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IL-17 Signaling: The Yin and the Yang

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Abstract

Interleukin (IL)-17 is the founding member of a novel family of inflammatory cytokines. While the pro-inflammatory properties of IL-17 are key to its host-protective capacity, unrestrained IL-17 signaling is associated with immunopathology, autoimmune disease and cancer progression. In this review, we discuss both the activators and the inhibitors of IL-17 signal transduction, and the physiological implications of these events. We highlight the surprisingly diverse means by which these regulators control expression of IL-17-dependent inflammatory genes, as well as the major target cells that respond to IL-17 signaling.

1. IL-17: The Yin and the Yang

IL-17 (IL-17A, originally called CTLA-8) was cloned in 1993, but its functions remained obscure for close to a decade [1]. In 2005, IL-17 came into prominence with the discovery of a new population of $CD4^+$ T helper (Th) cells characterized by expression of IL-17. This subset became known as “Th17 cells,” and a plethora of literature has since been devoted to understanding the mechanisms that direct development, differentiation and regulation of this lineage [2–5]. Although Th17 cells are typically considered the principal source of IL-17, $CD8^+$ cells have also been shown to make this cytokine, and are termed “Tc17.” In addition, a number of innate immune subsets make this cytokine, including innate-acting lymphocytes such as γδ-T cells, some natural killer T (NKT) cells and TCRβ+ ‘natural’ Th17 cells. Furthermore, IL-17-expressing Type 3 “innate lymphoid cells” (ILC3) have been described, which lack an antigen receptor and serve as the innate counterparts of Th17 cells [6]. Myeloid cells have also been reported to make IL-17, although not in large amounts, and in many cases the validity of this has been called into question [7]. Collectively, IL-17-producing cells, whether adaptive or innate, are often termed ‘Type 17’.

Antibodies targeting IL-17A (secukinumab and ixekizumab) were approved in 2016 for the treatment of moderate to severe plaque psoriasis [8, 9]. In many cases these drugs cause

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Conflicts of Interest

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almost complete clearance of psoriatic plaques [10, 11]. However, the efficacy of IL-17 blockade for other conditions has been less dramatic [7], though there are promising data from trials of ankylosing spondylitis and psoriatic arthritis [7, 12]. Disappointingly and rather surprisingly, trials of secukinumab and brodalumab (anti-IL-17RA) in Crohn's disease were terminated early due to worsening of disease in the treatment group [13, 14]. This observation contrasted with the efficacy of anti-IL12/23 therapies (ustekinumab, briakinumab) and anti-IL-6 receptor antibody (tocilizumab), which target cytokines that control Th17 differentiation and hence IL-17 secretion [15–17]. An explanation for this paradox came from studies in mice showing a dominant protective role for IL-17 in maintaining intestinal barrier integrity that apparently outweighs its tissue-damaging potential in inflammatory bowel disease [18–21]. Thus, targeting IL-17 is an effective therapy for certain conditions, but its clinical use has revealed new insights into how Th17 cells function in humans.

While IL-17 blockade is clinically beneficial in some settings, the downside of this and all immune-modulating drugs is susceptibility to opportunistic infection. Numerous studies in mice starting in the early 2000's indicated that IL-17R signaling is critical for protection against a variety of fungal and bacterial infections, particularly the commensal fungus *Candida albicans* and the pulmonary bacterium *Klebsiella pneumoniae* [22]. Humans with IL-17 defects are especially prone to chronic mucocutaneous candidiasis (CMC). For example, rare mutations in IL-17 signaling genes (e.g., *IL17RA, IL17RC, ACT1*) are associated with CMC [23–25]. Individuals with *AIRE* gene deficiency can also generate neutralizing autoantibodies against Th17 cytokines including IL-17A, and the presence of these antibodies is typically associated with CMC as well [26, 27]. However, only a small percentage of patients undergoing anti-IL-17 treatment (2–4%) experienced mucosal candidiasis, suggesting that blockade of this cytokines may need to be profound in order to cause this side effect [11, 28].

2. IL-17 Cytokines and Receptors

The IL-17 family consists of six structurally related cytokines IL-17A (IL-17), IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F. IL-17A and IL-17F are the most closely related and are co-expressed on linked genes and are usually co-produced by Type 17 cells [29]. Similarly, the IL-17R family comprises five receptor subunits, IL-17RA, IL-17RB, IL-17RC, IL-17RD and IL-17RE. IL-17RA is the founding member of the IL-17R family and is a co-receptor used by several other IL-17 family ligands. The expression and functions of the extended IL-17/IL17R family are reviewed in detail elsewhere, summarized in Figure 1 [30]. IL-17 and IL-17F exist either as homodimers or as a heterodimer, and all forms of the cytokine induce signals through an obligate dimeric IL-17RA and IL-17RC receptor complex. This review focuses on IL-17 signal transduction, but many of the principles will likely apply more broadly to this family.

3. Structural Features of the IL-17 Receptor Family: SEFIR and Beyond

Members of the IL-17R family are defined by conservation of a cytoplasmic motif known as the similar expression of fibroblast growth factor and IL-17R (SEFIR) domain, a motif that

is distantly related to the “Toll/IL-1R” (TIR) domain found in IL-1 and Toll-like receptor family members [31]. Act1, also known as Connection to IκB kinase and Stress-activated protein kinases (CIKS), is a unique cytosolic adaptor required for activation of all known IL-17-dependent signaling pathways [22, 32]. Act1 contains a SEFIR domain and interacts with IL-17RA and IL-17RC through homotypic SEFIR interactions [31, 33]. Consistent with this central role of Act1, soluble decoy peptides that mimic the predicted Act1:IL-17RA interface blocked both IL-17A and IL-25 (IL-17E) signaling activities [34].

In addition to the SEFIR domain, the first mutagenesis studies of IL-17RA identified a nonconserved region required for IL-17RA signaling function that extends ~100 residues beyond the SEFIR, termed a “SEFIR-Extension” (SEFEX) [35, 36]. Subsequent X-ray crystallographic studies of the human IL-17RA cytoplasmic domain confirmed that the SEFIR and SEFEX regions together comprise a single composite structural motif [37]. Deletion studies suggested that IL-17RC may also require at least a short sequence extending past the SEFIR region for receptor functionality [38]. There are SEFIR domains in the other IL-17R family members, though their functions are not well defined. Interestingly the IL-17RB SEFIR region appears to adopt a very different 3-dimensional topology from its counterpart in IL-17RA [37, 39], suggesting there may be unique twists to how other IL-17R family members operate.

The cytoplasmic tail of IL-17RA additionally contains a distal domain distinct from the SEFIR/SEFEX whose function is associated with negative regulation of signaling. The first studies of this motif were based on correlations with activation of the transcription factor CCAAT/Enhancer Binding Protein (C/EBP)β (see below) [35, 40]. Hence, this region was named a “C/EBPβ activation domain” (CBAD). Later studies showed association of the CBAD with two signaling inhibitors, TNF receptor associated factor 3 (TRAF3) and the ubiquitin-editing enzyme A20 [41–43]. Therefore, IL-17RA has at least two structurally and functionally discrete signaling domains within the cytoplasmic tail that control downstream signaling events.

The extracellular regions of IL-17R family members contain two fibronectin III-like (FN) domains, homologous to those in the extracellular regions of Class I and Class II cytokine receptors [31, 44, 45]. These domains mediate protein-protein interactions as well as ligand binding. Yeast-two hybrid studies and FRET analyses revealed that the membrane proximal FN domain in IL-17RA (FN2) is capable of self-dimerization and accordingly mediates pre-assembly of IL-17R complex. This motif thus functions similarly to the “pre-ligand assembly domain” found in the TNF receptor family and is another potential way that assembly or blockade of IL-17R receptors might be manipulated [46–48].

4. IL-17 Signal Transduction

IL-17 upregulates inflammatory gene expression either by inducing *de novo* gene transcription or by stabilizing target mRNA transcripts, and both of the pathways controlling these events are discussed in detail in the following sections (Figure 3). Although the IL-17R is expressed ubiquitously, non-hematopoietic cells are generally the primary responders to IL-17 (Figure 2B) [7]. The pro-inflammatory role of IL-17 was first demonstrated in

fibroblasts, where IL-17 was shown to activate NF-κB and induce NF-κB-dependent cytokines [49–51]. Subsequent studies delineated a characteristic IL-17 core gene signature that includes pro-inflammatory cytokines, chemokines, anti-microbial peptides (AMPs), matrix metalloproteinases (MMPs) and inflammatory effectors (Figure 2A). [52, 53]. Additionally, there is a distinct, tissue-specific pattern of IL-17-dependent genes that underlies the diverse physiologic functions of this cytokine (Figure 2B) [54]. For instance, IL-17 regulates several genes largely restricted to gut epithelia, such as occludin (*Ocln*), regenerating islet-derived protein 3 gamma (*Reg3g*) and mucin 1 (*Muc1*), which all contribute to maintenance of intestinal barrier integrity. In NK cells, IL-17 was reported to induce expression of GM-CSF (*Csf2*), one of the few documented examples of IL-17-dependent signaling in hematopoietic cells [55]. A recent report showed that IL-17 drives kallikrein 1 (*Klk1*) expression in renal epithelial cells to confer protection against disseminated candidiasis [56]. IL-17-induced induced receptor activator of NF-κB ligand (RANKL, also known as TNFSF11 or osteoprotegerin ligand, OPGL) expression in osteoblasts promotes differentiation and activation, perhaps accounting for some of the bone-destructive effects of IL-17 observed in models of arthritis or periodontal disease [57, 58], and IL-17 regulates expression of histatins in the salivary compartment that control infection with *C. albicans* [59]. Another vitally important facet of IL-17 function is its capacity to synergize (or at least cooperate) with numerous other inflammatory stimuli, further compounding its biological activities [60, 61].

In this review, we will discuss in detail the many activators and inhibitors of IL-17 signaling that amplify or dampen IL-17-mediated inflammation, respectively. These regulators play non-redundant roles in controlling expression of IL-17 target genes. Understanding their mechanism of action may provide strategies for designing novel therapeutic interventions for IL-17-mediated signaling and inflammation.

4a. Regulation of Transcription Factors

NF-κB and MAPKs—The IL-17R signaling pathway shares many features in common with IL-1R/TLR pathways, but there are notable differences, particularly in receptor-proximal signaling events. Most significantly, the earliest event in signaling following IL-17 receptor engagement is the induced association of the IL-17R with Act1 (CIKS), an adaptor not used by the IL-1R/TLR family. [33, 62]. In addition to its role as an adaptor, Act1 is a Lysine-63 (K63) E3 ubiquitin ligase, which recruits and ubiquitinates TRAF6, also a K63 E3 ligase. Ubiquitination of TRAF6 provides a scaffold for the recruitment and activation of the transforming growth factor β-activated kinase (TAK)1 and the inhibitor of NF-κB kinase (IKK) complex composed of IKKα, IKKβ and IKKγ (NEMO) [22, 62–65]a. IKK then phosphorylates the IκB subunit of the NF-κB:IκB complex, marking IκB for proteasomal degradation. Degradation of IκB exposes a nuclear localization signal on NF-κB, freeing it for rapid nuclear translocation and consequent inflammatory gene transcription (Figure 3) [66]. IL-17 signaling does not activate the non-canonical NF-κB pathway [30]. Consistently, most IL-17 target genes have essential NF-κB promoter elements [67].

While NF-κB is a undisputedly a key event in the IL-17 signaling cascade, IL-17 is consistently found to be only a modest activator of NF-κB [61]. Despite increased

understanding of factors controlling NF-κB activation, the underlying basis of this weak activation is not yet understood. Nonetheless, IL-17 is a powerful inducer of inflammatory cytokines due to its capacity to signal synergistically with other stimuli. Although best-studied in the case of TNFα, IL-17 also cooperates with lymphotoxin (LT), IFNγ and other inflammatory effectors [53]. Interestingly, the synergistic up-regulation of IL-17 and TNFα target gene expression is not mediated through NF-κB activation [60, 61]. Rather, co-stimulation with TNF-α and IL-17 results in stabilization of TNF-α-induced mRNA transcripts that are inherently unstable, which is characteristic of most chemokine and cytokine genes [68–71]. Recently, IL-17 was shown to synergize with the fibroblast growth factor FGF2 in colitis driven by dysregulated intestinal microbiota. In contrast to its positive role in IL-17R signaling, Act1 is a negative regulator of FGF2; FGF2 and IL-17 co-stimulation resulted in preferential binding of Act1 to IL-17RA, thus dampening its suppressive effect on FGF2 activity [21]. These combinatorial effects of IL-17 create a setting in which the physiological impact of IL-17 *in vivo* is profound, even though its "solo" effects in isolated experimental conditions do not always appear to be particularly potent. Nevertheless, some studies suggest that the activity of IL-17 is dependent on cellular context. For example, in a Reconstructed Human Epidermis (RHE) model, IL-17 was shown to regulate significantly more genes in differentiated versus undifferentiated keratinocytes. The differential IL-17 response was attributed to a higher expression of the transcription factor CCAAT/enhancer-binding protein β (C/EBPβ) in differentiated keratinocytes [72].

Many IL-17-dependent genes are regulated by Inhibitor of NF-κB Zeta (IκBζ), a non-canonical member of the NF-κB transcription factor family. Despite its name, IκBζ acts primarily as a driver of transcription rather than an inhibitor. IL-17 induces both IκBζ mRNA and protein expression, and IκBζ in turn positively activates numerous IL-17 target genes in cooperation with NF-κB [69, 70, 73–75]. Additionally, IκBζ facilitates IL-17-induced gene expression by suppressing expression of miR-23b, an inhibitor of IL-17 signaling [76]. The transcript encoding IκBζ (*Nfkbiz*) is intrinsically unstable, and IL-17 serves to enhance its stability and thereby indirectly upregulate expression of all its target genes (see below). One case in point is Lipocalin 2 (Lcn2, also known as 24p3 or NGAL), a prototypical IL-17 target gene (Figure 2) whose expression is exquisitely IκBζ-dependent [67, 69, 74]. Thus, IκBζ is a central regulator of IL-17 signaling, and identifying novel IκBζ target genes important for IL-17-mediated inflammation may be an informative area for future studies.

IL-17 also activates mitogen-activated protein kinase (MAPK) pathways, which include extracellular signal-regulated kinase (ERK), p38 and JUN N-terminal kinase (JNK), although the dominance of these pathways in response to IL-17 appears to vary somewhat by cell background (Figure 3) [61]. Support for a role for the MAPK pathway *in vivo* came from studies in which mice with impaired p38-MAPK signaling showed reduced pathology in IL-17-driven experimental autoimmune encephalomyelitis (EAE). Moreover, mice lacking the p38-MAPK inhibitor MKP1 (Dusp1) showed enhanced IL-17-dependent signaling in this setting [77]. The TPL2 kinase is also upstream of IL-17-mediated MAPK activation. Upon IL-17 stimulation, IKK mediates p105 phosphorylation, releases TPL2 from p105 and activates p38 and JNK. Interestingly, the TPL2-TAK1 axis activates IKK, creating a positive-feedback loop that reinforces gene induction. TPL2 deficiency is

associated with compromised IL-17-induced expression of chemokines and pro-inflammatory cytokines in CNS, and *Tpl2*$^{-/-}$ mice are resistant to EAE [78]. In the TLR and TNFR pathways, TPL2 mediates ERK1/2 activation; however TPL2 is dispensable for ERK activation in IL-17 signaling [78, 79]. Hence, the mechanism that activates ERK in the IL-17 pathway is still unclear. Another recent study showed that IL-17 activates a formation of a multi-protein signaling complex that comprises of IL-17R-ACT1-TRAF4-MEKK3-MEK5. This complex activates ERK5 but not NF-κB, p38, JNK, or ERK1/2, which induces IL-17 target genes resulting in keratinocyte proliferation and tumor formation [80].

Although the IL-17 signaling pathway is primarily activated by serine/threonine kinases that characterize NF-κB and MAPK pathway activation, IL-17 was recently reported to activate the spleen tyrosine kinase (Syk) tyrosine kinase in keratinocytes. Upon IL-17 stimulation, Syk associated with IL-17RA, Act1 and TRAF6, leading to activation of NF-κB [81]. Thus, there may be multiple avenues by which IL-17 activates NF-κB.

C/EBPs—CCAAT/enhancer-binding protein (C/EBP) transcription factors are additional transcriptional regulators used by IL-17. Both NF-κB and C/EBP binding sites are over-represented in promoters of IL-17 target genes [67], and expression of C/EBPβ and C/EBPδ is increased by IL-17 in a variety of settings [71]. Several gene promoters absolutely require C/EBPβ and/or C/EBPδ for IL-17-dependent induction (e.g., *Il6* and *Lcn2*), even when the NF-κB sites are intact [35, 82, 83]. Some data suggest that activation of C/EBP family members is part of the cooperative/synergistic activation of IL-17 with TNF-α [71]. C/EBPδ is primarily induced transcriptionally, whereas C/EBPβ is regulated by IL-17 post-transcriptionally (alternative translation) and post-translationally (phosphorylation). For example, there are three methionine start sites within the *Cebpb* gene, and IL-17 triggers a shift to use of the less dominant sites [71]. The biological significance of IL-17-induced changes in alternative translation is unclear, but one of the alternatively generated C/EBPβ isoforms contains only the DNA binding domain and is thus potentially a transcriptional repressor [71, 84]. C/EBPβ is also inducibly phosphorylated at multiple sites following IL-17 stimulation, an event that is associated with reduced signaling. Specifically, ERK and glycogen synthase kinase 3 β(GSK-3β) phosphorylate C/EBPβ on two threonine residues within its regulatory domain [40]. Intriguingly, both these alternative translation and phosphorylation of C/EBPβ are mediated by the IL-17RA CBAD domain [35, 40], linking C/EBPβ to negative regulation of IL-17.

4b. Control of mRNA Stability and Translation

In addition to turning on inflammatory genes by *de novo* transcription, IL-17 promotes expression of a large number of gene targets by controlling mRNA stability. Stabilized transcripts are stored in cytoplasmic granules, and can either be translated or degraded rapidly as needed [85]. Indeed, mRNA stabilization appears to be one of the mechanisms by which IL-17 synergizes with other cytokines such as TNFα [68, 69]. Moreover, many inflammatory cytokines and chemokines induced by IL-17 are intrinsically unstable. Therefore, since IL-17 is a poor stimulus for NF-κB and only induces transcription of inflammatory genes modestly, its capacity to indirectly control inflammatory gene

expression through control of factors like IκBζ is a fundamental feature of IL-17-mediated inflammation.

RNA Binding Proteins—IL-17-induced regulation of mRNA stability is controlled in several non-canonical ways. For example, tristetraprolin (TTP), one of the best-characterized AU-rich element (ARE)-binding factors known to be activated by IL-1β and TNFα, does not stabilize mRNA in response to IL-17 [86]. Like all known IL-17-dependent signals, the IL-17-mediated mRNA stability pathway is dependent on Act1, but surprisingly this was found to occur independently of TRAF6 [87]. Rather, Act1 is inducibly phosphorylated [38], which triggers a shift in TRAF factor usage and subsequently determines which downstream pathway is preferentially activated [88]. Specifically, using the *Cxcl1* mRNA transcript as a representative system, IL-17 was found to recruit the inducible IκB kinase (IKKi, also known as IKKε) to the IL-17R-Act1 complex, leading to phosphorylation of Act1 on Ser 311.

Phosphorylated Act1 favors recruitment of TRAF2 and TRAF5, which sequester an RNA decay factor (the mRNA splicing regulatory factor 2, SF2) away from the 3′ UTR of *Cxcl1* mRNA. This sequestration thus prevents degradation of *Cxcl1* [89]. At the same time, IL-17 recruits the RNA binding protein Human Antigen R (HuR, also known as ELAVL1) to the Act1/TRAF2/TRAF5 complex and activates HuR through Act1-dependent ubiquitination. HuR directly binds to the 3′UTR of the *Cxcl1* transcript. Since HuR and SF2 recognize similar sequences within the 3′UTR, HuR sterically competes with SF2 and prevents SF2-mediated RNA decay [90] (Figure 3). While phosphorylation of Act1 by IKKi on Ser 311 mediates IL-17-induced mRNA stability, phosphorylation of Act1 on three other Ser sites by IKKi and the IKK-related kinase, TANK binding kinase 1 (TBK1), suppresses IL-17 signaling (Figure 4). IL-17 activates TBK1, which associates with and phosphorylates Act1. Additionally, Act1 phosphorylation interferes with binding of TRAF6 to Act1 and inhibits NF-κB activation [91]. Thus, a complex series of events centered around the Act1 and TRAF proteins controls the activation of gene expression through both transcription and mRNA stability.

Although enhanced inflammation due to IL-17-mediated mRNA stabilization is beneficial during clearance of pathogens, constraint of this pathway is critical for prevention of severe inflammatory conditions. Recently we showed that the endoribonuclease MCPIP1 (MCP-1-induced protein 1, also known as Regnase-1) negatively regulates IL-17 signaling by degrading mRNAs encoding IL-17-dependent genes [74]. IL-17 induces MCPIP1 mRNA (*Zc3h12a*) and protein in non-hematopoietic cells [74, 92, 93]. Specifically, IL-17 induces MCPIP1 via NF-κB, but also stabilizes *Zc3h12a* transcripts through activation of the DEAD box protein DDX3X [74, 94]. DDX3X forms a complex with Act1 upon IL-17 stimulation and promotes stability of *Zc3h12a* mRNA though interestingly not of *Il6, Cxcl1* or *Cxcl5* mRNA [94] (Figure 3). In turn, MCPIP1 acts as a negative feedback inhibitor by degrading IL-17-induced mRNA transcripts such as *Il6* and *Nfkbiz* (encoding IκBζ, see above) through their respective 3′UTRs (Figure 4). Moreover, MCPIP1 indirectly regulates expression of other IκBζ-dependent IL-17 target genes by controlling IκBζ mRNA stability and ultimately protein expression. Consequently, MCPIP1-deficient mice exhibit enhanced IL-17 signaling which makes them less susceptible to infection (e.g. by *Candida albicans*)

while exacerbating IL-17-mediated pathology in mouse models of EAE, pulmonary inflammation and psoriasis [74, 95].

Intriguingly, MCPIP1 also degrades the mRNA transcripts encoding IL-17 receptor subunits *Il17ra* and *Il17rc.* Strikingly, this regulation occurs in a manner that is independent of the receptor genes' 3′UTR motifs, but rather through binding to sequences located within the coding region [74]. Recently, the RNA binding proteins Roquin-1 and Roquin-2 were shown to cooperate with MCPIP1 to repress mRNAs of T_H17 differentiating factors such as IL-6, thus regulating IL-17 production [96]. Moreover, Roquins also regulate IL-6 production downstream of IL-17 signaling. However, the role of Roquins and MCPIP1 are not fully redundant in IL-17 pathway, as knockdown of both enhances signaling more than knockdown of either alone [74]. Recently, MCPIP1 and Roquin-1 were shown to recognize stem-loop structural motifs in the 3′UTR of their target transcripts, rather than binding to specific sequences [97]. A similar mechanism of recognition is likely to exist in IL-17 signaling.

MicroRNAs—MicroRNAs are gene expression regulators that induce mRNA decay or suppress translation. In IL-17 signaling pathway, miR-23b was found to target signaling intermediates such as TAB2, TAB3 and IKK-α, which led to inhibition of NF-κB activation. IL-17 downregulates miR-23b transcription, resulting in feedback activation of IL-17 signaling [76]. In addition, miR-30a induces the degradation of *Traf3ip2* mRNA (encoding Act1) and consequently inhibits IL-17-induced NF-κB and MAPK activation (Figure 4) [98]. Doubtless more layers of miRNA directed regulation of IL-17 signaling will come to light.

4c. Ubiquitin-Mediated Signaling

Ubiquitin-related post-translational modifications play a major role IL-17 signaling. Ubiquitin ligases recognize and link ubiquitin chains to their respective substrate. Though all seven lysines present in ubiquitin can be used for the formation of ubiquitin chains, only K48 and K63 linked chains have been described thus far in IL-17 signaling. K48 ubiquitinated substrates typically undergo proteasomal degradation, whereas K63 chains promote signal transduction by enhancing protein-protein interactions [99]. As described above, E3 ubiquitin ligases such as Act1 and TRAF6 are central activators of IL-17 pathway through K63-linked ubiquination events. The β-transducin repeat–containing protein (β-TrCP) is an F-box E3 ubiquitin ligase that ubiquitinates phosphorylated Act1 on K48 residues under prolonged stimulation, thus triggering Act1 degradation and restricting IL-17 activity (Figure 4) [100]. Furthermore, heat shock protein 90 (Hsp90), a chaperone that helps in protein folding and assembly, maintains the integrity of Act1 at the protein level. Inhibition of Hsp90 leads to proteasomal degradation of Act1 and thus downregulates IL-17 activity [101] (Figure 3). As Act1 is the focal point of IL-17 signal transduction, it is not surprising that there are multiple pathways involved in fine-tuning Act1 expression and activation.

Ubiquitin ligases also influence signal transduction by competing for common substrates/complexes. Although the impact of their ubiquitin ligase activity is unclear, TRAF3 and

TRAF4 both act as inhibitors of IL-17 signaling (Figure 4) As noted, TRAF3 binds to the CBAD domain in IL-17RA and interferes with IL-17RA-Act1 interaction. In contrast, TRAF4 competes with TRAF6 for occupancy of TRAF binding sites on Act1. Consequently, deficiency of TRAF3 or TRAF4 results in enhanced IL-17-activated gene expression and therefore enhanced autoimmune disease severity [41, 102].

Removal of ubiquitin chains (mainly K63-linked) also serves to dampen IL-17-induced inflammatory response. This process is carried out by deubiquitinase enzymes (DUBs), and reverses the positive signaling induced by Act1-TRAF6. In the IL-17 pathway, A20 (encoded by *Tnfaip3*, a common autoimmune gene locus [99]) and Usp25 have both been shown to deubiquitinate TRAFs (Figure 4) [42, 103]. Mechanistically, A20 deubiquitinates TRAF6, which suppresses NF-κB and MAPK activation. Similarly, Usp25 deubiquitinates both TRAF5 and TRAF6 and thereby restricts downstream gene expression. Notably, A20 expression is upregulated by IL-17, making this another feedback regulatory response. Moreover, A20 is recruited to the CBAD domain of IL-17RA, explaining why deletion of this receptor region leads to exacerbated IL-17-dependent gene induction [35, 36]. Intriguingly, A20 interacts with the non-canonical adaptor Anaphase Promoting Complex Subunit 5 (ANAPC5, also called APC5), and knockdown of ANAPC5 enhances IL-17 signaling [104]. Notably, since these DUBs act on other inflammatory pathways (TNFα, IL-1R, etc), their activation by IL-17 can have ripple effects that serve to restrict inflammation more globally. Cumulatively, ubiquitin-related protein modifications are rheostats that help control the magnitude of IL-17-induced inflammatory gene expression.

5. Conclusion and perspectives

Although IL-17 is a critical mediator of inflammation, it is a modest activator of signaling compared to other inflammatory stimuli. Nonetheless, its capacity to synergize with other inflammatory signals makes this a vital inflammatory effector. This is, of course, highly biologically relevant in the context of an inflammatory environment, where conditions are not driven independently by a single cytokine, but rather as a result of concerted actions of multiple inflammatory mediators [60]. This review highlights the pathogenic and protective aspects of IL-17 and discusses multiple regulatory mechanisms that keep IL-17 signaling in check. Since the positively-acting proteins in the IL-17 pathway can drive pathogenicity if not held in check, negative inhibitors are vital to keep the inflammation under control.

It is not well understood why so many non-redundant mechanisms exist to turn on or off IL-17 signal transduction. One potential explanation is that these regulators individually are not sufficient to enhance or halt a response, but that a collective effort at multiple levels is necessary, a phenomenon described in many other immune settings [105]. Similarly, the kinetics of induction or activity of each regulator may contribute uniquely at different stages of signaling. Moreover, once induced, these inhibitors can also regulate other signaling pathways, thus serving to fine-tune inflammation. Biologically, it is imperative that the precarious balance between pathogenic (Yin) and protective (Yang) sides of IL-17 signaling be maintained. An uncontrolled acceleration of the system or failure of the brakes can both lead to persistent inflammation resulting in tissue damage and/or autoimmune diseases. Thus, gaining an in-depth understanding of these regulators may help in the rational design

of drug targets for maintaining balance during dysregulation or for treatment of diseases where IL-17 activity is beneficial. Furthermore, as more activators and inhibitors are identified, it will be critical to understand their specificity and the interplay between all these factors influencing IL-17-induced inflammation.

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Abbreviations

AMP	anti-microbial peptide
ANAP	Anaphase Promoting Complex
C/EBP	CCAAT/Enhancer Binding Protein
CIKS	Connection to IκB kinase and Stress-activated protein kinases
CMC	chronic mucocutaneous candidiasis
DUB	deubiquitinase
EAE	experimental autoimmune encephalomyelitis
FN	fibronectin III-like
Hsp	heat shock protein
IκBζ	Inhibitor of NF-κB-ζ
ILC	innate lymphoid cell
MCPIP1	MCP-1-induced protein 1
MMP	metalloproteinase
SEFEX	SEFIR-Extension
SEFIR	similar expression of fibroblast growth factor and IL-17R
Syk	spleen tyrosine kinase
TAK1	transforming growth factor β-activated kinase
TBK1	TANK Binding Kinase 1

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TRENDS BOX

IL-17-mediated inflammation is critical for microbial clearance, while unrestrained IL-17 signaling can promote immunopathology.

Signaling pathways activated by IL-17 lead to enhanced *de novo* gene transcription and also control of mRNA stability.

IL-17 activates multiple negative regulators of signaling to restrict bystander inflammation, which target transcriptional activators as well as regulators of mRNA stability

IL-17 induces a core set of signature genes common to most tissues, but tissue-specific gene targets are also identified that dictate the biology of this cytokine in different locations.

Therapeutics targeting the IL-17 pathway are approved for treating autoimmunity, and are especially effective in psoriasis. Applicability to other conditions is under investigation.

OUTSTANDING QUESTIONS

1. Why is strength of IL-17R signaling comparatively modest compared to traditional pro-inflammatory signaling pathways such as TNFα or TLR ligands? Is this due to an altered balance of negative regulators?
2. What are the molecular bases for synergy between IL-17 and other inflammatory effectors?
3. Why does IL-17 activate so many negative regulatory pathways? Can these be exploited to design drugs targeting the IL-17 inflammatory axis?
4. Does IL-17 participate in other forms of post-transcriptional RNA processing such as RNA splicing, transport, and translation? Are long non-coding RNAs (lncRNAs) involved in the regulation of IL-17 signaling?
5. Does IL-17 affect epigenetics or chromatin remodeling?

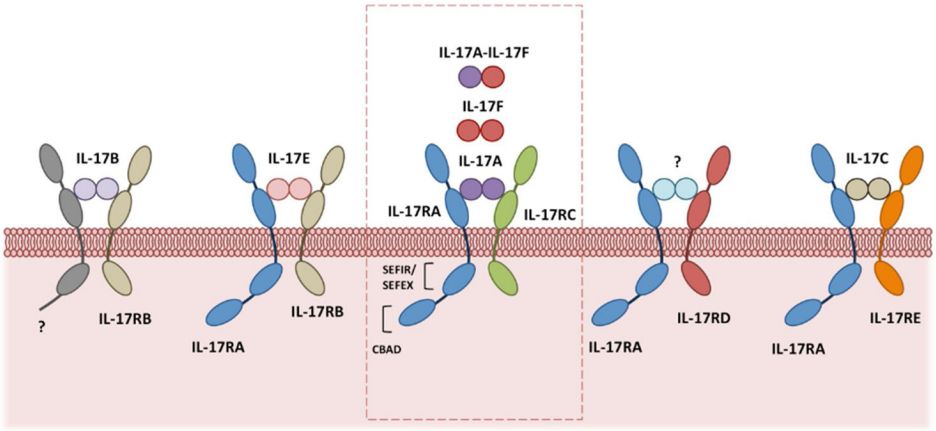

Figure 1. IL-17 Cytokine and Receptor Family

IL-17A is the prototypical cytokine of IL-17 family that includes five other cytokines. IL-17 receptor family consists of five different receptors, which share a common cytoplasmic motif known as SEFIR domain. IL-17RA, the common subunit for all the other receptors, also consists of an inhibitory CBAD domain [SEFIR:similar expression of fibroblast growth factor and IL-17Rs, SEFEX:SEFIR extension, CBAD:C/EBPβ activation domain]

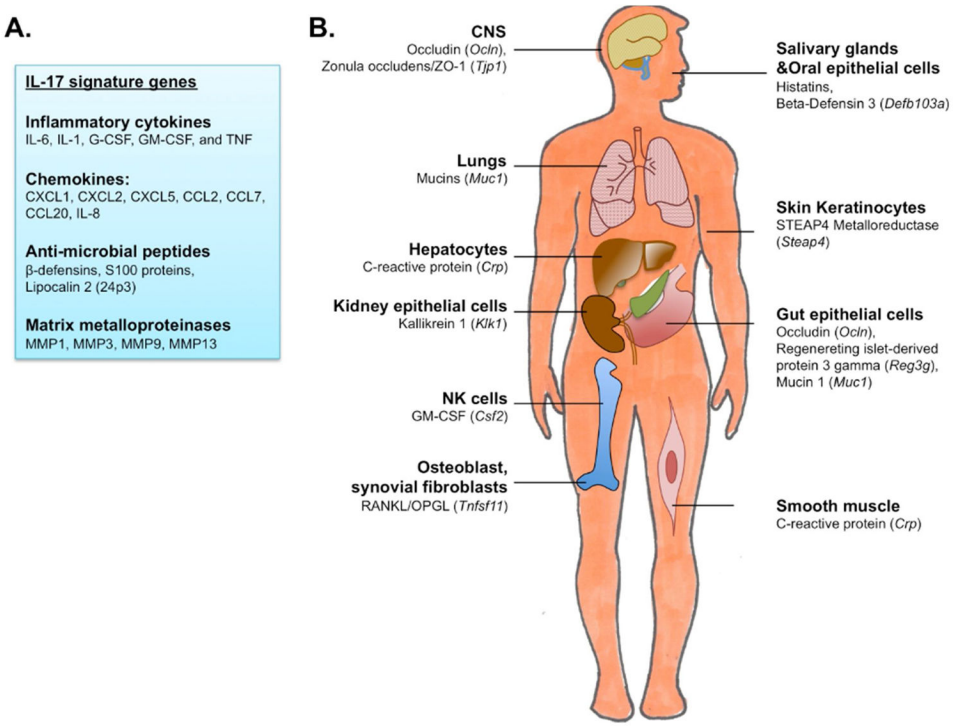

Figure 2. Major Inflammatory Genes Regulated by IL-17

IL-17 signaling controls inflammation by regulating expression of inflammatory genes in the cells of mostly non-hematopoietic compartment. The IL-17 signature genes (top left) are common inflammatory genes regulated by IL-17. Genes listed elsewhere are specific to respective tissue compartments and play a critical role in mediating tissue specific IL-17-dependent inflammation.

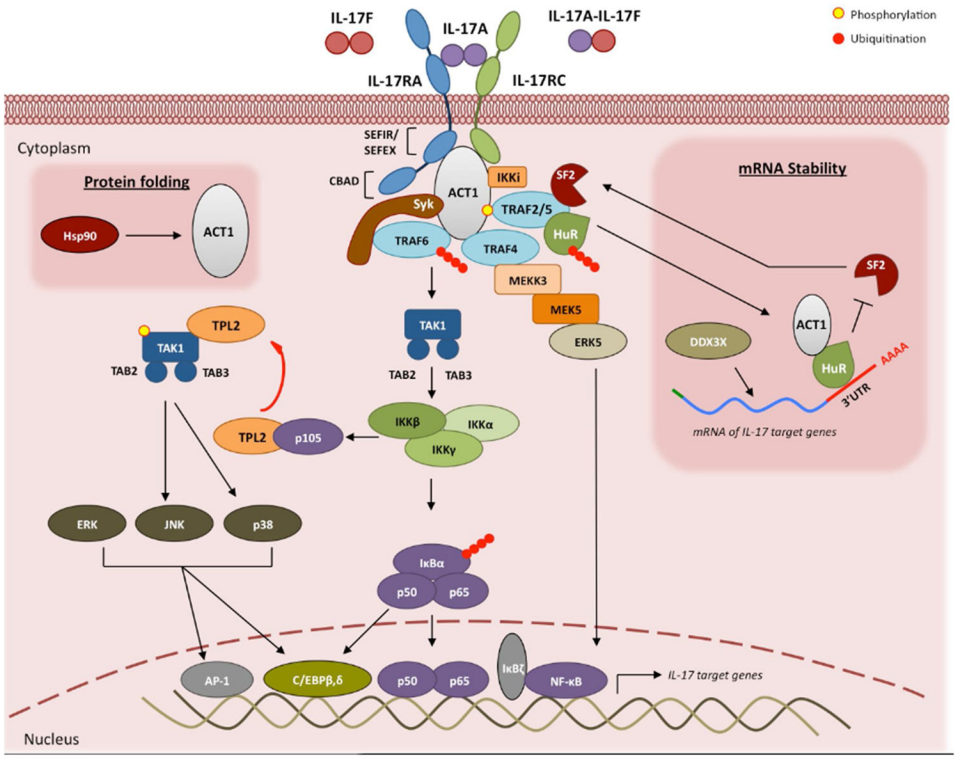

Figure 3. Activation of IL-17 Signal Transduction

IL-17 signaling starts with the binding of IL-17A/A, IL-17A/F or IL-17F/F cytokine to their receptors IL-17RA and IL-17RC. Upon ligand binding, Act1 activates multiple independent signaling pathways mediating through different TRAF proteins. Activation of TRAF6 results in the triggering of NF-κB, C/EBPβ, C/EBPδ and MAPK pathways. IL-17R-Act1 complex also associates with MEKK3 and MEK5 via TRAF4, resulting in the activation of ERK5. WhileTRAF6 and TRAF4-mediated IL-17 signaling results in transcription of inflammatory genes, IL-17 signaling through ACT1-TRAF2-TRAF5 complex results in the control of mRNA stability of IL-17 target genes. [Hsp: heat-shock protein, TRAF: TNF receptor associated factor, TAK1: TGF-β activated kinase 1, IKK: inhibitor of kappa B kinase, ERK: extracellular signal related kinase, JNK: Janus kinase, HuR: human antigen R, also known as ELVAL1, SF2: splicing factor 2]

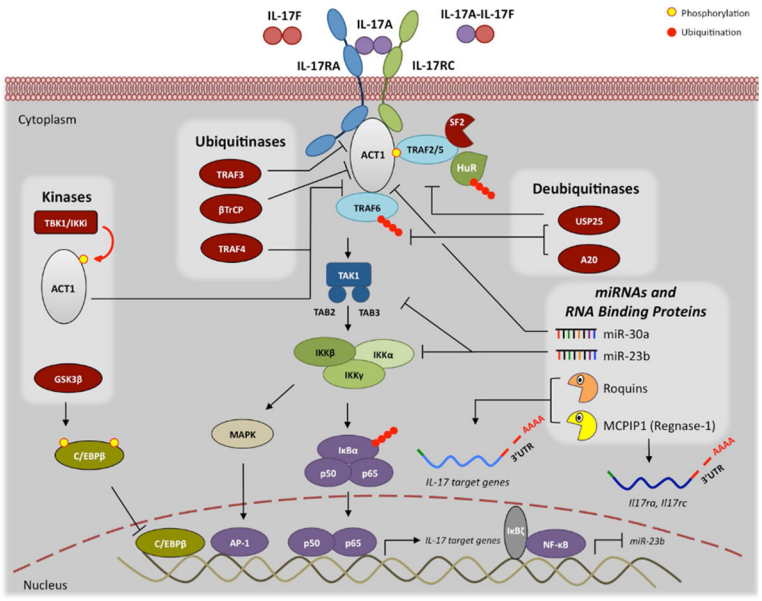

Figure 4. Negative regulation of IL-17 signal transduction

Different classes of inhibitors such as ubiquitinases (TRAF3, TRAF4 and βTrCP), deubiquitinases (A20 and USP25), kinases (TBK1, GSK3β), endoribonuclease (MCPIP1/ Regnase-1) and micro RNAs(miR-23b and miR-30a) negatively regulate IL-17 signaling through various independent mechanisms (see Table 1). [TRAF: TNF receptor associated factor, HuR: human antigen R, also known as ELVAL1, SF2: splicing factor 2, TAK1: TGF-β activated kinase 1, IKK: inhibitor of kappa B kinase, TBK1: TANK-binding kinase 1, GSK: glycogen synthase kinase, MAPK: mitogen-activated protein kinase]

Table 1

Proximal Activators and Inhibitors of the IL-17 Signaling Pathway

Reviewed in Refs. 22, 30, 65.

Classes	Molecules	Function
Ubiquitinases	**Act1**	Recruits and ubiquitinates TRAF6
	TRAF2	Mediates stability of IL-17 target gene transcripts
	TRAF5	Mediates stability of IL-17 target gene transcripts
	TRAF6	Mediates NF-κB and MAPK activation
	TRAF3	Interferes with formation of IL-17R-Act1-TRAF6 complex
	TRAF4	Competes with TRAF6 for association with Act1
	βTrCP	Degrades Act1
Deubiquitinases	**A20**	Deubiquitinates TRAF6
	USP25	Deubiquitinates TRAF5 and TRAF6
RNA Binding Proteins	**HuR**	Stabilizes *Cxcl1* and *Cxcl5* transcripts
	DDX3X	Stabilizes *Zc3h12a* (MCPIP1) transcripts
	SF2/ASF	Degrades *Cxcl1* transcripts
	MCPIP1/Regnase-1	Degrades IL-17 target gene transcripts and *Il17ra, Il17rc* transcripts
	Roquin-1/2	Degrades IL-17 target gene transcripts
micro RNAs	**miR-23b**	Targets TAB2, TAB3 and IKK-α
	miR-30a	Targets Act1
Chaperones	**Hsp90**	Mediates folding of Act1
Kinases	**MAPKs**	Activates AP-1
	IKKα/β/γ	Activates NF-κB
	TAK1, TAB2, TAB3	Activates NF-κB
	Syk	Mediates Act1-TRAF6 complex formation
	TPL2	Phosphorylates TAK1
	IKKi	Phosphorylates Act1 and mediates mRNA stability
	GSK3β	Phosphorylates C/EBPβ
	IκBα	Inhibits NF-κB
	TBK1/IKKi	Phosphorylates Act1 and inhibits Act1 and TRAF6 binding