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Semin Immunol. Author manuscript; available in PMC 2008 December 1.

Published in final edited form as:
Semin Immunol. 2007 December ; 19(6): 377–382.

Th17 cells and Mucosal Host Defense

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Abstract

Th17 cells are a new lineage of T-cells that are controlled by the transcription factor RORγt and develop independent of GATA-3, T-bet, Stat 4 and Stat 6. Novel effector molecules produced by these cells include IL-17A, IL-17F, IL-22, and IL-26. IL-17RA binds IL-17A and IL-17F and is critical for host defense against extracellular planktonic bacteria by regulating chemokine gradients for neutrophil emigration into infected tissue sites as well as host granulopoiesis. Moreover IL-17 and IL-22 regulate the production of antimicrobial proteins in mucosal epithelium. Although TGF-β1 and IL-6 have been shown to be critical for development of Th17 cells from naïve precursors, IL-23 is also important in regulating IL-17 release in mucosal tissues in response to infectious stimuli. Compared to Th1 cells, IL-23 and IL-17 show limited roles in controlling host defense against primary infections with intracellular bacteria such as *Mycobacterium tuberculosis* suggesting a predominate role of the Th17 lineage in host defense against extracellular pathogens. However in the setting of chronic biofilm infections, as that occurs with Cystic Fibrosis or bronchetctasis, Th17 cells may be key contributors of tissue injury.

Introduction

The critical role of CD4+ T-cells in host defense against variety of pathogens became clearly evident by the Acquired Immunodeficiency Syndrome (AIDS) epidemic. Large epidemiological studies across patients infected with Human Immunodeficiency Virus-1 and AIDS showed clear inverse relationships between CD4+ T-cell count in peripheral blood and the risk of infection with *Mycobacterium tuberculosis*, *Pneumocystis*, and *Toxoplasma gondii* [1] [2]. With the discovery of the T-cell subsets Th1 defined by interferon gamma production and Th2 cells defined by IL-4, IL-5, and IL-13 production and the use of selective gene deletions within these effector molecules, it became possible to ascribe specific infections with defects along these T-cell lineages. For example defects in the generation of the Th1 cell effector interferon-gamma resulted in susceptibility to *Mycobacterium tuberculosis* infection or an increase in susceptibility to *Toxoplasma* infection [3] [4] [5] [6] [7]. Moreover the lack of an effective Th2 response was shown to predispose to infection with helminths [8] [9]. In addition to these specific susceptibilities in CD4-deficient hosts, data in humans also suggested that Th1 and Th2 immune responses could be associated with specific pathologies. For example a strong Th1 response was associated with the tuberculoid form of leprosy, an infection caused by *Mycobacterium leprae* whereas; a Th2 response was associated with the less controlled variant, lepromatous leprosy [10].

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Although much of clinical HIV-associated risk of infection in the Western world could be understood under this paradigm, this dichotomy of T-cell subsets was incomplete. This particularly became evident as prophylaxis against the opportunistic pathogen *Pneumocystis* became widespread in the late 80's to the early 90's and bacterial pneumonia increased as a major a pulmonary complication of AIDS [11] [12]. Just like infections ascribed to Th1 or Th2 immunity, epidemiological data also suggested that lung infections with extracellular bacteria were also inversely associated with CD4+ T-cells in peripheral blood [11] [12]. However whether this susceptibility was due to a defect in Th1 or Th2 immunity was unclear. It was hypothesized that the susceptibility of HIV infected patients with low CD4+ T-cell counts could be due to lack of T-cell helper function and the generation of neutralizing or opsonic activity against pathogens such as *Streptococcus pneumoniae*, *Klebsiella pneumoniae* or *Pseudomonas aeruginosa*. However this immune defect would not necessary explain susceptibility to primary infection.

With the cloning of IL-17 in 1993 and its receptor in 1995 [13] [14] we undertook studies to determine if IL-17, a molecule shown to be expressed in subset of CD4+ memory T-cell could further explain the susceptibility of CD4+ T-cell deficient patients to infection. Particularly, as the original biological activity of IL-17 in vitro was to support the differentiation of human CD34+ cells along a granulopoietic lineage, it was reasonable to assume that IL-17 may regulate neutrophil responses in vivo; a cell that had previously been shown to be critical for many extracellular pathogens. Thus, we hypothesized that the differentiation and recruitment of neutrophils by IL-17 producing T-cells that may in part explain the susceptibility of CD4+ T-cell deficient host to extracellular pathogens.

IL-17 and granulopoiesis

Schwarzenberger and colleagues overexpressed IL-17 in mice and showed that IL-17 can markedly expand both neutrophil progenitors in bone marrow and spleen as well as mature neutrophils in peripheral blood [15] This expansion is not a direct effect of IL-17 as neutralization of granulocyte-colony stimulating factor or deficiency of transmembrane stem cell factor [15] [16] markedly attenuated the response to IL-17. Furthermore mice with a homozygous deletion of IL-17RA (IL-17RA KO mice) have normal circulating numbers of neutrophils in peripheral blood but are much more susceptible to sublethal gamma irradiation and show reduced neutrophil recovery [17]. These data suggest that stress-induced granulopoiesis requires IL-17RA signaling. In support of this, we examined neutrophil progenitor mobilization in a model of gram negative pneumonia using the bacterial strain *K. pneumoniae* [18]. Wild-type mice show a nearly 100% increase in CFU-GM and over a 200% increase in high proliferative potential colonies containing 50 or more cells (Figure 1). However this response is nearly absent in IL-17RA KO mice (Figure 1) despite higher levels of IL-17A ligand in the lungs of these mice [18] demonstrating that IL-17RA signaling is critical for this response. Again this effect is likely due the secondary mediators induced by IL-17 such as G-CSF and IL-6 [16] [18]. Using mice that have neutrophil adhesion defects, such as CD18 deficiency, which is associated with an expansion of circulating neutrophils in peripheral blood, Ley and colleagues have shown that this expansion of neutrophils is regulated G-CSF [19] [20]. This G-CSF response is regulated by gut derived IL-23 [21] and ultimately IL-17 production by T-cells as antibodies to IL-17 or a soluble receptor which antagonizes IL-17 binding, abrogates the neutrophilia observed in these mice [19]. Stark et al. have proposed a model by which the normal uptake of apoptotic neutrophils in the lamina propria of the gut antagonizes IL-23p19 expression and thereby negatively regulating IL-17 production by gut T-cells, thereby allowing precise physiological regulation of circulating neutrophil numbers [21]. However in the context of strong Toll-like receptor stimulation such as with TLR4 ligands higher levels of IL-23 can be produced to promote IL-17 induced granulopoiesis in the setting of infection [22].

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IL-17 regulation of chemokines

In addition to regulation of granulopoiesis, IL-17 has been shown to regulate the production of specific chemokine ligands of CXCR1/CXCR2 in fibroblasts and epithelial cells, along with emigration of neutrophils into mucosal sites [23] [24] [25]. IL-17A stimulation of human bronchial epithelial, venous endothelial cells, and human synoviocytes results in the production and release of CXCL8 (IL-8) [26] [27] [25]. IL-17A also induces CXCL6 in human bronchial epithelial cells [25] and CXCL5 in murine in osteoblasts in vitro [28]. It is important to note that these cells represent critical barriers for neutrophil invasion. IL-17A and IL-17F also induce CXCL1 and G-CSF in human bronchial epithelial response and this response to both ligands is antagonized by anti-IL-17RA monoclonal antibody suggesting that both IL-17A and IL-17F require IL-17RA for a functional signaling receptor complex [24]. In human synoviocytes in vitro, IL-17A induction of CXCL8 requires NF-kB and the PI-3 kinase/Akt pathway [29]. Moreover there is experimental evidence to support a role for p38 mitogen activated protein (MAP) kinases and extracellular signal regulated kinase (ERK), in the production of CXC chemokines to IL-17 in HBE cells [30] [31]. In many of these CXC chemokine responses, both IL-17A and IL-17F shown marked synergy with TNF-alpha [25]. Recently it has been demonstrated that in mouse embryonic fibroblasts the induction of CXCL1 by IL-17A and IL-17F requires the downstream adaptor Act1 and the induction of CXCL1 is only partly dependent on NF-κB [32]. Other potential transcription factors responsible for IL-17 induced CXCL1 gene expression include CEBPδ which has been shown to mediate some of the synergy of gene expression observed with IL-17A and TNF-alpha dual stimulation [33].

Although it has been reported that IL-17A lacks a direct effect on chemotaxis for human blood neutrophils in vitro, local administration of IL-17A into the lung or synovial space of experimental animals results in a significant accumulation of neutrophils into these specific tissue compartments in vivo [25] [34]. This neutrophil emigration in the context of the lung is blocked by a neutralizing and specific anti-IL-17 antibody or pretreatment with glucocorticoids [26] and cell emigration is likely the result of the local induction of CXCL1, CXCL2, and CXCL5 although the specific requirement of these individual chemokines has not been fully studied. This effect is also observed with IL-17C, IL-17E, and IL-17F however, IL-17E also results in significant emigration of eosinophils [35] consistent with its Th2 cytokine profile. In addition to eliciting the ligands for CXCR1 and CXCR2 and neutrophil emigration, local administration of IL-17A into the lungs of experimental animals results in an increase in neutrophil elastase and myeloperoxidase (MPO) activity in rats in vivo [36].

IL-17 and mucosal host defense

IL-17A, and IL-17F, is induced in a dose- and time-dependent fashion several models of infection including gram-negative bacteria such as *K. pneumoniae* [37] [18]. Just as IL-17 is potent inducer of CXCL1, 2 and 5, mice with a homozygous deletion of IL-17RA show reduced levels of CXCL2 in the lung upon challenge with the gram negative bacteria, K. pneumoniae [18]. This defective CXC chemokine response is associated with reduced neutrophil emigration into the lung. It is likely this defect, along with nearly an 85% reduction in G-CSF in IL-17RA −/− mice compared to wild-type controls that leads to the increased bacteremia and mortality observed in these mice [18]. In support of this, mice deficient in IL-23, a key survival factor for Th17 cells [38] [39] [40], show reduced survival and reduced IL-17 levels in response to *K. pneumoniae*. However restoration of local IL-17 levels in the lung, restores bacterial killing as well as the local levels of G-CSF, CXCXL1 and CXCL5 [40]. In addition to IL-17 regulating host defense to aerobic pathogens, Chung et al have shown that intraabdominal abscess formation due to the anaerobic bacterium *Bacteroides fragilis* requires IL-17A [41]. IL-23 has also been shown to be critical for mucosal host defense in the gut in response to infection with

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Citrobacter rodentium which is natural occurring pathogen in mice [42]. Interestingly in this model IL-17A was produced in both IL-23p19 deficient and wild-type suggesting that the susceptibility of IL-23p19 −/− mice is independent of IL-17A [42]. In addition to extracellular bacteria, Huang et al have shown that IL-17RA signaling is also required for optimal host defense against *Candia albicans* [43] and antibodies against IL-23p19 antagonize pulmonary IL-17 production, neutrophil emigration, and host defense against *Mycoplasma pulmonis* [44]. In addition to regulating CXCR1/2 ligands and G-CSF, IL-17 regulates antimicrobial peptide production of beta defensins [45] and calgranulins in human bronchial epithelial cells and keratinocytes. Recently it has been shown that IL-22 a product of Th17 cells synergizes with IL-17 in inducing these antimicrobial proteins in human keratinocytes which lends further support of the T-cell lineage in mucosal immunity [46]. Due to the fact that there is redundancy in the beta defensin and calgranulins gene family it will require further experimentation to determine the individual contributions of these proteins in ThIL-17 mediated mucosal immunity.

Cellular Sources of IL-17 to infection in vivo

Although the factors that regulate the differentiation of naive αβ T-cells into IL-17 producing T-cells is becoming much more clear with contributions of TGF-β, IL-6 and IL-23 [42] [47] [48], the regulation of IL-17 by T-cells in vivo is much more complex. For example Ley et al have shown that in maintaining neutrophil homeostasis, that approximately 60% of the IL-17 producing T-cells are γδ T cells, 25% NKT like cells, and only approximately 15% are CD4+ T cells [20]. In response to stimulation by lipopetides from *Borrelia burgdorferi*, IL-17A localizes to a subset of T-lymphocytes expressing tumor necrosis factor TNF-alpha and granulocyte-macrophage colony-stimulating factor (GM-CSF) [49]. Moreover, CD8+ T-cells have been shown to produce IL-17 in response to *K. pneumoniae* in vitro [22] and depletion of CD8+ cells partially abrogates lung IL-17 responses in vivo to the same infection [22]. Further evidence for a predominant role of T-cells is the fact that SCID mice show over a 90% reduction in IL-17A concentration within the lung after endotoxin exposure [22] [27]. Recently Michel et al have demonstrated that a critical source of IL-17 in the airway is a novel NK1.1 negative, α-gal-ser positive invariant NKT cell population and this population is critical for airway neutrophilia in response to endotoxin [50]. Lockhart et al have shown that γδ T-cells are the predominant source of IL-17 in *M. tuberculosis* infection in mice [51] however neither IL-23 [52] nor IL-17R signaling is required for host defense against primary TB infection (Figure 2), However in response to the extracellular pathogen E. coli, Shibata et al have shown that the Vγ1 subset of γδ T-cells are critical for IL-17 production in an intraperitoneal model of infection [53]. Thus it appears that IL-17 production is likely regulated by different cells and perhaps different cytokine control at different mucosal/serosal surfaces such as the skin, gut, and lung. In addition to T-lymphocytes, IL-17A message or intracellular protein has been detected in eosinophils and neutrophils and human blood monocytes but release of free, soluble IL-17A protein by these cells has not been reported [25].

Receptor utilization by IL-17A and IL-17F

Although the Act1 is been shown to be a critical adaptor protein of both IL-17A and IL-17F CXCL1 production [32] there is an emerging picture of ligand:receptor specificities in both mouse in human cells. Human IL-17A can bind to IL-17RA but with relatively weak affinity and IL-17F shows one log less affinity to IL-17RA [54]. Transfection of murine IL-17RA −/− fibroblasts with human IL-17RA poorly complements IL-17RA signaling to both potential ligands, IL-17A and IL-17F. However co-transfection of human IL-17RC has been shown to result in fully complement signaling to both IL-17A and IL-17F [54]. Moreover, in human 293 cells transfected with both IL-17RA and IL-17RC is possible to show these two proteins associate by co-immunoprecipitation [54]. However IL-17RA is an essential component for

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both IL-17A and IL-17F signaling in both mouse and human epithelial cells. Mouse IL-17RA −/− fibroblasts fail to produce CXCL1 in response to IL-17A or IL-17F and monoclonal antibodies raised against human IL-17RA block IL-17A and IL-17F CXCL1 production in HBE cells [24]. However soluble IL-17RA only antagonizes IL-17A signaling and lacks the affinity to effectively block IL-17F biding in HBE cells (Figure 3) [24]. Thus the use of soluble receptors or anti-receptor monoclonal antibodies could be exploited to specifically antagonize IL-17A, IL-17F, or both.

Role of IL-17 in vaccine-induced immunity

Although IL-17RA signaling has shown limited roles in primary infection with intracellular infections such as TB (Figure 2), recent evidence supports a critical role of IL-17 producing T-cells in vaccine induced protection to both extracellular and intracellular infections. Higgins et al have shown that vaccine induced protection against *Bordetella pertussis* with a whole cell pertussis vaccine induces TLR4-depednent Th1 and Th17 response and that the Th17 response was required for efficacy [55]. Furthermore there was a strong requirement for IL-1β in the generation of the TLR4-dependent Th17 response [55]. Malley and colleagues have shown a role for IL-17A in vaccine induced efficacy against the gram positive pathogen *Streptococcus pneumoniae* using a species-common cell wall polysaccharide as antigen [56] which was also dependent on the charged amino group on the polymer backbone by N-acetylation [56]. Potential mechanism of efficacy of vaccine induced Th17 cells is likely through the regulation of chemokines. Khader et al have shown that BCG induced protection against *M. tuberculosis* requires IL-23 and IL-17, and IL-17 is critical for the regulation of the CXCR3 ligands, CXCL9, CXCL10 and CXCL11 [57] thereby augmenting Th1 cell recruitment. Thus, adjuvants that induce IL-23 or the generation of Th17 cells may be particularly useful for vaccine efficacy in the setting of both extracellular and intracellular pathogens. However, there is need for some caution as in the setting of biofilm infections, such as mucoid *P. aeruginosa* infection, as occurs in bronchiectasis or cystic fibrosis, IL-23 contributes to tissue pathology [58]. These data suggest that in the presence of specific bacterial or host factors that prohibit clearance of the pathogen, vaccination to induce a Th17 response may be harmful. In contrast in the setting of chronic biofilm infection antagonizing Th17 immunity may be beneficial in preventing further tissue inflammation and injury [58]

Conclusions

Evidence clearly supports the notion that Th17 cells are a distinct lineage that may have evolved to mediate mucosal host defense against extracellular pathogens. Moreover there is emerging evidence that these cells are critical in mediating vaccine induced protection to a variety of pathogens. Part of this effect is likely mediated by regulation of chemokines. Further work is needed to determine if this protection can be exploited in terms of T-cell lineage specific adjuvants. Furthermore the longevity of antigen specific Th17 cells and their contributions to cellular and humoral memory also needs to be explored.

Acknowledgements

Funding for this project was provided, in part, by the Pennsylvania Department of Health, Tobacco Formula Funding and the National Institutes of Health

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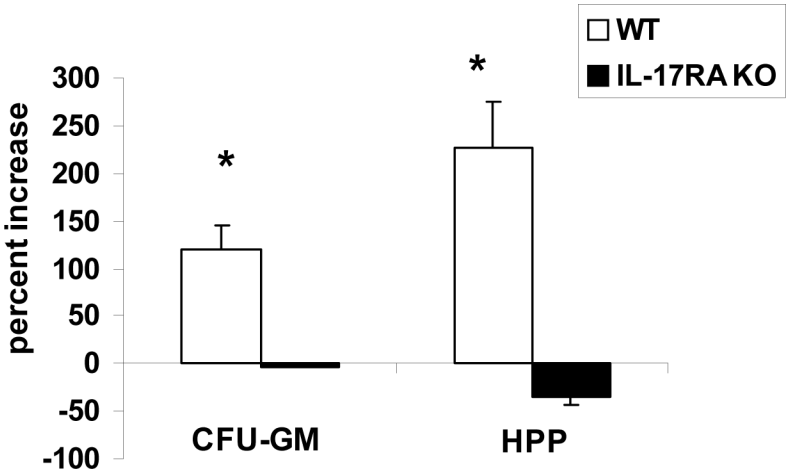

Figure 1.

Changes in splenic neutrophil progenitors eighteen hours after pulmonary challenge with *K. pneumoniae*. WT or IL-17RA KO mice were challenged with 10^4 CFU of *K. pneumoniae* and spleens were harvested at 18 hours and CFU-GM and high proliferative potential (HPP) colonies were measured using colony formation in methylcellulose (n=6−7 mice per group, * denotes $p < 0.05$ compared to WT control by Mann-Whitney non parametric testing).

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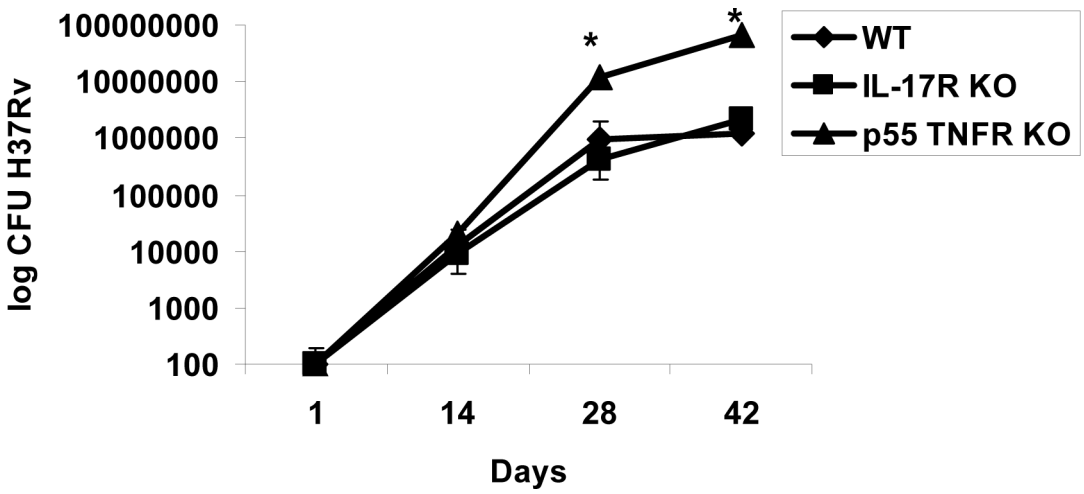

Figure 2.

Lack of susceptibility of IL-17RA deficient mice to primary Mycobacterium tuberculosis infection. WT or IL-17RA were challenged with 100 CFU of H37Rv *M. tuberculosis* and sacrificed at serial time points to determine lung CFU. As a positive control, TNFR p55 KO mice were infected as well. As opposed to mice deficient in TNFR p55 signaling, IL-17RA showed control of M tb growth similar to WT mice (n=6−7 mice per group, * denotes $p < 0.05$ compared to WT control by Mann-Whitney non parametric testing).

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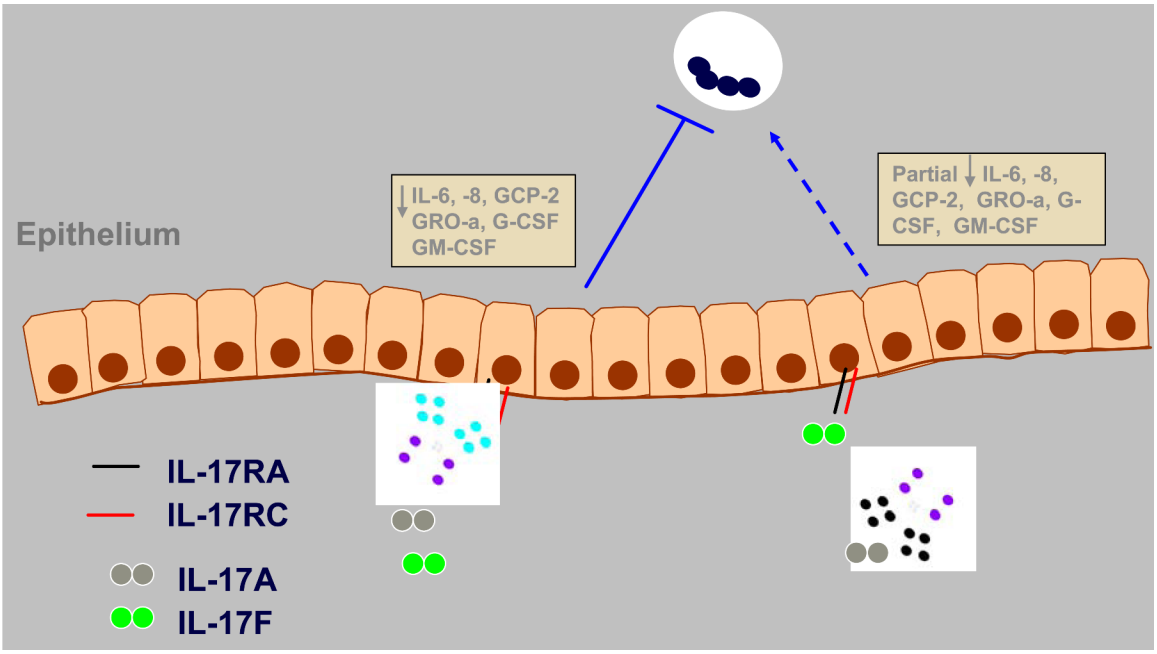

Figure 3.

Proposed model of IL-17 signaling in human airway epithelium. IL-17RA and IL-17RC can associate to potentially form a heterodimeric receptor. Antibodies against IL-17RA depicted in light blue can effectively block IL-17A and IL-17F. However due to the relatively lower affinity of soluble IL-17RA:Fc depicted in dark blue, can bind can neutralize IL-17A but is ineffective blocking IL-17F resulting in only partial abrogation of IL-17 induced CXC chemokines.