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Conflict of Interest
The authors declare no potential conflicts of interest.

Abbreviations
AHR, aryl hydrocarbon receptor; APC, antigen presenting cell; BA, bile acid; CAC, colitis-associated cancer; CD, Crohn's disease; DC, dendritic cell; DSS, dextran sulfate sodium; ETBF, enterotoxigenic B. fragilis; FMT, fecal microbiota transplant; GF, Germ-free; GPR,

Context-Dependent Regulation of Type17 Immunity by Microbiota at the Intestinal Barrier

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ABSTRACT

T-helper-17 (Th17) cells and related IL-17-producing (type17) lymphocytes are abundant at the epithelial barrier. In response to bacterial and fungal infection, the signature cytokines IL-17A/F and IL-22 mediate the antimicrobial immune response and contribute to wound healing of injured tissues. Despite their protective function, type17 lymphocytes are also responsible for various chronic inflammatory disorders, including inflammatory bowel disease (IBD) and colitis associated cancer (CAC). A deeper understanding of type17 regulatory mechanisms could ultimately lead to the discovery of therapeutic strategies for the treatment of chronic inflammatory disorders and the prevention of cancer. In this review, we discuss the current understanding of the development and function of type17 immune cells at the intestinal barrier, focusing on the impact of microbiota-immune interactions on intestinal barrier homeostasis and disease etiology.

Keywords: Type17 immunity; Intestinal microbiome; Intestinal barrier; Antigen presentation; Microbial metabolite; Inflammatory bowel diseases (IBDs), Colitis-associated cancer (CAC); RORγt

INTRODUCTION

Mammalian mucosal barriers of the intestine interact with the external environment and consequently are exposed to potential immune modulators, including microbiota and dietary antigens (Ags) (1-6). As such, maintaining the barrier's homeostasis requires a precise balance of immune surveillance and tolerance (1). Due to large communities of commensal microbes found in the gut, the intestinal barrier requires continual surveillance by immune cells (1-9). Along with their canonical protective activities, resident and recruited immune cells provide instructional signals to intestinal barrier compartments to stimulate healing (3,4,10,11) (**Fig. 1** left). In contrast, uncontrolled immune responses caused by gut microbiota disturbance can lead to life-threatening chronic inflammatory disorders such as inflammatory bowel disease (IBD) (2,12) and colitis-associated cancer (CAC) (3,13,14) (**Fig. 1** middle and right). Therefore, clarity around the interaction between immune cells and intestinal microbes, in addition to non-immune parenchymal compartments of the intestinal barrier, will contribute
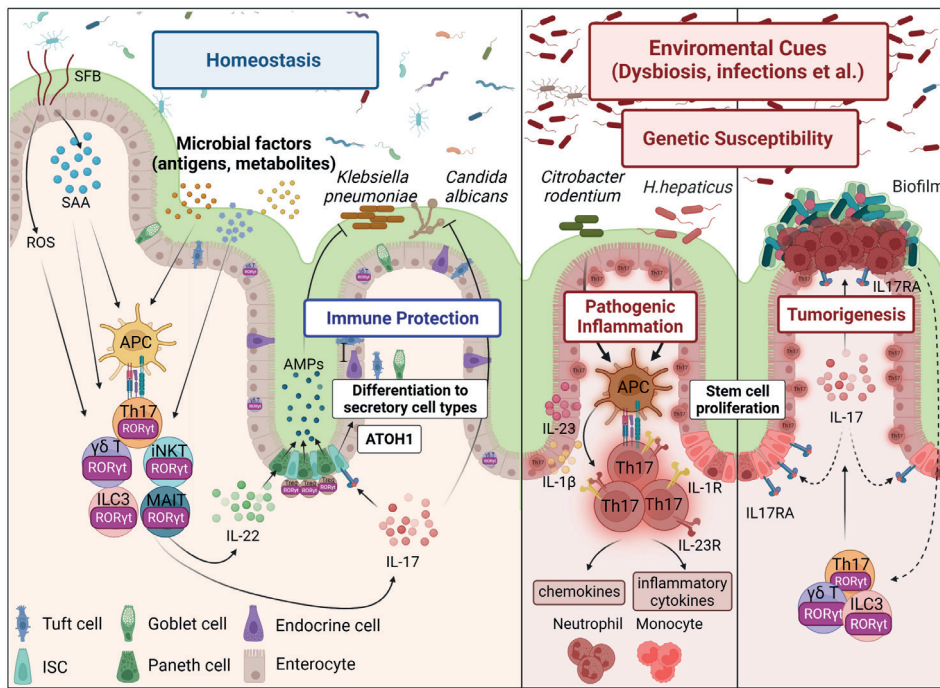
Figure 1. Dynamic interactions between the microbes and type17 immune cells at intestinal barrier in homeostasis and illness. Gut microorganisms have a critical role in the formation and function of type17 immune cells in the lamina propria. Colonization with SFB stimulates Th17 cell accumulation in the ileum via IEC-production of SAAs, which can induce Th17 differentiation by acting on APCs or directly influence Th17 effector functions. Moreover, microbial antigens and metabolites participate into regulation of type17 immunity, which is illustrated detailed on **Fig. 4**. Type17 immune cells secrete cytokines, including IL-22 which stimulates antimicrobial responses via intestinal epithelium AMPs production and immune effector functions. In addition, IL-17A/F mediated crosstalk between the immune cells and ISCs modulates the secretory cell lineage commitment and mucosal integrity. IL-17A/F promotes differentiation of ISCs into Tuft, goblet and endocrine cells by increasing ATOH1 expression. These actions of type17 cytokines contribute to immune defense against pathogenic microorganisms, such as *Klebsiella pneumoniae* and *Candida albicans*. On the other hand, when bacteria such as *Citrobacter rodentium* or *Helicobacter hepaticus* induce tissue inflammation by generating a pro-inflammatory Th17 response, this is referred to as microbial dysbiosis or immunological dysregulation. By secreting chemokines and proinflammatory cytokines, pathogenic Th17 cells recruit neutrophils and inflammatory monocytes to the inflamed intestinal lamina propria in response to IL-23 and IL-1β signaling. In genetically predisposed hosts, dysbiosis of gut microbiota and bacterial biofilm formation lead to intestinal inflammation, which is associated with cancer progression. The signaling of IL-17/IL-17RA promotes carcinogenesis by inducing the growth and survival of transformed IEC deficient Adenomatous polyposis coli (*APC*) gene expression.

G-protein-coupled receptor; HDAC, histone deacetylase; IBD, inflammatory bowel disease; IEC, intestinal epithelial cell; IEL, intraepithelial lymphocyte; ILC3, 3 innate lymphoid cells; iNKT, invariant natural killer T; ISC, intestinal stem cell; LRP1, low-density lipoprotein receptor-related protein 1; MAIT, mucosal-associated invariant T; mitoROS, mitochondrial ROS; mLN, mesenteric lymph nodes; MNP, mononuclear phagocyte; MR1, MHC class I–related protein 1; pTreg, peripheral Treg; SAA, serum amyloid A; SCFA, Short chain fatty acid; SFB, segmented filamentous bacteria; TFH, T follicular helper; Tr1, T regulatory type 1 cell; Trp, Tryptophan; UC, ulcerative colitis; VDR, vitamin D receptor; VIP, vasoactive intestinal peptide.

to our understanding of tissue homeostasis, which may lead to improved therapeutic strategies for infections, wound healing, and inflammatory diseases.

Type17 immunity, also known as type3 immunity, encompasses both innate and adaptive immune cells which are mediated by the transcription factor RORγt, and defined by the expression of cytokines IL-17A, IL-17F, and IL-22 (4-6). At epithelial barrier sites, the type17 signature cytokines stimulate antimicrobial immune responses and enhance wound healing and tissue regeneration following bacterial and fungal infections, particularly those caused by *Klebsiella pneumoniae* (15,16) and *Candida albicans* (6,17,18) (**Fig. 1** left). In human, mutations in the IL-17 signaling (*IL17RA, IL17RC, ACT1, IL17F*) and type17 master-regulating (signal transducer and activator of transcription 3 (*STAT3*), RAR Related Orphan Receptor C (*RORC*) genes have been linked to chronic mucocutaneous candidiasis (17,18). IL-17A signaling in Lgr5⁺ intestinal stem cells (ISCs) promotes secretory cell lineage commitment, such as Paneth, tuft, goblet, and enteroendocrine cell, by expression of transcription factor ATOH1 during homeostasis and injury responses (19) (**Fig. 1** left). These findings indicate that type17 immunity plays a dominantly protective role that maintains the integrity of the intestinal barrier. On the other hand, type17 immune cells are also important drivers of a variety of chronic inflammatory disorders, including autoimmune diseases and IBD, and have been linked to inflammation associated with epithelial carcinogenesis (20-22) (**Fig. 1** middle and right). The increased entry

of bacterial components into host epithelium and intestinal lamina propria can contribute to the formation of a tumor-promoting environment by activating type17 immune responses and promoting the tumorigenesis of colorectal cancer (21,23) (**Fig. 1** right).

The dynamic interaction between commensal microbiota and the mammalian immune system manifests in both homeostasis and disease (3-6,24,25). Specific species of the intestinal microbiota are essential for the formation and maturation of both innate and adaptive type17 immune cells, whereas type17 immunity orchestrates the maintenance of fundamental host-microbe symbiosis characteristics (24,25). In genetically susceptible hosts, perturbations in microbiota-immune interactions under specific environmental conditions result in the pathogenesis of a variety of type17-mediated disorders (4,6) (**Fig. 1**). In this review, we illustrate and discuss the current knowledge and key concepts that critically impact the microbiome's role in the development and function of the type17 immune system in intestinal lamina propria. We review the existing mechanistic dissections of complex microbiome-immune interactions within the intestinal barrier during homeostatic and diseased states. Additionally, we discuss the challenges and opportunities associated with studying disease pathogenesis of IBD and CAC and developing new type17-related therapeutic interventions using microbiome-targeted strategies.

MICROBIOME-MEDIATED TYPE17 IMMUNE RESPONSE

Numerous subsequent studies in mice (26-31) have shown that intestinal microbiota and the ability of the host to recognize and respond to its constituents are important in the generation and optimal function of local immune cells, especially Th17 cells and peripheral regulatory T cells. Intriguingly, microflora from IBD patients can trigger inflammatory Th17 responses and predispose mice to chronic colitis (32,33), suggesting that these bacteria may contribute to the pathogenic T cell responses observed in IBD patients. In addition to the extensively researched Th17 cells, type17 immunity also consists of lymphocytes with innate-like properties (4-6). The Innate-like and unconventional type17 lymphocytes, including group 3 innate lymphoid cells (ILC3), γδ T cells, intraepithelial lymphocytes (IELs), invariant natural killer T (iNKT) cells, and mucosal-associated invariant T (MAIT) cells, seed the intestinal barrier, and play a role in the long-term maintenance of homeostatic responses to microbiota (4-6) (**Fig. 1**). These unconventional type17 lymphocytes recognize entire groups of microbes simultaneously by detecting microbe-derived lipid and glycolipid Ags as well as microbial metabolic intermediates through monomorphic Ag-presenting molecules such as MHC class I–related protein 1 (MR1) and CD1d (34-36). Indeed, the capacity of innate-like type17 lymphocytes to respond to non-canonical Ags originating from a broad proportion of the microbiota makes them potent regulators of tissue physiology, such as intestinal barrier protection, wound healing, and the augmentation of conventional T cell-mediated responses (4-6). The following section summarizes our current understanding of microbiota immune recognition by type17 lymphocytes with a particular emphasis on the ontogeny, specificity, and function of commensal-specific responses at barrier sites.

Context-dependent Th17 responses to the microbiota

Two functionally distinct populations of Th17 cells develop differently in response to context-dependent environmental cues: tissue-resident, homeostatic Th17 cells that contribute to gut homeostasis (5,6), whereas proinflammatory Th17 cells are involved in the development of a variety of inflammatory disorders (37-39) (**Figs. 1** and **2**).

The microbiota plays a significant role in regulating the differentiation of homeostatic and pathogenic Th17 cells in the gut. Of this microbiota, the most studied segmented filamentous bacteria (SFB) attach to epithelial cells in the terminal ileum and induce naïve Ag-specific CD4⁺ T cells in the draining mesenteric lymph nodes (mLN) to increase transcription factor RORγt expression and differentiate into Th17 cells (6,26,27,32,40,41) (**Fig. 2** left). These Th17 cells then migrate to the intestinal lamina propria, where they perform homeostatic functions, such as wound healing (42-44). An SFB-triggered circuit in which ILC3 secretion of IL-22 is critical for local epithelial production of serum amyloid A (SAA)1 and SAA2, which act directly on poised Th17 cells to amplify effector cytokine production (42) (**Fig. 2** left). In the SFB-colonized ileum lamina propria, CD11c⁺ cells stimulate SFB-specific Th17 cells via MHCII loaded with bacterial Ags (32,40). Commensal-induced Th17 cells strengthen the epithelial barrier by increasing the expression of antimicrobial defensins, apical NADPH oxidase, and the transcytosis of secretory IgA, thereby enhancing the host's protection against pathogens (45) (**Figs. 1** and **2**).

While SFB induces non-inflammatory and protective Th17 cells, enteric pathogens, such as *Citrobacter rodentium* (*C. rodentium*) (39), trigger pathogenic Th17 cell differentiation in inflammatory conditions, indicating that Th17 cell function is context-dependent (**Fig. 2** right). Contrary to conventional pathogens that cause disease in healthy hosts, emerging data suggest that microbial species associated with chronic inflammation are typically harmless and widely colonize in healthy persons (46). These types of resident pathogenic microorganisms, such as *Helicobacter hepaticus* (*H. hepaticus*) (46-49), *Enterococcus faecalis* (50,51), have been referred to as "pathobionts" (46) because their pathogenic function is "dual-faced" depending on an additional factor such as genetic susceptibility or environmental context of the host. Particularly, *H. hepaticus* has been causally linked to large-bowel inflammation in immunocompromised mice (e.g. *IL-10/IL-10R*-knockout), but it induces no overt pathology in wild-type animals (47,52). At steady state, the majority of *H. hepaticus*-induced Th cells are RORγt⁺FOXP3⁺ peripheral Treg (pTreg), which are necessary for gut homeostasis maintenance (47) (**Fig. 2** left). In contrast, under inflammatory conditions and/or Treg dysfunctions, T cells specific for *H. hepaticus* differentiate into pathogenic Th17 cells with features including T-BET expression together with RORγt and pro-inflammatory cytokines IFN-γ and IL-17 (47) (**Fig. 2** right). Proinflammatory cytokines, IL-1β, IL-23 and SAAs signal
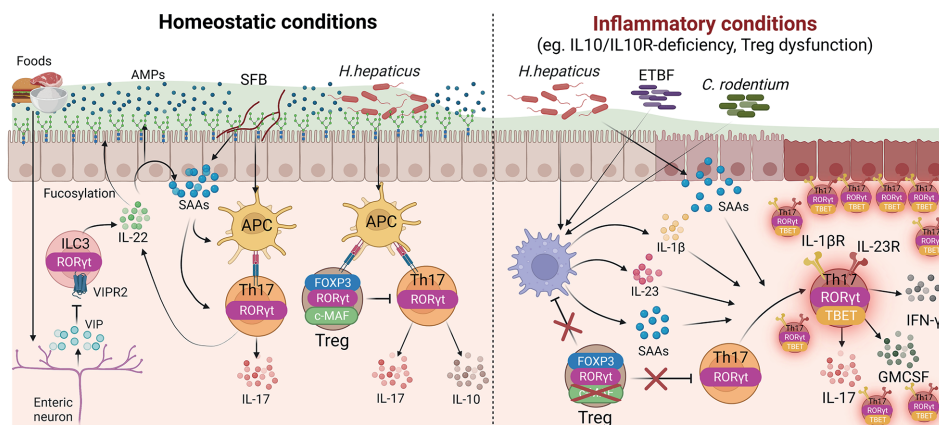

Figure 2. Context-dependent regulation of the Th17 plasticity during homeostasis and disease. During homeostasis, SFB colonization in the small intestine promotes homeostatic Th17 cell differentiation, whereas *H. hepaticus* induces RORγt⁺ Treg, expressing c-MAF, and limiting Th17 cells during homeostasis. The neuropeptide VIP released from enteric neurons following food intake induces IL-22 production in ILC3s, protecting the intestinal epithelial barrier integrity by promoting fucosylation and AMP production in IECs. Bacterial colonization in mice with immune dysfunction such as IL-10/IL-10 receptor loss or Treg dysfunction (MAF-deficient), leads to the development of a pathogenic Th17 phenotype, secreting the pro-inflammatory cytokines, GM-CSF and IFN-γ, which are induced by *H. hepaticus* through SAAs, IL-23R signaling, as well as IL-1R signaling.

into T cells promoting their proliferation and accumulation in the colon and favor the development of the IL-17A^{+}IFN-γ[+] pathogenic Th17 cells while inhibiting *FOXP3* expression (38,48,53) (**Fig. 2** right). Additionally, the transcription factor c-MAF is necessary for pTreg differentiation (54) (**Fig. 2**). c-MAF affects both the differentiation and function of CD4^{+} T cells in distinct T cell subtypes, including the regulation of IL-10 production in various Th cell populations and repression of IL-22 in Th17 cells, via a TGF-β-dependent mechanism involving direct binding of c-MAF to the IL-22 promoter (55). During colonization with *H. hepaticus*, the homeostatic state is maintained by RORγt[+] Treg, which mediate host tolerance to bacteria and inhibit pro-inflammatory Th17 cells in a c-MAF-dependent manner, however pTreg-specific deletion of c-MAF leads to impaired intestinal Treg differentiation and function, including diminished IL-10 production and promotes differentiation of bacteria-specific specific pathogenic Th17 cells and spontaneous colitis (**Fig. 2** right) (47).

Despite extensive *in vitro* and *in vivo* research (37,56,57), however, the local differentiation cues that distinguish homeostatic type17 functions, such as those that maintain intestinal epithelial integrity, from pathogenic type17 functions associated with the pathogenesis of chronic inflammatory diseases are not fully understood. For the development of more effective treatments, a deeper understanding of the upstream regulators that initiate cell type-specific and context-dependent pathogenic Th17 programs will be necessary.

ILC3 cells

ILC3 cells are Ag-independent innate-like type17 cells that express RORγt and contribute to maintaining intestinal homeostasis using a variety of mechanisms (57-60). Unlike the adaptive lymphocytes, which are activated in lymph nodes following Ag recognition and migrate to the inflammation site, activation of the tissue-resident ILC3s occurs directly in the intestine, mediated by inflammatory cytokines (58-61). ILC3s are a heterogeneous population that may develop into either the lymphoid tissue inducer (LTi) lineage or ILC3 cells that express the natural cytotoxic receptor (62). By stimulating intestinal epithelial cells (IECs) and regulating Th17 cell function, ILC3 cells play a key role in the control of host-microbiota interactions (63) (**Figs. 1** and **2**). The relationship between the intestinal microbiota and ILC3 is bidirectional; gut microbes and microbial metabolites regulate IL-22 production in ILC3s, while ILC3-secreted IL-22 acts on the microbiota both directly and indirectly through IEC regulation (61) (**Figs. 1** and **2**). ILC3-produced IL-22 induces antimicrobial peptide (AMP) production in IECs (61) and play a prominent role in epithelial fucosylation, which is required for the establishment of an environmental niche for commensal bacteria in the small intestine (64) (**Figs. 1** and **2**). ILC3s interact with non-immune parenchymal cells as well as gut microorganisms to control IL-22 production (65). The neuropeptide vasoactive intestinal peptide (VIP), which is generated by enteric neurons, is triggered by food intake and aids in nutrient absorption and mounts immunological responses by suppressing IL-22 production in ILC3s in a VIP receptor VIPR2-dependent manner, increasing host vulnerability to *C. rodentium* infection (65) (**Fig. 2** left).

MAIT cells

MAIT cells are another unconventional subset of T cell that responds to vitamin B2 derivatives such as ribityl-lumazines (7-hydoxy-6-methyl-8-d-ribityllumazine) and 6-(2-oxopropylideneamino)-6-d-ribitylaminouracil (5-OP-RU), which are generated by bacteria delivered through MR1 (66) (**Fig. 3-1**). MAIT cells identify MHC class Ib protein MR1 Ags through the invariant TCR (Vα19 Jα33 in mice and Vα7.2 Jα33 in humans) (35). The notion that the microbiota is critical for the formation and education of immune cells also pertains

to MAIT cells. MAIT cells are absent in animals deficient in microbiota, demonstrating that MAIT cell formation is dependent on commensal bacteria (2). Although the precise activities of these cells in host health and disease remain unclear, barrier-resident MAIT cells are RORγt⁺ and exhibit a type17 effector phenotype in mice (67). In response to local commensal sensing, skin MAIT cells produce IL-17A, which is IL-1 and IL-18 dependent (68) and promotes wound healing (69). MAIT cells provide resistance to various pathogen infections including *Escherichia coli*, *Mycobacterium*, *Klebsiella*, *Francisella*, and *Legionella* (70). MAIT cells also detect acute viral infections through IL-18, IL-15, and type I IFN sensing (71).

γδ T cells

γδ T cells, which are found between the intestinal epithelial cells as IELs, are the initial line of defense against enteric infections (72). γδ T cells are important early responders in a variety of infectious disease models, releasing cytokines such as IL-17 and IFN-γ (73). Certain commensals may increase the frequency of IL-17⁺IL-1R1⁺ T cells, therefore preventing disease (74). γδ T cells generate IL-17A, which protects mice against *Clostridium difficile* infection (75). Vγ9Vδ2⁺ and Vγ9Vδ1⁺ T cell subsets in humans recognize lipids and phosphoantigens such as (E)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP), a microbial precursor of isopentenyl pyrophosphate (76) (**Fig. 3-1**). Microbiota deficiency has no discernible influence on the formation or number of intestinal IELs (72). However, microbiota depletion results
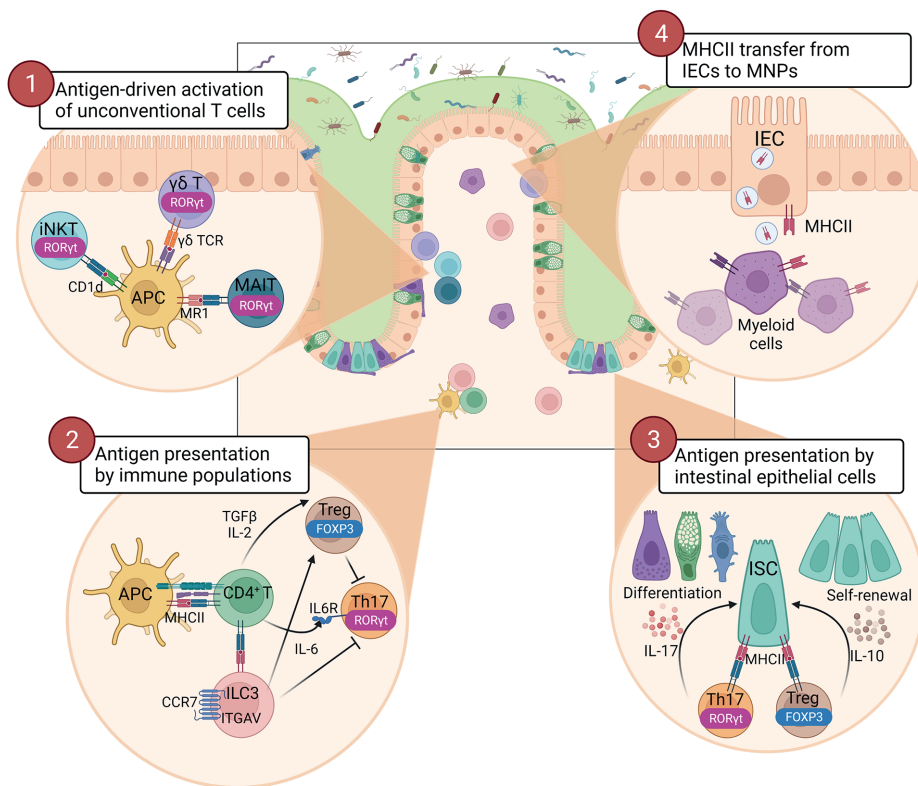

Figure 3. Antigen-dependent regulation of Type17 immune response. 1) Antigen-driven activation of unconventional T cells. NKT cells and MAIT cells recognize bacterial antigens loaded on the Cd1d molecule and MR1 molecule, respectively, which are expressed by APCs. Also, γδ T cells recognize the microbial antigens presented on APCs via γδ TCR. 2) Antigen presentation by immune populations. Professional antigen presenting cells, such as dendritic cells and macrophages, modulate T cell responses to microbiota through MHCII signaling. ILC3 cells also express MHCII molecules and directly interact with T cells. Antigen presentation by ILC3s is essential for Treg cell differentiation in response to *Helicobacter hepaticus* colonization in a CCR7⁻ and αV integrin (*ITGAV*)-dependent manner. 3) Antigen presentation by IECs. Intestinal epithelial expression of MHCII regulates the crosstalk between epithelial cells and CD4⁺ T cells. The contact between ISCs and Tregs promotes self-renewal of stem cells, whereas ISC-Th17 interactions induce differentiation. 4) MHCII transfer from IECs to MNPs. Epithelial MHCII might induce an immune response against microbes through MHCII molecule transfer from IECs to myeloid cells via exosomes.

in altered patterns of IEL localization along the crypt-villus axis, with a considerable shift toward the small intestine crypts due to their high mobility (72). Additionally, regenerating islet-derived protein type 3 (REGIII) synthesis is elevated in small intestine IELs in response to bacterial colonization and in colon-resident IELs following colonic injury caused by dextran sulfate sodium (DSS) (77,78).

iNKT cells

iNKT cells are a distinct type of unconventional T cell that recognize microbial and host-derived glycolipids through the MHC class Ib protein CD1d and express an invariant chain in conjunction with a limited number of TCR chains (34) (**Fig. 3-1**). When activated, iNKT cells rapidly release cytokines and in mice, subsets equivalent to Th1, Th2, and Th17 cells are identified based on their lineage-specific cytokine production (79); however, these features are less apparent in humans (79). Despite recent studies recognizing reciprocal crosstalk between iNKT cells and the microbiota (80), the processes that lead to the differentiation of iNKT cells, particularly those at barrier sites, remain poorly understood. Germ-free (GF) mice exhibit a greater number of immature, hyporesponsive iNKTs in the lamina propria and epithelium of the small intestine and colon (81). Increased CXCL16 chemokine production in the intestines of GF mice lead to increased iNKT cell accumulation compared to SPF animals (81). Additionally, the impact of altered gut microbiota on iNKT cell-dependent inflammation at mucosal surfaces has been reported in research employing GF mice that show CD1d-dependent severe tissue damage and inflammation in IBD (81).

MICROBIAL AG-SPECIFIC PRIMING OF TYPE17 IMMUNITY

Intestinal Ag presenting cells (APCs), which are required to initiate CD4+ T cell responses, are composed of a diverse population of subsets that are defined by cell surface features, transcription factor requirements, ontogeny, and function (82). Although APC subsets are associated with specific functions, the published data are confusing and these interactions are still debated (83-85). This is due to technical challenges associated with identifying all APC subsets in a variety of conditions, most notably during inflammation when multiple subsets change their cell surface markers and alternative subsets form (86). Although it is uncertain which APC subset(s) preferentially trigger or sustain intestinal Th17 or Treg responses, a more comprehensive understanding of this interaction will significantly impact IBD treatment. Recent research has shown that non-traditional APCs are critical regulators of mucosal homeostasis. The expression of MHCII by ILC3 is thought to be required for the clonal eradication of effector Th17 cells (87,88) (**Fig. 3-2**). Additionally, ISCs express MHCII and function as non-conventional APCs, and it is hypothesized that interactions with Th cells govern ISC renewal and differentiation in order to maintain the intestinal barrier integrity (89) (**Fig. 3-3**).

Microbial Ag presentation by immune populations

APCs are a heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting Ags for recognition by lymphocytes. Bacterial activation of Th17 cells in the gut is dependent on intestinal dendritic cells (DCs) presenting commensal bacterial Ags, such as from SFB through MHCII (90,91). During inflammation, the inflammatory DCs, differentiated from Ly6C^hi monocytes, are recruited to the site of inflammation where they present Ag to both CD4+ and CD8+ T cells (92). Inflammatory DCs promote the development of naive CD4+ T cells into Th17 cells via activation of STAT3 by IL6R signaling, which induces expression of the lineage-specific transcription factor RORγt

(70-72) (**Fig. 3-2**). On the other hand, ILC3s restrict the differentiation of Th17 cells by serving as unconventional APCs by directly triggering cell death of activated commensal bacteria-specific T lymphocytes (63) (**Fig. 3-2**). Unsurprisingly, deletion of MHCII on ILC3s leads to low-grade systemic inflammation as a consequence of CD4$^+$ T cell activation and spontaneous IBD formation due to elevated amounts of IL-17, IFN-γ, and TNF-α producing CD4$^+$ T cells in the colon (88,93). ILC3s are also required for microbiota-specific pTreg induction, carried out by the presentation of MHCII Ags, the chemokine receptor CCR7, and α$_v$ integrin (*ITGAV*) that regulates TGF-β activation (**Fig. 3-2**) (94). Additionally, ILC3 expression of MHCII negatively impact the interaction between T follicular helper (T$_{FH}$) cells and B cells, resulting in decreased mucosal IgA production in the colon and associated effects on the microbiota (95).

Ag presentation by IECs: MHCII linking IEC to mucosal immunity

MHCII expression on IECs was first described more than two decades ago (98), but its potential role in mucosal immunity has only recently drawn attention. However, the precise function of epithelial MHCII is still unknown. A recent study revealed that ISCs express MHCII and function as non-conventional APCs, and their interactions with Th cells control ISC renewal and differentiation, thereby shaping the gut microenvironment homeostasis (89) (**Fig. 3-3**). Treg and their major cytokine IL-10 contribute to the maintenance of the small intestinal LGR5$^+$ ISC niche, whereas Treg deficiency leads to aberrant epithelial cell differentiation, resulting in a decreased LGR5$^+$ ISC pool and an accumulation of developed cells (89) (**Fig. 3-3**). IEC-specific MHCII-deficient mice exhibit worse disease outcomes following T-cell transfer or chemical (DSS)-induced colitis, as well as greater susceptibility to enteric infection, while effector T-cell activation in mesenteric lymph nodes (mLNs) is unaffected (100). Moreover, mice with an IEC-intrinsic deletion of MHCII are healthy, but have reduced amounts of microbial-bound IgA, regulatory T cells (Tregs), and immunological repertoire selection due to altered interindividual microbiota diversity (101). Microbial adhesion-triggered endocytosis is another mechanism by which commensal bacteria affect the development and function of host T cells. This indicates that IECs acquire antigens from commensal bacteria by direct contact in order to generate T cell responses to the resident microbiota (102). Although this strategy is adequate to initiate a CD4$^+$ T cell response and commensal-specific homeostatic Th17 cell development, the mechanisms by which these Ags are processed and delivered to immune cells remain unknown (102). IECs can also secrete exosomes containing MHCII molecules, which intestinal mononuclear phagocytes (MNPs) can obtain and use to mediate adaptive responses to microbial Ags (101) (**Fig. 3-4**). Furthermore, Graft-versus-host disease model studies demonstrate that CD4$^+$ and CD8$^+$ T lymphocytes inhibit bone marrow transplantation-induced intestinal injury by targeting ISCs expressing MHCI and MHCII (99). Thus, MHCII on intestinal epithelium, in addition to conventional and unconventional APC immune compartments, is essential for limiting adaptive responses to gut microbial antigens and sustaining intestinal homeostasis.

REGULATION OF TYPE17 IMMUNITY BY NON-ANTIGENIC MICROBIOTA-DERIVED MOLECULES

Intestinal microbes drive differentiation of effector T cells not only by supplying Ags, but also by secreting metabolites and acting on epithelial cells in Ag-independent manner. In this section, we will cover the interplays between intestinal microorganisms and the host mediated by bacterial metabolites and host cytokine signals, which contribute to both homeostasis and inflammation in the gut via immune cell modulation.

Secondary bile acids (BAs)

BAs, a byproduct of cholesterol metabolism, are synthesized in the liver, secreted into the duodenum and flows to terminal ileum where most primary bile acids are reabsorbed. The remainder travel to the large intestine, in which they are metabolized by commensal bacteria to form secondary bile acids with modified chemical structures (103). Secondary BAs are well-known for their anti-inflammatory effects on CD4+ T cells in the intestine. Inhibiting secondary BA production in bacteria causes a drop in Th17 levels, whereas secondary BA therapy activates RORγt+FOXP3+ pTreg and reduces gastrointestinal inflammation (104) (**Fig. 4**). Both isoalloLCA and 3-oxoLCA, which are derivatives of lithocholic acid (LCA), are T cell regulators inhibiting the differentiation of Th17 cells while promoting the differentiation of Treg cells (105) (**Fig. 4**). 3-OxoLCA inhibits the differentiation of Th17 cells by directly binding to the key transcription factor RORγt, whereas isoalloLCA promotes the differentiation of Treg cells via the production of mitochondrial ROS (mitoROS), resulting in the upregulation of FOXP3 (105) (**Fig. 4**). The isoalloLCA-mediated enhancement of Treg cell differentiation requires an intronic Foxp3 enhancer, the conserved noncoding sequence3 (105). In addition, the nuclear hormone receptor NR4A1 is required for the isoalloLCA mediated Treg induction (106). Moreover, Bacteroidetes is the intestinal bacterial phylum capable of metabolizing 3-oxoLCA to isoalloLCA, which implies that a specific commensal bacterium can modulate the immune system by changing host metabolites (106).
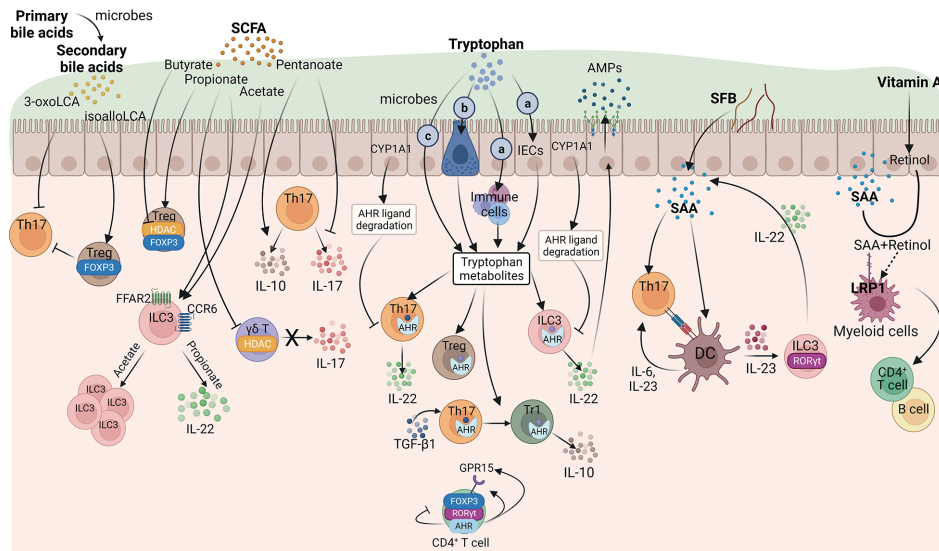

Figure 4. Regulation of type17 immunity by non-antigenic molecules. Bacterial metabolites shape intestinal immune responses using different mechanisms. Secondary bile acids regulate Th17/Treg balance by enhancing Treg differentiation and reducing Th17 cell differentiation. Among SCFAs, the most well-studied butyrate promotes Treg differentiation. Propionate suppresses IL-17- and IL-22-producing γδ T cells by inhibiting histone deacetylase. The SCFAs, propionate and acetate, are recognized by the colonic ILC3s through G protein-coupled receptor FFAR2 and these metabolites induce IL-22 production and proliferation of ILC3s, respectively. Pentanoate also acts on CD4+ T cells through HDAC-inhibition. Although it inhibits IL-17, IL-10 production in Th17 cells is induced by this SCFA. Dietary tryptophan is metabolized by host cells or microbes: a) The kynurenine pathway in IECs and immune cells, b) the serotonin pathway mediated by TPH1 in enterochromaffin cells and c) Direct conversion of tryptophan to smaller molecules, including AHR ligands by gut microbiota. Trytophan metabolites and AHR ligands may provoke distinct type17 cell subsets, including Tregs, Th17 cells, or ILC3s through AHR. Th17 cells transdifferentiate into Tr1 cells producing IL-10. This process is induced by TGF-β1 signaling and depends on AHR activity. IECs act as gatekeepers of AHR ligand supplies to the host by CYP1A1 expression. Dysregulated production of CYP1A1 results in Ahr-deficient state, which leads to loss of AHR-dependent ILC3 and Th17 cells and increased susceptibility to enteric infection. Moreover, AHR upregulates *GPR15* expression, which is positively regulated by FOXP3 and negatively regulated by RORγt in an AHR-dependent manner. On the other hand, SAAs produced by host cells in response to microbial stimuli, induce IL-6 and IL-23 production in CD11c+ cells, which promote Th17 cell differentiation. SFB stimulates IL-23 secretion from APCs, acting on ILC3 cells to upregulate the IEC-derived SAAs via IL-22 signaling. Vitamin A can also induce SAA-production in IECs. SAAs deliver retinol to intestinal myeloid cells via direct interaction with LRP1. The transfer of retinol promotes vitamin A-dependent adaptive immunity, inducing homing of both T cells and B cells to the intestine.

Short chain fatty acids (SCFAs)

SCFAs, such as formic acid (C1), acetic acid (C2), propionic acid (C3), butyric acid (C4), and valeric acid (C5), can induce immune responses or suppress inflammation through a variety of mechanisms, including histone deacetylase (HDAC) inhibition, Acetyl-CoA production, metabolic integration, and G-protein-coupled receptor (GPR) signaling (107) (**Fig. 4**). SCFAs promote T cell responses depending on the cytokine milieu or host circumstances (107). While SCFAs induce immunological tolerance via IL-10 in the steady state, they boost effector T cells during immune system activation against infection (107) (**Fig. 4**). Butyrate, which has been recognized for the favorable anti-inflammatory properties, produces functional Treg in the colon using a T-cell intrinsic epigenetic mechanism (108). The pentanoate alters the metabolism of CD4$^+$ effector T lymphocytes and B cells, and increases IL-10 production, which is independent of Treg (109). Similar to butyrate, which ameliorates colitis by acting on HDAC1 in Th17 cells, pentanoate suppresses IL-17A production by inhibiting HDAC in CD4$^+$ T cells (110) (**Fig. 4**). SCFAs also suppress the intestinal Th17 development upon SFB colonization of GF mice (110). Another SCFA metabolite, propionate, is a key regulator of IL-17 and IL-22 expression in γδ T cells of the lamina propria and represses IL-17-producing γδ T cells through suppression of HDAC in the caecum and colon (111). Moreover, propionate and acetate are essential for ILC3 homeostasis and IL-22 production in the colon, respectively. Both metabolites act through G protein-coupled receptor free fatty acid receptor 2, which mainly regulates CCR6$^+$ ILC3s through activation of AKT and STAT3 signaling pathways (112).

Tryptophan (Trp) metabolites and aryl hydrocarbon receptor (AHR) ligands

Trp is an essential amino acid degraded by gut microbes, intestinal epithelial, and immune cells across three main pathways: a) the kynurenine pathway in both IECs and immune cells, b) the serotonin (5-HT) pathway via Trp hydroxylase 1 (TPH1) in IECs called enterochromaffin, and c) direct conversion of Trp by gut microbes into smaller molecules, such as AHR ligands (113). The AHR, a transcription factor activated by small molecules derived from microbes, diet, and metabolism, contributes to immune homeostasis (114). AHR modulates the Treg/Th17 cell balance, and the direction of this AHR-dependent shift is mediated by the type of ligand that activates the AHR (115,116) (**Fig. 4**). A potent activator of AHR, 6-formylindolo[3,2-b]carbazole (FICZ), induces Th17 activation and IL-22 production (**Fig. 4**) (115). Inversely, the deletion of AHR prevents the localization of Th17 cells in the lamina propria and reduces the disease severity in a colitis mouse model (117). Moreover, AHR can mediate the cell plasticity of Th17 cells in the presence of TGF-β1, enhancing the transdifferentiation of Th17 cells to T regulatory type 1 cells (Tr1), which are IL-10 producers with immunosuppressive function independent of FOXP3 (118). Despite low levels of AHR detected in extraintestinal Treg, it is highly expressed in gut tissue-associated Treg (119). Supporting the functional role of AHR in intestinal homeostasis, the expression of FOXP3, the Treg lineage-defining transcription factor, is reduced in the absence of AHR, and an AHR agonist, dioxin, promotes Treg differentiation and depletes Th17 cells (115). Treg cell-specific deletion of the *AHR* attenuates intestinal Treg (119). AHR mediates expression of an essential intestinal-homing gene, *GPR15*, an AHR-target gene in Treg and Th17 cells regulated positively by FOXP3 and negatively by RORγt in an AHR-dependent manner (120) (**Fig. 4**). In cases of *AHR* deficiency, reduced levels of *GPR15* lead to defective intestinal-homing of Treg in the large intestine (120). Impaired AHR signaling attenuates ILC3, Th17 cells and IL-22 levels following AHR ligand-metabolizing enzyme, Cytochrome P450 Family 1 Subfamily A Member 1 (CYP1A1), dysregulation in IECs, and causes increased disease susceptibility by infection with *C. rodentium* (121).

Serum amyloid A (SAA)

SAAs comprise a family of acute-phase reactants that are abundantly produced during inflammation and often correlate with the severity of multiple Th17-associated chronic inflammatory disorders (38). In the intestine, colonization with SFB triggers SAA production, which in turn promotes Th17 cell differentiation directly, as well as indirectly by acting on dendritic cells of lamina propria (**Figs. 2** and **4**) (26). The epithelial expression of SAA1 and SAA2 is regulated by IL-23 and ILC3-derived IL-22 involving an immune circuit triggered by SFB (**Figs. 2** and **4**) (42). Recent research has shown that SAAs can substitute for TGF-β in the production of Th17 cells, but that they drive a distinct signaling pathway that results in a proinflammatory differentiation program (38,42) (**Fig. 2**). As a result, SAAs contribute *in vivo* to Th17-mediated pathophysiology, as demonstrated in chronic colitis and EAE in both gain- and loss-of-function models (38). In addition, SAAs support the *H. hepaticus*-driven colitis, inducing pathogenic features exemplified by T-BET expression during Th17 priming and sensitization of the T cells to cytokines essential for Th17-mediated autoimmune pathogenesis, such as IL-23 and IL-1β (38,42) (**Fig. 2**). It remains unclear what distinguishes the SAA-dependent properties associated with pathogenic versus homeostatic Th17 cells. It may be due to the milieu of T cell priming (e.g., lymph nodes draining a healthy small intestine versus an inflammatory large intestine), the presence of other cytokines, the concentration of SAAs encountered, or the cell types that make SAAs (122).

Vitamin A can also induce the SAA production in epithelial cells by retinoic acid-dependent activation of the transcription factor retinoic acid receptor β, which binds directly to SAA promoters (123) (**Fig. 4**). SAAs transfer retinol to intestinal myeloid cells that produce RA through low-density lipoprotein receptor-related protein 1 (LRP1) (**Fig. 4**) (124). Thus, SAA or myeloid cell-specific LRP1 deficiency causes impairments to vitamin A-mediated immunity, involving both B and T cell trafficking to gut IgA production (124). Although there is evidence suggesting that retinol and SAAs affect the Th17 cell function, it remains unclear whether these molecules influence the Th17 response through the LRP1 pathway.

DYSREGULATION OF HOST-MICROBIOTA INTERACTIONS

Defective host-bacteria interactions are associated with various intestinal diseases, including IBD and CAC (4,125). Recent advances in our understanding of the immunopathogenesis of IBD have revealed that dysbiosis and the resulting pathogenic type17 immunity may play a critical role in the etiology of IBD (33). This section discusses the relationship between the gut microbiota, type17 immunity and the pathophysiology of IBD and CAC. Additionally, we discuss treatment options for re-establishing a normal gut microbiota, including probiotics and fecal microbiota transplantation.

Inflammatory bowel disease (IBD)

IBD is a chronic inflammatory disorder in the gastrointestinal tract and manifests as either ulcerative colitis (UC) or Crohn's disease (CD) (125). IBD is characterized by a changed gut microbial composition, accumulated intestine resident type17 immune cells, and elevated type17 cytokine levels in inflammatory lesions of IBD patients and animal models of colitis (126,127).

Dysregulation of gut microbial composition and metabolites in IBD
Increased Proteobacteria and decreased *Firmicutes* species are associated with IBD (125) (**Table 1**). Levels of *Faecalibacterium prausnitzii (F. prausnitzii)*, one of the most abundant

commensal bacteria belonging to Firmicutes phylum, are lower in both UC and CD (125,128) (**Table 1**). Mouse studies demonstrate that *F. prausnitzii* play an anti-inflammatory role in colitis through the regulation of Th17/Treg balance by inhibiting IL-6/STAT3/IL-17 pathway and inducing FOXP3 (110). Moreover, several Clostridium strains derived from humans promote FOXP3$^+$ Treg via butyrate-production and induction of IL-10, TGF-β1, and inducible T cell costimulatory (ICOS), thereby suppressing mucosal inflammation in colitis mouse models (129). A significant decrease in *Roseburia hominis (R. hominis)*, a member of the *Clostridia* cluster XIVa, is observed in UC patients, whereas mouse studies reveal *R. hominis* upregulates genes involved in promoting gut barrier function, innate immunity, and Treg differentiation in a TLR5-dependent manner (130) (**Table 1**). Together with Firmicutes, Bacteroidetes dominate the intestine in healthy adults (131). *Bacteroidetes* species are also altered in IBD, with a decreased abundance in CD and increased numbers in UC (132,133). The *Bacteroidetes* species, *Bacteroides fragilis* (*B. fragilis*) and enterotoxigenic *B. fragilis* (ETBF), are present in the stool and biopsy specimens of healthy individuals, yet increased levels of toxin genes are observed in UC and CAC patients (134) (**Table 1**). Although the nontoxigenic *B. fragilis* promotes the anti-inflammatory function of Treg through secretion of Polysaccharide A in the mouse intestine, colonization of mice with ETBF upregulates activation of STAT3 in the colon and induces Th17 immune responses (125) by producing a metalloprotease toxin termed *B. fragilis* toxin (135).

Dysregulation of the metabolite-mediated host-microbiota crosstalk contributes to disease progression in IBD as well. SCFAs and SCFA-producing bacteria are present at reduced levels in IBD. In addition to the regulatory role of SCFAs in T cell differentiation and function, SCFAs act directly on γδ T cells and restrict IL-17 and IL-22 production by these cells (111). Given that human IL-17-producing γδ T cells accumulate in the intestinal mucosa of IBD patients (136), SCFAs, particularly propionate, are proposed to prevent chronic inflammation through their inhibitory effect on γδ T cell activity (111). Impaired BA metabolism and reduced levels of secondary BA-producing bacteria *Ruminococcaceae* have been identified in IBD (137). Intestinal BAs are essential for the maintenance of the colonic RORγ$^+$FOXP3$^+$ Treg in a BA-receptor, the vitamin D receptor (VDR)-dependent manner (104). Therefore, human VDR genetic variants may influence host susceptibility to disease through defective control of the intestinal Treg pool (104).

Type17 signatures in the disease lesions of IBD
Pathogenic heterogeneity of IBD significantly contributes to the failure of typically successful novel therapeutics (146). Recent advances in single-cell sequencing technologies allow for unbiased investigation of distinct cell types within a tissue during health and disease, facilitating our progressive knowledge of the interplay between immune cells and

Table 1. Altered microbiota during IBD that are associated with type17 immune modulation

Microbiota	Abundance	Function	Reference
Faecalibacterium prausnitzii	Decreased in IBD	Butyrate-producer, regulates Treg/Th17 balance.	(110)
Roseburia hominis	Decreased in IBD	Butyrate-producer, modulate Treg expansion.	(130)
Roseburia intestinalis	Decreased in IBD	Inhibits IL-17 secretion and stimulates Treg differentiation.	(138)
Bacteroides fragilis, non-toxigenic	Decreased in IBD	Induces CD4$^+$ T cells to produce IFN-γ and IL-10.	(139,140)
Enterotoxigenic *Bacteroides fragilis* (ETBF)	Increased in IBD	Stimulates STAT3 activation and Th17 response.	(141)
Akkermansia muciniphila	Decreased in IBD	Drives colonic Treg differentiation.	(142,143)
Bifidobacterium adolescentis	Decreased in IBD	Induces Th17 cells in the mouse small intestine.	(143,144)
Lactobacillus	Decreased in IBD	Upregulates Treg activity and suppresses Th1, Th17.	(143,145)
Clostridium clusters (IV and IXV)	Decreased in IBD	Increase the number and function of colonic Tregs.	(129)
Escherichia coli	Increased in IBD	Induces Th17 response.	(32,145)

non-immune cells (147). The integration of multi-omics data, including epigenomics, transcriptomics at the single-cell level, proteomics, metagenomics, and metabolomics will elucidate the crosstalk between different cell types of the intestine and their interactions with gut microbes (4).

Emerging studies that exploit single cell RNA sequencing (scRNA-seq) to identify the cellular and molecular events behind disease pathogenesis provide insights into cell subsets, as well as interactions that are involved in the progression of intestinal inflammation (148,149). The comparison of inflamed and non-inflamed tissues from CD patients and healthy individuals reveals that activated Th17 cells are increased in the IEL compartment of inflamed lesions, whereas CD8⁺T, γδT, T_{FH} and Treg cells are decreased (148). Moreover, greater levels of CD8⁺ and Th17 cells are observed in the lamina propria, alongside reduced T_{FH} cells and Treg (148). A recent study identified a distinct cellular module, consisting of IgG plasma cells, inflammatory MNP, activated T cells, and stromal cells in the inflamed tissue of CD patients and designated these modules as GIMATS, which are associated with anti-TNF therapy non-responsiveness (149). Both GIMATS-positive and -negative CD patients display an active T cells-driven inflammatory pathway, whereas activated DCs and monocyte-derived inflammatory macrophages accumulated within GIMATS-enriched lesions (149). Furthermore, MHCII molecules are enriched in distinct cell types of the intestinal epithelium and stromal lineages (149). Additionally, the genes in IL-17 signaling pathway are upregulated in some types of IEC and in fibroblasts (150). With the help of the scRNA-seq, a wider range of Th17 subtypes were identified, including classic CD4⁺ Th17 cells, that regulates the inflammation and the cytotoxic Th17-like subtype, which is a heterogeneous population of CD4⁺ and CD8⁺ T cells (149,151,152).

CAC

The chronic inflammation observed in the patients with IBD is a potent risk for colorectal cancer development, particularly CAC (153). CAC progresses rapidly and is associated with high mortality in 10%–15% of patients with IBD (153). The exact mechanisms underlying the progression from IBD to CAC are not clear, however an overproduction of pro-inflammatory cytokines, including IL-6, TNF-α and IL-17, by both immune and non-immune populations is related to cancer development (154). Recently, various studies report that the intestinal microbial composition is altered both in colitis and CAC and may be involved in chronic inflammation and the tumorigenesis. Increased levels of *Bacteroidetes* and decreased levels of *Firmicutes* are found in CAC patients compared to healthy individuals across various studies (155,156). Furthermore, a comparison between CAC patients and sporadic cancer patients reveals that CAC is associated with increases to the Enterobacteriacae family and *Sphingomonas* genus and reduced levels of *Fusobacterium* and *Ruminococcus* genus (157). On the other hand, some specific bacteria mitigate tumorigenesis. *B. fragilis* can prevent cancer progression by inhibiting the NLRP3-mediated inflammatory signaling pathway through butyrate production (158), whereas fecal microbiota transplant (FMT) can induce anti-cancer immunity by promoting Treg within the tumor microenvironment (159).

Treatment of IBD targeting type17 immunity

Due to increased levels of Th17 and related cytokines in IBD, several therapeutics were developed to target these cells (126,160,161) (**Table 2**). Anti-IL-17A antibodies are effective in the treatment of a variety of inflammatory diseases, including IBD (146). Anti-IL-17R Ab treatment exacerbate CD (162), whereas anti-p40 subunit antibodies (Ustekinumab, Briakinumab) (126,163) and anti-IL-6 receptor antibodies (Tocilizumab) target cytokines

that control Th17 cell differentiation and thus IL-17 secretion have shown efficacy (126) (**Table 2**). These findings suggest that IL-17 plays a protective role in inflammatory bowel disease by preserving the integrity of the intestinal barrier, which outweighs its potential for tissue destruction. Blockades of the key cytokine of Th17 cells, IL-17, exacerbate the disease outcome in patients with CD, implicating an enrichment of Th17 and increased levels of IL-17 might exhibit beneficial effects, such as promoting enterocyte proliferation, tight-barrier formation, and epithelial barrier integrity in the intestine (44), a cause for study termination. On the other hand, targeting IL-23 is effective in clinical trials treating Crohn's disease, specifically in patients with anti-TNF therapy resistance, displaying a good response to ustekinumab, an FDA-approved treatment for moderate-to-severe CD and UC (164). The JAK-STAT pathway is a promising target for the treatment of inflammatory diseases including IBD, however contradictory results are observed in patients with CD or UC (164). Clinical trials applying JAK inhibitor tofacitinib show improved disease outcomes in UC patients, a medication approved by the FDA and EMA for the treatment of moderate-to-severe UC in 2018 (164). Furthermore, selective JAK1 inhibitors, such as upadacitinib and filgotinib, show promising results in early clinical trials in CD (164). The clinical application of antibodies directed against IL-17 signaling provides insights into the function of IL-17 in humans.

As an alternative to immunosuppressive and anti-inflammatory therapies, microbiota-based therapies, including probiotics, prebiotics, and FMT may modulate dysregulated immune responses by correcting gut dysbiosis (125). Initial clinical studies of FMT exhibit promising results in improving UC, however subsequent results are varied (125). Compared to FMT, treatment with individual or a combination of specific microbial strains or bacterial metabolites with anti-inflammatory functions might be a safer therapy option. In particular, due the immune regulatory role of Treg, IL-10 producing Treg inducers such as *Faecalibacterium prausnitzii* (128), *Clostridium* species (129), and *Bacteroides* species (143) may be effective as live biotherapeutic products (LBP) to treat IBD, however there is currently no FDA-approved LBP. Clinical trials with a human-derived multibacterial FMT-derived spore-based drug product SER-287 by Seres Therapeutics failed in Phase IIb due to non-efficient therapy responses (165), whereas trials using the orally-administered rationally-defined bacterial consortium candidate VE202 produced Vedanta Biosciences are ongoing (166).

Table 2. Therapeutic agents for CD and UC targeting type17 immunity

Therapeutic agent	Target	Disease	Phase of clinical trials	Trial ID
Brazikumab	IL-23p19	CD	II/III	NCT03759288
		UC	II	NCT03616821
Guselkumab	IL-23p19	CD	II/III	NCT03466411
		UC	II/III	NCT04033445
Mirikizumab	IL-23p19	CD	III	NCT04232553, NCT03926130
		UC	III	NCT03519945, NCT03524092, NCT03518086
Risankizumab	IL-23p19	CD	III	NCT03105102, NCT03105128
		UC	II/III	NCT03398148
Tocilizumab	IL-6R	CD	II	NCT01287897
Filgotinib	JAK1	CD	III	NCT02914600
		UC	III	NCT02914535
Tofacitinib	JAK	UC	III	NCT03281304
Upadacitinib	JAK1	CD	III	NCT03345823
		UC	III	NCT03006068
Ustenikumab	IL-12/23p40	CD	III	NCT04963725
		UC	III	NCT02407236

CONCLUSION

Understanding of the immune system and its relationship with its symbionts has been revolutionized by the increased incorporation of the microbiome into our knowledge of host physiology. The exceptional plasticity and motility of immune cells and their dependence on the highly dynamic microbiota connect practically all physiological systems, making the immune system, particularly type17 immunity, and microbiota essential regulators of host homeostasis. At the same time, however, type17 immunity has been also linked to immunopathologies other than conventional inflammatory autoimmune disease, and mice models show a functional significance; nonetheless, decisive clinical studies have not been conducted in many instances. Contradictory results in the function of type17 cells demonstrate that the treatment strategy targeting the type17 axis must be modified according to tissue-specific and disease context-dependent manners. A comprehensive single-cell atlas that characterizes the pathogenicity of type17 immune cells at different inflamed organs will pave the way for a novel immunotherapy that allows us to specifically manipulate the function of pathogenic type17 cells in autoimmune disease, while preserving the immune homeostasis, for example, in the intestine, which is mediated by physiological type17 immunity.

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