HHS Public Access

Author manuscript

Nat Immunol. Author manuscript; available in PMC 2020 June 01.

Published in final edited form as:

Nat Immunol. 2019 December ; 20(12): 1594–1602. doi:10.1038/s41590-019-0514-y.

Interleukin 17 receptor-based signaling and implications for disease

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Abstract

Interleukin 17 (IL-17) is a highly versatile pro-inflammatory cytokine crucial for a variety of processes including host defense, tissue repair, inflammatory disease pathogenesis and cancer progression. In contrast to its profound impact *in vivo*, IL-17 exhibits surprisingly moderate activity in cell culture models, presenting a major knowledge gap regarding the molecular mechanisms of IL-17 signaling. Emerging studies reveal a new dimension of complexity in the IL-17 pathway that may help explain its potent and diverse *in vivo* functions. Discoveries of new mRNA stabilizers and receptor-directed mRNA metabolism provide insights into the means by which IL-17 cooperates functionally with other stimuli in driving inflammation, whether beneficial or destructive. Integration of IL-17 with growth receptor signaling in specific cell types offer new understanding in the mitogenic impact of IL-17 in tissue repair and cancer. This review summarizes new developments in IL-17 signaling and their pathophysiological implications.

Introduction

Il17a was discovered as a T cell-expressed transcript homologous to an open reading frame (ORF) in the T-cell tropic *Herpesvirus saimiri* virus[1]. Subsequent studies identified IL-17A (also known as IL-17) as the founding member of a distinct cytokine family with five additional members annotated as IL-17B though IL-17F. IL-17 did not gain wide attention until 2005, following the discovery of T_H17 cells[2, 3]. Through more than two decades of research, a plethora of physiological and pathogenic processes are now being attributed to IL-17 activity (Fig. 1)[4, 5]. Here in this review, we focus on how signaling by IL-17 is conducted at a molecular level and IL-17-mediated signaling events contribute to effector responses.

IL-17 receptor structure-function relationships

IL-17 signals through the IL-17RA and IL-17RC receptor subunits. IL-17F, the most closely related family member, also binds this receptor complex, as does the IL-17A/F heterodimer[6]. All three ligands mediate qualitatively similar but quantitatively distinct signals, with

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IL-17A > IL-A/F > IL-17F in terms of signaling potency[7]. Whereas IL-17RA is ubiquitously expressed, a more restricted expression of IL-17RC limits IL-17 signaling mostly to non-hematopoietic epithelial and mesenchymal cells. IL-17RA is a common subunit used by at least two other ligands (IL-17C and IL-17E/ also known as IL-25)[5]. A recent report suggests that IL-17RD may serve as an alternate receptor subunit for IL-17A, but surprisingly not IL-17F[8]. How these receptors function and their respective ligand/receptor relationships remains an active area of inquiry.

IL-17R family members are defined by a conserved region in the cytoplasmic tail known as the "SEF/IL-17R (SEFIR)"[9]. The only other known protein with a SEFIR is the multifunctional adaptor Act1, which is vital for nearly all known IL-17 signaling events[10, 11, 12]. The initiating event in IL-17 signaling is the recruitment of the multi-functional adaptor Act1 to the IL-17R via SEFIR interactions (Fig. 2a). Structure-function studies indicated that the SEFIR constitutes an interaction platform between Act1 and IL-17 receptors; hence peptides that block such interactions reduce IL-17-mediated pathology[13]. Act1 can be viewed as a multifunctional "hub" around which IL-17 signaling is induced. Act1 contains a TRAF-binding motif that recruits different TNF receptor associated factors (TRAFs) to initiate separate downstream pathways. Act1 also exhibits E3 ligase activity (targeting TRAFs) and direct RNA binding capacity, both of which are essential for the IL-17-induced transcriptional and post-transcriptional activation of gene expression[14, 15]. Befitting its central role in IL-17 signaling, Act1 is subjected to proteasomal degradation upon modification with lysine (K)48-linked polyubiquitin chain[16]. This process catalyzed by an F-box E3 ubiquitin ligase, β-transducin repeat-containing protein (β-TrCP), in response to prolonged IL-17 stimulation.

Although the SEFIR is the defining region of homology among IL-17 receptors, there are non-conserved extensions to this motif required for its function in at least some family members, and which are an essential part of its three dimensional structure[17, 18, 19, 20]. IL-17RA, the largest member of the family, additionally encodes a distinct C-terminal region that contains TRAF-binding sites and which is required to activate the transcription factor CCAAT/enhancer binding protein β (C/EBPβ); hence, this region has been dubbed a "CBAD" (C/EBPβ-activating domain)[18, 21]. There is no analogous domain in IL-17RC or other family members.

Transcriptional signaling by IL-17

In keeping with its homology to Toll-like receptor (TLR)/IL-1R cytokines[9], IL-17 signaling activates inflammatory transcription factors to induce gene expression via NF-κB and the activation of MAPK pathways (p38, ERK and JNK)[22] (Fig 2a). Consistently, IL-17-induced genes show enrichment of NF-κB and AP-1 binding sites in their proximal promoters[23], and blockade of the MAPK and NF-κB pathways typically impairs induction of IL-17-induced target genes[24]. The E3 ligase activity of Act1 is required for IL-17-induced NF-κB activation[14]. After the recruitment of Act1 to the IL-17 receptor complex, TRAF6 binds to the TRAF-binding motif in Act1, resulting in conjugation of K63-linked polyubiquitin chain to TRAF6[14]. Polyubiquitinated TRAF6 then activates TGFβ-activated kinase 1 (TAK1), leading to NF-κB activation. Notably, Act1-mediated TRAF6-activated TAK1 also

contributes to IL-17-induced activation of MAPK pathways for activation of transcription factors such as AP-1[10].

The TRAF6-mediated arm of IL-17 signaling is fine-tuned by several regulatory mechanisms to constrain IL-17-induced inflammation. A20 (*Tnfaip3*), a deubiquitinase associated with susceptibility to autoimmune syndromes including psoriasis, is upregulated by IL-17A through NF-κB. A20 is recruited via the CBAD to IL-17RA and removes Act1-mediated polyubiquitin chain on TRAF6, tempering activation in a negative-feedback circuit[25, 26]. Similarly, USP25 can also deubiquitinate TRAF6, limiting IL-17-induced signaling and the pathology of IL-17-dependent experimental autoimmune encephalomyelitis (EAE)[27]. In addition, TRAF4 competes with TRAF6 for the TRAF-binding motif on Act1. Consequently, deficiency of TRAF4 enhances IL-17-activated genes and sensitizes mice to EAE[28, 29](Fig. 2a). Likewise, TRAF3 binds to the CBAD in IL-17RA and competes with TRAF6 to restrict IL-17-induced expression of pro-inflammatory mediators. Accordingly, overexpression of TRAF3 attenuates the severity of EAE.

While the regulation of TRAF6-dependent NF-κB and MAPK pathways lowers the signaling output, IL-17 potentiates the inflammatory response through a feedforward mechanism that engages additional transcription factors such as IkBζ and CCAAT/Enhancer binding proteins (C/EBPs). IkBζ, encoded by *Nfkbiz*, positively promotes expression of IL-17-induced genes[30, 31, 32], though a comprehensive determination of its direct versus indirect targets has not been reported. Hence, *Nfkbiz*$^{-/-}$ mice show similarities to IL-17-deficient mice in disease resistance to imiquimod (IMQ)-induced dermatitis[33], a mouse model of psoriasis. The *Nfkbiz* gene is transcriptionally induced by IL-17 via NF-κB and the expression of IkBζ is further enhanced by IL-17-mediated post-transcriptional regulation[12, 33, 34]. Hence, orchestration of IkBζ expression is a focal point for the IL-17-dependent responses (Fig 2a).

Binding sites for C/EBPs are over-represented within the proximal promoters of genes induced upon IL-17 signaling[23]. C/EBPδ and C/EBPβ mediate the transcription of many of these IL-17 target genes[22, 35]. Similar to the mode of activation for IkBζ, IL-17 signaling results in increased expression of C/EBPδ and C/EBPβ. *Cebpd* is regulated transcriptionally, likely through NF-κB. In contrast, C/EBPβ is controlled at multiple levels, including translational start site selection that dictates the isoforms and abundance of the protein[18, 21, 24, 34, 36]. In addition, IL-17 signaling triggers phosphorylation of C/EBPβ by a MEK-dependent pathway and glycogen synthase kinase 3β (GSK3β) via the IL-17RA CBAD subdomain, an event linked to reduced IL-17 signaling[21](Fig 2a). The full spectrum C/EBP-dependent genes in the IL-17 pathway remains to be determined. Integration of these and other transcription factors depends upon the arrangement of the promoter of individual target genes, but thus far only a few target genes have been carefully interrogated in this regard.

Post-transcriptional signaling by IL-17

Inflammatory mRNA transcripts are often intrinsically unstable, a property driven by sequences in 3′ untranslated regions (UTR) that serve as binding platforms for RNA-binding proteins (RBPs)[37]. Hence, in addition to transcription, it is essential for IL-17 to

increase mRNA half-life to permit efficient production of effector proteins. The IL-17–driven post-transcriptional pathway is initiated by the recruitment of TRAF2 and TRAF5 to Act1 (Fig. 2b)[38]. These TRAFs activate RBPs that dictate the fate of client mRNAs. Some RBPs act in a positive capacity to increase expression of IL-17-target mRNAs, such as HuR, Act1, Arid5a and DDX3X[15, 34, 38, 39, 40]. Other RBPs promote RNA decay, such as the multifunctional RBP splicing factor 2 (SF2) and the endoribonuclease Regnase-1[39, 41].

IL-17 orchestrates RBPs to modulate mRNA metabolism in multiple ways. Intriguingly, Act1, the adaptor molecule for IL-17R, can also function as an RBP, and as such interacts with target mRNAs, including *Cxcl1*, *Csf2, Tnf*. Through its SEFIR domain, Act1 binds to a specific stem-loop structure (the SEFIR-binding element, SBE), in the 3′UTR of client mRNAs[15]. IL-17 induces the phosphorylation of Act1 at Ser111 by IκB kinase I (IKKi) and promotes Act1–IKKi nuclear translocation, causing phosphorylation of SF2 and therefore reducing SF2-mediated mRNA decay. In cytoplasmic RNP granules such as P-bodies Act1 mediates mRNA stability by inhibiting the mRNA-decapping enzymes Dcp1 and Dcp2 by via TBK1-mediated (TANK Binding Kinase 1) phosphorylation[15]. Additionally, Act1 facilitates HuR binding to mRNA, which drives client mRNAs such as *Cxcl1* into polysomes for translation[15, 40]. IL-17 also induces the expression of the RBP Arid5a, which stabilizes IL-17-induced transcripts by competing for 3′UTR occupancy with Regnase-1. Arid5a also promotes translation of certain IL-17 target mRNAs, in particular *Nfkbiz* and *Cebpb*[34], thereby amplifying IL-17-mediated responses[23, 30].

Several mechanisms exist at the post-transcriptional level to constrain IL-17-induced inflammation. IL-17 induces expression of *Zc3h12a*, which encodes Regnase-1, via NF-κB and stabilizes its transcript through DDX3X[42]. A potent inhibitor of the IL-17 response, Regnase-1 degrades mRNAs that are undergoing active translation; these include prototypical IL-17-induced transcripts such as *Il6* and *Nfkbiz*, but under some circumstances *Il17ra* and *Il17rc*[43]. Consequently, Regnase-1-deficient mice exhibit exacerbated IL-17-mediated pathology during EAE, pulmonary inflammation and IMQ-driven dermatitis; conversely, Regnase-1 deficiency improves IL-17-dependent immunity to *Candida albicans* infections[43, 44]. The negative-feedback control by Regnase-1 is counteracted by feedforward self-reinforcing mechanisms. IL-17-induces Arid5a, whichbinds to the 3′UTRs of pro-inflammatory transcripts such as*Il6* mRNA to inhibit Reganse1-mediated degradation. IL-17 also restrains Regnase-1 activity via phosphorylation by TBK1 and IKKi[45]. Regulation of Regnase-1 is dynamic, allowing for an initial period of Regnase-1-mediated mRNA decay, which is then constrained to return to homeostasis.

The activity of RBPs does not affect all IL-17-induced mRNAs in the same way, indicating that target-specific mechanisms exist, potentially opening up therapeutic opportunities. Exploiting RNA is attractive given the potential for exquisite specificity and targeting of otherwise “undruggable” targets. There are emerging options in development or in some cases approved that target RNA or RBPs pharmacologically[46]. For example, oligonucleotide “aptamers” representing the Act1 recognition site in the *Cxcl1* 3′UTR were shown to function in pre-clinical models of autoimmunity[15], and Arid5a was reported to be a target of the drug chlorpromazine (CPZ)[30].

IL-17 signaling can further be regulated by noncoding (nc) RNAs. The microRNA miR-23b was found to target mRNAs encoding TAB2, TAB3 and IKK-α, dampening NF-κB activation. Interestingly, IL-17 downregulates miR-23b transcription, causing feedback activation of IL-17 signaling activity[47] (Fig. 2a). Moreover, miR-30a degrades *Traf3ip2* mRNA (encoding Act1) and consequently inhibits IL-17 signaling[48]. Thus, the IL-17 signaling pathway is subject to multiple post-transcriptional and post-translational regulation.

Synergistic interactions with IL-17 signaling

IL-17 signals synergistically with numerous other ligands that activate surprisingly diverse signaling pathways. In addition to cooperating with cytokines that activate NF-κB such as TNFα or lymphotoxin, IL-17 signals cooperatively with IFN-γ (which activates STAT1), IL-13 (STAT6), TGF-β (SMADs). IL-17 also synergizes with microbial products such as bacterial LPS and candidalysin, a fungal pore-forming toxin produced by *Candida albicans* that signals through c-Fos[35, 49, 50, 51]. The ability of IL-17 signaling to regulate genes posttranscriptionally may explain this promiscuity. That is, regardless of how a given stimulus induces transcription, IL-17-induced events stabilize the resulting mRNA transcripts and/or facilitate their translation.

In addition to the classical synergy at transcriptional and post-transcriptional levels, recent studies have revealed surprising new ways in which IL-17 acts in conjunction with other receptor systems (Fig. 3). The integration of IL-17 signaling with growth factor receptors critically controls tissue homeostasis. Because these synergistic interactions act in a highly cell type- and context-specific manner, their existence and detailed mechanism of action have largely eluded the field until recently. An IL-17A–induced epidermal growth factor receptor (EGFR)-mediated Act1–TRAF4–ERK5 cascade has been identified in skin stem cells that are involved in wound healing and tumorigenesis[52, 53]. ERK5 activation is usually triggered by growth factor receptors via MEKK2- or MEKK3-MEK5 axis, which requires a tyrosine kinase for activation[54]. In the setting of IL-17 signaling, EGFR tyrosine kinase activity enables the MEKK3-MEK5 cascade[52]. Upon IL-17A stimulation, TRAF4 tethers EGFR to the IL-17R complex, which is followed by EGFR transactivation via Src recruitment through interactions with Act1[52]. Importantly, the extracellular domain of EGFR was dispensable[52], indicating that this cascade occurs independently of EGFR ligands. Notably, transactivation of EGFR by a heterologous ligand has been documented in other signaling pathways including platelet-derived growth factor receptor (PDGFR), insulin-like growth factor 1 receptor (IGF1R), G protein-coupled receptors (GPCRs), TLRs and IL-6R[55]. Thus, the IL-17R-EGFR-ERK5 axis illustrates an emerging concept in which the kinase activity of EGFR can be exploited by other receptors.

The crystal structure of the TRAF4 TRAF domain suggests that the protein exists as a trimer[56]. The TRAF4 trimer may promote the heterotrimerization of IL-17RA-IL-17RC-EGFR. Deletion analysis revealed that IL-17RA, IL-17RC and EGFR all contained TRAF4-binding motifs. As a mode of action, TRAF4 is known interact with growth factor receptors and promote their signaling activation[57], including EGF-induced activation[58]. Interestingly, TRAF4 binds to a motif in the juxtamembrane segment of EGFR in response to EGF to

promote autophosphorylation[58], whereas TRAF4 binds to the C-terminal tail of EGFR in response to IL-17A to promote EGFR transactivation[52]. Such versatile interactions with EGFR may enable TRAF4 to promote EGFR transactivation when EGF-induced EGFR activation (*cis*-activation) is hindered.

Compared to other cell types in the skin, the IL-17A–induced EGFR-mediated Act1–TRAF4–ERK5 signaling cascade was most strongly activated in a stem cell population marked by a negative regulator of EGFR, Lrig1[59], which exhibits a high level of TRAF4 expression[52]. Accordingly, expression of TRAF4 may dictate whether IL-17A can engage the EGFR-ERK5 cascade. Notably, IL-17A-induced EGFR-ERK5 signaling cascade drives the expansion and migration of Lrig1$^+$ stem cells and their progenies to participate in re-epithelialization in response to wounding. Thus, the integration of IL-17 signaling with EGFR links inflammation, wound healing and tumorigenesis.

The crosstalk between IL-17 and FGF2 in colonic epithelial cells represents another integration of IL-17 with growth factor signaling. IL-17A-induced ERK1/2 activation is associated with tissue regeneration and tumorigenesis, best defined in the intestine[60, 61, 62]. *In vivo*, the activation of ERK1/2 in colonic epithelial cells relies on cooperation between FGF2 and IL-17A[60]. At the nexus of this cooperation is Act1, which binds to the adaptor GRB2, preventing its association with guanine nucleotide exchange factor SOS1. Following IL-17 stimulation, Act1 is recruited to IL-17RA, thereby releasing GRB2 and enhancing FGF2-induced ERK1/2 phosphorylation. Activation of ERKs, including both ERK1/2 and ERK5, is clearly crucial for IL-17-mediated mitogenic effect. Curiously, despite their similarities, ERK1/2 and ERK5 regulate distinct sets of genes[63]. ERK5 plays a non-redundant role in IL-17-dependent KRAS G12D-driven skin tumorigenesis[52, 53, 64]. Future studies are required to delineate the unique function of ERK1/2 versus ERK5 and the interplay between IL-17A-induced ERK1/2 and ERK5 activation, which could have implications for therapy.

Integration of IL-17 with growth factor signaling is not restricted to mucosal tissues (i.e. skin and gut). In a similar fashion to the integration with EGFR, IL-17 engages the NOTCH receptor to promote neuroinflammation. In multiple sclerosis and EAE, tissue damage triggers the expansion and differentiation of oligodendrocyte progenitor cells (OPCs) for regeneration of the myelin sheath. Conditional deletion of Act1 in specific brain cell subsets demonstrated that OPCs are the major IL-17A target cell type in IL-17-induced EAE[65]. Mechanistically, there is a critical crosstalk between IL-17A and NOTCH1, regulating inflammatory and proliferative genes that promote demyelinating disease. IL-17 triggers interactions between IL-17RA and ligand-bound NOTCH1 receptor, promoting proteolytic release of the NOTCH1 intracellular domain (NICD1)[66]. NICD1 complexed with Act1 which co-translocate into the nucleus[66]. The E3-ligase activity of Act1 facilitates the assembly of a stable transcriptional complex, converting the DNA-binding protein RBP-J from a transcriptional repressor into an activator[66]. Consequently, Act1 and RBP-J are recruited to the promoters of several NOTCH1 target genes that mediate inflammation and cell proliferation. As a result, deletion of Act1, NOTCH1 or RBP-J in OPCs alleviated severity of EAE[66].

Notably, IL-17A co-signaling with NOTCH1 requires NOTCH1 ligands[66], which differs from its cooperativity with EGFR. In this scenario, IL-17 mediates cis-interactions between IL-17RA and NOTCH1, coupled with the Act1-interaction with NICD1, facilitates proteolytic activation of ligand-bound NOTCH1. A salient feature of the IL-17A-NOTCH integration is translocation of Act1 into the nucleus, also documented elsewhere[15]. Most prominently, Act1 can translocate into the nucleus to stabilize SEFIR-binding element-containing transcripts[15]. A question arises regarding what controls the specific activity of nuclear Act1. Interaction with and phosphorylation by IKKi is a distinct biochemical event on Act1 for IL-17A-mediated mRNA stabilization pathway[15] (Fig 3). It is plausible that this event commits Act1 for mRNA stabilization, whereas the interaction with NICD1 destines Act1 for the assembly of RBP-J containing transcriptional complex.

Anti-IL-17 biologics show remarkable efficacy for psoriasis[67]. Intriguingly, *CARD14* (CARMA2) is located in a psoriasis susceptibility locus, and numerous CARD14 variants occur in psoriasis patients. One mutant, CARD14E138A, is associated with especially strong NF-κB activation. Consistently, Card14$^{E138A/+}$ mice develop spontaneous psoriasis-like skin inflammation. Unexpectedly, a CARD14 deficiency impaired IL-17A-induced signaling to NF-κB, JNK1/2 and p38 by forming a complex with Bcl10 and MALT1 (the CBM complex), a pathway that is linked to TCR and Dectin signaling but not IL-17 family members[68]. Overexpressed CARD14 interacted with Act1 and TRAF6, which was enhanced by IL-17A stimulation[68]. In a separate study, Syk kinase was also shown to associate with Act1, TRAF6 and IL-17RA and to facilitate IL-17A-induced NF-κB[69]. Receptor-level crosstalk between IL-17R and C-type lectin receptors is not fully demonstrated, these data suggest that this is plausible. Moreover, since CARMA2 is now implicated in IL-17A signaling, it will be important to determine whether psoriasis patients with CARD14 variants will respond normally to biologics targeting the T_H17 pathway.

Discoveries of synergistic interactions between IL-17 and other signaling pathways has significantly extended our understanding of how IL-17 promotes physiological and pathogenic responses in diverse *in vivo* settings.

IL-17 in physiologic responses

IL-17 is evolutionarily ancient, and unsurprisingly, its major impact is on innate immunity[70]. IL-17 strongly induces neutrophils, an effect that is achieved indirectly by production of G-CSF, MCP-1 and CXC chemokines from non-hematopoietic target cells. Commensurate with this, IL-17 deficiency is nearly always associated with reduced neutrophil activation[5].

IL-17 is implicated in responses to extracellular bacteria (*Klebsiella, Staphylococcus, Enterobacteriae, Porphyromonas*), fungi (*Candida, Blastomyces*), and commensal microbiota[71]. IL-17 contributes to immunity to intracellular pathogens such as *Mycobacterim tuberculosis*, particularly vaccine responses, through promotion of tertiary immune bronchial-associated lymphoid tissue (iBALT)[72, 73]. Although poorly defined, there have been sporadic reports linking IL-17 to viral immunity[74, 75].

Enlightening observations made in patients with mutations encoding IL-17R components (*IL17RA, IL17RC, ACT1*) revealed a surprising dominance of mucocutaneous infections by

Candida albicans and *S. aureus* in humans (Table 1)[76]. Consistently, nearly all humans show T_H17 responses to *C. albicans*[77], which can exert broad cross-reactive immunity to other fungi, perhaps explaining evolutionary pressure to maintain *C. albicans* as a commensal organism[78, 79]. However, these anti-*Candida* T_H17 cells can also contribute to pathogenic allergic responses induced by *Aspergillus* species[78]. Nonetheless, candidiasis is only a minor problem in humans taking anti-IL-17 biologic drugs, a finding mirrored in mice given blocking antibodies to IL-17[67, 80], implying that only threshold levels of IL-17 are needed to prevent candidiasis.

IL-17 promotes immunity to other fungi, explaining in part why the early loss of T_H17 cells following HIV infection is associated with a remarkably high incidence of opportunistic fungal infections[81]. As with tuberculosis, IL-17 is needed for effective responses to experimental fungal vaccines, for example targeting *Blastomyces, Histoplasma* and *Coccidioides*[82, 83, 84, 85]. *Pneumocystis* is a true opportunist, in that T_H1, T_H2 and T_H17 cell responses act redundantly to mediate immunity to this fungus. In these settings, IL-17 can be derived from various cell types, including conventional T_H17 cells but also other CD4+, CD8+ T cell subsets as well as innate lymphoid cells and innate-like T cells[4], and in the case of *Aspergillus*, eosinophils[86]. Nonetheless, single IL-17 deficiency in humans due to anti-T_H17 biologic use or genetic deficiency does not seem to predispose to infections by these organisms.

In addition to host defense, IL-17 is also vital for barrier protection. On one hand, IL-17 protects mucosal barrier by maintaining the tight junctions of the intestinal epithelium and upregulating antimicrobial proteins such as β-defensins and calprotectin (S100A8/9) to control infection in the skin[4]. On the other hand, IL-17 also stimulates tissue regeneration to restore barrier function in case of tissue damage. During an immune response to invading pathogens, epithelia proliferate extensively to repair breached barriers and restore tissue integrity. In this regard, IL-17 is emerging as a driver of tissue regeneration. IL-17 regulates cell proliferation and differentiation in cultured primary keratinocytes[53, 87]. Blockade of IL-17 delays re-epithelialization of wounded mouse skin. IL-17 acts directly on $Lrig1^+$ stem cells in the hair follicle, which are central to tissue repair. Normally confined to hair follicles in unchallenged skin[52]. In response to inflammation or wounding, IL-17-activated $Lrig1^+$ cells give rise to progenies that mediate wound closure. Similar observations have been made in chemically induced colitis, where IL-17 signaling induces a population of rapidly proliferating progenitors that promote colon epithelium repair[62], which may occur in cooperation with fibroblast growth factor signaling[49]. Additionally, IL-17-induced expression of the anti-microbial peptide RegIIIγ is critical for wound closure in skin[88], and tissue plasminogen activator promotes tissue repair in gut[89]. These properties help explain why blockade of IL-17 is counterproductive in treating Crohn's disease; evidently the capacity of IL-17 to protect gut barrier tissue outweighs any potential negative effects of inflammation[49, 90].

IL-17 in pathogenic responses

While transient and regulated IL-17 elicits physiological responses for host defense and tissue repair, chronic IL-17 activity orchestrates pathogenic responses that promote cancer and autoimmunity.

A growing body of evidence strongly support a pathogenic role for IL-17 in carcinoma formation, including cancers of the colon, skin, pancreas[9191], liver, lung and myeloma[52, 61, 62, 91, 92, 93, 94, 95]. In the gut, IL-17 signaling contributes to adenoma formation by enhancing the proliferation and survival of enterocytes harboring mutations in the *Adenomatous polyposis coli* (*Apc*) gene[61]. The adenoma impairs gut barrier function, further amplifying an intra-tumoral IL-17 response that reinforces tumor growth. Epithelial IL-17 signaling has been shown to mediate colitis-associated and carcinogenic bacteria-induced tumorigenesis, as well as papilloma and squamous cell carcinomas in models of skin tumorigenesis[52, 53, 62, 92]. Interestingly, modulation of stem cell behavior appears to be a common underlying mechanism. In chemical-induced inflammation-associated and oncogenic Kras-driven wounding-induced skin cancer models, lineage tracing showed that progeny of Lrig1$^+$ cells contribute to tumorigenesis driven by IL-17[52]. In parallel, IL-17 promotes development of pancreatic tuft cells and stem cell features of pancreatic cancer cells, accelerating pancreatic neoplasia progression[91]. Additionally, IL-17-induced cytokines and chemokines mobilize myeloid suppressive cells (MDSCs), which promote angiogenesis and suppress anti-tumor immunity[94, 96, 97]. Collectively, it is clear that IL-17A promotes tissue regeneration, tumorigenesis and tumor progression.

The connection between IL-17 and autoimmune diseases was established considerably before the discovery of T_H17 cells[98, 99]. However, the discovery of T_H17 cells and the involvement of IL-23 in T_H17 cell function prompted a major realignment of our understanding of autoimmunity[100], inspiring intense interest in the IL-17 cytokine family. Mouse models such as collagen-induced arthritis (CIA, representing rheumatoid arthritis) and EAE (multiple sclerosis) demonstrated that T_H17 rather than T_H1 cells are the dominant instigators of autoimmune pathology[101]. Accordingly, blockade or deletion of IL-17 and IL-23 in mice reduced disease signs in several autoimmune model systems. Conceptually, the IL-17-driven proliferation of OPCs is reminiscent of the IL-17-dependent tissue repair seen in the skin and gut. It is possible that a non-resolving IL-17 activity during autoimmune response, like the chronic inflammation that drives IL-17-dependent tumor formation, amplifies and prolongs an otherwise transient IL-17-induced reparative proliferation of OPCs, resulting in suppression of their differentiation.

There were immediate clinical implications of these discoveries in treating human autoimmunity. IL-23 is comprised of a unique p19 subunit and a common p40 subunit shared with IL-12[102]. The anti-IL-12p40 biologic drug ustekinumab, which impairs IL-23 as well as IL-12, was already approved, and its success spurred development of more specific anti-IL-17–IL-17R and anti-IL-23 therapies[103]. The efficacy of anti-IL-17A biologics secukinumab and ixekizumab in psoriasis is particularly striking[67, 104], and these drugs also work in psoriatic arthritis, ankylosing spondylitis, and at least a subset of RA patients[105]. In preclinical settings, blockade of IL-17 also ameliorates pathologies triggered by environmental challenges in models of allergic asthma and chronic obstructive pulmonary

disease (COPD)[106]. Corticosteroids are the mainstay treatment for these conditions, but they fail to suppress T_H17-mediated airway inflammation in models of neutrophilic asthma[107]. Consistently, IL-17 airway activity positively correlates with disease severity in asthma and COPD patients[108, 109]. Ongoing efforts are focused on evaluating biomarkers of IL-17 activity to identify patients most likely to benefit from IL-17 blockade[109].

Emerging pathophysiological function of IL-17

IL-17 is classically considered to signal in non-immune sites, such as epithelium of skin and gut. IL-17 is dispensable for development of secondary lymphoid organs (SLOs), such as lymph nodes (LNs) and spleen. However, chronically inflamed tissues develop tertiary, or ectopic, lymphoid follicles that support local adaptive immunity. Like SLOs, tertiary lymphoid follicles are organized and supported by stromal cells called fibroblastic reticular cells (FRCs), which produce survival factors such as IL-7 and BAFF as well as chemokines. During inflammation the rapid increase in SLO size triggers proliferation of the resident FRCs to support and regulate adaptive immune immunity. Proliferation and cellular activation require increased metabolic function to support biosynthesis and bioenergetics, and recent studies have demonstrated that IL-17 signaling in FRCs drives increased glucose uptake and metabolic function[110]. IL-17 induces the transcriptional coactivator IkBζ, which is essential for the metabolic reprogramming of FRCs through genes that control mitochondrial function. IkBζ is required for increased glucose uptake and for expression of CPT1A, the rate-limiting transporter for fatty acid oxidation (FAO)[110]. Both glucose (through glycolysis) and FAO generate acetyl-CoA needed to feed the citric acid cycle, leading to enhanced oxidative phosphorylation in proliferating cells.

During infections with *Mycobacterium* or *Pneumocystis*, IL-17 induces stromal cell production of chemokines such as CXCL13 to attract and organize T and B cells in iBALT, and these structures support the local T_H17 response against pathogens[111, 112]. During EAE, T_H17 cells promote development of tertiary lymphoid follicles in the meninges surrounding brain and spinal cord, thought to contribute to disease chronicity[113, 114]. In EAE, IL-17 synergistically signals with lymphotoxin to drive differentiation of FRC-like cells from meningeal stromal cells[113]. During local LN inflammation that occurs in EAE and colitis, the absence of IL-17 signaling causes activated FRCs to experience nutrient stress and increased apoptosis, leading to failed expansion of these stromal cells despite LN hypercellularity[110]. Interestingly, only FRCs from previously activated LNs (e.g. from immunized mice) show a metabolic response to IL-17 stimulation, suggesting that IL-17 acts as a necessary ‘signal 2’ for metabolic reprogramming and proliferation of activated LN stromal cells. As discussed above, IL-17 promotes proliferation of several cell types including epithelium, and it will be interesting to determine whether similar metabolic changes accompany IL-17-driven proliferation in inflamed non-lymphoid tissues.

Summary

IL-17 first gained notoriety as a cytokine driving autoimmune and inflammatory diseases. New research has unraveled the critical roles of IL-17 in maintaining mucosal immunity and barrier integrity, two fundamental physiological functions that not only establish host

defense, but can drive tumorigenesis and cancer progression in pathological settings. These pathophysiological functions depend on the capacity of IL-17 to induce proinflammatory mediators, the mitogenic effect in tissue progenitor cells, and the ability to reprogram cellular metabolism. Mechanistically, these outcomes are governed at both transcriptional and post-transcriptional levels. Arguably, the most exciting discoveries in canonical IL-17 signaling have been the elucidation of receptor-directed regulation of mRNA metabolism, an emerging area that continues to evolve. Integration with non-IL-17 signaling pathways represents a new mechanism by which IL-17 contributes to biological responses beyond inflammation. Detailed mechanistic insights into canonical and noncanonical IL-17 pathways could ultimately inform the development of novel therapeutic agents such as small molecules, aptamers or stapled peptides.

Acknowledgements

SLG was supported by NIH grants DE022550 and AI107825. XL was supported by NIH grants P01CA062220, P01HL103453 and National Multiple Sclerosis Society grant RG5130A2/1. M.J.M was supported by NIH grant R01AI110822-01. There are no conflicts of interest.

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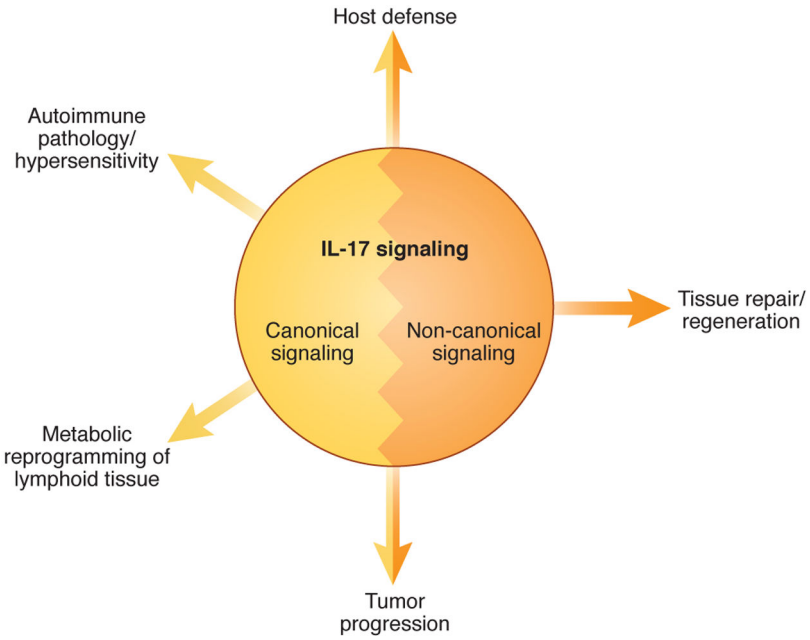

Figure 1. Overview of IL-17 signaling functions *in vivo*.

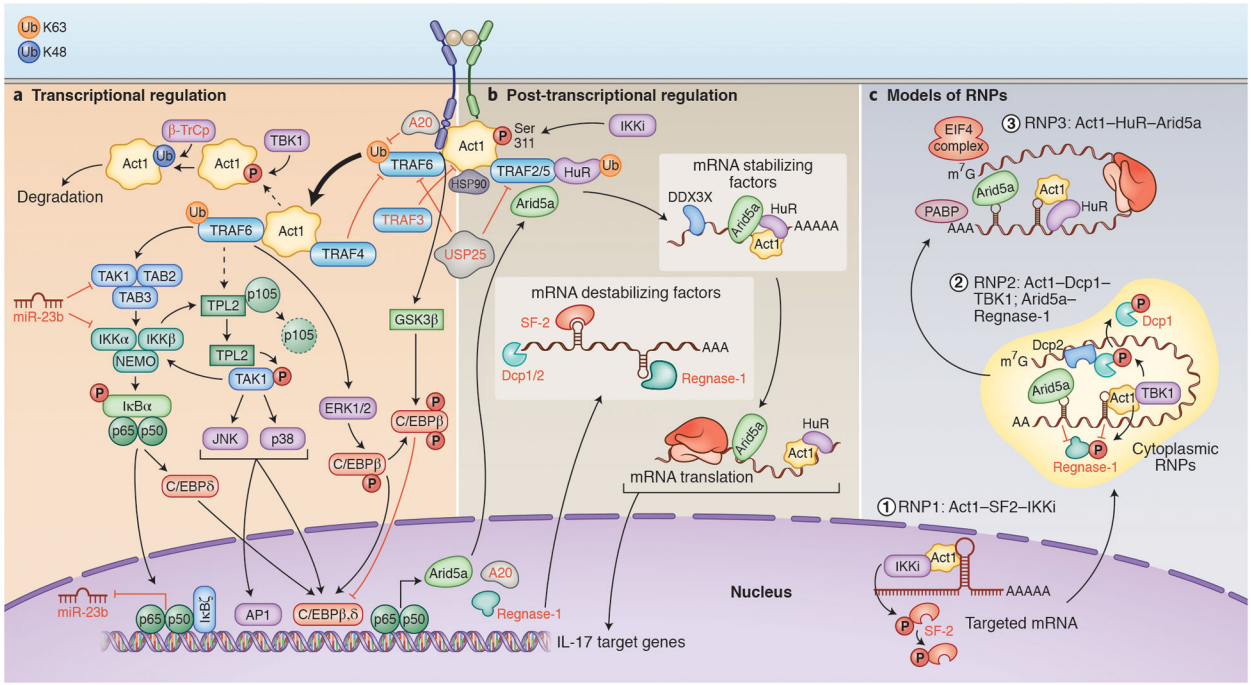

Figure 2. Canonical IL-17 signaling pathways

. A) Transcriptional regulation. Upon IL-17 binding to its heterodimeric receptors IL-17RA and IL-17RC, Act1 activates multiple signaling cascades operating through different TRAF proteins. Engagement of TRAF6 results in the activation of NF-κB, C/EBPβ, C/EBPδ, and MAPK pathways. ERK1/2 mediates phosphorylation of C/EBPβ on Thr-188 and CBAD domain of IL-17R is also required for IL-17A-mediated inducible phosphorylation of C/EBPβ on Thr-179 through GSK3β. IL-17 can also induce different feedback regulatory response by inducing/recruiting deubiquitnase enzymes (A20, USP25) or kinases (TBK1). Hsp90 maintains the integrity of Act1 at the protein level. **B) Post-transcriptional regulation**. IL-17 signaling through the Act1–TRAF2–TRAF5 complex results in the control of mRNA stability/translation of IL-17 target genes through multiple RNA-binding proteins, including mRNA stabilizing factors (Act1, HuR, Arid5a and DDX3X) or destabilizing factors (SF2 and Regnase-1). Mechanistically, in addition to its role as an adaptor, Act1 functions as an RBP by forming several RNPs **(as described in C)** contributing majorly to the receptor-mediated selectivity of mRNA stabilization and translation in response to IL-17 stimulation. As a feedforward mechanism, IL-17 induces the expression of Arid5a, which counteracts mRNA degradation mediated by Regnase-1 by recognizing similar sequences within the 3′-UTR of IL-17 targeted mRNA. Arid5 and HuR also promote translation of target mRNAs. **C) Models of RNPs**. IL-17 signaling results in the formation of multiple, compartmentally-distinct RNPs, controlling different steps of mRNA metabolism. Upon IL-17A stimulation, Act1 is phosphorylated by IKKi, followed by their translocation into the nucleus where Act1 binds to a stem-loop structure in the 3’UTR in the target mRNAs (RNP1). The binding of Act1 competes off SF2 from the mRNAs by bringing IKKi to phosphorylate SF2, preventing SF2-mediated mRNA decay. Act1 follows the mRNAs to cytoplasmic granules such as P-bodies (RNP2) inhibiting Dcp1/2-mediated mRNA decapping by employing TBK1 to phosphorylate Dcp1. Moreover, Arid5a can also

stabilize different IL-17-target mRNA in the cytoplasm by counteracting the negative effects of Regnase-1. In addition, IL-17 stimulates TBK1/IKKi-mediated phosphorylation of Regnase-1 in an Act1-dependent manner, removing it from target transcripts and preventing the degradation of mRNA. Finally, Act1-mRNAs are shifted to the polysomes to facilitate HuR's binding to mRNAs (RNP3) for protein translation. Arid5a is also inducibly associated with the eukaryotic translation initiation complex and facilitates the translation of IL-17 target genes (IκBζ and C/EBPβ).

Arid5a: AT-Rich Interaction Domain 5A; CBAD:C/EBPβ activation domain; Dcp: Decapping MRNA; DDX3X: DEAD-Box Helicase 3 X-Linked; ERK: extracellular signal related kinase; GSK: glycogen synthase kinase; Hsp90: Heat shock protein 90; HuR: human antigen R, also known as ELVAL1; IKK: inhibitor of kappa B kinase JNK: Janus kinase; PABP: Poly(A)-binding protein; SF2: splicing factor 2; TRAF: TNF receptor associated factor; TAK1: TGF-β activated kinase 1; TBK1: TANK-binding kinase 1; TPL2: Tumor progression locus 2; β-TrCP: beta-transducin repeat containing; USP25: Ubiquitin Specific Peptidase 25

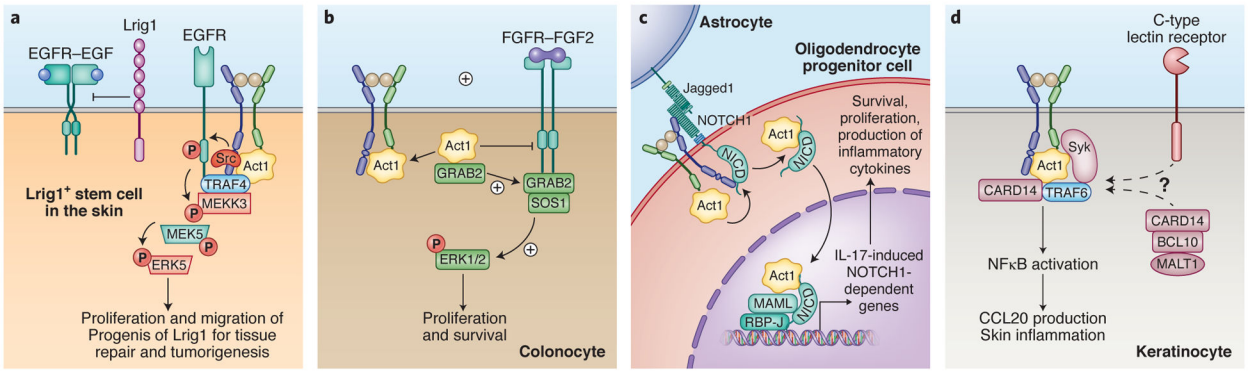

Figure 3. Noncanonical IL-17 signaling.

A) Integration of IL-17 signaling with EGFR. In Lrig1^{+} stem cells in the skin, IL-17 stimulation leads to the recruitment of EGFR to the IL-17 receptor complex by TRAF4. The close proximity of IL-17R and EGFR allows the adaptor protein Act1 to recruit *c-Src* for IL-17A–induced EGFR phosphorylation and subsequent activation of MEKK3-MEK5-ERK5 axis. Activation of this axis instigates the Lrig1^{+} cells to produce progenies for wound healing and tumorigenesis. **B) IL-17 cross-talk with FGF signaling**. In colonic epithelial cells, the IL-17 receptor adaptor Act1 constitutively binds to GRB2, suppressing FGF2-induced ERK1/2 activation. Upon IL-17 stimulation, Act1 is recruited to the IL-17 receptor, releasing GRB2 to associate with guanine nucleotide exchange factor SOS1 for RAS-RAF dependent ERK1/2 activation. The cooperativity between IL-17 and FGF2 plays a crucial role in the repair of damaged colonic epithelium during intestinal inflammation. **C) Integration of IL-17A signaling with NOTCH1**. In oligodendrocytes progenitor cells (OPCs), IL-17 stimulation induces the interaction between the extracellular domains of IL-17 receptor and Jagged1-bound NOTCH1, facilitating the cleavage of NOTHC1 intracellular domain (NICD1). The released NICD1 forms a complex with Act1 and translocates into the nucleus, promoting the assembly of RBP-J- and MAML-containing transcriptional machinery that mediates the expression of IL-17-induced NOTCH1 target genes for inflammation and cell proliferation. **D) Integration of IL-17 signaling with C-type lectin receptor components**. In keratinocytes, multiple signaling proteins that functions in C-type lectin receptor pathway have been implicated in IL-17 signaling. Both Syk and CARD14 can form complexes with Act1 and TRAF6 in response to IL-17 stimulation for NFκB activation.

Table1.

Human defects associated with IL-17 immunity

Genetic defects		Inheritance	Syndrome/disease susceptibility	Effects on IL-17 immunity	Ref
AIRE		AR	APECED (APS-I)/ enhanced susceptibility to CMC	AIRE deficiency associated witd high-titer neutralizing antibodies against T_H17 cytokines (IL-17A, IL-17F and/or IL22)	115
Mutations/ Polymorphisms affecting IL-17 signal transduction	IL-17RA	AR	CMC Staphylococcal skin lesions Pulmonary bacterial diseases (some cases)	Mutations of *Il17ra* which lead to tde absence of IL-17RA protein expression and impaired response to IL-17A and IL-17F homo- and heterodimers and IL-17E/IL-25	116
	IL-17RC	AR	CMC	Mutations of *Il17rc* which lead to tde absence of IL-17RC protein expression and impaired response to IL-17A and IL-17F homo- and heterodimers but normal response to IL-17E/ IL-25	117
	IL-17F	AD	CMC	Dominant-negative mutation at position 65 in tde IL-17F polypeptide chain. Tdis mutation abrogates signal transduction of mutant IL-17F homodimers, and wild-type IL-17A/mutant IL-17F and wild-type IL-17F/mutant IL-17F heterodimers	116
	ACT1	AR	CMC Staphylococcal skin lesions	Missense mutation in tde SEFIR domain of ACT1, which abolishes tde interaction of ACT1 witd IL-17R	118
		ND	Psoriasis	D10N variant of ACT1 which abrogates ACT1-HSP90 interaction	119
	CARD14	AD	Psoriasis	Gain-of-function mutation of *Card14* leading to a strong NF-κB activation and IL-17 signal transduction	68
Mutations affecting T_H17 cells generation	STAT3	AD	HIES/enhanced susceptibility to superficial fungal, bacterial and viral diseases	Dominant-negative mutations of *Stat3* which lead to tde impairment of T_H17 cells generation	120
	STAT1	AD	Superficial and invasive fungal, bacterial and viral diseases	Gain-of-function mutation of *Stat1* leading to enhanced transcription of STAT-1-dependent genes, which are known inhibitors of T_H17 cells generation	120
	RORγt	AR	CMC and mycobacterial diseases	Loss-of-function mutation of *Rorc* which lead to absence of T_H17 cells generation	120
	CARD9	AR	Superficial and invasive fungal diseases	Loss-of-function mutation of *Card9* which lead to impaired production of pro- T_H17 cytokines by phagocytes upon fungal recognition	120

AD: Autosomal dominant, AIRE: Autoimmune regulator gene, APS-I: Autoimmune polyendocrinopathy syndrome-I, APECED: Autoimmune polyendocrinopathy candidiasis ectodermal dystrophy, AR: Autosomal recessive, CMC: Chronic mucocutaneous candidiasis, HIES: Hyper-IgE syndrome, ND: not determined