IL-17: prototype member of an emerging cytokine family

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Abstract: IL-17 is a potent proinflammatory cytokine produced by activated memory T cells. The large-scale sequencing of the human and other vertebrate genomes has revealed the presence of additional genes encoding proteins clearly related to IL-17, thus defining a new family of cytokines. There are at least six members of the IL-17 family in humans and in mice. Initial characterization suggests that like IL-17, several of these newly identified molecules have the ability to modulate immune function. Neither the IL-17 family nor the cognate receptors that have been identified for these molecules bear obvious sequence similarity to other known families of proteins. Thus, they represent a distinct signaling system that appears to have been highly conserved across vertebrate evolution. The potent inflammatory actions that have been identified for several of these factors and the emerging associations with major human diseases suggest that these proteins may have significant roles in inflammatory processes. *J. Leukoc. Biol.* 71: 1–8; 2002.

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DISCOVERY OF THE INTERLEUKIN-17 FAMILY

Interleukin-17 (IL-17) was first identified as a rodent cDNA transcript, termed CTLA8, isolated from an activated T-cell hybridoma [1]. It bore a striking 58% identity to a predicted open-reading frame, HSVS13, in the T-lymphotropic herpesvirus *Herpesvirus samiri* [2]. Initial characterization recognized that this factor could promote the production of other cytokines and chemokines such as IL-6, IL-8, and granulocyte colony-stimulating factor (G-CSF) from a variety of epithelial, endothelial, and fibroblastic cell types and led to its proposed nomenclature as an IL [2–4]. IL-17 was striking in its uniqueness. It bore no resemblance to other known ILs, and moreover, beyond the viral ortholog, it bore no clear resemblance to any known protein or structural domain. Its uniqueness was further exemplified by the isolation of a receptor that binds IL-17 and is required for signaling [2]. IL-17 receptor (IL-17R) was not recognized to be related to any of the other known cytokine receptors, and remarkably, in spite of a relatively large size of 860 amino acids, it also did not possess similarity to any other known protein nor any recognizable domains. Thus, the IL-17 system appeared to be a distinct and potent signaling system involved in the control of the immune response.

The recent large-scale sequencing of expressed sequence tags (est) and genomes of several vertebrate species has led to the identification of additional genes that bear clear homology to IL-17 and thus define an emerging cytokine family [5–9]. There are at least six members of the family in the human genome (**Fig. 1**). IL-17B and IL-17C were identified based on est, and a fourth member, as yet unpublished but provisionally termed IL-17D, is also relatively abundantly represented in est databases (unpublished results). A fifth member of the IL-17 family, IL-17E, was first discovered in human genomic sequence [6]. The sixth known member of the family, IL-17F, is located adjacent to IL-17 in human genomic sequence [8]. Comparison of the human IL-17s with other species suggests that IL-17 family members are highly conserved across vertebrate evolution. In contrast, clear orthologs have not been identified in *Drosophila* or *Caenorhabditis elegans*. The IL-17s are all similarly sized, secreted proteins of 150–180 amino acids. They bear greatest similarity within the C-terminal 70 amino acids. Although there is not a strict conservation of spacing, there are four well-conserved cysteines and at least two additional cysteines that appear likely to be functionally conserved but with more variable spacing. Members of the IL-17 family are all expressed as dimers, and with the exception of IL-17B, they are covalent dimers (unpublished results). Recent structural analysis has revealed the unexpected finding that IL-17F and, therefore likely, the other IL-17s adopt a cysteine knot conformation [8].

BIOLOGICAL ACTIONS OF IL-17 AND FAMILY MEMBERS

The biological actions of IL-17 are quite proinflammatory in character. It increases the local production of chemokines such as IL-8 [10–12], monocyte chemoattractant protein-1 (MCP-1) [13, 14], and Groα [15], thereby promoting the recruitment of monocytes and neutrophils [16–18]. Further, it stimulates the production of the hematopoietic cytokines G-CSF and granulocyte macrophage (GM)-CSF that promote the expansion of these myeloid lineages [19–21]. Other actions such as the stimulation of IL-6 and PGE2 production enhance the local inflammatory environment [4, 22–24]. In addition, IL-17 also drives T-cell responses, notably through the induction of the

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Fig. 1. Sequence of IL-17 family members. Shown is a sequence alignment of the six known human IL-17 family members. Identical residues are boxed, and conserved cysteines are indicated by bullets.

costimulatory molecule intercellular adhesion molecule (ICAM) [25–27].

IL-17 has long been considered a molecule produced by activated memory T cells [1]. Studies designed to establish whether IL-17 could be classified according to the Th1/Th2 paradigm have been unable to provide clear categorization [28–30]. Although individual T-cell clones can be derived, which produce interferon-γ (IFN-γ) and IL-17, many IL-17-producing clones appear to produce neither IFN-γ nor IL-4. The significance of the observation that IL-17 was produced by activated $CD4^+CD45RO$ memory T cells has perhaps not been fully appreciated. One interpretation of this observation is that there exists within the memory T-cell compartment a population of T cells that were originally activated by unknown stimuli to produce IL-17. Having acquired this differentiated, polarized state, these cells are able to re-express IL-17 when subsequently restimulated with relatively nonspecific stimuli such as phorbol 12-myristate 13-acetate (PMA) and ionomycin. This interpretation has been given strong support by the recent observation that splenocytes from T-cell receptor (TCR) transgenic mice could be driven to produce IL-17 when primed with cognate peptide in the presence of microbial lipopeptides [31]. The study demonstrated that this outcome was not observed when cells were stimulated with peptide and the known Th1 driver IL-12 [32, 33]. Characterization of the cytokine expression profile of individual T cells within the population by cytometric single-cell analysis revealed that the IL-17-expressing cells represent a distinct population from the traditional Th1 profile [34–36] and are characterized by the production of IL-17, GM-CSF, and tumor necrosis factor α (TNF-α). This represents the first known physiological stimuli capable of directing the development of IL-17-expressing T cells. These data fit well with other observations that there is abundant IL-17 in various conditions that are impacted by microbial pathogens, including *Helicobacter pylori*-infected gastric mucosa [37] and synovial fluid of patients with Lyme arthritis [31].

Taken together, these data suggest a new paradigm for the consideration of IL-17 within the immune system. IL-17 may serve to mediate an adaptive immune response to pathogens that is characterized by a heavy reliance on cells thought to function primarily as mediators of the innate immune response. Thus, the immune system is able, by virtue of this memory T-cell response, to promote a more rapid recruitment of monocytes and neutrophils through IL-17-induced chemokine production [10–15, 38, 39]. Further, it is able to promptly begin to stimulate the production of additional myeloid cells through the production of GM-CSF by the activated IL-17/GM-CSF/TNF-producing T cells [31] and additional GM-CSF and G-CSF production from local IL-17-stimulated stromal cells [21–24]. However, the induction of ICAM by IL-17 acts to promote further T-cell responses, indicating the character of this adaptive response is not an exclusive reliance on phagocytic cells of the myeloid lineage.

The new IL-17s each appear to have very distinct expression patterns and therefore likely have distinct biological roles. The expression of IL-17 itself is very highly regulated, and IL-17 transcripts are essentially undetectable other than in select, activated T cells [11]. IL-17B is moderately expressed in several peripheral tissues as well as immune tissues [5, 7]. IL-17C was found to be quite rare, but like IL-17, its expression is highly regulated in inflammatory conditions (unpublished results). The expression of the unpublished molecule, here termed IL-17D, appears to be particularly high in skeletal muscle and the nervous system, suggesting its biology is likely to be quite different from IL-17. The expression of IL-17E is strikingly low but can be detected by polymerase chain reaction (PCR) in various peripheral tissues [6]. IL-17F mRNA expression seems most similar to IL-17, with expression generally very low, but clearly detectable in activated populations of T cells [8, 9]. Of these new members of the IL-17 family, IL-17E and IL-17F are currently the best characterized and so will be described in greater detail.

IL-17E has potent inflammatory effects in vitro and in vivo. Initial characterization of IL-17E indicated that it, analogous to IL-17, was able to stimulate activation of nuclear factor κB (NF-κB), a transcription factor that contributes to the signal transduction of several important proinflammatory molecules including TNF, IL-1β, and Toll-related receptors [40–42]. Consistent with this, it was shown to induce production of IL-8, a downstream target of each of these signaling pathways. Recently, the action of IL-17E has been characterized in the transgenic mouse setting [43]. Overexpression of IL-17E resulted in profound alterations of the immune system. Several features of the response had Th 2-like character [44, 45]. The mice displayed eosinophilia and increased serum immunoglobulin (Ig)E and IgG1 but not IgG2a. Serum levels of IL-13 and IL-5 were elevated. Further, elevated gene expression of several Th2 cytokines, including IL-4, IL-5, IL-10, and IL-13, was observed in multiple tissues. However, although the systemic response had Th2-like aspects, there were markedly different tissue-specific expression patterns of cytokines, chemokines, and adhesion molecules. For instance, high levels of TNF and

ICAM were expressed in liver. Elevated levels of G-CSF were expressed in several tissues and likely contributed to the substantial neutrophilia displayed in these mice. Moreover, exposure to IL-17E induced pathological changes in multiple tissues, particularly liver, heart, and lung, characterized by mixed inflammatory cell infiltration, epithelial hyperplasia, and hypertrophy. Thus, IL-17E appears to be a unique pleiotrophic cytokine that engages a systemic Th 2-like response with tissue-specific immunological and pathological changes.

The gene encoding human IL-17F is located adjacent to IL-17 (human genomic sequence in clone RP11-935B23; Genbank accession AL355513) [8]. IL-17 and IL-17F share 44% amino acid identity, whereas the other members of the IL-17 family share a more limited 15–27% amino acid identity, suggesting that IL-17A and IL-17F form a distinct subgroup within the IL-17 family. As mentioned above, IL-17F is produced by activated T cells. Whether this expression is in precisely the same population of cells that express IL-17 and whether there are differences in the stimuli that induce their expression are unresolved questions. IL-17F has also been demonstrated in activated monocytes [9]. IL-17F appears to have similar biological actions as IL-17 [8] and is able to promote the production of IL-6, IL-8, and G-CSF from a wide variety of cells. Similar to IL-17, it is able to induce cartilage matrix release and inhibit new cartilage matrix synthesis. Thus, like IL-17, IL-17F may potentially contribute to the pathology of inflammatory disorders such as rheumatoid arthritis (RA) [46–50]. IL-17F has also been shown to induce transforming growth factor-β (TGF-β) expression in human umbilical vein endothelial cells and decrease their ability to undergo capillary tube formation, suggesting a potential ability to inhibit angiogenesis [9].

STRUCTURE OF THE IL-17s

The apparent uniqueness of the sequences of IL-17 and its receptor has made it difficult to appreciate whether the IL-17 system is truly unrelated to other known signaling systems. Although it has not been possible to identify orthologs of these molecules outside of the vertebrates, they have the ability to engage components of the NF-κB and mitogen-activated protein kinase (MAPK) signaling pathways [2, 5, 6, 51, 52] and thus use signaling systems that are broadly distributed across metazoan evolution [53]. To better understand the character of the IL-17s, the crystal structure of one of the family members, IL-17F, has been determined recently [8]. Unexpectedly, the structure of IL-17F reveals that the protein adopts a cysteine knot fold and suggests that the family may have a relationship to the cysteine knot superfamily of proteins [54, 55]. IL-17F folds in a manner quite similar to that of nerve growth factor (NGF) [56] and the other neurotrophins [57]. In addition, IL-17F and NGF exist as dimers. The IL-17 family does not have any appreciable sequence identity with the neurotrophins. The cysteine knot superfamily is a diverse family and includes other proteins, such as the endocrine glycoprotein hormones (e.g., chorionic gonadotropin), the platelet-derived growth factors (PDGFs), and the TGF-β family, which also display limited sequence similarity [54]. Although IL-17 folds in a manner highly analogous to the cysteine knot superfamily, one of the cononical cysteine pairs, the pair that links through the ring formed by the other two pairs and thereby forms the "knot," is not present. Instead, a third cysteine bridge is formed by a spatially distinct pair of cysteines. Thus, although the members of IL-17 family clearly adopt a cysteine knot fold, actual evolutionary membership within the family cannot be assumed.

The tertiary structural similarity between the IL-17s and the neurotrophins raises some interesting speculations. The neurotrophins bind to two classes of receptors [58–61], the Trk tyrosine kinases and $p75^{NTR}$, a member of the TNF receptor superfamily. Neither the Ig domains within the extracellular domains of the Trk receptors nor the cysteine-rich extracellular domains that characterize membership in the TNF receptor family bear obvious similarity to the IL-17R. However, TNF has clear similarities to IL-17 in its ability to modulate immune function and promote an inflammatory response [40]. Another interesting speculation relates to the *Drosophila* protein späztle [62, 63], which has been predicted to adopt a neurotrophin fold [64] and has been shown genetically to be an endogenous ligand for the *Drosophila* Toll receptor [65, 66]. The Toll receptors are members of the leucine-rich repeat superfamily of proteins [67–70] and are clearly not related to the IL-17Rs. Nonetheless, it is possible that the IL-17 system may in some manner relate to this ancient, innate immune system.

IL-17R

Following the isolation of mouse [3, 71], rat [1], human [4, 28], and viral [1] homologs of IL-17, viral IL-17 was used to identify a mouse IL-17R that bound to all ortholog forms [2, 72]. In contrast to relatively restricted expression of IL-17 [1, 2], IL-17R was found to be ubiquitously expressed in all cell types examined [2, 10]. The mouse IL-17R is a type 1 membrane protein that contains 864 amino acids and eight putative *N*-linked glycosylation sites. The human homolog of mouse receptor exhibits 69% sequence homology. Direct binding assays using ^{125}I-labeled human (h)IL-17 on cells transfected with IL-17R have indicated that IL-17 binds to its receptor with relatively low affinity with a K_a value of approximately 2×10^7–2×10^8 M^{-1} [72]. This is a substantially low affinity for IL-17R, considering the low concentrations of IL-17 required for its biological activity, suggesting the potential presence of additional components of the IL-17R. However, in human fibroblast cell line HFF, an antibody to IL-17R blocks IL-6 production in response to IL-17.Fc ligand, indicating that binding to its receptor is necessary to generate an IL-17-specific response in these cells [72]. Initial studies of the new members of the IL-17 family suggest that they will use distinct, cognate receptors. IL-17E has been identified as a high-affinity ligand for a newly recognized receptor termed IL-17Rh1 [6] (also termed EVI27 and IL-17BR) [7, 73]. This receptor has also been suggested to interact with IL-17B although apparently with lower affinity. Comparison of IL-17R and IL-17Rh1 reveals conservation of several cysteines within the extracellular domains, suggesting they share similar structures. There are also conserved elements within the intracellular domain,

suggesting that these receptors likely engage similar intracellular machinery. This is supported by the observation that IL-17E, like IL-17, is able to induce the activity of NF-κB and similar downstream effector molecules. IL-17Rh1 was first shown as EVI27, a protein encoded whose expression was up-regulated as a result of retroviral integration in BXH2 murine myeloid leukemias [73]. IL-17F, which has similar activity to IL-17, also appears able to interact with the IL-17R (unpublished results), although the low affinity of this interaction makes it clear that additional components remain to be identified.

IL-17 SIGNALING

IL-17 is produced by activated T cells and mediates its proinflammatory effects via its receptor, IL17R, which is ubiquitously expressed on all cell types. However, the exact mechanisms of IL-17 signaling are still not fully elucidated. In chronic diseases including RA, IL-17 results in tissue damage, directly by matrix degradation [74–77] or indirectly by recruiting activated inflammatory cells and inducing other proinflammatory cytokines including IL-1β and TNF-α to the inflamed tissue [51]. The matrix degradation results from up-regulation of inducible nitric oxide synthase (iNOS) and NO in chondrocytes through a tyrosine kinase-dependent cascade, which is protein kinase A (PKA)- and, to a lesser extent, protein kinase C (PKC)-dependent [75, 78]. IL-17 activates all three subgroups of MAPKs, which are the p44 and p42 extracellular signal-regulated kinases (ERK1 and ERK2), stress-induced Jun NH_2-terminal kinases (JNK), and p38 [52, 75, 79, 80]. The IL-17-induced activation of JNKs (JNK1 and JNK2) results in up-regulation of iNOS and cyclooxygenase-2 (COX-2) genes [75]. NF-κB activation by IL-17 was seen in human fibroblasts [4, 28], intestinal epithelial cells [52], and chondrocyte cultures [75, 78]. The mechanisms by which IL-17 activates NF-κB are not resolved but appear to be dependent on TNF receptor-associated factor (TRAF)-6 [52, 81].

IL-17 has also been postulated to be a major vehicle by which T cells can communicate with the hematopoietic system [82]. For example, fibroblasts cultured with IL-17 were shown to support the growth of human $CD34^+$ hematopoietic progenitor cells and direct their maturation toward neutrophils [4]. More recently, it was shown that adenovirus-mediated gene transfer of murine IL-17 cDNA targeted to the liver stimulates granulopoiesis in mice [83]. In the hematopoietic system, using human monocytic leukemia cell line U937, IL-17 was shown to trigger tyrosine phosphorylation of several members of the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways [84]. These included Tyk2, JAK1, -2, and –3, and STAT 1, 2, 3, and 4, suggesting the possibility that the JAK/STAT pathway may be involved in mediating biological effects of IL-17.

Recently, we have shown that another member of IL-17 family, IL-17E, also activates NF-κB [6]. Furthermore, IL-17E and recently characterized IL-17F [8] promote the production IL-8 and IL-6 in vitro from responsive cell lines, activities shared with IL-17 and suggesting that the members of this family are capable of engaging similar intracellular machinery.

IL-17 IN DISEASE

IL-17 and RA

RA is characterized by chronic inflammation as well as progressive destruction of RA synovium and destruction of bone and cartilage [85]. In RA, T cells infiltrate into synovial membrane, and tissue pathogenesis occurs through a complex cell-cell interaction among T cells, antigen-presenting cells, endothelial cells, and synovium [86–89]. The structural changes associated with the disease are caused, in part, by contribution from increased NO production [90, 91]. Bioactive IL-17 is detected in RA and osteoarthritis (OA) [49, 92] synovial fluid. It stimulates the production of iNOS and NO levels and other catabolic enzymes in human chondrocytes, thereby resulting in decreased chondrocyte proliferation and proteoglycan synthesis [47, 93, 94]. Additionally, IL-17 together with (concomitantly or concurrently) IL-1β and TNF stimulate osteoblasts to secrete cytokines such as GM-CSF and IL-6, which in turn regulate osteoclast and chondrocyte-mediated resorption and hence, bone and cartilage destruction [95–101]. IL-17 also directly plays a destructive role in disease progression by inducing matrix metalloproteinases [48, 102, 103] (especially MMP-1) in synoviocytes, which in turn initiate tissue damage by proteolytic degradation of collagens and proteoglycans.

IL-17 and airway neutrophils

IL-17 can also play a proinflammatory role in the airways by recruiting and activating neutrophils [18–20, 104, 105]. Exacerbations of obstructive airway diseases, including bronchial asthma and chronic obstructive pulmonary disease (COPD), have resulted in increased neutrophilic granulocytes that are not associated with any detectable infection [106]. The neutrophil recruitment by IL-17 is mediated in part by CXC chemokine release [20] or by induction of endogenous tachykinins that act on natural killer (NK)-1 receptors to mediate neutrophil recruitment [18]. In addition to neutrophil recruitment, IL-17 can also stimulate neutrophil activity in the airways, because it stimulates release of neutrophil-activating cytokines IL-6 and IL-8 from bronchial epithelium and fibroblasts [4]. The IL-17-induced release of IL-6 and IL-8 is potentiated by IL-1β in bronchial epithelial cells [51, 107], which in turn can be regulated by IL-17, because increased IL-1β is present in obstructive airway diseases [108].

IL-17 in other diseases of chronic inflammation

Overproduction of IL-17 has been associated with several chronic disease conditions, suggesting a role in these diseases. Several studies point to the association among IL-17, transplant rejection [14, 109–111], systemic sclerosis [112], psoriasis [27, 28, 113], and promotion of tumor growth [114–116].

Blocking the effects of IL-17 using IL-17R:Fc inhibits proliferative responses of T cells to allo-antigens and also significantly prolongs major histocompatibility complex (MHC)-mismatched, nonvascularized and vascularized cardiac allograft survival in animal models [109, 110]. Systemic multiple sclerosis (SSc) is a connective tissue disease of unknown etiology characterized by fibrosis of the skin, lung, and gastrointestinal tract and by microvascular abnormalities of the skin and vis-

ceral organs [117]. Increased IL-17 expression is seen in $CD4^+$ T cells in the lymphocytes from peripheral blood and fibrotic lesions of the skin and the lung of affected patients [112]. Similarly, a presence of IL-17 is seen in $CD4^+$ and $CD8^+$ T-cell clones derived from biopsies from lesional psoriatic skin but not in nonlesional control biopsies [27, 113]. Last but not least, expression of IL-17 is seen in >50% of ovarian [114], endometrial [114], and cervical cancers [115]. Furthermore, in selected cervical cancer cell lines, IL-17 exhibited angiogenic effects, as tumors from IL-17-transducted cell lines resulted in increased tumor size [115], possibly because of IL-17-mediated, increased expression of IL-6 and macrophage recruitment.

CONCLUSION

The IL-17 family is unique among the known cytokine families in that all of the members of this family were first identified by sequence similarity. IL-17 itself was identified as a potentially interesting molecule based on similarity to the viral open reading frame HSVS13, and other recently identified family members have been expanded upon this recognized similarity. Thus, our knowledge of the IL-17 family, at present, is largely of proteins in search of biological function. Nonetheless, what has been learned to date of the functions of IL-17 and the new family members suggests that these molecules are capable of eliciting profound biological responses and are therefore likely to play important roles in the fine-tuning of our immune response. The association of several members of this family with inflammation and the induction of other cytokines that impact the inflammatory response suggest that there may be therapeutic use in the blocking or regulation of the function of these proteins.

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