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Recent advances in the IL-17 cytokine family

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Summary

The IL-17/IL-17 receptor family is the newest and least understood of the cytokine subclasses. Composed of ligands IL-17A-IL-17F and receptors IL-17RA-IL-17RE, these cytokines have many unique structural and functional features. Since the discovery of the "Th17" subset in 2005, particular attention has been paid to IL-17A and IL-17F and their cognate receptors. To date, far less is known about the rest of the family. This review discusses recent advances in the field, with an emphasis on IL-17A biology.

IL-17-producing cells: Th17 and beyond

IL-17 (IL-17A, CTLA-8, Table 1) was cloned in 1993, but came into the limelight with the recognition of a third effector CD4+ T cell population distinct from classic Th1 and Th2 lineages, which produces IL-17 as a signature cytokine and responds potently to IL-23. Dubbed "Th17," IL-17-producing CD4+ cells arise from multiple differentiation triggers, including TGFβ, IL-6, IL-1β, and IL-21 (Fig 1A). IL-23 is not required for Th17 differentiation per se, but is essential for maintenance and activity of these cells in vivo. The discovery of Th17 cells reconciled many of the long-standing discrepancies of the Th1/Th2 model, particularly the discordant roles of IFN γ and IL-12 (specifically, the IL-12p40 subunit shared with IL-23) [1]*. In addition, Th17 cells produce IL-17F, an IL-17A/F heterodimer, IL-22 and IL-26 (humans). Recent findings indicate that GM-CSF is another Th17-derived cytokine that contributes to the inflammatory pathology of Th17 cells, based on data from EAE models [2,3]. Understanding the integration and nuances of Th17-derived signals will doubtless continue to be an intensive area of research.

Although produced by T cells, IL-17 acts primarily on epithelial, endothelial and stromal cells. Genes induced by IL-17 encode antimicrobial proteins (AMPs; β defensins, cathelicidin, RegIII, lipocalin 2, salivary histatins), neutrophil-activating factors (G-CSF, CXC chemokines), and inducers of the acute phase response (IL-6) [4]. It was long evident that there must be innate sources of IL-17 that act rapidly during infection, prior to the onset of a bona fide adaptive T cell response [5]. Accordingly, a variety of studies have demonstrated IL-17 expression in γδ T cells, NKT cells, macrophages, LTi, TFh among others [6]**. These IL-17-producing cells play vital roles in mediating effects of IL-17, especially at mucosal surfaces [7].

Interconnections among T cell subsets

Although Th17 cells are often depicted as a committed lineage, in fact there are many interrelationships with other subpopulations, including functional cooperation, cells that express signature cytokines from multiple subsets (e.g., IL-17+IFNγ+ cells) and lineage plasticity. For example, Th17 cells and Tregs both arise from TGFβ-dependent signals, although the importance of TGFβ in Th17 generation continues to be controversial [8–10]. Th17 cells can convert to Tregs and vice versa or Th1-type cells, a process known as "plasticity" [11,12]. This occurs in part by T-bet-mediated repression of RORγt [13], a transcription factor considered the "master regulator" of Th17 cells [14]. IL-2, which promotes Tregs, suppresses Th17 generation through STAT5 [15,16]*. Conversely, Tregs can promote Th17 cells by acting as a "sink" for IL-2 through the high affinity IL-2R, thereby relieving IL-2-mediated repression of Th17 differentiation [17,18]. Although Th1 cells can suppress Th17 generation via inhibitory signals from IFNγ [19,20], IL-17 can positively regulate Th1 cell differentiation in certain intracellular infections or vaccination settings, including *M. tuberculosis*, *Francisella tularensis* and chlamydial infections [21–23]*. In one instance this is mediated by direct IL-17 signaling on DCs, leading to upregulation of IL-12 [21]*. An elegant fate-mapping study recently showed that Th17 cells exhibit variable plasticity, dependent on setting. Whereas conversion of Th17 cells to other subsets was observed at a high frequency in chronic EAE, conversion occurred rarely during acute fungal infection [24]. At a molecular level, plasticity is related to epigenetic modifications of genes encoding the transcription factors that specify lineage choice, namely T-bet (Th1), GATA-3 (Th2), RORγt (Th17) and Foxp3 (Treg). Analysis of different CD4+ subsets by ChIP-Seq showed that "permissive" chromatin modifications are frequently found in the promoters of transcription factors different from the lineage analyzed, suggesting that these regulators are poised for rapid transcription [25–27]. Thus, the immune system exhibits considerable flexibility, presumably to allow appropriate fine-tuning of the immune response throughout the course of different immune challenges.

IL-17 gene regulation

The genes encoding IL-17A and IL-17F are closely linked, and a comprehensive picture of gene regulation is starting to emerge [28] (Fig 1B). Within the intergenic DNA between *il17a* and *il17f* lies a conserved noncoding sequence region. The chromatin in this locus is extensively remodelled upon receipt of signals from TGFβ and IL-6, helping to explain coordinate regulation of these cytokines [29]. Early studies demonstrated the importance of NFATc1 in regulating the human IL-17A promoter, consistent with the cyclosporin-A sensitivity of IL-17 expression [30]. RORγt is essential for regulating the murine *il17a* and *il17f* promoters, although RORα can also accomplish this [14,31,32]. An independent analysis of the mouse *il17a* promoter showed that RORγt and RUNX1 bind directly to conserved noncoding elements upstream of the *il17a* start site. Notably, interactions of RUNX1 with Foxp3 inhibit transcription, providing a molecular explanation for the reciprocal development of Th17 and Treg cells [33]. BATF, a member of the AP-1 transcription factor family, is implicated in regulation of *il17a* and Th17 differentiation, binding to both proximal and intergenic regulatory regions [34]. STAT3, activated by Th17-inductive cytokines such as IL-6, IL-21 and IL-23, also binds the *il17a* promoter [35], and consistently, humans with STAT3 defects show reduced IL-17 production and sensitivity to Th17-dependent infections (see below, Table 2) [36]. A new report indicates that the positive activities of STAT3 are offset by competitive binding of STAT5 at the same locus, accounting for the dose-dependent and competitive regulation of IL-17A production by IL-6 (which signals through STAT3) and IL-2 (which signals through STAT5) [16]*. The role of TGFβ in Th17 differentiation was recently shown to be mediated by SMAD-mediated suppression of eomesodermin, which regulates both the RORγt and *il17a* promoters [37].

IL-17-mediated inflammation can be tempered by signals from Vitamin D. Notably, 1,25-dihydroxyvitamin D3, the hormonally active form of Vitamin D, interacts with its receptor (VDR) to suppress mouse and human IL-17 transcription by blocking NFAT, sequestering Runx1 and enhancing Foxp3 [38]. In another study, it was shown that VDR in mice suppresses IL-17A expression in T cells mainly through a post-transcriptional signal, at least at physiological levels of Vitamin D [39]. The IKKα kinase was also shown to regulate mouse *il17a* (but interestingly not *il17f*), where it activates histone H3 phosphorylation [40]. A complete understanding of the factors involved in regulating IL-17A expression has important ramifications for rational drug design to target autoimmunity.

IL-17 in fungal infections

Numerous studies identified a role for IL-17 in immunity against extracellular pathogens [5]. In particular, several new reports implicate IL-17 as a particularly vital mediator of host defense against fungi. *Candida albicans* is an opportunistic yeast that colonizes skin and mucosal tissues, and can cause systemic infections that are a serious problem in hospitals. In mice, deficiency of IL-17A and IL-17RA but not IL-17F causes increased susceptibility to disseminated candidiasis [41,42]. Similarly, IL-17R in mice is essential for immunity to mucosal candidiasis in the oral cavity as well as skin [43]*[44,45]. A requirement for Th17 cells has been demonstrated in an experimental vaccine that targets both *C. albicans* and *Staphylococcus aureus* [46]. In contrast, IL-17 and IL-23 have been suggested to be pathogenic in a model of gastric candidiasis [47], and their roles in vaginal candidal infections are thus far unclear. In addition, IL-17-dependent immunity in vaccine responses to various other fungal pathogens has been demonstrated [48]**, indicating that antifungal immunity is a general feature of IL-17.

A number of “experiments of nature” have begun to reveal that IL-17 activity appears to be surprisingly limited to just a few infections, particularly those caused by *Candida* and *Staphylococcus aureus* (Table 2). Humans with hyper-IgE Syndrome (HIES, Job’s Syndrome) have mutations in STAT-3. Presumably because of defects in Th17-inducing cytokines such as IL-6, IL-21 and IL-23, these patients exhibit a selective paucity of Th17 cells [49–51]. Although they exhibit a wide spectrum of clinical manifestations, HIES patients are highly susceptible to mucosal candidiasis and staphylococcal abscesses, implicating Th17 cells in immunity to these organisms. Interestingly, this is associated with reduced salivary antifungal activity, implying a direct role for IL-17 on the salivary gland [52]. The major pattern recognition receptors for *Candida* are C-type lectin receptors including Dectin-1, -2 and Mincle. These recognize fungal cell wall carbohydrates, and stimulate potent Th17 responses [53]. Notably, patients with defects in Dectin-1 or its signaling effector CARD9 experience severe chronic mucocutaneous candidiasis (CMC) [54,55]. Further direct evidence for a role for IL-17 comes from APS-1, in which patients with mutations in *Aire* develop neutralizing autoantibodies against Th17 cytokines and experience recurrent CMC [53,56,57]**. Moreover, rare patients with mutations in IL-17RA or IL-17F exhibit similar susceptibility to CMC and *Staphylococcus* [58]. Thus, data in humans argues for an immunoprotective role of IL-17 signaling in controlling *Candida* and *Staphylococcaal* infections.

IL-17 in autoimmunity, therapies

Even before the discovery of Th17 cells, it was evident that IL-17 promotes autoimmunity, particularly in the context of rheumatoid arthritis (RA) [59]. Analyses of collagen-induced arthritis (CIA) confirmed that Th17 cells rather than Th1 cells promote disease [60], and blocking IL-17 or its receptor relieves experimental symptoms [61]. Studies in EAE similarly indicated a dominant role of Th17 cells over Th1 cells [62]. In humans, a SNP in

the IL-23R (R381Q) is associated with reduced susceptibility to a variety of autoimmune disorders, and was recently linked to reduced IL-17 production in human T cells [63,64]. Accordingly, antibodies targeting IL-17A are in numerous clinical trials, and early reports are promising. Results, albeit from small numbers of patients, show efficacy in psoriasis, RA and autoimmune uveitis [65,66]*. Thus far side effects appear minimal, though much larger data sets will be needed to confirm this trend. However, findings from IL-17-deficient humans (Table 2) suggest that loss of IL-17 signaling may indeed predispose only to a limited number of infections.

IL-17 receptor structure and signaling

The receptor for IL-17A, IL-17F and the IL-17A/F heterodimer is composed of IL-17RA paired with IL-17RC [4]. The crystal structure of the human IL-17RA extracellular domain complexed to an IL-17F:F homodimer reveals an unusual fibronectin III domain conformation [67]**. Surface plasmon resonance studies showed stepwise association of receptor/ligand binding; namely, after either IL-17RA or IL-17RC bind their respective ligand, affinity for the reciprocal subunit is increased. This observation is consistent with studies showing ligand-inducible association of IL-17RA and IL-17RC on the cell surface [44,68]. There are notable differences between the human and mouse IL-17R systems, however. Human IL-17RA has much higher affinity for IL-17A than for IL-17F, and human IL-17RC binds both ligands with similar affinity. In contrast, murine IL-17RC alone binds primarily to IL-17F [67,69]. IL-17RA appears to be a component of at least one other receptor complex (IL-25R, Table 1), and may in fact be the common signaling subunit of the entire family [4,70].

The signal transduction pathway mediated by IL-17 is still poorly defined (Fig 2). IL-17R family members contain a conserved “SEFIR” motif, which has homology to TIR domains found in Toll and IL-1 receptors [71]**. However, structure-function mapping studies in IL-17RA and IL-17RC indicate that the SEFIR domain does not encompass the entire requisite signaling motif. In addition, there are large nonconserved regions within these receptors also essential for signal transduction [44,72,73]. Consistently, IL-17 does not engage TIR-containing adaptors such as MyD88, TRIF or IRAKs [72]. Rather, IL-17 signals through Act1, an adaptor and U-box E3 ubiquitin ligase that contains both a SEFIR and TRAF-binding domain [74–76]. IL-17 induces rapid phosphorylation of Act1 [44], though the target sites and relevant kinases are not yet reported. IL-17 activates the classical NF-κB pathway, albeit modestly, an event requiring both Act1 and TRAF6 [74,77]. In addition to NF-κB, IL-17 activates IκBζ and C/EBP transcription factors (mainly C/EBPδ and C/EBPβ) [78], as well as MAPK and possibly PI3K [4].

A striking feature of IL-17A, IL-17F and IL-17A/F is their modest signaling activity, even in high concentrations of ligand. However, they exhibit potent synergy, particularly with TNFα but also LTα, IFNγ and IL-1β [4,73]. The mechanisms underlying synergy are not fully defined, but a major component is cooperative enhancement of mRNA stability of certain IL-17 target genes. For example, IL-6 and CXCL1 are both induced weakly at the transcriptional level by IL-17 alone, but their transcript half-life is enhanced dramatically by a combination of TNFα and IL-17. This signal is Act1-dependent, but occurs in the absence of TRAF6 [79]. Surprisingly, the well-characterized mRNA destabilization factor tristetraprolin, which reduces the stability of inflammatory transcripts induced by IL-1β, LPS and TNFα, is dispensable for IL-17-mediated enhancement of CXCL1 (KC) mRNA [80]*. New data indicate that a different mRNA destabilization factor, SF2/ASF, associates with TRAF5 and TRAF2 following IL-17 activation, leading to enhanced stabilization of CXCL1 (T. Hamilton, personal communication). Thus, despite many parallels to IL-1/TLR signaling, IL-17R activates distinct pathways mediated through unique receptor subdomains.

Given its pro-inflammatory propensities, it is not surprising that there are inhibitory signaling events mediated by IL-17 that modulate its activity. Mapping studies of IL-17RA revealed a distal cytoplasmic domain that mediates suppressive signaling through dual phosphorylation of C/EBPβ. These phosphorylation events are mediated by ERK and GSK3β, and many IL-17 target genes are enhanced upon exposure to pharmacological inhibitors of these kinases [81]. This IL-17RA subdomain also controls alternative translation of C/EBPβ, and hence is termed the "C/EBPβ activation domain" (C-BAD) [72]. Recently, the C-BAD was found to contain a TRAF3-binding element that mediates suppressive signaling, and TRAF3-transgenic mice indeed exhibit reduced IL-17-dependent pathology in EAE [82]. The full range of molecular signaling events mediated by IL-17 is still poorly understood, and is likely to continue to yield unexpected findings in the future.

Summary and Perspectives

The recognition of Th17 cells has stimulated a surge of interest in IL-17 cytokines. Although much remains to be learned about this enigmatic family, intensive studies in mice have provided much new information about this cytokine and its fascinating cellular and molecular regulation. The advent of clinical trials targeting IL-17 and its receptor will no doubt shed new light on its biology in humans as well.

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Abbreviations

EAE	experimental autoimmune encephalomyelitis
CIA	collagen-induced arthritis
RA	rheumatoid arthritis
CMC	chronic mucocutaneous candidiasis
SF2/ASF	splicing factor 2/alternative splicing factor
VDR	vitamin D receptor
STAT	signal transducer and activator of transcription
HIES	hyper-IgE Syndrome
ChIP	chromatin immunoprecipitation
SNP	single nucleotide polymorphism
SEFIR	similar expression to FGF receptor/IL-17R

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Highlights

- IL-17, signature of the CD4+ “Th17” lineage, is also produced by innate cell types
- *il17a* gene regulation and epigenetics helps explain Th cell plasticity
- Data from animal models and humans reveals a vital role of IL-17 in fungal immunity
- Anti-IL-17 therapeutics show early promise in the clinic
- The IL-17 receptor activates noncanonical signal transduction pathways

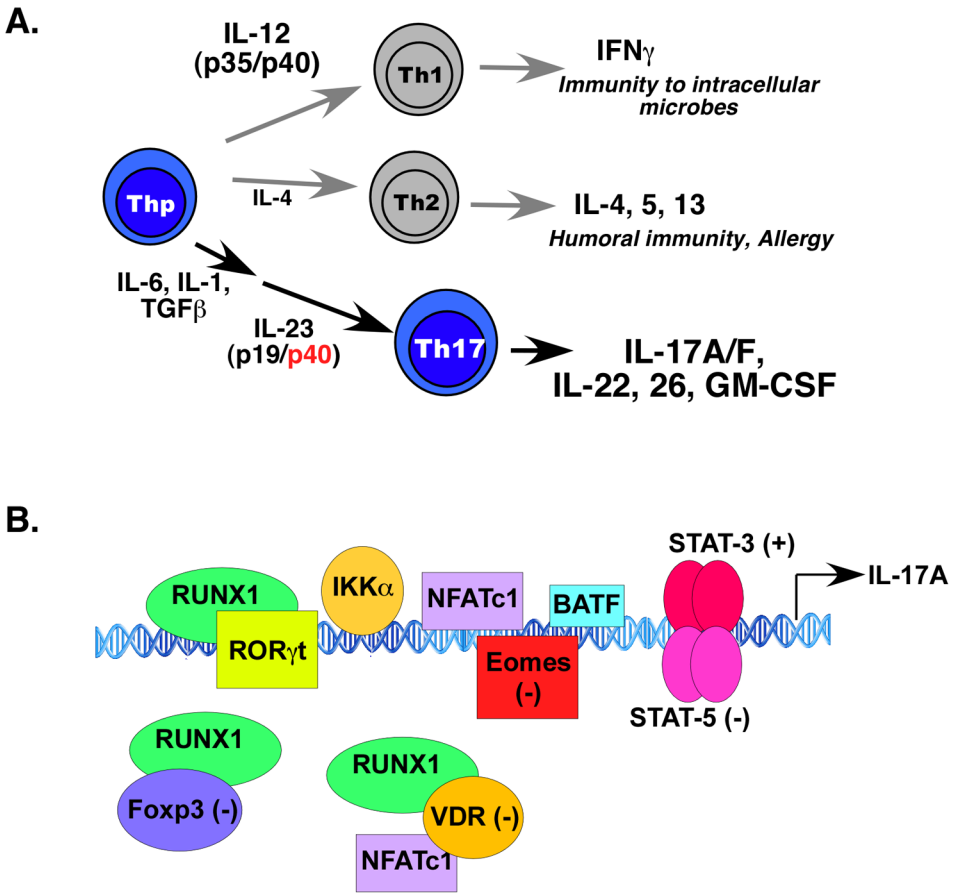

Figure 1. Th17 differentiation and IL-17A gene regulation

A. Th17 cells arise from differentiative signals from IL-1, IL-6 and TGFβ, while stability and maintenance of Th17 cells is mediated by IL-23. In addition to IL-17A, Th17 cells produce IL-17F, IL-17A/F, IL-22, IL-26 (humans only) and GM-CSF. **B**. Summary of studies from the human and mouse *il17a* promoters indicates involvement of various positively (+) and negatively (−) acting transcription factors.

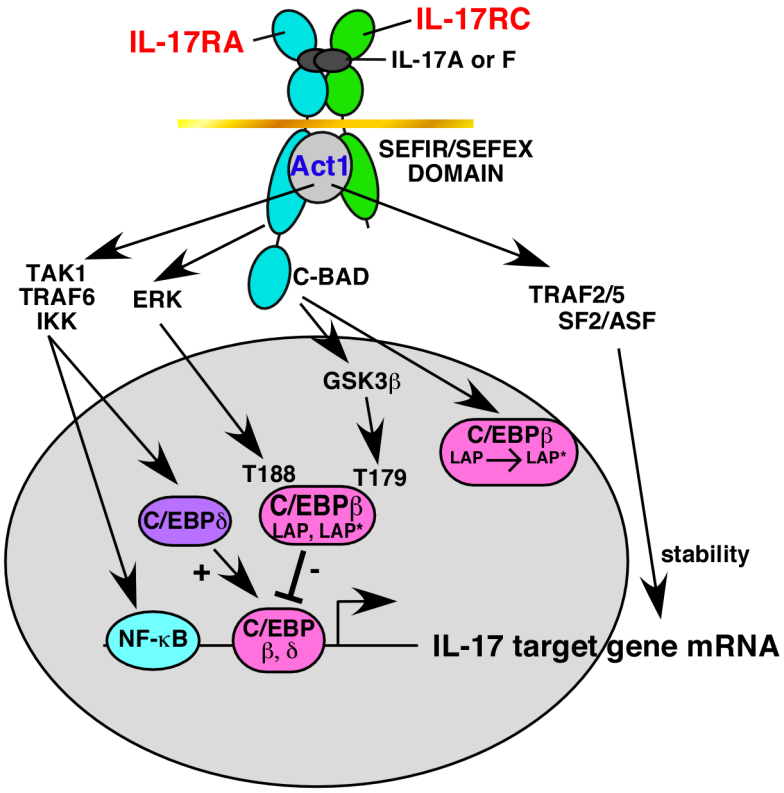

Figure 2. IL-17R Signaling

The IL-17R complex is composed of IL-17RA and IL-17RC. Major downstream signaling pathways mediated by this receptor are indicated.

Table 1

IL-17 receptor/ligand family

Receptor complex	Ligand(s)
IL-17RA/RC	IL-17A, IL-17F, IL-17A/F, vIL-17*
IL-17RA/RB	IL-17E (a.k.a., IL-25)
IL-17RD (SEF)	unknown
IL-17RA/RD	unknown
IL-17RE	IL-17C
unknown	IL-17D

* viral IL-17

Table 2

Human Genetic diseases involving IL-17

	Infections, other disease manifestations	How IL-17 is affected	Gene affected	References
Autoimmune polyendocrine syndrome-1 (APS-1)	CMC[a]	Neutralizing Abs to IL-17A, IL-17F (and IL-22)	Aire (LOF)[b]	[56,57]
Hyper-IgE Syndrome (Job's Syndrome)	CMC, Staph, eczema, cold absesses, bone problems, etc.	Reduction in Th17 cells, low IL-17A levels	STAT-3 (DN)[c]	[49,50]
Dectin1-deficiency	CMC	Reduced Th17 numbers	Dectin-1 (LOF)	[55]
CARD9-deficiency	CMC	Reduced Th17 cell numbers	CARD9 (LOF)	[54]
IL-17RA-deficiency	CMC, Staph	No expression of IL-17RA, failure to signal to IL-17A, F	IL-17RA (LOF)	[58]
IL-17F deficiency	CMC, Staph	Inhibition of IL-17A/F and IL-17F signaling	IL-17F (DN)	[58]
IL-23R SNP (R381Q)	protection from various autoimmune diseases (GWAS)[d]	Decreased IL-23 signaling in T cells, leading to reduced IL-17/IL-22 production	IL-23 receptor	[63,64]

[a] Chronic mucocutaneous candidiasis

[b] LOF, loss of function

[c] DN, dominant negative

[d] GWAS, genome wide association study