Biomedical Research and Clinical Practice

Review Article

ISSN: 2397-9631

Factors regulating Th17 cells: a review

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Abstract

This article aims to provide a broad coverage of over 300 studies on T helper 17 (Th17) cells published mainly between 2011 and 2016, with a focus on factors negatively regulating Th17 cell differentiation and functions. During the last decade, processes underlying Th17 cell differentiation and activation, as well as Th17-specific cytokines, chemokines, and transcription factors, have been characterized. Diverse modalities controlling Th17 cells range from factors modulating the state of regulatory T (Treg) cells or dendritic cells and indirectly regulating Th17 cells to cell-intrinsic factors, such as those that repress genes encoding Th17 signature cytokines, including artificial products. Since IL-17 is a major player in tissue-specific immune pathology, Th17 cells, a major source of the cytokine, have been a subject of intensive research and have been at the forefront of clinical studies. New approaches, including conditional knockout mice as well as transcriptome profiling, have revealed closely related developmental states in Th17 cells, reflecting their plasticity. For example, given that Th17 cells share a differentiation pathway with Treg cells that, in turn, control Th17 cells, the Treg/Th17 axis is important for fine-tuning the intensity of inflammatory responses. An emerging picture shows that a combination of many factors involving IL-23, IL-2, CCR6, the mammalian target of rapamycin (mTOR)-hypoxia-inducible factor (HIF) axis, metabolism (glycolysis and lipid synthesis), retinoic acid, glucocorticoids, melatonin, Wnt pathways, and salt act in synergy to regulate the Th17/Treg balance and inter-Th17 subset balance. Therapeutic interventions that can tune such balances would be efficacious when accompanied by our attentiveness to the spatial and temporal dynamics of Th17 cells. A comprehensive understanding of biochemical and cellular factors underlining these subtle regulations would give us a more integrated view that would hopefully help increase therapeutic options for many cases of autoimmune and inflammatory diseases and predisposed individuals.

Introduction - an overview of immunotherapy, IL-17, and Th17 biology

An understanding of the cytokines responsible for autoimmune diseases has changed the concept of their treatment. Prior to the identification of IL-17, several cytokines crucial for autoimmune diseases had been identified. The treatment of autoimmune diseases, including rheumatic arthritis (RA), has been revolutionized by the advent of targeted biological agents as well as improved use of conventional drugs. Inhibitors of TNF-α have shown benefits in many patients with RA and psoriasis [1-3]. This success was followed by the development of drugs targeting IL-6 and IL-1 [2,4,5]. After the discovery and characterization of IL-17A demonstrating that it induces IL-6 secretion from synoviocytes in patients with RA [6], blockade of IL-17A has been assessed in RA, psoriasis, and other related diseases and has shown some successful results [7]. (Henceforth "IL-17" indicates IL-17A, the founding member of the IL-17 family, unless otherwise noted.) Pathological roles of IL-17 in autoimmune diseases, as well as clinical trials targeting IL-17 or IL-23, have been reviewed by Beringer *et al.* [7], Waisman *et al.* [8], and Kim *et al.* [3]. Roles for IL-17 in central nervous system (CNS) diseases, including multiple sclerosis (MS) and infarction [8], and in cardiovascular diseases [9] have also been discussed. To avoid redundancy, we focus on T helper 17 (Th17) biology and mechanisms that inhibit Th17 cell development and activity, with emphasis on their therapeutic relevance. Notably, Th17 is not the only cell capable of producing IL-17; other types of cells, such as γδ-T cells and innate lymphoid cells (ILCs), are likely to be the main source of IL-17 in some cases [10,11].

Upon activation by an antigen, naive $CD4^+$ T cells proliferate and differentiate into various subsets of T helper (Th) cells, including Th1, Th2, and Th17 cells. Th17 cells develop mostly from naive T cells, produce proinflammatory cytokines IL-17A, IL-17F, and IL-22, and coordinate inflammatory responses for host defense [8,12]. Th17 cells have been shown to be important for mucosal host defense against microbial and fungal pathogens [13], but, on the other hand, are present at tissue inflammation sites and contribute to the pathogenesis of human autoimmune and chronic inflammatory disorders [12,14-17]. In mice, Th17 cells express the transcription factor retinoic acid-related orphan receptor γt (RORγt, corresponding to human RORc) as a master transcriptional regulator [18] along with the chemokine receptors CCR6 [19] and CCR2 [20]. Both RORγt and RORα, a closely related family member, are necessary for full Th17 cell development [18]. Multiple cytokines, including TGF-β, IL-6, IL-1β and IL-21 are known to induce differentiation of naive T cells to Th17 cells [12]. In particular, this differentiation can be initiated by a combination of TGF-β and IL-6 in mice [12], and is maintained by IL-23 [21,22]. It is now known that Th17 cells consist of subsets with differential inflammatory potential, ranging from a subset that is induced by TGF-β and IL-6, produces IL-10, and is a weak inducer of inflammation, to a highly inflammatory subset that produces GM-CSF/IFN-γ and is induced by IL-23 [23]. IL-23R is required for effector Th17 cell responses in vivo [24], and IL-23 appears to be a promising therapeutic target [25]. The importance of pleiotropic cytokine TGF-β for Th17 (as well as inducible regulatory T [Treg] cell) development was established by early findings [26]. As the differentiation state of dendritic cells (DCs) has profound effects on Th17 differentiation, the extrinsic effect of TGF-β mediated by TGF-β-signaling in DCs is also important [27].

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Received: October 08, 2016; **Accepted:** November 15, 2016; **Published:** November 17, 2016

We do not discuss IL-22, a Th17 signature cytokine, in detail, but instead suggest recent articles [28,29]. Both IL-17 and IL-22 play a central role in the pathogenesis of MS [30,31] and RA [32]. A recently proposed subset, Th22, shows similarity with Th17 [33], yet, one feature of Th22 cells is their dependency on aryl hydrocarbon receptors (AHR), rather than RORγt. Th22 cells play a pathological role in psoriasis, but their role in RA is less clear [34].

Cytokines and other factors present during T cell priming events can direct differentiation by inducing lineage-specifying transcription factors that act as master regulators. T-bet, signal transducer and activator of transcription (STAT)1, and STAT4 are the master regulators for Th1 cells; GATA3 and STAT6 direct the Th2 lineages, and STAT3 and RORγt direct differentiation of Th17 cells [18,35]. The induction of RORγt is dependent on STAT3, which is mainly activated by IL-6. PI3K/AKT signaling acts upstream to positively regulate the activation of protein kinase mammalian target of rapamycin (mTOR) C1, and this axis is a positive regulator of Th17 development [36,37]. mTORC1 positively modulates IL-17 expression through several pathways involving STAT3 and hypoxia-inducible factor 1α (HIF1α) [36,38].

This article focuses on recent reports of negative regulators that inhibit Th17 cell development or suppress their functions, with a limited coverage of the basics revealed in earlier studies. Nonetheless, given the therapeutic relevance of the overall tone of inflammation, and the indirect effect of non-T cells such as DCs, the macroscopic mechanisms governing the balance of various subsets of T cells are also important. Therefore, we begin with Th17/Treg balance, to which we aim to endow an introductory purpose. After the factors modulating Th17 development in an extrinsic manner are discussed, the regulatory factors intrinsic to T cells (i.e., without the aid of other cell types) are considered.

Cytokines, hormones, and vitamins that negatively regulate Th17 cells include retinoic acid [39,40], IFN- β, IL-10 [41,42], IL-27, Th1 and Th2 cytokines, IFN-γ and IL-4 [43,44]. Many of these factors act, at least in part, in an extrinsic manner, i.e., mediated by DCs and other cells. On the other hand, Th17 cell-intrinsic negative regulators include Foxp3 [45], interferon regulatory factor 4 (IRF4)-binding protein (also known as Def6 or SLAT) [46], peroxisome proliferator-activated receptor γ PPAR-γ [47], liver X receptors (LXRs) [48], and STAT5 [49], which we discuss in some depth. Other negative factors include NR2F6 (Ear-2) [50], growth factor independence 1 (Gfi-1) [51], suppressor of cytokine signaling 3 (SOCS3) [52], TNF receptor–associated factor 6 (TRAF6) [53], protein kinase B (PKB)/Akt signals [54], and E26 transformation-specific sequence 1 (Ets-1) [55,56], but we only briefly mention them in related sections, as these may be integrated into some axes. For example, Ets-1 is involved in the Ets-1-IL-2 axis [56].

IL-23 signaling as a target

IL-23 consists of the p40 subunit of IL-12 and an unrelated p19 peptide. There is a consensus that, in the presence of TGF-β IL-6 triggers differentiation of Th17 cells in mice. IL-23 is essential to establish and stabilize the differentiated states of Th17 cells. In support of this view, IL-23 is important in vaccination models [57]. In Khader *et al.'s* study, despite no involvement of IL-23 in primary resistance to *Mycobacterium tuberculosis*, vaccination with a defined peptide from *M. tuberculosis* established persistent IL-17-producing T cells in a manner dependent on IL-23 [57]. Thus-established IL-17-producing T cells, which appeared to accumulate in the lung, allowed accelerated recall response and protection against infection [58].

Setting aside evidence for IL-23 involvement, several studies have elucidated roles of memory Th17 cells in protection from several microbes. Wüthrich *et al.* showed the importance of Th17 cells in recall responses against several fungi, specifically, *Coccidioides posadasii, Histoplasma capsulatam,* and *Blastomyces dermatitidis* [59]. Chen *et al.* [60] showed the importance of memory Th17 cells established by vaccination for *Klebsiella pneumoniae*. In that study, Th17, but not IFN-γ was required for broader (i.e., serotype-independent) protection against *K. pneumoniae*. Using a baboon model of *Bordetella pertussis* infection, Warfel and Merkel showed the presence of IL-17-producing memory T cells and IFN-γ-producing memory T cells >2 years after infection [61].

Using an experimental autoimmune encephalomyelitis (EAE) model, Haines *et al.* [25] showed that memory cells were generated from IL-17$^+$RORγt$^+$ precursors, not noncommitted precursors. Compared to the cells on day 8 (after primary immunization), the cells on day 18 showed better Th17 phenotype stability in an IL-23-dependent manner, implying that the time length of primary immunization is critical for stability of the differentiation state of Th17 cells. Short immunization times allowed differentiation into IFN-γ-producing cells in their setting [25]. IL-23 promoted proliferation of memory Th17 cells and upregulated genes required for cell-cycle progression in Th17 cells. IL-23 also induced T-bet and IFN-γ in Th17 cells.

These findings implicated the therapeutic potential of blocking IL-23. Notably, tildrakizumab (MK-3222), a humanized anti-IL23p19 mAb improved psoriasis in a phase IIb randomized, placebo-controlled trial, although adverse effects, including bacterial arthritis, were reported [62].

Tregs, non-pathogenic Th17, and pathogenic Th17

After naive T cells were shown to differentiate into Th17 cells, it was noted that Treg and Th17 cells emerge from an overlapping developmental program (Figure 1) [63]. This close relationship between Treg and Th17 cells, along with the developmental plasticity of Th17 cells, led to recognition that Th17 cells play not only proinflammatory and defensive roles but also have regulatory roles. Treg cells are broadly classified into two groups: nTregs that develop in the thymus and iTregs that are induced in peripheral organs by TGF-β. Thus, both iTreg and Th17 cells can be induced from naive CD4$^+$ T cells in the periphery upon antigen stimulation and exposure to TGF-β. The notion that Treg and Th17 have a reciprocal (mutually exclusive) relationship [39] leads us to surmise that subtle modulations of Th17-iTreg cell balance can exert immense effects on the outcome of therapeutic interventions. Physiologically, switching differentiation between Treg and Th17 cells is mainly regulated by IL-6 [53]. TGF-β signaling alone leads to Foxp3 expression and induction of Treg, but costimulation with IL-6 can suppress *Foxp3* and, therefore, release RORγt from inhibition by Foxp3, promoting Th17 development.

Th17 cells can be derived from Treg cells if appropriate conditions are provided. In Veldhoen *et al.'s* study, in the presence of DC and ligands for TLR3, 4, or 9, coculture of naive CD4$^+$ T cells with Tregs resulted in the development of Th17 cells [64]. In another study, TGF-β likely produced by Tregs and DCs, was a key cytokine that promoted Th17 differentiation from naive CD4 T cells in the presence of dectin-1 agonists [65]. Later, Xu *et al.* used Foxp3-IRES-GFP knock-in mice, which ensured that only CD4$^+$CD25$^+$Foxp3$^+$ cells were used, and showed that these cells undergo self-induced Th17 differentiation [66]. Treg cells not only expressed TGF-β but also induced DCs to produce increased amounts of TGF-β [66]. A differentiation pathway from the

Foxp3$^+$ passing through the Foxp3$^+$/IL-17$^+$ double positive stage and then to the IL-17 single positive stage was also observed [66]. Thus, Treg cells can differentiate into Th17 cells in a manner dependent on TGF-β.

Several studies have focused on the relevance of IL-2 in Th17-iTreg balance. IL-2 is a cytokine that normally suppresses Th17 cell differentiation and function. Later, rather than TGF-β production by Treg cells, IL-2 depletion by Treg cells was proposed to be the key factor promoting early stages in Th17 development. Using an in vivo *Candida albicans* infection model, Pandiyan *et al.* found that the effect of Treg cells on the induction of IL-17 production from responding CD4$^+$ T cells is dependent on consumption of IL-2 by Treg cells at early time points [67]. Further, using a system in which diphtheria toxin can kill Foxp3$^+$ Tregs at a specific stage, Chen *et al.* showed that Treg cells promote Th17 cell development in vivo and this is mediated by consumption of IL-2. Strikingly, their analysis with *TGFb* knockout mice conditional to *Foxp3* expression showed that Treg cell production of TGF-β was not required for Th17 induction in vivo [68]. Cejas *et al.* showed that TRAF6-deficient mice exhibited enhanced Th17 cell differentiation, and this was at least partly explained by the finding that TRAF6-deficient CD4$^+$ T cells showed lower expression levels of IL-2 compared to those of wild-type CD4$^+$ T cells [53]. Thus, it is possible that negative regulation by IL-2 is playing a central role in suppressing Th17 cell differentiation in many unknown cases. In any case, Pandiyan *et al.* [67] and Chen *et al.* [68] showed that Treg cells are likely to promote priming of Th17 in vivo, although further evaluation appears to be necessary to establish the significance of Tregs as a source of TGF-β in vivo. The role of TGF-β in Th17 development is still controversial for human T cells [69]. Effects of IL-2 are also discussed in the following section.

Thus, several findings indicated or suggested derivation of Th17 cells or Foxp3$^+$IL-17$^+$ "double positive" cells from Foxp3$^+$ Treg cells. Of clinical importance, fate-mapping analysis by Komatsu *et al.* showed that Th17 cells arise from Foxp3$^+$ Treg cells by the loss of Foxp3 expression in the presence of synovial fibroblast-derived IL-6 in collagen-induced arthritis (CIA) model mice, suggesting that T cell plasticity, combined with the inflammatory rheumatic environment, facilitates Th17 polarization, altering the balanced Treg/Th17 ratio [70]. In another study using peripheral blood from patients with RA, Th17 cells were enriched with Helios-producing Foxp3$^-$ IL2RA$^-$ cells, suggestive of nTreg cells that had presumably lost suppressive capability [71]. Notably, Helios expression is indicative of the recent thymic origin of the cells, and IL-2RA- is abundantly expressed in Treg cells. Thus, in patients with RA, nTreg cells appear to have anomalously high chances of transdifferentiating into IL-17-producing cells.

Ueno *et al.* observed that the prevalence of circulating double positive (IL-17$^+$ Foxp3$^+$) CD4$^+$ T cells is increased in patients with inflammatory bowel diseases (IBDs) [72]. Basu *et al.* further showed that IL-1 signaling represses SOCS3, a molecule that normally inhibits STAT3. This was suggested to be the molecular basis for IL-1β-dependent increases in phosphorylated STAT3 and alterations of the STAT3/STAT5 balance resulting in Th17 generation, even in retinoic acid-mediated iTreg induction that is predominant in the normal intestine [63].

It is recognized that Th17 cells have functional plasticity, but can Th17 cells transdifferentiate into Tregs? By using a triple reporter mouse model that reports expression of IL-17A, IL-10, and Foxp3 genes, Gagliani *et al.* [73] showed that Th17 cells generated during *Staphylococcus aureus* infection can be converted into IL-10^{high} Foxp3^{lo} Tr-1-like cells. Besides being positive for lymphocyte-activation gene 3 (LAG-3) and negative for CCR6, the latter cells (referred to as Tr-1^{exTh17} cells) showed features of Tr-1 in transcriptome analyses. TGF-β promoted Th17 to Tr-1 conversion [73]. AHR ligand 6-formylindolo[3,2-b]carbazole (FICZ) also promoted Th17 to Tr-1 cell conversion [73]. Thus, Th17 cells can transdifferentiate into regulatory cells.

Recent notable reports include those of Gaublomme *et al.* [74] and Wang *et al.* [75]. Reflecting the functional diversity of Th17, in vitro polarized Th17 cells can either cause severe autoimmune responses upon adaptive transfer ("pathogenic," polarized with IL-1β + IL-6 + IL-23) or have little or no effect in inducing autoimmune responses ("non-pathogenic," polarized with TGF-β + IL-6) [76,77]. RNA-seq was performed for single CD4$^+$IL-17$^+$cells isolated in vivo from EAE model mice. Significant cellular variation was observed, and in vivo Th17 showed cell states were progressively changed from the lymph nodes (LNs) to the central nervous system (CNS) [74]. The in vitro Th17 cells were also analyzed after activation under non-pathogenic (TGF-β + IL-6) or pathogenic (IL-1β+ IL-6 + IL-23) conditions. The profiles of these sets of cells formed a spectrum with distinctions and similarities when compared with the profile of the in vivo Th17 [74]. Interestingly, pathogenic Th17 cells expressed T-bet, GM-CSF, and IL-23R, for example, while non-pathogenic Th17 cells expressed IL-10. Exposure of non-pathogenic Th17 cells to IL-23 converted them to a pathogenic phenotype (Figure 1). In humans, Th17 cells that coproduce IL-17 and IFN-γ are generated upon infection with *C. albicans*, and this state of Th17 appears to be similar to that of pathogenic Th17 cells [75]. Further, in humans, Th17 cells that coproduce IL-17 with IL-10 are induced upon *S. aureus* infection [78], and this state is more similar to the non-pathogenic Th17 cells [75]. Wang *et al.* further reported CD5L/AIM expression in non-pathogenic, but not in pathogenic, Th17 cells. CD5L behaved as a functional switch; its loss converted non-pathogenic Th17 cells into pathogenic Th17 cells. CD5L inhibits this conversion in a manner mediated by modulation of the intracellular lipidome, such as maintaining a high ratio of poly-unsaturated fatty acids (PUFA)/saturated fatty acids (SFA) and restriction of cholesterol synthesis, and, thereby, ligand availability of RORγt. Notably, cholesterol synthesis is considered to be linked to the production of RORγt ligands, including oxysterol [79]. Thus, it is reasonable to consider that lipid metabolism plays important roles in T cell-mediated immunity, helping Th17 cells adapt to protective, as well as inflammatory, immune responses.

IL-2

Treg cells are highly dependent on IL-2 for survival, and the number of Treg cells can be dramatically reduced by neutralization of IL-2 [80]. In contrast, Th17 cell responses have been shown to be inhibited by IL-2. As considered above, Chen *et al.* showed that IL-2 depletion by Tregs acts as a positive regulator in the priming of Th17 cells [68]. In an attempt to utilize the immunosuppressive effect of IL-2, several authors administered low-dose IL-2 treatments in animal models and patients with type I diabetes [81]. To cite a few reports, in an application for type I diabetes therapy/prevention, IL-2 induced a dose-dependent increase in the proportion of Treg cells, without inducing deleterious changes in glucose-metabolism variables [82]. Webster *et al.* found that the in vivo activity of IL-2 can be enhanced by coinjection of anti-IL-2 mAbs and, intriguingly, one particular IL-2 mAb, when injected into mice as IL-2/anti-IL-2-mAb complexes, selectively expanded Treg cells in many organs [83]. Thus-expanded Treg cells showed excellent suppressive functions, inducing resistance to EAE induction and conferrence of

tolerance to islet allografts. Further studies using IL-2/anti-IL-2-mAb complexes include that by Wang *et al.* that showed that this complex attenuates lung inflammation and heart failure progression in a congestive heart failure mouse model [84].

Ets-1 is a transcription factor belonging to the Ets family and is important in hematopoietic cell development [85]. Moisan *et al.* showed that Ets-1 is a negative regulator of Th17 development [55]. Ets-1-deficient cells produced less IL-2 than wild-type cells, and Ets-1-deficient mice expressed abnormally high levels of IL-17 in the lung [55]. Tsao *et al.* showed that Ets-1 promotes IL-2 expression, synergizing with nuclear factor of activated T-cells (NFAT) in the transcription of IL-2 [86].

Zelante *et al.* focused on a role of IL-2, especially from DCs, to adjust Th17 activity [87]. Using a mouse model of invasive pulmonary aspergillosis, the authors showed that lung $CD103^+$ DCs produce IL-2, leading to an optimally protective Th17 response. Mice conditionally lacking IL-2 in $CD11c^+$ DC cells exhibited unrestrained production of IL-23 and fatal hyperinflammation, which was characterized by the emergence of a Th17 stem-cell-like population [87].

IL-4

Early studies have shown that systemic IL-4 immunotherapy improves Th1/Th17- or Th17-mediated diseases, such as EAE [88], experimental colitis [89], nonobese diabetes [90], and psoriasis in humans [91]. Using several DC populations, Guenova *et al.* found that IL-4 abolished the capacity of DCs to produce IL-23 while promoting IL-12p70. Further, an IL-4 therapy attenuated Th17-related diseases through STAT6- and activating transcription factor 3 (ATF3)-dependent suppression of the IL-23/Th17 responses, despite simultaneous enhancement of IL-12/Th1 responses [92]. One merit of such cytokines for clinical use would be their long history of research, which could help prevent adverse effects.

STAT3 and a subset of $Foxp3^+$ Tregs regulating Th17 cells

STAT3 is a molecule responsible for programming Th17 effector cells; activation of STAT3 serves as the primary input to the genetic network that governs Th17 differentiation. In an influential study on a subset of Treg cells that regulate Th17, Chaudhry *et al.* [93] showed that STAT3 expression is important for a subset of Tregs that specifically regulate Th17 cells. Unlike *Foxp3* knockout mice that show generalized lymphadenopathy, STAT3-deficient mice conditional to *Foxp3* promoter activation showed only splenomegaly and enlargement of the mesenteric lymph nodes, suggesting specific deregulation of Th17, as Th17 cells are mainly located in the intestine. The conditional knockout did not affect the number of Treg cells, but led to a selective increase in Th17 responses. Th1 and Th2 were kept in check by the conditionally STAT3-deficient Treg cells. Intriguingly, their gene expression analysis showed that 20% of Foxp3-dependent genes are also dependent on STAT3 expression in Treg cells.

Koch *et al.* showed that Th1 immunity is under the control of Th1-specialized Tregs, namely, Treg1 cells, proposing the concept of lineage-specific Tregs [94]. Thus, Th1 and Treg1 share T-bet, and Th17 and Treg17 share STAT3. Key mediators of differentiation signals specific to a helper T cell subgroup are also utilized in a corresponding subgroup of $Foxp3^+$ Tregs, likely endowing unique homeostatic and migratory properties optimized for suppression of the corresponding Th cells. Such examples include CXCR3 in Th1 and Treg1, IRF4 for Th2 and Treg2, and CCR6 in Th17 and Treg17 [94-97]. Thus, a developmentally related Treg subgroup may have been evolutionarily integrated into the homeostasis of each Th subgroup. This could provide benefits to immune system homeostasis as inappropriate distribution of Treg cells in vivo leads to tissue-specific inflammatory disease [98].

Using STAT3-knockout mice conditional to Foxp3 expression, Kluger *et al.* recently showed that these mice showed increased peritoneal Th17 responses, compared to wild-type controls, after i.p. pristane injection that is known to induce SLE in mice [99]. They reported that the lack of Treg17 cells also caused severe pulmonary vasculitis, as well as, at 4 and 9 months after the injection, aggravation of lupus nephritis, accompanied by enhanced Th17 responses [99]. They also found a reduced level of CCR6 in the Tregs from the conditional KO mice, supporting the CCR6-dependent anti-inflammatory effect of Treg17 cells.

Antigen stimulation and anergy induction

A major part of this article discusses cytokines, reflecting our understanding that pathophysiological Th17 differentiation is profoundly regulated by cytokines. Yet, TCR signaling triggered by self-antigen as causative for autoimmune diseases has long been considered of pathological importance, although it is not easy to identify specific causative antigens in most settings. Using cell transfer analysis between SKG mice that develop autoimmune arthritis (due to the ZAP-70 mutation) and *Rag2*-knockout mice, Ito *et al.* presented a method to isolate arthritogenic TCR and revealed that the self-antigen was a ribosomal protein, RPL23A. The presence of anti-RPL23A antibody was confirmed in the serum of 16.8% of patients with RA, signifying the importance of this self-antigen [100]. Yet, although this work seems outstanding, it is generally difficult to determine such antigens due to ethical and technical problems. Even in the case of SKG mice, TCRs on arthritogenic $CD4^+$ T cells were found to be highly polyclonal and varied among individual mice. Is it possible to identify and use peptides to induce Th17 cell tolerance in a TCR-specific manner?

In general, successful vaccination requires targeting antigens to DCs as an appropriate method to stimulate immune responses [101]. As DCs express various receptors on their surface, including TLRs, mannose receptors, and DC-SIGN receptors, targeting such receptors for efficient delivery of antigens has been utilized for efficient anticancer immunotherapy [101]. DCs can take up mannosylated proteins, and present peptide antigen thereof, with a very high efficiency. Different stimulation methods of DCs, and their combinations (in receptor type and strength, for example), can lead to different immune responses. Hawiger *et al.* [102] showed that in vivo targeting of antigens selectively to steady-state (immature) DCs, by fusing them to an antibody against the DEC-205 endocytosis receptor, induced peripheral T cell tolerance in mice [102]. In Tseveleki *et al.'s* study, DCs loaded with myelin peptide conjugated to oxidized mannan induced anergy in antigen-specific Th1 and Th17 cells and tolerance in EAE in a transfer analysis [103]. Although further studies are needed to characterize the mechanism for the anergy induction, these findings suggest the potential usefulness of tolerance induction for therapeutic intervention in MS.

B7/CD28 costimulation - unexpected suppression

CD28 was the first costimulatory receptor identified on T cells, and signaling through this receptor usually initiates potent T cell activation [104]. CTLA4 expressed on Treg cells is considered to compete with CD28 on effector T cells for costimulatory ligands and, in the hope of utilizing this effect, treatment with CTLA-4–Ig (abatacept) has been attempted in both RA and psoriatic arthritis [e.g., 105]. Paradoxically,

treatment of EAE with Abs against B7 family members (i.e., anti-CD80 or anti-CD86 Abs) or injections of CTLA4-Ig actually exacerbated disease [106]. Moreover, the development of ulcerative colitis during CTLA4-Ig (abatacept) therapy in a patient with RA was reported [107]. These findings led to Bouguermouh *et al.'s* study showing that CD28 stimulation has a suppressive effect on Th17 cells. In a system with conventional plate-bound anti-CD3 stimulation of mouse peripheral $CD4^+$ T cells under Th17-polarizing conditions, CD28 costimulation decreased the proportion of IL-17-producing cells [108]. CD28 costimulation did not inhibit fully differentiated Th17 cells, but inhibited the polarization of naive $CD4^+$ T cells into Th17 [108]. The inhibitory effect of CD28 stimulation was dependent on IL-2 and IFN-γ, likely secreted by the T cells used ($CD4^+$ T cells) [104]. In support of the inhibition by CD28, coculture with bone marrow-derived DC (BMDC) and CTLA4-Ig showed that interrupting the B7 costimulatory pathway favored Th17 differentiation [108]. This CTLA4-Ig effect can, at least in part, explain the early observation that Tregs facilitate the differentiation of Th17 cells in a proinflammatory cytokine milieu [64,65]. Note, however, that a conflicting result has been reported; Ying *et al.* argued that addition of human (h)CTLA-Ig, that would mainly block CD28-CD80 interaction, suppressed the production of IL-17, as well as IL-4 and IFN-γ by anti-CD3-stimulated WT $CD4^+$ T cells. When it was applied to $CD28^{-/-}$ CD4 T cells, it enhanced IL-17 production, presumably by blocking CTLA4-CD80 interaction [109]. The cause for this discrepancy between the two studies [108,109] is not clear, but it may be due to differences in population or differentiation stage of T cells used.

Another case in which Tregs can enhance Th17-dependent inflammation has recently been reported by Watanabe *et al.* [110]. In their system, ovalbumin (OVA) epitope-specific iTregs, Th1, Th2, and Th17 cells were independently prepared in vitro and intravenously transferred to wild-type mice. Various combinations of cotransfer showed that the cotransferred iTregs suppressed Th1- and Th2-mediated colon thickening, but stimulated Th17-mediated colon thickening. Prior oral administration of OVA led to immunosuppression of Th2- and Th1-mediated colon thickening, but instead accelerated Th17-mediated colon thickening. The augmentation by iTregs of Th17-mediated intestinal inflammation depended on CTLA4 [110]. This corroborates Bouguermouh *et al.'s* results [108] showing an adverse effect of CD28 signaling on Th17 differentiation.

Dendritic cells (DCs) and extrinsic effects of TGF-β

As we have seen above, TGF-β promotes Th17 cell differentiation

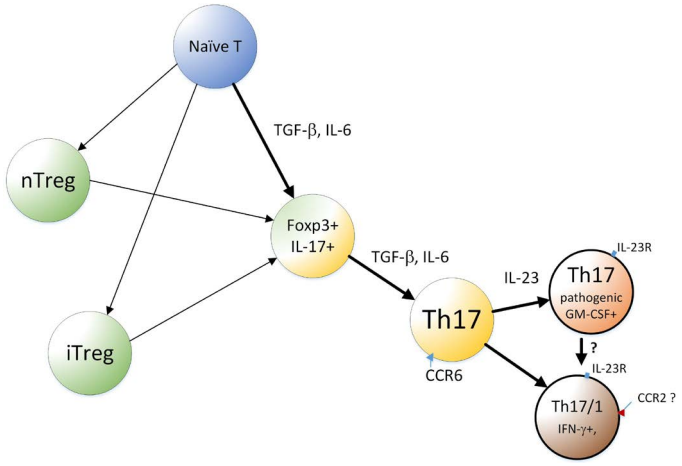

Figure 1. A simplified model of developmental pathway of Th17 and related cells.

Veldhoen *et al.* showed that mice expressing dominant-negative TGF-β receptor (TGF-βR)II showed resistance to EAE through a reduction in Th17 cells [26,64]. The inhibition of the protease thrombospondin-1 (TSP-1), that normally activates TGF-β delayed the onset of EAE [111], in accordance with the role of TGF-β-induced Th17 in EAE. However, TGF-β has long been considered to be an anti-inflammatory factor. In fact, early studies had shown that TGF administration reduced incidence and severity of EAE [112,113] and that injections of anti-TGFβ1 antibody worsened EAE both in incidence and severity [113]. How can we explain such disparity?

DCs can provide a microenvironment suitable for Th17 differentiation. DC development induced by retinoic acid has an impact on Treg and Th17 development, as discussed in the next section. Here, we focus on Speck *et al.'s* study that used mice with DC-specific knockout of TGF-βR to investigate the role of TGF-β in their EAE model [27]. DCs lacking TGF-β signaling showed a highly mature DC profile and caused severe inflammation and Th17 response in CNS [27]. Using in vitro experiments with bone-marrow precursors, the authors also showed that TGF-β controls (limits) DC numbers at a precursor level, but not at the mature stage. This study is important because, while the promotive effect of TGF-β on Th17 cannot be doubted, extrinsic effects of TGF-β on Th17 are complex, and this careful experimental setting revealed a rather suppressive extrinsic effect of TGF-β via DCs. For efficacious therapeutic intervention in the future, analyses addressing differences due to tissue/compartment, cell type, and timing should be helpful. Complexity of TGF-β effects is likely to manifest as sensitivity to details of intervention protocol such as timing, dose, and methods of delivery chosen for treatment.

Retinoic acid in intestinal mucosal immunity

Retinoic acid, a vitamin A metabolite, plays important roles in embryonic and adult tissue development including immune cells [114]. Retinoic acid promotes the differentiation of iTreg cells, and, in mucosal immunity, fine-tunes the Treg-Th17 balance [115,116]. Retinoic acid generally can: 1) suppress IL-12-mediated Th1 differentiation, 2) enhance IL-4-mediated Th2 response, and 3) enhance TGF-β-induced Treg differentiation by upregulating *Foxp3* [114,116].

Retinoic acid potentiates induction of gut-homing $Foxp3^+$ Treg cells, reciprocally inhibiting Th17 cells in vitro. Mucida *et al.* observed that exogenous retinoic acid inhibited TGF-β- and IL-6-dependent Th17 induction in vivo in an infection model, allowing Treg differentiation, but injection of retinoic acid receptor (RAR) antagonists caused a decrease in $Foxp3^+$Tregs in the lamina propria [39]. Thus, in conjunction with TGF-β, retinoic acid enhances the expression of Foxp3. Analyses of lamina propria by Denning *et al.* showed that there is normally a high production of cytokine TGF-β and IL-10 [117].

However, retinoic acid is not always immunosuppressive, its effect varying depending on the balance of various cytokines. Physiological concentrations of retinoic acid promote Th17 differentiation in vitro, whereas higher concentrations of retinoic acid inhibit Th17-cell responses in vitro and in vivo [118]. It is also unlikely that the findings in gut analyses can be extrapolated to non-gut phenomena; Pino-Lagos *et al.* showed that retinoic acid signaling in $CD4^+$ T cells is necessary for T cell tissue accumulation and skin-graft rejection, which represents a role of retinoic acid opposite to tolerance induction [119].

DCs and their expression of retinaldehyde dehydrogenase

(RALDH) activity are considered important for the immunological environment of the intestine. Broadly, the majority of retinoic acid functions in immunity are considered to be mediated by canonical RAR/retinoid X receptor (RXR) heterodimers, and by all-trans retinoic acid (ATRA) produced by retinaldehyde dehydrogenase 2 (RALDH2) and acting through RARα [116]. It is noted that most molecular studies highlighted immunosuppressive roles of retinoic acid. Xu *et al.* showed that retinoic acid stimulation leads to binding of RAR/RXR to the conserved enhancer region (enhancer I), causing increased histone acetylation in the region of the Smad3 binding site and subsequently increased binding of phosphorylated Smad3, thereby leading to Foxp3 expression [120].

In the intestine, DCs, stromal cells, epithelial cells, and macrophages are sources of retinoic acid as shown by high RALDH activity [121,122]. $CD103^+$ DCs in small intestine lamina propria and mesenteric LNs have higher *Raldh2* expression relative to DCs in other tissues [123]. Retinoic acid levels correlate with the ability of the intestinal DCs to induce gut-homing potential in T cells [121,124].

Retinoic acid induces T cell homing to mesenteric LNs and gut via the enhanced expression of the gut-homing receptors α4β7 integrin and CCR9 [114,121]. The intestine, lamina propria, and mesenteric LNs have $CD103^+$ DCs that produce TGF-β and retinoic acid, aiding development of $Foxp3^+$ Treg cells. In particular, $CD103^+$ $CD11b^+$ DCs are the most numerous DCs in the small intestinal lamina propria, and are major constituents of the tolerogenic $CD103^+$ DC population [125]. Although the impact of this subset ($CD103^+CD11b^+$) on Treg cells is difficult to isolate because of functional redundancy with $CD103^+CD11b^-$ DCs, a decrease in intestinal Treg cells was observed in animals lacking all $CD103^+$ intestinal DCs [126]. Many recent studies have focused on the effect of retinoic acid on differentiation and modulation of DCs. As an example, Klebanoff *et al.* showed that mice deprived of retinoic acid signaling show selective loss of splenic endothelial cell-specific adhesion molecule $(Esam)^{high}$ $CD11b^+$ cells that are developmentally related to the small intestine lamina propria $CD103^+CD11b^+$ DC subset [127]. Transferred pre-DCs differentiated into the $CD11b^+$ $CD8a^-$ subset, but transfer into vitamin A-deficient hosts caused differentiation to the $CD11b^+CD8a^+$ lineage [127].

Retinoic acid production and signaling in DCs can be enhanced by many factors, including retinoic acid itself [123], TLR signaling [128], GM-CSF [129], and IL-4 [129,130]. TLR2 signaling in DCs, in particular, appears to be important for maintaining host-microbiota mutualism [128]. Wang *et al.* showed that signaling of TLR1/2 induces retinoic acid-producing activity in splenic DCs, conferring the ability to imprint T cells for gut-homing [131].

Direct effects of retinoic acid on T cells have also been studied. Lu *et al.* showed that all-trans retinoic acid (ATRA) increased histone methylation and acetylation within the region including the promoter of *Foxp3a*, thereby promoting TGF-β-induced Treg development [132]. Nguyen *et al.* showed that retinoic acid treatment enhances TLR2-dependent IL-10 production by T cells and this, in turn, potentiates Treg cell generation [133]. Round *et al.* showed that symbiosis factor (PSA) from *Bacteroides fragilis* can induce $Foxp3^+$, IL-10-secreting Treg cells via TLR2 expressed on $CD4^+$ T cells, promoting immunological tolerance and colonization of *B. fragilis* on mucosal surfaces [134]. More cases showing synergy with other cytokines and signals for retinoic acid are likely to emerge in the near future.

Unlike vitamin D, whose in-serum level can be measured as 25-hydroxyvitamin D (25(OH)D), serum retinol level does not reflect the intracellular retinoic acid concentration, making clinical studies difficult. Nonetheless, several studies focused on the clinical relevance of retinoic acid. In a mouse model of allergic airway inflammation, ATRA treatment attenuated airway inflammation and decreased Th2- and Th17-related transcription factors [135]. In vitro analyses also showed that ATRA modified Treg/Th17 balance in favor of Treg cells [135]. Vitamin A level (measured as the retinol binding protein (RBP)/transthyretin (TTR) ratio) was negatively correlated with $CD4^+$ T cell proliferation in patients with MS [136], and vitamin A supplementation in patients with MS upregulated *TGF-β* and *Foxp3* expression in PBMCs [137]. Therapeutic modulation of RALDH activity appears to be a worthwhile approach. Manicassamy *et al.* [138] showed that Wnt/β-catenin signaling in intestinal DCs is required for *Raldh1* and *Raldh2* expression, as well as IL-10 and TGF-β and that β-catenin deletion in DCs led to lower Treg and higher Th1/Th17 cell differentiation making the host susceptible to inflammatory bowel diseases (IBD) [138].

Some studies have focused on retinoic acid receptors. Of note, RXRs (RXRα, RXRβ, and RXRγ) can form homo- as well as heterodimers with several nuclear receptors including RARs, vitamin D receptor (VDR), LXR, and PPARγ. $CD4^+$ T cells mainly express RXRα. ATRA binds to RAR and 9-*cis*–retinoic acid can bind to both RAR and RXR [139]. Recently, Chandraratna *et al.* showed that RXR activation by IRX4204 promotes iTreg formation, inhibits Th17 development, and can profoundly alleviate disease in EAE mouse models [140]. Brown *et al.* used mice carrying a dominant negative form of RARα and showed that loss of retinoic acid signaling in fully committed Th1 cells leads to transdifferentiation to cells that have features of Th17 lineage, implying that retinoic acid stabilizes the differentiation state of Th1 and suppresses Th17 pathways [141]. This suppression was necessary to prevent pathogenic Th17-biased responses in *Listeria monocytogenes* infection and OVA-specific TCR model mice. Retinoic acid-RARα antagonized the activity of transcription factors important for Th17 differentiation (IRF4, basic leucine zipper transcription factor (BATF), STAT3, and RORγt), without any signs of antagonizing Th2-cell-associated genes [141]. Taken together, RALDH, retinoic acid, and its receptors could be a target for therapeutic intervention for the suppression of Th17 cells. It is likely that in the near future further progress will be made in various subareas of vitamin A research.

Vitamin D

Vitamin D, or specifically, its active form $1,25(OH)_2$-cholecalciferol ($1,25\text{-}(OH)_2D_3$) is known for its role in maintaining systemic levels of calcium and phosphate. $1,25\text{-}(OH)_2D_3$ is derived from 25(OH)D by CYP27B1-mediated reactions and exerts its effects through VDRs. 25(OH)D is commonly used as a marker for vitamin D status. The $1,25\text{-}(OH)_2D_3$-VDR-RXR complex recruits coactivator or corepressor complexes, depending on the type of cell, thereby determining the transcriptional response from vitamin D response element (VDRE)-containing genes [142]. Several studies reported a negative correlation between circulating 25(OH)D and MS disease activity [e.g., 143]. In patients with MS with low vitamin D levels, an intervention with supplementary vitamin D significantly reduced disease progression [144]. However, the evidence for vitamin D as a treatment for MS is inconclusive, as all studies were underpowered due to small sample sizes [145]. Notably, Pozuelo-Moyano *et al.* suggested stratifying by HLA-DR15 (MS risk allele) status in future trials and including patients with progressive forms of MS, considering that the possible protective effect of vitamin D could be masked by subgroups of nonresponders.

Correlations between VDR alleles and MS susceptibility have

been reported [146,147], yet no association with VDR alleles was observed in a genome-wide association study despite the identification of 57 regions significantly associated with MS, suggesting weak or no appreciable association of VDR alleles [148]. For several specific alleles of *VDR*, functional impacts have been shown [142]. Although *CYP27B1* mutations are rare and do not contribute a genetic risk in the majority of disease cases, an analysis using an in vitro system allowing differentiation of DCs demonstrated that the risk allele of CYP27B1 is underexpressed in tolerizing DCs [149]. Overall, while genetic evidence for vitamin D involvement in autoimmune pathogenesis is increasing, it seems challenging to pinpoint the causative genes, due to the limited resolution hampering dissection of linkage disequilibrium blocks [149]. There could be multiple causative alleles with weak predisposing effects.

More unequivocal results on the protective effects of vitamin D have been obtained in rodent models. Th1, Th2, and Th17 cells were all shown to express *Vdr* transcripts and can be modulated by vitamin D [150]. 1,25-$(OH)_2D_3$ is likely to have no impact on fully differentiated rodent $CD4^+Foxp3^+$ T cells [151], although VDR-dependent downregulation and upregulation of *Foxp3* transcription in rodent $CD4^+Foxp3^+$ T cells have also been reported [142]. Mixed bone marrow chimera studies showed that 1,25-$(OH)_2D_3$ inhibited EAE induction in a manner dependent on *Vdr* expression in hematopoietic cells [151]. 1,25-$(OH)_2D_3$ failed to inhibit EAE induction in mice with knockout of *Vdr* specific to $CD4^+$ T cells [151]. On the other hand, mice with global knockout of *Vdr* had Th17 cells that overproduced IL-17 and a reduced number of tolerogenic DC cells [152]. These results support the suppressive role of vitamin D against Th17 functions.

Using cells from patients with hereditary vitamin D–resistant rickets (HDVRR), Tiosano *et al.* showed that TNF-α and IL-17 concentrations were significantly higher in HVDRR lymphocyte cultures than in controls. 25(OH)D suppressed IL-17 only in control, and not in HVDRR, lymphocytes [153]. However, as the authors discuss, the cohort of 35 patients with HVDRR did not show a higher incidence for infectious or autoimmune diseases, suggesting the presence of compensatory mechanisms that protect patients with HVDRR from such diseases.

Smad3 is a member of the Smad family that transmits TGF-β signaling [154]. Smad3 interacts with the VDR and promotes its function in transcriptional regulation. A recent study by Nanduri *et al.* showed that 1,25-$(OH)_2D_3$-VDR-RXR heterodimer directly binds to the VDRE in the *Smad7* promoter and inhibits its expression in Th17 cells [155]. Notably, Smad7 is known as one of the inhibitory Smads that negatively regulate TGF-β signaling in a feedback regulatory mechanism [156]. The VDR axis also activated extracellular signal-regulated kinase (ERK), inhibiting expression of Th17-specific genes.

Both animal and human studies have implicated 1,25-$(OH)_2D_3$ as a positive regulator of genes encoding receptor activator of nuclear factor kappa-B ligand (RANKL) and of cutaneous IL-10-producing iTreg cell induction, suggesting the usefulness of phototherapy during periods of light starvation for immune-mediated diseases [142,157]. Overall, however, vitamin D and human Th17 studies have so far provided conflicting data [142]. One relatively unnoticed confounding factor could be melatonin, a hormone that controls circadian rhythms and is immunosuppressive, as we discuss below. Specifically, it could be that the melatonin level is high in winter, assisting the maintenance of an immunotolerant environment, complementing the light starvation in winter that would lower the level of 1,25-$(OH)_2D_3$. In general, besides the direct effects on Th17, extrinsic effects mediated by Treg and other immune cells appear important for Th17 regulation by vitamin D.

STAT3 vs STAT1

STAT3 is the primary input to the genetic network that governs Th17 differentiation [158]. The effect of IL-6 on Th17 differentiation is mediated by JAKs that in turn activate STAT members, including STAT3. In contrast, STAT1 reacts negatively to Th17 differentiation. IL-27 is considered to be a potent inhibitor of Th17 differentiation and exerts its inhibitory effect in a STAT-1-dependent manner [159].

However, it was puzzling that IL-10 and IL-27, neither of which supports Th17 differentiation, can activate STAT3. Do other factors enable differential functions of the latter cytokines [158]? Recently, Peters *et al.* showed that, in STAT1-knockout mice, IL-27 "induced" Th17, suggesting that the ratio of activated STAT3/activated STAT1 is important for the Th17 differentiation program [158].

Hirahara *et al.* performed genome-wide transcriptome analysis [160]. Intriguingly, there was an extensive overlap of the transcriptomes induced by IL-6 and (Th17-inhibiting) IL-27 with few examples expressed in an opposite manner by the cytokines. They further showed that STAT3 is responsible for the overall transcriptional output for IL-6 and IL-27, whereas STAT1 shapes the specific signature superimposed upon STAT3's action, driving specificity. Hirahara *et al.* found that much of STAT1 binding to chromatin is dependent on STAT3, and most likely on heterodimer formation with STAT3.

Targeting RORγt

RORγt, the master transcription factor of Th17 cells, is indispensable for Th17 cell development, but not for other T-helper-cell lineages. RORγt not only promotes the production of IL-17 and IL-22 from Th17 cells, but also promotes these cytokines' production by lymphoid tissue inducer (LTi) cells and other $ROR\gamma t^+$ innate lymphocytes (ILCs), suggesting parallel functionalities of ILCs and Th17 cells during host defense [161]. Notwithstanding the presence of these $ROR\gamma t^+$ cells other than Th17, RORγt remains an attractive pharmacologic target for the treatment of Th17 cell-mediated immune disorders. Taking advantage of the ligand-binding pocket of RORγt, small-molecular weight compounds have been screened.

Digoxin has been shown to specifically inhibit the transcriptional activity of RORγt and suppress Th17 differentiation [162]. Digoxin showed no effect on CD4 T cell differentiation toward Th1 and no binding to RORα [162,163]. However, concentrations of 1-2 μM appear to be necessary in vitro, and collagen-induced arthritis (CIA) model mice required 2 mg/kg via thrice weekly injections. This concentration is high, calling for a careful assessment of adverse effects if therapeutic translation is conducted.

Another example is SR1001, a derivative of T0901317 that is an LXR ligand [164]. SR1001 was devoid of all LXR activity yet retained its ability to suppress the activity of RORα and RORγt. Xiao *et al.* identified three RORγt inhibitors (TMP778, TMP920, and GSK805) that suppress Th17 development and alleviate EAE in model mice [165]. Another molecule that inhibits RORγt is ursolic acid, a small molecule used in herbal medicine [166].

Interestingly, Lin *et al.* [166] discussed CD4 aptamer-RORγt short hairpin RNA (shRNA) chimeras that enabled CD4-specific shRNA delivery to suppress RORγt expression. To derive the aptamer part of the chimera, systematic in vitro ligand evolution was performed and target-specific aptamers were isolated from a random sequence

oligonucleotide library. This technique may enhance the efficacy of in vivo injection of shRNA recombinant plasmid DNA [e.g., 167]

Foxo1

Members of the forkhead box O (Foxo) family of transcription factors regulate many facets of cell physiology, including cell proliferation [168]. Phosphorylation by Akt downregulates their activity. Foxo members are important for specifying T cell differentiation, particularly in the pathway to Tregs [168]. It is still a matter of debate whether Foxo1 directly controls *Foxp3* [168], but Foxo1 is likely a T cell-intrinsic regulator of tolerance [169]. T cell-specific deletion of *Foxo1* caused spontaneous T cell activation and induction of inflammatory bowel diseases in a transfer model. Foxo1-deficient T cells had low IL-7R expression, compromising IL-7-induced T cell survival and proliferation, and in particular naive T cell homeostasis [169]. Foxo1 acts as a direct repressor of IL-23R expression [170]; the *Il23r* promoter is transactivated by RORγt in IL-23-restimulated Th17 cells and can be inhibited by Foxo1 [170]. Importantly, using a bone marrow chimera strategy, Laine *et al.* showed that Foxo1 does not need Tregs to negatively regulate Th17 cell differentiation, and this regulation depends on the direct binding of Foxo1 to RORγt [171]. Given the T cell-intrinsic suppressive activity of Foxo1, it is hoped that in the near future further analyses of this molecule may produce useful findings.

IL-35

IL-35 is an immunoregulatory cytokine that belongs to the IL-12 family and consists of the Epstein-Barr virus-induced gene 3 (EBI3) and the p35 subunit of IL-12 [172]. Notably, IL-27 and IL-35 share the EBI3 subunit. IL-35 is normally produced by $CD4^+Foxp3^+$ Tregs and iTr35, a regulatory T-cell population [173]. We only briefly discuss IL-35 here, given the excellent review articles available [e.g., 174,175].

IL-35 has shown its therapeutic effectiveness in several studies [175]. In Niedbala *et al.'s* study, recombinant IL-35 fusion protein (EBI3-p35-Fc fusion) suppressed CIA, at least in part, by increasing IL-10 in serum and suppressing Th17 cells [176]. In the latter system, IFN-γ was enhanced. Wirtz *et al.* showed that, compared with IL-27p28-deficient mice, EBI-3-deficient mice showed more severe features of colitis with increased numbers of T cells producing Th1 and Th17 cytokines in mucosa [177]. Recombinant IL-35 suppressed the colitis and reduced levels of systemic markers for Th1 and Th17 cells. Bettini *et al.* generated NOD transgenic mice in which IL-35 was expressed in pancreatic β-cells. This expression protected the NOD mice from autoimmune diabetes [178]. Kochetkova *et al.* found that IL-35 suppressed CIA in a mouse model and that $CD39^+CD4^+$ regulatory T cell expansion, a new subset of regulatory T cells, plays an important role in this protection [179]. It is possible that IL-35 effects are strongly dependent on IL-10 [179,180].

However, some studies showed proinflammatory functions of IL-35. In Thiolat *et al.'s* study [180], direct DNA injection followed by in situ electrotransfer into the cells of CIA mice unexpectedly aggravated the CIA and produced increased Th17/Treg ratios. Filková *et al.* showed an increased level of IL-35 in synovial tissue of patients with RA [181]. In both PBMCs and synovial fibroblasts in RA, in vitro stimulation with TNF-α-induced expression of IL-35. Strikingly, IL-35 treatment increased proinflammatory cytokine production by human PBMCs [181]. Cao *et al.* showed an enhanced IL-35 level in patients with sepsis as well as in cecal ligation and puncture (CLP)-induced sepsis in mice [182]. In the latter model, a blocking analysis showed that the IL-35 effect is generally suppressive against neutrophil recruitment and proinflammatory cytokine production, but that IL-35 facilitates bacterial dissemination.

IL-35 can activate both STAT1 and STAT4, but this balance is determined by the receptors [174]. STAT1 activation negatively effects Th17 differentiation, but STAT4 is controversial. While the findings of Varikuti *et al.* suggest that STAT4 is important for Th1 and Th2, but not for Th17 [183], McWilliams' data suggested that Th17 differentiation is influenced by STAT4 activation [184]. Dulek *et al.* also showed that STAT4 deficiency strongly affected Th1, but it also affected Th2 or Th17 responses [185].

T cell factor 1 (TCF-1) and Wnt

The Wnt proteins are a large family of palmitoylated secreted glycoproteins that regulate many processes, including cell development. Wnt signaling is important in T cell development as well as in cellular developmental processes and tumorigenesis. Review articles, including that by Ma *et al.* [186], generally suggest its immunosuppressive role. Among the (at least three) Wnt signaling pathways, a transcriptional coactivator β-catenin serves in the canonical Wnt signaling pathway, by interacting with transcription factors including TCF. Wnt/β-catenin signaling influences T cell polarization in favor of Th2 over Th1 [187] and potentiates the survival of nTregs [188]. Consistent with this, specific deletion of β-catenin in DCs led to low Treg and high Th1/Th17 differentiation [138].

As its name suggests, TCF-1 plays an important role in T cell development, involving transition from the $CD4^-CD8^-$ double negative to the $CD4^+CD8^+$ double positive (DP) state [189]. Ma *et al.* showed that TCF-1-deficient mice were susceptible to Th17-dependent EAE induction and had a higher proportion of Th17 cells compared to wild-type mice [190]. They observed that TCF-1 regulates Th17 differentiation affecting neither TGF-β-induced Treg differentiation nor expression of Th17 master factors like RORγt, STAT3, RORα, AHR [191], Runx1 [192], Ets-1, IRF4, or BATF. TCF-1 did not appear to affect Th17 differentiation at the mature T cell stage. Rather, analysis of histone acetylation and methylation states suggested that knockout of TCF-1 leads to opening up of the IL-17 locus in the thymus due to chromatin modifications. Thus, TCF-1 is likely to repress IL-17 gene expression via epigenetic modifications during T cell development [190], and is therefore important for the early stage of Th17 development.

Ye *et al.* compared $CD4^+$ T cell transcriptomes between patients with RA and healthy controls using microarray analysis and pathway analysis. Differentially expressed (DE) genes showed enrichment of immune response, T-cell response, and apoptotic signals [193]. The Wnt signaling pathway showed differential expression; the degree of enrichment of DE genes of STAT3 signaling and that of Wnt signaling were comparable, suggesting the importance of the Wnt signaling pathway in pathological roles of $CD4^+$ T cells in RA development.

Frizzleds are seven-pass transmembrane proteins similar to G-protein-coupled receptors and are the main proteins responsible for binding to Wnt on the plasma membrane. Secreted frizzled-related proteins (sFRPs) make up the largest family of Wnt inhibitors. sFRP1 functionalities involve inhibition of Wnt signaling by hindering Wnt binding to Frizzled and by forming nonfunctional complexes with Frizzled [194]. Lee *et al.* showed that sFRP1 potentiates IL-17 production from restimulated human memory $CD4^+$ T cells and promotes Th17 differentiation in a manner mediated by inhibition of the Wnt pathway. sFRP1 enhanced TGF-β activity in human T

cells, appearing to positively regulate Th17 differentiation [195]. They also showed that sFRP1 and IL-17 levels were high relative to those of patients with osteoarthritis and were positively correlated in the synovial fluid of RA.

TIGIT confers Treg cells suppressive ability specific to Th1 and Th17

T cell Ig and immunoreceptor tyrosine-based inhibition motif (ITIM) domain (TIGIT), also known as VSTM3, is a recently identified coinhibitory receptor that is found on NK cells, memory T cells, follicular Th cells, and on a subset of Tregs [196]. Similar to the well-known competition between CTLA-4 and CD28, TIGIT (on Tregs) and CD226 (on NK, Th1, and $CD8^+$ T cells) share ligands (e.g., CD155 on DCs). TIGIT is considered to have dual (or more) pathways to inhibit T cell responses. Besides the hindering CD226-CD155 interaction, engagement of TIGIT inhibits T cell responses via its cytoplasmic ITIM motifs and recruitment of the phosphatase SHIP-1. Interestingly, $TIGIT^+$ Tregs selectively suppress Th1 and Th17 responses, sparing Th2 responses [197]. Compared to TIGIT-deficient Treg cells, $TIGIT^+$ Treg cells abundantly express CTLA-4, CD25, IL-10, Foxp3, and fibrinogen-like protein 2 (Fgl2), signifying their high suppressive potency. Both soluble TIGIT administration and lentivirus-mediated expression of TIGIT ameliorated CIA in mouse models [198,199]. TIGIT ligation induces secretion of Fgl2, which is necessary for the potent suppression of Th1 and Th17, as well as for prevention of Th2 suppression [197]. Intriguingly, both in vivo and in vitro findings supported a view that IL-17 promoted production of Fgl2 in spleen cells, suggesting the presence of a homeostatic regulation loop [200]. Specific mechanisms for Fgl2 action await further elucidation.

IRF4, BATF and IRF4-binding protein (Def6) and ROCK2

Although we cover only a few studies on transcription factors, a complex picture of the gene network governing Th17 differentiation emerges even when focusing only on proteins associated with IRF4. IRF4, a member of the IRF family of transcription factors, is a key regulator of Th17 development, although its expression is also regulated in other T cells [46]. *Irf4*$^{-/-}$ mice show a lack of Th17 differentiation and are resistant to autoimmune diseases in models of EAE and colitis. Def6 acts as an inhibitor of IRF4. Def6-deficient mice developed a systemic lupus-like syndrome [201]. In Chen *et al.'s* study, Def6-deficient mice crossed to DO11.10 mice that carry a transgenic TCR recognizing a specific peptide exhibited spontaneous development of arthritis, large-vessel vasculitis, and enhanced production of IL-17 and IL-21 [202]. They also showed that Def6 sequesters IRF4 and prevents it from targeting the transcriptional regulatory regions of *Il-17* and *Il-21* [202]. Def6 can directly interact with IRF4 and prevent Rho-associated coiled-coil-containing protein kinase 2 (ROCK2)-mediated IRF4 activation (phosphorylation) necessary for binding to regulatory regions of *IL-17* and *IL-21* [202,203]. Notably, ROCK2 activation also plays an important role in Th17 differentiation, and Def6 generally acts to suppress ROCK2 activity [203]. Of practical importance, oral administration of the ROCK2 inhibitor KD025 in healthy humans downregulated the ability of PBMCs to secrete IL-21 and IL-17 upon stimulation [204]. KD025 and siRNA-mediated inhibition of ROCK2 negatively regulated STAT3 phosphorylation and reduced the levels of IRF4 and RORγt [204]. Treatment with KD025 successfully ameliorated chronic graft versus host disease (GVHD) in several mouse models [205].

Schraml *et al.* showed that the activating protein 1 (AP-1) transcription factor, BATF, is required for Th17 development [206]. BATF was found to bind conserved intergenic elements in the *Il-17a-Il-17f* locus and to the *Il-17*, *Il-21*, and *Il-22* promoters [206]. Chromatin immunoprecipitation (ChIP) analysis by Glasmacher *et al.* showed that, in Th17 cells, IRF4 targets sequences enriched for AP-1-IRF composite elements (AICEs) that are cobound by BATF [207]. Thus, both IRF4 and BATF are necessary for Th17 differentiation.

Is there any inhibitory factor against BATF useful for Th17 suppression? Miao *et al.* [208] showed that early growth response gene (Egr)-2, a zinc-finger transcription factor, interacts with BATF in $CD4^+$ T cells and suppresses its interaction with the *Il-17* promoter. Conditional Egr-2 knockout did not change the levels of STAT3 activation or RORγt expression. Thus, inhibition of BATF is a unique function of Egr-2, and the BATF pathway appears to be independent of STAT3 and RORγt. In Zhu *et al.'s* study [209], analysis of mice with Egr-2 knockout conditional to T cells showed hyperresponsiveness in response to TCR stimulation and Th1/Th17 bias resulting in lupus-like syndrome.

Among BATF-associated molecules, IRF8 is notable as a key factor regulating differentiation between Th1 and Th17 pathways. IRF8 can bind to BATF and negatively regulate Th17 differentiation [210]. Retinoic acid upregulates *Irf8* in Th1 differentiating cells, thereby suppressing Th17 cell genes [141].

Metabolic pathways and mTOR

Upon activation, T cells dramatically alter their metabolic activity to meet the increased metabolic demands for cell proliferation and effector functions. A number of studies have focused on the system integrating T cell activation and control of their metabolic state [211]. For instance, Chang *et al.* demonstrated that the effector function of T cells is coupled with the state of glucose metabolism [212]. They first showed that T cells grown with galactose, but not with glucose, shift to a state in which respiration (oxidative phosphorylation) is used, but aerobic glycolysis is not used in the main, for energy acquirement (i.e., generation of ATP). This finding is consistent with earlier reports, e.g., Rossignol [213]. Strikingly, T cells cultured in galactose had a severe defect in IFN-γ and IL-2 production. These findings indicated that the state utilizing aerobic glycolysis is coupled to cytokine production. In the absence of aerobic glycolysis, IFN-γ translation was blocked by enhanced GAPDH binding to IFN-γ mRNA [212]. Thus, engagement/disengagement of aerobic glycolysis allows the post-translational regulation of IFN-γ in T cells. Such coupling may ensure that, when T cells undergo antigen-driven proliferation during the immune response, effector cytokines are produced to meet their requirement; whereas when T cells undergo homeostatic proliferation, and such cytokine production is not necessary, they do not produce cytokines. Increased expression of PD-1 was also shown in the T cells cultured with galactose. Coculture experiments showed that the presence of tumor cells causes nutrient restriction to T cells that dampens cytokine production and, at the same time, increases PD-1 expression [212].

Multiple metabolic programs are controlled by mTOR signaling. After treatment with the mTOR-specific inhibitor rapamycin, effector T cell development was greatly diminished [211]. TCR signaling induces uptake of amino acids including leucine, which is important for activation of mTORC1 and metabolic reprogramming of T cells [214]. Notable studies on metabolism and Th17 development include that of Nakaya *et al.* showing that stimulation of naive $CD4^+$ T cells via TCRs and CD28 triggers the uptake of glutamine, the most abundant amino acid in plasma [215]. The amino acid transporter ASCT2, that was found to be crucial for glutamine uptake, was required for naive

T-cell differentiation to Th1 and Th17 cells, but not to Th2 cells. Amino acids can activate mTORC1 by targeting it to lysosomal membranes for activation [216,217]. ASCT2 was required for TCR and CD28-stimulated activation of mTORC1 pathways, but not for the activation of several other T-cell activation pathways, including the MAP kinase pathways [215].

mTORC1 increases expression of HIF1α [218]; HIF1α in turn, upregulates Glut1 expression increasing glucose uptake [219]. HIF1α was shown to be critical for the development of Th17 in both mice and humans [220,221]. Expression of the enzymes mediating rate-limiting steps in glycolysis are positively regulated by HIF1α [220]. T cells deficient in HIF1α showed impaired ability of Th17 cell differentiation, and this was explained by the decreased glycolysis [220]. Inhibition of glycolysis shifted the Th17/Treg balance in favor of Treg cells. Thus, the tuning of Th17/Treg balance is coupled to a very fundamental biochemical process (glycolysis); this is not specific to Th17, but shared at least by T cells [222]. These findings suggest that TCR- and CD28-stimulation promotes Th17 cells to an enhanced state in which, even in inflamed tissues that are inevitably hypoxic, Th17 cells can utilize glycolysis to generate ATP under the limited oxygen availability, as well as exert effector functions.

Liver kinase B1 (LKB1) is a serine threonine kinase identified as the tumor suppressor responsible for Peutz-Jeghers syndrome [223]. LKB1 is known to activate AMP-activated protein kinase (AMPK), which, in turn, suppresses mTOR activity [224]. As AMPK is considered a conserved guardian of cellular energy [225], there appeared to be an anticipation that LKB1-deficiency and AMPK-deficiency would lead to enhanced activation of Th17 cells. Using LKB1-knockout mice conditional to T cells, MacIver *et al.* reported that T cells lacking LKB1 show increased rates of glucose uptake and glycolytic activities, as well as enhanced expression of Glut1 [226]. LKB1-deficient T cells showed elevated IFN-γ and IL-17A production, as well as enhanced differentiation toward Th1 and Th17 lineages, relative to control T cells [226]. They further showed that AMPKα1-deficient T cells showed elevated glycolytic activities, but this deficiency did not show an effect on Th1, Th2, and Th17 effector cell differentiation and functions [226]. This unexpected result may represent the common challenge in this type of study: in genetic analyses using knockout and conditional knockout animals, the effect may become masked by compensation [227].

β-oxidation of FA produces copious acetyl-CoA that serves as a fuel for mitochondrial oxidation. Although acetyl-CoA can be derived from pyruvate (the glycolysis product), mitochondrial oxidative metabolism, in theory, can operate if acetyl-CoA is abundant even if pyruvate is not abundant. In general, it has been proposed that the two reciprocal processes (FA synthesis vs FA oxidation) are biased in favor of FA oxidation in iTreg cells, whereas FA synthesis is more important in activated Th17 cells to meet proliferation requirements [228]. This hypothesis postulates that Treg cells rely on mitochondrial FA oxidation to proliferate and this bias is, at least in part, caused by activation of AMPK [228].

Acetyl-CoA carboxylases (ACCs) catalyze the conversion of acetyl-CoA to malonyl-CoA, the key step for regulation of cellular FA metabolism. In both mice and humans ACCs have two isoforms, ACC1 (cytosolic) and ACC2 (associated with the outer membrane of mitochondria) [229]. Using ACC1–knockout mice conditional to T cells and soraphen A, an ACC1 and ACC2 inhibitor, Berod *et al.* showed that de novo FA synthesis controls the Th17/Treg differentiation pathway. Naive $CD4^+$ T cells cultured under the Th17 polarizing condition in the presence of soraphen A exhibited reduced expression of *Il-17f*, *Stat3*, and *Hif1a*, and enhanced phosphorylation levels of AMPK, all indicative of Treg/Th17 balance modulation in favor of Treg. However, this effect of ACC inhibition is not specific to Th17 lineages; it also suppressed proliferation of $CD4^+$ T cells cultured under Th1- and Th2-polarizing conditions [230].

PPARγ and LXRs - transrepression

Besides its roles in lipid metabolism, PPARγ exerts an anti-inflammatory response in murine and human macrophages [231]. This effect is likely mediated mainly by transrepression; liganded PPARγ inhibits the inflammatory activities of AP-1, STAT-1, NF-κB, and NFAT. This property of PPARγ enables it to promote Th2 cytokine production, decreasing Th1 cytokine production [232].

Using $CD4^+$ T cell-specific PPARγ-knockout mice, Klotz *et al.* indicated that PPARγ serves as a specific brake of Th17 differentiation. Treatment with the PPARγ agonist pioglitazone (PIO) suppressed Th17 differentiation, but showed no influence on Th1, Th2, or Treg differentiation [47]. Direct interaction of PPARγ with RORγt was not observed. Rather, PPARγ activation caused persistent binding of a corepressor, silencing mediator for retinoid and thyroid hormone receptors (SMRT), to the *RORγt* promoter. Notably, a ChIP assay showed that clearance of SMRT from the *RORγt* promoter normally precedes *RORγt* expression induced by TGF-β/IL-6 stimulation of $CD4^+$ T cells. Thus, anti-inflammatory actions of PPARγ ligands have much to do with stabilization of the repression state of NCoR1/SMRT [233]. Both NCoR1 and SMRT repress proinflammatory genes in macrophages, most of which are normally upregulated by NF-κB. The anti-inflammatory effect of PPARγ ligands involves prevention of NCoR1 dismissal [234]. Anti-inflammatory mechanisms of both PPAR and LXRs involve ligand-dependent self-sumoylation, which in turn inhibits NCoRI ubiquitination or phosphorylation induced by LPS, modifications normally leading to dismissal from promoters in proinflammatory conditions.

LXRs belong to the nuclear receptor superfamily that plays important roles in cholesterol and fatty acid metabolism, positively regulating genes for cholesterol efflux and bile acid synthesis [235]. LXRs have been shown to repress inflammatory gene expression in macrophages [234,236]. Both LXR isoforms (LXR-α and -β) are expressed in $CD4^+$ T cells [237]. Intriguingly, Cui *et al.* [48] showed that LXRs mediate negative effects on Th17 differentiation. Analysis of mice deficient for both LXR-α and -β showed that LXR protein itself acts to inhibit Th17 differentiation and initiation of EAE. Treatment with LXR agonists (GW3965 and T0901317) decreased expression of RORγt and profoundly inhibited Th17 differentiation. They further identified the E-box element, a putative Srebp-1-binding site, within the *IL-17* promoter and found that it is necessary for T0901317-dependent suppression of Th17 differentiation. They also showed that Srebp-1, whose gene is regulated by LXR, suppresses Th17 differentiation by binding the E-box element, thereby binding to and inhibiting the AHR that normally increases *Il-17* transcription.

Reflecting their involvement in many cellular processes, LXRs have multifaceted roles in immunity. In murine macrophages, LXR activation antagonizes the NF-κB pathway, thereby inhibiting TLR4-mediated LPS responses [236]. Reciprocal inhibition between TLRs and LXRs has been discussed [238]. However, in human macrophages LXR can potentiate LPS-induced responses [239]. In Korf *et al.'s* study, treatment with a synthetic LXR agonist showed increased resistance

to *M. tuberculosis* infection resulting from activation of LXR-signaling pathways, that was accompanied by increased Th1/Th17 function in the lungs [240]. This is reminiscent of Joseph *et al.* [236] that showed the requirement of LXRs for normal immunity to *L. monocytogenes*. Given such broader implications, assessment of many aspects of metabolism and immunity, as well as detailed evaluations regarding timing and dose, may become important if LXR-based therapeutics are pursued for Th17 suppression. Regarding PPARγ, further regulatory factors may also be elucidated in the near future. For example, T cell expression of epidermal fatty acid-binding protein (E-FABP) promotes Th17 differentiation, while counterregulating development of Foxp3$^+$ Tregs [241]. E-FABPs may act to sequester PPAR ligands in the cytoplasm, thereby inhibiting nuclear entry and PPAR activity [241].

A lipidome-based approach may provide a useful insight into integrate diverse aspects of Th17 development. As discussed above, newly described CD5L behaves as a functional switch; CD5L stabilizes non-pathogenic Th17 cells, inhibiting their change into pathogenic Th17 cells. This inhibition is mediated by intracellular lipidome modulation, such as maintenance of a high PUFA/SFA ratio and restriction of cholesterol synthesis, and, thereby, RORγt ligand availability [75]. From a biological perspective, little is known about the evolutionary advantages of such crosstalk between lipid metabolism and T cell development/functions.

Glucocorticoid and GILZ

Glucocorticoids (GCs) are the most widely used anti-inflammatory and immunomodulatory agents. Most physiological and pharmacological effects of natural and synthetic GCs involve activation of the glucocorticoid receptor (GR). The efforts to separate therapeutic from adverse effects of GCs led to the use of a protein induced by GCs as a drug that may mediate their anti-inflammatory effects [242]. GC-induced leucine zipper (GILZ) is a protein discovered during such efforts and has been suggested to be a key player in the anti-inflammatory activity of GCs [243]. GILZ is widely expressed in various cells, including lymphocytes, DCs, macrophages, and epithelial cells. General mechanisms for GC- and GILZ-mediated transrepression and transactivation have been discussed in Hoppstädter and Kiemer [244]. Using in vitro analyses, GILZ-deficient mice, and skin biopsy samples from patients with psoriasis, Jones *et al.* showed that GILZ plays suppressive roles against Th17 cells but is downregulated in patients with psoriasis [245].

Mesenchymal stromal (stem) cells (MSCs) deploy various modalities to suppress inflammation [246]. Luz-Crawford *et al.* showed that MSCs from wild-type, but not from GILZ knockout mice, have immunosuppressive potential when transferred into a CIA murine model. GILZ expression in MSCs was required for the generation of IL-10-producing regulatory Th17 cells [247].

IL-27 and Interferon (IFN)-β

IL-27 was initially described as an initiator of Th1 responses, but was later shown to exhibit ability to antagonize various T cells involving Th17 and to promote Treg cell responses [248]. We discussed IL-27 effects on Th17 cell development in section for STAT3 vs STAT1. Sweeney *et al.* provided in vivo and in vitro data suggesting that IFN-β exerts its therapeutic effects in patients with MS partly via the induction of IL-27, implicating IL-27 as an alternative therapy for patients with MS that do not respond to IFN-β [249]. In murine models of EAE, both Th1 and Th17 myelin oligodendrocyte glycoprotein-specific T cells were shown to induce EAE with similar severity, but resulted in different anatomical pathologies [250]. In a Th17-biased EAE mouse model, IL-27 suppressed EAE in an IL-10-independent manner [251]. This stands in contrast to the requirement of IL-10 for suppression of Th1-biased EAE by IL-27 [252]. When human naive CD4$^+$ T cells cultured in Th17-polarizing conditions were treated with IL-27 or IFN-β, IL-17 production was reduced to 50% or less relative to the control. Intriguingly, neutralizing anti-IL-10 Ab did not show effects on IL-27 and IFN-β, signifying the non-IL-10-mediated nature of the suppressive effect of IL-27 and IFN-β against Th17 [251].

Conflicting results in serum level in patients with MS have been reported. Tang *et al.* showed that patients with progressive MS had decreased plasma and mRNA expression levels of IL-27 [253]. On the other hand, in Naderi *et al.'s* study, plasma levels of IL-27 in patients with MS were increased significantly compared to the control subjects [254].

Melatonin, NFIL3, and ERK1/2

Intriguingly, melatonin, a hormone whose rhythmic production serves as an important day-night and seasonal endocrine signal, is linked to Th17-suppressive transcription factor nuclear factor, interleukin 3 regulated (NFIL3). NFIL3 (also known as E4BP4) is a basic leucine zipper transcription factor that has been shown to have an association with IBDs [255]. Yu *et al.* [256] showed that *Nfil3*$^{-/-}$ mice had higher IL-17A$^+$ and RORγt$^+$ Th17 cell frequencies than wild type mice in both small intestine and colon. NFIL3 suppresses Th17 cell development by direct binding and repression of the *RORγt* promoter [256]. A nuclear receptor, REV-ERBα is involved in the transcriptional network of the circadian clock and directly represses *Nfil3* transcription, thereby linking Th17 cell development to the circadian clock network [256,257]. Perturbed light-cycles caused increased Th17 cell frequencies in the intestine and spleen of mice in a manner dependent on the expression of REV-ERBα [256].

A cohort study by Farez *et al.* [258] demonstrated seasonality of MS relapses, specifically, a 32% reduction in the number of MS relapses occurring during fall and winter, in accordance with Jin *et al.* [259] and Spelman *et al.* [260]. Treatment with melatonin ameliorates disease in an EAE mouse model [258]. Under Th17-polarizing conditions, IL-17, but not IFN-γ production from human and murine CD4 cells was suppressed by melatonin. Farez *et al.* further showed that melatonin induces expression of NFIL3 and activation of ERK1/2, which is known to suppress Th17 [258,261]. Mechanistic details of melatonin signaling involving REV-ERBα have been shown by Farez *et al.* Unsurprisingly, melatonin effects are not specific to Th17; melatonin treatment induced Tr1 differentiation via ERK1/2 and RORα [258].

Targeting salt effects

Intriguing reports from Kleinewietfeld *et al.* and Wu *et al.* showed that mouse naive CD4$^+$ T cells cultured in high-salt (sodium chloride) medium had a higher expression of serum/glucocorticoid-regulated kinase 1 (SGK-1) and produced higher numbers of Th17 cells compared to those cultured in normal conditions [262,263]. This effect was mediated by the p38/MAPK-NFAT5 pathway [262]. Loss of SGK1 abrogated Na(+)-mediated Th17 differentiation in an IL-23-dependent manner [263]. Hernandez *et al.* observed that in a mouse model of MS, a high-salt diet exacerbated disease progression and impaired Treg function [264]. In an EAE mouse model, Jörg *et al.* suggested that a direct effect of NaCl on Th17 cells, rather than an effect primarily exerted via DCs, plays the key role [265]. We direct readers to a recent review by [266].

Epidemiological studies were also informative. In a cross-sectional analysis using a detailed questionnaire on 18555 individuals including 392 (self-reported) patients with RA, a logistic regression model showed that the odds for RA increased with daily sodium intake. A logistic multivariate model adjusted for many confounding factors (including age, sex, prevalent cardiovascular diseases, diabetes, and smoking) showed that the fourth quartile had an odds ratio of 1.5 ($P < 0.02$) [267]. Their case-control study replicated the dose-dependent association. Farez-Fiol *et al.* recently showed that sodium intake is associated with increased disease activity in MS [268]. Note, however, that McDonald observed no strong association between dietary salt intake and pediatric-onset MS risk [269].

In Monteleone *et al.'s* study, in vitro analysis using human lamina propria mononuclear cells showed enhanced expression of IL-17, IL-23R, TNF-α and RORγt following NaCl exposure in a p38/MAPK-dependent manner, while expression of IFN-γ was unchanged. In vivo analyses of mice fed a high-salt diet showed a consistent result [270]. Recent intriguing reports include that from Wen *et al.* Analyses with human subjects, as well as in vitro experiments with Jurkat cells, showed that potassium supplementation has a blocking effect on IL-17A production in T lymphocytes induced by salt loading. This protective effect was found to be mediated by the direct suppression of the p38/MAPK-SGK1 pathway [271].

Dopamine as a target

Several findings have suggested immunological effects of dopamine or its antagonists. This is interesting, because dopamine has long been therapeutically utilized, mainly as a neurotransmitter, although expression in many organs, including the gastrointestinal tract, is recognized [272]. As the comprehensive review by Levite discusses, expression of dopamine receptors (DR) on T cells, with differential balance among DR types depending on T cell subsets and stages, influences Th1/Th2/Th17 differentiation [272]. At least five DRs are known (D1R to D5R), all being G-protein coupled receptors. D1R/D5R couple with stimulatory Gα subunits, while the remaining receptors couple with inhibitory Gαs [273]. In many settings, dopamine suppresses Treg in an autocrine or paracrine manner, thereby enhancing effector T cell activities. Several studies support the view that dopamine also directly stimulates effector T cells. In some cases, anomalous expression of DR, or responses to dopamine, is reported for MS, RA, and SLE. Given the article by Levite [272], we cite only a few recent papers.

Using D5R knockout mice, Prado *et al.* showed that D5Rs expressed on DCs are able to modulate the development of T cells and, in particular, activate differentiation of Th17 cells. D5R-deficient DCs transferred into wild-type recipients reduced the severity of EAE [273,274]. However, conflicting results exist among analyses of patients. In Ferreira *et al.'s* study, PBMCs from patients with relapsing-remitting (RR)-MS showed increased proliferation and production of TNF-α, IL-6, and IL-17 upon stimulation with phytohemaglutinin (PHA) + dopamine, relative to cells from healthy controls [275]. Further, IL-17 and IL-6 production by T cells from patients with MS was less sensitive to glucocorticoid inhibition, supporting the idea that dopamine stimulates Th17 proliferation. However, in Melnikov *et al.'s* study [276], patients in the relapse stage of MS exhibited a high level of IL-17 and, intriguingly, lower level of dopamine in serum relative to healthy controls and patients in the remission stage. In that setting, dopamine treatment mildly reduced IL-17 in PBMC cultures from the relapse patients, although after the dopamine treatment IL-17 levels remained high relative to those of PBMC from patients in remission. It is not clear why dopamine promoted Th17 proliferation in Ferreira *et al.'s* study [275], but inhibited it in Melnikov *et al.'s* [276], yet Melnikov *et al.'s* finding of high IL-17 production after dopamine treatment of PBMCs from patients with RR-MS is consistent with that in Giorelli *et al.'s* study [277]. However, while these results reinforce the role of Th17 cells in MS activity [278], Melnikov *et al.'s* results represent a challenge in a dopamine-centered view of MS pathogenesis [276].

Gut microbiota, SCFA, and histone deacetylase (HDAC) inhibitors

Intestinal dysbiosis (microbial imbalance) has been shown to be associated with, or suggested to contribute to, the pathogenesis of various autoimmune diseases, including both IBD and non-IBD [279-284]. The importance of gut commensal bacteria in regulating the Treg/Th17 axis has been widely recognized [285]. Although recent studies showed that gut microbiota remotely regulated systemic disease by driving the induction and egress of T follicular helper (Tfh) cells of gut Peyer's patch [e.g., 286], here we briefly discuss microbiota relevance to Th17 cells.

Atarashi *et al.* discovered several strains of Clostridia that promote expansion of Treg cells and, upon oral administration, attenuate colitis and allergic diarrhea in mouse models [287,288]. Although they are minor among gut microbiota, mucosa-associated species such as segmented filamentous bacteria (SFB) can powerfully modulate host immunity [289]. SFB adhesion to small intestine epithelial cells leads to induction of Th17 [290,291]. In the K/BxN TCR transgenic mouse model of inflammatory arthritis used by Wu *et al.*, Th17 cells were essentially absent from the site in germ-free K/BxN mice but monocolonization of SFB was capable of triggering arthritis development in K/BxN mice through promotion of Th17 cell populations in the small intestine lamina propria and spleen [289]. Intriguingly, Kumar *et al.* recently showed that IL-17 receptor (IL-17R)-deficient mice exhibited an earlier onset and worsened severity in an EAE model. They also used IL-17R knockout mice conditional to enteric epithelium and found dysbiosis of SFB (SFB overgrowth), increased serum GM-CSF concentrations, enhanced predisposition to neuroinflammation, and unconstrained Th17 development [292].

Findings derived from many studies led to the consensus that symbiosis between Tregs and commensal microbes is important. In particular, Kawamoto *et al.* provided findings arguing that mucosal IgAs, diversified and selected in a manner dependent on $Foxp3^+$ T cells, contribute to the maintenance of diversified and balanced microbiota, which in turn facilitate the expansion of $Foxp3^+$ T cells, induction of germinal centers, and IgA responses in the gut, comprising a symbiotic regulatory loop [293]. Short chain fatty acids (SCFAs) and in particular, butyrate, have been shown to facilitate acetylation of the Foxp3 histone upregulating this gene, thereby promoting iTreg development [294,295]. Mechanistic insights were gained by the discovery of G-protein-coupled receptors (GPCRs) for SCFAs, which mediate their anti-inflammatory action [296].

For gut bacteria to play an integral role in maintaining intestinal immunity against pathogens and tolerance against self-antigens, metabolites from gut bacteria, including SCFA, are considered important. SCFA shows inhibitory activity against HDAC [297,298]. Koenen *et al.* reported a profound negative effect of the HDAC inhibitor trichostatin A on the emergence of IL-17-producing cells from Tregs, implying that Treg differentiation into Th17 cells depends on histone deacetylase activity [299]. In general, histone acetylation

often accompanies gene transcription, required for the appropriate tissue-specific induction of many genes, and is opposed by the activity of HDAC [132]. This is consistent with the view that, in the case of Tregs, histone acetylation-mediated upregulation of *Foxp3* expression may be important for stabilizing Treg status. Indeed, histone H3 and H4 acetylation was found to be associated with upregulation of *Foxp3,* which is important for Treg differentiation [132,300]. HDAC9 knockout mice showed increased numbers of Treg cells with increased suppressive capacity [300]. HDAC inhibitors (HDACi) are classified into two groups; those of Class II enhance the suppressive function of murine Treg cells, while Class I HDACi have shown mixed results [298].

The story of commensal bacteria, SCFA, and HDAC is illuminative, but HDACi treatment may face a challenge for therapeutic translation, as is often the case with interventions in intracellular phenomena that are often ubiquitous. The inhibitory effects of HDACi on effector $CD4^+$ T cells are absent or very weak after activation of these cells [298]. HDACi also enhance the function of cytotoxic $CD8^+$ T cells. Therefore, timing and procedure of treatment may need to be carefully optimized in approaches to modulate ubiquitous events. Yet, HDACi appears to have a good chance of efficacy in many pre-clinical and clinical settings, particularly when a short-term treatment can be critical. For example, Sugimoto *et al.* showed in an islet transplantation mouse model in which donor-specific blood perfusion (DST), when combined with HDACi treatment, dramatically improved graft survival [301]. This effect was accompanied by a pronounced decrease in IL-17 mRNA levels in the spleen and Treg cell induction in the thymus.

IL-25 (IL-17E)

IL-25 (also known as IL-17E) belongs to the IL-17 family, but, unlike IL-17A, IL-25 promotes Th2-type immune responses, contributing to atopic dermatitis and asthma [302]. IL-25 exhibits anti-inflammatory properties in many settings where IL-17 is involved [303]. IL-25-deficient mice are susceptible to EAE, exhibiting increased IL-23 levels and a subsequent increase in inflammatory cytokines involving IL-17 [304]. Several findings suggest that IL-25 is of particular importance in commensal bacteria-dependent induction of tolerance in the intestinal immune system. Notably, the number of Th17 cells in the large intestine increases (>3 fold) in the absence of commensal bacteria [305]. Zaph *et al.* also showed commensal-dependent expression of IL-25 by intestinal epithelial cells and that this inhibits macrophage production of IL-23, thereby limiting Th17 proliferation [305]. Intriguingly, IL-25 did not suppress *Il12a*, *Tgfb*, *Il6*, or *Il10* gene expression, showing specific negative regulation of IL-23 by IL-25. Later, Su *et al.* showed that IL-25 is markedly decreased in the sera and mucosa of patients with IBD and that IL-25 normally inhibits CD4 T-cell activation and differentiation into Th1/Th17 cells in an IL-10-dependent manner [306].

IL-17RA is likely to the most important receptor mediating the effects of IL-17A [307]. When IL-17RA is considered as a therapeutic target to reduce IL-17A effects, however, the outcome could be confounded by the IL-25 effect, as the biological activities of IL-25 require both IL-17RB and IL-17RA [303]. Unlike anti-IL-17A inhibitors that showed efficacy in patients with RA [308], trials using anti-IL-17RA (brodalumab) in patients with RA showed no efficacy [7,309,310]. This suggests that IL-17RA targeting abrogates the IL-25 effect. IL-25 (IL-17E) signaling may have to be retained during therapeutic intervention. On the other hand, when it comes to the therapeutic potential of IL-25 itself in patients with IBD, evaluation of adverse respiratory system events may become important [311]. This motivates us to seriously think about locally acting biologics not mediated by systemic circulation.

Aryl hydrocarbon receptor (AHR)

There are many other molecules and mechanisms regulating Th17, although we cannot exhaust them all here. AHR is important in T cell differentiation and function, although it was only briefly discussed above (in sections for "Tregs, non-pathogenic Th17, and pathogenic Th17"and "PPARg and LXRs). AHR-deficient mice have increased levels of Th17 and IL-17/IL-22-producing γδT cells in a skin-inflammation model [312]. However, in vitro studies suggest that AHR paradoxically promotes Th17 differentiation [313]. Various endogenous ligands with apparently differential effects on Treg/Th17 balance are present [314], and expression patterns of AHRs are broad and complex [191]. Broadly, there are two conflicting views. In Nguyen *et al.'s* study, AHR ligation in DCs is required for full Treg cell differentiation [315]. On the other hand, Stephens *et al.* showed that inhibition of kynurenin 3-monooxygenase that catabolizes kynurenin, an AHR ligand, in Th17 cells caused increased IL-17 production in vitro [316]. Further analyses of kynurenin, a tryptophan metabolite, and AHR activation in Th17 are warranted. It is generally difficult to predict the outcome of a therapeutic approach targeting AHR [191]. AHR has also been targeted in the context of ILCs. AHR is required for the development of $ROR\gamma t^+$ ILCs and the production of IL-22 from these cells [317]. AHR is also required for cryptopatches (CPs) and isolated lymphoid follicles (ILFs) in the intestine, with ILFs being a sort of inducible tertiary lymphoid organ in the intestine that develop from the CPs, (rudimentary lymphoid structures) [161,317].

Other modalities

Adenosine acts as an immunosuppressive molecule [246]. The role of the CD39/adenosine axis may have been underevaluated in Th17-mediated diseases. CD39 is an ectoenzyme that catalyzes the conversion of ATP to 5′-AMP, the substrate for CD73. CD73 catalyzes production of adenosine from 5′-AMP [246]. Importantly, in patients with juvenile autoimmune liver disease, $Th17^{CD39+}$ cells are markedly diminished and fail to generate AMP/adenosine, compared to healthy subjects, thereby limiting control of both target cell proliferation and IL-17 production [318]. In the near future, involvement of the CD39/adenosine axis in other diseases may also be elucidated.

miRNAs (micro-RNAs) are short fragments of non-coding RNA that bind to the 3′-UTR of complimentary mRNA, thereby repressing/silencing target RNAs [319,320]. miRNAs are important for the regulation of Th17 development and functions, but we do not cover many studies here, as there are excellent review articles [320,321]. The pathological roles and diagnostic potential of miRNAs in RA have been reviewed by Churov *et al.* [322]. miRNA roles in the pathogenesis of MS and IBD have been discussed by Wu and Chen [323] and Xu *et al.* [324], respectively. From the perspective of negative regulation of Th17 cells, miR-210 acts as a negative regulator of Th17 differentiation. Deletion of miR-210 promotes Th17 differentiation under hypoxic conditions [325]. Other miRNAs regulating Th17 cells include miR10, miR210, miR301, and miR326 [321]. miRNA's role in Treg and Th17 regulation is clearly important, but this area is still in its infancy [321]. In fact, besides the miRs discussed by Ueno *et al.*, Naghavian *et al.* showed that miR141 and miR200a are likely to be key miRNAs in the progression of MS through differentiation of Th17 cells and inhibition of differentiation of Treg cells [326]. In the coming years, more information on miRNAs relevant to Th17 will be elucidated through preclinical and clinical studies.

Perez *et al.'s* analysis using siRNA showed that lymphocytes (mouse and human) externalize calpains, calcium-activated proteases generally considered to act in cytosol. Extracellular calpains negatively regulated IL-17A production by lymphocytes by cleaving TLR2, and thereby preventing lymphocytes responding to TLR2 ligands. They further showed that low-dose IL-2 increased calpain secretion and decreased lymphocyte expression of TLR2, and that this decrease was abolished by calpastatin. Using peritonitis and autoimmune arthritis models, they further showed in vivo relevance of calpain externalization in regulating (reducing) IL-17A expression [327].

Several authors have suggested or indicated the negative effect of the antioxidant CoQ10 on inflammation and Th17 cells. Tawfik showed that intraperitoneal administration of CoQ10 not only potentiated the antiarthritic effect of methotrexate (MTX) but also alleviated MTX-induced hepatocellular injury [328]. Oral administration of CoQ10 ameliorated zymosan-induced arthritis in mice [329]. Splenocytes from CoQ10 treated mice showed decreases in IL-17, CCL20, and RORγt mRNA levels, and an increase in $Foxp3^+$ Treg cells [329].

Although the mechanistic explanation has yet to be given, Bcl2 family molecules have drawn attention in the pathogenesis of autoimmune disease. The Bcl2 family consists of three classes of proteins that can either promote or inhibit apoptosis [330]. B cell lymphoma 2–interacting (Bcl2-interacting) mediator (Bim) is considered to delete autoreactive lymphocytes through apoptosis. Paradoxically, Bim-deficient mice showed protection against the development of EAE and diabetes [330]. Other paradoxical reports related to Bcl-2 involve that of Iglesias *et al.* who showed that mice with T cell-specific overexpression of BCL2A1, an antiapoptotic Bcl2 family member, had attenuated development of CIA. Both in vivo and vitro, Th17 differentiation was impaired. In vitro TCR stimulation showed defective activation of p38 MAPK [331]. Characterization of the BCL2A1 interactome may reveal a novel pathway regulating the p38MAPK pathway [331].

Although we do not cover the subject broadly, several cases have been reported in which MSCs inhibit Th17 cell activity. Luz-Crawford *et al.* showed that MSCs inhibit Th1 activity in a manner dependent on soluble factors, but MSC-suppression of Th17 differentiation was mediated by direct contact [332]. Using antibodies to PD-L1 and PD-1, they showed that PD-L signaling was the key for this suppression [332]. Other studies that discussed PD-1-mediated suppression include that by Yang *et al.* who showed that PD-1-deficient mice develop severe CIA. When T cells from CIA mice were analyzed ex vivo, mice lacking PD-1 exhibited aberrant antigen-specific Th17 responses. Deregulated activation of PKC-θ and Akt was suggested as the cause for these aberrant responses [333].

Perspective

As we have seen above, some cytokines, including IL-2 and IL-23, showed robust negative regulation in many settings. However, for several factors, including TGF-β, AHR signaling, vitamin D, IL-35, IL-27, and dopamine, the effects depend on the cell type and complexity arising from interactions between non-T cells and Th17 cells, and their spatiotemporal dynamics appear to cause significant dependency of effects of these factors on timing, dose, location, and context.

Fine-tuning the balance between regulatory cells and Th17 cells is important. The same is true for pathogenic and non-pathogenic subsets of Th17 cells. Local imbalance, likely in the intestine, between such populations causing over-proliferation of Th17 cells results in exacerbation of autoimmunity in remote organs [99]. It is reasonable to interpret that necessity of the tight regulation of the balance favored the pairwise evolution of Th17 and Th17-targeted Treg cells sharing a developmental pathway and forming clusters in tissues. It is likely that, in the early phase of development, Th17 cells located in the vicinity of Tregs receive promotive stimuli from Tregs (TGF-β, IL-2 depletion, and CTLA-4 mediated suppression of CD28 signaling). Such time- and stage-sensitive roles of Tregs on Th17 cells might have evolved in such a way that Tregs enable a near-optimum time-course of Th17 functionality in protection against microbes, and at the same time, avoidance of autoimmune diseases. Such pair-wise evolution, which would enable evolution of well-coordinated dynamics, is also seen in cytokines. IL-17 families are basically proinflammatory, but IL-25 (IL-17E) exerts suppressive effects on Th17 in the IBD model, despite its sequence similarity to IL-17A. Analyses of molecular bases for differential physiological effects between IL-17A and IL-25 are desired, although such an issue is often difficult to study due to highly complex, context-dependent, non-specific, and degenerate features of intracellular signal transduction. It is likely that there are many more factors regulating this subtle balance; for instance, T cell expression of E-FABP promotes Th17 differentiation, while counterregulating development of Tregs [241]. E-FABP-deficient $CD4^+$ T cells display enhanced PPARγ expression and activity. This is an example of the intricate regulation of Treg/Th17 balance via lipid metabolism. It could be that FABPs act to sequester PPAR ligands in the cytoplasm, hence inhibiting nuclear entry and PPAR activity [241]. A deep understanding of lipid metabolism may enable fine-tuning of the balance between Treg and Th17 cells, and among Th17 subsets.

From a clinical perspective, the availability of drugs that explicitly act on specific cells or accumulate in local tissues/organs may become important, given that systemic drug administration is generally apt to lead to adverse events. It would be interesting to envisage that, in future, gene transduction could enable controllable accumulation of regulatory cells to a particular target organ so that the local Treg/Th17 balance can be modulated, without changing Th17 levels. As therapeutic approaches using aptamers exemplify, future therapeutics will be more directed toward local and cell type-specific interventions. To facilitate such organ/cell-specific approaches, understanding of the trafficking of effector T cells is important. CCR6 helps to recruit Th17 cells to inflamed tissues/organs in response to its ligand CCL20 [e.g., 334]. Genetic studies have demonstrated an association between susceptibility to RA and polymorphism of the gene for CCR6, the important chemokine receptor of Th17 [335]. Association of *CCR6* with lupus nephritis has also been reported [336]. Koga *et al.* assessed the effects of suppression of the CCR6/CCL20 axis and showed reduced kidney CCR6/CCL20 expression and serum IL-17 levels, as well as improved clinical and pathologic outcomes in a lupus nephritis-like kidney disease mouse model [337]. While these findings are informative, the migratory properties of effector T cells are poorly understood in general. For instance, Elhofy *et al.* showed that CCR6 is largely dispensable for EAE pathogenesis [338]; CCR6-deficient mice developed a significantly more severe chronic EAE compared with wild-type immunized animals. It should also be borne in mind that chemokines and their receptors have not been identified exhaustively. Kara *et al.* showed IL-23-dependent switches from CCR6 to CCR2 usage during Th17 cell development (Figure 1). This switch gives rise to $CCR6^-CCR2^+$ Th17 cells that represent an advanced differentiated state producing GM-CSF/IFN-γ and therefore has a very high proinflammatory potency [20]. It would be interesting to attempt administration of Tregs transfected with genes for CCR2 in autoimmune disease model mice.

Fine-tuning of Treg/Th17, and of the subsets of Th17 cells, appears important in the intestine, in particular. While clinical trials using IL-17A inhibitors for psoriasis, ankylosing spondylitis, and RA showed promising results, the trials on Crohn's disease instead showed increased disease activity and adverse events [339,340]. Inhibition of IL-17 activity should lead to susceptibility to infection. IL-17 and IL-22 produced by Th17 are considered to be important for epithelial cell production of β-defensin that has antifungal activity, and inhibition of this loop may lead to increases in fungi, leading to an enhanced innate immunity response in intestinal mucosa [341].

Studies on the roles of antigen recognition by TCR in autoimmune diseases have been relatively limited, but could be important. Induction of antigen-specific tolerance using chemically modified antigen peptides seems to be an interesting approach. An obvious challenge in clinics, however, would be that the cDNA sequences of TCRs and immunoglobulins from patients tell us little about the antigen peptides key to the patient. In Ito *et al.'s* study [100], mice expressing a single arthritogenic TCR were used for identification of peptide antigen, and this identification required auto-antibody/B cell analysis. This is elegant but still very intensive work. It would be nonetheless interesting to envisage that this approach could generate a panel of peptides from autoimmune arthritis in mice, and this information may facilitate, in combination with appropriate conjugation methods, induction of anergy of Th1 and Th17 cells in patients with RA [103].

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