

MUCOSAL IMMUNOLOGY

Essential immunologic orchestrators of intestinal homeostasis

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Over the past 25 years, substantial advances have been made in our understanding of the cellular and molecular pathways that are essential to maintain a state of health in the mammalian gastrointestinal tract, an organ that is densely colonized by both immune cells and trillions of microbes. Seminal studies in the 1990s identified that several cytokines, antigen-presentation molecules, and components of the T cell receptor were necessary to prevent the development of spontaneous intestinal inflammation in mice. Subsequent research revealed that these pathways orchestrate beneficial interactions with intestinal microbes, involve complex communication between innate and adaptive immune cells, and can be dysregulated in human inflammatory bowel disease. Here, we discuss how these early findings set the stage for numerous other advances and shaped our current knowledge of host-microbiota interactions and intestinal homeostasis in mammals. It is expected that continued investigation of these areas will define previously unknown immunologic mechanisms of tolerance and inflammation in the intestine that can be exploited to benefit human health.

INTRODUCTION

The anatomical landscape of the mammalian intestine creates a number of considerable challenges to maintain a state of health. The organ system has an enormous surface area in which a single layer of intestinal epithelial cells segregates a substantial portion of the immune system from trillions of intestinal microorganisms, termed the microbiota, which is composed of commensal bacteria, fungi, protozoa, and viruses (1). Intestinal homeostasis depends on a physical separation of the majority of intestinal microbiota from the mammalian immune system, and this is accomplished through numerous biophysical and biochemical barriers, such as the production of tight junctions, antimicrobial proteins, and mucus by the host epithelium. A breakdown in these protective barriers causes aberrant immune responses to the microbiota and is a hallmark of multiple chronic inflammatory diseases, including inflammatory bowel disease (IBD), HIV/AIDS, viral hepatitis, cardiovascular disease, and cancer (2). Despite physical separation, there is a dynamic and reciprocal dialogue between the microbiota, host epithelium, and immune system, which is also essential to regulate a state of intestinal health. The mammalian immune system recognizes and responds to intestinal microbiota, promoting protective innate and adaptive immune pathways that reinforce barrier function, prime protective immune responses to pathogens, and maintain tolerance to beneficial microbiota or food antigens (3). These immune responses also shape the composition of the intestinal microbiota by exerting pressure or tolerance against selective microbes or by providing nutrient substrates through mucus production or epithelial fucosylation (3). Here, we discuss specific immune pathways identified in mice and humans that are essential to regulate intestinal homeostasis and consider how these findings have shaped our understanding of host-microbe interactions and created a foundation for future therapeutic strategies in IBD.

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T CELL- AND CYTOKINE-DEPENDENT REGULATION OF INTESTINAL HEALTH

In 1993, three seminal studies identified that several lines of transgenic mice with deficiencies in the immune system develop spontaneous and chronic intestinal inflammation. These included mice deficient in interleukin-2 (IL-2), IL-10, major histocompatibility complex class II (MHC-II), and subunits of the T cell receptor (TCR) (4–6). The results of these studies were surprising and highlighted an essential role of the immune system in orchestrating intestinal homeostasis.

Although it was previously appreciated that IL-10 is a critical immunoregulatory cytokine that limits T cell and macrophage responses (7), the finding that *Il10*^{-/-} mice develop spontaneous intestinal inflammation solidified an essential role for this pathway in regulating intestinal health. Mice lacking IL-10 develop chronic colitis characterized by extensive mucosal hyperplasia and aberrant inflammatory leukocyte infiltration (4). Additional studies revealed that mice lacking a subunit of the IL-10 receptor, IL-10Rβ, also develop spontaneous intestinal inflammation (8). CD4⁺ T cells are major mediators of colitis in IL-10- and IL-10R-deficient mice, rather than B cells, and initial studies suggested an association with increased T helper 1 (T_H1) cells and interferon-γ (IFN-γ) production. IL-10 directly inhibits IL-12 production in myeloid cells and therefore limits T_H1 cell differentiation (9, 10). In addition to IL-12, IL-10 also suppresses IL-23 production through inhibition of the shared IL-12 p40 subunit at the transcriptional level (10). IL-23 is essential for the maintenance and expansion of pathogenic T_H17 cells, and therefore IL-10 also limits pathogenic T_H17 cell responses by controlling IL-23 induction during mucosal inflammation.

Despite these advances, the exact cellular and molecular pathways by which IL-10 mediates intestinal health were incompletely understood. T cells, B cells, macrophages, and dendritic cells (DCs), as well as several nonhematopoietic cells, have all been reported as potential cellular sources of IL-10 in the mammalian intestine (10). Cre-lox technology in mice permitted lineage-specific deletion of IL-10 and revealed that T cell-derived IL-10 was the critical cellular source to regulate mucosal homeostasis (11), and many of these phenotypes could be recapitulated with lineage-specific deletion of IL-10 in Foxp3⁺ regulatory T (T_{reg}) cells (12). Expression of IL-10R

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and signal transducers and activators of transcription 3 (STAT3) is also critical in Foxp3^+ T_{reg} cells to limit spontaneous intestinal inflammation; however, overexpression of a dominant negative IL-10R with a CD4-cre was not sufficient to induce spontaneous disease (13, 14). By contrast, expression of IL-10R, but not IL-10, was essential in myeloid cells to condition monocyte-derived anti-inflammatory macrophages and prevent spontaneous intestinal inflammation (15, 16). Thus, T_{reg} cell-derived IL-10 drives macrophages to execute tolerogenic functions and maintain mucosal homeostasis (Fig. 1). Recent studies have clarified that the molecular basis of the anti-inflammatory function of IL-10 in macrophages occurred in part through metabolic reprogramming. In response to inflammatory stimuli, IL-10 regulates cellular metabolism in macrophages by suppressing mammalian target of rapamycin (mTOR) activity through the induction of its inhibitor, DDIT4 (DNA damage-inducible transcript 4 protein), and preventing glucose uptake and glycolysis while promoting oxidative phosphorylation (17). In IL-10-deficient mice, dysfunctional mitochondria accumulate in macrophages, resulting in activation of the NLRP3 inflammasome and production of IL-1 β . Consistent with this, impairing the inflammasome with caspase-1 deficiency could

partially protect IL-10-deficient mice from the development of spontaneous intestinal inflammation.

IL-2-deficient mice develop spontaneous and progressive inflammation throughout the entire gastrointestinal tract (6). These results were paradoxical because previous studies had defined an important role of IL-2 in promoting T cell responses. Similar intestinal inflammation also develops in mice lacking the high-affinity IL-2 receptor α subunit, CD25 (18). Elevated levels of both T cells and B cells were characterized in the intestine lamina propria of aged IL-2- or CD25-deficient mice. The infiltrating T cells of these mice are substantially increased in numbers, activation, and proliferation (6, 18). Crossing IL-2-deficient mice with Rag2-deficient mice resulted in an absence of colitis, demonstrating an essential role for adaptive immunity in disease progression (19). It was initially hypothesized that the loss of IL-2-producing CD4^+ T_{H1} cells leads to a predominance of IL-4-producing T_{H2} cells and subsequent hyperreactivity of mucosal B cells. However, later studies demonstrated that T cells, not B cells, are required for spontaneous intestinal inflammation in IL-2-deficient mice (19). The IL-2-dependent regulation of CD4^+ T cells was later refined with the identification of additional

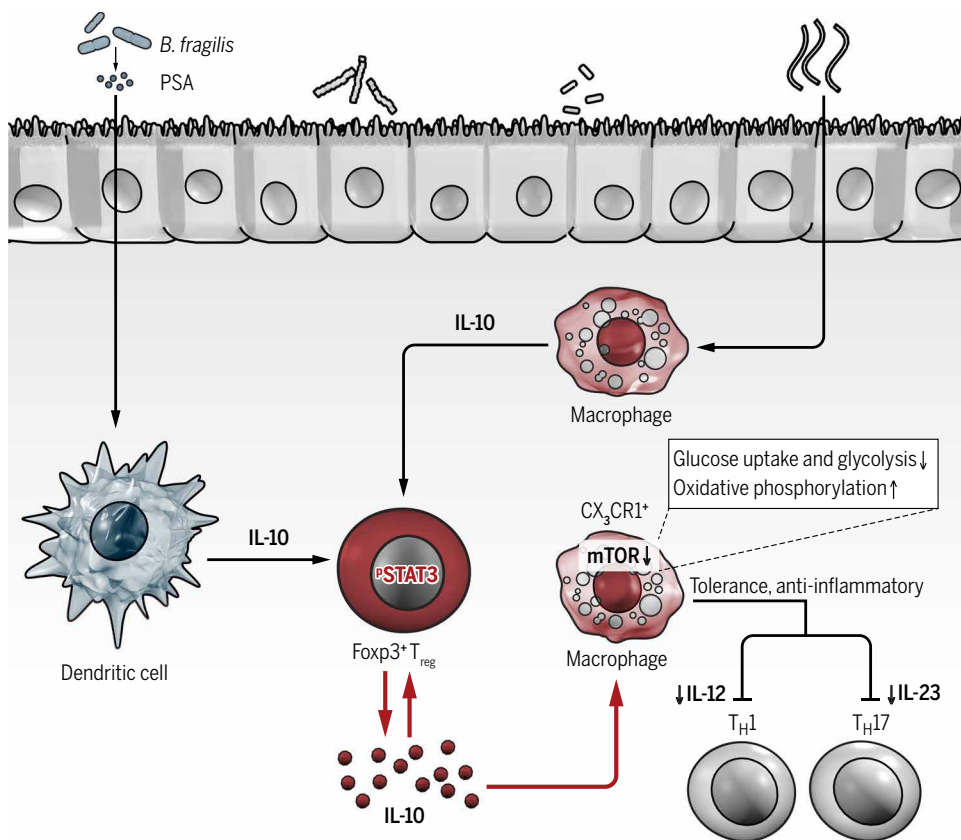


Fig. 1. IL-10-dependent regulation of intestinal health. T cells, especially T_{reg} cells, are the critical cellular source of IL-10 in the mammalian intestine. The gut microbiota is critical for the induction of intestinal T_{reg} cells and IL-10 production. *B. fragilis*-derived PSA acts on DCs, resulting in IL-10 expression. In addition, bacteria-stimulated macrophage can also directly secrete IL-10 and support T_{reg} cell development. Thus, DC-derived IL-10 binds to IL-10R expressed on T_{reg} cells, which induces STAT3 activation and the expression of abundant IL-10. IL-10 limits T_{H1} and T_{H17} cell differentiation through inhibition of IL-12 and IL-23, respectively. T_{reg} -derived IL-10 drives macrophages to execute tolerogenic functions and maintain intestinal homeostasis. In addition, IL-10 regulates cellular metabolism in macrophages by suppressing mTOR activity, thus reducing glucose uptake and glycolysis while promoting oxidative phosphorylation. Essential pathways that prevent spontaneous inflammation are highlighted in red.

heterogeneity of T helper cells, and it is now appreciated that IL-2 promotes the differentiation of T_{H1} cells, T_{H2} cells, and T_{reg} cells while inhibiting T_{H17} cells (20). Among these findings, the appreciation of IL-2-dependent T_{reg} cells was one of the most important advances. T_{reg} cells are vital for preventing autoimmunity, limiting inflammatory responses, and maintaining immune homeostasis, particularly within the gastrointestinal tract (21). The development and expansion of inducible T_{reg} cells require IL-2, and IL-2 sequestration is also a critical mechanism by which T_{reg} cells can suppress effector T cell responses (21). Consistent with this, T_{reg} cells are largely absent in IL-2- or IL-2R-deficient mice, and lineage-specific deletion of the IL-2R on T_{reg} cells was recently found to promote spontaneous intestinal inflammation and other autoimmune diseases (22). The relevant cellular sources of IL-2 in regulating intestinal homeostasis have yet to be defined, but expression has been observed in T cells, DCs, natural killer cells, and innate lymphoid cells (ILCs) (21). In short, these studies define a critical role for T cells as a target of IL-2 and led to a greater understanding of T_{reg} cells in intestinal homeostasis (Fig. 2).

Beyond IL-2 and IL-10, spontaneous and chronic intestinal inflammation was also reported in mice lacking $\text{TCR}\alpha$, $\text{TCR}\beta$, $\text{TCR}\delta$, or MHC-II (5). The intestinal disease in these mice exhibits chronic diarrhea, a wasting syndrome associated with anorectal prolapse. However, athymic or $\text{Rag1}^{-/-}$ mice did not exhibit

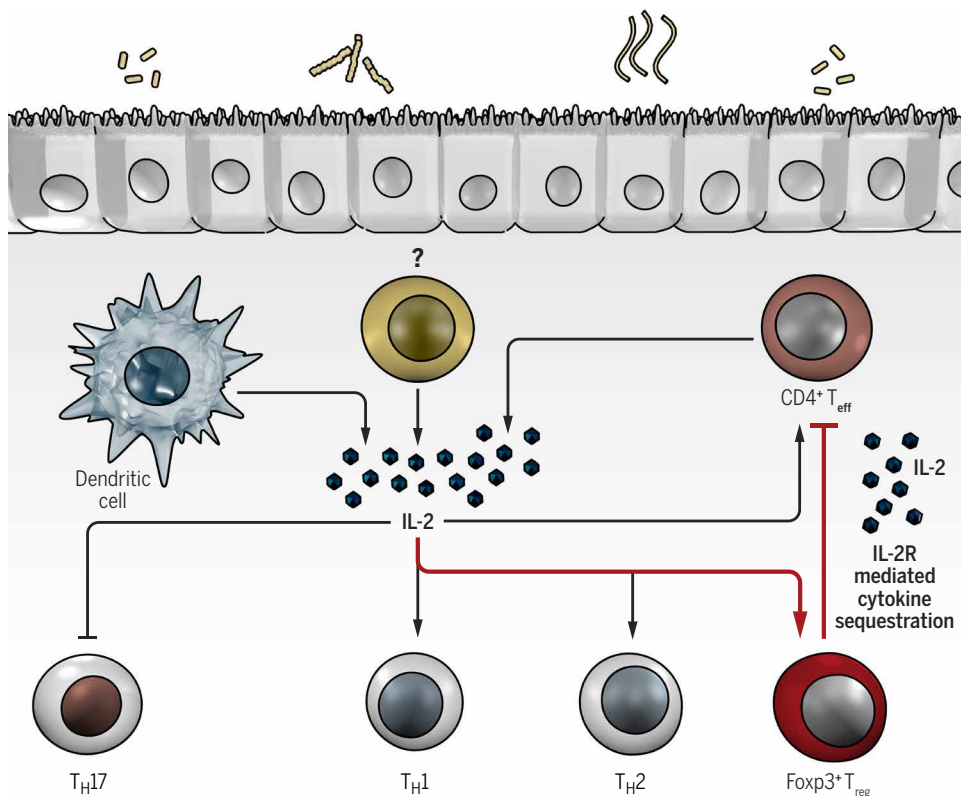


Fig. 2. IL-2-dependent regulation of intestinal health. During intestinal homeostasis, IL-2 is produced by activated CD4⁺ T cells, DCs, and other unknown cells. IL-2 is mainly consumed by regulatory T cells and activated CD4⁺ T cells. It is now widely appreciated that IL-2 promotes the differentiation of TH1 cells, TH2 cells, and T_{reg} cells while inhibiting TH17 cells. Moreover, T_{reg} cells efficiently sequester IL-2 from effector T cells and use it to maintain high levels of CD25 and Foxp3 expression, enhancing its suppressive capacity. Essential pathways that prevent spontaneous inflammation are highlighted in red.

any spontaneous disease, suggesting that dysfunction of $\alpha\beta$ T cells, especially MHC-II-restricted CD4⁺ T cells, may underlie the pathogenesis of intestinal inflammation (5). A recent study found that the absence of MHC-II on conventional DCs resulted in chronic intestinal inflammation as well, suggesting that DC-mediated CD4⁺ T cell priming and subsequent adaptive immune responses, including T_{reg} differentiation, are essential to maintain homeostasis (Fig. 3) (23). Collectively, these seminal findings drove a field forward toward extensive investigation into immunoregulatory cytokines, CD4⁺ T cells, and innate immune populations to better understand intestinal health and disease.

RECIPROCAL HOST-MICROBIOTA INTERACTIONS CRITICALLY INFLUENCE INTESTINAL HEALTH

Housing conditions can dramatically influence the onset and location of intestinal disease in many of the above-described transgenic mice, and enteric microbes were subsequently found to be necessary for the development of spontaneous intestinal inflammation (1). IL-10-deficient mice that were rederived under germ-free conditions failed to develop colonic inflammation, and this could be recapitulated by treatment with broad-spectrum antibiotics before disease onset. Antibiotics also attenuate disease severity in *Il10*^{-/-} mice after the development of spontaneous colitis, and germ-free

Il10^{-/-} mice develop chronic colitis after colonization with normal enteric microflora or selected species of microbes derived from healthy wild-type mice (24, 25). *Helicobacter* is indispensable for colonic inflammation in *Il10*^{-/-} mice; however, *Helicobacter* alone is insufficient to induce disease, suggesting that alteration in the microbial community or change in bacterial metabolism may affect colitis development (26). Consistent with this, IL-10-deficient mice have reduced probiotic bacteria, such as *Lactobacillus*, and treating IL-10-deficient mice with different species of *Lactobacillus* effectively prevents or attenuates colitis (27). A probiotic bacteria mixture containing a combination of eight bacteria treatment could also substantially ameliorate the development of colitis in *Il10*^{-/-} mice with established disease (28). Thus, IL-10 can influence the colonization of selective bacteria species in the gastrointestinal tract, and reciprocally, the microflora exerts a crucial role in preventing or controlling disease progression.

Attenuated colitis is also observed in IL-2-, TCR α -, or TCR β -deficient mice housed in a specific pathogen-free environment, and there was no clinical or histologic evidence of colitis in germ-free conditions, although a mild, focal, and nonlethal colonic inflammation was reported in older gnotobiotic IL-2-deficient mice (29, 30). Subsequent studies revealed that abundant *Escherichia coli* accumulate in *Il2*^{-/-} mice, whereas limited *E. coli* was detected in control mice. Monocolonization of gnotobiotic *Il2*^{-/-} mice with the *E. coli* strain mpk, but not *E. coli* Nissle, is sufficient to induce colonic inflammation. Also, *Bacteroides vulgatus* mpk protects against *E. coli* mpk-induced colitis in gnotobiotic *Il2*^{-/-} mice (31, 32). In addition, the absence of MHC-II on conventional DCs resulted in intestinal inflammation, which could be alleviated by antibiotic treatment and entirely averted under germ-free conditions (23). Together, these studies demonstrate that the intestinal microbiota are essential for the development of spontaneous intestinal inflammation in mice and are likely targets of aberrant immune responses when there is a disruption in immunologic homeostasis. Furthermore, they imply that there are strain-specific differences in microbes that critically influence intestinal disease.

Subsequent seminal studies have revealed that the intestinal microbiota critically influence the composition of lamina propria CD4⁺ T cell subsets, in particular TH17 and T_{reg} cells. Colonization of mice with segmented filamentous bacteria (SFB) results in a marked expansion of TH17 cells. SFB could penetrate the mucus layer in the terminal ileum and closely interact with the epithelial cells, resulting in TH17 differentiation within the lamina propria through MHC-II-dependent antigen presentation of SFB antigens by intestinal DCs and induction of serum amyloid A from intestinal epithelial cells (33–35). Recently, it was also found that a number of other intestinal

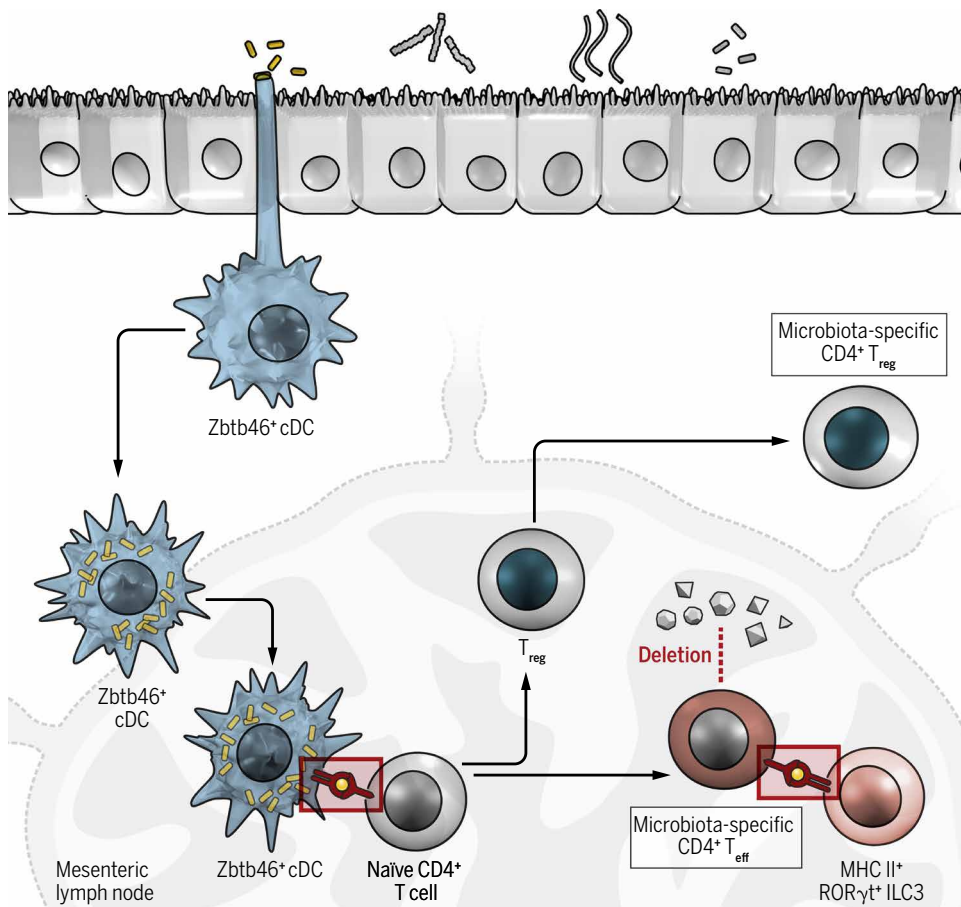


Fig. 3. Regulation of intestinal health by antigen presentation. Microbiota are sampled by intestinal Zbtb46⁺ conventional DCs (cDCs), and bacteria-loaded cDCs then migrate to the draining mesenteric lymph nodes and activate naïve CD4⁺ T cells by presenting commensal bacteria-derived antigen via MHC-II, resulting in the differentiation of effector and regulatory microbiota-specific CD4⁺ T cells. MHC-II⁺ RORγt⁺ ILC3s contact antigen-experienced T effector cells, resulting in deletion of commensal bacteria-specific CD4⁺ effector T cells, a process termed intestinal selection. In addition, activated CD4⁺ T cells partly differentiate into T_{reg} cells, which migrate to lamina propria and regulate intestinal homeostasis. Essential pathways that prevent spontaneous inflammation are highlighted in red.

microbes are sufficient to induce T_H17 cell responses in the intestine, in part through similar epithelial adhesion mechanisms (36). Gut microbes are also important for intestinal T_{reg} cell differentiation. Colonization of gnotobiotic mice with a complex cocktail of cluster IV and XIV *Clostridia* strains increased the development of IL-10-expressing inducible T_{reg} cells, which occurs in part through potent induction of transforming growth factor-β (37, 38). *Bacteroides fragilis*-derived polysaccharide A (PSA) can also promote accumulation of colonic IL-10-expressing T_{reg} cells via the TLR2-MyD88 signaling pathway (Fig. 1) (39). Furthermore, *Clostridia* species produce short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate, resulting from the fermentation of dietary fiber. SCFAs are absorbed by colonic epithelial cells or diffuse into lamina propria and help to induce colonic T_{reg} cell differentiation through multiple proposed mechanisms (40–42).

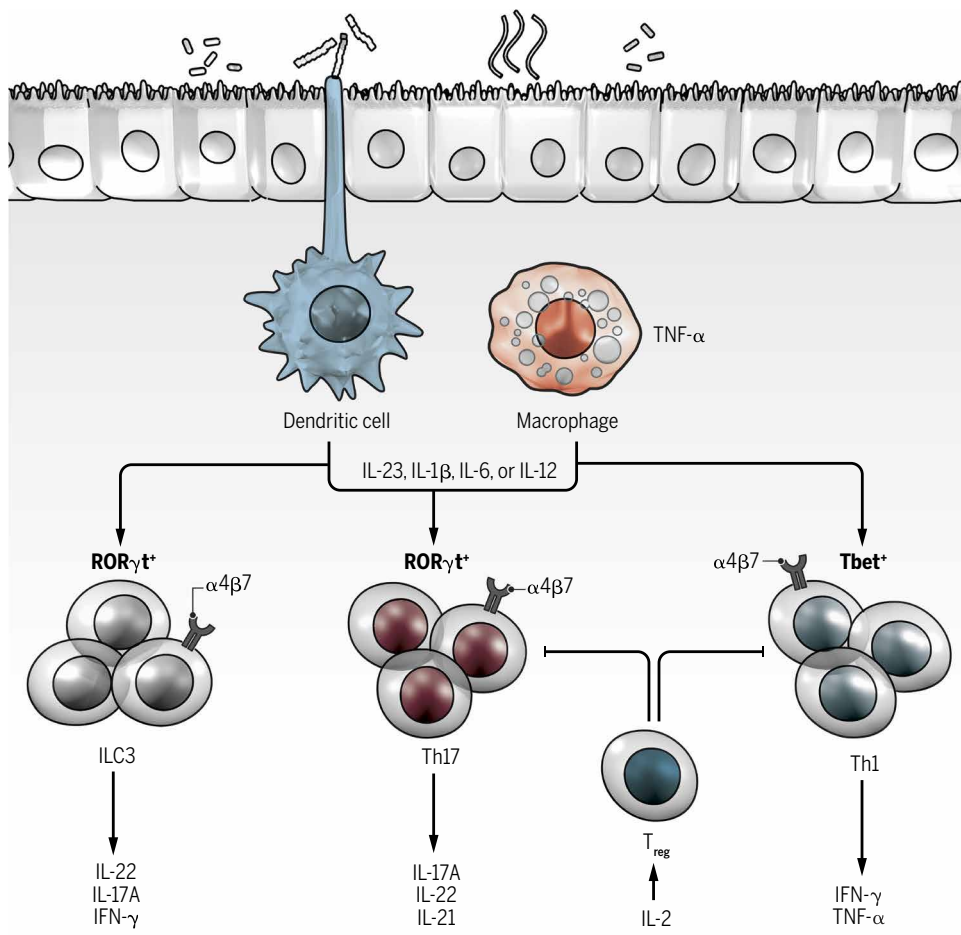
Defects in the host immune system reciprocally influence microbial communities and cause intestinal dysbiosis, which, in some contexts, is sufficient to drive chronic inflammation in the gut. For example, mice lacking both the transcription factor T-bet and Rag2, named

TRUC mice, develop spontaneous colonic inflammation in a microbiota-dependent manner. This phenomenon was horizontally transmissible to wild-type mice by either cohousing or adoptive transfer of the TRUC mice microbiota. It was proposed that loss of T-bet in the innate immune system leads to overproduction of tumor necrosis factor-α (TNF-α) in DCs and subsequently induces epithelial cell death (43). Later studies uncovered that *Helicobacter typhlonius* may drive excess TNF-α production and promote colitis in TRUC mice (44). Another example of dysbiosis driven by immunologic defects is observed in mice deficient for the inflammasome component NLRP6. These mice displayed spontaneous colitis that was communicable to wild-type mice after cohousing. *Prevotellaceae* was recognized as a causative agent of this inflammatory phenotype (45). However, these results have been called into question by a recent report that did not observe dysbiosis or spontaneous disease in littermate controls (46). These findings suggest that disruption of immune responses in the gut can induce microbial dysbiosis, and dysbiosis alone can drive the intestinal inflammation in several contexts.

ILC REGULATION OF INTESTINAL HOMEOSTASIS

The IL-10Rβ chain is also used by another member of the IL-10 cytokine family, IL-22, which critically influences intestinal health and homeostasis by acting exclusively on nonhematopoietic cells. IL-22 is a pleiotropic cytokine that promotes intestinal tissue repair, protects from intestinal pathogens, and anatomically restricts select intestinal microbiota (47–49). These functions are in part due to IL-22-mediated induction of mucus or antimicrobial proteins in intestinal epithelial cells—including REGIIIβ, REGIIIγ, S100A8, and S100A9—that limit colonization with commensal bacteria, such as SFB. Conversely, IL-22 also induces fucosylation of intestinal epithelial cells, which promotes colonization with beneficial bacteria and protects from *Salmonella typhimurium* and *Citrobacter rodentium* infection (50–52). IL-22 is also context-dependent and can promote intestinal inflammation in response to *Toxoplasma gondii* infection or in models of innate cell-mediated colitis (47).

Although originally thought to be a T cell-derived cytokine, studies of IL-22 contributed to recent revolutionary findings in mice and humans that identified populations of innate lymphocytes, known as ILCs, and defined these cells as critical regulators of immunity, inflammation, and homeostasis in the intestine. ILCs are subdivided into three subgroups on the basis of their transcription factor expression profile, including T-bet⁺ group 1 ILCs (ILC1), GATA3⁺ group 2 ILCs (ILC2), and RAR-related orphan receptor-γt⁺ (RORγt⁺) group 3



Microbes:
Fecal microbiota transplantation*

Integrin:
α4β7 (Vedolizumab, Etrolizumab, and Natalizumab)*

Signaling and transcription factors:
JAK-STAT (Tofacitinib, ABT494, and Filgotinib)*
RORγt#

Cytokines:
TNF (Infliximab, Adalimumab, Golimumab, and Certolizumab pegol)*
IL-12/23 p40 (Ustekinumab and Briakinumab)*
IL-23 p19 (Risankizumab)*
IL-2 (Low-dose exogenous cytokine)*
IL-6 (PF-04236921)*
IL-22 (blockade and exogenous cytokine)#
IFN-γ (Fontolizumab)*
IL-17A/IL-17RA (Secukinumab, Brodalumab)*

Fig. 4. Current and potential therapeutic targets in IBD. A number of current and potential future targets exist to provide therapeutic benefit in the context of IBD. These targets influence the generation, maintenance, or effector function of innate and adaptive immune cells. Symbol definitions: ♦, efficacy exhibited in clinical trials; *, FDA-approved and providing clinical benefit; #, promising preclinical target in mouse models; ✖, failed or poor efficacy in clinical trials.

ILCs (ILC3) (53). ILC3s contribute to intestinal health through several distinct pathways. ILC3s have a bidirectional relationship with the gut microbes because the development and activation of ILC3 are regulated by intestinal microbiota-derived signals, and further, the effector function of ILC3 influences microbial composition and intestinal homeostasis (54). In response to myeloid cell-derived IL-1β and IL-23 after recognition of microbial signals or microbiota-derived metabolites (such as aryl hydrocarbon receptor ligands), ILC3s produce IL-22, IL-17, IFN-γ, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (54, 55). Among these cytokines, IL-22 is dominantly produced by ILC3 in the intestine and associated lymphoid tissues. During homeostasis, disruption

of the ILC3–IL-22 pathway leads to defects in anatomical containment of selective microbiota that reside in the lymphoid tissue, termed lymphoid tissue–resident commensal bacteria (LRCs) (48). LRCs also induce IL-22 production by ILC3 and myeloid cell–derived IL-10, which collectively enhance LRC colonization and protected mice from lethal intestinal damage (56). IL-22 production by ILC3 is also essential for regulating the composition of intestinal microbes and facilitating colonization resistance. Resistance to intestinal *C. rodentium* infection in mice is dependent on IL-22 signaling, and ILC3 is the dominant source of IL-22 in the first week after infection; then, T cell–derived IL-22 and B cells contribute largely to resistance and clearance of the infection (49, 57). Other than IL-22, ILC3-derived IL-17, which can act alone or synergistically with IL-22, promotes antimicrobial peptide production from intestinal epithelial cells and induces chemokine expression to recruit neutrophils during pathogen infection (47, 49).

ILC3s also regulate intestinal homeostasis or inflammation through direct and indirect interaction with adaptive immune responses. ILC3s secrete lymphotoxin-α3 or express surface lymphotoxin-α1β2, which stimulates the T cell–dependent or –independent production of immunoglobulin A, respectively, modulating the composition of the gut microflora (58). ILC3s regulate homeostasis of myeloid cells in the intestine through production of GM-CSF, which promotes T_{reg} cell responses to food antigens and maintains oral tolerance (55). ILC3s were also found to express high levels of MHC-II and directly present antigens to CD4⁺ T cells. Surprisingly, this interaction results in the inhibition of microbiota-specific CD4⁺ T cells, and genetic deletion of ILC3-intrinsic MHC-II leads to the development of spontaneous CD4⁺ T cell–dependent intestinal inflammation (59). Mechanistically, MHCII⁺

ILC3 mediated cell death of microbiota-specific CD4⁺ T cells in the intestine; this has been termed “intestinal selection,” given a number of similarities to what occurs during thymic selection, and further establishes a paradigm of how antigen presentation regulates intestinal health (Fig. 3) (60).

ESSENTIAL IMMUNOLOGIC PATHWAYS IN HUMAN IBD

Human IBD involves a complex interplay between genetic risk factors and extrinsic environmental triggers, such as the microbiota. Genome-wide association studies (GWASs) have identified about

200 susceptibility genes associated with IBD, most of which are involved in regulating intestinal barrier function and host-microbe interactions (61, 62). These analyses helped to provide insight into disease pathobiology and promote advances in diagnostics and therapies. IL-10 signaling and IL-10R signaling were recognized early on as human IBD risk alleles through GWASs (61, 63), and further studies also identified IL-2 and IL-2R (64). Human lymphocyte antigen polymorphisms also highly segregate IBD cohorts, suggesting a critical role for antigen presentation (62). Genomic loss-of-function mutations in *IL10*, *IL10RA*, *IL10RB*, and *IL2RA* have also been described to cause a particular form of IBD—termed very early onset IBD (VEO-IBD)—that develops at early stages of life and is thought to be the result of a monogenic mutations (65). However, these mutations only represent a small population of VEO-IBD patients, and advances in whole-exome sequencing are rapidly identifying additional variants.

The role of ILCs in human IBD is still in the early stages of investigation; however, several studies have reported that ILC frequencies or responses are altered in the context of Crohn's disease. An expansion of IL-17- and IL-22-producing ILC3 was noted in the inflamed mucosa of patients with Crohn's disease, and these were dependent on the fecal stream, suggesting either a pathogenic or a compensatory protective role (66, 67). By contrast, other studies have suggested that a reduction in ILC3 occurs in Crohn's disease and that human ILC3 may exhibit plasticity, differentiate into proinflammatory ILC1 or ex-ILC3, and produce IFN- γ (68). Furthermore, the expression of MHC-II on ILC3 is lower in patients with Crohn's disease as compared with healthy controls, and the reduced expression of MHC-II is inversely correlated with intestinal T_H17 cells, which suggests that ILC3 may limit pathogenic T cells through MHC-II in Crohn's disease, as described in mice (59, 60).

Various therapeutic advances have been applied to clinical management of patients with IBD (Fig. 4). Among these therapeutic strategies, blockade of TNF has provided substantial therapeutic benefit in some but not all patients, and further, patients can go on to lose responsiveness (69). There has been an urgent search for other effective cytokine blockade strategies. IL-12 p35-p40 and IL-23 p19-p40 are two heterodimeric proinflammatory cytokines that are induced in the inflamed mucosa in patients with Crohn's disease and represent promising targets. Ustekinumab, an anti-p40 monoclonal antibody therapy, was recently approved by the U.S. Food and Drug Administration (FDA) for treatment of moderate to severe Crohn's disease. However, several cytokine blockade trials have yielded disappointing results. For example, blockade of IL-17 resulted in aggravation of Crohn's disease and increased susceptibility to fungal infections in a number of patients (70)—possible reasons being the protective roles of IL-17 on intestinal epithelial cells or disrupting ILC3–IL-17-mediated protection from opportunistic fungal infection (54, 71). Other promising therapies that were recently approved, or are in the clinical or preclinical trials, include targeting the integrin α 4 β 7 to limit immune cells' recruitment to the intestine and small-molecule inhibitors targeting transcriptional regulators or kinases downstream of cytokine receptors (69). Targeting the ILC3 and T_H17 cell transcription factor ROR γ t may hold particular promise, given its ability to selectively target proinflammatory responses while preserving tissue protection and innate immunity (72).

The balance of effector and T_{reg} cells in intestinal homeostasis suggests a therapeutic potential of boosting T_{reg} cells in human IBD.

Clinical trials and studies have shown that low-dose IL-2 specifically expands and activates T_{reg} cell populations and thus might be a promising strategy for human IBD therapy (73). Furthermore, other strategies aim at delivering T_{reg} cell-inducing microbiota or microbiota-derived products; however, the clinical efficacy of probiotic or fecal microbiota transplantation in IBD has thus far demonstrated limited efficacy.

FUTURE DIRECTIONS AND PERSPECTIVES ON HOST-MICROBIOTA INTERACTIONS AND INTESTINAL HOMEOSTASIS

Since the discovery of several transgenic mouse lines that develop spontaneous intestinal inflammation, there have been an astounding number of exciting scientific and technical advances that paved the way for a better understanding of the immune mechanisms that maintain a state of health in the mammalian gastrointestinal tract. Immunologic mediators remain the primary therapeutic targets to limit inflammation in IBD, but there is an urgent need to develop safe and effective strategies that hold preventative or ideally curative potential. Recent appreciation of sophisticated and reciprocal host-microbiota interactions will also allow advanced determination of whether we can harness the microbiota or related by-products as a tractable treatment or target. These goals can only be achieved through the continued investigation of mouse models and innovative exploration of patient-oriented translation research that will continually challenge paradigms and advance our scientific understanding of intestinal health toward preventative and curative strategies of intestinal diseases.

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Abstract

One-sentence summary: This Review discusses how seminal findings have shaped our current understanding of homeostasis and host-microbiota interactions in the mammalian intestine.

Essential immunologic orchestrators of intestinal homeostasis

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