IL-17 cytokines in immunity and inflammation

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Interleukin 17 (IL-17) and its closest relative, IL-17F, have recently drawn much attention in the field of immunology. IL-17 and IL-17F are expressed by a distinct type of T cells, T helper 17 cells and certain other lymphocytes. These cytokines play key regulatory roles in host defense and inflammatory diseases. In this review, we summarize the recent findings in IL-17 biology and the progress towards understanding the regulatory mechanisms of IL-17 expression and signaling mechanisms. This knowledge will benefit the development of novel immune modulators that enhance immunity to various infections and reduce inflammatory damage in infected patients.

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INTRODUCTION

There are six members in the interleukin 17 (IL-17) cytokine family, including IL-17A (commonly referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F. Among all the members, the biological function and regulation of IL-17A and IL-17F are best understood. These two cytokines share the strongest sequence homology. The genes encoding IL-17A and IL-17F are close to each other on the same chromosome in both mouse and human, underscoring their shared patterns of expression.¹ Functionally, both IL-17A and IL-17F mediate pro-inflammatory responses, with certain differences depending on the type and site of inflammation.²⁻³ IL-25 has the least sequence similarity with IL-17A, only 16% compared with 50% in the case of IL-17F. Correspondingly, IL-25 plays distinct roles in immunity, mainly regulating the T helper (Th) 2 response against helminthic parasites and allergic inflammation.⁴⁻⁵ IL-17B, IL-17C and IL-17D have been shown to induce the production of pro-inflammatory cytokines, but their biological function is largely unknown.⁶⁻¹⁰ Recent studies by three different groups highlighted the function of IL-17C in mucosal immunity and autoimmune responses.¹¹⁻¹³

IL-17 family cytokines mediate their biological functions via surface receptors on target cells. IL-17RA was the first identified IL-17 receptor, and four other IL-17R family members, IL-17RB, IL-17RC, IL-17RD and IL-17RE, were subsequently identified, largely based on their sequence similarity with IL-17RA. Functional receptors for IL-17 family cytokines often exist in the form of heterodimers, with IL-17RA as a common subunit. For example, the receptor complex consisting of IL-17RA and IL-17RC recognizes IL-17A and IL-17F, whereas IL-17RA pairs with IL-17RB, followed by binding to IL-25.¹⁴⁻¹⁵ Recently, IL-17RE was identified as a receptor for IL-17C in complex with IL-17RA.¹¹⁻¹³ In this article, we summarize recent developments in our understanding of the function, signaling and regulation of IL-17A and IL-17F cytokines.

CELLULAR SOURCES OF IL-17A AND IL-17F

Specialized T cells, called Th17 cells, are the major source of IL-17A and IL-17F in many types of adaptive immunity. Recent studies in the field also identified other contributors to IL-17A and IL-17F production, mainly in the innate arm of the immune system. IL-17 derived from innate and adaptive sources may fight against pathogen invasion at different phases and locations of infection, which may add further complexity and a safeguard to the defensive immune response.

Th17 cells

IL-17A was initially reported to be mainly expressed by activated cluster of differentiation 4⁺ (CD4⁺) T cells.¹⁶ Naive CD4⁺ T cells can differentiate into the Th1 or Th2 lineage upon stimulation, depending on the exogenous cytokine environment. IL-12 and IL-4 drive the development of Th1 and Th2 lineage cells, respectively.¹⁷ As separate lineages, Th1 and Th2 cells express unique transcription factors, secrete a distinct set of cytokines and mediate specific immune responses. Earlier studies did not classify IL-17A-producing CD4⁺ T cells into either Th1 or Th2 subsets.¹⁸⁻²⁰ The discovery that inducible T-cell costimulator and IL-23 selectively regulate IL-17A-producing CD4⁺ T cells suggests that these cells are a separate helper cell subset.²¹⁻²³ Two reports conclusively demonstrated that antigen-specific IL-17A⁺ CD4⁺ T cells could be efficiently generated, independent of Th1 or Th2 cell development.²⁴⁻²⁵ In agreement with this idea, the differentiation of IL-17A-producing CD4⁺ T cells requires a novel set of transcription factors that do not overlap with those factors required for Th1 or Th2 cells, including signal transducer and activator of transcription 3 (Stat3), retinoic acid receptor-related orphan receptor γ (RORγ), retinoic acid receptor-related orphan receptor α, nuclear factor kappa-light-chain-enhancer of activated B (NF-kB) cells, inhibitor zeta (IκBζ) and basic leucine zipper transcription factor (Batf), reinforcing IL-17A- and IL-17F-producing Th17 cells as a new T-cell lineage.²⁶ The upregulation and function of these factors require signals from the cytokines transforming growth factor (TGF)-β and IL-6.²⁷

IL-17A-producing Th17 cells are barely detectable in unmanipulated mice according to Hirota and colleagues,²⁸ who used an IL-17A reporter system. The researchers generated mice with Cre under the control of the IL-17A promoter. These mice were then crossed with reporter mice expressing enhanced yellow fluorescence protein (eYFP)
following Cre upregulation. Any cells that expressed IL-17A would be marked as eYFP-positive. When the reporter mice were challenged with myelin oligodendrocyte peptide to induce experimental autoimmune encephalomyelitis (EAE), Th17 cells were gradually induced and represented the major IL-17A-expressing cell population infiltrating the spinal cords of the diseased mice. The coexistence of eYFP IL-17A CD4⁺ cells together with eYFP IL-17A CD4⁻ cells suggested the plasticity of Th17 cells under autoimmun-inflammatory conditions. In contrast, Th17 cells generated during acute inflammation against Candida albicans maintained their signature cytokine expression, most of which were eYFP IL-17A⁺.

Although Th17 cells are blamed for IL-17-driven autoimmune diseases, not all Th17 cells are pathogenic. Recent studies by Kuchroo's group identified a subpopulation of Th17 cells that is highly pathogenic and can induce EAE. Generation of the pathogenic Th17 cells requires IL-23 stimulation following IL-6 and TGF-β1 stimulation, which induces production of TGF-β3 in Th17 cells. TGF-β3 together with IL-6 drives the development of Th17 cells with a distinct gene expression profile compared with their non-pathogenic counterparts, which are induced by TGF-β1 and IL-6. Consistent with the molecular signature, pathogenic Th17 cells have a higher expression and activity of the signal transducers and activators of transcription 3 and 5, whereas Smad2 and Smad3 are more active in non-pathogenic Th17 cells. The above data suggest the existence of functionally diverse Th17 subpopulations. Further investigation to understand the differential regulatory mechanisms of these cells will be of great therapeutic importance for the manipulation of Th17 cells under specific clinical situations.

γδT cells

In addition to Th17 cells, there are several types of innate immune cells that also produce IL-17A and IL-17F, among which γδT cells are the best understood. γδT cells are a special population of T cells that comprises 1%–5% of the total lymphocytes in both human and mouse. These cells are localized to mucosal tissues, such as the intestine, skin and lung, which constantly interact with the outside environment and can respond via their expression of Toll-like receptors. γδT cells can rapidly react to antigen and initiate an innate-like immune response by producing immunoregulatory mediators as the first line of defence. This phenomenon is especially true for the IL-17-producing subset of γδT cells. Many studies have shown that γδT cells and the IL-17 that these cells produce are important in early defense against bacterial infection. Early reports suggested the functional involvement of IL-17-producing γδT cells during Listeria monocytogenes and Mycobacterium infection.

A more recent publication described the dominant role of IL-17-producing γδT cells in controlling cutaneous Staphylococcus aureus infection at the innate stage. There is an early wave of IL-17A and IL-17F production observed in infected control mice, which peaks at 8 h and disappears by 24 h post-inoculation. However, this phenomenon is not present in γδT cell-deficient mice. A parallel analysis also showed that γδT cells are the exclusive source of IL-17A and IL-17F in skin lesions. Mice deficient in γδ but not γβT cells are highly susceptible to S. aureus compared with control mice and have increased bacterial load, substantially larger skin lesions and impared neutrophil recruitment. This defect in γδT cell-deficient mice closely resembles that of IL-17R-mutant mice and can be rescued by exogenous IL-17A. In a different case of C. albicans infection, IL-17-producing γδT cells worked together in the acute phase, with progressive involvement by Th17 cells, to clear the fungi invading the body.

Other IL-17-producing cells

In addition to γδT cells, another innate subtype of T cells that expresses IL-17 during intestinal bacterial infection has recently been identified. The authors named this special T-cell subtype innate Th17 (iTh17) cells. iTh17 cells are γδβT cells residing in the lamina propria of the intestine. These cells promptly respond to the enteric bacteria Citrobacter rodentium and Salmonella typhimurium at the early stage of infection and are the major producers of IL-17 in the cecum. The development of iTh17 cells requires IL-6 and nucleotide-binding oligomerization domain-containing protein 1/nucleotide-binding oligomerization domain-containing protein 2 signaling. Despite this interesting finding, the development, regulation and function of iTh17 cells require further investigation.

Lastly, IL-17 can also be produced by several other innate immune cell types, such as lymphoid tissue inducer cells, natural killer and natural killer T cells, macrophages and Paneth cells (reviewed in references 39 and 40). The functional importance of the IL-17 produced by these cell types during inflammation is not very well characterized.

IL-17A AND IL-17F IN HOST DEFENSE AND INFLAMMATORY DISEASES

Function of IL-17A and IL-17F in defensive immunity

IL-17A and IL-17F play protective roles in host defense against certain pathogens at epithelial and mucosal barriers. These cytokines are important for the clearance of the extracellular bacteria S. aureus, C. rodentium and Klebsiella pneumoniae, which infect the skin, colon and lungs, respectively. IL-17A and IL-17F have largely redundant function in defense against S. aureus because animals become more sensitive to the bacterium only when both cytokines are defective. However, the two cytokines are both required in the case of C. rodentium. At an early stage of infection (day 7), IL-17A and IL-17F are equally important in controlling the bacterial burden, whereas at later stages (days 14 and 21), IL-17F is more critical, and IL-17A becomes less important, despite still being functional. IL-17A also contributes to pro-inflammatory cytokine and chemokine production upon K. pneumoniae challenge, as Il17a⁻/⁻ mice display a significantly decreased level of these inflammatory mediators. It has also been reported that IL-17A-producing cells are detected upon infection with intracellular bacteria such as Mycobacterium tuberculosis, L. monocytogenes and S. typhimurium. A defect in IL-17A or IL-17RA results in increased bacterial dissemination, correlating with reduced inflammatory mediators and neutrophil recruitment.

In addition to its role in bacterial immunity, IL-17A is involved in controlling fungal infection. In one study, a blockade of IL-17A by neutralizing antibodies during Pneumocystis carinii infection significantly increased the pathogen burden and exacerbated the disease. IL17a⁻/⁻ mice also show increased susceptibility to systemic C. albicans infection, with a much lower survival rate compared with wild-type controls. Human patients with hyper-IgE syndrome, who have defective IL-17A/F production due to a genetic mutation in the STAT3 gene, suffer from high susceptibility to S. aureus, Streptococcus pneumoniae and C. albicans infection, further indicating the protective roles of IL-17A and IL-17F in immune responses against these pathogens. IL-17A and IL-17F mediate their immunological function by inducing pro-inflammatory cytokine, anti-pathogenic peptide and chemokine secretion by responder cells. The release of these pro-inflammatory molecules triggers the recruitment of innate immune cells to the site of infection and elimination of the pathogen.
Involvement of IL-17A and IL-17F in chronic inflammation and autoimmunity

Although crucial in protecting the host from invasion by many types of pathogens, dysregulated IL-17A and IL-17F production can result in excessive pro-inflammatory cytokine expression and chronic inflammation, which lead to tissue damage and autoimmunity. IL-17 family cytokines have been linked to many autoimmune diseases, including multiple sclerosis (MS), rheumatoid arthritis (RA), inflammatory bowel disease and psoriasis. MS, for a long time, was considered as a Th1-dependent disease, until studies revealed the key role of Th17 cells and IL-17 family cytokines in the development of MS using EAE, a mouse model resembling human MS.\textsuperscript{21,25} Th17 cells and associated cytokines are the major force that drives the related central nervous system inflammation and lesion formation.\textsuperscript{21,25}

IL-17A is readily detected in the synovial fluids and synovium of RA patients.\textsuperscript{46} Several studies using mouse models of RA have demonstrated a key role for IL-17A in the progression of disease.\textsuperscript{22,47–50} A blockade of IL-17 after disease onset effectively prevents bone and cartilage erosion and reduces the severity of clinical symptoms.\textsuperscript{49} The broad involvement of IL-17A in many autoimmune diseases makes this cytokine an ideal drug target. Indeed, humanized IL-17A antibodies have been developed for the treatment of RA, psoriasis and uveitis, with favorable outcomes.\textsuperscript{51,52}

Distinct roles of IL-17A and IL-17F

IL-17A and IL-17F, which have identical receptors, may easily be assumed to function redundantly in promoting inflammation. However, these two highly related cytokine genes also play non-overlapping, and even opposite, roles in certain cases.\textsuperscript{2,3} In the EAE model, only Il17a\textsuperscript{−/−} mice show a significantly reduced disease score, indicating the requirement for IL-17A but not IL-17F in the initiation of EAE. In addition, IL-17A promotes inflammation in an asthma model, with a reduction of eosinophil infiltration into the airway in Il17a\textsuperscript{−/−} mice. In contrast, Il17f\textsuperscript{−/−} animals exhibit higher Th2 cytokine and eosinophil infiltration,\textsuperscript{3} suggesting a suppressive function for IL-17F in asthma. Furthermore, IL-17A is protective, whereas IL-17F is pathogenic, in dextran sulfate sodium-induced acute colitis.

MECHANISMS OF IL-17A AND IL-17F SIGNALING

Responder cells of IL-17A and IL-17F

IL-17A mainly mediates its immune regulatory function by promoting the generation of pro-inflammatory cytokines and chemokines, which leads to the attraction of neutrophils and macrophages to the inflammation site. The receptor for IL-17A is widely expressed among non-haematopoietic cells, such as fibroblasts and epithelial cells, and among innate immune cells, such as macrophages and neutrophils. The treatment of fibroblasts with IL-17A results in the upregulation of several cytokines, including chemokine (C–X–C motif) ligand 1 (CXCL1), chemokine (C–C motif) ligand 2 (CCL2), CCL7, CCL20 and matrix metalloproteinase 3 and 13.\textsuperscript{2,25} Similar results were obtained using a lung epithelial cell line.\textsuperscript{25} Due to strong sequence homology with IL-17A, IL-17F can induce the production of pro-inflammatory cytokines (IL-6, granulocyte colony-stimulating factor and granulocyte-macrophage colony-stimulating factor) and chemokines (CXCL1, CXCL2 and CXCL5) and promote granulopoiesis and neutrophil recruitment, albeit less potently than IL-17A.\textsuperscript{2,53,54}

IL-17A, IL-17F and the IL-17A/F heterodimer mediate their function through a heterodimeric receptor complex of IL-17A and IL-17RC.\textsuperscript{15} A lack of either IL-17RA or IL-17RC completely abolishes the inflammatory function of both cytokines. However, IL-17RA and IL-17RC are not equal in binding affinity for the two cytokines, which may affect the cytokine activity, thereby contributing to the functional differences of IL-17A and IL-17F.\textsuperscript{55–57} In humans, IL-17A is selectively inhibited by soluble IL-17RA, whereas soluble IL-17RC inhibits IL-17F, and the soluble heterodimeric IL-17RA/IL-17RC protein suppresses IL-17A/IL-17F function.\textsuperscript{55} The expression patterns of IL-17RA and IL-17RC are also different. In contrast to the ubiquitously expressed IL-17RA, IL-17RC is mainly detected in tissue-resident and non-hematopoietic cells.\textsuperscript{59} The partially overlapping expression patterns of IL-17RA and IL-17RC provide a further explanation for the redundant yet distinct functions of IL-17A and IL-17F.

Signal transduction of IL-17A and IL-17F

Signaling downstream of IL-17R mediates NF-κB and mitogen-activated protein kinase (MAPK) activation, leading to the production of pro-inflammatory cytokines and chemokines and subsequent myeloid cell recruitment to the inflamed tissue.\textsuperscript{58,59} Although the signaling events induced by IL-17A/F are not fully understood, several key signaling molecules have been successfully identified.

**NF-κB activator 1 (Act1).** Act1 was previously reported to associate with TRAF6 and to mediate NF-κB and activator protein 1 activation.\textsuperscript{60} Act1 shares sequence homology with the cytoplasmic domain of the IL-17R family and is reported to directly interact with the cytoplasmic domain of IL-17RA.\textsuperscript{62} Therefore, it is reasonable to hypothesize that Act1 may function as an adaptor and recruit TRAF6 to IL-17RA. Act1-deficient cells fail to activate NF-κB and MAPKs upon IL-17A stimulation and thus cannot produce pro-inflammatory molecules, such as IL-6 and CXCL1.\textsuperscript{62,64} Consistent with the in vitro data, Act-1-deficient mice show much reduced inflammatory disease in vivo in both autoimmune encephalomyelitis and dextran sulfate sodium-induced colitis.\textsuperscript{65} TRAF6 is dispensable for IL-17A-induced colitis.\textsuperscript{66} TRAF6 is also dispensable for IL-17A-induced extracellular signal-regulated kinase and p38 activation, which promotes the stabilization of certain chemokine mRNA, suggesting the presence of an Act1-mediated but TRAF6-independent pathway downstream of IL-17R.\textsuperscript{66} Because IL-17F shares its receptor with IL-17A, Act1 also plays an indispensable role in IL-17F signaling.\textsuperscript{3}

**IkB kinase 1 (IKKi).** As an E3 ubiquitin ligase, Act1 mediates the K63 ubiquitination and activation of TRAF6. However, how Act1 is activated and regulated is unknown. Work performed by the Li's\textsuperscript{67} group provided new insights into the answer to this question. The authors identified IKKi as a binding partner of Act1 and confirmed the association in primary mouse embryonic fibroblasts. Experiments using
airway epithelial cells from IKKi-deficient mice demonstrated the unique role of IKKi in IL-17A-induced, Act1-dependent MAPK activation, but IKKi was dispensable for TRAF6-dependent NF-κB activation. Cells lacking IKKi are defective in pro-inflammatory molecule induction and chemokine mRNA stabilization. Indeed, IKKi-deficient mice display decreased lung inflammation with reduced amounts of CXCL1 expression and neutrophil infiltration when challenged with IL-17A intranasally. IKKi associates with Act1 and phosphorylates Act1 on Ser311 upon IL-17A stimulation. This phosphorylation is functionally important because mutation at this site abolishes Act1-dependent MAPK activation and chemokine mRNA stabilization but leaves the NF-κB pathway intact. These findings established the unexpected role of IKKi as an Act1 kinase specifically upstream of the Act1–MAPK signalling cascade but not the Act1–TRAF6–NF-κB axis. IKKi and the related TANK-binding kinase 1 are best known as key signal transducers in innate immune signaling pathways that activate interferon regulatory factors upon viral infection.

**Ubiquitin-specific processing protease 25 (USP25).** IL-17 is of great importance for the immune response to certain pathogens. Unbalanced IL-17A production or dysregulated IL-17R signaling in responder cells can lead to excessive inflammation and autoimmune symptoms. Little is known about the molecular mechanism that controls downstream signaling from the IL-17R complex. The Act1-mediated, K63-linked ubiquitination of TRAF6 is a key signaling event leading to the activation of NF-κB. To understand the regulatory mechanism of this process, Zhong and colleagues coexpressed various deubiquitinating enzymes with an NF-κB luciferase reporter construct and examined the reporter activity upon IL-17A stimulation. The assay revealed that the overexpression of the USP25 significantly and specifically inhibited IL-17A- but not TNF-α-mediated NF-κB activation and the expression of inflammatory mediators. USP25 binds to and deubiquitinates TRAF5 and TRAF6, thereby attenuating NF-κB and MAPK signal transduction downstream of the IL-17R complex. USP25-deficient mice displayed an enhanced IL-17A-mediated inflammatory response when challenged with IL-17A in vivo or when subjected to IL-17A-related airway inflammation or EAE. These findings demonstrate the physiological function of USP25 as a negative regulator of the IL-17R signal transduction pathway.

**CONCLUDING REMARKS**

Recent studies on IL-17A and IL-17F significantly enhance our understanding of protective inflammation during pathogen infection and chronic inflammation associated with autoimmune diseases. Further dissection of the source and regulation of IL-17A and IL-17F expression and these cytokines’ signaling mechanisms may provide ways for us to modulate the immune system in infectious and inflammatory diseases.

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