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Review Series

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Pouring fuel on the fire: Th17 cells, the environment, and autoimmunity

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Introduction

The random rearrangement of adaptive antigen receptors allows for incredible diversity of antigen receptor specificity but comes at the cost of creating potentially autoreactive T and B lymphocytes. Although many potentially autoreactive clones are deleted during development or are prevented from causing disease by the various mechanisms of peripheral tolerance, others go on to induce autoimmune disease. Unfortunately, the incidence of autoimmune diseases such as MS, type 1 diabetes (T1D), and inflammatory bowel disease (IBD) has been increasing in the last three to four decades (1–3). Thus it is more important than ever to understand the pathways that promote the differentiation and effector function of self-reactive CD4 Th cells into pathologic effector subsets.

One of the principal means by which Th cells coordinate immune responses is by producing cytokines. Over 20 years ago, Mosmann and Coffman recognized that Th cells can be divided into distinct subsets on the basis of unique patterns of cytokine production (4). While many different subsets have been identified in the ensuing 20 years, the most well-defined effector Th subsets include Th1 cells, which make IFN-γ; Th2 cells, which produce IL-4; and Th17 cells, which generate IL-17 (Figure 1). The patterns of cytokine production of these subsets endow them with different functional properties, and these subsets therefore clear different types of pathogens by inducing distinct types of inflammation. Cytokines also play critical roles in regulating the differentiation of naive Th cells into different effector subsets, independently of antigen specificity, by inducing expression of subset-defining transcriptions factors (5). Thus, cytokines control the differentiation of Th cells as well as their effector function.

Given the importance of cytokines in regulating Th cells, it is not surprising that polymorphisms or environmental stimuli that alter the normal regulation of cytokines are frequently identified as risk factors for the development of autoimmune disease. In particular, mutations or stimuli that result in the dysregulation of cytokines that control Th17 cells appear to particularly predispose to the development of several autoimmune diseases (6, 7). In this Review we focus on the role of cytokines in controlling Th17 cell differentiation and effector function and discuss how environmental factors, such as diet and the intestinal microbiota, may predispose to the development of a pathogenic subset of Th17 cells that can promote autoimmune disease.

Cytokine regulation of Th17 differentiation

The observation that IFN-γ–producing Th cells are prevalent in many autoimmune diseases, such as MS and RA, led to the hypothesis that Th1 cells were critical for disease pathogenesis. Paradoxically, in mouse models of RA and MS (collagen-induced arthritis or EAE), mutations in key Th1-related genes such as *Ifng*, *Ifngr*, and *Stat1* lead to increased susceptibility to disease, rather than protection from disease (8–10). Moreover, while mice deficient for the p40 subunit of IL-12 were resistant to EAE, p35 subunit–deficient mice were still susceptible. This apparent conundrum was resolved by the recognition that another subunit, p19, could also pair with p40 to form the cytokine IL-23 and that mice lacking p19 were resistant to EAE despite having normal Th1 responses (11–13). Rather than promoting Th1 differentiation, as IL-12 does, IL-23 induced IL-17–producing Th cells, later termed Th17 cells, which can induce autoimmune tissue inflammation (13, 14). Moreover, IL-23 was also found to be crucial to developing intestinal inflammation in several mouse models of IBD (15–17). Thus, IL-23 plays a vital role in promoting T cell–mediated tissue inflammation in murine models of human autoimmune disease, in large part by promoting Th17 differentiation.

While IL-23 is clearly critical for the development of Th17 cells in vivo, naive Th cells do not express IL-23 receptor (IL-23R) (18), suggesting that other cytokines are responsible for the initial

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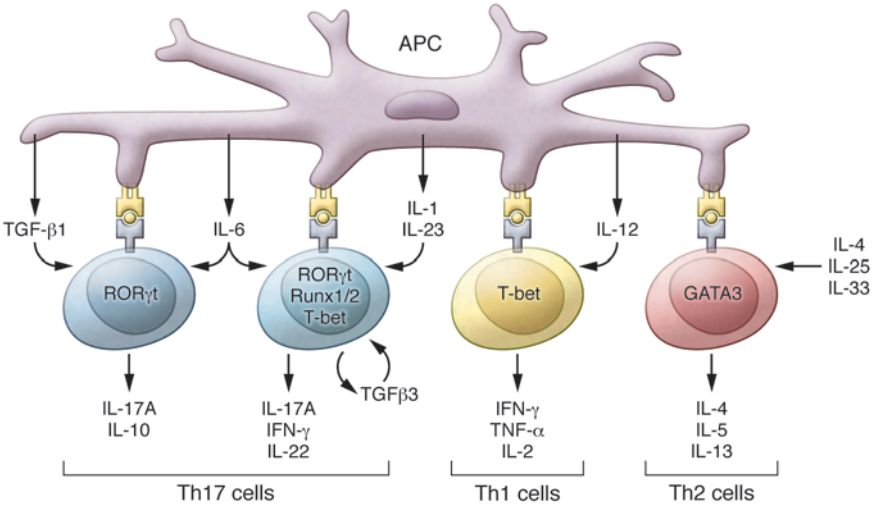

Figure 1. Effector T cell subsets. The subsets of effector Th cells are shown, along with the cytokines that drive their differentiation, lineage-defining transcription factors, and the cytokines they produce. Within the Th17 subset, two distinct subtypes of cells have been described with differing abilities to induce autoimmunity: a pathogenic subtype that produces both IL-17 and IFN-γ and a nonpathogenic subtype that produces IL-17 and IL-10.

induction of this lineage. The combination of TGF-β1 and IL-6 efficiently induces IL-17–producing murine T cells in vitro and highlights the reciprocal relationship between induced Tregs, which are generated by TGF-β1 alone, and Th17 cells (19, 20). A series of studies demonstrated that IL-21, a γ_c-dependent cytokine, could promote the differentiation of Th17 cells (21–23). In combination with TGF-β, IL-21 induces IL-17 production from naive Th cells and promotes the expression of both RORγt, the lineage-defining transcription factor of Th17 cells, and IL-23R (23, 24). IL-21 could also inhibit the generation of TGF-β–induced FOXP3$^+$ Tregs, and analysis of IL-6–deficient mice revealed that the ability of IL-21 to generate Th17 cells from Th cells was independent of IL-6 (21). Both IL-6 and IL-21 can induce Th17 cells themselves to produce IL-21. This led to a model of Th17 cell differentiation in which IL-6 elicits autocrine IL-21 production, which then amplifies the Th17 response by inducing itself and upregulating IL-23R, allowing for the stabilization and terminal differentiation of the lineage through IL-23. While IL-21 can clearly promote Th17 differentiation in vitro, it is not absolutely required in vivo. In particular, both IL-21– and IL-21R–deficient mice are not protected from EAE, indicating that IL-21 may have a redundant role in Th17 differentiation in this setting (25, 26). In contrast, IL-21 is absolutely required in the NOD model for development of spontaneous diabetes, as loss of either *Il21* or *Il21r* makes mice resistant to the development of disease (27, 28). Moreover, SNPs in *IL21* and *IL21R* have been implicated in several human autoimmune diseases (29–34).

Interestingly, Th17 cells differentiated with just TGF-β1 and IL-6 are inefficient at inducing autoimmunity when transferred in vivo, in part due to their co-production of IL-10 (35). However, the addition of IL-23 to TGF-β1 and IL-6 induces Th17 cells that trigger EAE after transfer, supporting a key role for IL-23 in promoting the ability of Th17 cells to induce tissue-specific autoimmunity (36). Interestingly, the role of TGF-β1 in human Th17 cell differentiation is less clear cut, as studies have shown variable importance of this cytokine for human Th17 cell differentiation (37–39). Moreover, human Th17 cells can be efficiently induced by the combination of IL-1β, IL-6, and IL-23, and subsequent work suggests that TGF-β1–dependent Th17 cells may have different functional properties than those differentiated with IL-1β (38, 40). Murine Th17 differentiation can also be induced in the absence of TGF-β1 signaling, via the combination either of IL-1β, IL-6, and IL-23 or of TGF-β3 and IL-6 (41, 42). These TGF-β1–independent Th17 cells can efficiently induce autoimmune tissue inflammation upon adoptive transfer, a trait that led to them being termed "pathogenic" Th17 cells. Additionally, they possess a gene expression profile distinct from that of "nonpathogenic" Th17 cells, which are differentiated with TGF-β1 and IL-6.

These observations have led to two competing hypotheses. The first posits that IL-23 cements Th17 lineage commitment such that Th17 cells induced with TGF-β1 and IL-6 are insufficiently committed to the lineage and cannot induce autoimmune tissue inflammation. The second suggests that there are distinct subtypes of Th17 cells whose differentiation is dependent on distinct combinations of cytokines. The latter hypothesis is supported by the finding that pathogenic Th17 cells express higher levels of several Th1 lineage–associated transcripts, such as the transcription factor T-bet and IFN-γ, and have been shown to be derived from IL-17 single producers by fate mapping experiments (43, 44). Similarly, an important feature of human Th17 cells, as well as those isolated from inflamed tissues in mouse models of Th17-mediated disease, is that they coproduce IL-17 with other cytokines, leading to distinct functional roles (45–47). For instance, human Th17 cells that produce both IL-10 and IL-17 preferentially respond to *Staphylococcus aureus*, while those that produce both IL-17 and IFN-γ recognize *Candida albicans*, suggesting that distinct pathogens induce distinct subtypes of Th17 cells (40). IL-17/IFN-γ coproducers have been ascribed pathogenic functions in the CNS during EAE; however, it has been difficult to reliably differentiate such cells in vitro. Repeated rounds of in vitro culture in the presence of either Th1-inducing cytokines or IL-23 can induce IL-17/IFN-γ coproducers, albeit at moderate percentages. The transcription factors T-bet, RUNX1, and RUNX3 appear to be important in the acquisition of this phenotype (48, 49).

Large-scale transcriptional analysis of Th17 differentiation at very high temporal resolution has begun to elucidate the molecular networks that control this process, and is a promising approach to the identification of novel regulatory molecules that control pathogenic Th17 differentiation (50, 51). In fact, Th17 development is controlled

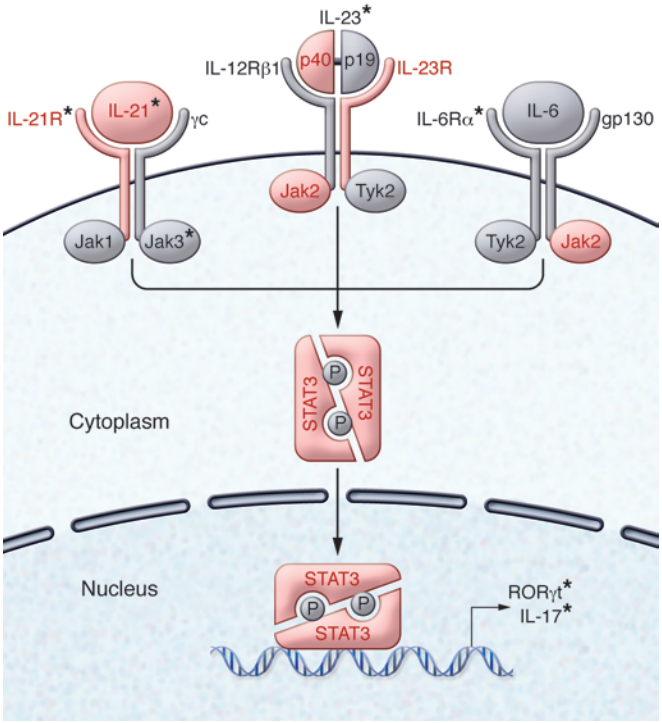

Figure 2. STAT3-dependent cytokines in autoimmunity. Cytokines that activate STAT3, including IL-6, IL-21, and IL-23, play a critical role in promoting Th17 differentiation and have been implicated in human autoimmune disease. The signaling pathways of IL-23, IL-21, and IL-6 are shown. Genes marked in red have SNPs that have been implicated in human autoimmune diseases. Genes marked with an asterisk have targeted therapeutics either approved or in active clinical development for treatment of autoimmune disease.

by two self-reinforcing, mutually antagonistic modules: a positive module containing 22 genes that promote Th17 differentiation and a negative module of 5 genes that inhibit Th17 development. These mutually antagonistic modules are essential for maintaining a balance between Th17 cells and other T cell subsets. Thus, a growing amount of evidence suggests that there may be at least two distinct subtypes of IL-17–producing Th cells and that these subtypes may mediate distinct immunologic functions, although the underlying molecular basis for these subtypes is just beginning to be identified.

IL-23 and autoimmunity

Mice that overexpress IL-23 develop a spontaneous inflammatory disease similar to ankylosing spondylitis, while mice lacking tristetraproline, which regulates *Il23* mRNA stability, develop spontaneous systemic inflammation, highlighting the importance of this cytokine in regulating inflammatory T cell populations (52, 53). Moreover, IL-23 is essential for the induction of the pathogenic Th17 cell gene expression profile (41). Thus, it is not surprising that the IL-23R is expressed at higher levels in pathogenic Th17 cells and is required for Th17-mediated induction of EAE (41). The pathways activated downstream of IL-23R that are required for pathogenicity are just beginning to be identified. One such molecule, the salt-sensitive kinase SGK1, was recently identified through use of transcriptional networks and predicted protein-protein interactions, experimentally verified to be downstream of IL-23R, and shown to be required for the induction of pathogenic Th17 cells (50, 54, 55). Additionally, the IL-23R–mediated induction of the cytokine GM-CSF is required for the pathogenicity of Th17 cells, although by itself it is not sufficient to induce EAE in vivo (56, 57). Thus, while further investigation into the molecular basis for the differentiation of pathogenic Th17 cells is clearly needed, the critical role of IL-23 in this process is evident.

The importance of IL-23 in promoting autoimmune tissue inflammation is further highlighted by the finding that polymorphisms in genes related to IL-23 and its signaling pathway are associated with several human autoimmune diseases, including IBD, ankylosing spondylitis, psoriasis, and autoimmune thyroiditis (Figure 2 and refs. 58–60). SNPs in *IL23R* are associated with both Crohn's disease and ulcerative colitis, consistent with the crucial role IL-23 has in mouse models of IBD (15, 17, 61). One IBD-associated *IL23R* SNP, which encodes the mutation R381Q, lies within exon 9 of *IL23R* and appears to be protective, with a reduced frequency in patients compared with controls. After activation, T cells isolated from individuals expressing IL-23R^{Q381} have a reduced frequency of IL-23R$^+$ Th cells and decreased phosphorylation of STAT3 after stimulation with IL-23 (62). Moreover, SNPs in the gene encoding IL-12/23p40, which could affect both IL-12 and IL-23 function, have also been linked to psoriasis, psoriatic arthritis, and IBD (63–66). Thus, SNPs affecting the IL-23 pathway are commonly found in human autoimmune disease, and a SNP that results in decreased IL-23R function is protective against the development of intestinal inflammation. These data suggest that the proper regulation of IL-23 is critical to prevent autoimmunity.

STAT3 represents an important downstream mediator of IL-23R signaling, as well as several other inflammatory cytokines, including IL-6 and IL-21, and is crucial for Th17 differentiation in both humans and mice. SNPs in *STAT3* have been linked to many of the same human autoimmune diseases associated with the IL-23 pathway, including psoriasis, IBD, and ankylosing spondylitis (66–68). Loss-of-function mutations in *STAT3* lead to the development of autosomal-dominant hyper-IgE syndrome, manifestations of which include chronic mucocutaneous candidiasis and recurrent staphylococcal infections. These patients have markedly decreased frequencies of IL-17– and IL-22–producing T cells (69–72). In contrast, several patients have recently been identified who had very early onset multi-organ autoimmune disease and were found to have novel *STAT3* mutations that resulted in increased STAT3 activity (73, 74). Such patients have a reduced frequency of circulating FOXP3$^+$ Tregs, and one patient responded clinically to blockade of IL-6R with tocilizumab with a marked decrease in the frequency of IL-17–producing CD4$^+$ T cells (74). Thus, mutations in *STAT3* can alter Th17 differentiation, and *STAT3* mutations and polymorphisms can predispose to the development of autoimmune disease, highlighting the importance of this molecule.

Regulation of Th17 differentiation by environmental factors

The relatively recent increase in the incidence of a variety of autoimmune diseases in which Th17 cells and IL-23 have been implicated, including MS and IBD, suggests that environmental factors

may lead to altered immune responses and promote autoimmunity. Given the importance of cytokines in regulating Th17 differentiation and the apparently crucial role of IL-23 in promoting a pathogenic Th17 subset, it is important to understand how environmental stimuli can influence regulation of Th17-related cytokines, particularly IL-23. Mucosal tissues such as the intestine have emerged as a key physiologic site for the differentiation and regulation of Th17 cells, suggesting that these cells may be particularly sensitive to perturbations from changes in environmental stimuli.

Microbiota. The intestine is home to both a vast array of commensal microbes and a multitude of immune cells, and the interplay between these two populations has been increasingly recognized to affect immune homeostasis. At steady state, a significant proportion of the Th cells residing in the lamina propria of the small intestine are Th17 cells (24). Colonization of germ-free mice with normal intestinal microbiota induces the upregulation of a number of cytokines, including TNF-α, IFN-γ, IL-1, IL-6, IL-10, and IL-17; however, the induction of IL-17 in this setting is profound, showing an increase of over 1,000-fold (75–77). Consistent with this, the development of intestinal Th17 cells requires the presence of the intestinal microbiota, as these cells are absent in germ-free mice (76). The intestinal microbiota are also required for the maintenance of intestinal Th17 cells, as antibiotic treatment, particularly antibiotics with activity against Gram-positive organisms, results in marked depletion of this population (76, 77). Thus, normal commensal microbes induce an environment that promotes the differentiation of Th17 cells.

Ivanov and colleagues made the observation that mice from Taconic Farms have a substantially higher frequency of IL-17$^+$ Th cells in the lamina propria than do mice from The Jackson Laboratory (76). Cohousing of Jackson and Taconic mice led to an increased frequency of lamina propria Th17 cells in Jackson mice, suggesting that the bacteria responsible could be transmitted between mice (76). A single Gram-positive bacterial species, termed segmented filamentous bacteria (SFB), appears to be primarily responsible for inducing intestinal Th17 cells. This Clostridial-related species is non-culturable, sporulating, and strongly adherent to ileal epithelium and is nearly absent in mice from The Jackson Laboratory (78, 79). Inoculation of Jackson mice with fecal microflora from SFB-monocolonized mice potently induces expansion of intestinal IL-17$^+$IL-22$^+$ Th cells (79). The majority of these cells are specific for SFB-derived antigens, although there are conflicting data regarding whether recognition of cognate antigen is required for their differentiation (80–83). SFB colonization also induces development of secondary and tertiary lymphoid structures in the intestine, and the development of SFB-specific Th17 cells requires such organized structures (84). Thus, a single commensal microbial species is able to exert a marked effect on Th cell differentiation, augmenting the differentiation of a subset important in the pathogenesis of autoimmune disease.

The intestinal microflora, and in particular the presence of SFB, has been demonstrated to alter the course of a number of mouse models of autoimmune disease. In a Th cell transfer model of colitis, which requires the presence of intestinal microbiota, reconstitution of mice with a mixture of SFB and conventional murine microbiota led to colitis, whereas either one alone led to attenuated disease (85). Inflammatory autoimmune arthritis can be mitigated in the K/BxN mouse model by treatment with either anti–IL-17 or antibiotics that cover Gram-positive organisms, is significantly attenuated in germ-free mice, and recurs upon either conventionalization or SFB monocolonization (86). A spontaneous model of relapsing/remitting EAE has been found to be dependent on the presence of commensal microbiota (87). Similarly, in germ-free animals, EAE induced by immunization with complete Freund's adjuvant/myelin oligodendrocyte glycoprotein is attenuated compared with EAE in conventionalized mice, and these mice show an increased frequency of Tregs and decreased numbers of IL-17$^+$ CD4$^+$ cells (88). After monocolonization with SFB, germ-free mice are once again susceptible to EAE, with markedly enhanced Th17 responses in both the spinal cord and small intestine. This suggests that the SFB-induced microenvironment can foster the differentiation of autoreactive Th17 cells that can then circulate throughout the body and induce inflammatory disease at distal sites, depending on the specificity of the TCRs of the T cells. This possibility is further supported by the finding that adoptively transferred naive Th cells that express an SFB-specific TCR upregulate RORγt in an SFB-dependent manner and can be found in both the intestine and the spleen (81). In contrast, in the case of the NOD model of T1D, SFB colonization actually appears to be protective, as SFB-positive NOD mice have a dramatically reduced incidence of diabetes (89). Thus, SFB-induced intestinal Th17 cells can variably modulate the course of organ-specific autoimmune disease.

The mechanisms by which SFB induce intestinal Th17 cells are still being elucidated. Despite playing a critical role in regulating intestinal epithelial homeostasis, TLR-derived MyD88-dependent signals appear to be dispensable for SFB-induced intestinal Th17 differentiation (75, 76, 90). However, several studies have suggested an important role for intestinal APCs in promoting the differentiation of microbiota-dependent intestinal Th17 cells via both antigen-dependent and -independent mechanisms (75, 79–81). Intestinal Th17 cells show a substantial degree of reactivity to SFB-derived antigens and fail to develop in the absence of MHC class II on CD11c$^+$ cells (80, 81, 83). ATP derived from lumenal microbes specifically induces upregulation of IL-23p19, IL-6, and TGF-β–activating integrins in a CD70^{hi}CD11c^{lo} population uniquely present in the lamina propria that can support the differentiation of Th17 cells in vitro (75). Intriguingly, mice lacking *Entpd7*, which encodes an extracellular ATP hydrolase preferentially expressed on small intestinal epithelium, have both increased luminal ATP and higher frequencies of intestinal Th17 cells (91). Moreover, while *Entpd7*-deficient mice are resistant to *Citrobacter rodentium* infection, they develop more severe EAE than WT mice. Thus, microbial-derived peptides and metabolites contribute to the induction of intestinal Th17 cells.

Type 3 innate lymphoid cells (ILC3s), which resemble Th17 cells with regard to the cytokines they produce, appear to regulate intestinal Th17 cell differentiation in a microbiota-dependent manner. Mice lacking Ahr, IL-22, IL-23p19, or IL-23R have relative outgrowth of SFB and increased intestinal Th17 cells, and this appears to be due to a marked decrease in IL-22–producing immune cells, particularly ILC3s (92–94). IL-22 is critical for maintaining intestinal barrier function, and in the absence of IL-22, SFB increase in relative abundance, leading to an increased

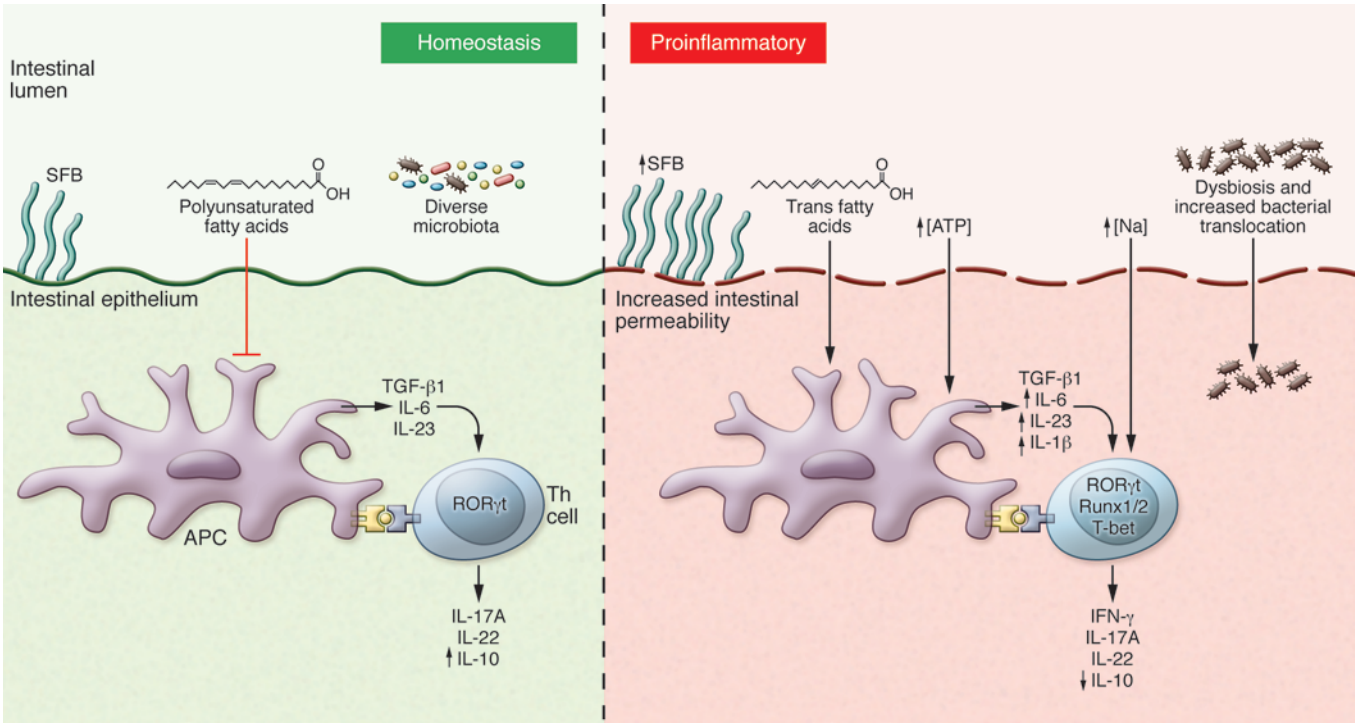

Figure 3. Factors that alter the intestinal microenvironment can affect Th17 differentiation. The small intestine plays an important role in promoting Th17 differentiation in vivo, and changes in dietary intake or the intestinal microbiota can alter cytokine production in that microenvironment and promote the differentiation of Th17 cells with a pathogenic phenotype. This more pro-inflammatory environment may predispose to the development of autoimmune disease. Intriguingly, many of these same factors can also predispose to the development of metabolic diseases such as type 2 diabetes. Thus, dysregulation of Th17-related cytokines may also play a role in the pathobiology of these diseases as well as in full-blown autoimmunity.

frequency of Th17 cells in both the intestine and distal secondary lymphoid tissue (93, 95, 96). IL-23–induced IL-22 also appears to be critical for prohibiting microbiota from entering normally restricted anatomical compartments, as mice deficient in both IL-23R and RAG2 have elevated levels of LPS in both the spleen and liver (93). Furthermore, selective depletion of ILCs results in systemic dissemination of *Alcaligenes* spp., a normal enteric commensal (97). Dissemination of *Alcaligenes* induced a systemic inflammatory response that was prevented by the administration of exogenous IL-22. Intriguingly, pediatric patients with Crohn's disease had higher titers of anti-Alcaligenes antibodies compared with healthy controls, suggesting that dissemination of these bacteria may occur in patients with IBD as well. Finally, ILC3s have also been found to express MHC class II and induce peripheral tolerance to commensal-derived antigens, as selective deletion of the MHC class II locus in ILC3s leads to spontaneous intestinal inflammation associated with expansion of intestinal Th17 cells (80, 92). Thus, the interplay between ILC3s and intestinal microbiota can modulate in vivo Th17 differentiation by a number of distinct mechanisms.

Diet. The increased incidence of autoimmune disease over the last several decades has mirrored the widespread adoption of a diet dependent on processed foods rich in salt, fats, and both sugar and artificial sweeteners. While it is currently unclear whether these two things are related, there is a clear association between obesity and the adoption of a diet heavy in processed foods. Recent work has clearly highlighted the extent to which obesity is an inflammatory state, with increased production of cytokines known to promote Th17 differentiation, including IL-1 and IL-6 (98). Moreover, mice placed on a high-fat diet demonstrate increased expression of IL-17, IL-23p19, and RORγt consistent with increased Th17 responses and have more rapid onset of colitis (99). Similarly, mice placed on a diet rich in trans fatty acids, which are found in processed hydrogenated vegetable oil, develop more severe intestinal inflammation in response to dextran sodium sulfate, and this is associated with an increase in both IL-17 and RORγt expression (100). Trans fatty acids also directly induce increased expression of IL-23p19 in peritoneal macrophages. However, addition of polyunsaturated fatty acids (PUFAs), which have been shown to mitigate obesity-associated metabolic pathology, results in decreased colitis severity in mice placed on a high-fat diet that otherwise would exacerbate disease, and this correlates with decreased levels of a number of Th17-related cytokines (101–103). Interestingly, observational data from the Nurse's Health Study suggest a possible correlation between dietary PUFA intake and a reduced risk of ulcerative colitis, whereas high intake of trans-unsaturated fats was associated with an increased risk of developing ulcerative colitis (104). Thus, both obesity and dietary fat intake can alter the production of cytokines involved in Th17 differentiation and potentially predispose to the development of autoimmunity.

In addition to fats, processed foods are also rich in salt, and recent work has shown that a diet high in salt may promote both Th17 differentiation and induction of autoimmunity (54, 55). This appears to be directly mediated by the salt-sensitive kinase,

SGK1, which was identified as an important downstream target of IL-23R signaling (50, 54). Increased salt concentrations preferentially induced Th17 cells with a pathogenic, pro-inflammatory gene signature. Consistent with this, mice placed on a high-salt diet develop more severe EAE (54, 55). While a high-salt diet induces multiple physiological changes, it appears that it alters EAE severity by directly affecting T cell priming, since mice with a T cell–specific deletion of *Sgk1* have reduced EAE severity and do not develop exacerbated disease on a high-salt diet (54). Given how tightly mammals regulate the plasma sodium concentration, it is tempting to speculate that the high-sodium diet may exert its effect by altering the differentiation of intestinal Th17 cells toward a pathogenic phenotype, since they would be in close proximity to the increased concentration of sodium in the intestinal lumen; however, this remains to be demonstrated. Although there is no conclusive evidence, a number of recent studies support the concept that a high-salt diet may predispose to the development of human autoimmune diseases. One such study found a positive correlation between sodium intake and disease activity in patients with relapsing-remitting MS, as patients with higher salt intake had higher lesion load by MRI and higher disability scores (105). Similarly, the combination of high sodium intake and smoking was associated with a significantly increased incidence of developing RA (106). Thus, high salt concentrations can promote the differentiation of pathogenic Th17 cells, and increased dietary salt intake may promote autoimmune disease in both mice and humans.

The IL-23/IL-17 axis as a therapeutic target in autoimmunity

The identification of the IL-23/IL-17 axis as critical for human autoimmune disease has led to the rapid development of many novel therapeutic agents. Monoclonal antibodies to a variety of cytokines and cytokine receptors and small-molecule inhibitors of RORγt and JAKs are in active preclinical and clinical development (Figure 2). Clinical trials of these agents in human autoimmune diseases suggest that they hold promise as therapeutics and illuminate the distinct roles these cytokines play in different autoimmune diseases.

Humanized monoclonal antibodies to both IL-17 (secukinumab) and IL-17RA (brodalumab) significantly improved moderate to severe psoriasis as well as psoriatic arthritis (107–110). Moreover, a Phase II clinical trial with secukinumab in MS has been completed, and preliminary results have been reported to be positive (ClinicalTrials.gov identifier: NCT01051817). In contrast, a Phase II study on RA patients with inadequate response to methotrexate reported no significant response to secukinumab, while a Phase Ib study of brodalumab failed to show efficacy in patients with moderate to severe RA, suggesting that inhibition of IL-17, one of the many cytokines produced by Th17 cells, may not be efficacious in RA (111, 112). Additionally, in Crohn's disease, trials of secukinumab and brodalumab failed to show efficacy and even exacerbated disease activity in some patients (113). This is in line with evidence that IL-17A may be protective in murine colitis models (114). Thus, the clinical utility of targeting IL-17 depends greatly on the disease and highlights that IL-17 can play both pathogenic and protective roles in autoimmunity.

Agents targeting IL-23 are also in development. Monoclonal antibodies targeting IL-23/IL-12p40 have shown clinical efficacy for both psoriasis and Crohn's disease. Ustekinumab, an antibody to the shared IL-12/23p40 subunit, dramatically improves psoriasis, performing better than etanercept (115–117). Intriguingly, ustekinumab showed benefit in patients with Crohn's disease, including those with TNF-antagonist refractory disease (118). This is stark contrast to the results seen with inhibition of IL-17 and suggests that IL-23 and IL-17 may play distinct roles in the pathobiology of Crohn's disease.

Conclusions

Interactions between diet, the microbiota, and intestinal immune cells can markedly alter both systemic immune function and host metabolism, and this appears to be largely mediated by cytokines, particularly those in the IL-23/IL-17 axis. In this regard, intestinal ILC3s and Th cells demonstrate reduced production of IL-22 in response to IL-23 in some mouse models of obesity, leading to altered intestinal barrier function (119). Remarkably, administration of exogenous IL-22 not only rescued barrier function and reduced evidence of inflammation, but also led to improvement in glycemic control and dyslipidemia, highlighting the importance of interactions between the immune system, the microbiota, and host metabolic pathways in maintaining homeostasis. It is also important to note that the development of atherosclerosis is accelerated in several systemic human autoimmune diseases, particularly RA (120). It is thus intriguing to speculate that there are similar pathobiologic processes in play for both autoimmunity and metabolic diseases with an inflammatory component, such as type 2 diabetes and atherosclerosis.

While the past several decades have seen marked changes in diet, it is also likely that improvements in hygiene, the development of antibiotics, and widespread vaccination have resulted in significant changes in the intestinal microbiota (121, 122). This raises the possibility that altered regulation of cytokines as a consequence of changes in diet, metabolism, and commensal microbes, particularly in the intestinal microenvironment, may contribute to the increased incidence of autoimmune diseases, especially those involving the IL-23/IL-17 axis (Figure 3). Further investigation of the manner in which these complex and interrelated systems affect cytokine regulation represents a promising area of investigation to better understand the pathobiology of autoimmune disease and is already bearing fruit for identifying promising therapeutic targets to ease the human burden of these diseases.

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