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Development and survival of Th17 cells within the intestines: the influence of microbiome- and diet-derived signals

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Abstract

Th17 cells have emerged as important mediators of host defense and homeostasis at barrier sites, particularly the intestines, where the greatest number and diversity of the microbiota resides. A critical balance exists between protection of the host from its own microbiota and pathogens and the development of immune-mediated disease. Breaches of local innate immune defenses provide critical stimuli for the induction of Th17 cell development, and additional cues within these tissues promote Th17 cell survival and/or plasticity. Normally, this results in eradication of the microbial threat and restitution of homeostasis. When dysregulated, however, Th17 cells can cause a range of immune-mediated diseases, whether directed against antigens derived from the microbiota, such as in inflammatory bowel disease, or against self-antigens in a range of autoimmune diseases. This review highlights recent discoveries that provide new insights into ways that environmental signals impact Th17 cell development and function in the intestines.

Further defining the role of transforming growth factor-β and interleukin-6 in Th17 development

Transforming growth factor-β (TGF-β) performs a critical role in the extrathymic generation of “peripheral” Treg cells (pTreg cells, to be distinguished from “thymic” Treg, or tTreg cells) (1, 2), and the absence of TGF-β results in decreased $FoxP3^+$ T cells that is associated with severe autoimmune disease (3, 4). Based on the immune suppressive role of this cytokine, the discovery that TGF-β is also important for the development of pro-inflammatory Th17 cells seemed contradictory (5–8). However, maintenance of the equilibrium between the immune system and the intestinal microbiota has proved to reflect a balance between the effects of Treg cells to repress inflammation directed against normal constituents of the microbiome and that of Th17 cells to mount inflammatory responses that clear organisms that traverse the intestinal barrier (9). This balance is achieved, at least in in part, through the dual role of TGF-β in promoting developmental pathways of both of these important T cell subsets.

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TGF-β signaling induces the expression of both FoxP3 and RORγt in antigen-stimulated naïve T cells through a SMAD-dependent mechanism (reviewed in (10)). Interestingly, FoxP3 acts to inhibit RORγt through a direct protein-protein interaction, while also suppressing *Il17a* transcription through a DNA-binding mechanism (11, 12). High concentrations of TGF-β result in increased levels of FoxP3 and subsequent induction of Treg cells that develop in the peripherary. In contrast, lower concentrations of TGF-β are capable of synergizing with inflammatory cytokines (e.g. IL-6 and IL-1) to induce the development of Th17 cells (11). Thus, while high TGF-β levels act to suppress Th17 development, lower levels coupled with other inflammatory signals promote the Th17 lineage. Through mechanisms that are yet to be fully defined, inflammatory cytokines are also able to reverse the FoxP3-mediated suppression of RORγt in established pTreg cells, providing a mechanism for Treg plasticity in the setting of infection (12). The balance between pro- and anti-inflammatory responses in the GI tract, therefore, is in part based on local levels of TGF-β and other cytokines, as well as other stimuli generated by the microbiota or the immune response to this flora (13). This balance affects not only local immune regulation in the gut, but has been shown to have global effects on the immune system and host health (14–19).

Recent discoveries have further elucidated the relationship between the immune system and the microbiota and the mechanisms for the generation of Th17 cells within the intestines (9, 20). The gastrointestinal tract represents the largest organ of the immune system. Within the intestinal tract, approximately 100 trillion organisms comprise the microbiome, residing in symbiosis with the host (21). The host immune system and the intestinal microbiota interact continuously following colonization of the intestines over the first few days of life. A major function function of the host immune system is to restrain inflammatory responses to normal constituents of the microbiota while retaining the capability to mount vigorous responses against potential pathogens, whether they derive from the resident microbiota or result from infection.

Dendritic cells (DCs) are a critical component in the interaction between the immune system and the microbiota, and act to bridge the innate and adaptive immune responses. Within the intestinal mucosa, DCs are grouped based on the expression of CD103 (integrin α_E) and CD11b, with numbers of each subset varying according to differing segments of the GI tract (22–25). $CD103^+$ DCs reside primarily within the lamina propria, with low numbers contained in the epithelium where they can migrate along the basement membrane. Recent studies indicate that these cells can project intraepithelial dendrites into the intestinal lumen that act to phagocytose bacteria and, somewhat less efficiently, sample luminal antigen (26). Following encounter with pathogenic bacteria, e.g. *Salmonella*, additional $CD103^+$ DCs are recruited from the lamina propria in a TLR and chemokine-dependent manner (26). Additional data indicate that luminal antigens may also be passed to underlying $CD103^+$ DCs via goblet cells (27). After antigenic challenge, DCs upregulate CCR7 and migrate to mesenteric lymph nodes (MLNs) (28–30) where they present antigen and initiate the adaptive immune response (30–33).

The presentation by DCs of antigens derived from the microbiota or pathogens initiates the development of effector T cells. Lineage-specifying signals are transmitted to naïve T cells

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along with antigen by DCs, contingent on their activation by through toll-like receptors (TLRs) and other pattern recognition receptor (PRR) pathways (34). Other signals also provide critical stimuli for determining mature T cell fate within the MLNs. $CD103^+$ DCs present in the MLNs were initially demonstrated to promote pTreg development via increased TGF-β secretion and retinoic acid (31), while the $CD103^-$ DCs were responsible for producing inflammatory signals. Further studies demonstrated that the $CD103^+CD11b^+$ and $CD103^+CD11b^-$ DC subsets promote different mature T cell lineages (23). These studies revealed that the $CD103^+CD11b^+$ subset, as well as the $CD103^-$ subset, were capable of promoting Th17 development, primarily through secretion of IL-6 (35). Thus, evidence indicates that the balance of pro- and anti-inflammatory signals is at least partially dependent on the nature of the cell presenting intestinal antigens to T cells within the MLN.

Additional studies have revealed other mechanisms for regulating the immune balance in the intestinal tract. Phagocytosis of apoptotic cells by host DCs results in the production of TGF-β, which can promote pTreg development. However, ingestion of infected apoptotic cells results in the additional secretion of IL-6 (in a TLR-dependent manner), which alternatively promotes the development of Th17 cells (36). Specific microorganisms have now also been shown to induce the development of Th17 cells through similar mechanisms. It has been demonstraed that intestinal colonization with a single bacterial strain, so-called segmented filamentous bacteria (SFB), is capable of inducing Th17 development in the intestines. SFB colonization of the ileum, and Peyer's patches in particular, up-regulates expression of serum amyloid A, which is capable of inducing increased IL-6 and IL-23 secretion by LP DCs (37). Th17 cells present within the small intestine lamina propria (SILP) recognize and respond to SFB antigens, while these same antigens do not induce cytokine production from non-Th17 cells (38, 39). SILP Th17 cells possess a distinct TCR repertoire, enriched for Vβ14, capable of recognizing multiple SFB-encoded peptides (38, 39). Interestingly, presentation of SFB antigens appears to occur within the lamina propria, not in secondary lymph tissues, and requires MHC class II on $CD11c^+$ APCs (38). Interestingly, colonization with SFB also induces a non-specific Th17 response that occurs in the absence of organized lymph tissues (40). Other types of bacteria have been shown to preferentially induce Treg responses in the intestines. Colonization with certain *Clostridium* species (specifically clusters IV, XIVa, and XVIII), spore-forming members of the normal microbiota, increased TGF-β secretion by intestinal epithelial cells through a PRR-independent mechanism. (41, 42).

Recently, another member of the TGF-β family, TGF-β3, was proposed to induce a more pathogenic Th17 cell capable of inducing increased severity of experimental autoimmune encephalitis (EAE) in mice (43). TGF-β3 is normally produced by endothelium and other sources (including Th17 cells), and is present in normal plasma (44). Both TGF-β1 and TGF-β3 form a ternary complex with type I and II receptors (TβRI and TβRII, respectively), but with differing affinity (45) and it is possible that differential binding to the TGF-β receptor by TGF-β3 plays a role in altered T cell differentiation. It is unclear how much TGF-β3 is normally present in the intestinal mucosa and what role the microbiota might have in altering TGF-β3 levels.

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Despite the relatively early discovery of the importance of TGF-β and IL-6 on Th17 development, much remains unknown regarding the mechanisms controlling production of these cytokines and the impact of the balance of cytokine-induced signals (TGF-β, IL-6 and others) to maintaining the immune homeostasis within the intestinal mucosa. Further details also remain to be elucidated regarding the influence of the microbiome on TGF-β, IL-6, and other critical cytokines that impact the development of Th17 and Treg cells within the GI tract.

IL-23 signaling is critical for both Th17 survival and plasticity

Interleukin-23 (IL-23) is a heterodimeric protein consisting of the unique p19 subunit and the p40 subunit, which is shared with IL-12 (which consists of the p40 and p35 proteins). Prior to the identification of IL-23, experimental colitis models were thought to be secondary to IL-12 signaling, resulting in enhanced Th1 development. Subsequent studies identified IL-23 as a unique cytokine and found that it has an indispensable role in mediating autoimmune disease (46, 47). IL-23 also provides critical developmental and survival signals for Th17 cells.

TGF-β and IL-6 promote the development of Th17 cells from naïve $CD4^+$ T cells and induce up-regulation of the IL-23 receptor (IL-23R). IL-23 signaling acts to further up-regulate IL-23R expression (48). While IL-23 is not required for the initial differentiation of Th17 cells, absence of IL-23 signals results in abbreviated Th17 maturation and decreased Th17 proliferation (49). The generation of Th17 memory cells and the generation of secondary recall responses also appears to be critically dependent on IL-23 signaling (50). The absence of IL-23 signals results in reduced Th17 production of GM-CSF and IL-22, two critical cytokines in Th17-mediated host protection and inflammation (51, 52).

Th17 cells have a high propensity for developmental flexibility (or “plasticity”), including the up-regulation of IFN-γ production (53–55). Following acquisition of IFN-γ, these Th17 cells become either IL-17–IFN-γ dual producers or can down-regulate RORγt and IL-17 (and other Th17 mediators) and up-regulate Tbet to become an IFN-γ producer with many features of Th1 cells (53–55). These converted Th17 cells have been designated Th17/Th1 or Th1-like cells to discriminate from *de novo* Th1 cells. We and others have demonstrated an important role for IL-23 in the conversion of Th17 precursors to Th1-like cells, both *in vitro* and *in vivo* (53, 54). Thus, IL-23 is an important cytokine in determining the both the survival and ultimate developmental fate of Th17 cells.

IL-23 in the GI tract is produced primarily by tissue-resident DCs and macrophages (56). In particular, $CD103^-$ DCs within the GI tract have been demonstrated to produce inflammatory cytokines, and specifically IL-23 (31). Classically $CD103^+$ DCs have not been demonstrated to secrete significant levels of IL-23, but instead seem poised to promote Treg development (see previous section). However, studies have shown that $CD103^+CD11b^+$ DCs are capable of inducing Th17 cells (35). Recently, TLR5-expressing $CD103^+CD11b^+$ DCs were shown to produce increased IL-23 levels in response to bacterial flagellin, which binds TLR5. The production of IL-23 by these cells further induces the production of IL-22 within the lamina propria of exposed mice (57). Finally, lamina propria (LP) $CD11c^+$ DCs were

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also shown to secrete increased IL-23 upon co-culture with serum amyloid A, a protein produced by SFB (37).

IL-23 has been shown to be an important mediator of GI disease, including inflammatory bowel disease (IBD) and intestinal graft versus host disease (GVHD) of the intestines (58–61). In murine models, IL-23 is critical for the development of severe disease in the $CD4^{+}CD45RB^{hi}$ transfer colitis model colitis (58). Blockade of IL-23 signaling in transferred T cells was associated with decreased tissue levels of IFN-γ and reduced pathology. IL-23 signaling was associated with increased numbers and proliferation of IL-17–IFN-γ dual positive cells, suggesting a critical role in the transition from Th17 to Th1-like cells (58). In a TCR transgenic colitis model, Th17 cells expressing the CBir1 TCR (specific for an immunodominant microbiota antigen) induced severe colitis, which was associated with increased IFN-γ and Th1-like cells present within diseased tissue (62). Blockade of IL-17A reduced disease in these mice. Mechanistic studies revealed that Th17-produced IL-17 induced DC release of IL-23 and IL-12 which, in turn, promoted the transition from Th17 to Th1-like cells.

Both ulcerative colitis (UC) and Crohn's disease (CD) have been linked to IL-23 signaling, although Crohn's has classically been deemed a Th1-dependent disease whereas UC has not. In studies utilizing LP $CD4^{+}$ T cells from patients with IBD, both patient groups demonstrated increased expression of IL-23R on LP T cells. Further, $CD4^{+}$ T cells from patients with UC up-regulated *IL17A* mRNA and secreted increased IL-17A in response to IL-23, while $CD4^{+}$ T cells from patients with CD up-regulated IFN-γ (63). Whether these differential effects of IL-23 are a feature of all patients with UC or CD is unknown, but suggests a critical role for IL-23 in the pathogenesis of both forms of IBD.

The resident microbiota can contribute directly to local IL-23 levels in the intestinal mucosa through several mechanisms. Colonization with the normal flora has been shown to increase IL-23 levels in the murine GI tract. Through a TLR-dependent mechanism, colonization with microbiota down-regulated DC expression of miR-10a, a microRNA that is expressed at increased levels in the murine intestine (64). Normally, miR-10a acts to repress the p40 subunit of IL-12 and IL-23, and levels of this miRNA were higher in germ-free mice. Restoration of the normal gut flora resulted in decreased miR-10a and increased levels of IL-23. In addition, lower levels of miR-10a were seen in IL-10 knockout colitis mice (64). Another microRNA, miR-107, also acts to control intestinal inflammation by repressing IL-23p19 in the GI tract, particularly within intestinal epithelial cells (IEL) and $CD11c^{+}$ macrophages and DCs. Presence of the intestinal microbiota downregulates miR-107 levels through a MyD88-dependent mechanism, resulting in increased IL-23 levels (65). Another mechanism of microbiota-induced regulation of IL-23 is through dietary metabolites produced by lumenal bacteria. Butyrate is a short-chain fatty acid (SCFA) produced by constituents of the microbiome. SCFAs are known to reduce inflammation in the GI tract (see later section), however, high levels of oral butyrate increased IL-23 secretion by DCs that resulted in increased Th17 cells (66). Further, in this model, increased butyrate exacerbated dextran sulfate sodium (DSS)- induced colitis (66).

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In addition to its role in modulating the host response to the resident microbiota, IL-23 is critical to host defense against certain intestinal pathogens. *Citrobacter rodentium* is a murine pathogen that normally induces a self-limiting enteritis that mimics enteropathogenic *Escherichia coli* and enterohemorrhagic *E. coli* infection in humans. Infection by *C. rodentium* induces increased IL-23 expression in the intestines of infected mice. Deficiency or neutralization of IL-23 renders the host lethally susceptible to *C. rodentium* colitis (7), largely due to the absence of IL-23-mediated IL-22 secretion, whether by innate lymphoid cells or $CD4^+$ T cells (51, 67, 68). Similarly, *Clostridium difficile* is associated with elevated levels of IL-23 in human samples as well as in mouse models of the disease, although IL-23 neutralization in mice with *C. difficile* colitis ameliorated disease and reduced mortality (69).

Similar to its effects in T cell models of colitis, IL-23 acts through both IL-17/Th17 and/or the IFN-γ/Th1 (Th1-like) pathways in infectious colitis models. Infection with enterotoxigenic *Bacteroides fragilis* (ETBF) induces a severe colitis and inflammation-induced cancer in mice (70). The disease is mediated by IL-23, and IL-23R blockade abrogates colitis and carcinogenesis. The inflammatory T cells present in lamina propria primarily produce IL-17, with only small amounts of IFN-γ. Additionally, increased levels of IL-6, TGF-β, and IL-1β are present in the inflamed tissues. Murine colitis due to *Helicobacter hepaticus* infection has also been demonstrated to be dependent on excess IL-23 levels (71). However, it was found that disease is associated with increased infiltrating $CD4^+$ were primarily IFN-γ secreting (either IL-17–IFN-γ dual positive or IFN-γ single positive) (72). Moreover, when IL-17-positive cells were harvested from colitic mice and transferred to secondary hosts, disease was induced and the transferred cells progressively transitioned to Th1-like cells. Using fate-reporter mice (55), it was demonstrated that the $CD4^+$ T cells progress through an early Th17 phase and ultimately develop into a Th1-like cell throughout the course of the infection (72). Thus, IL-23 appears to primarily sustain Th17 responses in some circumstances or facilitate the transition from a Th17 to a dominant Th1-like response in others.

While IL-23 has emerged as a central cytokine in Th17–mediated host protection and immune-mediated disease, it precise function is incompletely understood. Similarly, the relative importance of Th17-derived IL-17 and IFN-γ single positive cells, as well as the IL-17–IFN-γ dual positive cells, in host protection and intestinal inflammation and tissue damage has not been completely defined. And how the balance between IL-23 driven Th17 versus Th1-like differentiation is controlled is currently unknown, although TGF-β—mediated down modulation of STAT4 activation downstream of IL-23 signaling, and thus blunting of the transition to a Th1-like program (53), might be contributory. Another important signal that may be quite influential in strengthening IL-23-induced Th17 stability is the cytokine IL-1β.

Role of IL-1β in stabilizing the Th17 phenotype

As detailed previously in this review, TGF-β and IL-6 were initially demonstrated to be important in Th17 development from naïve CD4 T cells in murine studies (5, 7). Early data in humans, however, demonstrated an important role for IL-1β (IL-1), but not TGF-β, in promoting the Th17 lineage (73). Furthermore, studies in the Th17-mediated EAE mouse

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model also indicated that IL-1 signaling was important for disease (74). The IL-1 receptor (IL-1R1) is up-regulated in developing Th17 cells, and its expression appears to be induced by IL-6 and IL-23 signaling (75, 76). IL-1 signaling has been shown to be important for promoting both Th17 development and maintenance (75). IL-1 synergizes with IL-6 to enhance expression of IRF4 and RORγt (75), both of which are important transcription factors required for Th17 development (77, 78). IL-1 also acts to suppress TGF-β-mediated FoxP3 up-regulation (79). IL-1–induced Th17 proliferation, on the other hand, appears to be mediated by the mTOR signaling pathway, and this can be inhibited by the SIGIRR receptor, an important receptor for immune tolerance in the intestinal mucosa (80).

Although many cells can produce IL-1, IL-1β is produced primarily by DCs and macrophages activated by microbe-derived ligands for PRRs. For example, the nucleotide oligomerization domain 2 (NOD2)-ligand muramyldipeptide (MDP) has been demonstrated to induce DC production of IL-1 and IL-23 secretion with subsequent Th17 development (81). Irrespective of the factor(s) that induces IL-1 expression, it is expressed as a pro-peptide that must be cleaved to become active. In the intestines, a key mediator of IL-1 cleavage is the NLRP3 inflammasome. The NLRP3 inflammasome is made up of the NLRP3 member of the nucleotide-binding domain and leucine-rich repeat containing (NLR) family of proteins. Following activation, NLRP3 forms a complex with pro-caspase-1 and apoptosis-associated speck-like protein containing a CARD (ASC), with pro-caspase-1 then undergoing cleavage and activation. Active caspase-1 then cleaves pro-IL-1β and pro-IL-18 precursors to the active forms of these cytokines.

Absence of NLRP3 results in increased susceptibility to experimental colitis in murine models (82, 83). This is due to decreased levels of both IL-1β and IL-18, which results in increased intestinal epithelial permeability and decreased production of β-defensins (82, 83). Hyperactive NLRP3 mutations, on the other hand, result in increased IL-1β levels with concomitantly increased Th17 development in mice and humans (84, 85). Mice with a hyperactivating NLRP3 mutation demonstrate increased levels of IL-1 and increased number of Th17 cells and increased tissue levels of Th17-associated cytokines. Co-culture of $CD11b^+$ DCs from NLRP3 mutant mice with wild-type $CD4^+$ T cells resulted in increased IL-1–dependent Th17 development (84). Furthermore, patients with various hyperactive NLRP3 mutations demonstrate increased serum IL-17 as well as increased numbers of circulating Th17 cells. DCs from these patients secrete increased levels of IL-1, and treatment of these patients with anti-IL-1 therapy results in resolution of these findings (85).

Recent studies have highlighted the importance of IL-1β in maintaining Th17 development in the intestinal mucosa. In $CD4^+CD45RB^{hi}$ transfer colitis model studies, IL-1 was demonstrated to be important for the development of disease and was associated with increased levels of IL-6 and IL-17, as well as Th17 cell numbers. Absence of IL-1 signaling was shown to result in decreased Th17 survival, but not development, within the intestinal mucosa that was associated with lower levels of anti-apoptotic protein *Bcl2* and *Bclx1* transcripts (76). These studies indicated an essential role for IL-1 in promoting colitis through its promotion of Th17 cell survival and accumulation within the intestines.

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The intestinal microbiota has also been shown to have a direct impact on Th17 development through the generation of IL-1β. The absence of IL-1 or IL-1R signaling in mice was shown to result in decreased Th17 cells within the intestinal lamina propria (LP). $CD11b^+$ macrophages were identified as the source of intestinal IL-1 secretion, and IL-1 production occurred in a MyD88-dependent manner (86). Th17 cell development was dependent on T cell-specific IL-1 signaling. Interestingly, germ-free mice demonstrated recapitulation of the Th17 cell population following IL-1β treatment, indicating a critical role for microbiota in regulating intestinal Th17 cells through the induction of IL-1β production (86).

IL-1β also provides important signals for the maintenance of intestinal homeostasis and host-microbiota symbiosis. Absence of NLRP3 signaling (with concomitantly decreased IL-1β) results in dysbiosis in mouse models, with increased intestinal colonization of pathogenic species including *Enterobacteriaceae*, *Mycobacterium*, and *Clostridium* (83). Further, infection with *C. difficile* induces severe colitis resulting in damage to the intestinal epithelial barrier. Altered intestinal epithelium was shown to be associated with translocation of commensal bacteria, with subsequent IL-1 induction through an NLRP3-dependent process. Increased IL-1 acts in a feedback loop to promote clearance of *C. difficile*, and absence of this cytokine results in increased susceptibility to infection and mortality (87).

Augmentation of intestinal Th17 immunity is an important role of IL-1β. It is not yet certain exactly how this cytokine regulates the development and/or survival of Th17 cells within the intestines, but decreased or absent IL-1β signals result in lower Th17 cell numbers within the GI tract. Additionally, human data implicates increased levels of this cytokine in Th17-mediated inflammation and disease.

Importance of AhR ligands and ATP produced by microbiota on Th17 development and survival

The symbiotic relationship between the host and its intestinal microbiota is a multifaceted one, and we are only beginning to understand the factors that maintain this relationship. It is clear that one beneficial role for the intestinal microbiota is the production of important non-dietary factors (such as vitamins) that the host is incapable of synthesizing or metabolizing. Other factors, such as ligands of the aryl hydrocarbon receptor (Ahr) or adenosine triphosphate (ATP), are derived from the diet and/or produced by the microbiota and can directly affect mucosal immunity, and specifically Th17 development.

The aryl hydrocarbon receptor is a member of the basic helix-loop-helix Per/Arnt/Sim (bHLH/PAS) receptor family, and resides in the cytosol in a complex with protein chaperones (e.g. Hsp90), where it encounters and binds a variety of ligands, including xenobiotic and naturally arising toxins. After ligand binding, the Ahr complex translocates to the nucleus where it forms heterodimers with other member of the bHLH/PAS receptor family and acts to control the transcription of multiple genes through Ahr-responsive elements (88).

Initial studies revealed that Th17 cells express Ahr, and that an Ahr ligand, the photosynthesized tryptophan metabolite 6-formylindolo [3,2-b] carbazole (FICZ), augments

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Th17 development (89, 90). T cells derived from mice lacking Ahr demonstrated reduced up-regulation of IL-17 and IL-22 under Th17-promoting conditions *in vitro*, and reduced severity of Th17-mediated disease(89, 91). In a collagen-induced arthritis model, Ahr signaling was shown to be critical for increasing Th17 cell numbers and disease severity (92). This might be due, at least in part, to altered Th17 survival, as studies have demonstrated that absence of Ahr signaling results in decreased levels of anti-apoptotic genes, such as *Bcl2* and *Bcl2l1* (93). A contributor to Ahr-dependent up-regulation of IL-17 is the microRNA-132/212 cluster, and absence of miR-132/212 resulted in decreased Th17-dependent CNS inflammation in an EAE model (94). Ahr signaling through miR-132/212, however, did not influence IL-22 levels (94).

More recently, however, Ahr-deficient mice have been shown to have increased Th17 cell numbers within the peripheral blood and GI tract, particularly the small intestine (95, 96). These studies reveal that the absence of Ahr signaling *in vivo* results in increased intestinal colonization with SFB, secondary to decreased Ahr-dependent production of IL-22, which results in increased Th17 cell numbers. Furthermore, the increased levels of IL-17-single and IL-17–IFN-γ dual positive cells resulted in increased intestinal pathology (96). Consistent with these findings, Ahr-deficient mice have been found to have increased levels of both TGFβ1 and TGFβ3 (97). Collectively, these studies also highlight an important differential effect of Ahr signaling on Th17 cell development and survival compared to Th22 cells, which are markedly reduced in Ahr deficient mice (67, 96).

Regardless of the apparently discrepant findings on Ahr signaling and Th17 development, it is clear that a tightly regulated balance exists between the microbiota, host diet, and the immune cells present in the intestinal mucosa. Ahr ligands are derived from dietary and non-dietary sources. Dietary Ahr ligands are typically found within fruits and vegetables and include flavonoids, such as kaempferol and quercetin, and indole-3-carbinol (as well as others) derived primarily from cruciferous vegetables (98, 99). Other sources include curcumin metabolites (contained in spices) and resveratrol (red wine) (100, 101). Endogenous Ahr ligands (especially kynurenines) also play a significant role in modulating host immunity, and have been shown to be important in murine colitis and tumor models (102, 103). Recently, another endogenous Ahr ligand, cinnabarinic acid, has been shown to induce T cell expression of interleukin-22 (104).

The microbiota itself can produce Ahr ligands that are capable of promoting a host immune response that, in turn, alters the immunologic response to the microbiota. Elegant studies demonstrated that the *Lactobacillus* speciez, *L. reuteri*, metabolizes tryptophan through the enzyme aromatic amino acid aminotransferase (ArAT) to produce a potent Ahr ligand, Indole-3-aldehyde (IAld), which signals through Ahr to induce increased IL-17 and IL-22 levels within GI tissues of colonized mice (105). In the absence of indoleamine 2,3-dioxygenase 1 (IDO1), an important enzyme responsible for degradation of tryptophan into immunologically active metabolites, mice demonstrated increased gastric colonization with *L. reuteri*, resulting in a compensatory increase in IL-22 production which provided host resistance to *C. albicans* and ameliorated dextran sodium sulfate (DSS)-induced inflammation (105). Another member of the *Lactobacillus* family, *L. bulgaricus* OLL1181 (*L. helviticus*), has also been shown to activate Ahr signaling through a distinct, unknown

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mechanism (106). Other contituents of the resident microbiota (such as *C. sporogenes*) have demonstrated the ability to produce tryptophan derivatives that bind and activate Ahr (107).

The microbiota also produce ATP, a vital energy source that enables innumerable cell functions. ATP secretion by multiple intestinal bacteria has been demonstrated, and occurs via a glycolytic process that is dependent on luminal glucose levels (108, 109). ATP within the gut lumen can increase Th17 cell numbers in the colonic lamina propria (110). It was found that ATP produced by the mirobiota binds to purinergic receptors expressed on lamina propria DCs (specifically the $CD70^{high}CD11c^{low}$ population) to enhance production of IL-6, TGF-β, and IL-23 in a TLR-independent fashion. These DCs were capable of promoting Th17 cell development *in vitro*, and absence of resident microbiota and/or treatment with an ATP antagonist resulted in markedly decreased colonic Th17 cell numbers (110). DCs have also been shown to produce increased IL-1β levels following ATP binding, which could contribute to Th17 cell development (111).

ATP-binding purinergic receptors are expressed by multiple different cell types. Recent studies have demonstrated that intestinal epithelial cells (IECs) also express these receptors and, upon binding microbiota-produced ATP, IECs produce IL-6 and TGF-β and stimulate local DCs to produce additional IL-6 and TGF-β, as well as IL-23 (112). Furthermore, T cells express purinergic receptors and have been shown to produce increased IL-17 levels after direct ATP binding (111).

Levels of extracellular ATP are closely regulated by the host through the expression of a family of enzymes called ecto-nucleoside triphosphate diphosphohydrolases (ENTPDases). The most extensively studied of this family, ENTPDase1 or CD39, has an important role in controlling inflammation and autoimmunity (113, 114). Absence of this enzyme increases susceptibility to colitis in mice, and human mutations are associated with increased risk of IBD (114). Another ENTPDase, ENTPDase7 is expressed on endothelial cells in the small intestine and acts to metabolize luminal ATP produced by the microbiota (115). Absence of ENTPDase7 resulted in augmented Th17 cell numbers within the lamina propria, which was associated with increased severity of EAE but resistance to *C. rodentium* infection (115). This study serves to highlight the importance of regulated balance within the intestinal mucosa. Heightened ATP levels resulting from increased bacterial colonization and/or infection are detected by the host, with a subsequent increase in Th17 development for host protection. Important regulatory mechanisms are required to degrade excess ATP, however, in order to prevent unchecked Th17 response resulting in enteritis and autoimmunity.

Other environmental and dietary effects on Th17 development

Constituents of the microbiota, particularly members of the *Bacteroidetes* and *Firmicutes* phyla, are responsible for metabolism of dietary fiber into short-chain fatty acids (SCFAs) within the GI tract (42, 116). The most studied of the SCFAs are acetate, isovalerate, propionate, and butyrate. SCFAs provide an energy source to colonic epithelial cells that is important for maintenance of a healthy mucosa (117). Butyrate has been specifically shown to maintain intestinal epithelial tight junctions and decrease bacterial translocation (118, 119). SCFAs also dampen the intestinal immune response through increased production of

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TGF-β (42) and through suppression of inflammatory cytokines, including IL-6, IL-17, and IFN-γ (120–122). Luminal acetate has been shown to bind to the GPR43 receptor expressed by intestinal epithelial cells and neutrophils, and down-regulates the inflammatory response in DSS-induced colitis (120). Butyrate and propionate appear to be the most potent SCFAs in abrogating inflammatory signals within the intestinal mucosa (123). This appears to be secondary to their ability to inhibit histone deacetylase (HDAC), thereby resulting in increased H3 acetylation of the FoxP3 promoter and CNS1 enhancer, which enhance Foxp3 expression, but also through acetylation and stabilization of FoxP3 protein itself (124, 125). In addition, butyrate exposure resulted in increased dendritic cell-mediated Treg development. This effect is likely due to repression of pro-inflammatory genes, including *Il12*, *Il6*, and *Relb* in butyrate-exposed DCs (124).

SCFAs are critical regulators of the Th17 response, and are the subject of ongoing research in the pathogenesis and treatment of IBD and dysbiosis. Additionally, other dietary substances can induce IL-23 secretion and potentially alter the Th17 balance within the intestines. These “food-derived bioactives” demonstrate the ability to up-regulate IL-23R expression and Th17-associated cytokines in various cell lines, through mostly unknown mechanisms (126).

Other local environmental signals can influence intestinal immunity. Recently, increased dietary sodium levels have been shown to induce the development of pathogenic Th17 cells and exacerbate autoimmunity (127, 128). Human and murine naïve $CD4^+$ cells exposed to physiologically relevant increased sodium concentrations produced more IL-17 and other Th17-associated cytokines (e.g. GM-CSF) when stimulated *in vitro* under Th17-promoting conditions (128). *In vivo* studies revealed that mice fed a high sodium diet developed worsened manifestations of experimental autoimmune encephalitis (EAE). These effects were mediated by an NFAT5- and SGK1-dependent mechanism (128). Notably, SGK1 levels are initially induced by TGF-β but stable expression is mediated by IL-23 signaling (127). Furthermore, SGK1 increases IL-23R expression, thereby establishing a positive feedback mechanism whereby heightened sodium promotes heightened IL-23 signaling in Th17 cells.

Surprisingly, increased sodium did not result in increased IFN-γ levels, despite up-regulation of T-bet (127, 128). Although the mechanism underlying this observation is unclear, it appears that heightened sodium exposure can increase Th17 cell proliferation and survival while preventing Th1-like conversion. Future studies that explore the role of sustained dietary sodium levels on development of autoimmunity and how the apparent fixed Th17 phenotype alters the manifestations of disease should be informative. In any case, these studies provide additional support for the importance of dietary factors in maintaining and/or altering mucosal immunity within the intestinal tract, and specifically address the role for luminal environment in promoting host Th17 development and inducing inflammation and/or autoimmunity.

Recently, another environmental factor—oxygen tension, particularly hypoxia—has also been demonstrated to have an important role in modulating Th17 development. Oxygen levels decrease throughout the GI tract, reaching levels <5 torr within the distal colon and rectum (129). Important initial studies revealed that hypoxia-inducible factor 1 (HIF-1) is

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important for Th17 development, and in particular, for controlling the balance of Th17 and Treg cell differentiation (130, 131). HIF-1 is a heterodimer composed of the HIF-1α and HIF-1β subunits. The HIF-1α subunit is oxygen-sensitive while HIF-1β is constitutively expressed. Up-regulation of HIF-1α expression occurs in a STAT3-dependent manner and HIF-1α induces glycolysis pathways that are crucial for Th17 cell differentiation (131). HIF-1α also influences the Th17-Treg developmental balance by activating RORγt transcription, while complexing with FoxP3 protein and von Hippel-Lindau protein (VHL) to target both proteins for proteosomal degradation (130). The microRNA miR-210 was recently demonstrated to have an important role in regulating Th17 development under hypoxic conditions. T cell receptor stimulation under hypoxic conditions induces HIF-1α which acts to increase expression of miR-210, in a PI(3)K pathway-dependent manner. miR-210 subsequently acts in a negative feedback loop to decrease *Hif1a* gene expression (132). Thus, aerobic/anaerobic conditions within the GI tract environment, which are regulated in part by the microbiota, also influence development of Th17 cells.

Conclusion

It has been speculated that Th17 cells are the most primitive of the effector $CD4^+$ T cell subsets in evolutionary terms and that they emerged in parallel with pTreg cells to provide vertebrates a means to harness the metabolic potential of a diverse intestinal microbiota (133). As more has been learned regarding the special interplay between these barrier lymphocytes and the microbiota, this possibility seems all the more compelling. Nowhere is the need to finely balance immune tolerance and clearance mechanisms so critical as the intestinal tract, where the greatest concentration and diversity of antigens, microbial and ingested, are in intimate contact with the greatest number of innate and adaptive immune cells throughout life. Moreover, as it has become appreciated that the intestinal microbiota is a latent threat to promote Th17-mediated disease that extends well beyond the intestines, the urgency to better understand the factors that regulate Th17 and pTreg biology in the gut has grown. In view of the remarkable advances that have been made in the decade since discovery of Th17 cells, the prospects for new understanding that informs better therapies for immune-mediated disease driven by the Th17 pathway would appear great.

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