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Interleukin-17: A novel inflammatory cytokine that bridges innate and adaptive immunity

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1. ABSTRACT

Interleukin-17 (IL-17A) is a pro-inflammatory cytokine that is primarily secreted from T lymphocytes, mediators of adaptive immunity. Recently, IL-17 was shown to be the defining cytokine of a new T helper subset termed "Th17." Discovery of the Th17 population was a groundbreaking discovery that has triggered major revisions of the prevailing paradigms in T cell biology. Although produced by T cells, IL-17 promotes expansion and recruitment of innate immune cells such as neutrophils, and also cooperates with TLR ligands, IL-1 beta, and TNF alpha to enhance inflammatory reactions and stimulate production of beta-defensins and other antimicrobial peptides. Its receptor, IL-17RA, is ubiquitously expressed and shares many features with classical innate immune receptors such as shared intracellular tail motifs and convergence on common inflammatory transcription pathways. The role of IL-17 in periodontal disease is still uncertain, since IL-17 has been shown to promote bone destruction in arthritis, but is nonetheless essential to protect the host from pathogens, including periodontopathic organisms. Recent evidence has shown that Th17 cells are more osteoclastogenic than other T helper subsets such as Th1 or Th2. Ablation of IL-17 signaling prior to onset of infection with *Porphyromonas gingivalis* increases susceptibility to periodontal bone loss, but this finding does not rule out the efficacy of therapeutic inhibition of IL-17 after onset of severe disease. IL-17 sits at the center of many complex diseases that integrate innate and adaptive immune mechanisms and requires careful study to maximize host protective effects and minimize host deleterious effects.

2. INTRODUCTION

Innate immune cells in mammals, represented primarily by monocytes/macrophages, dendritic cells and granulocytes, are activated by pathogen-associated molecular patterns (PAMPs) and act to remove foreign bodies from the host as well as process and transport antigens to lymphocytes. The adaptive immune system, represented by B and T lymphocytes, are characterized by clonal expansion of cells that bind to a highly specific antigen. Although often described separately, crosstalk between the adaptive and innate immune systems is frequent, and a relatively new cytokine, interleukin-17 (IL-17) represents an intriguing new bridge between adaptive and innate immunity.

3. INTERLEUKIN-17: AN INNATE IMMUNE CYTOKINE

Interleukin-17 (IL-17A, CTLA-8) is the founding member of a novel family of pro-inflammatory cytokines. Since its discovery in 1993 (1), many studies have demonstrated that IL-17 plays a non-redundant role in directing innate immune responses. Its receptor, IL-17RA, is nearly ubiquitous and is expressed on hematopoetic cells as well as many non-immune cell types such as osteoblasts, fibroblasts, endothelial cells and epithelial cells (2, 3). Gene expression studies have demonstrated that signaling through IL-17RA promotes the expression of numerous genes relevant to the recruitment of innate immune cells to sites of infection or tissue damage (4-9). Inflammatory proteins such as matrix metalloproteases (MMPs), acute phase proteins, IL-6 and chemokine ligands, particularly

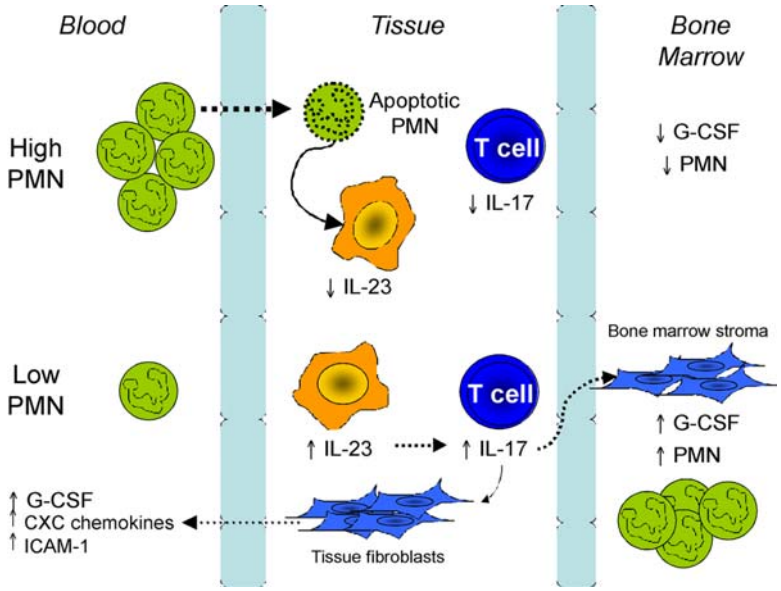

Figure 1. Regulation of neutrophil recruitment and homeostasis by IL-17. IL-17 promotes the production of CXC chemokines, G-CSF and increased ICAM-1 from tissues, which in turn increase neutrophil tethering, recruitment and expansion. In order to maintain steady-state levels of neutrophils, excess neutrophils migrate into tissues and are phagocytosed by macrophages. This event inhibits production of IL-23, whose absence then limits IL-17 production by a failure to expand the Th17 population. In turn, the reduced levels of IL-17 lead to decreased production of G-CSF and thus a loss of new neutrophils from the bone marrow. Conversely, in the absence of apoptotic neutrophils, tissue macrophages produce IL-23, which stimulates IL-17 production from T cells by inducing expansion of the Th17 population, which specifically expresses IL-23R. Secretion of IL-17 by Th17 cells leads to increased production of G-CSF and subsequent granulopoiesis in the bone marrow (17).

CXC chemokines that function to recruit neutrophils, are among the gene products that are most strongly regulated by IL-17 (4, 7, 10, 11).

Several *in vivo* infection studies have demonstrated a non-redundant role for IL-17 in neutrophil recruitment for host protection. Mice with selective ablation in IL-17RA signaling (IL-17RA^{KO} mice) have been shown to be significantly more susceptible to fatal outcomes associated with systemic *Candida albicans* and pneumonic *Klebsiella pneumoniae* infections (4, 12). Similarly, IL-17RA^{KO} mice are unable to control *Toxoplamsa gondii* infections (13) and are more susceptible to alveolar bone loss induced by *Porphyromonas gingivalis* (see section 6) (14). In each of these cases, the increased susceptibility to infection was associated with an impaired neutrophil recruitment to infected tissues and decreased production of neutrophil chemokines (e.g. LIX, Groalpha/KC and MIP-2) as well as neutrophil growth factors such Granulocyte Colony Stimulating Factor (G-CSF) (4) (reviewed in (15, 16)). Because of this strong association with neutrophil-mediated immunity, functional IL-17 and IL-17RA signaling is necessary for host defense against numerous pathogens, especially extracellular pathogens that are particularly susceptible to neutrophil-based attacks.

In addition to mediating neutrophil defenses in the context of infection, IL-17 plays an important role in regulating neutrophil homeostasis (Figure 1). An intriguing study demonstrated that excess circulating neutrophils can emigrate to peripheral tissues, where they become apoptotic and are engulfed by tissue phagocytes (17). Phagocytosis of apoptotic neutrophils suppresses production of interleukin-23 (IL-23), an IL-12-family cytokine that drives IL-17 production by T cells (see also section 5) (18). Specifically, the authors noted a specific reduction in the expression of p19 (the IL-23-specific subunit) and p40 (the subunit shared between IL-23 and IL-12), but no change in p35 (the IL-12-specific subunit). This reduction in IL-23 in turn decreases IL-17 production, leading to decreased production of G-CSF, which is responsible for granulocyte expansion. Thus, the ultimate outcome of excess neutrophil infiltration is a decreased production of neutophils from bone marrow (17). IL-17 sits at the center of this negative-feedback loop to maintain neutrophil levels at steady-state equilibrium.

While IL-17-dependent regulation of neutrophil activities is essential for host defense in many settings, IL-17 has also been shown to promote a variety of other inflammatory reactions. For example, IL-17 increases prostaglandin E2 production via upregulation of cyclooxygenase-2 (COX-2) (8, 19). Stimulation of Inducible Nitric Oxide Synthase (iNOS) by IL-17 increases nitric oxide (NO), another important mediator of inflammation (19-21). IL-17 promotes the production of numerous matrix-metalloproteases (MMP) such as MMP-3 and MMP-13 in bovine chondrocytes, subepithelial myofibroblasts, fetal mouse metatarsals and human synovial fibroblasts (22-25). Other studies showed that IL-17 increases MMP-1 and MMP-9 in various settings (26-28). MMPs have been implicated in tissue penetration of

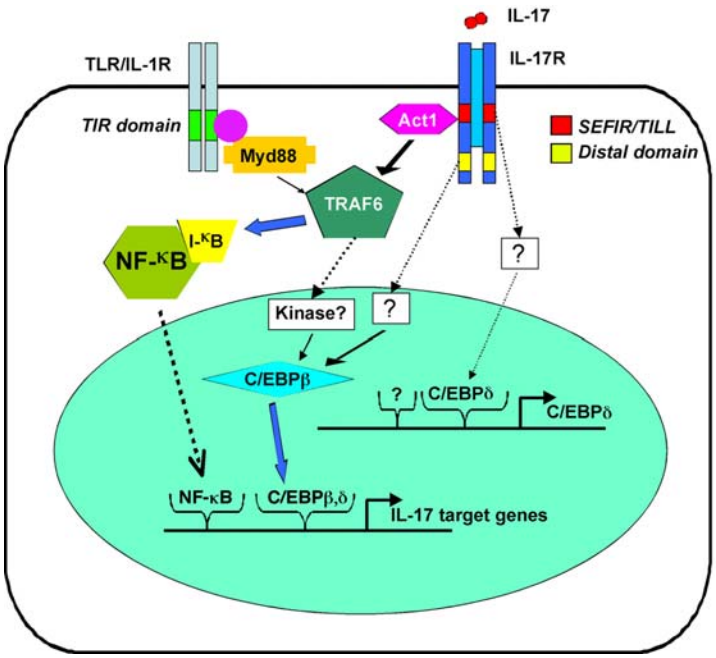

Figure 2. Similarities of IL-17RA to TLR and IL-1R signaling. TLR/IL-1 receptors recruit the adaptor proteins such as MyD88 via a conserved structural motif in the cytoplasmic tail, termed a "Toll-IL-R (TIR) domain". MyD88 is upstream of the ubiquitin ligase TRAF6, which then initiate a cascade of events resulting in the liberation of NF-kappaB and transcription of TLR/IL-1-responsive genes (74). Similarly, the SEFIR and TILL domains of IL-17RA recruit the SEFIR-containing adaptor protein Act1, which activates TRAF6 and leads to transcription of IL-17-responsive genes (36-39). The SEFIR/TILL domain is also upstream of several other signaling pathways, including ERK1/2 and C/EBPbeta and C/EBPdelta (6, 37). Additionally, a poorly-defined distal domain within IL-17RA also contributes to C/EBPbeta activation, a transcription factor also required for the induction of many IL-17-responsive genes (31, 37).

inflammatory cells and play an important role in pathologic settings such as arthritis as well as in recruiting immune cells to combat infection.

Although IL-17 promotes the production of chemokines and inflammatory proteins, its activity is potently augmented when combined with other innate immunity cytokines such as Tumor Necrosis Factor-alpha (TNFalpha) and IL-1beta (5, 6, 29) Several studies have shown that IL-17 and TNFalpha synergistically increase production of IL-6, chemokines, beta-defensins, COX-2 and the anti-bacterial protein 24p3 from fibroblasts and osteoblasts (6, 7). IL-17 also cooperates with TLR ligands to promote inflammatory gene expression (5), and the combination of IL-17 with IL-22 promotes the synergistic production of anti-microbial peptides (30). Although the precise mechanisms of this functional cooperation is still incompletely defined, the intracellular pathways of IL-17RA and other innate cytokine signaling receptors appear to converge on similar pathways such as Mitogen Activated Protein Kinase (MAPK) and C/EBP activation (6, 7, 31, 32).

4. IL-17RA SIGNALING: CORRELATIONS WITH TOLL-LIKE RECEPTORS (TLR) AND IL-1R

Analyses of proximal events in IL-17 signaling have been difficult since IL-17RA is a unique cytokine receptor with no homology to other known cytokine families (2). Moreover, the IL-17 binding complex was recently shown to include IL-17RC (IL-17RL), a poorly-understood member of the IL-17 receptor superfamily (33). Recent studies analyzing the IL-17RA cytoplasmic tail have uncovered motifs that share features with a signaling moiety found in TLR-IL-1R (TIR) superfamily (34), termed the SEFIR domain (Similar Expression to FGF receptor, IL-17 receptor, Toll-IL-1R) (Figure 2) (35). The TIR domain is critical for recruitment of the MyD88 adaptor by IL-1beta and TLRs, but IL-17 does not require MyD88 for signaling (36, 37). Rather, it was recently shown that SEFIR domain recruits the adaptor protein Act1, which also contains a SEFIR domain. Act1 then leads to the recruitment of the kinase TAK1 and E3 ubiquitin ligase TNF-Receptor Associated Factor 6 (TRAF6) to activate NF-kappaB (36, 38, 39). Thus, IL-17 activates a parallel pathway to IL-1R and TLR receptors, with different proximal signaling intermediates.

We recently reported an extensive structure-function analysis of the IL-17RA tail and discovered additional similarities to TIR domains (37). Specifically, the intracellular domains of TIR family members share conserved structural features called BB-loops that are critical for the TIR domain function; indeed, a single point mutation in the TLR4 BB-loop causes LPS insensitivity in C3H/HeJ mice (40, 41). Although the crystal structure of IL-17RA has not been solved, this receptor contains a BB loop-like sequence termed TILL (TIR-Like Loop) (Figure

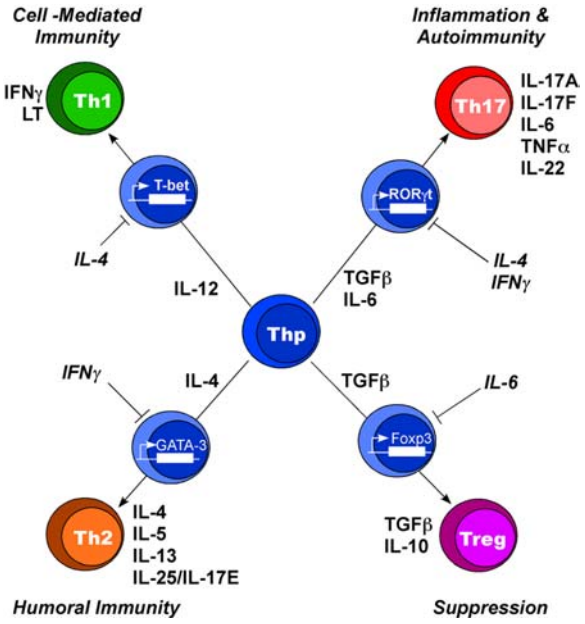

Figure 3. Th17 cells arise as an independent lineage. Based on numerous studies in mouse systems, Th17 cells are produced from T helper progenitor (Thp) cells in the context of IL-6 and TGFbeta. IFNgamma and IL-4 inhibit Th17 differentiation, while simultaneously promoting differentiation of Th1 and Th2 cells, respectively. Treg cells develop in the presence of TGFbeta stimulation in the absence of an inflammatory signal such as IL-6 (reviewed in (46)).

2). The functional significance of the TILL domain in IL-17RA was confirmed experimentally by mutating selective residues in the TILL domain and observing the loss of IL-17RA signaling. However, not all structural features of *bona fide* BB-loops are preserved within IL-17RA, so it is clear that this family remains unique in many structure and functional aspects (37). These studies illustrate similarities between IL-17RA and other innate cytokine receptors, and may be useful in determining how IL-17 augments the activities of other innate cytokines.

5. IL-17 BRIDGES INNATE AND ADAPTIVE IMMUNITY

Although IL-17 clearly has functional and structural similarities to innate immune molecules, the vast majority of IL-17 is T cell-derived (8). Indeed, IL-17 was discovered in a cDNA library of a murine cytotoxic T lymphocyte hybridoma and originally termed Cytotoxic T Lymphocyte Antigen 8 (CTLA-8) (1). Soon after its discovery, IL-17 was found to be secreted from CD4+ T cells with an effector memory phenotype (42), and was correlated with T cell-mediated autoimmune diseases such as rheumatoid arthritis (RA) (43, 44). Early attempts in humans to classify IL-17 into a particular T helper subset (i.e. Th1 or Th2) were inconsistent and unconvincing. For example, human T cell clones isolated from arthritic synovial fluid have been characterized as Th1 (secrete IFN-gamma but not IL-4), Th2 (secrete IL-4 but not IFN-gamma) or Th0 (secrete both IFN-gamma and IL-4). Among these subsets, IL-17 was found to be secreted from Th1 and Th0 cells, but not Th2 cells (45). Thus, for some time, IL-17 was considered a Th1 or pre-Th1 cytokine.

However, recent studies examining requirements for IL-17 production in T cells in mice have resulted in an upheaval in the Th1-Th2 paradigm (reviewed in (46, 47)). While CD4+ T cells have been classically divided as either Th1 or Th2, which secrete IFNgamma or IL-4, respectively (Figure 3), there is now ample evidence for the existence of a new T helper effector subset, termed Th17, and is distinguishable in lineage and function from Th1 and Th2 cells. Th17 cells arise from T helper progenitor (Thp) cells in a cytokine environment consisting of transforming growth factor-beta (TGF-beta) and IL-6 (Figure 3) (46, 48-50). This differentiation is under the control of the transcription factor retinoic acid orphan receptor gamma t (RORgammat) (51) and is inhibited by interferon-gamma (IFNgamma) and IL-4 (9), and by extension, inhibited by Signal Transducer and Activator of Transcription 1 (STAT1)/T-bet and STAT6/GATA-3 (52). Th17 cells secrete IL-17 and a related family member IL-17F, as well as TNFalpha, IL-6 (53) and IL-22 (30, 54). Similar to IL-17, Th17 cells function to promote inflammation for host defense or, in other contexts, to promote pathology through excess inflammation (reviewed in (55)).

Another source of IL-17 that is likely to be highly significant is the gamma-delta T cell population. Unlike conventional CD4+ or CD8+ T cells with highly diverse alpha-beta T cell receptor (TCR), gamma-delta-T cells are enriched at mucosal and epithelial surfaces such as the gut, lung, and skin and express a limited TCR antigen-binding repertoire. The role of gamma-delta T cells at these sites is uncertain, but studies have shown that IL-17 production from gamma-delta T cells is important in controlling mouse *Mycobacterium tuberculosis* lung infections (56) as well as mouse intraperitoneal *Escherichia coli* infections (57). These discoveries help explain the observation that pathology in IL-17RA^{KO} mice occurs within a few days of infection, before mature effector T cell responses are likely to be involved (4). Therefore, IL-17 from gamma-delta T cells may be important for initiating an immediate and early neutrophil response to mucosal infections. Furthermore, IL-17 may be a mechanism by which gamma-delta T cells provide defense responses until adaptive immune cells are recruited to combat remaining pathogens.

6. IL-17: BONE BIOLOGY AND PERIODONTAL DISEASE

Soon after its discovery, IL-17 was linked to the bone destructive pathology seen in RA (43, 44). Overexpression of IL-17 by adenovirus or direct intraarticular injection of IL-17 resulted in joint erosion (58, 59). IL-17 increases membrane expression of Receptor Associated with NF-kappaB Ligand (RANKL) in osteoblasts, which in turn promote osteoclastogenesis (59). Moreover, IL-17 augments the activity of other osteoclastogenic factors such as TNF- alpha and IL-1beta (27), which is likely to further increase bone erosion.

Recently, a study directly compared the osteoclastogenic potential of Th17 cells with Th1 and Th2 cells (60). This group showed that co-culture of osteoclast precursors with Th17, but not Th1 or Th2 cells resulted in the formation of mature osteoclasts capable of resorbing bone *in vitro*. This study also found that mice deficient in the gene encoding Interferon-gamma receptor 1 (*Ifngr1*, which binds the Th1 cytokine IFNgamma) and STAT6 (a signaling component for the Th2 cytokine IL-4) were capable of resorbing bone *in vivo*, whereas IL-17-deficient or IL-23-deficient mice were protected from bone destruction. Prior to this study, Th1 cells had been associated with bone pathology in rheumatoid arthritis, but few groups could explain why IFNgamma receptor-deficient mice showed accelerated bone destruction in collagen-induced arthritis rather than protection from bone loss (61, 62). The revision of the Th lineage model to include Th17 cells has explained many of these paradoxes.

Similar to RA, periodontal disease is also associated with T cell-mediated pathology. Both SCID mice and T cell-deficient mice orally infected with *P. gingivalis* are protected from alveolar bone loss (63, 64). In humans, a recent study showed that mononuclear cell infiltrates into periodontal gingival tissues were 45% T cells, 50% B cells and 5% monocytes, and more than 50% of the T cells and 90% of the B cells expressed RANKL (65). The contribution of Th1 or Th2 cells to bone pathology is highly debated. While some data supports a role for Th1 cells in periodontal bone pathology ((66) and reviewed in (67)), it has also been hypothesized that a Th1 immune response is associated with a stable gingivitis lesion, whereas a transition to a Th2 immune response is associated with progressive periodontitis (reviewed in (68)). Th17 cells are rapidly emerging as pathologic effector cells in numerous inflammatory diseases, and are likely to play a role in periodontal disease as well.

Periodontal disease is a highly complex disorder initiated by the colonization of periodontopathic bacteria and results in alveolar bone destruction. Resolution of inflammation and subsequent healing tends to be difficult in many patients, and often cannot take place without therapeutic intervention. Because of the strong association of IL-17 with bone destruction, it is compelling to postulate that IL-17 plays a role in the pathogenesis of periodontal disease. The central role of lymphocytes in the pathogenesis of periodontal disease also suggests that IL-17 from T cells may play an important role in disease progression. To date, only a few studies have attempted to directly address the relationship of IL-17 and periodontal disease. In 2004, it was reported that the concentration IL-17 positively correlated with the gingival sulcus depth as the depth increased from 3 mm to 5 mm, but was significantly decreased as the gingival sulcus depth was increased to 6 mm (69). In this study, the authors suggested that IL-17 might play a role only in certain stages of periodontal disease, such as the early transition from gingivitis to periodontitis. In a separate study, IL-17 levels in gingival crevicular fluid (GCF) of chronic periodontitis patients were found to be higher than healthy controls (70). Yet another study showed that tissue samples from 9 out of 23 (39.1%) periodontitis patients were positive for IL-17 mRNA (71). By comparison, IFNgamma mRNA was detected in 30.4% of the tissue samples from periodontitis patients, IL-4 in 4.3% of samples, and IL-10 in 47.8% of samples. Finally, a recent study reported increased numbers of gingival fibroblast cells positive for IL-1beta, TNFalpha and IL-17 in periodontitis tissues compared to healthy controls (72). Together, these studies suggest that IL-17 is present in some active periodontal lesions, but may be present only in certain stages of the disease.

Like many inflammatory cytokines, IL-17 is a double-edged sword (73). In some settings such as RA, IL-17 is a pathologic factor that promotes bone destruction. In the context of infectious disease, however, IL-17 clearly plays an essential role in protecting the host by recruiting neutrophils to infected tissues (16). Although RA and periodontal disease share features of bone destruction, one major difference is that RA is understood to be a sterile disease process, whereas periodontal disease is initiated by bacterial infection in the oral cavity. On the molecular level, IL-17 may be playing a similar role in promoting inflammation. However, although inflammation is clearly detrimental to the host in RA, inflammation for host defense may be beneficial to the host in periodontal disease.

Although previous studies showed that IL-17 is present in some active periodontal lesions, it is unclear whether the overall effect of IL-17 is to combat ongoing infection or contribute to bone destruction by promoting osteoclastogenesis. We recently addressed this potential paradox by examining IL-17 function in a mouse model of periodontal disease. IL-17RA^{KO} mice were infected by oral gavage with *P. gingivalis*. When compared to similarly-treated wild-type mice or Sham controls, IL-17RA^{KO} mice were found to be significantly more susceptible to alveolar bone loss (14). This phenotype was attributable to a neutrophil deficiency, as mice were deficient in production of chemokines LIX/CXCL5 and KC/Groalpha/CXCL1 and failed to recruit neutrophils to infected gingival tissue. This work illustrates the importance of IL-17RA signaling in preventing alveolar bone loss initiated by periodontopathic organisms, at least in an acute colonization model. These findings raise a cautionary note in the potential use of therapeutics that target IL-17 for other inflammatory diseases such as RA, which may compromise resistance to periodontal disease and other commensal or mild infections. Clearly, further studies need to be done to clarify the role of IL-17 during ongoing periodontitis and whether therapeutic inhibition of IL-17 prevents or promotes further bone destruction.

7. CONCLUSION

Complex diseases such as periodontal disease are often multifactorial in nature, involving many systems in the initiation, pathogenesis and resolution of the disease. IL-17 is at the center of two major arms of the immune system, innate and adaptive immunity. IL-17 is secreted primarily from T cells, and many diseases that involve IL-17 include recruitment and activation of T cells. Signaling

through IL-17RA however, parallels the signaling observed in innate cytokine receptors such as IL-1R and TLRs and converges to similar endpoints, such as activation of MAPK, NF-kappaB and C/EBP. Nonetheless, IL-17RA is a unique cytokine receptor in its own family of receptors, with unique signaling adaptors and structure that is only just beginning to be elucidated. Future studies that investigate the differences between IL-17RA and other innate receptors may result in beneficial therapeutic strategies for specific diseases. In the context of periodontal disease, IL-17 plays an important role in protecting the host from periodontopathic organisms, but may also contribute to the T cell-mediated alveolar bone destruction in later, more chronic stages of the disease. Potential therapies that target IL-17 must balance the benefits of reducing inflammation and bone pathology with the problems of an increased risk of future infections.

8. ACKNOWLEDGEMENTS

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