Published in final edited form as:
Cytokine. 2013 November ; 64(2): . doi:10.1016/j.cyto.2013.07.022.

IL-17 family: cytokines, receptors and signaling

Chunfang Gu[1], **Ling Wu**[1,2], and **Xiaoxia Li**[1]

[1]Department of Immunology, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio, USA

[2]Department of Pathology, Case Western Reserve University, School of Medicine, Cleveland, Ohio, USA

Abstract

The interleukin 17 (IL-17) family, a subset of cytokines consisting of IL-17A-F, plays crucial roles in host defense against microbial organisms and in the development of inflammatory diseases. Although IL-17A is the signature cytokine produced by T helper 17 (Th17) cells, IL-17A and other IL-17 family cytokines have multiple sources ranging from immune cells to non-immune cells. The IL-17 family signals via their correspondent receptors and activates downstream pathways that include NFκB, MAPKs and C/EBPs to induce the expression of anti-microbial peptides, cytokines and chemokines. The proximal adaptor Act1 is a common mediator during the signaling of all IL-17 cytokines so far and is thus involved in IL-17 mediated host defense and IL-17-driven autoimmune conditions. This review will give an overview and recent updates on the IL-17family, the activation and regulation of IL-17 signaling as well as diseases associated with this cytokine family

Keywords

interleukin 17; IL-17R; signaling transduction; Act1

1. Introduction

The interleukin-17 (IL-17) family consists of a subset of cytokines that participate in both acute and chronic inflammatory responses. Since the discovery of IL-17A (also called IL-17 or CTLA8) in 1993, five other members of this family IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F have been identified based on amino acid sequence homology [1–6]. While some are well characterized, others have remained understudied.

The most widely investigated cytokine of this family, IL-17A, is a pro-inflammatory cytokine that plays an essential role in host defense against microbial infections and is implicated in various inflammatory conditions such as autoimmune diseases, metabolic disorders, and cancer [7–16]. Through the production of a variety of molecules including cytokines, chemokines, acute phase proteins, anti-microbial peptides, mucins, and matrix

Correspondence should be addressed to Dr. Xiaoxia Li, 9500 Euclid Avenue, Cleveland, OH 44195, USA, Lix@ccf.org, Phone: +01 (216) 445-8706, Fax: +01 (216) 444-9329.

The authors have no conflicting financial interests.

metalloproteinases [17, 18], IL-17A can propagate cascades of events that lead to neutrophil recruitment, inflammation and host defense. Pathological production of IL-17A leads to excessive inflammation and overt tissue damage. It has received considerable attention upon the discovery of a subset of helper CD4+ T cells that is distinct from the classical T helper 1 (Th1) and T helper 2 (Th2) lineages, which produce IFN-γ and IL-4respectively. This T helper 17 (Th17) lineage produces IL-17A as a signature cytokine and plays a pathological role in inflammatory and autoimmune diseases. Differentiation of naïve CD4+ T cells to Th17 cells is triggered and tightly controlled by a set of cytokines that include IL-6, IL-1β, IL-21, IL-23, and TGFβ, which leads to the activation of RORγt to enable Th17 programming [19]. Overabundance of these cytokines is associated with pathological conditions.

Though Th17 cells were thought as a major source of IL-17A, IL-17A can also be produced by other cell types, the most prominent of which are the innate immune cell populations [20]. IL-17 producing innate immune cells mediate the rapid release of IL-17A in response to pathogens or tissue injury [20–22]. For example, γδ T cells express pattern recognition receptors (PRRs) such as dectin-1 and Toll-like receptor 2 (TLR2), which allow for rapid IL-17 production in response to bacteria encounter [22–25]. LTi cells, key components of the machinery required for the construction of the lymphoid structures, produce IL-17A rapidly after challenge with the yeast cell wall product zymosan [26]. IL-17A is also produced by a subset of CD8+ T cells, known as Tc17 cells which can participate in host defense against viruses and contribute to autoimmunity [27, 28]. More recently, previously unappreciated populations such as B cells were found to be a major source of IL-17A and IL-17Fduring *Trypanosoma cruzi* infection. The *T. cruzi* surface antigen, trans-sialidase, drives the formation of IL-17^+ B cells, which via IL-17A production, promotes the control of this parasite [29].

2. The IL-17 receptor family

In 1995, IL-17 receptor A (IL-17RA) was identified as a new cytokine receptor for IL-17A and was later found to be part of a cytokine receptor family unrelated to existing cytokine receptor family [30]. The IL-17 receptor family now consists of 5 members (IL-17RA, RB, RC, RD and RE), all of which, like their ligands, share sequence homology (Fig. 1). IL-17RA is ubiquitously expressed on a wide range of tissues and cell types. Upon the stimulation with IL-17, IL-17RA initiates the activation of downstream signaling pathways to induce the production of pro-inflammatory molecules. However, IL-17RA alone is insufficient to mediated IL-17signaling. Further evaluation revealed that IL-17 signals through a heterodimeric receptor complex composed of IL-17RA and IL-17RC [31–33] (Fig. 1). It is proposed that the binding of ligand to the first IL-17 receptor subunit alters the affinity and specificity of the second binding event, thereby promoting the formation of a heterodimeric rather than a homodimeric receptor complex [34, 35]. Sharing the greatest sequence homology(56%) with IL-17A, IL-17F also signals through the same receptor complex, though IL-17F binds to IL-17RAwith ~100 to 1000 times lower affinity than does IL-17A, while the binding affinities for IL-17RC is comparable between the two cytokines [36, 37]. IL-17F is located adjacent to IL-17A on the same chromosome [6], and is produced by similar cells, often in conjunction with IL-17A [38]. Crystal structures have revealed that while IL-17A and IL-17F can form IL-17A/A or IL-17F/F homodimers, IL-17A/F heterodimers are also formed [6, 36, 39,40]. Though some studies have indicated that IL-17A and IL-17F may have disparate roles in inflammation, the aspects that distinguishes the two cytokines have remained largely elusive [16, 38, 41, 42]

3. Homotypic interaction of the SEFIR domains

At the C-terminus of the IL-17 receptors is a conserved region known as the SEFIR (similar expression of fibroblast growth factor genes and IL-17Rs) domain, which helped to group the receptors into a receptor family[43]. This region is closely related to the TIR (Toll/Interleukin-1 receptor) domain in toll-like receptors (TLRs) and IL-1 receptors (IL-1Rs). Due to this similarity, the STIR (SEFIR and TIR) domain superfamily now includes the TLRs, the IL-1Rs, and the IL-17 receptors. Interestingly, the SEFIR domain is also present in a cytosolic protein called Act1 (NFκB activator 1, also known as CIKS or TRAF3IP2). Act1 was originally discovered as anNFκB activator during a search for NFκB binding proteins [44, 45]. It was shown to activate IKK, an upstream kinase of NFκB, through a helix-loop-helix (HLH) domain near its N-terminus. The involvement of the TIR domain in TLR-IL-1R/MyD88 signaling implicated a possible role for Act1 in IL-17 signaling. Indeed, Act1 is recruited to the IL-17 receptor complex through the homotypic interactions of the SEFIR domains upon IL-17stimulation (Fig. 1). Act1-deficiency results in a loss of IL-17-dependent NFκB activation and pro-inflammatory cytokine production [46, 47]. Further detailed studies involving domain mapping showed that a coiled-coiled(CC) loop in the SEFIR domain is essential for the interaction of Act1 with IL-17RA. The interaction was blocked by a cell-permeable decoy peptide that mimicked the structure of the CC loop [48]. The crystal structure of the IL-17RB SEFIR domain was used to model the SEFIR-SEFIR domain interaction between IL-17RB and Act1 [49]. Key residues located within the SEFIR domain of IL-17RB (Leu419 and Leu422) and within the CC loop of Act1 (Leu474, His475, Lys477, and Tyr478) are crucial for this homotypic association. These four key residues in the CC loop of Act1 are likely to be critical for Act1's interaction with the SEFIR domains of other IL-17 receptors.

4. IL-17-dependent inflammation and signaling

4.1 IL-17A synergizes with other molecules to enhance pro-inflammatory responses

Previous studies have reported that IL-17A-dependent NFκB activation was dependent on TRAF6 [50, 51]. Following Act1-binding to the receptor complex, TRAF6 is recruited through the interaction with Act1's TRAF binding motifs (Fig 2). The enzymatic U-box domain of Act1 serves as an E3-ubiquitin ligase that facilitatesLys63-linked ubiquitination of its target proteins for subsequent protein-protein interactions [51]. Ubiquitinated forms of TRAF6 are detectable in wild-type cells but not in cells lacking Act1 upon IL-17A stimulation. *In vitro*ubiquitination assays revealed that Act1 mediates Lys63-linked TRAF6 ubiquitination through its U-box domain. Deletion and point mutations of the U-box abolished Act1-mediated TRAF6 ubiquitination and attenuated IL-17-dependent responses. Poly-ubiquitinated TRAF6 further activates downstream TRAF6-dependent TGFβ-activated kinase 1 (TAK1) for NFκB activation.

IL-17A alone, however, is a weak NFκB activator. But what makes it such a pathogenic cytokine is its ability to synergize with other cytokines like TNF-α to promote and prolong pro-inflammatory responses. While TNF-α, a strong NFκB activator, induces the expression of highly unstable pro-inflammatory mRNAs, IL-17A enhances the chemokine expression through stabilizing these mRNAs [52–54]. This mechanism involves two other TRAF molecules, TRAF2 and TRAF5, as well as a kinase called IKKi (also known as IKKε). IKKi is recruited to the IL-17R–Act1 complex upon IL-17A stimulation, where it specifically phosphorylates Act1 at Ser311. This generates a docking site that recruits TRAF2 and TRAF5, but not TRAF6, to form anAct1/TRAF2/TRAF5/arginine- and serine-rich splicing factor SRSF1 (SF2 (ASF)) complex. The formation of this complex prevents ASF from binding to the 3' UTR of CXCL1 mRNA for cleavage and thereby enhancesCXCL1 mRNA stability [53, 54]. Whereas TRAF6 is essential for IL-17A-dependent activation of NFκB

and MAPK cascades, TRAF2 and TRAF5 are involved in IL-17A-dependent mRNA stabilization through the activation of IKKi. IKKi-deficiency abolished the formation of the Act1/TRAF2/TRAF5/ASF complex and resulted in a loss of mRNA stability without affecting Act1-TRAF6-NFκB activity. Deficiency of TRAF6 in mouse embryonic fibroblasts resulted in the loss of NFκB and JNK activation as well as IL-6 production upon IL-17Astimulation, whereas IL-17A-dependent mRNA stability was unaffected [50, 55]. In addition to theAct1/TRAF2/TRAF5/SF2(ASF) complex, we recently found that an SF2(ASF)-independent complex composed of Act1/TRAF2/TRAF5 and HuR, an RNA-binding protein, can mediate IL-17A-dependent mRNA stabilization[56]. IL-17A stimulation led to Act1-dependent HuR polyubiquitination, which was necessary for HuR to bind the 3'-UTRs of its target mRNAs like CXCL1. Thus, IL-17 induced mRNA stabilization via the TRAF6-independent pathway plays an important role in regulating the coordinated expression of pro-inflammatory cytokines and chemokines.

4.2. Regulation of IL-17A signaling

IL-17A stimulation also leads to TRAF4 recruitment to the IL-17 receptor complex. TRAF4 is a negative modulator of IL-17-signaling and utilizes the same TRAF binding sites as that of TRAF6 on Act1, competing with TRAF6 for Act1 binding [57]. TRAF4-deficient mice displayed markedly enhanced IL-17–dependent signaling and cytokine expression [57]. TRAF3 has also been shown to be an important negative regulator in the IL-17 signaling cascade, binding directly to the IL-17R to interfere with the formation of the IL-17R-Act1-TRAF6 complex [58]. Knockdown of TRAF3 promoted NFκB and MAPK activation as well as enhanced IL-17A-dependent pro-inflammatory gene expression [58]. IL-17 stimulation also triggers the dual phosphorylation of C/EBPβ at Thr188 and Thr179 by ERK and glycogen synthase kinase 3β (GSK3β), respectively [59]. These phosphorylation events on C/EBPβ led to inhibition of IL-17-dependent pro-inflammatory gene induction [60].

The binding of IL-17 to the receptors triggers a series of phosphorylation and ubiquitination events. A recent study described a previously unknown function for the deubiquitinating enzyme USP25 in restricting IL-17Rsignaling [61]. *In vitro*, IL-17A treated USP25 deficient cells resulted in the hyper-ubiquitination of TRAF5 andTRAF6, prolonging the half-life of CXCL1-encoding mRNAs and enhancing the phosphorylation of JNK and the inhibitor IκBα. As a result, USP25-deficiency led to exaggerated IL-17A-dependent chemokine and cytokine production. In vivo, USP25-deficient mice exhibited enhanced IL-17 mediated pulmonary inflammation. These observations indicate that USP25 may negatively regulate IL-17 signaling, in part by restricting the ubiquitination status of TRAF5 and TRAF6. Another deubiquitinase, A20, a tumor suppressor encoded byTNFAIP3 (TNF-a–induced protein 3), was recently found to interact directly with the distal domain of IL-17RAand associated with TRAF6 in an IL-17–dependent manner to restrict the IL-17–dependent activation of NFκBand MAPK [62].

IL-17-dependent NFκB activation can also lead to downregulation of a micro-RNA, miR-23b, in human fibroblast-like synoviocytes, mouse primary kidney cells and astrocytes [63]. MiR-23b suppresses NFκB activity and inflammatory cytokine expression by targeting several upstream signaling mediators, including Tab2, Tab3and IKK-α. Thus, inhibition of miR-23b by IL-17 provides a positive feedback loop for activation of the NFκB pathway and the expression of pro-inflammatory genes in response to IL-17 [63, 64]. Activation of NFκB can also be positively regulated by an IL-17 induced transcription factor NFκBIZ. It is reported that NFκBIZ is required for IL-17A-induced human beta-defensin 2 in epithelial cells and neutrophil gelatinase-associated lipocalin [65, 66].

One IL-17 receptor has been shown to participate in regulating IL-17 signaling. IL-17RD, originally identified as an inhibitor of FGF signaling, co-localizes with IL-17RA and has

recently been implicated to regulate IL-17Asignaling [67, 68]. Interestingly, IL-17RD-deficiency resulted in enhanced IL-17A-dependent NFκB activation and increased IL-6 and KC expression, yet reduced MAPK activation and decreased MIP2 expression upon IL-17A stimulation. Furthermore, IL-17RD-deficiency resulted in impaired IL-17-induced pulmonary neutrophilia. It was shown that IL-17RD interacts with IL-17RA and Act1 through SEFIR-SEFIR domain interaction as a means to disrupt Act1-TRAF6 binding, thereby inhibiting NFκB activation for IL-6 and KC expression. However, the mechanism by which IL-17RD positively transmits IL-17A-dependent MAPKs activation remains to be delineated. Additional studies are required to determine whether IL-17RD also participates in the receptor complexes for other IL-17 cytokine members.

More recently, we identified Act1 as a client protein of the molecular chaperone, Hsp90. The highly conserved N-terminus of Act1 is necessary for Hsp90 interaction. Deletions and mutations occurring at the N-terminus impacted its ability to bind to Hsp90 and abrogated IL-17-dependent signaling, possibility due to improper folding of the adaptor protein. Interestingly, the interaction between Act1 and Hsp90 was enhanced after IL-17stimulation, suggesting a possible role for Hsp90 as a scaffolding protein in the IL-17 signaling cascade. Such role for Hsp90 has previously been observed in the nitric oxide signaling cascade [69]

4.3 IL-17 is essential for host defense against microbial pathogens

IL-17A and IL-17F are both major contributors to host defense against bacterial and fungal pathogens, and functions via neutrophil recruitment, anti-microbial molecule and acute phase protein production [13, 32]. The protective role of IL-17 family in host defense against microbial pathogens was first illustrated in studies showing that IL-17RA knockout mice have increased mortality in intrapulmonary *Klebsiella pneumoniae*infections [13]. This was further supported by data showing that IL-23, a cytokine necessary for the expansion and maintenance of the Th17 population, was critical for host defense against *K. pneumoniae* [70, 71]. By using genetic ablation of IL-17RA or IL-17 in murine models or by using neutralizing antibodies to either the receptor or the ligand, impaired IL-17 signaling was linked to host susceptibility to a variety of pathogens. These include *Salmonella enterica* [72], *Streptococcus pneumoniae* [73], *Listeria monocytogenes* [25, 74],*Staphylococcus aureus* [16, 75], *Helicobacter pylori* [76], *Citrobacter rondentium* [16], herpes simplex virus [77],*Trypanosoma cruzi* [78, 79] and *Candida albicans* [15, 80]. IL-17RC-deficiency in mice also resulted in increased susceptibility to *C. albicans* infection [81]. In humans, chronic mucocutaneous candidiasis can result from autosomal dominant IL-17F deficiency, autosomal recessive IL-17RA deficiency, or mutations that inhibit IL-17 immunity [82, 83].

Act1 has also been demonstrated to be involved in antiviral signaling [84]. A zebrafish Act1 protein is able to trigger antiviral gene expression in human cells, suggesting an evolutionary conserved role of Act1 in the host defense against viruses. Furthermore, small interfering RNA-mediated knockdown of Act1 in primary human skin fibroblasts reduced the expression of antiviral genes induced by polyinosinic-polycytidylic acid (poly I:C). Interestingly, a respiratory bacterial pathogen *Chlamydia pneumoniae* produces a secreted protein that binds to Act1, which might provide an immune evasion strategy for the organism by inhibiting IL-17RA signaling [85].

4.4 How things can go wrong: pathogenic roles of IL-17 in autoimmunity

It is now well established that IL-17A is one of the major drivers for several inflammatory and autoimmune diseases. High IL-17A levels were found in patients with diseases like multiple sclerosis (MS), psoriasis, asthma, Crohn’s disease and rheumatoid arthritis [86–92]. In an animal model for MS, experimental autoimmune encephalomyelitis (EAE), mice

deficient in IL-17-signaling exhibited attenuated disease severity compared to wild-type controls [47, 93]. Deficiency of Act1 showed attenuated EAE, confirming the pathogenic role of IL-17 in MS pathogenesis. Cell-specific-deletion of Act1 demonstrated that IL-17-signaling in neuroectoderm-derived cells, but not endothelial cells, macrophages, or microglials, contributed to demyelination and axonal injury in EAE [94]. Moreover, in cuprizone-induced demyelination models, loss of IL-17-signaling (using IL-17A-, IL-17RC- and Act1-deficient mice) was accompanied by decreased microglial and polydendrocyte cellular reactivity, and thus, decreased demyelination. More specifically, loss of IL-17-signaling in astrocytes reduced the severity of cuprizone-induced demyelination [95].

Genome-wide association studies have identified a series of single nucleotide polymorphisms (SNPs) in the genome of psoriasis patients linking the IL-17 cytokine network to psoriasis susceptibility [96–99]. Likewise, murine models of psoriasis have also shown the importance of the Th17 cytokine network in mediating the pathogenesis of skin inflammation. In mice, intra-dermal IL-23 injection resulted in skin hyperplasia and acanthosis that was alleviated with IL-17RA-deficiency, IL-17A-deficiency or anti-IL17 neutralization [100]. Imiquimod (a TLR7/8 agonist that induces Th17-mediated skin inflammation) application led to attenuated skin inflammation in IL-17RA-deficient mice [101]. However, a loss of function Act1 variant (Act1 D10N) was also linked to increase susceptibility for psoriasis. We recently showed that this variant failed to interact with the molecular chaperone, Hsp90 and consequently was unable to transduce IL-17-signaling events. Paradoxically, the loss of IL-17 signaling increases the susceptibility to psoriasis. Act1-deficient mice developed spontaneous skin inflammation, with elevated Th17 cytokines like IL-17A, IL-17F and IL-22 [69, 102]. Absence of IL-17signaling resulted in a hyperactive Th17 population with elevated IL-22 that contributed to the skin phenotype. Previously, it was shown that IL-17RA-deficient mice had more IL-17A-producing cells, suggesting a role for IL-17A in Th17 homeostasis [103]. Similarly, antigen-specific hyperactive Th17 cells have been seen in IL-17RC-deficent mice upon $MOG_{33–55}$ immunization [104]. Moreover, in murine models of skin inflammation, IL-23 injection intra-dermally resulted in elevated IL-22 expression in IL-17A-deficient and IL-17RA-deficient mice compared to wild-type controls [100, 101], while short term TPA (12-O-Tetradecanoylphorbol-13-acetate)treatment resulted in elevated, though not significant, expressions of IL-17A, IL-17F, and IL-22 if anti-IL17A was administered [105]. These observations suggest that IL-17A, though itself a pro-inflammatory cytokine, contributes to immune homeostasis whereby in the absence of its signaling, can lead to dysregulated and exaggerated production of other pro-inflammatory cytokines.

4.5 IL-17, intestinal diseases and microbiota

This dysregulation can be extrapolated to the gut, where IL-17 can play both a exacerbating and a protective role in intestinal inflammation. IL-17A, IL-17F, and Th17 cells are abundantly upregulated in the intestinal mucosa of Crohn's disease and ulcerative colitis patients [106–109]. Indeed, a variety of studies have shown the pathogenic role of IL-17 in experimental models of inflammatory bowel diseases. For example, IL-17R-deficiency protected mice from acute trinitrobenzenesulfonic acid (TNBS)-induced colitis [110], while IL-17A aggravates dextran sodium sulfate (DSS)-induced colitis [111]. Similarly, IL-17F–deficient animals were protected from DSS-induced colon pathology [41], indicating that IL-17A and IL-17F may have redundant roles in promoting murine intestinal chronic inflammation [112].

While IL-17 can contribute to intestinal inflammation, several lines of evidence suggest that it plays a protective role as well. IL-17A was demonstrated to be protective in T-cell mediated colitis by inhibiting Th1 polarization for IFN-γ dependent inflammation [113]. Furthermore, the loss of function variant of Act1 (D10N) was linked to extraintestinal

manifestations of Crohn's disease, suggesting that a loss of IL-17 signaling may contribute to increase susceptibility for developing these Crohn's disease-associated cutaneous manifestations [114]. Recent studies have also revealed the crucial role of the gut microbiota in intestinal immune homeostasis, including the development and the regulation of intestinal Th17 cells. Segmented filamentous bacteria (SFB) can promote the generation of Th17 cells, while the gut commensal bacterium *Bacteroides fragilis* restrains IL-17 production, suggesting that the gut microbiota plays a crucial role in balancing IL-17 production and response [115–117]. Th17 cells in the intestine are also dramatically reduced in antibiotic-treated or germ-free animals [118, 119].

Higher IL-17 expression is associated with poor prognosis in patients with colorectal cancer [120]. Ablation of IL-17A decreases the progression of intestinal tumorigenesis in the Apc $^{Min/+}$ mouse model [121], suggesting an important role for IL-17A in colorectal cancer promotion. On the contrary, a recent study showed that IL-17F-deficiency in mice resulted in increased colonic tumor numbers and tumor area, indicating a protective role for IL-17F in colon tumorigenesis [42]. As IL-17 plays a critical role in host defense against microbes, the gut microbiome has been emerging as a major environmental factor that affects colorectal tumorigenesis [122, 123]. By using next generation sequencing technology, it was demonstrated that an altered microbiota composition existed in colon cancer patients [122]. While the overall bacterial levels did not differ in normal versus cancer group, significantly higher Bacteroides to Prevotella ratio was observed in colon cancer patients. The higher bacteroides level in cancer patients was associated with elevated IL-17-expressing cells, which was undetectable in healthy controls. Consistent with this observation, *Bacteroides enterotoxigenic fragilis*, promoted tumorigenesis in Apc knockout mice via the activation of Th17 responses as anti-IL-17 neutralizing antibody inhibited bacterial-induced tumor formation [124]. Furthermore, colorectal tumors exhibited higher epithelial permeability to commensal bacteria and microbial products, which promoted IL-23/IL-17-mediated tumor growth [125]. Taken together, these findings illustrate the importance of the interaction between IL-17 and the gut microbiota in colon tumorigenesis.

5. IL-17E potentiates type 2 allergic responses

IL-17E (IL-25), sharing the least sequence homology (29%) with IL-17A, functions very differently from IL-17A. Whereas IL-17A promotes inflammation through the induction of cytokines and chemokines for neutrophil recruitment, IL-25 is associated with type 2 responses, promoting the production of type 2 cytokines such as IL-4, IL-5, and IL-13 for eosinophil recruitment and contributes to host defense against helminth and parasitic infections [126–129]. IL-25 is produced by a variety of cells, including immune cells ($CD4^+$ cells, CD8+ T cells, macrophages, dendritic cells, mast cell, and eosinophil) and non-immune cells (epithelial and endothelial) and in a pathological setting it can potentiate allergic inflammation [130, 131].

IL-25 signals through a heterodimeric receptor complex composed of IL-17RA and IL-17RB [33, 132]. IL-17RB is expressed by a variety of cell types with highest expression level in kidney, liver and brain [5]. Deficiency or antibody neutralization of either IL-17RA or IL-17RB can abrogate IL-25-dependent responses. Similar to IL-17A signaling, Act1 is recruited to the receptor complex upon IL-25 stimulation through the homotypic interactions of the SEFIR domains [133–135]. IL-17RB was reported to possess a putative TRAF6 binding domain. Mutation of IL-17RB E338, which is located within this domain, initially showed attenuated NFκB activation [136]. However, a recent paper showed mutations at S337A, E338A or I339A within the putative TRAF6-binding sequence did not have any effect on the interaction between IL-17RB and TRAF6, arguing against the existence of a TRAF6 binding domain within this region of IL-17RB [49].

IL-25 stimulation also led to TRAF6-independent activation of MAPKs like ERK, p38 and JNK [136]. A death domain (DD) within SEFIR domain of IL-17RB was identified based on alignment analysis with DDs of the apoptosis-stimulating fragment (FAS) receptor and tumor necrosis factor (TNF) receptor 1 [137]. IL-25 was reported to induce caspase-mediated apoptosis in breast cancer cells, which exhibited high expression of IL-25R. IL-25-induced caspase activation was dependent on the DD of IL-17RB as deletion of the DD resulted in a loss of caspase activation. Furthermore, DD adaptor proteins, FAS-associated protein with death domain(FADD) and TNF-R1–associated death domain protein (TRADD), were shown to interact strongly with IL-17RBin response to IL-25 stimulation, suggesting that this pathway can be exploited for cancer therapy [137].

Since type 2 responses are essential for helminth expulsion, it is no surprise that in IL-25 deficient mice, expulsion of helminth parasites was delayed [138–140]. Studies using Act1-deficient mice showed diminished type 2 responses (as indicated by reduced levels of IL-4 and IL-13) and delayed helminth expulsion [126]. More specifically, epithelial cells rather than T cells and macrophages, were crucial for IL-25 mediated worm expulsion, highlighting the importance of epithelial cells in IL-25 mediated host defense. Furthermore, IL-25produced by epithelial cells mediated the expansion of $Lin^{-}c\text{-}Kit^{+}$ innate cells to potentiate type 2 responses for worm expulsion [126].

IL-25 can induce lung inflammation by promoting the differentiation of naïve T cells to effector Th2 cells [134, 141]. In human asthmatic tissue, both IL-25 and IL-17RB expression were elevated compared to healthy controls [142]. Presumably, allergens induce the expression of IL-25 by the epithelium and the increased IL-25 can feedback on T cells and innate lymphoid cells to promote type 2 responses [134, 139, 141–144]. Similarly, in the OVA-allergen model, Act1 was shown to be crucial for IL-25 mediated allergic airway inflammation [133,134]. Cell type-specific deletion of Act1 in the epithelial compartment resulted in abolished IL-25-induced cytokine production and eosinophilia [134]. Likewise, a cell-permeable decoy peptide that inhibited the interaction of Act1 with IL-17RA, inhibited IL-25–signaling *in vitro* and prevented IL-25–induced pulmonary inflammation *in vivo* [48].

6. IL-17C and others

IL-17C is mainly produced by epithelial cells and was recently found to be important in promoting cytokines and anti-microbial peptides production in the gastrointestinal tract [32, 145]. Similar to IL-17A, IL-17C is implicated in protection against microbial infection as well as in the pathogenesis of autoimmune disease including psoriasis and multiple sclerosis [146–149]. IL-17C signals through the IL-17RA/IL-17RE receptor complex and Act1 to promote innate host defense and regulate the intestinal inflammation and barrier function [32, 145, 146, 150]. IL-17RE is upregulated on Th17 cells upon differentiation and has been shown to promote Th17 differentiation through the induction of NFκBIZ [146]. Mice lacking IL-17C are partially resistant to EAE. NFκB and MAPK pathways were activated by IL-17C in colon epithelial cells but not in IL-17RE deficient cells [32]. IL-17C was demonstrated to be important for early mucosal responses to *C. rodentium* infection [32]. IL-17C was substantially induced in colon epithelial cells as early as day 4 post *C. rodentium* challenge and synergized with IL-22 for anti-microbial peptides production. In the absence of its functional receptor, IL-17RE, mice exhibited impaired anti-microbial peptide, cytokine and chemokine production during *C. rodentium* infection and succumbed to infection within 13 days. IL-17C has also been shown to have a protective role in intestinal inflammation as mice lacking IL-17C exhibited exacerbated DSS-induced colitis. Moreover, IL-17C directly promoted the expression of the tight junction molecule occludin by colonic epithelial cells, suggesting the critical role of IL-17C in maintaining intestinal barrier function [150]. Furthermore, IL-17C is also involved in skin inflammation.

Deficiency of IL-17C led to attenuated imiquimod-induced skin inflammation [145], while over-expression of IL-17C in keratinocytes led to spontaneous psoriasiform skin inflammation in mice [147].

IL-17B was detected in several organs with high expression in chondrocytes and neurons [3, 130, 151]. IL-17B was reported to bind to IL-17RB, though with lower affinity than IL-25 and stimulated the production of TNF-α and IL-1β by the monocytic cell line, THP-1 [3, 5]. Furthermore, it was highly expressed in the cartilage derived from the paws of collagen-induced arthritis mice, suggesting a potential pro-inflammatory role in disease processes [152]. IL-17D was also detected in several organs, whereas in immune cells, IL-17D is only express in resting $CD4^+$ T cell and $CD19^+$ B cells [4]. The biological function of IL-17B and IL-17D are still poorly understood. The receptor for IL-17D has yet to be solved.

7. Concluding remarks and perspective

The IL-17 cytokine family, derived from a wide array of cell types, coupled to the differential expression of their receptors on various cells and tissues, illustrate the complexity of this cytokine family network in modulating the immune response for host defense and how its dysregulation could lead to pro-inflammatory diseases. Recent advances that uncovered IL-17 sources, and studies dissecting the activation and regulation of the signal transduction pathways have extensively expanded our knowledge in understanding the biological functions of the IL-17 family in human diseases. However, given the complexity of IL-17's pro-inflammatory and tissue protective roles in different diseases, it is unclear how current therapeutic developments including anti-IL-17A and anti-IL-17RA antibodies for autoimmune diseases like psoriasis and rheumatoid arthritis [153–155] may affect patients in the long run. Nevertheless, better understanding of IL-17 signaling in inflammatory and autoimmune settings will be crucial for the discovery of new therapeutic targets that will enable us to design more suitable treatments for patients who do not respond to conventional therapies.

References

1. Rouvier E, Luciani MF, Mattei MG, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a herpesvirus saimiri gene. J Immunol. 1993; 150(12):5445–5456. [PubMed: 8390535]
2. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, et al. Human IL-17: a novel cytokine derived from T cells. J Immunol. 1995; 155(12):5483–5486. [PubMed: 7499828]
3. Li H, Chen J, Huang A, Stinson J, Heldens S, Foster J, et al. Cloning and characterization of IL-17B and IL-17C, two new members of the IL-17 cytokine family. Proc Natl Acad Sci U S A. 2000; 97(2):773–778. [PubMed: 10639155]
4. Starnes T, Broxmeyer HE, Robertson MJ, Hromas R. Cutting edge: IL-17D, a novel member of the IL-17 family, stimulates cytokine production and inhibits hemopoiesis. J Immunol. 2002; 169(2): 642–646. [PubMed: 12097364]
5. Lee J, Ho WH, Maruoka M, Corpuz RT, Baldwin DT, Foster JS, et al. IL-17E, a novel proinflammatory ligand for the IL-17 receptor homolog IL-17Rh1. J Biol Chem. 2001; 276(2): 1660–1664. [PubMed: 11058597]
6. Hymowitz SG, Filvaroff EH, Yin JP, Lee J, Cai L, Risser P, et al. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. EMBO J. 2001; 20(19):5332–5341. [PubMed: 11574464]
7. Ouyang W, Kolls JK, Zheng Y. The biological functions of T helper 17 cell effector cytokines in inflammation. Immunity. 2008; 28(4):454–467. [PubMed: 18400188]
8. Milner JD. IL-17 producing cells in host defense and atopy. Curr Opin Immunol. 2011; 23(6):784–788. [PubMed: 22019285]

9. Kuchroo VK, Ohashi PS, Sartor RB, Vinuesa CG. Dysregulation of immune homeostasis in autoimmune diseases. Nat Med. 2012; 18(1):42–47. [PubMed: 22227671]
10. Ahmed M, Gaffen SL. IL-17 in obesity and adipogenesis. Cytokine Growth Factor Rev. 2010; 21(6):449–453. [PubMed: 21084215]
11. Trinchieri G. Cancer and inflammation: an old intuition with rapidly evolving new concepts. Annu Rev Immunol. 2012; 30:677–706. [PubMed: 22224761]
12. Gallimore AM, Godkin A. Epithelial barriers, microbiota, and colorectal cancer. N Engl J Med. 2013; 368(3):282–284. [PubMed: 23323906]
13. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, et al. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. J Exp Med. 2001; 194(4):519–527. [PubMed: 11514607]
14. Chung DR, Kasper DL, Panzo RJ, Chitnis T, Grusby MJ, Sayegh MH, et al. CD4+ T cells mediate abscess formation in intra-abdominal sepsis by an IL-17-dependent mechanism. J Immunol. 2003; 170(4):1958–1963. [PubMed: 12574364]
15. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-Candida albicans host defense in mice. J Infect Dis. 2004; 190(3):624–631. [PubMed: 15243941]
16. Ishigame H, Kakuta S, Nagai T, Kadoki M, Nambu A, Komiyama Y, et al. Differential roles of interleukin-17A and -17F in host defense against mucoepithelial bacterial infection and allergic responses. Immunity. 2009; 30(1):108–119. [PubMed: 19144317]
17. Chang SH, Dong C. Signaling of interleukin-17 family cytokines in immunity and inflammation. Cell Signal. 2011; 23(7):1069–1075. [PubMed: 21130872]
18. Gaffen SL. An overview of IL-17 function and signaling. Cytokine. 2008; 43(3):402–407. [PubMed: 18701318]
19. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 Cells. Annu Rev Immunol. 2009; 27:485–517. [PubMed: 19132915]
20. Cua DJ, Tato CM. Innate IL-17-producing cells: the sentinels of the immune system. Nat Rev Immunol. 2010; 10(7):479–489. [PubMed: 20559326]
21. Sutton CE, Lalor SJ, Sweeney CM, Brereton CF, Lavelle EC, Mills KH. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity. Immunity. 2009; 31(2):331–341. [PubMed: 19682929]
22. Martin B, Hirota K, Cua DJ, Stockinger B, Veldhoen M. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals. Immunity. 2009; 31(2):321–330. [PubMed: 19682928]
23. Umemura M, Yahagi A, Hamada S, Begum MD, Watanabe H, Kawakami K, et al. IL-17-mediated regulation of innate and acquired immune response against pulmonary Mycobacterium bovis bacille Calmette-Guerin infection. J Immunol. 2007; 178(6):3786–3796. [PubMed: 17339477]
24. Shibata K, Yamada H, Hara H, Kishihara K, Yoshikai Y. Resident Vdelta1+ gammadelta T cells control early infiltration of neutrophils after Escherichia coli infection via IL-17 production. J Immunol. 2007; 178(7):4466–4472. [PubMed: 17372004]
25. Hamada S, Umemura M, Shiono T, Tanaka K, Yahagi A, Begum MD, et al. IL-17A produced by gammadelta T cells plays a critical role in innate immunity against listeria monocytogenes infection in the liver. J Immunol. 2008; 181(5):3456–3463. [PubMed: 18714018]
26. Takatori H, Kanno Y, Watford WT, Tato CM, Weiss G, Ivanov II, et al. Lymphoid tissue inducer-like cells are an innate source of IL-17 and IL-22. J Exp Med. 2009; 206(1):35–41. [PubMed: 19114665]
27. Huber M, Heink S, Pagenstecher A, Reinhard K, Ritter J, Visekruna A, et al. IL-17A secretion by CD8+ T cells supports Th17-mediated autoimmune encephalomyelitis. J Clin Invest. 2013; 123(1):247–260. [PubMed: 23221338]
28. Nigam P, Kwa S, Velu V, Amara RR. Loss of IL-17-producing CD8 T cells during late chronic stage of pathogenic simian immunodeficiency virus infection. J Immunol. 2011; 186(2):745–753. [PubMed: 21148794]
29. Bermejo DA, Jackson SW, Gorosito-Serran M, Acosta-Rodriguez EV, Amezcua-Vesely MC, Sather BD, et al. Trypanosoma cruzi trans-sialidase initiates a program independent of the

transcription factors RORgammat and Ahr that leads to IL-17 production by activated B cells. Nat Immunol. 2013; 14(5):514–522. [PubMed: 23563688]

30. Yao Z, Fanslow WC, Seldin MF, Rousseau AM, Painter SL, Comeau MR, et al. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. Immunity. 1995; 3(6):811–821. [PubMed: 8777726]
31. Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, et al. Cutting edge: interleukin 17 signals through a heteromeric receptor complex. J Immunol. 2006; 177(1):36–39. [PubMed: 16785495]
32. Song X, Zhu S, Shi P, Liu Y, Shi Y, Levin SD, et al. IL-17RE is the functional receptor for IL-17C and mediates mucosal immunity to infection with intestinal pathogens. Nat Immunol. 2011; 12(12):1151–1158. [PubMed: 21993849]
33. Rickel EA, Siegel LA, Yoon BR, Rottman JB, Kugler DG, Swart DA, et al. Identification of functional roles for both IL-17RB and IL-17RA in mediating IL-25-induced activities. J Immunol. 2008; 181(6):4299–4310. [PubMed: 18768888]
34. Ely LK, Fischer S, Garcia KC. Structural basis of receptor sharing by interleukin 17 cytokines. Nat Immunol. 2009; 10(12):1245–1251. [PubMed: 19838198]
35. Liu S, Song X, Chrunyk BA, Shanker S, Hoth LR, Marr ES, et al. Crystal structures of interleukin 17A and its complex with IL-17 receptor A. Nat Commun. 2013; 4:1888. [PubMed: 23695682]
36. Wright JF, Bennett F, Li B, Brooks J, Luxenberg DP, Whitters MJ, et al. The human IL-17F/IL-17A heterodimeric cytokine signals through the IL-17RA/IL-17RC receptor complex. J Immunol. 2008; 181(4):2799–2805. [PubMed: 18684971]
37. Kuestner RE, Taft DW, Haran A, Brandt CS, Brender T, Lum K, et al. Identification of the IL-17 receptor related molecule IL-17RC as the receptor for IL-17F. J Immunol. 2007; 179(8):5462–5473. [PubMed: 17911633]
38. Chang SH, Dong C. IL-17F: regulation, signaling and function in inflammation. Cytokine. 2009; 46(1):7–11. [PubMed: 19233684]
39. Gerhardt S, Abbott WM, Hargreaves D, Pauptit RA, Davies RA, Needham MR, et al. Structure of IL-17A in complex with a potent, fully human neutralizing antibody. J Mol Biol. 2009; 394(5):905–921. [PubMed: 19835883]
40. Liang SC, Long AJ, Bennett F, Whitters MJ, Karim R, Collins M, et al. An IL-17F/A heterodimer protein is produced by mouse Th17 cells and induces airway neutrophil recruitment. J Immunol. 2007; 179(11):7791–7799. [PubMed: 18025225]
41. Yang XO, Chang SH, Park H, Nurieva R, Shah B, Acero L, et al. Regulation of inflammatory responses by IL-17F. J Exp Med. 2008; 205(5):1063–1075. [PubMed: 18411338]
42. Tong Z, Yang XO, Yan H, Liu W, Niu X, Shi Y, et al. A protective role by interleukin-17F in colon tumorigenesis. PLoS One. 2012; 7(4):e34959. [PubMed: 22509371]
43. Novatchkova M, Leibbrandt A, Werzowa J, Neubuser A, Eisenhaber F. The STIR-domain superfamily in signal transduction, development and immunity. Trends Biochem Sci. 2003; 28(5):226–229. [PubMed: 12765832]
44. Li X, Commane M, Nie H, Hua X, Chatterjee-Kishore M, Wald D, et al. Act1, an NF-kappa B-activating protein. Proc Natl Acad Sci U S A. 2000; 97(19):10489–10493. [PubMed: 10962024]
45. Leonardi A, Chariot A, Claudio E, Cunningham K, Siebenlist U. CIKS, a connection to Ikappa B kinase and stress-activated protein kinase. Proc Natl Acad Sci U S A. 2000; 97(19):10494–10499. [PubMed: 10962033]
46. Chang SH, Park H, Dong C. Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. J Biol Chem. 2006; 281(47):35603–35607. [PubMed: 17035243]
47. Qian Y, Liu C, Hartupee J, Altuntas CZ, Gulen MF, Jane-Wit D, et al. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. Nat Immunol. 2007; 8(3):247–256. [PubMed: 17277779]
48. Liu C, Swaidani S, Qian W, Kang Z, Sun P, Han Y, et al. A CC' loop decoy peptide blocks the interaction between Act1 and IL-17RA to attenuate IL-17- and IL-25-induced inflammation. Sci Signal. 2011; 4(197):ra72. [PubMed: 22045852]

49. Zhang B, Liu C, Qian W, Han Y, Li X, Deng J. Crystal structure of IL-17 receptor B SEFIR domain. J Immunol. 2013; 190(5):2320–2326. [PubMed: 23355738]
50. Schwandner R, Yamaguchi K, Cao Z. Requirement of tumor necrosis factor receptor-associated factor (TRAF)6 in interleukin 17 signal transduction. J Exp Med. 2000; 191(7):1233–1240. [PubMed: 10748240]
51. Liu C, Qian W, Qian Y, Giltiay NV, Lu Y, Swaidani S, et al. Act1, a U-box E3 ubiquitin ligase for IL-17 signaling. Sci Signal. 2009; 2(92):ra63. [PubMed: 19825828]
52. Hartupee J, Liu C, Novotny M, Li X, Hamilton T. IL-17 enhances chemokine gene expression through mRNA stabilization. J Immunol. 2007; 179(6):4135–4141. [PubMed: 17785852]
53. Bulek K, Liu C, Swaidani S, Wang L, Page RC, Gulen MF, et al. The inducible kinase IKKi is required for IL-17-dependent signaling associated with neutrophilia and pulmonary inflammation. Nat Immunol. 2011; 12(9):844–852. [PubMed: 21822257]
54. Sun D, Novotny M, Bulek K, Liu C, Li X, Hamilton T. Treatment with IL-17 prolongs the half-life of chemokine CXCL1 mRNA via the adaptor TRAF5 and the splicing-regulatory factor SF2 (ASF). Nat Immunol. 2011; 12(9):853–860. [PubMed: 21822258]
55. Hartupee J, Liu C, Novotny M, Sun D, Li X, Hamilton TA. IL-17 signaling for mRNA stabilization does not require TNF receptor-associated factor 6. J Immunol. 2009; 182(3):1660–1666. [PubMed: 19155515]
56. Herjan T, Yao P, Qian W, Li X, Liu C, Bulek K, et al. HuR Is Required for IL-17-Induced Act1-Mediated CXCL1 and CXCL5 mRNA Stabilization. J Immunol. 2013
57. Zepp JA, Liu C, Qian W, Wu L, Gulen MF, Kang Z, et al. Cutting edge: TNF receptor-associated factor 4 restricts IL-17-mediated pathology and signaling processes. J Immunol. 2012; 189(1):33–37. [PubMed: 22649194]
58. Zhu S, Pan W, Shi P, Gao H, Zhao F, Song X, et al. Modulation of experimental autoimmune encephalomyelitis through TRAF3-mediated suppression of interleukin 17 receptor signaling. J Exp Med. 2010; 207(12):2647–2662. [PubMed: 21078888]
59. Maitra A, Shen F, Hanel W, Mossman K, Tocker J, Swart D, et al. Distinct functional motifs within the IL-17 receptor regulate signal transduction and target gene expression. Proc Natl Acad Sci U S A. 2007; 104(18):7506–7511. [PubMed: 17456598]
60. Shen F, Li N, Gade P, Kalvakolanu DV, Weibley T, Doble B, et al. IL-17 receptor signaling inhibits C/EBPbeta by sequential phosphorylation of the regulatory 2 domain. Sci Signal. 2009; 2(59):ra8. [PubMed: 19244213]
61. Zhong B, Liu X, Wang X, Chang SH, Liu X, Wang A, et al. Negative regulation of IL-17-mediated signaling and inflammation by the ubiquitin-specific protease USP25. Nat Immunol. 2012; 13(11):1110–1117. [PubMed: 23042150]
62. Garg AV, Ahmed M, Vallejo AN, Ma A, Gaffen SL. The deubiquitinase a20 mediates feedback inhibition of interleukin-17 receptor signaling. Sci Signal. 2013; 6(278):ra44. [PubMed: 23737552]
63. Zhu S, Pan W, Song X, Liu Y, Shao X, Tang Y, et al. The microRNA miR-23b suppresses IL-17-associated autoimmune inflammation by targeting TAB2, TAB3 and IKK-alpha. Nat Med. 2012; 18(7):1077–1086. [PubMed: 22660635]
64. Hu R, O'Connell RM. MiR-23b is a safeguard against autoimmunity. Nat Med. 2012; 18(7):1009–1010. [PubMed: 22772548]
65. Kao CY, Kim C, Huang F, Wu R. Requirements for two proximal NF-kappaB binding sites and IkappaB-zeta in IL-17A-induced human beta-defensin 2 expression by conducting airway epithelium. J Biol Chem. 2008; 283(22):15309–15318. [PubMed: 18362142]
66. Karlsen JR, Borregaard N, Cowland JB. Induction of neutrophil gelatinase-associated lipocalin expression by co-stimulation with interleukin-17 and tumor necrosis factor-alpha is controlled by IkappaB-zeta but neither by C/EBP-beta nor C/EBP-delta. J Biol Chem. 2010; 285(19):14088–14100. [PubMed: 20220144]
67. Rong Z, Wang A, Li Z, Ren Y, Cheng L, Li Y, et al. IL-17RD (Sef or IL-17RLM) interacts with IL-17 receptor and mediates IL-17 signaling. Cell Res. 2009; 19(2):208–215. [PubMed: 19079364]

68. Mellett M, Atzei P, Horgan A, Hams E, Floss T, Wurst W, et al. Orphan receptor IL-17RD tunes IL-17A signalling and is required for neutrophilia. Nat Commun. 2012; 3:1119. [PubMed: 23047677]
69. Wang C, Wu L, Bulek K, Martin BN, Zepp JA, Kang Z, et al. The psoriasis-associated D10N variant of the adaptor Act1 with impaired regulation by the molecular chaperone hsp90. Nat Immunol. 2013; 14(1):72–81. [PubMed: 23202271]
70. Happel KI, Zheng M, Young E, Quinton LJ, Lockhart E, Ramsay AJ, et al. Cutting edge: roles of Toll-like receptor 4 and IL-23 in IL-17 expression in response to Klebsiella pneumoniae infection. J Immunol. 2003; 170(9):4432–4436. [PubMed: 12707317]
71. Happel KI, Dubin PJ, Zheng M, Ghilardi N, Lockhart C, Quinton LJ, et al. Divergent roles of IL-23 and IL-12 in host defense against Klebsiella pneumoniae. J Exp Med. 2005; 202(6):761–769. [PubMed: 16157683]
72. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, et al. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes Salmonella dissemination from the gut. Nat Med. 2008; 14(4):421–428. [PubMed: 18376406]
73. Lu YJ, Gross J, Bogaert D, Finn A, Bagrade L, Zhang Q, et al. Interleukin-17A mediates acquired immunity to pneumococcal colonization. PLoS Pathog. 2008; 4(9):e1000159. [PubMed: 18802458]
74. Xu S, Han Y, Xu X, Bao Y, Zhang M, Cao X. IL-17A-producing gammadeltaT cells promote CTL responses against Listeria monocytogenes infection by enhancing dendritic cell cross-presentation. J Immunol. 2010; 185(10):5879–5887. [PubMed: 20956351]
75. Cho JS, Pietras EM, Garcia NC, Ramos RI, Farzam DM, Monroe HR, et al. IL-17 is essential for host defense against cutaneous Staphylococcus aureus infection in mice. J Clin Invest. 2010; 120(5):1762–1773. [PubMed: 20364087]
76. Algood HM, Allen SS, Washington MK, Peek RM Jr, Miller GG, Cover TL. Regulation of gastric B cell recruitment is dependent on IL-17 receptor A signaling in a model of chronic bacterial infection. J Immunol. 2009; 183(9):5837–5846. [PubMed: 19812196]
77. Suryawanshi A, Veiga-Parga T, Rajasagi NK, Reddy PB, Sehrawat S, Sharma S, et al. Role of IL-17 and Th17 cells in herpes simplex virus-induced corneal immunopathology. J Immunol. 2011; 187(4):1919–1930. [PubMed: 21765013]
78. da Matta Guedes PM, Gutierrez FR, Maia FL, Milanezi CM, Silva GK, Pavanelli WR, et al. IL-17 produced during Trypanosoma cruzi infection plays a central role in regulating parasite-induced myocarditis. PLoS Negl Trop Dis. 2010; 4(2):e604. [PubMed: 20169058]
79. Miyazaki Y, Hamano S, Wang S, Shimanoe Y, Iwakura Y, Yoshida H. IL-17 is necessary for host protection against acute-phase Trypanosoma cruzi infection. J Immunol. 2010; 185(2):1150–1157. [PubMed: 20562260]
80. Conti HR, Shen F, Nayyar N, Stocum E, Sun JN, Lindemann MJ, et al. Th17 cells and IL-17 receptor signaling are essential for mucosal host defense against oral candidiasis. J Exp Med. 2009; 206(2):299–311. [PubMed: 19204111]
81. Ho AW, Shen F, Conti HR, Patel N, Childs EE, Peterson AC, et al. IL-17RC is required for immune signaling via an extended SEF/IL-17R signaling domain in the cytoplasmic tail. J Immunol. 2010; 185(2):1063–1070. [PubMed: 20554964]
82. Puel A, Cypowyj S, Bustamante J, Wright JF, Liu L, Lim HK, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity. Science. 2011; 332(6025): 65–68. [PubMed: 21350122]
83. Liu L, Okada S, Kong XF, Kreins AY, Cypowyj S, Abhyankar A, et al. Gain-of-function human STAT1 mutations impair IL-17 immunity and underlie chronic mucocutaneous candidiasis. J Exp Med. 2011; 208(8):1635–1648. [PubMed: 21727188]
84. Ryzhakov G, Blazek K, Lai CC, Udalova IA. IL-17 receptor adaptor protein Act1/CIKS plays an evolutionarily conserved role in antiviral signaling. J Immunol. 2012; 189(10):4852–4858. [PubMed: 23066157]
85. Wolf K, Plano GV, Fields KA. A protein secreted by the respiratory pathogen Chlamydia pneumoniae impairs IL-17 signalling via interaction with human Act1. Cell Microbiol. 2009; 11(5):769–779. [PubMed: 19159390]

86. Matusevicius D, Kivisakk P, He B, Kostulas N, Ozenci V, Fredrikson S, et al. Interleukin-17 mRNA expression in blood and CSF mononuclear cells is augmented in multiple sclerosis. Mult Scler. 1999; 5(2):101–104. [PubMed: 10335518]

87. Lock C, Hermans G, Pedotti R, Brendolan A, Schadt E, Garren H, et al. Gene-microarray analysis of multiple sclerosis lesions yields new targets validated in autoimmune encephalomyelitis. Nat Med. 2002; 8(5):500–508. [PubMed: 11984595]

88. Kagami S, Rizzo HL, Lee JJ, Koguchi Y, Blauvelt A. Circulating Th17, Th22, and Th1 cells are increased in psoriasis. J Invest Dermatol. 2010; 130(5):1373–1383. [PubMed: 20032993]

89. Lowes MA, Kikuchi T, Fuentes-Duculan J, Cardinale I, Zaba LC, Haider AS, et al. Psoriasis vulgaris lesions contain discrete populations of Th1 and Th17 T cells. J Invest Dermatol. 2008; 128(5):1207–1211. [PubMed: 18200064]

90. Kobayashi T, Okamoto S, Hisamatsu T, Kamada N, Chinen H, Saito R, et al. IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. Gut. 2008; 57(12):1682–1689. [PubMed: 18653729]

91. McAllister F, Henry A, Kreindler JL, Dubin PJ, Ulrich L, Steele C, et al. Role of IL-17A, IL-17F, and the IL-17 receptor in regulating growth-related oncogene-alpha and granulocyte colony-stimulating factor in bronchial epithelium: implications for airway inflammation in cystic fibrosis. J Immunol. 2005; 175(1):404–412. [PubMed: 15972674]

92. Bullens DM, Truyen E, Coteur L, Dilissen E, Hellings PW, Dupont LJ, et al. IL-17 mRNA in sputum of asthmatic patients: linking T cell driven inflammation and granulocytic influx? Respir Res. 2006; 7:135. [PubMed: 17083726]

93. Komiyama Y, Nakae S, Matsuki T, Nambu A, Ishigame H, Kakuta S, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. J Immunol. 2006; 177(1):566–573. [PubMed: 16785554]

94. Kang Z, Altuntas CZ, Gulen MF, Liu C, Giltiay N, Qin H, et al. Astrocyte-restricted ablation of interleukin-17-induced Act1-mediated signaling ameliorates autoimmune encephalomyelitis. Immunity. 2010; 32(3):414–425. [PubMed: 20303295]

95. Kang Z, Liu L, Spangler R, Spear C, Wang C, Gulen MF, et al. IL-17-induced Act1-mediated signaling is critical for cuprizone-induced demyelination. J Neurosci. 2012; 32(24):8284–8292. [PubMed: 22699909]

96. Perera GK, Di Meglio P, Nestle FO. Psoriasis. Annu Rev Pathol. 2012; 7:385–422. [PubMed: 22054142]

97. Strange A, Capon F, Spencer CC, Knight J, et al. Genetic Analysis of Psoriasis, C., C. the Wellcome Trust Case Control. A genome-wide association study identifies new psoriasis susceptibility loci and an interaction between HLA-C and ERAP1. Nat Genet. 2010; 42(11):985–990. [PubMed: 20953190]

98. Ellinghaus E, Ellinghaus D, Stuart PE, Nair RP, Debrus S, Raelson JV, et al. Genome-wide association study identifies a psoriasis susceptibility locus at TRAF3IP2. Nat Genet. 2010; 42(11): 991–995. [PubMed: 20953188]

99. Huffmeier U, Uebe S, Ekici AB, Bowes J, Giardina E, Korendowych E, et al. Common variants at TRAF3IP2 are associated with susceptibility to psoriatic arthritis and psoriasis. Nat Genet. 2010; 42(11):996–999. [PubMed: 20953186]

100. Rizzo HL, Kagami S, Phillips KG, Kurtz SE, Jacques SL, Blauvelt A. IL-23-mediated psoriasis-like epidermal hyperplasia is dependent on IL-17A. J Immunol. 2011; 186(3):1495–1502. [PubMed: 21172868]

101. El Malki K, Karbach SH, Huppert J, Zayoud M, Reissig S, Schuler R, et al. An alternative pathway of imiquimod-induced psoriasis-like skin inflammation in the absence of interleukin-17 receptor a signaling. J Invest Dermatol. 2013; 133(2):441–451. [PubMed: 22951726]

102. Matsushima Y, Kikkawa Y, Takada T, Matsuoka K, Seki Y, Yoshida H, et al. An atopic dermatitis-like skin disease with hyper-IgE-emia develops in mice carrying a spontaneous recessive point mutation in the Traf3ip2 (Act1/CIKS) gene. J Immunol. 2010; 185(4):2340–2349. [PubMed: 20660351]

103. Smith E, Stark MA, Zarbock A, Burcin TL, Bruce AC, Vaswani D, et al. IL-17A inhibits the expansion of IL-17A-producing T cells in mice through "short-loop" inhibition via IL-17 receptor. J Immunol. 2008; 181(2):1357–1364. [PubMed: 18606690]
104. Hu Y, Ota N, Peng I, Refino CJ, Danilenko DM, Caplazi P, et al. IL-17RC is required for IL-17A-and IL-17F-dependent signaling and the pathogenesis of experimental autoimmune encephalomyelitis. J Immunol. 2010; 184(8):4307–4316. [PubMed: 20231694]
105. Nakajima K, Kanda T, Takaishi M, Shiga T, Miyoshi K, Nakajima H, et al. Distinct roles of IL-23 and IL-17 in the development of psoriasis-like lesions in a mouse model. J Immunol. 2011; 186(7):4481–4489. [PubMed: 21346238]
106. Fujino S, Andoh A, Bamba S, Ogawa A, Hata K, Araki Y, et al. Increased expression of interleukin 17 in inflammatory bowel disease. Gut. 2003; 52(1):65–70. [PubMed: 12477762]
107. Rovedatti L, Kudo T, Biancheri P, Sarra M, Knowles CH, Rampton DS, et al. Differential regulation of interleukin 17 and interferon gamma production in inflammatory bowel disease. Gut. 2009; 58(12):1629–1636. [PubMed: 19740775]
108. Seiderer J, Elben I, Diegelmann J, Glas J, Stallhofer J, Tillack C, et al. Role of the novel Th17 cytokine IL-17F in inflammatory bowel disease (IBD): upregulated colonic IL-17F expression in active Crohn's disease and analysis of the IL17F p.His161Arg polymorphism in IBD. Inflamm Bowel Dis. 2008; 14(4):437–445. [PubMed: 18088064]
109. Nielsen OH, Kirman I, Rudiger N, Hendel J, Vainer B. Upregulation of interleukin-12 and -17 in active inflammatory bowel disease. Scand J Gastroenterol. 2003; 38(2):180–185. [PubMed: 12678335]
110. Zhang Z, Zheng M, Bindas J, Schwarzenberger P, Kolls JK. Critical role of IL-17 receptor signaling in acute TNBS-induced colitis. Inflamm Bowel Dis. 2006; 12(5):382–388. [PubMed: 16670527]
111. Ito R, Kita M, Shin-Ya M, Kishida T, Urano A, Takada R, et al. Involvement of IL-17A in the pathogenesis of DSS-induced colitis in mice. Biochem Biophys Res Commun. 2008; 377(1):12–16. [PubMed: 18796297]
112. Leppkes M, Becker C, Ivanov II, Hirth S, Wirtz S, Neufert C, et al. RORgamma-expressing Th17 cells induce murine chronic intestinal inflammation via redundant effects of IL-17A and IL-17F. Gastroenterology. 2009; 136(1):257–267. [PubMed: 18992745]
113. O'Connor W Jr, Kamanaka M, Booth CJ, Town T, Nakae S, Iwakura Y, et al. A protective function for interleukin 17A in T cell-mediated intestinal inflammation. Nat Immunol. 2009; 10(6):603–609. [PubMed: 19448631]
114. Ciccacci C, Biancone L, Di Fusco D, Ranieri M, Condino G, Giardina E, et al. TRAF3IP2 gene is associated with cutaneous extraintestinal manifestations in Inflammatory Bowel Disease. J Crohns Colitis. 2013; 7(1):44–52. [PubMed: 22445837]
115. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell. 2009; 139(3):485–498. [PubMed: 19836068]
116. Gaboriau-Routhiau V, Rakotobe S, Lecuyer E, Mulder I, Lan A, Bridonneau C, et al. The key role of segmented filamentous bacteria in the coordinated maturation of gut helper T cell responses. Immunity. 2009; 31(4):677–689. [PubMed: 19833089]
117. Round JL, Lee SM, Li J, Tran G, Jabri B, Chatila TA. The Toll-like receptor 2 pathway establishes colonization by a commensal of the human microbiota. Science. 2011; 332(6032): 974–977. [PubMed: 21512004]
118. Ivanov II, Frutos Rde L, Manel N, Yoshinaga K, Rifkin DB, Sartor RB, et al. Specific microbiota direct the differentiation of IL-17-producing T-helper cells in the mucosa of the small intestine. Cell Host Microbe. 2008; 4(4):337–349. [PubMed: 18854238]
119. Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, Onoue M, et al. ATP drives lamina propria T(H)17 cell differentiation. Nature. 2008; 455(7214):808–812. [PubMed: 18716618]
120. Liu J, Duan Y, Cheng X, Chen X, Xie W, Long H, et al. IL-17 is associated with poor prognosis and promotes angiogenesis via stimulating VEGF production of cancer cells in colorectal carcinoma. Biochem Biophys Res Commun. 2011; 407(2):348–354. [PubMed: 21396350]

121. Chae WJ, Gibson TF, Zelterman D, Hao L, Henegariu O, Bothwell AL. Ablation of IL-17A abrogates progression of spontaneous intestinal tumorigenesis. Proc Natl Acad Sci U S A. 2010; 107(12):5540–5544. [PubMed: 20212110]

122. Sobhani I, Tap J, Roudot-Thoraval F, Roperch JP, Letulle S, Langella P, et al. Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One. 2011; 6(1):e16393. [PubMed: 21297998]

123. Sobhani I, Amiot A, Le Baleur Y, Levy M, Auriault ML, Van Nhieu JT, et al. Microbial dysbiosis and colon carcinogenesis: could colon cancer be considered a bacteria-related disease? Therap Adv Gastroenterol. 2013; 6(3):215–229.

124. Wu S, Rhee KJ, Albesiano E, Rabizadeh S, Wu X, Yen HR, et al. A human colonic commensal promotes colon tumorigenesis via activation of T helper type 17 T cell responses. Nat Med. 2009; 15(9):1016–1022. [PubMed: 19701202]

125. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature. 2012; 491(7423):254–258. [PubMed: 23034650]

126. Kang Z, Swaidani S, Yin W, Wang C, Barlow JL, Gulen MF, et al. Epithelial cell-specific Act1 adaptor mediates interleukin-25-dependent helminth expulsion through expansion of Lin(−)c-Kit(+) innate cell population. Immunity. 2012; 36(5):821–833. [PubMed: 22608496]

127. Pan G, French D, Mao W, Maruoka M, Risser P, Lee J, et al. Forced expression of murine IL-17E induces growth retardation, jaundice, a Th2-biased response, and multiorgan inflammation in mice. J Immunol. 2001; 167(11):6559–6567. [PubMed: 11714825]

128. Ballantyne SJ, Barlow JL, Jolin HE, Nath P, Williams AS, Chung KF, et al. Blocking IL-25 prevents airway hyperresponsiveness in allergic asthma. J Allergy Clin Immunol. 2007; 120(6): 1324–1331. [PubMed: 17889290]

129. Saenz SA, Taylor BC, Artis D. Welcome to the neighborhood: epithelial cell-derived cytokines license innate and adaptive immune responses at mucosal sites. Immunol Rev. 2008; 226:172–190. [PubMed: 19161424]

130. Iwakura Y, Ishigame H, Saijo S, Nakae S. Functional specialization of interleukin-17 family members. Immunity. 2011; 34(2):149–162. [PubMed: 21349428]

131. Song X, Qian Y. The activation and regulation of IL-17 receptor mediated signaling. Cytokine. 2013

132. Angkasekwinai P, Chang SH, Thapa M, Watarai H, Dong C. Regulation of IL-9 expression by IL-25 signaling. Nat Immunol. 2010; 11(3):250–256. [PubMed: 20154671]

133. Claudio E, Sonder SU, Saret S, Carvalho G, Ramalingam TR, Wynn TA, et al. The adaptor protein CIKS/Act1 is essential for IL-25-mediated allergic airway inflammation. J Immunol. 2009; 182(3):1617–1630. [PubMed: 19155511]

134. Swaidani S, Bulek K, Kang Z, Liu C, Lu Y, Yin W, et al. The critical role of epithelial-derived Act1 inIL-17- and IL-25-mediated pulmonary inflammation. J Immunol. 2009; 182(3):1631–1640. [PubMed: 19155512]

135. Swaidani S, Bulek K, Kang Z, Gulen MF, Liu C, Yin W, et al. T cell-derived Act1 is necessary for IL-25-mediated Th2 responses and allergic airway inflammation. J Immunol. 2011; 187(6): 3155–3164. [PubMed: 21856933]

136. Maezawa Y, Nakajima H, Suzuki K, Tamachi T, Ikeda K, Inoue J, et al. Involvement of TNF receptor-associated factor 6 in IL-25 receptor signaling. J Immunol. 2006; 176(2):1013–1018. [PubMed: 16393988]

137. Furuta S, Jeng YM, Zhou L, Huang L, Kuhn I, Bissell MJ, et al. IL-25 causes apoptosis of IL-25R-expressing breast cancer cells without toxicity to nonmalignant cells. Sci Transl Med. 2011; 3(78):78ra31.

138. Fallon PG, Ballantyne SJ, Mangan NE, Barlow JL, Dasvarma A, Hewett DR, et al. Identification of an interleukin (IL)-25-dependent cell population that provides IL-4, IL-5, and IL-13 at the onset of helminth expulsion. J Exp Med. 2006; 203(4):1105–1116. [PubMed: 16606668]

139. Owyang AM, Zaph C, Wilson EH, Guild KJ, McClanahan T, Miller HR, et al. Interleukin 25 regulates type 2 cytokine-dependent immunity and limits chronic inflammation in the gastrointestinal tract. J Exp Med. 2006; 203(4):843–849. [PubMed: 16606667]

140. Zhao A, Urban JF Jr, Sun R, Stiltz J, Morimoto M, Notari L, et al. Critical role of IL-25 in nematode infection-induced alterations in intestinal function. J Immunol. 2010; 185(11):6921–6929. [PubMed: 20974983]

141. Angkasekwinai P, Park H, Wang YH, Chang SH, Corry DB, Liu YJ, et al. Interleukin 25 promotes the initiation of proallergic type 2 responses. J Exp Med. 2007; 204(7):1509–1517. [PubMed: 17562814]

142. Wang YH, Angkasekwinai P, Lu N, Voo KS, Arima K, Hanabuchi S, et al. IL-25 augments type 2 immune responses by enhancing the expansion and functions of TSLP-DC-activated Th2 memory cells. J Exp Med. 2007; 204(8):1837–1847. [PubMed: 17635955]

143. Suzukawa M, Morita H, Nambu A, Arae K, Shimura E, Shibui A, et al. Epithelial cell-derived IL-25, but not Th17 cell-derived IL-17 or IL-17F, is crucial for murine asthma. J Immunol. 2012; 189(7):3641–3652. [PubMed: 22942422]

144. Saenz SA, Siracusa MC, Perrigoue JG, Spencer SP, Urban JF Jr, Tocker JE, et al. IL25 elicits a multipotent progenitor cell population that promotes T(H)2 cytokine responses. Nature. 2010; 464(7293):1362–1366. [PubMed: 20200520]

145. Ramirez-Carrozzi V, Sambandam A, Luis E, Lin Z, Jeet S, Lesch J, et al. IL 17C regulates the innate immune function of epithelial cells in an autocrine manner. Nat Immunol. 2011; 12(12): 1159–1166. [PubMed: 21993848]

146. Chang SH, Reynolds JM, Pappu BP, Chen G, Martinez GJ, Dong C. Interleukin-17C promotes Th17 cell responses and autoimmune disease via interleukin-17 receptor E. Immunity. 2011; 35(4):611–621. [PubMed: 21982598]

147. Johnston A, Fritz Y, Dawes SM, Diaconu D, Al-Attar PM, Guzman AM, et al. Keratinocyte overexpression of IL-17C promotes psoriasiform skin inflammation. J Immunol. 2013; 190(5): 2252–2262. [PubMed: 23359500]

148. Johansen C, Riis JL, Gedebjerg A, Kragballe K, Iversen L. Tumor necrosis factor alpha-mediated induction of interleukin 17C in human keratinocytes is controlled by nuclear factor kappaB. J Biol Chem. 2011; 286(29):25487–25494. [PubMed: 21628458]

149. Johansen C, Usher PA, Kjellerup RB, Lundsgaard D, Iversen L, Kragballe K. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. Br J Dermatol. 2009; 160(2): 319–324. [PubMed: 19016708]

150. Reynolds JM, Martinez GJ, Nallaparaju KC, Chang SH, Wang YH, Dong C. Cutting edge: regulation of intestinal inflammation and barrier function by IL-17C. J Immunol. 2012; 189(9): 4226–4230. [PubMed: 23024280]

151. Shi Y, Ullrich SJ, Zhang J, Connolly K, Grzegorzewski KJ, Barber MC, et al. A novel cytokine receptor-ligand pair. Identification, molecular characterization, and in vivo immunomodulatory activity. J Biol Chem. 2000; 275(25):19167–19176. [PubMed: 10749887]

152. Yamaguchi Y, Fujio K, Shoda H, Okamoto A, Tsuno NH, Takahashi K, et al. IL-17B and IL-17C are associated with TNF-alpha production and contribute to the exacerbation of inflammatory arthritis. J Immunol. 2007; 179(10):7128–7136. [PubMed: 17982105]

153. Hueber W, Patel DD, Dryja T, Wright AM, Koroleva I, Bruin G, et al. Effects of AIN457, a fully human antibody to interleukin-17A, on psoriasis, rheumatoid arthritis, and uveitis. Sci Transl Med. 2010; 2(52):52ra72.

154. Patel DD, Lee DM, Kolbinger F, Antoni C. Effect of IL-17A blockade with secukinumab in autoimmune diseases. Ann Rheum Dis. 2013; 72(Suppl 2):iii116–iii123.

155. Spuls PI, Hooft L. Brodalumab and ixekizumab, anti-interleukin-17-receptor antibodies for psoriasis: a critical appraisal. Br J Dermatol. 2012; 167(4):710–713. discussion 714–5. [PubMed: 23013312]

156. Ruddy MJ, Wong GC, Liu XK, Yamamoto H, Kasayama S, Kirkwood KL, et al. Functional cooperation between interleukin-17 and tumor necrosis factor-alpha is mediated by CCAAT/enhancer-binding protein family members. J Biol Chem. 2004; 279(4):2559–2567. [PubMed: 14600152]

Highlights

IL-17 is essential for host defense against microbial pathogens.

IL-17 signaling is tightly controlled at different levels of the signaling cascade.

Things can go wrong: pathogenic roles of IL-17 in autoimmunity.

The microbiota-regulated IL-17 production contributes to intestinal inflammation and tumorigenesis.

IL-17E potentiates type 2 allergic responses.

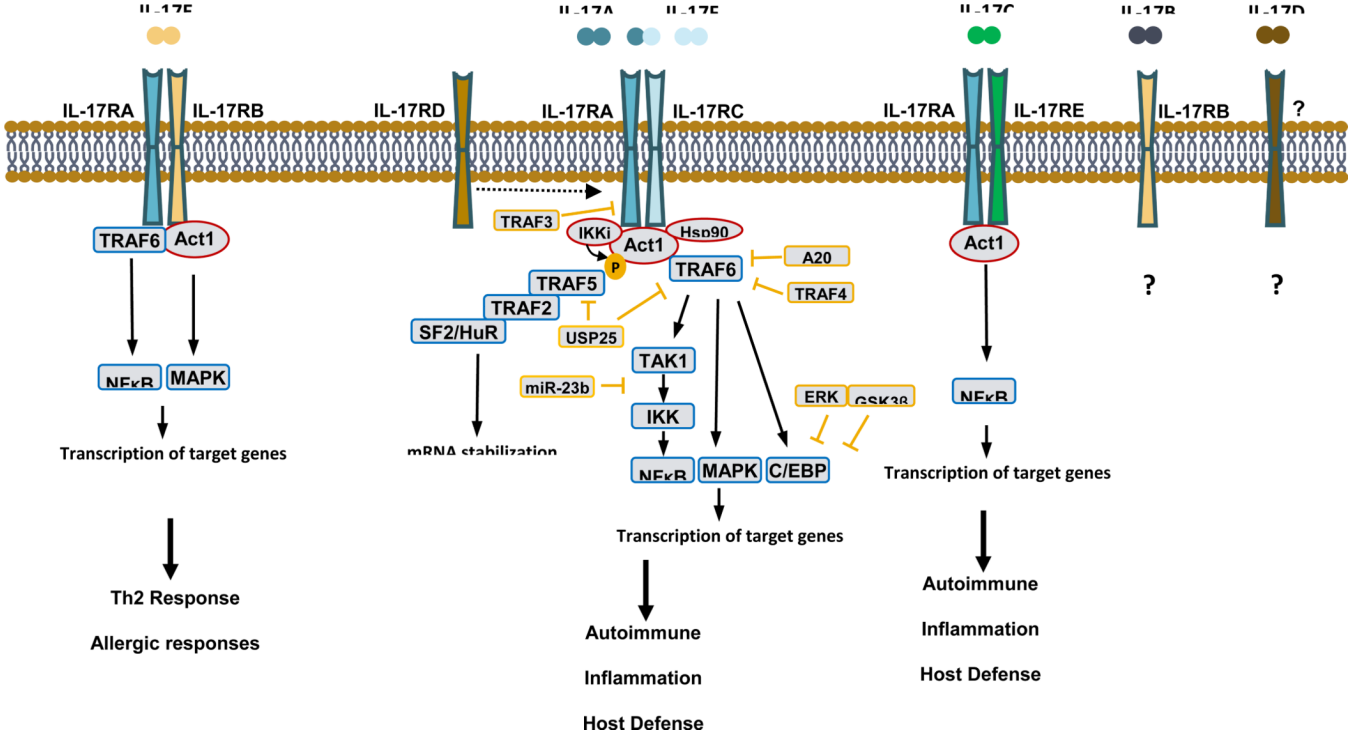

Figure 1. IL-17 cytokines, receptors and signaling

The IL-17 family consists of six members IL-17A-F, while the IL-17 receptor family consists of five members IL-17RA to IL-17RE. IL-17RA is a common receptor that forms heterodimeric complexes with IL-17RB, IL-17RC, and IL-17RE. Thus far, all of the IL-17 receptors recruit Act1 as an adaptor molecule for downstream signaling. IL-17A and IL-17F signals through the IL-17RA-RC complex, triggering TRAF6-dependent target gene transcription and TRAF6-independent IKKi-dependent mRNA stabilization, both of which are important for host defense and contributes to the pathogenesis of autoimmune diseases and cancer. IL-17 signaling is tightly controlled at different levels of the signaling cascade. At the receptor level, IL-17RD interacts with Act1 basally, sequestering it from IL-17RA and TRAF6 until IL-17 stimulation. TRAFs like TRAF3 and TRAF4 act to disrupt downstream signaling complex formation. While TRAF3 binds to the IL-17R to prevent the recruitment of Act1 and TRAF6, TRAF4 competes with TRAF6 for Act1 binding. Deubiquitinating enzymes like USP25 and A20 regulate the ubiquitination status of TRAFs (like TRAF5 and TRAF6), placing a brake on the signaling cascade. The IL-17A-dependent micro-RNA, miR-23b, regulates NFκB activation. IL-17A-induced transcription factors such as C/EBPδ inhibits inflammatory gene expression. IL-17E (IL-25) signaling through the IL-17RA-RBreceptor complex induces Th2 responses by activating MAPK and NFκB pathways. IL-17C signals through the IL-17RA-RE complex mediates host defense and like IL-17A, contributes to the pathogenesis of autoimmune diseases. IL-17B have been shown to interact with IL-17RB, however, its biological function is as yet unclear. The receptor for IL-17D is unknown.

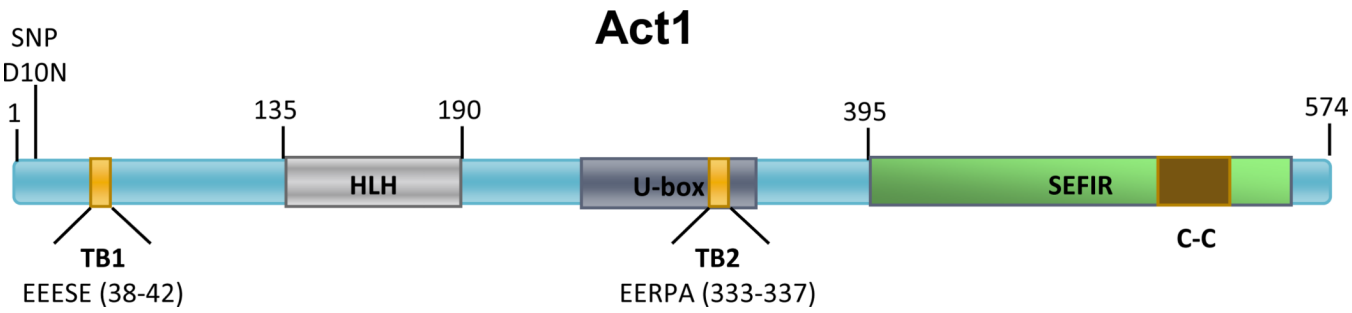

Figure 2.

The structure of Act1. Act1 contains two TRAF binding motifs (TB1 and TB2) that mediate TRAF6 and TRAF4 interactions following IL-17 stimulation. The U-box E3 ligase domain is functionally important for mediating the ubiquitination of its target proteins, like TRAF6 and HuR. The SEFIR domain of Act1 is necessary for the recruitment of Act1 to the IL-17 receptor upon IL-17 stimulation. At the N-terminus, a highly conserved region is required for Act1's interaction with the molecular chaperone, Hsp90.

Table I

Regulators of IL-17 signaling

Name	Description	Reference
Negative		
TRAF4	Competes with TRAF6 for Act1 binding	[57]
TRAF3	Binds to the IL-17R to interfere with the formation of the IL-17R-Act1-TRAF6 complex	[58]
USP25	Restricts the ubiquitination of TRAF5 and TRAF6 to down-regulate IL-17 signaling and mRNA stabilization	[61]
A20	Interacts directly with the distal domain of IL-17RA and mediates deubiquitination of TRAF6	[62]
C/EBPβ	Becomes phosphorylated by ERK and Gsk-3β and inhibit the expression of IL-17 target genes	[60]
miR23b	Inhibits IL-17 induced NFκB activation	[63]
IL-17RD	Disrupts the interaction of Act1 and TRAF6 to inhibit NFκB activation	[67, 68]
Positive		
NFκBIZ	Required for IL-17A induced gene expression	[65, 66]
IL-17RD	Enhances IL-17A-dependent MAPK signaling and neutrophil recruitment through MIP-2	[67, 68]
C/EBPδ	Essential for IL-27-dependent IL-6 expression	[156]