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IL-17 family member cytokines: Regulation and function in innate immunity

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ABSTRACT

Recently, the IL-17 family member cytokines have become prominent subjects of investigation. IL-17 (IL-17A) is the best-described member of this family where its production has been mainly attributed to a specialized T helper subset of the adaptive immune response termed Th17. However, recent research on this and other Th17 cytokines has revealed new sources and functions of IL-17 family members in the innate immune response. This review will highlight recent advances in the field of IL-17 family member cytokines and will predominately focus on the innate regulation and function of IL-17, IL-17F, and IL-25.
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1. Introduction

The IL-17 family of cytokines consists of six family members of varying homology and function: IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F. In general, these cytokines range from 20 to 30 kDa and incorporate four conserved C-terminal cysteine residues [1,2]. The cytokines IL-17 and IL-17F share the strongest homology, which is likely the reason why these mediators are thought to use similar signaling mechanisms in exerting their pro-inflammatory functions [1,3,4]. Little is known about the regulation and function of IL-17B and IL-17C; however, there is some evidence that these cytokines are also regulators of the inflammatory response as well [5–7]. IL-25 has the least homology with IL-17A, which may translate to its unique abilities in regulating allergy and T helper (Th) 2 responses [8–10]. A summary of the known sources and functions of the IL-17 family of cytokines is presented in Table 1.

The cytokines IL-17 and IL-17F have been associated with a distinct lineage of CD4+ T helper lymphocytes (Th) known as Th17 cells [11,12]. However, recent reports have strongly suggested that IL-17 and IL-17F expression is not strictly limited to Th17 cells or for that matter T cells at all. Additionally, the sources of IL-25 include both innate immune cells as well as cells from non-hematopoietic origins. Thus, this review will highlight recent developments in IL-17A, IL-17F, and IL-25 biology, with a special emphasis on the innate sources and functions of these cytokines.

2. IL-17 and IL-17F

IL-17 has been extensively studied since its discovery in human peripheral blood [13,14]. The identification of IL-17 led to the unearthing of the specialized Th17 subset that was found to produce the cytokines IL-17 as well IL-17F [15–17]. Upon recognition of cognate ligands, naïve CD4+ helper T (Th) cells differentiate into various effector lineages that can be characterized by the induction of specialized transcription factors and their subsequent patterns of cytokine expression. Naïve Th cells, however, do not simply autonomously decide their fate; environmental signals present during the initial activation events instead determine their effector properties [18,19]. These environmental factors, produced by innate cells following host insult, are crucial for Th17 lineage commitment and maintenance and include transforming growth factor beta (TGFβ), IL-6, IL-1β, and IL-23 [17,20]. However, the hallmark of inflammation is the rapid production of pro-inflammatory factors that are vital in the recruitment and activation of infiltrating leukocytes with the overall goal of combating host insult [21]. Therefore, due to the known importance of IL-17 and IL-17F in the promotion of inflammation, there are likely many other sources of these cytokines, including the innate arm of immunity, which would provide a rapid means for IL-17 effector function.

2.1. The pro-inflammatory function of IL-17A and IL-17F

IL-17F was also discovered through homologous IL-17 sequence comparison in humans following the identification of IL-17 [4,22]. Both IL-17 and IL-17F readily form homodimers, however, there is evidence that suggests that an IL-17/IL-17F heterodimer forms as well, where IL-17, IL-17F, or IL-17/IL-17F bind to ubiquitously

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Table 1
The IL-17 family member cytokines.

Cytokine	Receptor	Source	Known functions	Role in disease	References
IL-17A (IL-17)	IL-17RA, IL-17RC	CD4+ and CD8+ T cells, γδ T cells, NKT cells, other innate cells	Induce pro-inflammatory cytokines and chemokines in various target cells which promote inflammation and neutrophil recruitment	Pro-inflammatory functions in host defense against extracellular bacteria, fungi, and possibly some viral infections and cancers. Promotes inflammation associated with autoimmunity	[11,15,17,59, 146–148]
IL-17B	IL-17RB	Pancreas, gut, cartilage, neurons, embryonic limb buds	Stimulates TNFα and IL-1β from monocytes; stimulates chondrocyte proliferation	Associated with arthritis; bone fracture healing	[5,7,149–151]
IL-17C	?	Prostate, kidney, psoriatic skin, pneumonia-infected lung	Stimulates TNFα and IL-1β in THP-1 cells	Expression correlates with arthritis and psoriasis; upregulated following pneumonia infection	[5–7,26,152]
IL-17D	?	Nervous system, muscle, heart, adipose	Stimulates IL-6, IL-8, and GM-CSF from endothelial cells	Reduced in psoriasis	[152,153]
IL-17E (IL-25)	IL-17RB, IL-17RA	Epithelial ells, myeloid cells, eosinophil, basophil, mast cells	Induces Th2 cytokines in NBNT, monocytes and NKT cells; promotes Th2 differentiation, enhances Th9 differentiation	Promotion of type 2 helper responses in vivo, promotes allergic lung disease, important in host defense against parasites; possible roles in autoimmune inflammatory disorders	[8,9,114,118, 120,121,130]
IL-17F	IL-17RA, IL-17RC	CD4+ and CD8+ T cells, γδ T cells, epithelial cells and other innate cells	Induces pro-inflammatory mediator production in hematopoietic and non-hematopoietic cells (less potent than IL-17A), involved in neutrophil recruitment, induces IP-10 from bronchial epithelial cells	Similar pro-inflammatory functions to IL-17; not as important as IL-17A in EAE; inhibitory in asthma and colitis; potent in psoriasis	[1,11,17,30, 50,154,155]

expressed receptors, IL-17RA, IL-17RC, or IL-17RA/IL-17RC, respectively [1,23–26]. The cytokines IL-17 and IL-17F employ the adaptors TRAF6 and Act1 in their signaling transduction pathways as well [27,28]. Both IL-17 and IL-17F readily activate innate and tissue resident cells, such as fibroblasts and epithelial cells, to induce the production of pro-inflammatory cytokines and chemokines (reviewed in [29]). Although somewhat redundant in function, research has shown that in some cases IL-17F is less potent compared to IL-17 in activating target cells to produce pro-inflammatory products [30]. Moreover, other pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), have been shown to cooperate with IL-17 to synergistically enhance the inflammatory capacity of innate cells [31,32]. Overall, one of the major outcomes attributed to considerable IL-17 and IL-17F production is the recruitment and subsequent activation of neutrophils during inflammation [3].

In vivo, IL-17 and IL-17F perform a wide variety of immunoregulatory roles during infection. For example, IL-17 production is readily induced following infection with the extracellular bacterium, *Klebsiella pneumoniae* [33–35]. In humans, *Pseudomonas aeruginosa* infection stimulates IL-17 and IL-17F production [36]. Blocking IL-17 during fungal infection, such as that observed in a model of *Pneumocystis carinii*, leads to exacerbated disease [37]. Taken together, these examples along with many other studies (extensively reviewed in [29]) demonstrate the importance of IL-17 and IL-17F in combating microbial infections, through the activation of innate cells as well as the recruitment of inflammatory leukocytes.

Besides infection, one of the most prominent roles associated with IL-17 and IL-17F production is in the regulation of autoimmunity, where dysregulation of Th17 and other IL-17-producing cells may lead to severe disease. During multiple sclerosis (MS), Th17 cells and their associated cytokines have been shown to be critical for lesion development and central nervous system (CNS) inflammation [15,38,39]. In contrast, the mouse model of human MS, experimental autoimmune encephalomyelitis (EAE) still develops, albeit partially, in mice lacking IL-17 expression (reviewed in [29]). This evidence suggests that although IL-17 is important during EAE pathogenesis, it is not the sole pro-inflammatory mediator contributing to CNS inflammation. Moreover, in models of rheumatoid arthritis, both IL-17 and IL-23 have been implicated in joint destruction [40–42]. Blocking IL-17 following arthritis induction results in a protective effect [43]. Furthermore, IL-17 deficiency results in a similar protection in other autoimmune inflammatory disease models, including colitis [44], and IL-17 and IL-23-producing cells have known roles in promoting psoriasis [45–48].

2.2. Differential regulation and function of IL-17A and IL-17F

Research into the differential regulation requirements for IL-17 and IL-17F to date has been minimal. However, there is one such report that suggests that inducible T cell kinase (Itk) expression, an important mediator for T cell receptor (TCR) signaling, is required for IL-17 induction [49]. Ikt-deficient T cells had impaired ability to produce IL-17 but not IL-17F, even though Ikt levels did not influence RORγ activity. Further analysis revealed that the promoter for IL-17 contained an NFATc1 binding site but the IL-17F promoter did not, providing mechanistic insight into this differential regulation. Thus, IL-17 and IL-17F are not always necessarily induced in the same manner, where further examination is needed to determine what other factors can regulate IL-17 or IL-17F-specific responses.

Although IL-17 and IL-17F are generally accepted to have redundant functions in promoting inflammation, there are a few prominent examples of differential functions of these highly related cytokines. In a seminal paper by our group, we examined many different aspects of IL-17 and IL-17F function [30]. For example, IL-17F, like IL-17, was able to induce inflammatory molecules from MEF cells in vitro, however IL-17F was not nearly as effective when MEF cells were stimulated at similar concentrations of IL-17 and IL-17F. In vivo, IL-17 was shown to be critical in the early priming phase of EAE, possibly through the regulation of IFNγ-producing cells, whereas IL-17F was almost dispensable. In an allergic airway inflammation model, IL-17F-deficient animals, but not IL-17−/−, exhibited substantially decreased CXCL5 expression, which corresponded to reduced neutrophila. Conversely, in a mouse model of asthma IL-17-deficent animals

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