STAT3 over STAT5 phosphorylation contributing to a favorable balance between Th17 inhibition and Treg preservation [63,64]. At the cellular intervention frontier, low-dose IL-2 therapy has demonstrated selective Treg expansion and clinical efficacy across multiple autoimmune diseases [65], and novel engineered IL-2 fusion proteins with enhanced Treg selectivity are under active investigation [66]. Chimeric antigen receptor (CAR)-Treg cell therapy targeting gut-specific antigens represents another innovative precision approach, with emerging preclinical and patient perspective studies supporting its feasibility for antigen-specific immunosuppression in IBD without compromising systemic immunity [67,68]. Furthermore, nanoparticle-based delivery systems have been developed to locally modulate the gut microenvironment and promote Treg differentiation, offering a non-systemic alternative for restoring mucosal immune homeostasis [69,70]. These strategies collectively represent a paradigm shift from broad immunosuppression toward pathway-specific, Treg/Th17-targeted precision medicine in IBD management.

Current Challenges and Future Directions in the Field

Core Challenges

Although extensive research has been conducted on the role of Treg/Th17 balance in IBD, and some interventional strategies have been applied in clinical practice, current research still faces two core bottlenecks that severely hinder the translation of basic research into clinical treatment.

First, a significant bench-to-bedside translation gap persists. Most current mechanistic studies are based on rodent models, which cannot fully replicate the complex pathophysiological processes of human IBD. On the one hand, there are marked differences in the gut microbiota structure and mucosal immune microenvironment between rodents and humans, making it difficult to simulate the specific types of Treg functional deficiency and the characteristics of the inflammatory microenvironment in human IBD [71,72]. On the other hand, most animal models are acute colitis models, which cannot replicate the chronic, persistent, and recurrent course of human IBD, resulting in limited response rates in clinical trials for a large number of interventional strategies that show significant efficacy in animal models.

Second, the challenge of tissue-specific precision regulation remains unresolved. Treg/Th17 cells in different regions of the intestinal mucosa exhibit significant tissue specificity, with distinct phenotypic characteristics, functional status, and regulatory mechanisms from those in the circulation [73,74]. Current systemic intervention strategies used in clinical practice cannot achieve precise targeted regulation of intestinal inflammatory sites. While correct-

ing local immune imbalance, they may interfere with systemic immune homeostasis, leading to an increased risk of adverse events such as infection and tumorigenesis. Furthermore, Treg/Th17 balance is a dynamic and finely regulated process. How to achieve long-term maintenance of immune homeostasis after effective suppression of acute inflammation, while avoiding the induction of new immune deviation, remains a key unresolved challenge in current research.

Future Research Directions

Recent spatial transcriptomics studies in IBD have revealed distinct immune cell niches in ulcerative colitis and Crohn disease tissues, identifying spatially organized granuloma-associated immune landscapes and region-specific Treg/Th17 distribution patterns correlated with clinical outcomes. First, using single-cell multi-omics and spatial transcriptomics to map the heterogeneity of the mucosal immune microenvironment, including the spatial distribution of immune cell subsets across distinct intestinal regions and their interactions with local stromal cells and microbial communities. Single-cell multi-omics technology enables simultaneous analysis of multi-dimensional information including gene expression profiles, chromatin accessibility, and epigenetic modifications at single-cell resolution, thereby precisely identifying functionally impaired Treg/Th17 cell subsets in the intestinal mucosa of IBD patients and elucidating the specific signaling pathways driving their abnormal differentiation and activation [75,76]. Spatial transcriptomics technology combines molecular data with tissue spatial architecture to systematically map the spatial distribution and interaction patterns of Th17 cells, Tregs, IECs, and microbiota colonization sites in inflamed regions, revealing the dynamic regulatory mechanisms of the local microenvironment on immune cell function. The integrated application of these technologies will provide a panel of novel tissue-specific biomarkers and potential interventional targets for IBD precision medicine.

Second, developing gut-targeted, antigen-specific precision regulatory strategies. To address the off-target effects and systemic immune interference commonly associated with current systemic interventions, future research should prioritize the construction of drug delivery systems that can precisely target intestinal inflammatory foci, and the development of CAR-Treg cell therapies targeting commensal bacterial antigens or inflammation-specific antigens. These strategies will enable targeted regulation of the local Treg/Th17 balance in the intestinal mucosa, re-establishing local immune homeostasis while avoiding impacts on the systemic immune system. In addition, the development of individualized microbial interventions and TCM treatment regimens based on the patient's individual microbiota structure, immune phenotype, and disease subtype is also an important direction for achieving precision IBD treatment.

Recent studies have demonstrated the feasibility of intestinal organoid-immune cell co-culture systems for investigating Treg/Th17 responses in a patient-specific context. For instance, colon organoids derived from IBD patients have been successfully co-cultured with autologous $CD4^+$ T cells to recapitulate disease-specific inflammatory microenvironments. Third, establishing clinically relevant humanized model systems and large-scale clinical cohort studies. Given that existing animal models are difficult to replicate the complex pathological characteristics of human IBD, future research should focus on establishing *in vitro* and *in vivo* models that are closer to the human physiological environment, such as humanized gut microbiota mouse models and intestinal organoid-immune cell co-culture models. These models can more realistically simulate the intestinal mucosal microenvironment and the chronic inflammatory process of IBD, thereby improving the efficiency of translating basic research findings into clinical practice. Meanwhile, systematic dissection of the Treg/Th17 imbalance profile in patients with different disease subtypes and disease stages via large-sample, multi-center clinical cohorts will provide a solid clinical basis for stratified treatment and individualized intervention of IBD [11].

Conclusion

The maintenance of intestinal mucosal Treg/Th17 cell homeostasis is not governed by a single molecule or pathway. Instead, it is determined by a distributed regulatory network shaped by the signaling microenvironment, cellular plasticity, tissue regional heterogeneity, and the tripartite interaction among microbiota, epithelium, and immune cells. Research on Treg/Th17 cells in IBD is undergoing a paradigm shift: from describing imbalance phenomena to deciphering system-level locking mechanisms, and from pursuing normalization of cell ratios to restoring immune resilience. This shift requires both technological advances, such as single-cell multi-omics, spatial transcriptomics, and humanized animal models, and a conceptual embrace of a more complex biological reality: mucosal immune homeostasis is an inherently dynamic, multi-factor coupled system in which single-target intervention strategies can rarely achieve long-term remission alone. The core challenge for future research, therefore, lies in translating this complexity into actionable clinical decision-making frameworks.

Availability of Data and Materials

Not applicable.

Author Contributions

Conceptualization: JW and BQZ; Methodology: JW and BQZ; Literature search and Data curation: JW and MWS; Writing – original draft: JW; Writing – review & editing: MWS, BQZ. All authors gave final approval of the

version to be published. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This study was funded by grants from the Shandong Provincial Traditional Chinese Medicine Science and Technology Project (No. Z20240223) and the Shandong Provincial Medical Staff Science and Technology Innovation Plan Joint Project (No. SDYWZGKCJHLH202436).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Iliev ID, Leonardi I. Fungal dysbiosis: immunity and interactions at mucosal barriers. Nature Reviews. Immunology. 2017; 17: 635–646. https://doi.org/10.1038/nri.2017.55

[2] Vanciková Z. Mucosal immunity–basic principles, ontogeny, cystic fibrosis and mucosal vaccination. Current Drug Targets. Immune, Endocrine and Metabolic Disorders. 2002; 2: 83–95.

[3] Le Berre C, Honap S, Peyrin-Biroulet L. Ulcerative colitis. Lancet (London, England). 2023; 402: 571–584. https://doi.org/10.1016/S0140-6736(23)00966-2

[4] Rivera Rodríguez R, Johnson JJ. Terpenes: Modulating anti-inflammatory signaling in inflammatory bowel disease. Pharmacology & Therapeutics. 2023; 248: 108456. https://doi.org/10.1016/j.pharmthera.2023.108456

[5] Chang Y, Zhai L, Peng J, Wu H, Bian Z, Xiao H. Phytochemicals as regulators of Th17/Treg balance in inflammatory bowel diseases. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2021; 141: 111931. https://doi.org/10.1016/j.biopha.2021.111931

[6] Giudice A, Brescia C, Morano D, Viglietto G, Luzza F, Amato R, et al. Th17/treg balance in Inflammatory Bowel Disease: the role of microbial, and genetic regulators in disease modulation. Frontiers in Cell and Developmental Biology. 2026; 14: 1774790. https://doi.org/10.3389/fcell.2026.1774790

[7] Agak GW, Mouton A, Teles RM, Weston T, Morselli M, Andrade PR, et al. Extracellular traps released by antimicrobial TH17 cells contribute to host defense. The Journal of Clinical Investigation. 2021; 131: e141594. https://doi.org/10.1172/JCI141594

[8] Mikami N, Kawakami R, Sakaguchi S. New Treg cell-based therapies of autoimmune diseases: towards antigen-specific immune suppression. Current Opinion in Immunology. 2020; 67: 36–41. https://doi.org/10.1016/j.coi.2020.07.004

[9] Ueno A, Jeffery L, Kobayashi T, Hibi T, Ghosh S, Jijon H. Th17 plasticity and its relevance to inflammatory bowel disease. Journal of Autoimmunity. 2018; 87: 38–49. https://doi.org/10.1016/j.jaut.2017.12.004

[10] Edwards M, Brockmann L. Microbiota-dependent modulation of intestinal anti-inflammatory $CD4^+$ T cell responses. Seminars in Immunopathology. 2025; 47: 23. https://doi.org/10.1007/s00281-025-01049-6

[11] Huang C, Mei Q, Lou L, Huang Z, Fu Y, Fan J, et al. Ulcerative Colitis in Response to Fecal Microbiota Transplantation via Modulation of Gut Microbiota and Th17/Treg Cell Balance. Cells. 2022; 11: 1851. https://doi.org/10.3390/cells11111851

[12] Liu Z, Chen L, Xiong D, Zhan Y, Liu J, Ouyang L, et al. Salidroside affects the Th17/Treg cell balance in aplastic anemia via the STAT3/HIF-1α/RORγt pathway. Redox Report: Communications in Free Radical Research. 2023; 28: 2225868. https://doi.org/10.1080/13510002.2023.2225868

[13] Zhang S, Zhong R, Tang S, Chen L, Zhang H. Metabolic regulation of the Th17/Treg balance in inflammatory bowel disease. Pharmacological Research. 2024; 203: 107184. https://doi.org/10.1016/j.phrs.2024.107184

[14] Yuan M, Chang L, Gao P, Li J, Lu X, Hua M, et al. Synbiotics containing sea buckthorn polysaccharides ameliorate DSS-induced colitis in mice via regulating Th17/Treg homeostasis through intestinal microbiota and their production of BA metabolites and SCFAs. International Journal of Biological Macromolecules. 2024; 276: 133794. https://doi.org/10.1016/j.ijbiomac.2024.133794

[15] Guo M, Liu H, Yu Y, Zhu X, Xie H, Wei C, et al. *Lactobacillus rhamnosus* GG ameliorates osteoporosis in ovariectomized rats by regulating the Th17/Treg balance and gut microbiota structure. Gut Microbes. 2023; 15: 2190304. https://doi.org/10.1080/19490976.2023.2190304

[16] Brockmann L, Tran A, Huang Y, Edwards M, Ronda C, Wang HH, et al. Intestinal microbiota-specific Th17 cells possess regulatory properties and suppress effector T cells via c-MAF and IL-10. Immunity. 2023; 56: 2719–2735.e7. https://doi.org/10.1016/j.immuni.2023.11.003

[17] Cui H, Wang N, Li H, Bian Y, Wen W, Kong X, et al. The dynamic shifts of IL-10-producing Th17 and IL-17-producing treg in health and disease: A crosstalk between ancient "Yin-Yang" theory and modern immunology. Cell Communication and Signaling. 2024; 22: 99. https://doi.org/10.1186/s12964-024-01505-0

[18] Soongsathitanon J, Homjan T, Pongcharoen S. Characteristic features of *in vitro* differentiation of human naïve $CD4^+$ T cells to induced regulatory T cells (iTreg) and T helper (Th) 17 cells: Sharing of lineage-specific markers. Heliyon. 2024; 10: e31394. https://doi.org/10.1016/j.heliyon.2024.e31394

[19] Joetham A, Schedel M, Ning F, Wang M, Takeda K, Gelfand EW. Dichotomous role of TGF-β controls inducible regulatory T-cell fate in allergic airway disease through Smad3 and TGF-β-activated kinase 1. The Journal of Allergy and Clinical Immunology. 2020; 145: 933–946.e4. https://doi.org/10.1016/j.jaci.2019.09.032

[20] Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annual Review of Immunology. 2009; 27: 485–517. https://doi.org/10.1146/annurev.immunol.021908.132710

[21] Li C, Park JH. Assessing IL-2-Induced STAT5 Phosphorylation in Fixed, Permeabilized $Foxp3^+$ Treg Cells by Multiparameter Flow Cytometry. STAR Protocols. 2020; 1: 100195. https://doi.org/10.1016/j.xpro.2020.100195

[22] Prado DS, Cattley RT, Shipman CW, Happe C, Lee M, Boggess WC, et al. Synergistic and additive interactions between receptor signaling networks drive the regulatory T cell versus T helper 17 cell fate choice. The Journal of Biological Chemistry. 2021; 297: 101330. https://doi.org/10.1016/j.jbc.2021.101330

[23] Zou Q, Zhang W, Xie H, Ying S, Zeng X, Yao Y, et al. Inflammatory bowel disease through the lens of microbe-host interactions:

immunomodulation, metabolic effects, and genetic susceptibility in microbiota dysbiosis. Frontiers in Cellular and Infection Microbiology. 2026; 16: 1745929. https://doi.org/10.3389/fcimb.2026.1745929

[24] Aso K, Kono M, Kanda M, Kudo Y, Sakiyama K, Hisada R, et al. Itaconate ameliorates autoimmunity by modulating T cell imbalance via metabolic and epigenetic reprogramming. Nature Communications. 2023; 14: 984. https://doi.org/10.1038/s41467-023-36594-x

[25] Li J, Zhao J, Chen L, Gao H, Zhang J, Wang D, et al. α-Synuclein induces Th17 differentiation and impairs the function and stability of Tregs by promoting RORC transcription in Parkinson's disease. Brain, Behavior, and Immunity. 2023; 108: 32–44. https://doi.org/10.1016/j.bbi.2022.10.023

[26] Yoo JS, Oh SF. Unconventional immune cells in the gut mucosal barrier: regulation by symbiotic microbiota. Experimental & Molecular Medicine. 2023; 55: 1905–1912. https://doi.org/10.1038/s12276-023-01088-9

[27] Zhou L, Zhang M, Wang Y, Dorfman RG, Liu H, Yu T, et al. Faecalibacterium prausnitzii Produces Butyrate to Maintain Th17/Treg Balance and to Ameliorate Colorectal Colitis by Inhibiting Histone Deacetylase 1. Inflammatory Bowel Diseases. 2018; 24: 1926–1940. https://doi.org/10.1093/ibd/izy182

[28] Kibbie JJ, Dillon SM, Thompson TA, Purba CM, McCarter MD, Wilson CC. Butyrate directly decreases human gut lamina propria CD4 T cell function through histone deacetylase (HDAC) inhibition and GPR43 signaling. Immunobiology. 2021; 226: 152126. https://doi.org/10.1016/j.imbio.2021.152126

[29] Sharma A, Sharma G, Im SH. Gut microbiota in regulatory T cell generation and function: mechanisms and health implications. Gut Microbes. 2025; 17: 2516702. https://doi.org/10.1080/19490976.2025.2516702

[30] Seguí-Pérez A, Castillo-González R, Sancho-Temiño L, Cruz-Adalia A. Newly identified cell types crucial for gut commensal tolerance. Trends in Cell Biology. 2025; 35: 186–189. https://doi.org/10.1016/j.tcb.2024.12.008

[31] Hayashi Y, Nakase H. The Molecular Mechanisms of Intestinal Inflammation and Fibrosis in Crohn's Disease. Frontiers in Physiology. 2022; 13: 845078. https://doi.org/10.3389/fphys.2022.845078

[32] Hu Y, Yang Y, Li Y, Zhang Q, Zhang W, Jia J, et al. Th17/Treg imbalance in inflammatory bowel disease: immunological mechanisms and microbiota-driven regulation. Frontiers in Immunology. 2025; 16: 1651063. https://doi.org/10.3389/fimmu.2025.1651063

[33] Jang S, Lee EJ, Park S, Lim H, Ahn B, Huh Y, et al. Spatial host-microbiome profiling demonstrates bacterial-associated host transcriptional alterations in pediatric ileal Crohn's disease. Microbiome. 2025; 13: 189. https://doi.org/10.1186/s40168-025-02178-8

[34] Shen J, Liang W, Zhao R, Chen Y, Liu Y, Cheng W, et al. Cross-tissue multi-omics analyses reveal the gut microbiota's absence impacts organ morphology, immune homeostasis, bile acid and lipid metabolism. IMeta. 2025; 4: e272. https://doi.org/10.1002/imt2.272

[35] Liu L, Davidorf B, Dong P, Peng A, Song Q, He Z. Decoding the mosaic of inflammatory bowel disease: Illuminating insights with single-cell RNA technology. Computational and Structural Biotechnology Journal. 2024; 23: 2911–2923. https://doi.org/10.1016/j.csbj.2024.07.011

[36] Chen X, Zhang Y, Zhang G, Wang D, Dou L, Wang Y, et al. Spatial microbiome-metabolic crosstalk drives $CD8^+$ T-cell exhaustion through the butyrate-HDAC axis in colorectal cancer. Frontiers in Microbiology. 2025; 16: 1704491. https://doi.org/10.3389/fmicb.2025.1704491

[37] Lee JY, Yoo JH, Kim JE, Bae JW, Lee CK. Translating Gut Microbiota into Diagnostics: A Multidimensional Approach for the Diagnosis of Inflammatory Bowel Disease. Gut and Liver. 2026; 20: 199–212. https://doi.org/10.5009/gnl250360

[38] Chen H, Yu S, Zhang M, Tian B, Yang L, Lu J. Gut microbial metabolites in inflammatory bowel disease: immunological mechanisms regulating Treg/Th17 balance and therapeutic potential. Frontiers in Immunology. 2026; 17: 1780865. https://doi.org/10.3389/fimmu.2026.1780865

[39] Zakerska-Banaszak O, Tomczak H, Gabryel M, Baturo A, Wolko L, Michalak M, et al. Dysbiosis of gut microbiota in Polish patients with ulcerative colitis: a pilot study. Scientific Reports. 2021; 11: 2166. https://doi.org/10.1038/s41598-021-81628-3

[40] Zhang D, Dong B, Chen J, Zhang Z, Zeng W, Liao L, et al. Fecal Microbiota Transplantation Modulates Th17/Treg Balance via JAK/STAT Pathway in ARDS Rats. Advanced Biology. 2025; 9: e00028. https://doi.org/10.1002/adbi.202500028

[41] Tong L, Hao H, Zhang Z, Lv Y, Liang X, Liu Q, et al. Milk-derived extracellular vesicles alleviate ulcerative colitis by regulating the gut immunity and reshaping the gut microbiota. Theranostics. 2021; 11: 8570–8586. https://doi.org/10.7150/thno.62046

[42] Jiang Z, Wu C. Reciprocal Interactions Between Regulatory T Cells and Intestinal Epithelial Cells. Frontiers in Immunology. 2022; 13: 951339. https://doi.org/10.3389/fimmu.2022.951339

[43] Múnera-Rodríguez AM, Leiva-Castro C, Chacón P, Palomares F, López-Enríquez S. Unraveling the role of γδ T cells in inflammatory bowel disease: Development and prevention strategies. International Review of Cell and Molecular Biology. 2025; 397: 47–71. https://doi.org/10.1016/bs.ircmb.2025.03.006

[44] Huang HI, Xue Y, Jewell ML, Tan CY, Theriot B, Aggarwal N, et al. A binary module for microbiota-mediated regulation of γδ17 cells, hallmarked by microbiota-driven expression of programmed cell death protein 1. Cell Reports. 2023; 42: 113143. https://doi.org/10.1016/j.celrep.2023.113143

[45] Prakhar P, Alvarez-DelValle J, Keller H, Crossman A, Tai X, Park YK, et al. The small intestine epithelium exempts Foxp3+ Tregs from their IL-2 requirement for homeostasis and effector function. JCI Insight. 2021; 6: e149656. https://doi.org/10.1172/jci.insight.149656

[46] Li X, Chen M, Chen T, Xie L, Luo Q, Fan X, et al. The intricate interplay among microbiota, mucosal immunity, and viral infection in the respiratory tract. Journal of Translational Medicine. 2025; 23: 488. https://doi.org/10.1186/s12967-025-06433-2

[47] Choi J, Kim BR, Akuzum B, Chang L, Lee JY, Kwon HK. T_{REG}king From Gut to Brain: The Control of Regulatory T Cells Along the Gut-Brain Axis. Frontiers in Immunology. 2022; 13: 916066. https://doi.org/10.3389/fimmu.2022.916066

[48] Ma Z, Akhtar M, Pan H, Liu Q, Chen Y, Zhou X, et al. Fecal microbiota transplantation improves chicken growth performance by balancing jejunal Th17/Treg cells. Microbiome. 2023; 11: 137. https://doi.org/10.1186/s40168-023-01569-z

[49] Pan B, Yao Y, Wu H, Ye D, Zhang Z, Zhang X, et al. N-glycosylated LTβR increases the Th17/Treg cell ratio in liver cancer by blocking RORC ubiquitination and FOXP3 transcription. Cell Death & Disease. 2025; 16: 421. https://doi.org/10.1038/s41419-025-07738-2

[50] Liu X, Zhou M, Dai Z, Luo S, Shi Y, He Z, et al. Salidroside alleviates ulcerative colitis via inhibiting macrophage pyroptosis and repairing the dysbacteriosis-associated Th17/Treg imbalance. Phytotherapy Research: PTR. 2023; 37: 367–382. https://doi.org/10.1002/ptr.7636

[51] Palatella M, Kruse F, Ji H, Loriani Fard AK, Becker M, Daniel C, et al. Acsbg1 maintains intestinal immune homeostasis and controls inflammation by regulating $ST2^+$ Tregs. Mucosal Immunology. 2026; 19: 1526–1537. https://doi.org/10.1016/j.mu

cimm.2025.10.009

[52] Ge S, Ren H, Guo Q, Wang X, Liu Y, Lin B, et al. Wuweixiaoduyin regulates TAZ-mediated immunoregulatory properties of Treg/TH17 cells in chronic osteomyelitis. Biotechnology & Genetic Engineering Reviews. 2023; 39: 980–999. https://doi.org/10.1080/02648725.2023.2166706

[53] Zhou M, Liu X, He J, Xu X, Ju C, Luo S, et al. High-fructose corn syrup aggravates colitis via microbiota dysbiosis-mediated Th17/Treg imbalance. Clinical Science (London, England: 1979). 2023; 137: 1619–1635. https://doi.org/10.1042/CS20230788

[54] Jacobse J, Brown RE, Li J, Pilat JM, Pham L, Short SP, et al. Interleukin-23 receptor signaling impairs the stability and function of colonic regulatory T cells. Cell Reports. 2023; 42: 112128. https://doi.org/10.1016/j.celrep.2023.112128

[55] Ullrich KAM, Derdau J, Baltes C, Battistella A, Rosso G, Uderhardt S, et al. IL-3 receptor signalling suppresses chronic intestinal inflammation by controlling mechanobiology and tissue egress of regulatory T cells. Gut. 2023; 72: 2081–2094. https://doi.org/10.1136/gutjnl-2023-329818

[56] Musacchio E, Valvason C, Botsios C, Ostuni F, Furlan A, Ramonda R, et al. The tumor necrosis factor-{alpha}-blocking agent infliximab inhibits interleukin 1beta (IL-1beta) and IL-6 gene expression in human osteoblastic cells. The Journal of Rheumatology. 2009; 36: 1575–1579. https://doi.org/10.3899/jrheum.081321

[57] Cheru NT, Osayame Y, Sumida TS. Breaking tolerance: an update of Treg dysfunction in autoimmunity. Trends in Immunology. 2025; 46: 611–613. https://doi.org/10.1016/j.it.2025.06.007

[58] Mohebali N, Weigel M, Hain T, Sütel M, Bull J, Kreikemeyer B, et al. Faecalibacterium prausnitzii, Bacteroides faecis and Roseburia intestinalis attenuate clinical symptoms of experimental colitis by regulating Treg/Th17 cell balance and intestinal barrier integrity. Biomedicine & Pharmacotherapy = Biomedecine & Pharmacotherapie. 2023; 167: 115568. https://doi.org/10.1016/j.biopha.2023.115568

[59] Wang X, Sun B, Wang Y, Gao P, Song J, Chang W, et al. Research progress of targeted therapy regulating Th17/Treg balance in bone immune diseases. Frontiers in Immunology. 2024; 15: 1333993. https://doi.org/10.3389/fimmu.2024.1333993

[60] Long M, Allegretti JR, Danese S, Germinaro M, Baker T, Alvarez Y, et al. Efficacy and safety of subcutaneous guselkumab induction therapy in participants with moderately to severely active ulcerative colitis (ASTRO): a double-blind, treat-through, randomised, placebo-controlled, phase 3 trial. The Lancet. Gastroenterology & Hepatology. 2026; 11: 284–298. https://doi.org/10.1016/S2468-1253(25)00322-X

[61] Nasim H, Siddiqui AH, Khan SJ, Fatima K, Naz A, Yousafzai ZA, et al. Efficacy and safety of risankizumab in moderate-to-severe Crohn's disease: a systematic review and meta-analysis. Therapeutic Advances in Gastroenterology. 2026; 19: 17562848261454195. https://doi.org/10.1177/17562848261454195

[62] Puca P, Parello S, Colantuono S, Tursi A, Coppola G, Lopetuso LR, et al. Interleukin-23 Inhibitors in Inflammatory Bowel Disease. BioDrugs: Clinical Immunotherapeutics, Biopharmaceuticals and Gene Therapy. 2026; 40: 479–492. https://doi.org/10.1007/s40259-026-00781-1

[63] Vermeire S, Colombel JF, Danese S, Panaccione R, Peyrin-Biroulet L, Beck K, et al. Benefit-risk profile of upadacitinib: exploratory post hoc analysis of phase 2b/3 studies in patients with moderately to severely active ulcerative colitis or Crohn's disease. Journal of Crohn's & Colitis. 2026; 20: jjaf198. https://doi.org/10.1093/ecco-jcc/jjaf198

[64] Panaccione R, Colombel JF, Dubinsky M, Ma C, Kujawski M, Cheng E, et al. Efficacy of Upadacitinib Retreatment or Dose Escalation After Loss of Response in Ulcerative Colitis: Data From the Open-Label Extension of the U-ACTIVATE Study. Gastro Hep Advances. 2026; 5: 100969. https://doi.org/10.1016/j.gastha.2026.100969

[65] Rosenzwajg M, Lorenzon R, Cacoub P, Pham HP, Pitoiset F, El Soufi K, et al. Immunological and clinical effects of low-dose interleukin-2 across 11 autoimmune diseases in a single, open clinical trial. Annals of the Rheumatic Diseases. 2019; 78: 209–217. https://doi.org/10.1136/annrheumdis-2018-214229

[66] Lin Y, Wang X, Qin Y, Wang C, Zhou T, Zhang L, et al. A single-agent fusion of human IL-2 and anti-IL-2 antibody that selectively expands regulatory T cells. Communications Biology. 2024; 7: 299. https://doi.org/10.1038/s42003-024-05987-z

[67] Kümmel J, Schlegel N, Wagner JC. Opportunities and challenges harnessing antigen-specific CD4+ regulatory T cells in inflammatory bowel disease. Frontiers in Immunology. 2025; 16: 1667053. https://doi.org/10.3389/fimmu.2025.1667053

[68] Vent-Schmidt J, Goldsmith LJ, Steiner TS. Patients' Willingness and Perspectives Toward Chimeric Antigen Receptor T-Regulatory Cell Therapy for Inflammatory Bowel Diseases. Crohn's & Colitis 360. 2020; 2: otaa085. https://doi.org/10.1093/crocol/otaa085

[69] Park N, Lee B, Jeon HJ, Yeon Kim J, Park S, Kim SE, et al. Inulin-Butyrate Nanogel for Modulation of Gut Microbiome, Intestinal Barrier, and Regulatory T-Cells in Colitis. Small (Weinheim an Der Bergstrasse, Germany). 2026; 22: e13252. https://doi.org/10.1002/smll.202513252

[70] Tang X, Shang Y, Yang H, Song Y, Li S, Qin Y, et al. Targeted delivery of Fc-fused PD-L1 for effective management of acute and chronic colitis. Nature Communications. 2024; 15: 1673. https://doi.org/10.1038/s41467-024-46025-0

[71] Renault C, Veyrenche N, Mennechet F, Bedin AS, Routy JP, Van de Perre P, et al. Th17 CD4+ T-Cell as a Preferential Target for HIV Reservoirs. Frontiers in Immunology. 2022; 13: 822576. https://doi.org/10.3389/fimmu.2022.822576

[72] da Rocha GHO, de Paula-Silva M, Broering MF, Scharf PRDS, Matsuyama LSAS, Maria-Engler SS, et al. Pioglitazone-Mediated Attenuation of Experimental Colitis Relies on Cleaving of Annexin A1 Released by Macrophages. Frontiers in Pharmacology. 2020; 11: 591561. https://doi.org/10.3389/fphar.2020.591561

[73] Schnell A, Littman DR, Kuchroo VK. T_H17 cell heterogeneity and its role in tissue inflammation. Nature Immunology. 2023; 24: 19–29. https://doi.org/10.1038/s41590-022-01387-9

[74] Dominguez-Villar M, Hafler DA. Regulatory T cells in autoimmune disease. Nature Immunology. 2018; 19: 665-673. https://doi.org/10.1038/s41590-018-0120-4.

[75] Herrick MK, Tansey MG. Is LRRK2 the missing link between inflammatory bowel disease and Parkinson's disease? NPJ Parkinsons Disease. 2021; 7: 26. https://doi.org/10.1038/s41531-021-00170-1

[76] Hosseini ST, AminianToosi K, Nemati F, BishehKolaei R, Deng Y. Deciphering immune and cellular reprogramming during the progression from inflammatory bowel disease to colorectal cancer using multi-omics single-cell and spatial transcriptomics. Journal of Translational Medicine. 2026; 24: 591. https://doi.org/10.1186/s12967-026-08158-2