Chapter 5
Th17 Differentiation and Their Pro-inflammation Function

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Abstract CD4$^+$ T helper cells are classical but constantly reinterpreted T-cell subset, playing critical roles in a diverse range of inflammatory responses or diseases. Depending on the cytokines they release and the immune responses they mediate, CD4$^+$ T cells are classically divided into two major cell populations: Th1 and Th2 cells. However, recent studies challenged this Th1/Th2 paradigm by discovering several T-helper cell subsets with specific differentiation program and functions, including Th17 cells, Treg cells, and Tfh cells. In this chapter, we summarize the current understanding and recent progresses on the Th17 lineage differentiation and its effector impacts on variety of inflammatory responses or disease pathogenesis.

**Keywords** T-cell differentiation · Th17 cells · IL-17 · IL-22 · Inflammation

5.1 Introduction

Upon various pathogens or injuries challenging, our body initiates both innate and adaptive inflammatory responses to protect us from infection or insult. CD4$^+$ T helper cells are critical components for appropriate establishment of adaptive immune responses. After engagement of T-cell receptor (TCR) and co-stimulatory molecules, naive CD4$^+$ T cells differentiate into different effector T helper cells under the control of distinct cytokines produced by particular pathogens or injuries activated antigen presenting cells (APCs). Over 25 years, Mosmann and Coffman's Th1/Th2 paradigm in CD4$^+$ T helper cells development shapes our view of the landscape of adaptive immunity [189]. Although this paradigm helps us a lot for

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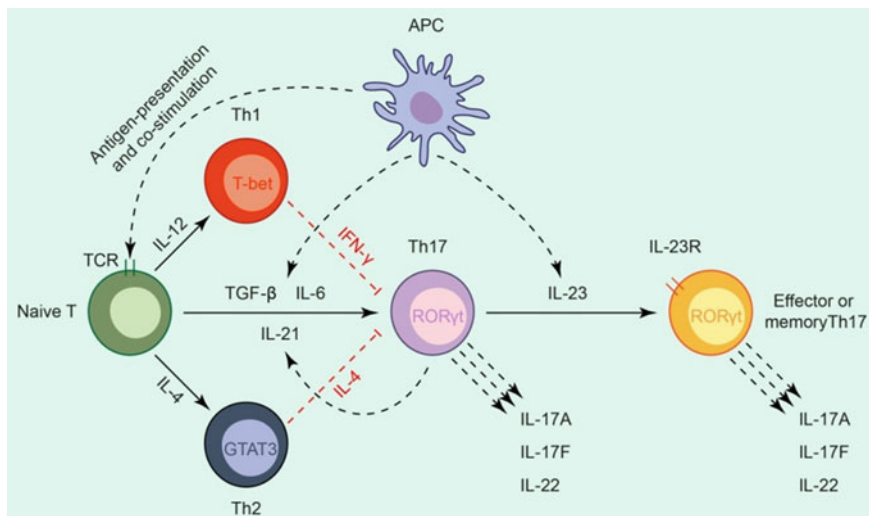
Fig. 5.1 The differentiation of Th17 cells. Naïve T cells can differentiate into three subsets of effector T helper cells under the control of distinct sets of cytokines. After TCR ligation, IL-12 and IL-4 promote Th1 and Th2 differentiation respectively, while the Th17 differentiation is controlled by TGF-β, IL-6, IL-23, IL-1β, and self-secreted IL-21. The differentiation of Th17 cells is inhibited by IFN-γ or IL-4. T-bet (also named Tbx21), GATA3, or RORγt (also known as Rorc) represents the linage-specific transcription factors for Th1, Th2, or Th17, respectively

understanding many aspects of adaptive immunity, some intriguing phenomena cannot be explained until the discovery of a third T helper cells lineage: the Th17 subset, which produces Interleukin-17 (IL-17, also called IL-17A) as its signature cytokine [129] (Fig. 5.1). The function of this newly emerged effector T helper cell subset appears to be distinct from those of Th1 and Th2 subsets and even reinforces certain roles of adaptive immunity system such as host defense and tissue repair responses, which cannot be fully achieved by the Th1/Th2 paradigm [129]. However, Th17 cells are also strong inducers of local tissue inflammation. Persistent and uncontrolled inflammation triggered by Th17 cells becomes a major stimulator in the pathogenesis of many human chronic diseases, which include autoimmune diseases and cancer [129]. The cytokines and the key transcription factors for its differentiation, maintenance, and expansion have been identified. The signaling pathways mediated by IL-17 and the responses mediated by its effector cytokines have also been elucidated.

In this chapter, we review the current understanding of the regulation of Th17 differentiation by the key cytokines and transcription factors and recent progresses of Th17 cell fate commitment and plasticity in both mouse and human. We also discuss the interplay of Th17 cells with other effector T cells such as Th1 and Treg cells. More importantly, Th17 cells produce characterized cytokines like IL-17A,

IL-17F, and IL-22. All those unique cytokines mediate Th17-driven inflammatory responses in both physiological and pathogenic conditions. The signaling pathways and the efforts mediated by those cytokines are also addressed here.

5.2 The Discovery of Th17 Cells

Autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA) are chronic inflammatory diseases. Experimental autoimmune encephalo-myelitis (EAE) and collagen-induced arthritis (CIA) mouse models are the most common tools to study those human autoimmune disorders [19, 257]. From a long time, those diseases were associated with uncontrolled self-reactive Th1 responses, since the IFN-γ level was highly correlated with the pathogenesis of EAE and CIA. Blockage of the key Th1 differentiation cytokine IL-12 with antibodies eliminated the progression of EAE and CIA [148, 172]. Rodent genetic evidences demonstrated that both Th1 favorite transcription factors *Tbx21*- and *Stat4*-deficient mice were protected from EAE [17, 35]. All the above evidences indicate that the IFN-γ-producing self-reactive Th1 cells are responsive for the induction of those auto-immune responses. However, this Th1-dominant presumption was intrigued by some experimental contradictions: either the *Ifng*- or its receptor deficient mice were unexpectedly noticed to be susceptible to EAE, rather than resistant to EAE [132, 274]. Similar phenotypes were also observed in both *Il12p35* (one subunit of IL-12)-and *Il12rb2*-deficient mice in EAE model [78, 318]. This paradox raises a question that whether there are unperceived cell populations required for the pathogenesis of EAE. In 2000, IL-12p40 was found to form a novel cytokine IL-23 with a newly identified subunit IL-23p19 [210]. Thus, IL-12p40 is a common subunit for both IL-12 and IL-23, but IL-12p35 and IL-23p19 are the unique subunit for IL-12 and IL-23, respectively. By comparing *Il12p35*-deficient mice with *Il23p19*-deficient mice in EAE or CIA model, researchers found that IL-23 rather than IL-12 was critical for the induction in both models [142, 44, 192]. These results also well explained the phenotype paradox between IL-12 antibodies blockage and *Il12p35*- or its receptor deficient mice in EAE, since blockage strategies targeted IL-12p40 subunit, which also affect the function of IL-23. Following studies showed that IL-23 was crucial for the development of IL-17-producing T helper cells, which was then named as Th17 cells [87, 215].

5.3 Th17 Cell Differentiation

Th17 cells are characterized by production of effector cytokines IL-17 as well as IL-17F, IL-21, and IL-22. Comparing with Th1 and Th2 lineages, Th17 lineage is a more plastic population in its fate determination and its differentiation is controlled by a distinct set of cytokines: after TCR activation and co-simulation, TGF-β and

IL-6, which activate transcription factors Smads and STAT3 respectively, induce the expression of Th17 polarized transcription factor retinoid-related orphan receptor (ROR) γt to initialize Th17 differentiation from naive T cells. IL-21, the cytokine produced by Th17 cells, further promotes this process in a positive feedback manner. After upregulation of IL-23R by the above cytokines in Th17 cells, IL-23 binds to its receptor to drive the terminal differentiation of Th17 cells for their fully function achievement. Other Th17 cell commitment promoting or regulatory cytokines and transcription factors are also identified in recent years, and we will also discuss them in detail as below (Fig. 5.2).

5.3.1 Positive Regulation of Th17 Differentiation by Cytokines

5.3.1.1 TGF-β

TGF-β is a pleiotropic cytokine in T-cell functions and its contribution in Th17 cell differentiation remains contradictory in different conditions [151]. *In vivo* evidences shown that *Tgfb1*-transgenic mice resulted in enhanced generation of Th17 cells and aggressive EAE phenotype when immunized with MOG$_{35-55}$ in CFA [16]. Dominant negative *Tgfbr2*-transgenic mice did not develop the pathological signs of EAE and have no Th17 cells in the spinal cords [282]. T-cell specific *Tgfb1*-deficient mice also did not develop any clinical sign of EAE, and the number of Th17 cells was greatly reduced in those mice [153]. Although Treg derived TGF-β was shown to induce Th17 differentiation *in vitro* [281], but it was not required for Th17 differentiation *in vivo,* since mice with Foxp3-Cre-mediated disruption of TGF-β had similar Th17 cells and comparable EAE pathogenesis when compared with wild-type controls [84]. However, Ox40-Cre-mediated deletion of TGF-β in both activated CD4$^+$ T cells and Tregs resulted in reduced Th17 cell frequencies and ameliorated EAE clinic signs [84], indicating that the production of TGF-β is critical for the pathogenic effector T cells during the organ specific autoimmune diseases. This study also found that, among the activated CD4$^+$ T cells, the Th17 cells themselves produced considerable TGF-β to further promote their functions in an autocrine manner [84].

However, how TGF-β contributes to Th17 cell differentiation remains unclear. TGF-β was reported as an inhibitory cytokine for both Th1 and Th2 cell differentiation by suppressing the transcription factors T-bet and GATA-3, respectively [77, 199]. It was likely that TGF-β promote Th17 differentiation in an indirect way by inhibiting the fate determination of other effector T-cell subsets such as Th1 and Th2 cells. The studies have also shown that TGF-β enhanced Th17 responses by suppressing the transcription factors Eomes and Gfi1, which are critical for Th1 and Th2 related cytokines production [108, 331]. Indeed, comparing with IL-6 which activates STAT3 pathway, TGF-β induced much less expression of RORγt in T
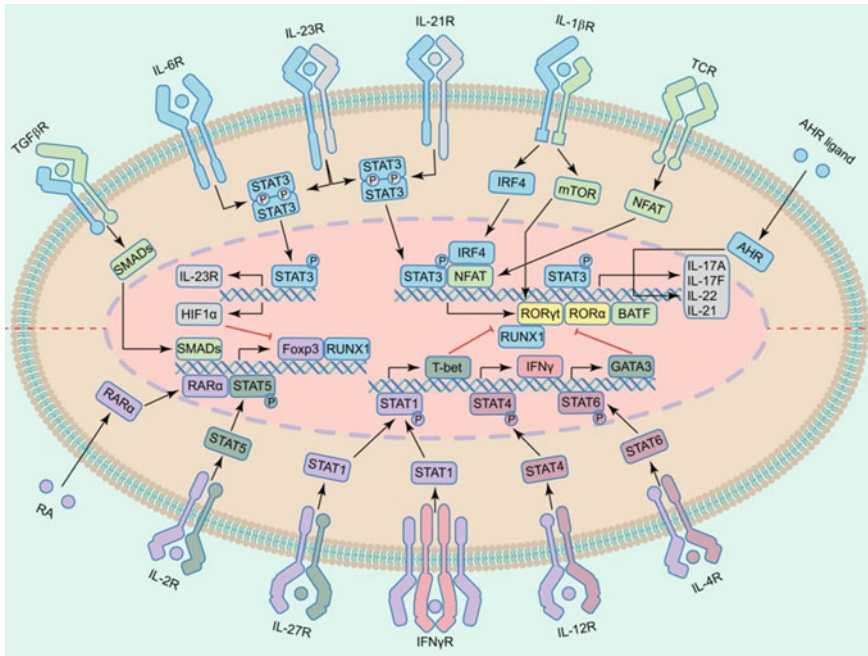
Fig. 5.2 The regulation of Th17 cell differentiation. Upon TCR activation, Th17 cells can be induced in presence of cytokines IL-6, IL-23, and IL-21 that activate STAT3. Activated STAT3 binds to the promoter regions and activates transcription of RORγt and RORα. Transcription factors BATF and IRF4 play a central role in RORγt mediated Th17 cell differentiation. Together with STAT3, RORγt, and RORα activate the expression of Th17 effector cytokines IL-17A, IL-17F, as well as IL-21 and IL-22. IL-6 mediated STAT3 activation also increases the expression of IL-23R, thus promoting the polarizing of Th17 cells. STAT3 activation also induces the expression of HIF1α to inhibit Foxp3 and promotes Th17 differentiation. IL-21 secreted by early Th17 cells functions as a self-amplified autocrine cytokine through IL-21 receptor. IL-1β promotes Th17 polarization by activation of MAPK and Akt/mTOR pathway. IL-1β also induces IRF4 to promote IL-21 secretion. Th17 differentiation is also promoted by activation of aryl hydrocarbon receptors (AHR). TGF-β signals through Smads to limit expression of genes encoding T-bet, Gata3 and other Th1 and Th2-related factors, thus enhancing the Th17 differentiation. TGF-β signaling cooperates with retinoic acid (RA) and IL-2-induced STAT5 activation to promote Foxp3 induction and Treg differentiation. Both Foxp3 and RORγt form complexes with Runx1 and regulate each other reciprocally. IL-12 and IFN-γ, which activate STAT4 and STAT1, respectively, promote Th1 differentiation by induction of T-bet and IFN-γ and then inhibit Th17 polarization. IL-27 also activates STAT1 to upregulate T-bet expression and thus inhibit Th17 development. Similarly, IL-4 signaling through STAT6 to induce GATA3 to suppress Th17 polarization and promotes Th2 differentiation

cells [327]. The IL-6 plus TGF-β produced stronger expression of RORγt than IL-6 alone [327], it is still unclear how TGF-β mechanistically contributes to Th17 cell differentiation. One study found that Th17 cells generated by IL-23, IL-6, and IL-1β rather than those induced by TGF-β and IL-6 caused the pathogenesis of EAE in a transfer model [74]. It seems that Th17 cells generated by TGF-β and IL-6 were not

pathogenic, but they are regulatory Th17 cells which produced high amount of IL-10 [74, 180]. Thus, TGF-β in low concentrations could efficiently initiate the Th17 cell differentiation in cooperated with IL-6, but under this condition, its signaling was insufficient to generate inflammatory Th17 responses [281]. In the contrast, the high concentration of TGF-β favored the generation of induced FOXP3$^+$ regulatory T cells (iTregs) rather than Th17 cells by inhibiting the expression of IL-23R and disrupting the function of RORγt [328], and high concentration TGF-β also inhibited IL-22 expression to generate IL-17$^+$IL-22$^-$ cells [324]. The plastic interplay between Th17 cells and iTregs will be discussed further in the section below.

5.3.1.2 IL-6

IL-6 is also a multiple functional cytokine in immune system and is produced by many immune and stromal cell types [279]. IL-6 binds to its receptor complex IL-6Rα and gp130 to activate STAT1 and STAT3 for downstream biological activities [94]. Its roles in autoimmune diseases have been studied. Several lines of clinic evidences revealed that the patients with MS or RA exhibit higher levels of IL-6 in their cerebrospinal fluid or synovial fluids than normal controls [97, 243]. Previous studies found that *Il6*-deficient mice are protective from CIA and EAE [5, 206, 235] and anti-IL-6 receptor antibodies blockage in mice also suppressed the progression of both CIA and EAE diseases [65, 243]. More importantly, in human, the therapy by Tocilizumab, a humanized anti-IL-6 receptor antibody, had become a novel therapeutic strategy to prevent many autoimmune diseases including RA [200]. The resistance phenotype of *Il6*-deficient mice in the models of EAE and CIA has been poorly explored until different groups identified that IL-6 as a critical differentiation factor for Th17 cell generation. As described above, IL-6 was a strong suppressor of the TGF-β-driven induction of Foxp3 in T cells, instead, IL-6 plus TGF-β induced a unique transcriptional program resulting in the differentiation of Th17 cells [16]. At this condition, TGF-β also induced the expression of IL-6Rα and gp130 indicating that TGF-β is crucial to maintain the responsiveness of T cells to IL-6 [298]. IL-6 then binds to IL-6Rα and gp130 to recruit and phosphorylate the transcription factors STAT3. Deficiency of STAT3 in T cells impaired the induction of RORγt and RORα and consequentially abrogates the generation of Th17 cells [306, 307]. Accordingly, CD4-Cre-mediated STAT3 depletion in T cells protected mice from EAE [88]. Thus, IL-6 is a key switch factor that favors Th17 cell differentiation while suppressing the generation of Tregs.

5.3.1.3 IL-21

IL-21 was firstly described in 2000 by showing that this cytokine has a role in the proliferation of natural killer (NK) cell, B cell, and T-cell populations in different conditions [216]. IL-21 is a member of IL-2 family of cytokines and signals though

the common γ chain of this family and IL-21R [159]. Although it can be produced by several activated CD$^+$ T cells, IL-21was found to be highly produced in T follicular helper (Tfh) cells and Th17 cells [128, 165, 203, 327]. IL-6 served as a strong inducer of IL-21 [263] though the transcription factor STAT3 but not RORγt [327]. It was found that IL-21 plus TGF-β can also generate Th17 cells *in vitro* as IL-6 plus TGF-β [128, 203, 327], while the relative contribution of IL-6 and IL-21 to Th17 cell differentiation *in vivo* was still controversial. Whereas Th17 can secrete IL-21, it is likely to keep a similar role as IFN-γ and IL-4 in Th1 and Th2 cell development, IL-21 is also a positive feedback amplification factor for Th17 cells. Although IL-21 was induced by IL-6 in Th17 cells, IL-6 plus TGF-β induced Th17 cell differentiation was independent of IL-21 signaling and both *Il21*- and *Il21r*-deficient mice shown similar susceptibility to the control mice in EAE model [42, 249]. Those data suggest that IL-6, rather than IL-21, plays a dominant role in Th17 differentiation in inflammatory conditions where IL-6 is massively produced. While in the absence of inflammation, IL-21 might contribute to the maintaining of precursor pool of Th17 cells, as the memory Th17 cell frequency was reduced in *Il21r*-deficient mice [128]. Thus, it is likely that IL-21 helps to maintain and amplify the pool of Th17 precursors when the level of IL-6 is relative low while under inflammatory conditions when IL-6 is highly produced, IL-21 is dispensable for the differentiation of Th17 cells.

5.3.1.4 IL-23

As discussed above, IL-23 was described as a novel heterodimer cytokine which is composed by IL-23p19 and IL-12p40 subunits in 2000 [210]. Later, researchers found that *Il23p19*-deficient mice, rather than *Il12p35*-deficient mice were protective from the induction of EAE and harbored very few IL-17-producing cells in CNS [44, 142]. The capability of IL-23 in promoting IL-17 production in activated T cells led to a notion that IL-23 was strongly connected with the generation of Th17 cells [2]. Since IL-23R is not expressed on naïve T cells, it is likely that IL-23 is dispensable for the *de novo* generation of Th17 cells. After the discovery of initiation factors for Th17 cell differentiation (IL-6, IL-21, and TGF-β), it became clear that IL-23 was not required for the *de novo* differentiation of Th17 cells but critical for the maintaining and expansion of differentiated Th17 cells. At the present of IL-6, IL-21, and TGF-β, naïve T cells began to differentiate into Th17 cells under the control of transcription factors STAT3 and RORγt, which were critical for the expression of IL-23R in those cells [174, 203, 327]. More recently, one study found that increased sodium chloride concentrations markedly boost the induction of both murine and human Th17 cells and this induction was dependent on NFAT5 and SGK1 [125]. The kinase SGK1 is critical for regulating the expression of IL-23R and thus stabilizing the Th17 cell fate [296]. Increased salt concentration induced its expression, in turn to promote IL-23R expression and enhance Th17 cell-mediated autoimmune responses [296]. Beside to Th17 cells, IL-23 signaling was also crucial for the production of IL-17 or IL-22 in many innate

immune cells [45]. Several genome-wide association studies showed the associations of *Il23r* gene SNPs with Crohn's disease and psoriasis in human [23, 58, 160].

5.3.1.5 IL-1β

The cytokine IL-1β has a broad range of influence on infectious diseases as well as autoimmune disorders [52]. More recently, studies showed that both IL-1β and IL-18 have a role in promoting IL-17 production from Th17 cells [140, 264]. Both cytokines synergized with IL-23 to enhance IL-17 secretion from TCR stimulated T cells [140, 264]. As IL-23, mice lacking IL-1β signaling was resistant to both EAE and CIA induction [169, 264). Following studies showed that IL-1β signaling was required for the early stage of Th17 differentiation by converting Foxp3$^+$ T cells into Th17 cells [36]. After polarization, IL-1β also favored Th17 cells to maintain their own fate [36]. Mechanically, IL-1β signaling promoted Th17 cell function by induction of transcription factor RORγt and IRF4 [36]. The processing of functional IL-1β requires two signals; conversely, inactive pro-IL-1β is produced by TLR signaling in innate immune cells (Signal 1) and then is cleaved by the caspase-1 to become mature and active cytokines (Signal 2) [275]. *Caspase1*- or other inflammasome components such as *Asc*- and *Nlrp3*-deficient mice were all found to be resistant to EAE induction, indicating that they may function though processing of IL-1β [67, 79, 109, 116, 244]. A *Nlrp3* gene mutation, which hyper activated inflammasome, promoted a Th17-dominant responses though uncontrolled production of IL-1β [183]. The inflammasome agonists such as uric acid crystal and extracellular ATP were all reported to promoted Th17 differentiation though inflammasome-derived IL-1β [9, 40].

5.3.1.6 TNFα

TNFα is another important inflammatory cytokine with diverse function in immune system [14]. It was found that both *Il1b*- and *Tnf*-deficient mice were resistant to spontaneous arthritis in SGK mice [90]. In CIA model of DBA/1 mice, antibodies blockage of either IL-1β or TNFα had therapeutical effects on joint pathology [120]. *Tnf*-deficient mice were also protected from EAE induction [111]. Although neither of these cytokines, alone or together, was sufficient for initiation step of Th17 differentiation, TNFα as well as IL-1β was found to amplify Th17 differentiation *in vitro* [281]. Together with IL-1β, the DC cell-derived TNFα promoted IL-6 plus TGF-β directed Th17 differentiation [196, 281]. TNFα or IL-1β can also indirectly promote Th17 development by induction of IL-6. It is likely that cytokines such as inflammatory environments derived IL-1β and TNFα contribute to Th17 differentiation by generating an inflammatory niche which favors its differentiation. As IL-17 is a strong inducer of both TNFα and IL-1β, it is possible for Th17 cells to interact with local or infiltrated cells to set up a positive feedback loop in such an inflammatory niche.

5.3.1.7 IL-17C

IL-17C was primitively described as a novel IL-17 family cytokine, which shared similar proinflammatory effects with IL-17 [105, 150, 302]. Recently, we and others identified IL-17RE, an orphan receptor of IL-17 receptor family, as the functional receptor for IL-17C [28, 224, 253]. IL-17RE was found to be highly expressed on intestinal epithelial cells and critical for IL-17C-mediated mucosal immunity to pathogen infection or colitis [224, 227, 253] (discussed below). While surprisingly, comparing to other CD4$^+$ T cells, Th17 cells also harbored high level of IL-17RE [28], indicating that IL-17C may also contribute to autoimmune response by targeting Th17 cells. The expression of IL-17RE was induced by IL-6 plus TGF-β and was fully upregulated at the present of IL-23 in T cells [28]. Deficient of its ligand, IL-17C, protected mice from EAE induction [28]. IL-17C bound to its receptor IL-17RE in Th17 cells and induced the expression of IκBζ, a nuclear IkappaB family member, to promote the production of IL-17 and Th17 cell response [28].

5.3.2 Positive Transcription Factors

5.3.2.1 RORγt and RORα

The T-bet, GATA3, and Foxp3 represent the lineage-specific transcription factors for Th1, Th2, and Treg cells, respectively. RORγt (also named as Rorc), a splicing variant of RORγ expressed in T cells [93, 181], was found to be the linage-specific transcription factor for Th17 cells [114]. However, in *Rorc*-deficient mice, the frequencies of Th17 cells were not absent but only reduced, indicating that other transcription factors play redundant role in controlling Th17 fate determination. Another ROR family member, RORα, was subsequently identified as a coordinator factor with RORγt to promote Th17-cell differentiation [307]. The deficiency of both RORγt and RORα completely abolished the generation of Th17 cells both *in vitro* and *in vivo* [307]. Both RORγt and RORα were synergistically induced by IL-6 or IL-21 plus low amounts of TGF-β [102, 307]. However, the mechanisms by which RORγt and RORα regulate IL-17 production have not yet been fully elucidated.

5.3.2.2 STAT3

Both IL-6 and IL-21 activate STAT3 in T cells, indicating a master role of STAT3 in Th17 cell programming. T-cell specific deletion of STAT3 impaired Th17 differentiation [306, 307], while retroviral overexpression of a constitutively active STAT3 in T-cells can enhance IL-17 production [179]. The STAT3 directly controlled expression of RORγt, RORα, and IRF4, which were transcriptional factors required for Th17 differentiation [59]. More importantly, STAT3 also bound

directly to the promoters of IL-17A, IL-17F, IL-21, IL-6R, and IL-23R, indicating a direct control of STAT3 on the Th17 differentiation [31, 59, 203]. Patients with Hyper IgE syndrome (HIES) harbored a dominant negative form of STAT3 which led to a serious impairment of Th17 generation in those patients [49, 99, 166, 185, 186, 226]. The mutation of STAT3 and subsequent impairment of IL-17 production may explain the inefficient cleanup of bacterial and fungal infections in those patients.

5.3.2.3 IRF4

IRF4, a transcription factor which has been shown to be critical for the differentiation of the Th1 and Th2 cells [162, 225], was also found to be essential for the development of Th17 cells. *Irf4*-deficient mice were resistant to EAE induction and its deficient-T cells were unable to induce the expression of RORγt and RORα and consequently could not be differentiated into Th17 cells when those cells were treated with TGF-β plus IL-6 or IL-21 [21, 102], while restitution of RORγt and RORα in those cells could partially compensate for the reducing of IL-17 production [102]. In addition, the expression of Foxp3 was increased in *Irf4*-deficient T cells, suggesting the interplay of the Foxp3 and RORγt balance in Treg /Th17-cell differentiation [21]. IRF-4 was negatively regulated by a binding protein named IBP (IRF-4-binding protein), which is shown to play a regulatory role in Th17-cell differentiation [29]. IBP prevented IRF-4 from binding to the transcriptional elements of *Il17* and *Il21* genes and mice lacking IBP developed arthritis-like syndrome and enhanced Th17 responses [29].

5.3.3 Negative Regulation of Th17 Differentiation

5.3.3.1 STAT5

STAT5 is an essential downstream transcription factor of IL-2 signaling, which is critical for the survival of T cells. Genetic abolishment or antibody neutralization of IL-2 promoted differentiation of the Th17 cells *in vivo* [144]. This inhibition effect of IL-2 on Th17 differentiation was independently of Foxp3 and RORγt [308]. Whereas STAT3 is a critical positive regulator of RORγt and Th17 development, disruption of STAT5 led to increased Th17 cell development, probably due to the loss of IL-2-mediated inhibitory effect [144]. This suppressive effect of STAT5 on the differentiation of Th17 might be due to its competition with STAT3 to bind to the same locus sites encoding *Il17* [308].

5.3.3.2 Gfi1

Gfi1 was highly expressed in Th1 and Th2 cells and its expression was controlled by IFN-γ/STAT1 and IL-4/STAT6 pathways. TGF-β, which is critical for either Th17 or Tregs differentiation, suppressed Gfi1 expression [107]. Over-expression of Gfi1 strongly repressed IL-17A expression in both human EL4 T-cell line and primary T cells. This suppressive effect was mainly due to the blockage of RORγt recruitment to the promoter region of IL-17A. In contrast, *Gfi1*-deficient T cells produced more IL-17A than wild-type T cells under Th17 favored differentiation conditions [107]. However, the influences of Gfi1 on iTregs were not as obvious as on Th17 cells [107].

5.3.3.3 LXR

Liver X receptors (LXRs) are nuclear receptors which are originally involved in cholesterol homeostasis and are activated by endogenous oxysterols or oxidized cholesterol derivatives [323]. Recently, LXR was found as a negative regulator for Th17 differentiation. LXR suppressed Th17 responses by promoting the transcription factors Srebp-1 to bind to the *Il17* promoter region, and thus interfering with the AhR-mediated *Il17* transcription [46]. Over-expression of LXR inhibited mouse Th17 differentiation and *Lxr*-deficiency mice were more susceptive to EAE induction than wild-type mice [46].

5.3.3.4 TCF1

T-cell factor 1 (TCF-1) is a transcription factor to activate canonical Wnt pathway and is crucial for normal T cell development [254]. TCF1 was showed to regulate differentiation and maintenance of memory CD8^{+} cells [329]. Recently, it was also found that TCF1 suppressed IL-17 expression by directly binding to the regulatory region of *Il17* and thereby repressing its transcription [312]. Induction of IL-17 in TCF1 depletion T cells was coupled with up-regulation of RORγt and STAT3 in those cells [168]. Moreover, *Tcf1*-deficient Th17 cells expressed increased levels of IL-7Rα, which potentially enhanced Th17 cell survival [312]. Accordingly, *Tcf1*-deficient mice showed exacerbated EAE phenotype [168, 312]. TCF1 might also repress Th17 responses by induction of Eomes [329].

5.3.3.5 Eomes

Cytotoxic activities of T cells were noticed under controlling of T box transcription factors including T-bet and Eomes through up-regulation of perforin, FasL and granzyme B [63, 223]. Eomes interacted with GATA3 to prevent its binding to IL-5 promoter in memory Th2 cells or functioned together with T-bet to mediate

generation of IFN-γ producing CD8^{+} cells [62, 76, 207]. In Th17 cells, ectopic expression of Eomes inhibited Th17 cell differentiation through directly binding to the promoter region of *Rorc* and *Il17*. Depletion of Eomes expression could substitute for TGF-β in induction of Th17 cell differentiation [108].

5.3.3.6 NFIL3

NFIL3, also called E4BP4, is a transcription factor with basic leucine zipper structure which regulates multiple immune responses [171]. Recently, it was found that this transcription factor suppressed Th17 cell differentiation though directly binding and inhibiting the *Rorc* promoter [313]. More interestingly, NFIL3 was negatively regulated by the transcription factor REV-ERBα, which is critical for circadian clock pathways [187]. Consequently, Th17 lineage frequency varied diurnally and was altered in *Rev-erbα*-deficient mice [313]. Disruption of light cycle elevated intestinal Th17 cell level and increased susceptibility to intestinal inflammatory disorders [313].

5.3.4 Negative Regulation of mTOR in Th17 Differentiation

The mTOR signaling is critical for regulating organism growth and homeostasis [143]. Recently, mTOR signaling is found to represent a crucial regulator of T-cell differentiation [95]. The mTOR signaling pathways have two distinct complexes: mTORC1 and mTORC2. The conditional depletion of Rictor, a key component of mTORC2, impaired the differentiation of Th1, Th2, and Tregs but not Th17 cells [146], while mTORC1 signaling was found to selectively regulate Th17 differentiation [51]. Recently, it was found that IL-1β signaling induced the activation of JNK and mTOR kinases in Th17 cells. IL-1β-induced Th17 proliferation was impaired in *Mtor*-deficient Th17 cells, indicating the critical role of mTOR activation in Th17 development [82]. Meanwhile, the study also found a negative regulator of IL-1β and TLR signaling, named SIGIRR, was induced during Th17 cell development and SIGIRR inhibited Th17 differentiation and expansion by suppression of IL-1β signaling. Comparing to wild-type Th17 cells, *Sigirr*-deficient Th17 cells shown increased IL-1β-induced JNK and mTOR activation [82]. IL-1β-induced mTOR activation was dependent on AKT, which was constitutively suppressed by GSK3α medicated phosphorylation. Thus, GSK3α severed as a brake to prevent over-expansion of Th17 cells. Upon IL-1β stimulation, a kinase IKKi was found to phosphorylate GSK3α and in turn to release the negative regulation of GSK3α on mTOR activation in Th17 cells [81].

5.3.5 MicroRNA in Th17 Differentiation

MicroRNAs (miRNAs) are about 19–24 nucleotide (nt) single-stranded RNA molecules that post-transcriptionally regulate the expression of genes [333]. In mammals, it was suggested that nearly 85% of microRNA-mediated decay of mRNA [83]. More than 600 different microRNAs were expressed in T cells and many of them were critical regulators for the differentiation stage and activation status of different T-cell populations [124]. As helper T-cell subsets are critical for autoimmune pathogenesis and proper host defense responses, the regulation of lineage commitment by microRNAs are studied to a greater extent. T-cell specific deletion of Dicer, a critical enzyme for microRNA biogenesis resulted in reduced T cells proportion in the thymus or periphery lymph tissues [39, 191]. Recent studies also showed that specific miRNAs are involved in regulation of certain types of T help cell development. T-cell deficiency of miR-155 led the activated CD4$^+$ T cells to favorite a Th2 bias under neutral conditions *in vitro* [230, 270]. It is noticed that miR-155 inhibited the function of Th2 transcriptional factor c-Maf to promote the differentiation of Th1 cells [230]. However, the Th1 differentiation was negatively regulated by miR-29. MiR-29 was reported to suppress Th1 differentiation by targeting the Th2 favored transcription factor T-bet and Eomes or the cytokine IFN-γ [167, 247, 255]. Beside to Th1 and Th2 cells, the microRNAs which regulate Th17 cells function have also been identified. A recent study showed that miR-326 targeted Est-1, a negative regulator of Th17 differentiation, to promote Th17 cell expansion and Th17 related autoimmune pathogenesis [56]. Likewise, miR-301a promoted Th17 differentiation by inhibiting PIAS3, which negatively regulated IL-6-IL-23-STAT3 cascades [195]. MiR-155 also enhanced STAT signaling through suppression of SOCS1 and this might explained the depressed Th17 differentiation and ameliorated EAE phenotype in *Mir155*-deficient mice [194, 310]. More recently, miR-21 was showed to promote Th17 differentiation by disrupting Smad-7, a negative regulator for TGF-β signaling. Like MiR-155, *Mir21*-deficient mice also protected from EAE induction [75]. Meanwhile, microRNA let-7a was recently found to be a negative regulator of Th17 differentiation by suppressing IL-6 secretion in a mouse model of Con A-induced hepatitis [320].

5.4 Interplay Between Th17 Cells and Other T Helper Cells

5.4.1 Interplay Between Th17 and Th1, Th2 Cells

The effector T-helper cell subsets was noticed as distinct and terminal differentiated lineages by studies showing that, once naive T cells have been programmed into Th1 or Th2 cells, these polarities could not be reversed even when new polarizing conditions were reintroduced [193]. The discoveries of specific master transcription factors, T-bet for Th1 while GATA3 for Th2 differentiation, had also improved this

lineage model. Furthermore, several studies showed that Th1 and Th2 antagonized each other to favor their own stable terminally differentiated phenotype [53, 198, 266]. As the crosstalk between Th1 and Th2 cells, cross regulation may also exist between Th17 and Th1 or Th2 cells. Either IFN-γ or IL-4 inhibited Th17 differentiation and IL-17 induction [87]. In addition, the IL-12 family cytokine IL-27, which induced T-bet and IL-12Rβ2 expression to promote Th1 responses inhibited Th17 cell differentiation through activation of STAT1 [13, 258]. Loss of T-bet in T cells strongly promoted IL-17 expression in Th17 cells [178, 309]. As discussed above, IL-4 could induce Gfi-1 to favor optimal Th2 cell differentiation [332] and suppressed Th17 or iTreg cells differentiation [331]. Thus, both Th1 and Th2 favored signaling are inhibitors for Th17 development, while the effects of Th17 derived cytokines on Th1 and Th2 differentiation are still need to be addressed.

Th17 cells are distinct T-helper cell subset and are not derived from the Th1 lineage, since those cells lacking T-bet or Stat4 also expressed RORγt and developed into Th17 cells under Th17 polarizing condition [114]. However, under both homeostatic and inflammatory conditions, IFN-γ$^+$IL-17$^+$ cells can be easily detected, suggesting that intricacy is existed between the Th1 and Th17 cell differentiation. *In vitro* polarizing Th17 cells could lose both IL-17 and IL-17F expression when IL-6 and TGF-β stimulation was withdrawn [149]. T cells cultured in Th17 polarizing conditions still failed to keep IL-17 and IL-17F expression and could be converted to Th1 or Th2 cells when those cells were stimulated with IL-12 or IL-4, respectively [147, 149]. *In vitro* polarized Th17 cells failed to keep their IL-17-producing memory when transferred into mice and many of them converted into IFN-γ-producing Th1 cells under a colitis condition [147]. Similar phenomenon was also noticed when Th17 cells were introduced into NOD-SCID mice [15]. In contrast, *in vivo* memory Th17 cells with CD4$^+$CD62L^{low} marker appeared more resistant to conversion [149], suggesting *in vivo* generated Th17 cells are a stable and distinct lineage of T helper cells.

As described above, Th17 cells polarized by TGF-β and IL-6, but without IL-23, were shown to express IL-10 [180]. Since Th17 cells are abundant in the lamina propria of intestine even in steady state, this containment is critical to control over-activated Th17 cells in gut. Upon infection or injury, these Th17 cells can easily become inflammatory Th17 cells when other Th17 polarizing cytokines are released by the local environment, and these cells can also rapidly convert into Th1-like cells for intracellular pathogens cleanup. As Th17-mediated inflammatory responses also cause serious tissue destruction, these pathogenic Th17 cells may be appropriately and timely re-shifted toward protective IL-10-producing Th17 cells when dangerous signals are removed.

5.4.2 Interplay Between Th17 and Treg Cells

TGF-β signaling was essential for formation of immune tolerance, in part due to its capability for induction of peripheral iTreg cells and for maintenance of thymus

derived nTreg cells [30, 152, 175]. However, at lower concentration, TGF-β was also critical for induction of proinflammatory Th17 cells [16, 174, 281]. Mice deficient in TGF-β failed to develop ethier Foxp3$^+$ Treg or Th17 cells and had uncontrolled autoimmune disorders which was caused by aggressive Th1 cells responses [152, 282], indicating a close relationship between Treg and Th17 cell development program in against Th1 differentiation. After TCR ligation, TGF-β could induce both Foxp3 and RORγt expression in CD4$^+$ T cells [328]. These Foxp3$^+$ RORγt$^+$ T cells were found both in murine and human and noticed as a transitional state for Treg and Th17 cells [284, 328]. In small intestine, the Foxp3$^+$ RORγt$^+$ cells produced less IL-17 than Foxp3$^-$RORγt$^+$ cells [328]. In agreeing with this, Foxp3 abolition led to a notable increase in IL-17 production without affecting RORγt expression [70], indicating that Foxp3 may antagonize RORγt function to favor Treg development. Indeed, Foxp3 suppressed Th17 responses by directly interacting with both RORγt and RORα [57, 307, 328]. Foxp3$^-$RORγt$^+$ T cells induced by TGF-β do not produce much IL-17 and have the dual potential to develop into either Treg or Th17 cells depending on the different inflammatory environment. As described, a proinflammatory environment (IL-6, IL-23, IL-1, and IL-21) plus low concentration or TGF-β inhibited Foxp3 function while further enhanced RORγt expression in favor of Th17 differentiation. In contrast, high concentration TGF-β further firmed Foxp3 expression and thus promoted Treg differentiation rather than Th17 cells [328]. This Treg favored shift was further enhanced by IL-2 and retinoic acid (RA) signaling, both of which were suppressors for RORγt but enhancers for Foxp3 expression [41, 144, 190, 261]. As mentioned before, several transcription factors have been noticed to modulate the Foxp3 and RORγt balance during CD4$^+$ T-cell differentiation. Runx1 was found to cooperate with RORγt to promote Th17 cell differentiation [317]. Additionally, in Treg cells, Runx1 and Foxp3 were also indicated to from a complex which was required for inhibition of IL-2 and IFN-γ expression and Treg suppressive activity [209]. Thus, Runx1 is required for governing potential plasticity in Foxp3$^+$ RORγt$^+$ T cells. IRF4 is critical for Th17 cell differentiation and its absence led to increased Foxp3 expression, reduced RORγt expression, and thus loss of IL-17 secretion [21]. Stat3, a transcription factor that was commonly activated by IL-6, IL-21, or IL-23, was also crucial for Th17 cell differentiation by binding to the promoter regions of *Il17* and *Il17f* [31]. These proinflammatory cytokines were found to inhibit TGF-β-induced Foxp3 expression in a Stat3-dependent manner [306, 327].

5.4.3 Epigenetic Regulation Between Th17 and Other T Helper Cells

Epigenetic regulation is critical for controlling gene expression through changing chromatin structure, histone or DNA modifications, and small noncoding RNAs expression and T helper cells are also under control of these regulatory strategies

[8, 184, 290]. Recent studies by using chromatin immunoprecipitation on gene array chips (ChIP-chip) and high-throughput sequencing (ChIP-Seq) found several histone modification and DNA methylation changes accompanying with CD4$^+$ T-cell differentiation. Trimethylation of histone H3 lysine 4 (H3K4me3) was a permissive mark, while H3 lysine 27 (H3K27me3) was a silence mark to be found at the promoters and the enhancers of different subset specific genes [289]. In Th1 cells, H3K4me3 mark was found at the *Ifng* locus while H3K27me3 mark was found at the *Il4* and *Il17* loci. In Th2 cells, however, *Il4* locus was modified with H3K4me3 while *Ifng* and *Il17* loci were modified with H3K27me3. Notably, the gene *Tbx21* and *Gata3* showed a bivalent status in Th2 and Th1 cells respectively, indicating cell lineage interconversion may occur between these two types of cells [133, 289]. However, *Rorc* locus was suppressed in both Th1 and Th2 cells, indicating that these two types of cells can hardly reprogrammed into Th17 cells. Consistent with the high plasticity of Th17 cells, the gene *Tbx21* and *Gata3* all showed a bivalent status in Th17 cells, indicating that Th17 cells can easily transmit into Th1- or Th2-like cells under appropriate conditions [133]. *Tbx21*, *Gata3*, or *Rorc* sites were all found to be bivalent modified in Treg cells, suggesting that, like Th17 subset, Tregs are also highly dynamic cell population. However, nTreg cells derived from thymus and iTreg cells derived from peripheral showed different reprogramming propensity. In iTreg cells, the *Il17* locus was silenced by H3K27me3 modification whereas H3K4me3 was found at the *Rorc* locus, agreeing with the notion that TGF-β induced RORγt expression in T cells, but the differentiation of Th17 cells was inhibited by Foxp3 [289, 328]. However, both H3K4me3 and H3K27me3 bivalently existed at the *Rorc* locus in nTreg cells, allowing for the generation of Foxp3$^+$RORγt$^+$ cells [289]. When nTreg cells were subjected to Th1- or Th17-polarizing culture conditions, a remarkable number of IFN-γ$^+$Foxp3$^+$ or IL-17$^+$Foxp3$^+$ cells appeared without affecting the expression of Foxp3 [289, 300, 305]. However, TGF-β-induced Treg cells easily lost Foxp3 expression and gained IL-17 expression when these cells were cultured in a Th17 cell-favoring condition [305].

5.5 Human Th17 Differentiation

Sooner after the discovery of cytokines and transcription factors that promote mouse Th17 cell differentiation, efforts were made to induce the differentiation of human Th17 cells. As mouse Th17 cells, human Th17 cells also highly expressed the master transcription factors RORC2, the human homologue to RORγ t [7, 291], and forced expression of RORC2 in cord blood derived T helper cells induced IL-17A, IL-17F, and IL-26, but not IL-22 expression [173]. The functional roles of other Th17-related transcription factors in human Th17 cell development are not fully understood. It was reported that transduction of RORA in human cord blood cells led to increased IL-17 expression [173], indicating that this human homologue to RORα also cooperates with RORC2 to induce Th17 cells as in mice. STAT3 was

also found to be important for the development of human Th17 cells. Patients with hyper-IgE sydrome carried dominant negative mutations in STAT3 gene and T cells obtained from these patients fail to develop into Th17 cells *in vitro* due to the lacking of IL-6-induced STAT3 activation and subsequently RORC2 expression [99, 166, 186]. AHR was also expressed in human Th17 cells [280], but it is still not clear whether it contributes to these cells development.

The cytokines required for the differentiation of human Th17 cells appeared similar to mouse Th17 cells, including IL-6, IL-23, IL-1, and IL-21, however, there were some debates on the necessity of TGF-β in human Th17 differentiation [129]. Several studies found that TGF-β was not required for human Th17 cells differentiation [1, 291]. But one study argued that these cells used above were not totally equal to naïve T cells in mouse. Other studies reported that the human naive cord blood T cells were dependent on TGF-β for their differentiation into Th17 cells. TGF-β was required for induction of RORC, but excess TGF-β inhibited its expression and function [173, 283, 303].

Given the complexity of TGF-β for human Th17 differentiation, the requirement of TGF-β in mouse Th17 differentiation has been re-checked. *Tbx21*- and Stat6-deficient T cells could differentiate into Th17 cell when stimulated with IL-6 alone, even in the absence of TGF-β [48], indicating that TGF-β indirectly regulated IL-17 production by inhibition of factors that required for other cell fates [145]. In addition, the IL-23R was induced in the absence of TGF-β, and IL-23 addition could further induce this receptor expression. In addition, the combination of IL-6, IL-23, and IL-1 was sufficient to induce IL-17 production in a TGF-β independent way [74]. Consistently, Th17 cells were also found in the gut of *Tgfb1*-deficient mice [74, 221].

5.6 Th17 Effective Cytokines

5.6.1 IL-17A and IL-17F

5.6.1.1 IL-17 Family Cytokines

Th17 cells secret characteristic cytokines IL-17A (also called IL-17) and IL-17F. IL-17 family also contains other four cytokines IL-17B, IL-17C, IL-17D, and IL-17E (also named IL-25), which are homologous to the fundamental member IL-17A by bioinformatics analysis. The IL-17 family of receptors, which contains IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE, are signal transmembrane receptors with unique structure architecture among the members. All receptor members harbor two fibronectin III-like domains in their extracellular region and a SEF/IL-17R (SEFIR) domain in their intracellular part [68]. IL-17RA (also called IL-17R) has been long known as the receptor of IL-17. However, recent findings indicate that IL-17RA may sever as a common receptor for all IL-17 family cytokines. Other receptors like IL-17RB, IL-17RC, or IL-17RE have been
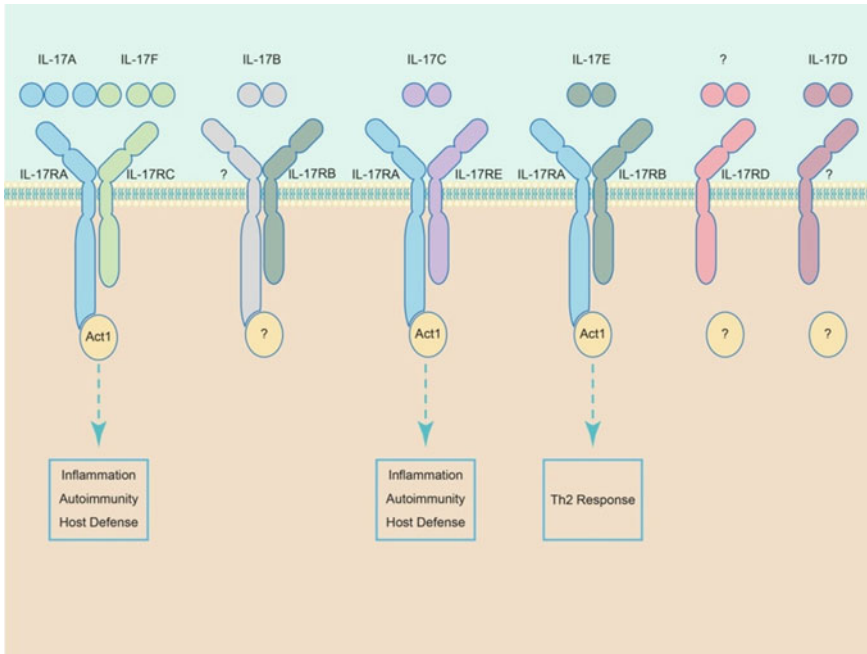
Fig. 5.3 The IL-17 family cytokines and their receptors. IL-17 family cytokines contain six members: IL-17A to IL17F, while the receptor family has five members: IL-17RA to IL-17RE. The most studied members, IL-17A and IL-17F, form homo- or hetero-dimer to bind IL-17RA and IL-17RC receptor complex and activate downstream signaling for host defense, autoimmune diseases and other inflammation responses. Although IL-17B was found as a ligand of IL-17RB, the *in vivo* functional evidences for this pair are still largely unclear. IL-17C binds to IL-17RA and IL-17RE receptor complex to trigger downstream signaling for host defense and autoimmune diseases. IL-17E associated with IL-17RA and IL-17RB receptor complex to mediate Th2 responses. Neither the receptor for IL-17D nor the legend for IL-17RD has been found. The adaptor protein Act1 has been considered as a key adaptor in IL-17A, IL-17F, IL-17C, as well as IL-17E mediated signaling

discovered as specific receptors for IL-17E, IL-17A, as well as IL-17F or IL-17C, respectively. IL-17RD (also called Sef), a negative regulator of FGF signaling, has recently been identified to have a role in IL-17A signaling [182, 231] (Fig. 5.3).

In murine, IL-17F shares the highest homology in amino acid sequence to IL-17 (about 50%), while IL-17B, IL-17C, IL-17D, and IL-17E share 16–30% sequence identity to IL-17 [115]. The high similarity of IL-17 and IL-17F may be responsible for the similar pro-inflammatory outcomes they mediate. IL-17 and IL-17F form homo/hetero-dimer to bind to their receptors, IL-17RA and IL-17RC, and therefore activate NF-κB, MAPKs, and C/EBPs signaling pathways which consequently upregulate the expression of proinflammatory genes [336]. IL-17 also cooperates with other inflammatory cytokines such as TNFα to synergistically induce certain chemokines expression by stabilizing their mRNAs [336]. Recently, we also found

IL-17 enhanced NF-κB activation though an alternative way by downregulating the expression of microRNA-23b in residential cells of several autoimmune diseases [335].

As discussed above, IL-17 and IL-17F are considered to be predominantly produced in the Th17 cells. The differentiation of Th17 cells is controlled by a unique set of cytokines (TGF-β, IL-6, IL-1β, IL-23, and IL-21) and transcription factors (RORγt, RORα, STAT3, IRF4, BATF, AHR, Runx1, and IκBξ). However, beside to Th17 cells, a subset of CD8$^+$ T cells named Tc17 cells can also produce those two cytokines. In addition, several innate immune cells have also been found to release IL-17 and IL-17F. These cells, which include γδT cells, iNKT cells, NK cells, LTi cells, and neutrophils, are noticed as major sources for innate IL-17 and IL-17F. Furthermore, nonlymphoid cells such as intestinal Paneth cells and colonic epithelial cells may also have the capability to produce IL-17 or IL-17F [45, 115]. The rapid releasing of IL-17 or IL-17F by those cells may contribute to appropriate immune responses against many pathogens.

IL-17E (also called IL-25) functions distinctly different from IL-17 and IL-17F. IL-17E promotes Th2 cell responses by inducing the expression of IL-4, IL-5, and IL-13. Il25-transgenic mice or mice treated with ectopic IL-17E showed increased releasing of Th2 factors along with eosinophilia [105, 123, 213, 268]. In contrast, due to reduced Th2 response, Il25-deficient mice displayed impaired Th2 responses, thus were more susceptible to parasite infection but were resistant to allergic responses in lung [11, 64, 212, 268, 322]. Either immune cells (macrophages, dendritic cells, mast cells, eosinophils, basophils, and T cells) or nonimmune cells (epithelial cells and Paneth cells) could release IL-17E under certain conditions. As its producing cells, IL-17E can target diverse cell types such as Th2, Th9, NKT, monocytes, macrophages, non-B non-T (NBNT), and epithelial cells [115]. IL-17E is activated downstream signaling through the IL-17RA and IL-17RB receptor complex [228]. The adaptor protein Act1 was also found to mediate IL-17E signaling [38, 121, 265]. Recently, one study showed that intestinal commercial bacteria induced IL-17E production from intestinal epithelia cells and IL-17E in turn inhibited Th17 expansion by suppression of IL-23 production in macrophages [314]. In addition, Il25-deficient mice were susceptible to EAE induction [126], indicating a negative role of IL-17E in controlling Th17 responses.

Although the biological functions of IL-17B and IL-17D remain largely unknown [252], recent findings have begun to uncover the functional roles of IL-17C. We and others demonstrated that IL-17C was the ligand for the orphan receptor IL-17RE and delivered its signal through IL-17RA and IL-17RE complex [28, 224, 253]. IL-17C is specifically induced in epithelial cells and keratinocytes by pathogens or inflammatory cytokines and acted as an autocrine cytokine on those cells. Similar to IL-17, IL-17C activates common signaling pathways including NF-κB and MAPKs cascades [224, 253]. IL-17C also targeted Th17 cells for promoting IL-17 production [28]. In vivo studies from Il17c- or Il17re-deficient mice demonstrated that this pathway was critical for protection against intestinal pathogens as well as the progression of several autoimmune diseases including psoriasis, IBD and MS [28, 224, 253].

5.6.1.2 IL-17A and IL-17F Medicated Signaling

Positive regulator

Soon after it was cloned from activated murine T lymphocyte hybridoma cDNA library [232], the downstream signaling pathways of IL-17A were revealed. Typically, IL-17A activates NF-κB, MAPKs, and C/EBPs cascades to upregulate expression of inflammatory genes [251]. IL-17A also synergizes with TNFα to induce gene expression through stabilization of TNFα-induced mRNAs [251]. Other studies also found that it can activate JAK-PI3K and JAK-STAT pathways, although detailed downstream molecular mechanisms were still poorly understood [101, 234]. Recently, we found that IL-17A downregulated microRNA-23b to promote inflammatory responses in tissue resident cells [335]. IL-17RA was initially noticed as the receptor for *Il17a-* and *Il17ra*-deficient fibroblasts have no response to IL-17A stimulation [273, 304, 311]. Later, IL-17RC was found as a receptor component for IL-17A signaling by interacting with IL-17RA as well as IL-17A. Deficiency of IL-17RC in mice impaired IL-17A induced downstream gene expression [304]. Thus, upon IL-17A ligation, IL-17RA binds to IL-17RC to form a heterodimeric receptor complex to initiate intracellular signaling pathways. The receptor proximal signaling mechanisms have been uncovered recently (Fig. 5.4).

TRAF6 was firstly found as a positive adaptor in IL-17A signaling, and it was essential for IL-17A-induced activation of NF-κB and JNK pathways and expression of downstream genes such as IL-6 [240]. However, the intercellular region of IL-17RA did not contain any predicted TRAF6 binding motif and TRAF6 was found not responsible for IL-17A-induced mRNA stabilization pathway, suggesting that additional adaptors upstream of TRAF6 might exist for both TRAF6 dependent or independent pathways [89].

By bioinformatic searching, all IL-17R family receptors were found to harbor an intracellular SEFs and IL-17Rs (SEFIR) domain. Furthermore, this SEFIR domain structure also was also noticed in a cytosolic protein called Act1 (also known as CIKS) [202]. After IL-17 stimulation, IL-17R recruited Act1 to its intracellular region through SEFIR-SEFIR domain interaction [27, 220]. Act1 then recruited TRAF6 to IL-17R complex. Act1 was not only a simple adaptor for downstream molecules recruitment, but also was noticed as a U-box like E3 ligase, which mediated Lys63-linked ubiquitination of TRAF6 through recruitment of the Ubc13-Uev1A E2 complex [157]. We recently found that IL-17A downregulated the expression of microRNA-23b (miR-23b) through NF-κB pathway and subsequently releasing its suppression effect on TAB2 and TAB3 to further amplify NF-κB activation [335]. Thus, IL-17A can trigger a positive feedback loop through removing the suppression of miR-23b on NF-κB activation. Since the SEFIR domains are required for the interaction between Act1 and IL-17R, a detailed domain mapping study found that SEFIR domains contain a CC' loop structure and this structure was responsible for the interaction of adaptor and receptor [158]. A mimicking decoy peptide of Act1 CC' loop inhibited IL-17 induced inflammatory responses [158]. Though the SEFIR domain is important for IL-17A signaling
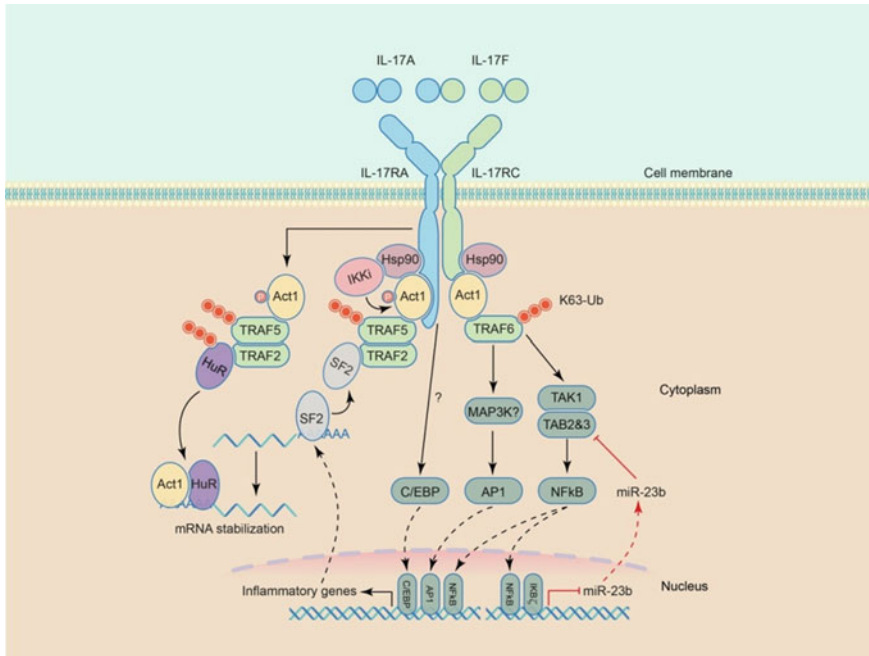
Fig. 5.4 The activation of IL-17 signaling. After IL-17A or IL-17F binding to the receptors, Act1 is recruited to the IL-17RA and IL-17RC receptor complex. Act1 then recruits and poly-ubiquitinates TRAF6 for the activation of NF-κB and JNK pathways. IL-17A-induced NF-κB signaling also suppresses the miR-23b expression and therefore releases its inhibition on TAB2 and TAB3 complex to amplify NF-κB activation. Act1 is also critical for IL-17A induced activation of C/EBP pathway. In addition, Act1 also recruits TRAF2 and TRAF5 to mediate mRNA stabilization pathway. Normally SF2 is bound to certain mRNAs for their degradation. Upon IL-17A challenging, Act1/TRAF5/TRAF2 complex recruits SF2 form mRNA and thus protect them from degradation. The phosphorylation of Act1 at Ser-311 by the kinase IKKi is crucial for the interaction of Act1 with TRAF2 or TRAF5. Meanwhile, Act1 also recruits and ubiquitinates an ARE-binding protein HuR through TARF2 and TRAF5. Act1/HuR complex then bind to the SF2 free mRNA to stabilize them. Hsp90 has been shown to be required for IL-17A signaling by promoting the function of Act1

transduction and inflammatory gene production, other studies also found that, beside to SEFIR domain, the C-terminal region and "TIR-like loop" (TILL) motif of IL-17RA, the cytoplasmic tail region of IL-17RC and the N-terminal domain of Act1, were also critical for IL-17A-mediated signaling [98, 170, 208, 248].

Act1 but not TRAF6 was required for IL-17A-mediated mRNA stabilization of KC induced by TNFα [89], indicating that Act1 mediates either TRAF6 dependent or independent pathways for IL-17A signaling. Recently, the inducible kinase IKKi (also called IKKε) was found for the Act1-mediated mRNA stabilization pathway. IKKi was showed to bind to Act1 upon IL-17 stimulation in mouse fibroblasts. Deficiency of IKKi in airway epithelial cells did not influence IL-17 induced NF-κB activation, but largely impaired IL-17-mediated KC mRNA stabilization in those

cells [22]. IKKi directly phosphorylated Act1 at residue Ser-311 after IL-17A stimulation and the phosphorylation of this site was critical for IL-17A-mediated mRNA stabilization of KC but not for NF-κB activation [22]. Another study showed that The Ser-311 phosphorylation of Act1 was required for recruiting TRAF2 and TRAF5 to generate an Act1-TRAF2-TRAF5 complex. IL-17A induced formation of Act1-TRAF2/TRAF5 complex further recruit mRNA splicing factor 2 (SF2) to prevent its binding and cleavaging of KC mRNA [262]. Besides, Act1 also recruited and ubiquitinated an ARE-binding protein HuR to stabilize the mRNA which released from SF2 [96]. More importantly, deficiency of HuR in epithelium resulted in impaired IL-17A-mediated inflammation in lung, agreeing with the essential role of Act1 in epithelium of lung [96]. More recently, upon IL-17A exposure, heat shock protein 90 (Hsp90) was found to be associated with Act1 and this interaction was critical for the binding of Act1 with other signaling molecules [285]. Inhibitors of Hsp90 prevented the signaling complex formation and in turn inhibited the activation of downstream signaling pathways [285]. Interestingly, Hsp90 lost a psoriasis associated Act1 mutant D10N [60, 104, 256] and this mutation failed to activate downstream signaling mediated by IL-17A [285]. To date, Act1 cooperates with Hsp90 to generate a receptor proximal anchor platform to assemble two distinct IL-17A-mediated cascades: (1) TRAF6-dependent pathway and (2) IKKi-TRAF2-TRAF5-dependent pathway.

IL-17F shares the same receptor set IL-17RA-IL-17RC with IL-17A for downstream signaling. Surface plasmon resonance (SPR) analysis found that human IL-17RA had a higher binding affinity to human IL-17A while human IL-17RC preferred to bind to human IL-17F [138, 295]. Although the binding affinities of those two cytokines are different, they mediated inflammatory responses completely required either IL-17RA or IL-17RC [98, 100, 273, 295, 304], suggesting their mediated downstream signaling all through the IL-17RA and IL-17RC heterodimer complex. Similar to IL-17A, IL-17F also needed Act1 and TRAF6 for downstream signaling [304] and induced NF-κB, MAPKs, and C/EBP activation in different cell types [122, 304, 330].

Negative regulator

As IL-17A exhibits a broad influence on driving inflammatory responses, its signaling is under strict control to prevent harmful persistent inflammation (Fig. 5.5). One early study found that IL-17A activated the kinases GSK-3β and ERK to phosphorylate C/EBPβ at Thr188 and Thr179 in its regulatory 2 domain, and this dual-phosphorylation in turn inhibited IL-17A induced expression of proinflammatory genes [245].

TRAF3 was a critical adaptor for TLRs and RIG-I induced type I interferon production in antiviral responses or was a negative regulator for CD40 or BAFF induced noncanonical NF-κB activation [33, 85, 92, 131, 204, 276, 299]. We recently identified that TRAF3 was an important negative regulator for IL-17A signaling [334]. Forced expression of TRAF3 in cells prevented IL-17A-mediated signaling activation and downstream cytokine production, while silencing of TRAF3 enhanced the activation of NF-κB and MAPKs pathways as well as expression of downstream genes. TRAF3 was found to directly bind to IL-17R for
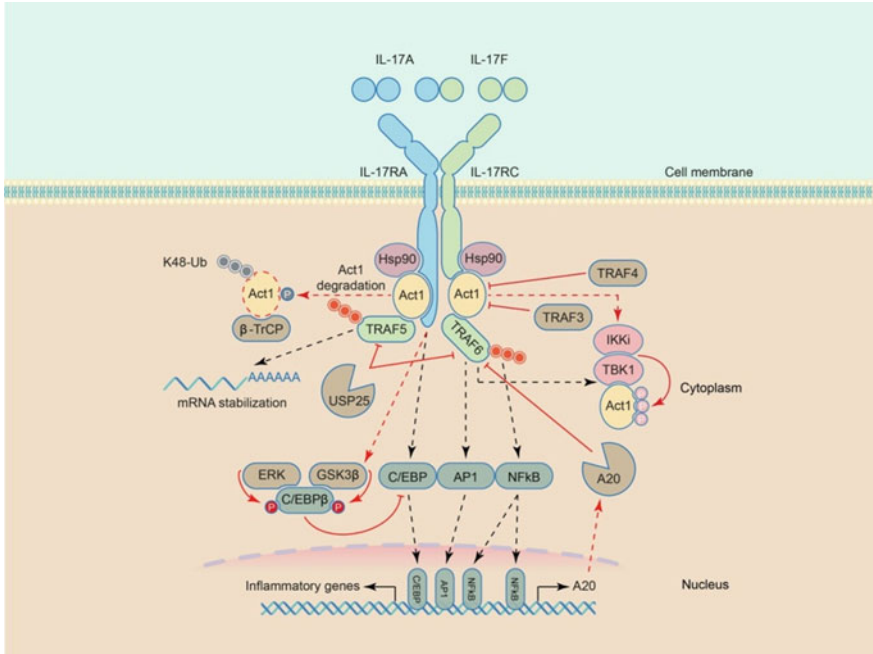
Fig. 5.5 The regulation of IL-17 signaling. Once IL-17 signaling is activated, several mechanisms are adopted to prevent over activation of the signaling. Upon activation, TRAF3 is recruited to IL-17RA and IL-17RC complex to interfere the formation of IL-17R/Act1/TRAF6 signaling complex, while TRAF4 binds to Act1 to disrupt the Act1/TRAF6 signaling complex formation. Although IKKi is required for IL-17A mediated mRNA stabilization pathway, IKKi and TBK1 also triple-phosphorylate Act1 to disrupt the interaction between Act1 and TRAF6 to suppress activation of NF-κB in a TRAF6-dependent negative feedback manner. IL-17A also activates ERK and GSK3β to phosphorylate C/EBPβ and thus suppresses C/EBP activation. USP25, a deubiquitinase, directly removes both TRAF5 and TRAF6 ubiquitination to inhibit IL-17-induced signaling. Another deubiquitinase A20 specifically removes the ubiquitination of TRAF6 to suppress IL-17-mediated NF-κB activation. With persistent IL-17A exposure, Act1 is phosphorylated and then ubiquitinated and degraded by SCF$^{β-TrCP}$ E3 ubiquitin ligase complex, therefore avoiding over activation of the signaling

disrupting the interaction complex of IL-17R, Act1, and TRAF6, thus suppressed IL-17 signaling activity. Transgenic TRAF3 in mice inhibited the IL-17 induced inflammatory responses and subsequently controlled EAE progression [100]. Thus, TRAF3 was identified as the first receptor proximal negative regulator of IL-17A signaling.

Similar to TRAF3, TRAF4 was lately identified to negatively control IL-17A signaling. Upon IL-17A treatment, deficiency of TRAF4 in cells led to remarkable exacerbated activation of IL-17A signaling and increased expression of chemokines. Genetic depletion of TRAF4 caused earlier onset of Th17 cell induced EAE

pathogenesis. TRAF4 suppressed IL-17A signaling by disruption the binding between Act1 and TRAF6 [316]. Therefore, in an alternative way, TRAF4 also interferes with the formation of positive signaling complex for controlling IL-17A signaling.

Ubiquitin-proteasome pathway mediated Protein degradation is a widely used strategy to desensitized specific signaling by erasing key signaling adaptors [197]. We recently found that Act1 protein level significant decreased upon IL-17A persistent stimulation, without affecting its mRNA level. Mechanically, Act1 was degraded in a Lys48-linked polyubiquitination manner by the $SCF^{\beta\text{-}TrCP\text{-}1/2}$ E3 ubiquitin ligase complex, which was the same for degradation of the inhibitor of nuclear factorκBα (IκBα), indicating that both negative and positive signaling events of IL-17 is controlled by the same degradation complex [246]. The degradation of Act1 eventually led to dismissing of downstream pathway activation and consequently desensitized cells to IL-17 exposure.

As described, IKKi phosphorylated Act1 at Ser-311 for IL-17A-mediated mRNA stabilization pathway [22]. Recently, we also found that both IKK-related kinases IKKi and TBK1 were recruited to Act1 upon IL-17A stimulation [222]. Both kinases phosphorylated Act1 on three serine sites different from Ser-311 and phosphorylation of those sites interfered with the association of Act1 with TRAF6 and subsequently suppressed IL-17A induced NF-κB activation. Notably, TRAF6 itself was needed for the activation of TBK1 and Act1 [222]. Therefore, in addition to its positive role in IL-17A signaling by phosphoryting Act1 at Ser-311, IKKi also displayed a redundant role with TBK1 though phosphorylation of Act1 on other Serine sites to control the signaling.

Since Act1 is an E3 ligase for TRAF6 to promote the signaling of IL-17A, the deubiquitinating enzyme (DUB) for negative regulation may exist. Recently, the ubiquitin-specific protease USP25 was found as a negative regulator of IL-17A signaling [326]. Overexpression of this deubiquitinating enzyme inhibited IL-17A induced downstream signaling. By contrast, deficiency of USP25 in MEFs or primary lung epithelial cells led to enhanced IL-17A-mediated responses [326]. Genetic depletion of USP25 in mice consequently enhanced IL-17A induced respiratory inflammation and exacerbated EAE induction [326]. USP25 was found to directly remove TRAF5 and TRAF6 ubiquitination induced by IL-17A and subsequently erase the signals for both TRAF6 dependent and independent pathways [326]. More recently, A20, another deubiquitinating enzyme, was identified as a negative regulator of IL-17A induced NF-κB and MAPK activation [69]. Notably, A20 itself was induced by IL-17A exposure and in turn formed a negative feedback control for IL-17A signaling. Deficiency of A20 in cells led to exacerbated IL-17A induced inflammatory gene expression [69]. Mechanically, IL-17R signaling directly recruited A20 to the distal domain of the receptor and therefore erased the ubiquitination of TRAF6 and also the activation of TRAF6 dependent cascades [69].

5.6.2 Th17 Effector Cytokines in Inflammatory Diseases

5.6.2.1 Th17 Effector Cytokines in Host Defense Against Infection

Th17 cells are found to be critical for host defense responses by releasing its effector cytokines IL-17A, IL-17F, and IL-22. The secreted IL-17A, IL-17F, or IL-22 in turn induces expression of host defense molecules in epithelial cells or keratinocytes to protect host from specific pathogens. Deficiency of IL-17A and IL-17F in mice caused increased susceptibility to the infection of extracellular pathogens, including *Klebsiella pneumonia*, *Citrobacter rodentium*, and *Staphylococcus aureus* [10, 110]. It was found that, an intestinal commensal bacterium, segmented filamentous bacteria (SFB), preferentially induced gut Th17 differentiation in steady state. Mice without SFB led to reduced Th17 proportion in intestine and were more susceptible to *Citrobacter rodentium* infection [113]. However, another study demonstrated that it was *Il22*-deficient mice but not *Il17rc* (a specific receptor for IL-17A and IL-17F)-deficient mice were susceptible to the infection [325]. IL-22 is a critical cytokine for mucosal immunity. It could directly promote epithelia proliferation to keep the epithelia barrier integrity during the infection of pathogens. IL-22 also acted alone or in synergy with other cytokines, such as IL-17A, IL-17F, IL-17C, or TNFα, to induce the expression of antimicrobial proteins such as S100A-proteins, β-defensins, or RegIII family proteins in host defense responses [10, 155, 253, 293, 294, 325]. In addition, IL-22 also induced the expression of multiple mucus proteins in globet cells, which are important for mucosal damage protection [260]. Furthermore, as IL-17A and IL-17F, this cytokine also stimulated the production of numerous inflammatory chemokines and cytokines production during infection [10, 155, 293]. Upon *Klebsiella pneumoniae* infection, neutralizing IL-22 led to remarkable bacterial dissemination in the lung and spleen [10]. Comparing with wild-type mice, the survival rate of infected animals treated with anti-IL-22 decreased significantly [10]. In this study, Th17 derived IL-22 acted in synergy with IL-17 to promote lung epithelia proliferation. The combination of IL-22 with IL-17 also induced several pro-inflammatory cytokines and chemokines or antimicrobial peptides expression in lung epithelial cells [10]. Another study also found that, comparing with wild-type mice, *Il22*-deficient mice died quickly after *Klebsiella pneumoniae* infection [301]. As described above, after *Citrobacter rodentium* infection, deficiency of IL-22 in mice led to increased intestinal damage, bacterial load and mortality [325].

In addition to extracellular pathogens, IL-17A or IL-22 also protected mice from intracellular bacterial and fungal infection. Upon *Francisella tularensis* infection, either neutralization or genetic depletion of IL-17A increased the bacterial burden in mice [156]. It was found that IL-17A, but not IL-17F or IL-22, was responsible for IL-12 production from dendritic cells and promoted Th1 activity during the infection [156]. IL-22, however, was found to protect *Il12p35*-deficient mice from liver necrosis upon *Salmonella enterica* serovar Enteritidis infection. Neutralization of IL-22 in *Il12p35*-deficient mice led to increased cell necrosis in the *Salmonella*

enterica serovar Enteritidis infected liver, indicating a protective role of IL-22 against this pathogen [239]. Th17 differentiation was strongly induced by an oral opportunistic fungus, *Candida albicans* [233]. Deficiency of IL-17A, but not IL-17F in mice, remarkably increased the susceptibility to oral candidiasis, indicating that IL-17A is critical against this pathogen-mediated pathogenesis [233]. In addition, in *Il17ra*-deficient mice, without IL-17A and IL-17F signaling, neutralization of IL-22 in mice increased *Candida albicans* burden in stomach [50]. Similarly, increased fungal burden in the kidney and stomach was found in *Il22*-deficient mice when these mice were intravenously infected with *Candida albicans* [50]. Mice intragastrically infected with *C. albicans* showed upregulated IL-22 in the stomach while several antimicrobial peptides such as S100A8, S100A9, Reg-IIIβ, and RegIIIγ were all decreased in *Il22*-deficient mice in this model [50], indicating that IL-22 protects against pathogen infections through inducing antibacterial genes in the epithelium.

5.6.2.2 Th17 Effector Cytokines in Autoimmune Diseases

Autoimmune diseases, such as MS and RA, have long been noticed as Th1, Th2, or B cells related diseases. Recently growing evidences showed that the Th17 subset and its unique cytokines IL-17A, IL-17F, and IL-22 display board effects on the pathogenesis of MS and RA as well as many other autoimmune diseases including inflammatory bowel disease, psoriasis, systemic lupus erythematosus, and type 1 diabetes mellitus [336].

MS is a central nervous system autoimmune disease characterized with loss of protective myelin sheaths around the brain and spinal cord axons. It was found that the expression of IL-17A as well as its producing T cells was highly elevated in the brain lesion regions of MS patients [161, 277]. Deficiency of IL-23p19, a specific cytokine subunit critical for Th17 cell differentiation, protected mice from EAE [142]. Genetic depletion of either IL-17A or its specific receptor IL-17RC suppressed the induction of EAE in mice [100, 127, 304]. However, it was found that IL-17F was not required for the initiation stage of EAE but the later stage of this disease seems decreased in *Il17f*-deficient mice [304]. One study identified that *Il22ra2* is a MS risk gene [18]. However, another study showed that *Il22*-deficient mice were still susceptible to EAE induction, suggesting that IL-22 appears not required for EAE [134].

RA is a systemic autoimmune disease which is characterized by symmetric inflammation that causes progressive joint cartilage destruction. Comparing with healthy volunteers and osteoarthritis patients, patients with RA showed remarkable increased IL-17A level in their rheumatoid synovium [130, 337]. In experimental murine models of RA, neutralizing of IL-17A ameliorated, while forced expression of IL-17A aggravated diseases progression [163, 164]. *Il17a*-deficient mice were protected from either collagen induced arthritis (CIA) or spontaneous autoimmune arthritis developed in *Il1rn*-deficient mice [110, 196]. The contribution of IL-17F to the arthritis pathogenesis was found to be extremely limited [110]. Increased IL-22

in serum was also found in human patients of RA, and its expression level was shown to correlate with disease activity [47]. In the CIA model, IL-22 level was increased and deficiency of IL-22 protected mice from CIA induction [71]. Blockade of IL-22 in *Il1rn*-deficient mice significantly reduced the inflammation and bone erosion [176]. However, another study revealed that mice treated with IL-22 prior to the onset of CIA had delayed progression of CIA and neutralization of IL-10 abrogated IL-22 protective effect [236]. These studies indicated that the role of IL-22 in RA still needs to be further characterized.

Inflammatory bowel diseases (IBD) is a chronic autoimmune intestinal inflammatory disease, which is caused by abnormal innate or/and adaptive immune responses. IBD can be classified into two major types, Crohn disease (CD) and ulcerative colitis (UC). IL-17A level was found to be upregulated in either CD or UC patients specimens [66, 259]. The expression of IL-17F was also higher in CD patients compared with UC patients [241]. Genome-wide association study (GWAS) data also identified IL-23R, STAT3, CCR6, as well as Act1, which were either critical for Th17 differentiation or IL-17 signaling, were IBD-associated genes [12, 37, 58, 286]. However, in murine models of IBD, the roles of IL-17A were still controversial. Antibody blockage of IL-17A or genetic depletion of IL-17A in mice caused exacerbated dextran sodium sulfate (DSS) induced colitis, indicating that IL-17A has a protective role of in this model [205, 304]. In contrast, comparing with wild-type mice, *Il17a*-deficient mice were protected from DSS induced colitis in another study [112]. The inconformity of those studies may largely due to the differences of gut microbiota among different facilities. In a parallel study of IL-17A, IL-17F was identified to enhance the inflammation of intestine as *Il17f*-deficient mice were protected from colitis induced by DSS [304]. Increased IL-22 expression has also been found in IBD patients [6, 20] and its serum level was correlated with disease severity [237]. The expression of its receptor IL22RA1 was also increased in UC patients tissues [117, 242]. Both antibody blockade of IL-22 function and genetic depletion of IL-22 or STAT3 in mice led to increased severe colitis, body weight loss and histological score, indicating IL-22 has a protective function in this model [218, 260, 315]. By contrast, IL-22 gene delivery reduced local intestine inflammation and induced the expression of mucus-associated proteins from goblet cells [260].

Psoriasis is a chronic skin immune disorder characterized by hyperplasia of dermis which is probably due to dysregulated interaction between immune cells and keratinocytes. Both IL-17A and IL-17F were remarkably upregulated in psoriatic skin biopsies from psoriasis patients [118, 119, 291]. As GWAS studies in IBD, similar approach also identified *Act1* and *Il23r* as psoriasis-associated genes in psoriasis specimens [23, 60, 104, 256]. In mice, skin intradermal delivery of IL-23 could cause a psoriasis-like symptoms and the skin hyperplasia was meliorated in either *Il17a*- or *Il22*-deficient mice [229]. IL-17A cooperated with other cytokines like TNFα, IFN-γ, or IL-22 to induce the expression of inflammatory genes and antibacterial molecules in human keratinocytes [4, 34, 86, 155, 269]. IL-22 has also been found as a critical mediator in the psoriatic pathology. Increased serum IL-22 level was found in psoriatic patients and showed correlation with the disease

severity [294]. IL-22-transgenic mice had acanthosis and hypogranularity symptoms which resembles psoriasis. These mice were born with stiff and shiny skin and then died quickly after broth [292]. Consistently, IL-23-mediated dermal inflammation was decreased in *Il22*-deficient mice [324]. Similarly, in an autoimmune psoriasis model, neutralization of IL-22 in wild-type mice showed either no development or very mild development of the disease [278]. Like IL-17A, IL-22 also could synergize with several other cytokines to promote the progression of psoriasis [211].

IL-17A is also found to be involved in the pathogenesis of other autoimmune diseases like SLE and T1DM. It was noticed that IL-17A was highly expressed in both SLE patients-derived double negative (DN) T cells and MRL/lpr mice [43, 321]. In a mouse model of SLE, comparing with *Fcgr2b*-deficient mice, recent study identified that *Il17a* and *Fcgr2b*-double deficient mice were resistance to the development of lupus [219]. IL-17A could activate inflammatory genes and auto-antibodies production in peripheral blood mononuclear cells (PBMC) isolated from lupus patients [55]. These studies suggest that IL-17 is critical for the pathogenesis of SLE. Although the function of IL-17A in human T1DM progression remains unclear, in murine model of T1DM, IL-17A was noticed to aggravate autoimmune diabetes progression. Antibody blockage of IL-17A ameliorated autoimmune diabetes pathogenesis in non-obese diabetic (NOD) mice [61]. However, deficiency of IL-17A in NOD mice led to comparable hyperglycemia when compared with control NOD mice [127]. It was also noticed that plasma IL-22 levels decreased and correlated with disease severity in SLE patients [32]. However, the role of IL-22 in lupus still needs to be further studied.

As IL-17A signaling is critical for mutiple autoimmune diseases progression, the usage of blocking antibodies against IL-17 or IL-17RA to treat different autoimmune diseases such as RA or psoriasis has shown promising outcomes in clinical trials [72, 73, 103, 214]. Two humanized IL-17A antibodies, AIN457 and LY2439821, were in phase II trials for RA, MS, and psoriasis therapy and were shown no strong adverse safety concerns [73, 103]. A fully human monoclonal antibody to IL-17RA, Brodalumab, was developed to block IL-17R-mediated signaling and was undergoing in phase II trials for psoriasis and RA [214]. As IL-17RA is a common receptor subunit shared by other members of IL-17 family, the strategy for targeting IL-17RC, which is also critical for IL-17A-mediated signaling, maybe more specific.

5.6.3 Th17 Effector Cytokines in Allergy

Allergic diseases such as allergic asthma and atopic dermatitis (AD) are common chronic inflammatory diseases, which are characterized by infiltration of eosinophil, mast cells, and T cells. It was found that both IL-17A and IL-17F were remarkably

increased in bronchial specimens from asthma patients [3, 54, 188]. Enforced expression of both IL-17A and IL-17F led to increased infiltration of neutrophil, but no eosinophil in lung [105, 304]. In OVA-induced airway allergic model, IL-17A was noticed to promote while IL-17F suppressed the allergic responses [110, 196, 304]. However, IL-17F was also showed not required for OVA induced neutrophilia in lung [110]. It was found that host dust mite induced airway inflammation was also dependent on IL-17A [139]. More recently, IL-17A, but not IL-17F, was found to promote airway hyper-responsiveness by directly enhancing the contraction of airway smooth muscle [137]. However, IL-22 has been found to play a protective role in allergic diseases. Increased IL-22 expression was found in both atopic dermatitis (AD) patients and asthmatic patients [201, 217]. In a mouse asthma model, neutralization of IL-22 increased the eosinophil recruitment into the lung [267]. One group showed that IL-22 inhibited antigen-induced airway inflammation by decreasing IL-25 production in lung epithelia cell [267]. Another group showed that IL-22 attenuated allergic responses by inhibiting DC functions [238].

5.6.4 Th17 Effector Cytokines in Cancer

Th17 cells had been implicated to associate with cancer development in human, although its roles in tumor progression are still in controversy between different studies. In hepatocellular carcinoma or colorectal cancer specimens, patients characterizing with high level of IL-17A expression correlated with a poor prognosis [272, 319]. By contrast, patients with ovarian cancer had poor prognosis when the infiltrated IL-17A producing cells numbers and IL-17A expression level were low [135], indicating that the influences of IL-17A on tumorigenesis are largely dependent on the type and stage of tumors.

Several studies by using *Il17a*-deficient mice implicated that IL-17A mainly has a pro-tumorigenic role among different tumor models. Subcutaneous transplantation of bladder carcinoma cell line MB49 or melanoma cell line B16 in *Il17a*-deficient mice led to delayed growth rate of those cells [287]. In either spontaneous or chemical-induced colon cancer models, disruption of IL-17A in mice caused reduced intestinal tumor development in those mice [26, 106]. More recently, it was noticed that either *Il23p19-* or its receptor deficient mice on an *Apc*-CRC background displayed reduced tumorigenesis in intestine, agreeing with the early studies with *Il17a*-deficient mice [80]. Enterotoxigenic *Bacteroides fragilis* (ETBF), an intestinal commensal bacteria, was found to promote intestinal tumorigenesis in *Apc*$^{min/+}$ mice through promoting Th17 responses [297]. As described, this hematopoietic IL-23-Th17-IL-17A axis was found to mediate microbiota-driven tumor growth. However, we also found that IL-17C contributed to this process in a different way. Unlike IL-17A, which was produced by Th17 cells, IL-17C was specifically secreted by IECs [250]. Furthermore, IL-23 and IL-17A were shown to

be critical for tumor cell growth but not survival during intestinal tumorigenesis [80, 250]. By contrast, IL-17C signaling was critical for IEC survival but not proliferation during the early stage of intestinal tumorigenesis [250]. Although IL-17C has been reported to promote Th17 differentiation [28], we found that the intestinal local resident cells rather than infiltrated hematopoietic cells such as Th17 were critical for IL-17C-mediated tumorigenesis, suggesting that IL-17C-mediated IEC survival instead of Th17 cell differentiation is critical for promoting intestinal tumorigenesis [250]. Both IL-17A and IL-23 were also found to promote other cancers such as cutaneous chemical carcinogenesis, as *Il17a*-, *Il17ra*-, or *Il23p19*-deficient mice developed remarkably decreased skin tumors [91, 141, 288].

As mentioned above, Th17 cells were also correlated with ameliorated prognosis in some studies. Similarly, in some mouse models, those IL-17A producing cells were also found to suppress tumor progression. One study showed that Th17 transplantation inhibited tumor growth through the activation of anti-tumor CD8^{+} cells [177]. Although there were studies showed that IL-17A enhanced tumor metastasis by showing that deficiency of IL-17A in mice reduced lung metastasis [24, 154, 287], other studies found controversial results by showing that IL-17A ablation led to increased lung metastasis [136, 177]. Thus, it is likely that the pro- or anti-tumor property of IL-17A is mainly dependent on the different tumor types and stages. The role of IL-17F in tumor development remains unclear. Similar to IL-17A, IL-17F was noticed to be critical for intestinal tumorigenesis in $Apc^{min/+}$ mice [25]. By contrast, IL-17F played a protective role in in chemical induced colon cancer model [271].

5.7 Conclusion and Perspective

The discovery of Th17 cells as a distinct T helper cell subset refreshes our understanding of both adaptive immunity and its related immune disorders. Th17 effector cytokines, IL-17A, IL-17F, and IL-22, show unique proinflammatory properties comparing to the typical cytokines of either Th1 or Th2 subsets. Recent progresses of Th17 differentiation and plasticity also expand our knowledge about T-cell development and complexity between different subpopulations. Recent advances in uncovering the molecular mechanisms of signal transduction of Th17 cytokines IL-17A, IL-17F, and IL-22, coupling with largely expanded understanding of their roles in human inflammatory diseases as well as in the relevant mouse models, provide great opportunities to develop new targets and therapeutic strategies. Further investigation of the programs of Th17 differentiation and the signaling mediated by Th17 effector cytokines will benefit for the understanding and therapy of human inflammatory diseases.

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