Review

Biology of recently discovered cytokines: Interleukin-17 – a unique inflammatory cytokine with roles in bone biology and arthritis

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Abstract

IL-17 and its receptor are founding members of an emerging family of cytokines and receptors with many unique characteristics. IL-17 is produced primarily by T cells, particularly those of the memory compartment. In contrast, IL-17 receptor is ubiquitously expressed, making nearly all cells potential targets of IL-17. Although it has only limited homology to other cytokines, IL-17 exhibits proinflammatory properties similar to those of tumor necrosis factor-α, particularly with respect to induction of other inflammatory effectors. In addition, IL-17 synergizes potently with other cytokines, placing it in the center of the inflammatory network. Strikingly, IL-17 has been associated with several bone pathologies, most notably rheumatoid arthritis.

Keywords: bone, cytokines, interleukin-17, inflammation, synergy

Introduction

The cytokine IL-17, originally termed CTLA-8, was isolated as a CD4-specific transcript from a rodent cDNA library [1]. Shortly thereafter, IL-17 was discovered in humans, and its receptor (IL-17R) was cloned and characterized [2–4]. The most striking feature of both IL-17 and IL-17R is that they are distinct in sequence from previously described cytokine/receptor families. However, they are highly homologous among mice, rats, and humans. In addition, an IL-17R homolog in zebrafish (termed SEF [similar expression of FGF genes]) has been described that functions in embryonic development [5], and mammalian homologs of SEF were also recently identified [6,7]. Consequently, IL-17 and IL-17R are now recognized to be the founding members of an emerging new family that, in mammals, contains at least six cytokines and five receptors (Table 1 [8,9]). This review focuses primarily on the original IL-17 cytokine (also known as IL-17A), because its roles in bone physiology and arthritis are most clearly defined, but the biology of the remaining family members promises to be a fascinating emerging story within the field of 'high numbered' cytokines.

Interleukin-17 and interleukin-17 receptor structure

Even though IL-17 and IL-17R have been recognized for many years, there is still much to learn about their respective structures and functions. IL-17 is secreted primarily by $CD4^+$ T cells in a mix of both nonglycosylated and *N*-glycosylated forms, which migrate in SDS-PAGE at 28 kDa and 33 kDa, respectively [2]. Secreted IL-17 apparently exists as a homodimer, but the specific contact points between IL-17 subunits or between IL-17 and IL-17R have never been defined [2,10]. IL-17B and IL-17F also exist as dimers [10,11]. While the amino acid sequence of IL-17 did not permit it to be classified as a

CCL = CC chemokine ligand; C/EBP = CCAAT/enhancer binding protein; CIA = collagen induced arthritis; CXCL = CXC chemokine ligand; DC = dendritic cell; IFN = interferon; IL = interleukin; IL-17R = IL-17 receptor; MAPK = mitogen-activated protein kinase; NF-κB = nuclear factor-κB; OPG = osteoprotegerin; RA = rheumatoid arthritis; RANKL = receptor activator of nuclear factor-κB ligand; TNF = tumor necrosis factor; TRAF = tumor necrosis factor receptor-associated factor.

Table 1

The IL-17 superfamily: cellular sources, receptors, and major functions

Cytokine	Other names	Cellular source	Receptor	Major functions
IL-17	IL-17A, CTLA-8	T cells (memory)	IL-17R (also known as, IL-17AR)	Inflammation, neutrophil recruitment, cytokine secretion, bone metabolism
IL-17B		Multiple organs	IL-17BR (also known as, IL-17Rh1/Evi27)	Cytokine secretion, inflammation
IL-17C		Unknown	Unknown	Regulation of Th1 cytokines
IL-17D	IL-27	Multiple organs	Unknown	Cytokine secretion
IL-17E	IL-25	Th2	IL-17BR (also known as, IL-17Rh1/Evi27)	Regulation of Th2 cytokines
IL-17F	ML-1	$CD4^+$ T cells and monocytes	IL-17R?	Angiogenesis, cytokine secretion, regulation of Th1 cytokines
HVS13	vIL-17	Herpesvirus saimiri infected cells	IL-17R?	Unknown (not required for cellular transformation)

References and further information on this family can be found in the report by Moseley and coworkers [24]. CTLA, cytotoxic T-lymphocyte associated antigen; IL, interleukin; IL-17R, interleukin-17 receptor; Th, T-helper.

member of any known cytokine families, X-ray crystallographic studies of IL-17F – its closest homolog – have been performed. Interestingly, the three-dimensional structure of IL-17F takes on a 'cystine knot fold', and hence resembles the neurotrophin family of growth factors, the canonical member of which is nerve growth factor [10].

The IL-17R is also particularly interesting because of its unique primary structure. It contains a single transmembrane domain and has an unusually large cytoplasmic tail [4,12]. This receptor is expressed in most cell types. One exception is in naïve T cells in mice, which do not bind IL-17 detectably (Dong C, personal communication). However, several mouse and human T cell lines do contain detectable mRNA encoding IL-17R, and so this receptor may be present in at least low levels in T cells (Gaffen SL, unpublished data) [12]. As a result of its ubiquitous expression, nearly all cells are potential targets of this cytokine, but it is still unclear which cells *in vivo* are the most physiologically relevant targets. Most studies to date have been performed in cells of fibroblast/osteoblast or epithelial origin, because these appear to be particularly responsive to IL-17. Although there was originally thought to be a unique cytokine–receptor relationship between IL-17 and IL-17R, more recent studies indicate that IL-17F binds, albeit weakly, to IL-17R [10]. Whereas IL-17 is composed of a homodimer of identical subunits, the configuration and stoichiometry of the receptor remain undefined. In this regard, discrepancies between IL-17 binding constants and concentrations needed to elicit biologic responses have hinted that an additional subunit might be involved in IL-17 signaling [10,12]. However, IL-17R is clearly an essential subunit, because cells from $IL\text{-}17R^{-/-}$ mice fail to bind to IL-17.

Sources, regulation, and biologic functions of interleukin-17

IL-17 is produced almost exclusively by T lymphocytes, primarily those of the $CD4^+$ memory ($CD45RO^+$) compartment [2,13,14]. Consequently, IL-17 does not obviously polarize to either the T-helper-1 or -2 lineages, although the literature is somewhat inconsistent in this regard [15–19]. Consistent with its production by memory cells, several recent studies have shown that IL-23, which is produced by dendritic cells (DCs) and acts mainly on memory T cells, is a potent stimulator of IL-17 secretion [20,21]. However, it should be noted that signaling through the T-cell receptor alone is sufficient to promote IL-17 production even in the absence of DCs or IL-23 (Liu X, Clements J, Gaffen S, unpublished data), and IL-23 deficient mice are still capable of producing IL-17, albeit at reduced levels [22]. In addition, IL-15 has been shown to induce IL-17 production [23].

The gene encoding human IL-17 resides on human chromosome 6, adjacent to the gene encoding IL-17F [10], whereas other IL-17 family members are located elsewhere in the genome [24]. We recently showed that a minimal regulatory promoter element exists about 250 bases upstream of the transcriptional starting point [25]. In this regard, the signaling pathways leading to IL-17 gene regulation by any of these stimuli are poorly defined, although several studies indicated that the calcineurin/NFAT (nuclear factor of activated T cells) pathway is essential [23,25] (Liu X, Clements J, Gaffen S, unpublished data). Other studies also indicate a role for the cAMP/protein kinase A pathway, although this signal may ultimately converge on NFAT signaling [13,14,26]. Like many cytokines, IL-17 gene expression is likely to be

at least partially controlled at the level of mRNA stability, because AU-rich elements exist in the 3′-untranslated region that could target the transcript for rapid degradation [2,27,28]. Clearly, much still remains to be learned about how IL-17 expression is controlled biologically.

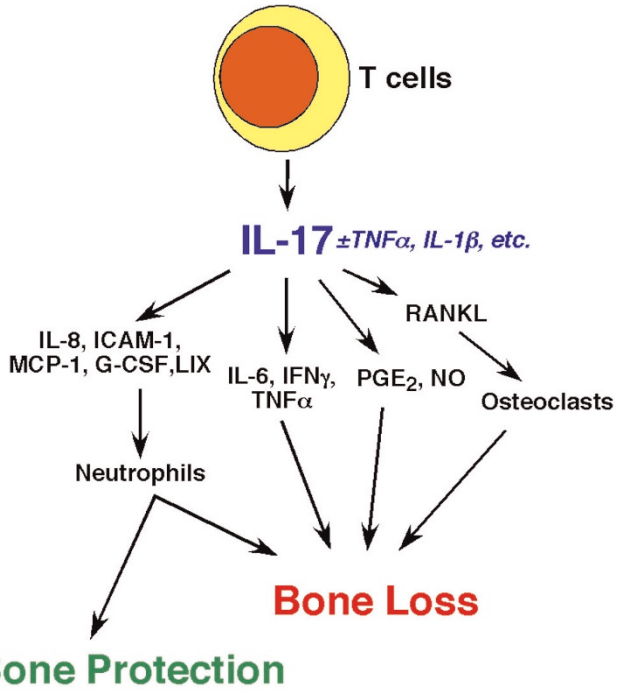
Functionally, IL-17 has been classified as a pro-inflammatory mediator, based on its ability to induce a wide array of inflammatory effectors in target cells (Fig. 1). Among these are cytokines (e.g. IL-6, tumor necrosis factor [TNF]-α, IL-1β, IFN-γ, and granulocyte colony-stimulating factor), chemokines (e.g. CXC chemokine ligand [CXCL]2/MIP-2/IL-8, CXCL1/Groα/KC, CC chemokine ligand [CCL]2/MCP-1, CCL5/RANTES, and CXCL5/LIX), and other effectors (e.g. cyclo-oxygenase-2, prostaglandin E_2, nitric oxide, and intercellular adhesion molecule-1; for review [8]). Moreover, IL-17 cooperates either additively or synergistically with various inflammatory cytokines or agonists, thus placing this cytokine in the midst of a complex network that amplifies inflammation (see below). In this sense, IL-17 appears to function as an activator of the innate immune system, analogous to TNF-α and IL-1β, with which it shares many target genes. However, because IL-17 is produced by T cells rather than by monocytes or other innate cells, it presumably comes into play during adaptive or memory immune responses. Consequently, the function of IL-17 may be to trigger innate immune responses shortly after a second encounter with antigen, when the memory response is activated but when concentrations of antigen are still too low to trigger a full-scale innate immune response.

Interleukin-17 as a synergistic cytokine

A prominent feature of IL-17 is its ability to synergize with other cytokines to enhance inflammation (for review [29]). In particular, IL-17 has been shown to synergize with IL-1β and TNF-α to drive expression of numerous inflammatory effectors [18,30–35]. IL-17 also synergizes with CD40 ligand, a TNF receptor family member, to upregulate target gene expression [36]. Similarly, IL-17 synergizes with IFN-γ to promote chemokine gene expression [37]. Microarray analysis of an osteoblast cell line examining synergy between IL-17 and TNF-α revealed that all genes induced by IL-17 alone were induced more potently in cooperation with TNF-α. This finding suggests that a primary function of IL-17 may be to amplify ongoing inflammatory responses [34,35].

Although the molecular mechanisms that mediate cytokine synergy are not fully understood, several have been proposed. For example, IL-17 cooperates with TNF-α or IL-1β to enhance mRNA stabilization of the CXCL1/Groα/KC chemokine transcript in peritoneal mesothelial cells [33]. In its synergy with CD40 ligand, IL-17 upregulates expression of CD40, thus enhancing all CD40 ligand dependent responses [36]. However, this is not true of

Figure 1



Opposing roles of IL-17 in bone turnover. IL-17 is produced by T cells (particularly memory T cells), and acts on a wide variety of target cells to trigger expression of inflammatory effectors. Most of these effectors have been shown to have an impact on bone metabolism. Those factors that promote osteoclastogenesis indirectly favor bone destruction. Conversely, chemotactic factors promote neutrophil recruitment and activation, which can exert both bone protective and bone destructive effects. G-CSF, granulocyte colony-stimulating factor; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; LIX, LPS-inducible CXC chemokine; MCP, monocyte chemotactic protein; PGE_2, prostaglandin E_2; RANKL, receptor activator of nuclear factor-κB ligand; TNF, tumor necrosis factor.

IL-17 synergy with TNF-α, because IL-17 does not appear to enhance TNF receptor expression in osteoblasts [35]. Although IL-17 synergy with IFN-γ has been reported to occur via enhancement of the nuclear factor-κB (NF-κB) pathway [37], this is not the mechanism by which IL-17 synergizes with TNF-α [35]. Rather, we recently showed that IL-17 synergizes with TNF-α to promote IL-6 production by upregulating expression of CCAAT/enhancer binding protein (C/EBP)δ (also known as NF-IL-6β), a member of the bZIP family of transcription factors. The conserved C/EBP site in the IL-6 proximal promoter is essential for expression of IL-6, and thus cooperative upregulation of C/EBPδ mediated by IL-17 and TNF-α helps in turn to enhance transcription of the IL-6 gene [35,38]. Another report suggested that p38/mitogen-activated protein kinase (MAPK) may be a target of cooperative signaling between IL-17 and TNF-α [39]. In addition to transcription and RNA stability, synergistic signaling may affect regulation of chromatin

remodeling, cytokine secretion, and possibly other levels of gene or protein regulation. Given the proclivity of IL-17 to function in concert with other cytokines, it will be very important to dissect the multiple mechanisms by which this cytokine promotes cooperative/synergistic signaling.

The immune system and bone homeostasis

Bone undergoes a continuous cycle of remodeling that is required for its maintenance and healing, and recent advances have elucidated many of the molecular mechanisms that regulate or have an impact on this process (for review [40,41]). Two major types of cells are involved in bone remodeling. Osteoblasts, cells that are crucially involved in bone formation, are derived from mesenchymal stem cells and are closely related to fibroblasts, adipocytes, and muscle cells [42]. Osteoclasts, the cells responsible for bone degradation, are derived from hematopoietic precursors, and are thus related to macrophages and DCs [43]. In normal physiology, osteoblasts trigger the formation of osteoclasts, thus helping to maintain homeostasis in bone remodeling. Conversely, the bone resorbing activity of osteoclasts causes the release of various growth factors and bone cell mitogens that induce proliferation and differentiation of osteoblasts [40]. Importantly, a number of pathologic conditions adversely affect bone by altering the balance between osteoblast and osteoclast activity, causing localized or systemic osteoporosis (or, less frequently, osteopetrosis) [41,44]. Such conditions may have severe medical and economic consequences. For example, it is estimated that as many as 15% of adults suffer from periodontal disease severe enough to cause tooth loss, and the acute crippling in advanced rheumatoid arthritis (RA) can have devastating consequences for the quality of life of its victims. Therefore, it is paramount to understand the network of factors that control bone homeostasis, in order to develop optimal avenues of intervention and treatment in diseases that involve bone loss.

Recent discoveries have significantly advanced our understanding of the molecular basis for bone turnover (for review [41,45]). At a molecular level, osteoblasts express a receptor called RANKL (receptor activator of NF-κB ligand; also termed osteoprotegerin [OPG] ligand). RANKL is a member of the TNF receptor superfamily and is central in controlling osteoclastogenesis, and hence bone degradation [46,47]. RANKL acts by engaging its counter-receptor RANK (receptor activator of NF-κB) on osteoclast precursors, thereby triggering their maturation and activation in conjunction with signals from the growth factor macrophage colony-stimulating factor [48]. The interaction between RANK and RANKL can be further modulated by a soluble 'decoy' receptor called OPG, which also binds to RANK but does not induce osteoclastogenesis [49]. The relative balance between OPG and RANKL dictates the magnitude of osteoclastogenesis.

For many years it has been recognized that the immune system exerts a profound effect on bone cell activity, explaining why infectious diseases such as periodontal disease or autoimmune diseases such as RA are associated with bone destruction (for review [50]). In particular, both T cells and inflammatory cytokines have been implicated in this process. Interestingly, activated T cells inducibly express RANKL, and can thus bypass osteoblasts in triggering osteoclastogenesis, ultimately tipping the balance in favor of bone destruction [51]. Inflammatory cytokines such as TNF-α or IL-1β (and IL-17; see below) act on osteoblasts to upregulate RANKL, either directly or indirectly through the production of other cytokines/chemokines [52]. Clinical strategies to block cytokines such as TNF-α and IL-1β have been quite effective in treating RA, and efforts are underway to influence the RANK–RANKL axis directly through the therapeutic use of OPG [45,53].

Evidence for a role of interleukin-17 in bone and arthritis

A number of studies have implicated IL-17 in bone metabolism. Most prominently, IL-17 is found at significantly elevated levels in the synovial fluid of patients with RA, and is present in osteoarthritic joints as well [54]. IL-17 has also been found in patients with relatively severe periodontitis, where it could potentially contribute to bone destruction [55]. In addition, IL-17 exerts many of its effects on bone cells in culture [54,56], including induction of both membrane-bound and soluble RANKL in primary mouse osteoblast/stromal cell cultures [52]. IL-17 is strongly implicated in several mouse models of RA. Enhancement of RANKL following IL-17 stimulation was not observed in several osteoblast or stromal cell lines, including MC3T3-E1 or ST-2 cells (Kirkwood KL, personal communication). However, *in vivo* bone erosion mediated by over-expression of IL-17 has been shown to occur through alterations in the RANKL/OPG ratio [57]. Furthermore, IL-17 knockout mice are highly resistant to collagen induced arthritis (CIA) [58], and blocking IL-17 reduces inflammatory symptoms and bone loss in mice with CIA [59,60]. Conversely, excess IL-17, as provided by adenovirus-mediated gene vectors, exacerbates disease [61–64]. Remarkably, mice deficient in the T cell costimulatory molecule ICOS (inducible co-stimulator) are also profoundly resistant to CIA, and the only cytokine deficiency detected in these mice was a reduction in IL-17 [65].

It is also striking that most IL-17-induced factors tend to be bone resorptive in nature (Fig. 1; for review [66]). For example, IL-6 has been shown to be a contributing factor to estrogen mediated bone loss [67] as well as bone loss due to periodontal disease [68]. Similarly, CXCL8/IL-8, prostaglandin E_2, and nitric oxide have all been implicated in the pathogenesis of periodontitis [69]. However, the role played by neutrophils in bone turnover is more

complex. During chronic inflammation, neutrophils are thought to contribute to bone destruction. However, neutrophils are generally considered to be bone protective in the context of periodontal disease-induced bone loss (for review [70,71]). IL-17 is a potent activator of neutrophil recruitment and activation, due in large part to its ability to promote chemokine secretion. Thus, IL-17 could potentially play a positive role in situations where neutrophil activity is bone protective.

In summary, IL-17 clearly has an impact on bone metabolism, and in the context of arthritis it appears to be a bone destructive cytokine.

Interleukin-17 in other diseases

IL-17 has been implicated in numerous other disease settings. Intriguingly, IL-17 is highly homologous to an open reading frame found in the T cell tropic Herpesvirus saimiri, although its physiologic significance within the context of this virus remains unknown [12,72]. However, addition of the gene encoding murine IL-17 into the vaccinia virus enhanced its virulence significantly, suggesting a possible pathogenic role for this cytokine in viral infections [73]. The role played by IL-17 in tumorigenesis is complex. IL-17 was shown to promote growth and tumorigenicity of human cervical tumors in athymic (nude) mice [74]. In contrast, IL-17 also inhibited the growth of hematopoietic tumors in immunocompetent but not nude mice [75]. IL-17 has also been found at elevated levels in the context of bacterial infections, such as periodontitis [55] and *Helicobacter pylori* infections [76]. Finally, IL-17 plays an important role in immune responses in the lung. Specifically, IL-17R$^{-/-}$ mice are highly susceptible to lung airway infections due to a failure to recruit neutrophils [77]. Human bronchial epithelial cells induce chemokines following IL-17 stimulation, and local administration of IL-17 in mouse lung tissue causes neutrophil recruitment and increases in elastase and myeloperoxidase activities (for review [78,79]). Finally, data from IL-17$^{-/-}$ and IL-17R$^{-/-}$ mice indicate that this cytokine is also involved in a variety of other T cell dependent events. For example, delayed type hypersensitivity and contact hypersensitivity responses are severely impaired in IL-17$^{-/-}$ mice [80]. Interestingly, attempts to over-express IL-17 transgenically have not been successful, perhaps because of a generalized inflammation that is lethal to developing embryos [81]. Thus, IL-17 is important for numerous immune functions related to regulation of inflammation, and can play both pathogenic and protective roles *in vivo*.

Interleukin-17 and interleukin-17 receptor signaling

The signaling mechanisms used by IL-17 to regulate its downstream targets are surprisingly poorly defined. As indicated above, the IL-17R is the founding member of a new subclass of cytokine receptors that do not bear homology to type I or II cytokine receptors, TNF receptors, or other receptor families [12,82]. Because so little is known about signaling pathways induced by this class of receptor, few predictions can be made based its primary amino acid structure.

Recently, however, it was suggested that IL-17 receptors may contain a putative TIR (Toll/IL-1 receptor) domain in the intracellular region [7], and the IL-17R tail also contains at least two putative TNF receptor-associated factor (TRAF)-binding domains (Gaffen SL, unpublished observations) [83]. Although early reports suggested that IL-17 activates the transcription factor NF-κB [12], careful comparisons show that NF-κB induction is generally quite modest as compared with that triggered by TNF-α or Toll-like receptor agonists [35]. Other signaling pathways implicated in IL-17 signaling include the MAPK, protein kinase A and JAK/STAT (Janus kinase/signal transducer and activator of transcription) pathways (for review [8]). However, only in a few cases have these pathways been linked to specific signaling outcomes. One study showed convincingly that IL-17 recruits the adaptor molecule TRAF6 in murine embryonic fibroblast cells, which are among the few cell types that induce NF-κB strongly. In these cells, TRAF6 lies upstream of signaling leading to IL-6 and intercellular adhesion molecule-1 expression [84]. Based on paradigms in the TNF and Toll-like receptors, TRAF6 probably also lies upstream of MAPK signaling, although this remains to be proven for the IL-17R [85]. In another study, the IL-17-induced MAPK pathway was linked to IL-6 gene expression via stabilization of IL-6 mRNA [39]. Similarly, IL-17 alone mediates cyclo-oxygenase-2 mRNA stability in a p38-MAPK dependent manner [86]. To date, no detailed mutagenesis studies of IL-17R have been performed, and so regions of the receptor required for activation of various signaling pathways have not yet been determined.

Conclusion

IL-17 is the prototypical member of a fascinating new family of cytokines. Although it is clear that IL-17 is proinflammatory in nature, its physiologic significance is only just beginning to be elucidated. The unique structure of IL-17 and its receptor hint at exciting new discoveries in the area of signal transduction as well as potential therapeutic intervention strategies. With respect to

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arthritis, IL-17 appears to be largely pathogenic. However, findings in IL-17 and IL-17R knockout mice indicate a nonredundant role for this cytokine in regulating host immunity to infection. Future work on the IL-17 family will no doubt yield many surprises, and will probably establish new paradigms for cytokine biology.

Competing interests

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