Published in final edited form as:
Semin Immunopathol. 2010 March ; 32(1): 33–42. doi:10.1007/s00281-009-0185-0.

IL-17RC: A partner in IL-17 signaling and beyond

Allen W. Ho[1,2] and **Sarah L. Gaffen**[1,2,*]

[1]University at Buffalo, State University of New York, Buffalo, Department of Oral Biology, New York 14214, USA

[2]University of Pittsburgh, Department of Medicine, Division of Rheumatology and Clinical Immunology, Pittsburgh, Pennsylvania 15261, USA

Abstract

The IL-17 cytokine family members IL-17A and IL-17F mediate inflammatory activities via the IL-17 receptor (IL-17R) complex, comprised of the IL-17RA and IL-17RC subunits. Proper regulation of the IL-17 signaling axis results in effective host defense against extracellular pathogens, while aberrant signaling can drive autoimmune pathology. Elucidating the molecular mechanisms underlying IL-17 signal transduction can yield an enhanced understanding of inflammatory immune processes and also create an avenue for therapeutic intervention in the treatment of IL-17-dependent diseases. To date, the fundamental signaling mechanisms used by the IL-17R complex are still incompletely defined. While current structure-function studies have primarily focused on the IL-17RA subunit, recent research indicates that the IL-17RC subunit plays a key role in modulating IL-17 responses. This review will examine what is known regarding IL-17RC function and provide a framework for future work on this subunit and its impact on human health.

Keywords

IL-17 receptor; Th17; autoimmunity; IL-17RC; signal transduction

Introduction

Cytokines play an integral role in the coordination of the innate and adaptive arms of the immune system to achieve host defense. Cytokine release following immunological insult results in the activation of innate immunity to prime immune signaling networks, recruitment of effector cells to the site of infection, induction of site-specific host defense effector mechanisms, and initiation of adaptive immunity to promote pathogen clearance and specific immunologic memory. While there have been remarkable advances in understanding how individual branches of the immune system function, specific mechanisms by which these systems interface remain incompletely understood. The newly-described IL-17 cytokine family, produced by a recently-defined subset of CD4+ T helper (Th) cells known as “Th17,” have helped to bridge this gap, as Th17 cells connect the adaptive and innate immune responses [1]. This review centers on IL-17 signal transduction and, more specifically, a newly-identified and essential subunit of the IL-17 receptor complex, IL-17RC.

Contrary to archetypal effectors of adaptive immunity, Th17 cells promote innate effector mechanisms of inflammation. The differentiation and priming of Th17 cells from naive CD4 + T cells requires a pro-inflammatory cytokine milieu, including IL-6, TGF-β and IL-1. In

*To whom correspondence should be addressed: University of Pittsburgh, Division of Rheumatology and Clinical Immunology, BST S708, 3500 Terrace St, Pittsburgh, Pennsylvania 15261. Ph. 412-383-8903. Fax. 412-383-8864. sig65@pitt.edu .

addition, the survival and stabilization of the Th17 subset requires IL-23, a pro-inflammatory cytokine closely related to IL-12 (reviewed in [2,3]). Once fully differentiated and activated, Th17 cells secrete IL-17A, IL-17F, IL-21, IL-22, IL-26 and a number of chemokines. These cytokines regulate inflammatory responses by driving the production of innate mediators such as IL-6, CXC chemokines, antimicrobial factors and acute phase proteins [4,5]. Th17 cells play a major role at mucosal surfaces to promote inflammation, providing a beneficial function in an infection setting and deleterious one in an autoimmune context [6,7]. The generation and function of IL-17-producing cells and the effects of their cognate cytokines have been reviewed extensively elsewhere [2,3,8,9].

The IL-17 and IL-17 receptor family

Th17 effector function results from the IL-17 cytokine / IL-17 receptor signaling axis, which is strikingly different in sequence and structure from other cytokine families. The IL-17 cytokine family includes six structurally related isoforms: IL-17A, IL-17B, IL-17C, IL-17D, and IL-17F [10]. IL-17E, more commonly called IL-25, shares structural features with other IL-17 family members, though its biologic functions differ considerably [11,12]. IL-17A and IL-17F (which are ~55% homology) are both produced by Th17 cells, and are the best-characterized family members to date [13]. Both IL-17A and IL-17F function as homodimers, and recently, an IL-17A/F heterodimer was described [14–16]. The IL-17A homodimer was found to be the most potent IL-17 family effector molecule based on its induction of the target gene CXCL1, followed by the IL-17A/F heterodimer, and finally the IL-17F homodimer [15]. Additionally, both IL-17A and IL-17F have been shown to promote the inflammatory pathology of a number of autoimmune diseases such as rheumatoid arthritis, lupus, psoriasis and asthma (discussed in detail in subsequent sections) [17,18].

IL-17 cytokine family members induce downstream signaling through interactions with a specific cell surface receptor complex, but the nature of this receptor is poorly understood. The IL-17 receptor (IL-17R) subfamily includes IL-17RA, IL-17RB, IL-17RC, IL-17RD, and IL-17RE (reviewed in [10,13]). IL-17RD is also known as Similar Expression to the Fibroblast Growth Factor Receptor (SEF), as it was initially described as having the same expression pattern as the Fibroblast Growth Factor Receptor (FGFR) during zebrafish development [19]. The best-characterized IL-17R molecules are the IL-17RA and IL-17RC subunits, in part because of their interaction to form a receptor complex capable specific for IL-17A and IL-17F [20,21] (see details below). Several studies and recent reviews have focused on IL-17RA and its signaling properties [22]. IL-17RC, however, remains relatively unexplored. This review focuses on what is currently known regarding IL-17RC, and addresses its contribution to IL-17 signal transduction with reference to IL-17RA.

Overview of the IL-17 binding complex

Studies of IL-17RA have provided a framework for understanding the role of IL-17RC in IL-17A- and IL-17F-mediated signaling. Prior to the recognition that IL-17RC was an integral part of the IL-17R complex, fluorescence resonance energy transfer (FRET) studies of IL-17RA indicated that IL-17RA multimers exist on the cell surface in the absence of ligand [23,24]. However, following binding of either IL-17A or IL-17F, a rapid conformational shift occurs resulting in a loss of FRET signal. This observation could be due to a complete dissociation of the IL-17RA subunits with each other, a large re-orientation of the cytoplasmic tails, and/or the recruitment of another unknown subunit or cytoplasmic signaling intermediate [23]. This report was followed by the discovery that IL-17RA co-immunoprecipitates with IL-17RC in a ligand-dependent manner, raising the possibility that the ligand-dependent loss of FRET between IL-17RA subunits results from oligomerization with IL-17RC [21]. Consistent with this, IL-17RC also forms large, multimeric complexes consistent with

oligomerization with IL-17RA [25]. The precise stoichiometry of the IL-17R complex, either with or without ligand, still remains undefined.

The IL-17R complex activates a number of different downstream effector signaling pathways. IL-17RA induces the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and mitogen-activated protein kinase (MAPK) signaling pathways to trigger many transcription factors, including the CCAAT/enhancer binding protein (C/EBP) transcription factors and AP1 (Figure 1) [26–28]. Like most cytokine receptors, IL-17R family members do not contain intrinsic enzymatic activity, but induce signaling via recruitment of signaling intermediates. The TRAF6 adaptor serves as a molecular scaffold for a number of immune receptors, including the CD40 receptor (CD40R), the B cell-activation factor receptor (BAFFR) and IL-17RA[29,30]. However, unlike the CD40R and the BAFFR, IL-17RA does not encode an obvious TRAF6-binding site. Rather, the adaptor Act1/CIKS links IL-17RA to TRAF6 [31,32]. The N-terminus of Act1 contains a TRAF-binding domain while its C-terminus contains a SEFIR (SEF/IL-17R) domain, uniquely found on IL-17R-family members [33]. Accordingly, Act1 plays a critical role in IL-17 signal transduction. Act1-deficient cells display severely blunted activation of IL-17 target genes such as IL-6 and CXC chemokines [31,32]. Moreover, Act1−/− mice developed reduced inflammatory pathology in IL-17-dependent autoimmune encephalomyelitis (EAE) and colitis models. However, IL-17RA signaling pathways independent of Act1 may also exist. In Act1−/− cells, extracellular signal-regulated kinases (ERKs) are activated in response to IL-17 signaling, raising the possibility of novel IL-17RA signaling intermediates that warrant further investigation [31].

As noted above, IL-17R family members encode a novel, conserved signaling motif termed SEF/IL-17R (SEFIR) that bears homology to the Toll/IL-1R (TIR) signaling domain on the Toll-like/IL-1 receptors [34]. A BB-loop structure embedded within the TIR domain of the Toll-like receptors is critical for signaling, and IL-17RA contains a homologous motif termed the TIR-like loop (TILL) located downstream of the C-terminus of the IL-17RA SEFIR [35]. The TILL domain is vital for IL-17 signal transduction, as mutations specific to this region abrogate all IL-17-induced responses tested. Of note, the TILL appears to be unique to the IL-17RA SEFIR, which may explain why it is needed to partner with multiple IL-17R subunits [22]. The cytoplasmic tail of IL-17RC also contains the conserved SEFIR signaling domain (Figure 1,2) [34]. The IL-17RC SEFIR, however, has no obvious TILL structure, and thus far no empirical studies have proven a functional role for the SEFIR in IL-17RC-dependent signaling.

The role of IL-17RC in mediating signaling is unclear. It is currently unknown whether Act1, TRAF6 or other signaling intermediates bind directly to IL-17RC. It is plausible that IL-17RC recruits novel adaptor intermediates to help create signaling scaffolds at the receptor complex, although none have been reported to date (Figure 1A). Alternatively, IL-17RC may simply provide the necessary signaling domains to ensure an adequate number of signaling intermediates to promote effective signal transduction, analogous to the tumor necrosis factor receptor (TNFR) system (Figure 1B)[36–38].

IL-17RC gene expression and regulation

Although The IL-17RA and IL-17RC subunits operate in concert to mediate IL-17 signaling, IL-17RC possesses a number of features that differentiate it from IL-17RA. Initially termed IL-17R-like (IL-17RL), IL-17RC was discovered via homology searches of mammalian expressed sequence tag (EST) databases and bears only 22% sequence homology with IL-17RA [39]. Alignment against the human genome indicates that the *il17rc* gene contains 19 exons on chromosome 3 and spans 16,550 base pairs within the chromosomal region 3p25.3 to 3.24.1 (Figure 2). The murine *il17rc* gene contains 18 exons on chromsome 6 and spans

11,565 base pairs on the chromosomal arm 6q. The full-length human IL-17RC (hIL-17RC) contains 720 amino acids, and the murine IL-17RC (mIL-17RC) contains 698 amino acids. In both species, *il17rc* encodes a single pass type I transmembrane protein where the transmembrane domain is encoded in exon 17.

Intriguingly, the expression profile and tissue distribution of IL-17RC suggest that the gene regulation of IL-17RC differs considerably from IL-17RA. Specifically, epithelial cells of the prostate, kidney, and joints express high levels of IL-17RC mRNA, while low levels of expression are detected in the hematopoietic cell compartments [39–41]. Conversely, IL-17RA is highly expressed in the bone marrow, thymus, and spleen, but relatively low levels are detected in colon, small intestine, and lung [26,40,42]. The biological significance of this reciprocity in tissue expression is unknown, but raises a number of interesting possibilities. IL-17RC or IL-17RA may bind a set of distinct ligands necessitating a different tissue distribution. Indeed, IL-17RA oligomerizes with IL-17RB to form a receptor complex that interacts with IL-25/IL-17E; accordingly, tissues sensitive to IL-25 may express higher levels of IL-17RA [43]. In addition, the differential gene regulation may be a mechanism to influence tissue specific signaling by IL-17A, IL-17F, and IL-17A/F, because these ligands exhibit different binding affinities to the IL-17RC and IL-17RA subunits, discussed in more detail below.

Unlike IL-17RA, which does not undergo alternative RNA splicing, IL-17RC exists in numerous splice forms. An EST database search and mRNA analysis of human prostate cancer cell lines revealed more than 90 different IL-17RC variants, some of which use cryptic splice sites (Figure 2A) [39]. While most IL-17RC variants are spliced at sites in the extracellular domain, some mRNA transcripts suggest the existence of soluble receptors that could presumably influence IL-17 signaling [39]. A similar database search of mouse EST databases revealed only four mIL-17RC variants, none of which appear to be soluble (Figure 2B) [41]. If they exist, soluble IL-17RC molecules could act as decoy receptors to dampen signaling, analogous to the IL-1 receptor antagonist (IL-1Ra) or RANKL/osteoprotogerin (OPG) systems [44]. Alternatively, soluble IL-17RC could function analogously to the IL-6 receptor (IL-6R) system, in which a soluble IL-6Rα subunit promotes IL-6 binding to the gp130 receptor on cells that lack IL-6R, a process known as “trans-signaling” [45,46]. Interestingly, mIL-17RC variants also appear to bind IL-17A and IL-17F with differing affinities, providing another level of potential signal modulation (Figure 3). Moreover, some mIL-17RC variants bind neither of these two cytokines, hinting that there may be novel ligands or functions for IL-17RC (Figure 3) [41].

Biological activity of IL-17RC

Investigations into the biological functions of IL-17RC have revealed a number of interesting observations. For example, there is a species-dependent cytokine binding and signaling role for IL-17RA and IL-17RC (Figure 3). For example, hIL-17RA fails to reconstitute IL-17A and IL-17F dependent signaling in mIL-17RA−/− fibroblasts, whereas mIL-17RA rescues signaling. Only co-expression of hIL-17RC with hIL-17RA permits effective IL-17 signaling, suggesting that hIL-17RA cannot pair with the mIL-17RC endogenously expressed in murine cells [21]. This finding also indicates that, despite species distinctions, IL-17RC is required for IL-17 signal transduction in both systems [21,41].

These studies also revealed that IL-17RC is not merely a ligand-binding component, but its cytoplasmic tail somehow contributes to signal transduction. Expression of hIL-17RA with an hIL-17RC lacking the cytoplasmic tail is not sufficient for IL-17-mediated induction of the CXCL1 target gene. The necessary portion of the IL-17RC tail needed for signaling is unknown, although the SEFIR domain is predicted to be important [34]. Consistent with these

data, mIL-17RC−/− fibroblasts do not produce IL-6 or GM-CSF in response to IL-17A or IL-17F stimulation, lending further support to the necessity of IL-17RC for signaling [47]. Thus far, IL-17RC-specific binding partners that interact with the cytoplasmic tail have not been identified.

The differences between the human and murine systems extend to IL-17A and IL-17F cytokine binding affinities. hIL-17RA binds preferentially to IL-17A and has a relatively low binding affinity to IL-17F. In contrast, hIL-17RC binds IL-17A and IL-17F with the same affinity [41]. In the murine system, the inverse is true: mIL-17RA binds IL-17A and IL-17F with equal affinities, but mIL-17RC binds preferentially to IL-17F. Therefore, in both humans and mice, IL-17RC appears to serve as a contact point for IL-17F (Figure 3) [41]. The difference in IL-17RC binding affinities for IL-17A and IL-17F is of interest because this may serve as one mechanism to control and modulate IL-17 signaling. Although IL-17A and IL-17F have many overlapping effects including immunity to extracellular pathogens and neutrophil recruitment, their respective cytokine knockout models indicate that IL-17A plays a more significant role in driving autoimmunity [40,48]. Moreover, in certain models of colitis, IL-17A plays a protective role while IL-17F has a pathogenic function [48–50]. These studies have also suggested that IL-17A can induce signals in murine T cells, which appear to lack IL-17RC, whereas IL-17F does not exert any T cell specific effects [40,42,50]. This phenomenon raises the intriguing possibility that in T cells, IL-17RA homomultimers are sufficient for IL-17 signaling, or that there exists a yet-to-be determined subunit that pairs with IL-17RA. It is also tempting to speculate that, given the tissue specific expression level differences, there may exist receptor complexes with different ratios of IL-17RA and IL-17RC subunits in specific tissues, possibly explaining differential effects of IL-17A and IL-17F. Furthermore, the potential existence of agonistic soluble IL-17RC receptors could explain IL-17 dependent signaling in those tissues lacking IL-17RC expression, analogous to trans-signaling in the IL-6 system [45,46]. Indeed, the differences in cytokine binding affinities and the central role IL-17RC possesses in the IL-17 signaling axis makes a clear understanding of its specific contributions necessary to understand how IL-17 mediates its effects.

IL-17RC and Disease

Dysfunction of the IL-17 signaling axis has been implicated in a number of human diseases. As expected given its central role in regulating inflammation, IL-17 mediates many autoimmune diseases and protects against a variety of extracellular pathogens (reviewed in [3]). Most evidence to date suggests that IL-17RC contributes to human disease pathogenesis resulting from its function in the IL-17 signaling axis rather than via a specific pathogenic role.

Currently, evidence indicates that both the IL-17 signaling axis and IL-17RC, specifically, may play an important role in the development of certain cancers, although the detailed mechanisms remain uncharacterized. The initial discovery of IL-17RC was based on its high levels of expression in human prostate cancer cells [25,39,51]. Specific overexpression of IL-17RC protects prostate cancer cell lines from TNFα-induced apoptosis. This protection is not mediated through any of the canonical survival pathways such as via Bcl-2 and Bcl-X_L and is apparently not dependent on any known IL-17-family ligands. Thus, IL-17RC may interact with novel signaling intermediates and ligands in the prostate cancer setting, although none have been identified [25].

Furthermore, in the murine B16 melanoma tumor model, IL-17A mediates a pro-tumor function that involves IL-6 induction to activate Stat3 in both tumor cells as well as the tumor microenvironment [52]. IL-6 activation of Stat3 in tumor cells results in increases in antiapoptotic, pro-proliferative, and pro-angiogenic genes, as well as suppression of certain proinflammatory genes [53]. In further support of the contribution of IL-17 signaling and

IL-17RC to tumor regulation, ecotopic overexpression of IL-17A by cervical carcinoma, fibrosasrcoma, and lung cancer cell lines results in accelerated growth *in vivo* [54–56]. In humans, IL-17A-positive ovarian and lung cancer specimens displayed higher levels of angiogenesis compared to those devoid of IL-17A [54,57].

The specific function of IL-17A and signaling via the IL-17R complex in the cancer setting, however, remains controversial [58–61]. Ectopic overexpression of IL-17A in hematopoietic tumor and sarcoma cells leads to enhanced anti-tumor immunity in immunocompetent mice [62,63]. Growth enhancement of metastatic colon cancer cells in IL-17A-deficient mice with an accompanied reduction in IFNγ-producing NK and tumor specific T cells support a protective function for IL-17A [64]. Moreover, adoptive transfer of Th17 or IL-17-positive CD8+ T cells resulted in tumor regression in the B16 melanoma model, albeit in a IFNγ-dependent and IL-17-independent manner [65,66]. These differences likely result from the different tumor models originating from tumors of different tissues. It is conceivable that the differences in tissue distribution of IL-17RC and IL-17RA may account for some of the differences in biologic activity of IL-17, but this issue has not been defined.

IL-17RC also contributes to autoimmune disease pathogenesis. The role of Th17 cells in autoimmunity is beyond the scope of this review, but a few reports highlight the contributions of IL-17RC to this spectrum of diseases. The IL-17 signaling axis has been implicated as pathogenic in the development of rheumatoid arthritis (RA), which is characterized by the chronic inflammation of synovial tissues in multiple joints associated with bone and cartilage damage. IL-17A knockout mice develop significantly less severe arthritis, and treatment with IL-17A neutralizing antibodies or soluble receptors alleviates joint inflammation [67–69]. Certain animal models that develop spontaneous arthritis including the IL-1Ra-deficient mice and SKG mice also require IL-17A expression for disease progression [70,71]. Moreover, human RA patients have high levels of IL-17A, IL-17F, IL-17RA, and IL-17RC in sera and inflamed synovium [72–74]. Higher levels of synovial IL-17A are predictive of more severe joint damage in RA, supporting a causal role [75]. Furthermore, based on RNAi blocking experiments, both IL-17RA and IL-17RC are required for the pro-inflammatory factors secreted by RA synoviocytes [76]. These studies suggest that to effectively treat RA, the effects of IL-17RC signaling should be targeted.

Impaired IL-17 signaling also drives the pathogenesis and disease progression of psoriasis, a chronic inflammatory disease of the skin characterized by epidermal hyperplasia, dermal angiogenesis, and leukocytic infiltration. IL-17A and IL-17F are overexpressed in the serum and lesions of psoriatic patients [77–79]. Surprisingly, gene transcript analyses of psoriatic lesions revealed an impairment of IL-17RC mRNA expression [80]. Perhaps this defect in IL-17RC expression leads to a compensatory effect, which could result in overactive Th17 cells and an inflammatory program. Accordingly, clinical targeting of Th17 cells by antibodies that neutralize the IL-12/IL-23 p40 subunit results in a significant improvement in disease pathology in psoriatic patients, associated with a decrease in the mRNA of the p19 subunit of IL-23 [81,82]. Thus, neutralizing a cytokine required for Th17 cell survival in the psoriatic setting results in clinical benefit, underscoring the role of aberrant IL-17 signaling in disease.

Although the specific contribution of IL-17 to the development of inflammatory bowel disease (IBD) remains unclear, there is good evidence that IL-17 signaling affects the development and progression of this disorder. In mice, T cells deficient in IL-17A or IL-17RA mediate a more severe form of colitis, indicating a protective role for IL-17A in an adoptive transfer model of IBD [50]. Furthermore, IL-17A also serves a protective function in a chemically-induced model of colitis [49]. IL-17F, however, was found to be pathogenic in this model of colitis, inducing the secretion of pro-inflammatory chemokines that exacerbated disease [48]. Additionally, IL-17F expression correlates with IBD development. Specific to the IBD

spectrum, Crohn's disease patients have significantly higher intestinal IL-17F levels than ulcerative colitis patients [83]. A report investigating the *in vitro* effects of IL-17A noted that it inhibits intestinal epithelial cell proliferation, an important mechanism of repair necessary to maintain epithelial integrity in a disease setting that destroys intestinal epithelium [84]. The functional differences between IL-17A and IL-17F in IBD may result from tissue specific distribution of IL-17RC and IL-17RA because of the high affinity of IL-17F for IL-17RC. The relative levels of the receptors and the existence of soluble variants of IL-17RC may drive the nuanced differences the cytokines play in the different models of IBD.

The IL-17 signaling axis may also contribute to cardiac pathology and be amenable to therapeutic targeting. IL-17A correlates with autoimmune myocarditis, an inflammatory condition thought to result from immune targeting of cardiac myosin following myocardial infection [85]. Moreover, neutralization of IL-17A leads to alleviation of disease in an experimental myocarditis model [86,87]. IL-17A stimulation of cardiac fibroblasts results in the production of a number of metalloproteases, suggesting that it may be partially responsible for tissue destruction and allowing access to inflammatory cells [88]. Furthermore, high glucose treatment of cardiac fibroblasts results in higher levels of IL-17A and IL-17RA expression, but fails to modulate IL-17RC expression [89]. Thus, in hyperglycemic conditions, IL-17A and IL-17RA may potentiate myocardial inflammation, injury, and remodeling.

Given the role of IL-17RC as a receptor for IL-17F, evidence linking IL-17F to airway inflammation suggests that IL-17RC may be instrumental in this setting. Transgenic lung-specific IL-17F expression in mice caused lymphocytic and macrophage infiltration and mucus hyperplasia [48]. Furthermore, neutrophil recruitment associated with allergen-induced airway inflammation by *Aspergillus* protease extract is reduced in IL-17F-deficient but not IL-17A-deficient mice [90]. However, this reduction is also observed in IL-17RA-deficient mice, suggesting that IL-17F potentiates allergen responses in an IL-17RA-dependent and probably IL-17RC-dependent manner. In an OVA-alum induced asthma model, IL-17F restricts the pathogenic role of Th2 cells, whereas IL-17A and IL-17RA promote Th2 responses in the lung [48,91,92]. While the specific role of IL-17RC has not been investigated in this setting, it is highly likely that IL-17RC also mediates these differences. In humans, a polymorphism in IL-17F leading to a missense mutation (His161Arg) is linked with protection against asthma development in a Japanese population [93]. Again, it is tempting to speculate that IL-17RA and IL-17RC expression levels skew the differences in cytokine function and biologic activity, but the role of IL-17RC is unknown. Additionally, IL-17 clearly plays an integral role in host defense against extracellular pathogens, specifically gram negative bacteria and fungi at mucosal surfaces [9,94]. Further studies are needed to determine if the effects of IL-17RC in this setting extend from its role in mediating the IL-17 signaling axis or from an IL-17RC specific function.

Recent studies have also shown that IL-17 affects bone formation and remodeling. IL-17 clearly plays a pathogenic, bone destructive role in arthritis, in part by inducing the expression of Receptor Activator of NF-κB ligand (RANKL) on osteoblasts and other mesenchymal cells [95–97]. Accordingly, IL-17A, IL-17RA, and IL-17RC have been found to localize to the site of bone fracture and the epiphesyeal growth plate [98]. Counter to this, signaling via IL-17RA protects against periodontal bone loss in a mouse oral *P. gingivalis* infection model, through a neutrophil recruitment mechanism [99]. Recently, using a murine model of ovariectomy-induced osteoporosis, IL-17RA signaling was shown to protect from systemic bone loss due to estrogen deficiency [100]. Thus, IL-17 signaling may directly affect bone remodeling and organization in the sterile settings of arthritis and fracture healing, while indirectly protecting from bone loss in other conditions such as infection or hormonal imbalances. The specific role of IL-17RC in these settings has not been defined.

Taken together, these studies illustrate the potential role of IL-17RC in disease pathogenesis and progression. IL-17RC may contribute directly to disease pathology or have indirect effects owing to its function as a receptor for IL-17F and as a subunit for the IL-17R complex. Either way, IL-17RC serves as an attractive therapeutic target in IL-17-dependent diseases.

Implications and Conclusions

Although IL-17RC may act mainly through its function as an integral part of the IL-17R signaling complex, emerging data indicates that IL-17RC may play a more broad and nuanced role. The differences in genomic structure, splicing and tissue distribution of IL-17RC compared to IL-17RA raise the prospect that IL-17RC may have distinct and/or complementary activities, and thus provide a level of control and modulation of cytokine signaling. Although these findings are provocative, much more work is needed to dissect the molecular biology and biological activities of this system. In terms of therapeutic implications, the biology and function of IL-17RC in disease pathogenesis suggest that it may be exploited as a clinical target. Due to the relatively similar affinities of the cytokines IL-17A and IL-17F to hIL-17RC, soluble hIL-17RC molecules may prove to be effective in treating inflammatory diseases, including autoimmunity and certain cancers. No doubt the next few years will bring new insights into this intriguing member of the IL-17 receptor family.

Acknowledgments

This work was supported by the Medical Scientist Training Program at the University at Buffalo (SUNY) School of Medicine and Biomedical Sciences. SLG was supported by the NIH (AR054389), Amgen and the Alliance for Lupus Research. We thank Dr. Brett N. Tomson for valuable comments and assistance with the manuscript.

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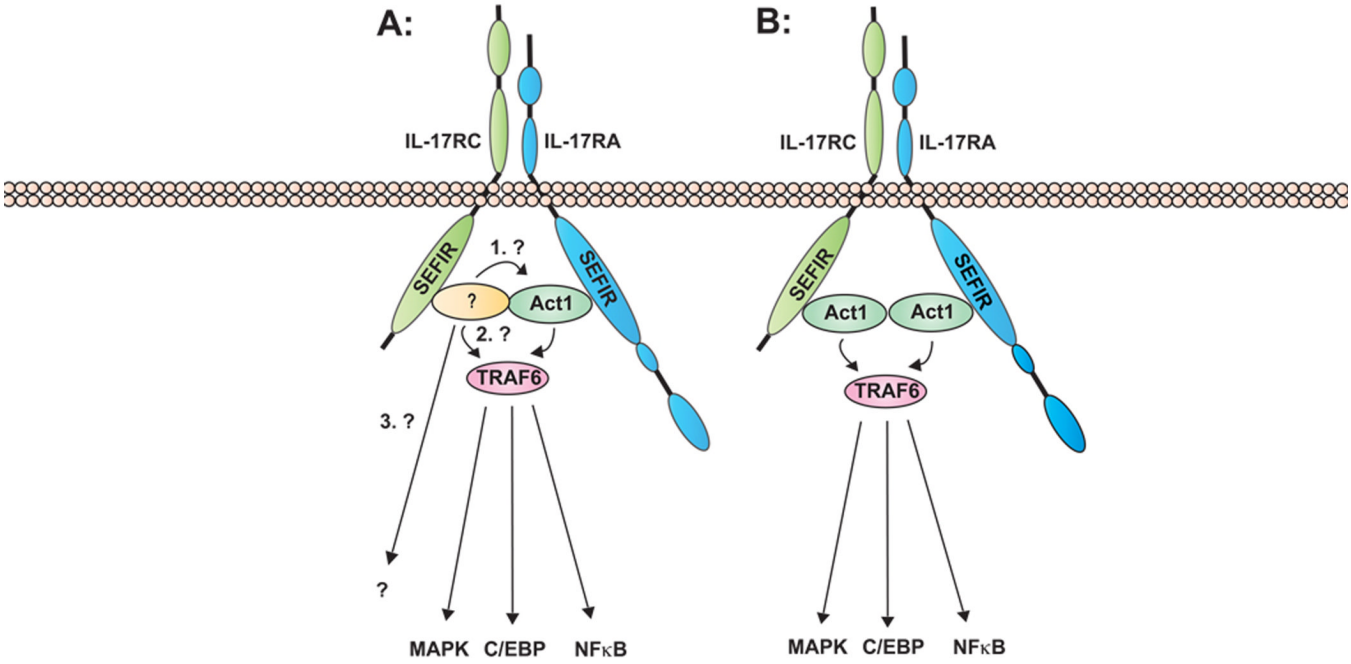

Figure 1. Alternative models of IL-17RC downstream signaling events

Two possible ways in which IL-17RC may participate in signaling are depicted. A. Upon ligand binding, IL-17RC recruits a novel signaling intermediate, resulting in the following downstream effector functions: (1) possible post-translational modifications on Act1, (2) recruitment of TRAF6, and/or (3) activation of novel effector signaling pathways. These events result in the creating of an appropriate molecular scaffold necessary for IL-17-dependent signaling. B. Upon ligand binding, IL-17RC recruits Act1 through a homotypic SEFIR docking interaction. IL-17RC-bound Act1 oligomerizes with IL-17RA-bound Act1, resulting in an effective recruitment of intermediates for efficient IL-17-dependent signal transduction.

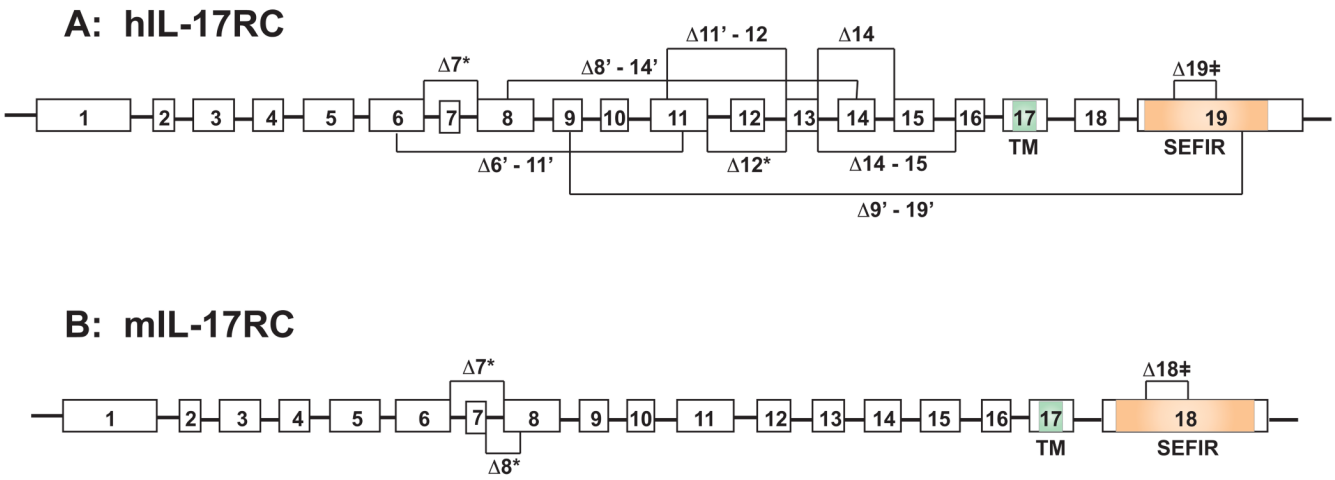

Figure 2. Genomic structure and predicted splice variants of hIL-17RC and mIL-17RC

A. hIL-17RC contains 19 exons. The transmembrane (TM) domain is encoded by exon 17 and spans amino acids 468 – 487. The SEFIR domain is encoded by exon 19 and spans amino acids 522 – 666. Exons with (') have multiple splice sites. Variants labeled with (‡) indicate multiple variants within the exon were found. Variants labeled with (*) have been independently verified [39,41]. B. mIL-17RC contains 18 exons. The TM domain is encoded by exon 17 and spans amino acids 465 – 484. The SEFIR domain is encoded by exon 18 and spans amino acids 495 – 645.

A: Human

Receptor	hIL-17A	hIL-17F
hIL-17RC	+	+
hIL-17RCΔ7	+	+
hIL-17RCΔ12	-	-
hIL-17RCΔ7,12	-	-
hIL-17RA	+	-

B: Mouse

Receptor	mIL-17A	mIL-17F
mIL-17RC	-	+
mIL-17RCΔ7	-	+
mIL-17RCΔ8	-	-
mIL-17RCΔ7,8	-	-
mIL-17RA	+	-

Figure 3. Cytokine binding capacities of human and murine IL-17RA and IL-17RC

A. hIL-17RA and hIL-17RC splice variants that have been independently verified and tested for cytokine binding capacity are displayed. A (+) indicates the presence of an interaction while (−) indicates a lack of one. B. mIL-17RA and mIL-17RC splice variants that have been independently verified and tested for cytokine binding capacity are displayed [41].