Published in final edited form as:

Cytokine. 2008 September ; 43(3): 402–407. doi:10.1016/j.cyto.2008.07.017.

An Overview of IL-17 Function and Signaling

Sarah L. Gaffen^{1,2}

¹University at Buffalo, SUNY, Dept. of Oral Biology, 3435 Main Street, Buffalo NY 14214,
sgaffen@buffalo.edu

Abstract

Since the discovery of interferons over 50 years ago, efforts to understand the biochemistry, molecular biology and biological activities of cytokines have been intense and rewarding. Although there are several hundred cytokines and receptors currently recognized, they in fact fall into a fairly limited set of subfamilies (reviewed in [1,2]). Within these families (and in some cases even outside them), cytokines share many structural and functional features that have provided a framework for understanding their biological activities and signal transduction mechanisms. This review will focus on interleukin (IL)-17, the founding member of the newest subclass of cytokines, which has received considerable attention in the last several years due to its central role in the Th17 system.

2. IL-17 and its receptor

The gene encoding IL-17 was discovered in 1993 in a rodent T cell library by subtractive hybridization. Then termed CTLA-8, IL-17 was recognized to have homology to an open reading frame encoded within a T cell-tropic γ -herpesvirus, *Herpesvirus Saimiri* [3], but did not resemble any known cytokines. The significance of the viral homology is still unclear. Nonetheless, the distinct sequence nature of IL-17 relative to other cytokine families was evident, and a human IL-17 homologue was identified that was also shown to be a T cell-derived factor with cytokine-like activity [4]. At the same time, an IL-17-binding receptor was cloned, which bound to the mouse, human and viral forms of IL-17. Like IL-17, the IL-17R was unique compared to other known groupings of cytokine receptors, and was a single transmembrane receptor with an unusually long cytoplasmic tail [5,6]. Thus were described the founding members of a new cytokine subfamily, which has since expanded to include 7 ligands (including the viral homologue ORF13 or vIL-17) and 5 receptor subunits (reviewed in [2,7,8]) (Table 1). The ligand-receptor relationships are still poorly defined for this family, as there are several orphan receptors and orphan ligands. Whether they cooperate to form composite receptor complexes or interact with non-IL-17R subunits remains to be determined.

IL-17 (also known as IL-17A) is most homologous to IL-17F (~60%), and the genes encoding them are proximally located on chromosome 6. IL-17 and IL-17F exist as homodimers [9], and it was recently shown that IL-17A and IL-17F, which are both produced by Th17 cells (see xx below) also form a heterodimeric cytokine termed IL-17A/F (Table 1) [10,11]. IL-17F is the only member of the subfamily whose 3-dimensional crystal structure has been solved [12].

Unexpectedly, it forms a cysteine knot structure also found in the NGF and PDGF cytokines,

²Present address: University of Pittsburgh, Division of Rheumatology & Clinical Immunology, 3500 Terrace St, Pittsburgh PA 15261, 412-383-8000

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

and the conserved cysteine alignment and computer modeling of IL-17A indicates it almost certainly adopts a similar structure.

Similar to their cognate cytokines, IL-17 receptor complexes are multimeric. IL-17 appears to bind to a receptor composed of at least two IL-17RA subunits and one IL-17RC subunit, though the precise stoichiometry has not been determined [13,14]. Similar to many receptor complexes such as the TNF and Toll-like receptors [15,16], IL-17RA subunits are pre-assembled in the plasma membrane prior to ligand binding. In IL-17RA, this occurs through an extracellular fibronectin III-like domain [13,17]. This pre-assembly presumably enables the receptor to respond rapidly and specifically to ligand, while preventing unproductive interactions with other receptors [15,18].

It is not yet clear whether IL-17RC is also part of the pre-assembled complex. IL-17F also uses IL-17RA and IL-17RC to signal, though the relative binding affinity of IL-17F to IL-17RC appears to be much stronger than to IL-17RA [19]. Interestingly, IL-17RC exists in a large number of splice isoforms that differ in the extracellular domain [7,20]. It is not known whether these different splice forms vary in their ability to bind ligands or assemble with IL-17RA, but this type of regulation could ultimately determine the nature of the signaling outcome in target cells. There are apparently important structural issues in signaling, however, because mouse IL-17RC cannot pair with human IL-17RA despite quite high homology between these receptors [14]. Additionally, soluble forms of IL-17RC mRNA have been identified, which could serve to antagonize IL-17 or IL-17F signaling [20]. Thus, there is potential for considerable variability in receptor complex formation and hence signaling responsiveness among these subunits, which will be an important area of inquiry in the future.

3. IL-17 regulates innate immunity

Early studies with IL-17 showed that it activates induction of IL-6, IL-8 and G-CSF in non-immune cells such as fibroblasts and epithelial cells, at least in part through activation of the NF- κ B transcription factor [4,9]. As our understanding of IL-17 function has improved, this general theme has held true, and the major gene targets for IL-17 include pro-inflammatory chemokines, hematopoietic cytokines, acute phase response genes and anti-microbial substances (reviewed in [2]). Indeed, a hallmark “Th17” signature has now become evident from a series of studies in both cell lines and *in vivo* (Table 2) [21–23]. Although the specific expression of each of these genes probably varies somewhat by tissue or disease state, the overall Th17 gene profile has been remarkably consistent among such studies.

In vivo studies indicated that IL-17 is an especially potent activator of neutrophils, both through expansion of the lineage through regulation of G-CSF and the G-CSF receptor as well as recruitment through regulation of chemokine expression. Ectopic expression of IL-17 stimulated a strong neutrophilic response [24] and IL-17 deficiencies in mice are associated with neutrophil defects leading to disease susceptibility (reviewed in [25,26]). For example, mice deficient in IL-17RA are highly susceptible to extracellular pathogens, including the bacteria *Klebsiella pneumonia* and *Porphyromonas gingivalis*, the yeast *Candida albicans*, and the parasite *Toxoplasma gondii* [27–30]. IL-17-deficient mice also exhibit reduced DTH responses and antibody responses [31]. Importantly, neutrophil function in IL-17RA^{−/−} mice is intrinsically normal, as neutrophils from these mice migrate normally and produce normal levels of MPO [30]. Rather, the defect appears to lie in neutrophil expansion via reduced G-CSF and recruitment to tissue via reduced CXC chemokine expression (reviewed in [32]). In mice, the key target chemokines seem to be CXCL1/KC/Groa and CXCL5/LIX [27,30,33–35], whereas in humans IL-8 is probably the most important neutrophil-attracting gene induced by IL-17 [9]. Thus, IL-17 appears to act on neutrophils indirectly.

In addition to affecting neutrophils, IL-17 promotes expression of various anti-microbial genes. For example, the acute phase protein lipocalin 2/24p3 is strongly regulated by IL-17 in numerous cell types [36]. Although roles for 24p3 in controlling mammalian development have been described, its major role in host defense lies in the ability to bind to bacterial siderophores. Siderophores are iron-scavenging molecules that are necessary for bacterial survival in the body, where free iron is generally highly sequestered. 24p3 acts by binding and inhibiting catecholate-type siderophores, and thus limiting iron uptake by bacteria such as *E. coli* and *K. pneumoniae* [37]. Several recent studies have shown that 24p3 is a critical IL-17-regulated gene *in vivo* [21,22]. In addition, IL-17 regulates expression of molecules with direct antimicrobial activity, such as β -defensins, calgranulins and mucins [38–41]. Defensins, in particular, act as natural antibiotics in the lung, skin and gut [42,43]. Interestingly, certain β -defensins also exhibit chemotactic activity. For example, human β -defensin 2 binds to CCR6 and mediates recruitment of DCs [44].

Another IL-17 target gene is CCL20 (MIP3 α), a chemokine that recruits DCs and T cells and plays a role in pathology in RA [45]. CCL20 is regulated by IL-17 in epithelial cells and synoviocytes [45,46], is expressed by Th17 cells [47] and has been linked to Th17 recruitment to inflamed sites [48]. Like β -defensins, CCL20 has chemotactic activity for T cells and DCs. There is an interesting connection between CCL20 and defensins, as many chemokines including CCL20 exert anti-bacterial and anti-fungal activities *in vitro* [49]. Like hBD2, CCL20 binds to CCR6, which is a marker for Th17 cells. Thus, both CCL20 and BDs may provide a positive feedback loop for IL-17 amplification by recruiting Th17 cells to inflamed sites.

However, IL-17 is not always beneficial in protecting the host from infection. In schistosomiasis and some forms of *Candida albicans* infections in mice, IL-17 appears to stimulate a pathogenic inflammatory response that can be alleviated with antibodies to IL-17 [50,51]. Elevated IL-17 levels are also associated with severe periodontal disease (reviewed in [18]), suggesting that in certain chronic infectious settings, IL-17 may be deleterious.

4. IL-17 promotes autoimmune pathology

Several studies in the late 1990s implicated IL-17 in the pathogenesis of autoimmunity. Elevated IL-17 levels were found in RA, SLE, psoriasis, patients, though it was not clear from these studies how important a role it might play in disease pathogenesis (reviewed in [32,52]). Consistent with these observations, rodent models of RA such as collagen-induced arthritis (CIA) indicated that IL-17, rather than being “just another cytokine,” might play a particularly key role in disease pathogenesis. Although Th1 cells had long been considered to be essential for driving pathology in autoimmunity, IFN γ did not appear to be a major driver of autoimmunity since IFN γ –/– mice were still susceptible to disease (reviewed in [53]). Conversely, antibodies to IL-17 reduced inflammation and bone erosion in CIA quite dramatically [54,55]. Moreover, mice deficient in ICOS (“inducible costimulator,” a co-stimulatory molecule for activation of T cells), were completely resistant to CIA and showed a large deficit in IL-17 levels, even though they produced normal levels of TNF α and IFN γ [56]. Consistently, IL-17–/– mice are also resistant to CIA [57]. IL-17 also seems to be important for various animal models of arthritis, including IL-1 (reviewed in [54]).

The significant effects of IL-17 blockade are seemingly at odds with its weak functions *in vitro*, as high levels of cytokine are needed to stimulate typical pro-inflammatory signals such as NF- κ B or IL-6 secretion [58]. However, IL-17 exhibits extremely potent synergy in combination with other cytokines, such as IL-1 β and TNF α [58–61]. The strong synergy of IL-17 with TNF α also suggests a potential mechanism by which blockade of TNF α might serve to reduce IL-17 function and thus explain the success of anti-TNF biologics for treating RA [62].

However, the real breakthrough in understanding the role of IL-17 in autoimmune disease occurred with the discovery of a unique, IL-17-secreting T cell subset, which will be discussed below.

5. IL-17 signal transduction

Because the IL-17 receptor family is distinct in sequence from other cytokine family, studies defining its signaling mechanisms have lagged behind other cytokine families. Early studies showed that IL-17 could activate NF- κ B and MAPK pathways, which was not surprising given the pro-inflammatory nature of IL-17 target genes (Table 2, [2]). Moreover, TRAF6 was shown to be important for activation of NF- κ B and ICAM-1 expression [63]. Although a few reports implicated the JAK-STAT pathway, the data are not very convincing and have usually relied on relatively nonspecific JAK kinase inhibitors (reviewed in [2]). An important insight occurred with the observation that IL-17R family cytoplasmic tails show some homology with the IL-1/Toll-like receptor family of cytokines. Novatchkova *et al.* used a bioinformatics algorithm that predicted the existence of a functional domain in IL-17R receptors with similarities to a “TIR” domain, which they termed “SEFIR” for SEF/IL-17R [64]. The TIR domain is a protein-protein interaction motif found in Toll-like receptors (TLRs) and IL-1 receptors that serve to recruit adaptor molecules such as MyD88, TRIF, etc. (reviewed in [65]). This group also noted that Act1, an activator of NF- κ B that had been linked to BAFF and CD40L signaling [66], also encoded an apparent SEFIR domain [64]. Indeed, it was later demonstrated empirically that the SEFIR domain in IL-17RA is essential for IL-17 signaling, as deletions of this region in IL-17RA impair its signaling capability [67,68]. Moreover, Act1-deficient cells fail to respond to IL-17 for most signals, and IL-17RA binds to Act1 through mutual SEFIR-dependent interactions to activate NF- κ B and TAK1 [68,69]. Interestingly, Act1 is also needed for IL-17-dependent mRNA stability [70]. However, there are Act1-independent signaling events such as activation of ERK [68], and so the complete IL-17 receptor signaling cascade is far from being completely defined.

6. Sources of IL-17: The Th17 lineage and beyond

In 1986 Mossman and Coffman proposed a model wherein CD4⁺ T helper cells can be modulated by their environment to produce different profiles of cytokines, termed Th1 and Th2 [53,71]. Th1 cells produced IFN γ and activated a macrophage-dominated “cell mediated” response, while Th2 cells produced IL-4, IL-5 and IL-13 and mediated an antibody-dominated “humoral” response. Th1 cells are driven to differentiate by IL-12, and Th2 cells by IL-4 (Fig. 1). This framework was extremely valuable for explaining many aspects of disease. However, in the ensuing years this paradigm was vastly over-interpreted [53]. Indeed, many T cell derived cytokines including IL-17 did not fall into either category; in fact, a prescient paper indicated that IL-17 might be characteristic of a distinct Th cell subset induced by an extracellular bacterium, *Borrelia* [72].

Multiple lines of research led to the revision of Th development model, which have been elegantly and comprehensively reviewed elsewhere [52,73]. Briefly, the discovery of IL-23, a heterodimeric cytokine that shares its p40 subunit with IL-12, led to the recognition that “IL-12-knockout mice”, based on which many conclusions about Th1 cells were made, were in fact deficient in another subset of T cells that produce IL-17 and IL-17F. Subsequent studies showed that the Th17 subset is a separate lineage driven by a complex set of cytokines (namely, TGF β , IL-6, IL-21 and IL-1, with some variations between mice and humans). IL-23, while not needed for development of this lineage per se, is required for the pathogenicity and expansion of these cells [74]. Hence, IL-23-deficient mice but generally not IL-12-deficient mice were susceptible to autoimmune disease models including CIA, EAE and IBD [75, 76]. Similarly, Th17 cells to a far greater extent than Th1 cells were capable of transferring

autoimmune disease. Importantly, a polymorphism in the IL-23 receptor, which is expressed almost exclusively on IL-17-secreting cells, has been linked to susceptibility to Crohn's disease, thus forging a direct link to pathology in humans [77]. Th17 cells express characteristic chemokine receptors, namely CCR6 and CCR4 [78], which help to target these cells to mucosal surfaces such as lung and gut.

It is important to note that Th17 cells produce additional cytokines besides IL-17A and IL-17F. IL-22, an IL-10 family cytokine, activates many of the same innate inflammatory genes as IL-17. Indeed, IL-17 and IL-22 act cooperatively or synergistically, especially on epithelial cells, to induce inflammatory gene expression [40]. Another important Th17 cytokine is IL-21, which promotes antibody secretion and class switching and serves as an important positive feedback cytokine to reinforce differentiation of Th17 cells [79–81]. Lastly, IL-17 is made by other cells apart from CD4⁺ Th17 cells. CD8⁺ cells and $\gamma\delta$ T cells are important sources of IL-17 [82,83]. NKT cells have also been reported to be a significant source of IL-17 [84]. Thus, IL-17 bridges innate and adaptive immunity, in that it is produced by both adaptive and “innate” T cells, and activates a gene expression program typical of the innate immune response.

As described above, IL-17-expressing cells have been found to be vital for immunity to a variety of diseases, particularly extracellular pathogens. However, as would be predicted, Th1 cells are more important than Th17 cells in mediating viral immunity and host defense against intracellular microorganisms such as *Mycobacterium tuberculosis* [85]. Nonetheless, these distinctions are not “all or nothing.” IL-23-expressing and IL-17-expressing vaccinia viruses appear to promote immunity to vaccinia viruses in a mouse model [86], and IL-17 contributes to immune memory in a vaccine model of TB [87]. Both Th2 and Th17 cells mediate pathology in asthma and airway hypersensitivity [26], and Th1 cells can still impart some level of disease upon adoptive transfer in certain autoimmune models such as EAE [75]. Moreover, certain cells produce both IFN γ and IL-17, thus blurring the lines between Th1 and Th17 responses.

Since IL-17 has potent pathogenic properties, it is not surprising that a number of mechanisms contribute to suppressing its production or function. Both Th1 and Th2 cytokines suppress Th17 development [88,89]. IL-27 and IL-2 also limit Th17 activity or development [90]. Th17 cells produce IL-10, which mitigates their pro-inflammatory function; IL-10 production is counter-acted by IL-23, which explains the essential role of IL-23 in mediating autoimmunity despite the fact that it is dispensable for Th17 differentiation [74].

7. Implications for therapy

Anti-cytokine therapy for treating autoimmunity has been extremely successful. Interestingly, most of anti-cytokine drugs currently in use impact the Th17 pathway, even though they were developed before its discovery (reviewed in [52]). The discovery of the central role of IL-17 and autoimmune disease has naturally stimulated development of antibodies against IL-17 or IL-17RA as well as IL-23 [62]. Understanding the functional role of IL-17 in various forms of disease will be critical for optimal targeting of this cytokine for effective use in therapy.

Acknowledgments

SLG was supported by the NIH (AR054389), and the Alliance for Lupus Research.

References

1. Ozaki K, Leonard WJ. Cytokine and cytokine receptor pleiotropy and redundancy. *J Biol Chem* 2002;277:29355–29358. [PubMed: 12072446]
2. Shen F, Gaffen SL. Structure-function relationships in the IL-17 receptor: Implications for signal transduction and therapy. *Cytokine* 2008;41:92–104. [PubMed: 18178098]

3. Rouvier E, Luciani M-F, Mattei M-G, Denizot F, Golstein P. CTLA-8, cloned from an activated T cell, bearing AU-rich messenger RNA instability sequences, and homologous to a Herpesvirus Saimiri gene. *J. Immunol* 1993;150:5445–5456. [PubMed: 8390535]
4. Yao Z, Painter SL, Fanslow WC, Ulrich D, Macduff BM, Spriggs MK, Armitage RJ. Cutting Edge: Human IL-17: A novel cytokine derived from T cells. *J. Immunol* 1995;155:5483–5486. [PubMed: 7499828]
5. Yao Z, Fanslow WC, Seldin MF, Rousseau A-M, Painter SL, Comeau MR, Cohen JI, Spriggs MK. Herpesvirus Saimiri encodes a new cytokine, IL-17, which binds to a novel cytokine receptor. *Immunity* 1995;3:811–821. [PubMed: 8777726]
6. Yao Z, Spriggs MK, Derry MJ, Strockbine L, Park LS, VandenBos T, Zappone J, Painter SL, Armitage RJ. Molecular characterization of the human interleukin-17 receptor. *Cytokine* 1997;9:794–800. [PubMed: 9367539]
7. Moseley TA, Haudenschild DR, Rose L, Reddi AH. Interleukin-17 family and IL-17 receptors. *Cytokine Growth Factor Rev* 2003;14:155–174. [PubMed: 12651226]
8. Aggarwal S, Gurney AL. IL-17: A prototype member of an emerging family. *J. Leukoc. Biol* 2002;71:1–8. [PubMed: 11781375]
9. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, Maat C, Pin J-J, Garrone P, Garcia E, Saeland S, Blanchard D, Gaillard C, Das Mahapatra B, Rouvier E, Golstein P, Banchereau J, Lebecque S. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J. Exp. Med* 1996;183:2593–2603. [PubMed: 8676080]
10. Chang SH, Dong C. A novel heterodimeric cytokine consisting of IL-17 and IL-17F regulates inflammatory responses. *Cell Res* 2007;17:435–440. [PubMed: 17452998]
11. Wright JF, Guo Y, Quazi A, Luxenberg DP, Bennett F, Ross JF, Qiu Y, Whitters MJ, Tomkinson KN, Dunussi-Joannopoulos K, Carreno BM, Collins M, Wolfman NM. Identification of an Interleukin 17F/17A Heterodimer in Activated Human CD4+ T Cells. *J Biol Chem* 2007;282:13447–13455. [PubMed: 17355969]
12. Hymowitz SG, Filvaroff EH, Yin JP, Lee J, Cai L, Risser P, Maruoka M, Mao W, Foster J, Kelley RF, Pan G, Gurney AL, de Vos AM, Starovasnik MA. IL-17s adopt a cystine knot fold: structure and activity of a novel cytokine, IL-17F, and implications for receptor binding. *Embo J* 2001;20:5332–5341. [PubMed: 11574464]
13. Kramer J, Yi L, Shen F, Maitra A, Jiao X, Jin T, Gaffen S. Cutting Edge: Evidence for ligand-independent multimerization of the IL-17 receptor. *J Immunol* 2006;176:711–715. [PubMed: 16393951]
14. Toy D, Kugler D, Wolfson M, Vanden Bos T, Gurgel J, Derry J, Tocker J, Peschon JJ. Cutting Edge: Interleukin-17 signals through a heteromeric receptor complex. *J. Immunol* 2006;177:36–39. [PubMed: 16785495]
15. Chan FK. Three is better than one: pre-ligand receptor assembly in the regulation of TNF receptor signaling. *Cytokine* 2007;37:101–107. [PubMed: 17449269]
16. Latz E, Verma A, Visintin A, Gong M, Sirois CM, Klein DC, Monks BG, McKnight CJ, Lamphier MS, Duprex WP, Espevik T, Golenbock DT. Ligand-induced conformational changes allosterically activate Toll-like receptor 9. *Nat Immunol* 2007;8:772–779. [PubMed: 17572678]
17. Kramer J, Hanel W, Shen F, Isik N, Malone J, Maitra A, Sigurdson W, Swart D, Tocker J, Jin T, Gaffen SL. Cutting Edge: Identification of the pre-ligand assembly domain (PLAD) and ligand binding site in the IL-17 receptor. *J Immunol* 2007;179:6379–6383. [PubMed: 17982023]
18. Kramer J, Gaffen S. Interleukin-17: A new paradigm in inflammation, autoimmunity and therapy. *J. Periodontol* 2007;78:1083–1093. [PubMed: 17539723]
19. Kuestner R, Taft D, Haran A, Brandt C, Brender T, Lum K, Harder B, Okada S, Osatrander C, Kreindler J, Aujla S, Reardon B, Moore M, Shea P, Schreckhise R, Bukowski T, Presnell S, Guerra-Lewis P, Parrish-Novak J, Ellsworth J, Jaspers S, Lewis K, Appleby M, Kolls J, Rixon M, West J, Gao Z, Levin S. Identification of the IL-17 receptor related molecule, IL-17RC, as the receptor for IL-17F. *J Immunol* 2007;179:5462–5473. [PubMed: 17911633]
20. Haudenschild D, Moseley T, Rose L, Reddi AH. Soluble and transmembrane isoforms of novel interleukin-17 receptor-like protein by RNA splicing and expression in prostate cancer. *J Biol Chem* 2002;277:4309–4316. [PubMed: 11706037]

21. Raffatellu M, Santos RL, Verhoeven DE, George MD, Wilson RP, Winter SE, Godinez I, Sankaran S, Paixao TA, Gordon MA, Kolls JK, Dandekar S, Baumler AJ. Simian immunodeficiency virus-induced mucosal interleukin-17 deficiency promotes *Salmonella* dissemination from the gut. *Nat Med* 2008;14:421–428. [PubMed: 18376406]
22. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, Reinhart TA, McAllister F, Edeal J, Gaus K, Husain S, Kreindler JL, Dubin PJ, Pilewski JM, Myerburg MM, Mason CA, Iwakura Y, Kolls JK. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. *Nat Med* 2008;14:275–281. [PubMed: 18264110]
23. Shen F, Ruddy MJ, Plamondon P, Gaffen SL. Cytokines link osteoblasts and inflammation: microarray analysis of interleukin-17- and TNF-alpha-induced genes in bone cells. *J Leukoc Biol* 2005;77:388–399. [PubMed: 15591425]
24. Schwarzenberger P, La Russa V, Miller A, Ye P, Huang W, Zieske A, Nelson S, Bagby GJ, Stoltz D, Mynatt RL, Spriggs M, Kolls JK. IL-17 stimulates granulopoiesis in mice: Use of an alternate, novel gene therapy-derived method for in vivo evaluation of cytokines. *J. Immunol* 1998;161:6383–6389. [PubMed: 9834129]
25. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity* 2004;21:467–476. [PubMed: 15485625]
26. Linden A, Laan M, Anderson G. Neutrophils, interleukin-17A and lung disease. *Eur Respir J* 2005;25:159–172. [PubMed: 15640338]
27. Ye P, Rodriguez FH, Kanaly S, Stocking KL, Schurr J, Schwarzenberger P, Oliver P, Huang W, Zhang P, Zhang J, Shellito JE, Bagby GJ, Nelson S, Charrier K, Peschon JJ, Kolls JK. Requirement of interleukin 17 receptor signaling for lung CXC chemokine and granulocyte colony-stimulating factor expression, neutrophil recruitment, and host defense. *J Exp Med* 2001;194:519–527. [PubMed: 11514607]
28. Kelly MN, Kolls JK, Happel K, Schwartzman JD, Schwarzenberger P, Combe C, Moretto M, Khan IA. Interleukin-17/interleukin-17 receptor-mediated signaling is important for generation of an optimal polymorphonuclear response against *Toxoplasma gondii* infection. *Infect Immun* 2005;73:617–621. [PubMed: 15618203]
29. Huang W, Na L, Fidel PL, Schwarzenberger P. Requirement of interleukin-17A for systemic anti-*Candida albicans* host defense in mice. *J Infect Dis* 2004;190:624–631. [PubMed: 15243941]
30. Yu J, Ruddy M, Wong G, Sfintescu C, Baker P, Smith J, Evans R, Gaffen S. An essential role for IL-17 in preventing pathogen-initiated bone destruction: Recruitment of neutrophils to inflamed bone requires IL-17 receptor-dependent signals. *Blood* 2007;109:3794–3802. [PubMed: 17202320]
31. Nakae S, Komiyama Y, Nambu A, Sudo K, Iwase M, Homma I, Sekikawa K, Asano M, Iwakura Y. Antigen-specific T cell sensitization is impaired in IL-17-deficient mice, causing suppression of allergic cellular and humoral responses. *Immunity* 2002;17:375–387. [PubMed: 12354389]
32. Yu J, Gaffen SL. Interleukin-17: A novel inflammatory cytokine that bridges innate and adaptive immunity. *Front. Biosci* 2008;13:170–177. [PubMed: 17981535]
33. Witowski J, Pawlaczyk K, Breborowicz A, Scheuren A, Kuzlan-Pawlaczyk M, Wisniewska J, Polubinska A, Friess H, Gahl GM, Frei U, Jorres A. IL-17 stimulates intraperitoneal neutrophil infiltration through the release of GRO alpha chemokine from mesothelial cells. *J Immunol* 2000;165:5814–5821. [PubMed: 11067941]
34. Ruddy MJ, Shen F, Smith J, Sharma A, Gaffen SL. Interleukin-17 regulates expression of the CXC chemokine LIX/CXCL5 in osteoblasts: Implications for inflammation and neutrophil recruitment. *J. Leukoc. Biol* 2004;76:135–144. [PubMed: 15107456]
35. Yu J, Ruddy M, Conti H, Boonantananasarn K, Gaffen SL. The IL-17 receptor plays a gender-dependent role in host protection against *P. gingivalis*-induced periodontal bone loss. *Infect. Immun.* 2008in press
36. Shen F, Hu Z, Goswami J, Gaffen SL. Identification of common transcriptional regulatory elements in interleukin-17 target genes. *J Biol Chem* 2006;281:24138–24148. [PubMed: 16798734]
37. Flo TH, Smith KD, Sato S, Rodriguez DJ, Holmes MA, Strong RK, Akira S, Aderem A. Lipocalin 2 mediates an innate immune response to bacterial infection by sequestering iron. *Nature* 2004;432:917–921. [PubMed: 15531878]

38. Kao CY, Chen Y, Thai P, Wachi S, Huang F, Kim C, Harper RW, Wu R. IL-17 markedly up-regulates beta-defensin-2 expression in human airway epithelium via JAK and NF-kappaB signaling pathways. *J Immunol* 2004;173:3482–3491. [PubMed: 15322213]
39. Zheng Y, Danilenko DM, Valdez P, Kasman I, Eastham-Anderson J, Wu J, Ouyang W. Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature* 2007;445:648–651. [PubMed: 17187052]
40. Liang SC, Tan XY, Luxenberg DP, Karim R, Dunussi-Joannopoulos K, Collins M, Fouser LA. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of antimicrobial peptides. *J Exp Med* 2006;203:2271–2279. [PubMed: 16982811]
41. Chen Y, Thai P, Zua Y-H, Ho Y-S, DeSouza M, Wu R. Stimulation of airway mucin gene expression by interleukin (IL)-17 through IL-6 paracrine/autocrine loop. *J Biol Chem* 2003;278:17036–17043. [PubMed: 12624114]
42. Ganz T. Defensins and host defense. *Science* 1999;286:420–421. [PubMed: 10577203]
43. Oppenheim JJ, Biragyn A, Kwak LW, Yang D. Roles of antimicrobial peptides such as defensins in innate and adaptive immunity. *Ann Rheum Dis* 2003;62:ii17–ii21. [PubMed: 14532141]
44. Yang D, Chertov O, Bykovskaia SN, Chen Q, Buffo MJ, Shogan J, Anderson M, Schröder JM, Wang JM, Howard OMZ, Oppenheim JJ. β -Defensins: Linking innate immunity and adaptive immunity through dendritic and T cell CCR6. *Science* 1999;286:525–528. [PubMed: 10521347]
45. Kao C-Y, Huang F, Chen Y, Thai P, Wachi S, Kim C, Tam L, Wu R. Upregulation of CC chemokine ligand 20 expression in human airway epithelium by IL-17 through a JAK-independent but MEK-NF-kappaB-dependent signaling pathway. *J Immunol* 2005;175:6676–6685. [PubMed: 16272323]
46. Zrioual S, Toh ML, Tournadre A, Zhou Y, Cazalis MA, Pachot A, Miossec V, Miossec P. IL-17RA and IL-17RC receptors are essential for IL-17A-induced ELR+ CXC chemokine expression in synoviocytes and are overexpressed in rheumatoid blood. *J Immunol* 2008;180:655–663. [PubMed: 18097068]
47. Wilson NJ, Boniface K, Chan JR, McKenzie BS, Blumenschein WM, Mattson JD, Basham B, Smith K, Chen T, Morel F, Lecron JC, Kastelein RA, Cua DJ, McClanahan TK, Bowman EP, de Waal Malefyt R. Development, cytokine profile and function of human interleukin 17-producing helper T cells. *Nat Immunol* 2007;8:950–957. [PubMed: 17676044]
48. Hirota K, Yoshitomi H, Hashimoto M, Maeda S, Teradaira S, Sugimoto N, Yamaguchi T, Nomura T, Ito H, Nakamura T, Sakaguchi N, Sakaguchi S. Preferential recruitment of CCR6-expressing Th17 cells to inflamed joints via CCL20 in rheumatoid arthritis and its animal model. *J Exp Med* 2007;204:2803–2812. [PubMed: 18025126]
49. Yang D, Chen Q, Hoover D, Staley P, Tucker K, Lubkowski J, Oppenheim J. Many chemokines including CCL20/MIP-3 α display antimicrobial activity. *J Leukoc Biol* 2003;74:448–455. [PubMed: 12949249]
50. Rutitzky LI, Lopes da Rosa JR, Stadecker MJ. Severe CD4 T cell-mediated immunopathology in murine schistosomiasis is dependent on IL-12p40 and correlates with high levels of IL-17. *J Immunol* 2005;175:3920–3926. [PubMed: 16148138]
51. Zelante T, De Luca A, Bonifazi P, Montagnoli C, Bozza S, Moretti S, Belladonna ML, Vacca C, Conte C, Mosci P, Bistoni F, Puccetti P, Kastelein RA, Kopf M, Romani L. IL-23 and the Th17 pathway promote inflammation and impair antifungal immune resistance. *Eur J Immunol* 2007;37:2695–2706. [PubMed: 17899546]
52. Ghilardi N, Ouyang W. Targeting the development and effector functions of Th17 cells. *Semin Immunol* 2007;19:383–393. [PubMed: 18083530]
53. Steinman L. A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med* 2007;13:139–145. [PubMed: 17290272]
54. Lubberts E. IL-17/Th17 targeting: on the road to prevent chronic destructive arthritis? *Cytokine* 2008;41:84–91. [PubMed: 18039580]
55. Lubberts E, Koenders MI, Oppers-Walgreen B, van den Bersselaar L, Coenen-de Roo CJ, Joosten LA, van den Berg WB. Treatment with a neutralizing anti-murine interleukin-17 antibody after the onset of collagen-induced arthritis reduces joint inflammation, cartilage destruction, and bone erosion. *Arthritis Rheum* 2004;50:650–659. [PubMed: 14872510]

56. Nurieva RI, Treuting P, Duong J, Flavell RA, Dong C. Inducible costimulator is essential for collagen-induced arthritis. *J Clin Invest* 2003;111:701–706. [PubMed: 12618524]
57. Nakae S, Nambu A, Sudo K, Iwakura Y. Suppression of immune induction of collagen-induced arthritis in IL-17-deficient mice. *J Immunol* 2003;171:6173–6177. [PubMed: 14634133]
58. Ruddy MJ, Wong GC, Liu XK, Yamamoto H, Kasayama S, Kirkwood KL, Gaffen SL. Functional cooperation between interleukin-17 and tumor necrosis factor- α is mediated by CCAAT/enhancer binding protein family members. *J Biol Chem* 2004;279:2559–2567. [PubMed: 14600152]
59. Chabaud M, Fossiez F, Taupin JL, Miossec P. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by rheumatoid arthritis synoviocytes and its regulation by Th2 cytokines. *J Immunol* 1998;161:409–414. [PubMed: 9647250]
60. Chabaud M, Miossec P. The combination of tumor necrosis factor alpha blockade with interleukin-1 and interleukin-17 blockade is more effective for controlling synovial inflammation and bone resorption in an ex vivo model. *Arthritis Rheum* 2001;44:1293–1303. [PubMed: 11407688]
61. Miossec P. Interleukin-17 in rheumatoid arthritis: if T cells were to contribute to inflammation and destruction through synergy. *Arthritis Rheum* 2003;48:594–601. [PubMed: 12632409]
62. Kikly K, Liu L, Na S, Sedgwick JD. The IL-23/Th(17) axis: therapeutic targets for autoimmune inflammation. *Curr Opin Immunol* 2006;18:670–675. [PubMed: 17010592]
63. Schwandner R, Yamaguchi K, Cao Z. Requirement of tumor necrosis factor-associated factor (TRAF) 6 in interleukin 17 signal transduction. *J. Exp. Med* 2000;191:1233–1239. [PubMed: 10748240]
64. Novatchkova M, Leibbrandt A, Werzowa J, Neubuser A, Eisenhaber F. The STIR-domain superfamily in signal transduction, development and immunity. *Trends Biochem Sci* 2003;28:226–229. [PubMed: 12765832]
65. Kawai T, Akira S. TLR signaling. *Semin Immunol* 2007;19:24–32. [PubMed: 17275323]
66. Li X. Act1 modulates autoimmunity through its dual functions in CD40L/BAFF and IL-17 signaling. *Cytokine* 2008;41:105–113. [PubMed: 18061473]
67. Maitra A, Shen F, Hanel W, Mossman K, Tocker J, Swart D, Gaffen SL. Distinct functional motifs within the IL-17 receptor regulate signal transduction and target gene expression. *Proc. Natl. Acad. Sci, USA* 2007;104:7506–7511. [PubMed: 17456598]
68. Qian Y, Liu C, Hartupée J, Altuntas CZ, Gulen MF, Jane-Wit D, Xiao J, Lu Y, Giltiay N, Liu J, Kordula T, Zhang QW, Vallance B, Swaidani S, Aronica M, Tuohy VK, Hamilton T, Li X. The adaptor Act1 is required for interleukin 17-dependent signaling associated with autoimmune and inflammatory disease. *Nat Immunol* 2007;8:247–256. [PubMed: 17277779]
69. Chang SH, Park H, Dong C. Act1 adaptor protein is an immediate and essential signaling component of interleukin-17 receptor. *J Biol Chem* 2006;281:35603–35607. [PubMed: 17035243]
70. Hartupée J, Liu C, Novotny M, Li X, Hamilton T. IL-17 enhances chemokine gene expression through mRNA stabilization. *J Immunol* 2007;179:4135–4141. [PubMed: 17785852]
71. Mosmann TR, Cherwinski H, Bond MW, Giedlin MA, Coffman RL. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins. *J Immunol* 1986;136:2348–2357. [PubMed: 2419430]
72. Infante-Duarte C, Horton HF, Byrne MC, Kamradt T. Microbial lipopeptides induce the production of IL-17 in Th cells. *J Immunol* 2000;165:6107–6115. [PubMed: 11086043]
73. McGeachy MJ, Cua DJ. Th17 cell differentiation: the long and winding road. *Immunity* 2008;28:445–453. [PubMed: 18400187]
74. McGeachy MJ, Bak-Jensen KS, Chen Y, Tato CM, Blumenschein W, McClanahan T, Cua DJ. TGF- β and IL-6 drive the production of IL-17 and IL-10 by T cells and restrain T(H)-17 cell-mediated pathology. *Nat Immunol* 2007;8:1390–1397. [PubMed: 17994024]
75. Langrish CL, Chen Y, Blumenschein WM, Mattson J, Basham B, Sedgwick JD, McClanahan T, Kastelein RA, Cua DJ. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. *J Exp Med* 2005;201:233–240. [PubMed: 15657292]
76. Langrish CL, McKenzie BS, Wilson NJ, de Waal Malefyt R, Kastelein RA, Cua DJ. IL-12 and IL-23: master regulators of innate and adaptive immunity. *Immunol Rev* 2004;202:96–105. [PubMed: 15546388]
77. Duerr RH, Taylor KD, Brant SR, Rioux JD, Silverberg MS, Daly MJ, Steinhart AH, Abraham C, Regueiro M, Griffiths A, Dassopoulos T, Bitton A, Yang H, Targan S, Datta LW, Kistner EO,

- Schumm LP, Lee A, Gregersen PK, Barmada MM, Rotter JI, Nicolae DL, Cho JH. A Genome-Wide Association Study Identifies IL23R as an Inflammatory Bowel Disease Gene. *Science* 2006;314:1461–1463. [PubMed: 17068223]
78. Acosta-Rodriguez EV, Rivino L, Geginat J, Jarrossay D, Gattorno M, Lanzavecchia A, Sallusto F, Napolitani G. Surface phenotype and antigenic specificity of human interleukin 17-producing T helper memory cells. *Nat Immunol* 2007;8:639–646. [PubMed: 17486092]
 79. Korn T, Bettelli E, Gao W, Awasthi A, Jager A, Strom TB, Oukka M, Kuchroo VK. IL-21 initiates an alternative pathway to induce proinflammatory T(H)17 cells. *Nature* 2007;448:484–487. [PubMed: 17581588]
 80. Nurieva R, Yang XO, Martinez G, Zhang Y, Panopoulos AD, Ma L, Schluns K, Tian Q, Watowich SS, Jetten AM, Dong C. Essential autocrine regulation by IL-21 in the generation of inflammatory T cells. *Nature* 2007;448:480–483. [PubMed: 17581589]
 81. Zhou L, Ivanov II, Spolski R, Min R, Shenderov K, Egawa T, Levy DE, Leonard WJ, Littman DR. IL-6 programs T(H)-17 cell differentiation by promoting sequential engagement of the IL-21 and IL-23 pathways. *Nat Immunol* 2007;8:967–974. [PubMed: 17581537]
 82. Stark MA, Huo Y, Burcin TL, Morris MA, Olson TS, Ley K. Phagocytosis of apoptotic neutrophils regulates granulopoiesis via IL-23 and IL-17. *Immunity* 2005;22:285–294. [PubMed: 15780986]
 83. Liu XK, Clements JL, Gaffen SL. Signaling through the murine T cell receptor induces IL-17 production in the absence of costimulation, IL-23 or dendritic cells. *Mol Cells* 2005;20:329–337.
 84. Rachitskaya AV, Hansen AM, Horai R, Li Z, Villasmil R, Luger D, Nussenblatt RB, Caspi RR. Cutting Edge: NKT Cells Constitutively Express IL-23 Receptor and ROR γ t and Rapidly Produce IL-17 upon Receptor Ligation in an IL-6-Independent Fashion. *J Immunol* 2008;180:5167–5171. [PubMed: 18390697]
 85. Khader SA, Cooper AM. IL-23 and IL-17 in tuberculosis. *Cytokine* 2008;41:79–83. [PubMed: 18218322]
 86. Kohyama S, Ohno S, Isoda A, Moriya O, Belladonna ML, Hayashi H, Iwakura Y, Yoshimoto T, Akatsuka T, Matsui M. IL-23 enhances host defense against vaccinia virus infection via a mechanism partly involving IL-17. *J Immunol* 2007;179:3917–3925. [PubMed: 17785829]
 87. Khader SA, Bell GK, Pearl JE, Fountain JJ, Rangel-Moreno J, Cilley GE, Shen F, Eaton SM, Gaffen SL, Swain SL, Locksley RM, Haynes L, Randall TD, Cooper AM. IL-23 and IL-17 in the establishment of protective pulmonary CD4(+) T cell responses after vaccination and during *Mycobacterium tuberculosis* challenge. *Nat Immunol* 2007;8:369–377. [PubMed: 17351619]
 88. Harrington LE, Hatton RD, Mangan PR, Turner H, Murphy TL, Murphy KM, Weaver CT. Interleukin 17-producing CD4+ effector T cells develop via a lineage distinct from the T helper type 1 and 2 lineages. *Nat Immunol* 2005;6:1123–1132. [PubMed: 16200070]
 89. Park H, Li Z, Yang XO, Chang SH, Nurieva R, Wang YH, Wang Y, Hood L, Zhu Z, Tian Q, Dong C. A distinct lineage of CD4 T cells regulates tissue inflammation by producing interleukin 17. *Nat Immunol* 2005;6:1133–1141. [PubMed: 16200068]
 90. Stumhofer JS, Laurence A, Wilson EH, Huang E, Tato CM, Johnson LM, Villarino AV, Huang Q, Yoshimura A, Sehy D, Saris CJ, O'Shea JJ, Hennighausen L, Ernst M, Hunter CA. Interleukin 27 negatively regulates the development of interleukin 17-producing T helper cells during chronic inflammation of the central nervous system. *Nat Immunol* 2006;7:937–945. [PubMed: 16906166]
 91. Laan M, Cui A-H, Hoshino H, Lötval J, Sjöstrand M, Gruenert DC, Skoogh B-E, Lindén A. Neutrophil recruitment by human IL-17 via C-X-C chemokine release in the airways. *J Immunol* 1999;162:2347–2352. [PubMed: 9973514]
 92. Van Kooten C, Boonstra JG, Paape ME, Fossiez F, Banchereau J, Lebecque S, Bruijn JA, De Fijter JW, Van Es LA, Daha MR. Interleukin-17 activates human renal epithelial cells in vitro and is expressed during renal allograft rejection. *J Am Soc Nephrol* 1998;9:1526–1534. [PubMed: 9697677]
 93. Andoh A, Yasui H, Inatomi O, Zhang Z, Deguchi Y, Hata K, Araki Y, Tsujikawa T, Kitoh K, Kim-Mitsuyama S, Takayanagi A, Shimizu N, Fujiyama Y. Interleukin-17 augments tumor necrosis factor- α -induced granulocyte and granulocyte/macrophage colony-stimulating factor release from human colonic myofibroblasts. *J Gastroenterol* 2005;40:802–810. [PubMed: 16143885]

94. Laan M, Prause O, Miyamoto M, Sjostrand M, Hytonen AM, Kaneko T, Lotvall J, Linden A. A role of GM-CSF in the accumulation of neutrophils in the airways caused by IL-17 and TNF-alpha. *Eur Respir J* 2003;21:387–393. [PubMed: 12661990]
95. He R, Shepard LW, Chen J, Pan ZK, Ye RD. Serum amyloid A is an endogenous ligand that differentially induces IL-12 and IL-23. *J Immunol* 2006;177:4072–4079. [PubMed: 16951371]
96. Patel DN, King CA, Bailey SR, Holt JW, Venkatachalam K, Agrawal A, Valente AJ, Chandrasekar B. Interleukin-17 stimulates C-reactive protein expression in hepatocytes and smooth muscle cells via p38 MAPK and ERK1/2-dependent NF-kappaB and C/EBPbeta activation. *J Biol Chem* 2007;282:27229–27238. [PubMed: 17652082]
97. Chabaud M, Garnero P, Dayer JM, Guerne PA, Fossiez F, Miossec P. Contribution of interleukin 17 to synovium matrix destruction in rheumatoid arthritis. *Cytokine* 2000;12:1092–1099. [PubMed: 10880256]
98. Bamba S, Andoh A, Yasui H, Araki Y, Bamba T, Fujiyama Y. Matrix metalloproteinase-3 secretion from human colonic subepithelial myofibroblasts: role of interleukin-17. *J Gastroenterol* 2003;38:548–554. [PubMed: 12825130]
99. Jovanovic DV, Martel-Pelletier J, Di Battista JA, Mineau F, Jolicoeur F-C, Benderdour M, Pelletier J-P. Stimulation of 92-kd gelatinase (matrix metalloproteinase 9) production by interleukin-17 in human monocyte/macrophages. *Arthritis & Rheum* 2000;43:1134–1144. [PubMed: 10817568]
100. Rifas L, Arackal S. T cells regulate the expression of matrix metalloproteinase in human osteoblasts via a dual mitogen-activated protein kinase mechanism. *Arthritis Rheum* 2003;48:993–1001. [PubMed: 12687541]
101. Yamazaki S, Muta T, Matsuo S, Takeshige K. Stimulus-specific induction of a novel nuclear factor-kappaB regulator, IkappaB-zeta, via Toll/Interleukin-1 receptor is mediated by mRNA stabilization. *J Biol Chem* 2005;280:1678–1687. [PubMed: 15522867]

Figure 1.
Th cell differentiation

Table 1**IL-17 family ligands and receptors**

IL-17 family ligands	Produced mainly by	Binding receptor(s)
IL-17 (IL-17A, CTLA-8)	T cells	IL-17RA, IL-17RC (IL-17RL)
IL-17A/F heterodimer	T cells	IL-17RA, IL-17RC
IL-17B	Numerous tissues	IL-17B?
IL-17C	Prostate, fetal kidney	
IL-17D	Numerous tissues	
IL-17E/IL-25	Numerous tissues	IL-17RB (IL-25R)
IL-17F	T cells	IL-17RA, IL-17RC
vIL-17 (ORF13)	<i>H. Saimiri</i>	IL-17RA, IL-17RC?
unknown		IL-17RD (SEF)
unknown		IL-17RE

Table 2

Th17 signature target genes

Th17 signature genes	references
Chemokines	CXCL1 (KC, Gro α) [9] CXCL2 (MIP2) [9] CXCL5 (LIX, GCP2) [34] CXCL8 (IL-8) [91] CXCL9 (MIG) [87] CXCL10 (IP10) [87] CCL2 (MCP-1) [92] CCL20 (MIP3 α) [45]
Cytokines	IL-6 [5] G-CSF [9] TNF α [93] G-CSF (CSF3) [9] GM-CSF (CSF2) [94]
Acute Phase Response	SAA [95] CRP [96]
Tissue Remodeling	Lipocalin 2/24p3 [21–23,36] MMP1 [97] MMP3 [98] MMP9 [99] MMP13 [100] TIMP1 [97]
Anti-microbial	β -defensins [38] Mucins [41] Calgranulins (S100 proteins) [40]
Transcription	NF- κ B ζ (MAIL) [23,101] C/EBP β [58] C/EBP δ [58]