

# T<sub>H</sub>17 Cytokines: Characteristics, Regulation, and Biological Function

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**Abstract** The recently identified Interleukin 17 (IL-17) cytokine family, which comprises of six members, contributes to immunity in infectious and chronic inflammatory diseases. IL-17 and the most structurally related cytokine, IL-17F, are produced by T<sub>H</sub>17 cells, a novel subset of CD4+ helper T cells. Although IL-17 and IL-17F have similar regulation and functions in vitro, they are involved differently in chronic inflammatory diseases and bacterial infection. The aim of this article is to summarize recent work in understanding the function and regulation of T<sub>H</sub>17 cytokines, focusing mainly on IL-17 and IL-17F. Elucidation of the function and regulation of these cytokines may yield immuno-therapeutic strategies for the prevention and treatment of inflammatory diseases.

## 1 Introduction

Cytokines are key players in the regulation of the development and function of immune cells. Several cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6 are recognized as pro-inflammatory cytokines with functions in promoting inflammation, while others such as IL-27 and IL-10 are involved in inhibiting inflammation. In recent years, extensive attention has been drawn to the recently identified IL-17 cytokine family, especially the founding member IL-17 that becomes an important pro-inflammatory cytokine in auto-immune diseases and in immunity to certain bacterial and fungal infections. The IL-17 cytokine family is comprised of six members, including IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and

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IL-17F. Among the IL-17 family members, IL-17 shares the highest homology to IL-17F, and IL-25 is the least related; they are the most investigated cytokines in this family. We will discuss the structure, function and regulation of IL-17 and IL-17F in this article.

## 2 Structure of IL-17 Family Cytokines

IL-17 was initially cloned by Rouvier et al. by subtractive hybridization of activated T cell-specific library and was originally named CTLA-8 (cytotoxic T lymphocyte associated antigen 8) (Rouvier et al. 1993; Yao et al. 1995a). Murine IL-17 displayed 57% identity in amino acid sequence to the ORF13 gene of T lymphotropic herpes virus, *Herpesvirus saimiri* (Rouvier et al. 1993). Subsequently, the human counterpart of murine IL-17 was cloned based on alignment of nucleotide sequences of HSV13 and mIL-17 (Fossiez et al. 1996; Yao et al. 1995b). The IL-17 gene is located on mouse chromosome 1A and human chromosome 2q31. Sequence homology searches for IL-17-related cytokines led to the identification of five additional family members, IL-17B, IL-17C, IL-17D, IL-25, and IL-17F (Fort et al. 2001; Hymowitz et al. 2001; Lee et al. 2001; Li et al. 2000a, b; Shi et al. 2000; Starnes et al. 2001, 2002). All members of the IL-17 family have a similar protein structure with considerable sequence divergence at the N termini. They share four highly conserved cysteine residues, all of which have been shown to form a cystine knot in the crystal structure of IL-17F (Hymowitz et al. 2001). IL-17 family cytokine is therefore recognized as a member of the cystine knot fold superfamily and dimerizes similarly to members of the NGF subfamily. In both human and mouse, IL-17A and IL-17F are closely related, with approximately 50% sequence identity (Hymowitz et al. 2001; Starnes et al. 2001). Structural features of IL-17 suggest that each of members is likely produced as a homodimer (Fossiez et al. 1996). However, our group and others reported that IL-17A and IL-17F were not only secreted as homodimeric proteins but can also form heterodimers in both human and mouse (Chang and Dong 2007; Liang et al. 2007; Wright et al. 2007). Compared with the IL-17A and IL-17F homodimer, the IL-17A and IL-17F heterodimer has intermediate biological activity (Chang and Dong 2007; Liang et al. 2007; Wright et al. 2007). Gene encoding human IL-17F is located adjacent to IL-17A and transcribed in opposite direction, suggesting that both cytokine genes may have been derived during evolution through gene duplication and thus may share same regulatory elements. Multiple non-coding sequences within the IL-17 and IL-17F locus were found to be conserved across species (Akimzhanov et al. 2007). These elements were associated with acetylated histone 3 in a lineage-specific manner and may serve as potential regulatory regions (Akimzhanov et al. 2007).

IL-25 diverges significantly from IL-17A and F with less than 17% homology to IL-17 (Lee et al. 2001). IL-25 cDNA predicts a secreted protein with 177 amino acids with overall conserved characteristics of the IL-17 family, including N-linked

glycosylation site and conserved cystine residues (Lee et al. 2001). Several lines of evidence so far indicate that IL-25 possesses different activities compared to other IL-17 family cytokines.

### 3 Expression and Regulation of IL-17 and IL-17F

#### 3.1 *T<sub>H</sub>17 Cells as a Novel Effector T<sub>H</sub> Lineage*

IL-17 was originally found to be mainly expressed by an activated CD4<sup>+</sup> T cells, predominantly in memory subset, but not by resting T cells (Yao et al. 1995a). The expression of IL-17 is increased in many chronic inflammatory diseases such as rheumatoid arthritis and multiple sclerosis (Aarvak et al. 1999; Albanesi et al. 2000; Lenarczyk et al. 2000). Naïve T helper cells after activation can differentiate into T<sub>H</sub>1 and T<sub>H</sub>2 lineage depending on exogenous cytokine IL-12 and IL-4, respectively (Mosmann et al. 1986). T<sub>H</sub>1 and T<sub>H</sub>2 cells secrete specific cytokines and function differently. Earlier characterization does not provide clear classification of IL-17 in neither T<sub>H</sub>1 nor T<sub>H</sub>2 subsets (Aarvak et al. 1999; Albanesi et al. 2000; Lenarczyk et al. 2000).

Co-stimulatory molecules are important in determining T helper cell differentiation. Unexpectedly, our initial characterization of mice lacking inducible co-stimulatory molecules (ICOS) showed reduced IL-17 expression in these mice (Dong and Nurieva 2003). The reduction of IL-17 but not IFN- $\gamma$  production in ICOS-deficient mice was found to be associated with their resistance to collagen-induced arthritis (CIA) (Dong and Nurieva 2003). Moreover, IL-23-deficient mice showed reduced IL-17 expression and alleviated experimental auto-immune encephalomyelitis (EAE) symptoms (Cua et al. 2003). Further studies indicated that IL-23 is critical for expanding pathogenic IL-17-producing T cells that are distinct from T<sub>H</sub>1 or T<sub>H</sub>2 (Langrish et al. 2005; Murphy et al. 2003). Later, Park et al. and Harrington et al. provided more conclusive evidence indicating that IL-17 was indeed produced by a distinct cell lineage (Harrington et al. 2005; Park et al. 2005). The T<sub>H</sub>17 lineage is identified to be a third lineage that plays prominent roles in regulating tissue inflammation. Antigen-specific IL-17-producing cells were shown to be efficiently generated in the absence of T<sub>H</sub>1 and T<sub>H</sub>2 cell development (Park et al. 2005). The generation of IL-17-producing T cells did not require a master regulator for T<sub>H</sub>1 or T<sub>H</sub>2, including T-bet, GATA3, STAT1, STAT4, and STAT6 (Harrington et al. 2005; Park et al. 2005). Thus, these studies provide direct evidence that IL-17 producing T cells are a novel T lineage that possess different transcriptional program.

Further studies have demonstrated that several other cell types, including  $\gamma\delta$ -T cells, NKT cells, NK cells, Paneth cells, and neutrophils are capable of producing IL-17 (Li et al. 2010; Lockhart et al. 2006; Michel et al. 2007; Takahashi et al. 2008). It shows that IL-17 can participate in both innate and the adaptive immune response. IL-17 and IL-17F produced by innate immune cells may contribute to early stage immunity following infection but T<sub>H</sub>17 cells are the major cell type producing both cytokines during chronic inflammatory diseases.

## 3.2 The Regulation of $T_H17$ Cells

### 3.2.1 Cytokine Regulation of $T_H17$ Differentiation

Cytokines are important in determining the fate of Th lineage differentiation. IL-12 and IL-4 are critical for driving  $T_H1$  and  $T_H2$  differentiation, respectively (Mosmann et al. 1986). Studies by three independent groups found that a combination of immunoregulatory cytokine, TGF- $\beta$  and pro-inflammatory cytokine, IL-6 potentially induced the differentiation of  $T_H17$  cells from naïve T cells both in vitro and in vivo (Bettelli et al. 2006; Mangan et al. 2006; Veldhoen et al. 2006a). IL-6 was found to be critical for the inhibition of Foxp3 expression induced by TGF- $\beta$ , while promoted the differentiation of IL-17-producing T cells (Bettelli et al. 2006; Mangan et al. 2006; Veldhoen et al. 2006a). Furthermore, mice lacking a functional receptor for TGF- $\beta$  or mice with a deleted TGF- $\beta$  only in T cells had defect in  $T_H17$  generation and were resistant to EAE (Li et al. 2007; Veldhoen et al. 2006b). These data indicate the critical roles of both cytokines in regulating the differentiation of  $T_H17$  lineage. IFN- $\gamma$  and IL-4, produced by  $T_H1$  and  $T_H2$  cells, respectively, auto-amplify the generation of its own lineage; IL-17 could not act as a growth factor of  $T_H17$  cells. We and others identified that  $T_H17$  cells produced an autocrine IL-21 (Korn et al. 2007; Nurieva et al. 2007; Zhou et al. 2007). IL-21 produced from  $T_H17$  cells can amplify its own expression, and function in promoting and sustaining the differentiation of  $T_H17$ . IL-21 was induced by IL-6 through STAT3; both TGF- $\beta$  together with IL-6 or IL-21 suppressed FOXP3 expression and induced the differentiation of IL-17 (Korn et al. 2007; Nurieva et al. 2007; Zhou et al. 2007).

During  $T_H17$  differentiation initiated by TGF- $\beta$  and IL-6, pro-inflammatory cytokines such as TNF- $\alpha$  and IL-1 $\beta$  seem to play important roles in enhancing the production of IL-17 (Veldhoen et al. 2006a). IL-1 was found to be critical for the induction of  $T_H17$  cells in humans (Acosta-Rodriguez et al. 2007). More recently, the role of IL-1 in directly regulating  $T_H17$  cells was reported (Ben-Sasson et al. 2009; Chung et al. 2009). IL-1R1 was upregulated in  $T_H17$  cells and IL-6 appeared to be the most important inducer for IL-1R1 expression (Chung et al. 2009). Further characterization by using mixed bone-marrow (BM) chimeras of CD45.1+ WT and CD45.2+ IL-1R1-KO BM cells indicated that IL-1 signaling in CD4+ T cells is necessary to promote the early  $T_H17$  differentiation and for proper  $T_H17$  cell differentiation in vivo (Chung et al. 2009). Moreover, IL-1 appeared to play important roles in maintaining differentiated  $T_H17$  cells even without TCR stimulation (Chung et al. 2009). Similarly, IL-1R1 expression on CD4+ T cells in humans was also shown to be important for both initiation and maintenance of human  $T_H17$  cells (Lee et al. 2010).

TNF receptors expressed on T cells play distinct roles in co-stimulation. We showed that a tumor necrosis factor receptor family member, death receptor 3 (DR3; also known as TNFRSF25), is selectively elevated in  $T_H17$  cells (Pappu et al. 2008). Indeed, TL1A, its cognate receptor was required for the optimal differentiation as well as effector function of  $T_H17$  cells (Pappu et al. 2008).

Besides the mentioned positive regulators, some cytokines can inhibit the differentiation of T<sub>H</sub>17 lineages. IL-27 was identified to have an antagonizing effect against IL-17 expression (Stumhofer et al. 2006). The inhibitory activity of IL-27 was dependent on the intracellular signaling molecule STAT1 (Stumhofer et al. 2006). Mice deficient in IL-27 showed increased susceptibility to EAE and generated more IL-17 producing T cells (Stumhofer et al. 2006). Another well-described negative regulator for T<sub>H</sub>17 differentiation is IL-2 (Laurence et al. 2007). IL-2 inhibits the production of IL-17 through STAT5 and its deficiency resulted in enhanced IL-17 production (Laurence et al. 2007). In addition, IFN- $\beta$  was recently found to suppress T<sub>H</sub>17 generation through STAT1 activation (Guo et al. 2008). Thus, therapeutics intervention by applying these inhibitory cytokines is important in treating chronic inflammatory diseases mediated by T<sub>H</sub>17 cells.

### 3.2.2 Transcriptional Regulation of T<sub>H</sub>17 Differentiation

Members of the signal transducer and activator of transcription (STAT) gene family, which are important in cytokine receptor signaling pathway, play crucial roles in determining T<sub>H</sub> lineage commitment. While STAT1 appears to inhibit T<sub>H</sub>17 differentiation, STAT4 and 6, which are critical for T<sub>H</sub>1 and T<sub>H</sub>2 differentiation, are not involved (Harrington et al. 2005; Park et al. 2005). It has been shown that Socs3 (suppressor of cytokine signaling 3), a negative regulator of STAT3 was found to negatively regulate the expression of IL-17 and its deficiency enhanced IL-17 expression (Chen et al. 2006; Pappu et al. 2008; Wong et al. 2006). We subsequently found that STAT3 is indeed a critical factor for T<sub>H</sub>17 differentiation (Yang et al. 2007). Overexpression of a hyperactive form of STAT3 promoted the expression of IL-17 and IL-17F, whereas STAT3-deficient T cells showed greatly reduced expression of both cytokines (Yang et al. 2007). Following the identification of cytokines mediating T<sub>H</sub>17 differentiation, STAT3 was found to be activated by IL-6, IL-21, and IL-23 in regulating IL-17 expression (Nurieva et al. 2007; Yang et al. 2007).

In a DNA microarray analysis, retinoic-acid-related orphan receptor ROR $\gamma$ t was identified as a first T<sub>H</sub>17-lineage specific transcription factor (Ivanov et al. 2006). ROR $\gamma$ t is selectively expressed in T<sub>H</sub>17 cells generated in vitro and in a subset of lamina propria IL-17<sup>+</sup> T cells (Ivanov et al. 2006). ROR $\gamma$ t<sup>-/-</sup> mice had impaired T<sub>H</sub>17 differentiation and reduced EAE (Ivanov et al. 2006). In these mice, however, T<sub>H</sub>17 cytokine expression was not completely abolished. A subsequent study showed us that another member of the retinoid nuclear receptor family, ROR $\alpha$  plays a role in T<sub>H</sub>17 differentiation and commitment (Yang et al. 2008c). T<sub>H</sub>17 cells selectively expressed not only ROR $\gamma$ t, but also ROR $\alpha$  (Pappu et al. 2008). Co-expression of ROR $\alpha$  and ROR $\gamma$ t synergistically regulates T<sub>H</sub>17 differentiation (Yang et al. 2008a, b, c). Furthermore, mice with T cells deficient in both transcription factors exhibited completely abolished T<sub>H</sub>17 generation and were completely protected from EAE (Yang et al. 2008c). Thus, the expression of both ROR $\alpha$  and ROR $\gamma$ t are essential for the determination of T<sub>H</sub>17 cells. Treatment with TGF- $\beta$  and IL-6 or IL-21 induced the expression of ROR $\gamma$ t and ROR $\alpha$ , while treatment solely with TGF- $\beta$  drove the

generation of FOXP3<sup>+</sup> T cells, suggesting a reciprocal relationship between T<sub>H</sub>17 and regulatory T cell development. By utilizing an RFP-IL-17F reporter mouse that we generated together with GFP-FOXP3 reporter mouse, we found the presence of a RFP<sup>+</sup>GFP<sup>+</sup> transient phase upon T cell activation in vitro and in vivo (Yang et al. 2008b). Induction of Foxp3 by TGF- $\beta$  inhibited T<sub>H</sub>17 differentiation by antagonizing the function of ROR $\gamma$ t and ROR $\alpha$ , possibly by blocking their binding of a co-activator (Yang et al. 2008b). In contrast, IL-6 overcame this suppressive effect of Foxp3 and, together with IL-1, induced genetic reprogramming in Foxp3<sup>+</sup> regulatory T cells (Yang et al. 2008b). Consistent with our data, Zhou et al. demonstrated that ROR $\gamma$ t and Foxp3 are co-expressed in TGF- $\beta$ -treated naive CD4<sup>+</sup>T cells and in a subset of T cells in the lamina propria of the mouse (Zhou et al. 2008). Adding increased concentration of TGF- $\beta$  can augment Foxp3 expression and reduced IL-23R expression (Zhou et al. 2008). Thus, cytokine-regulated balance of ROR $\gamma$ t determines the decision of regulatory T cell and T<sub>H</sub>17 cell development.

Besides the transcription factors mentioned above, several other factors are shown to regulate T<sub>H</sub>17 cells. The aryl hydrocarbon receptor (AHR), a ligand-dependent transcription factor known for mediating the toxicity of dioxin, was selectively expressed in T<sub>H</sub>17 cells (Quintana et al. 2008; Veldhoen et al. 2008). AHR ligation induced the production of the T<sub>H</sub>17 cytokine IL-22 and caused accelerated onset of EAE (Veldhoen et al. 2008). Furthermore, the interferon regulatory factor-4 (IRF4) was identified as an important transcription factor necessary for T<sub>H</sub>17 lineage differentiation (Brustle et al. 2007). The deficiency of IRF4 was associated with the decreased ROR $\gamma$ t expression and increased FoxP3 expression that may negatively impact T<sub>H</sub>17 differentiation (Brustle et al. 2007). In addition, it has been shown that Runt-related transcription factor 1 (Runx1) also regulates the expression of IL-17 through a complex that can affect ROR $\gamma$ t inhibition by FOXP3 (Zhang et al. 2008). More recently, a basic leucine zipper transcription factor, ATF-like (BATF) belonging to the AP-1 protein family, was identified to be essential for the T<sub>H</sub>17 differentiation (Schraml et al. 2009). BATF was highly expressed in T<sub>H</sub>1, T<sub>H</sub>2, and T<sub>H</sub>17 cells compared to naive T cells. BATF-deficient T cells displayed normal T<sub>H</sub>1 and T<sub>H</sub>2 differentiation but had a defect in T<sub>H</sub>17 generation (Schraml et al. 2009). In contrast, overexpression of BATF in T cells showed increased IL-17 production in both CD4<sup>+</sup> and CD8<sup>+</sup> T cells. Further in vivo analysis indicated that mice deficient in BATF were completely resistant to EAE (Schraml et al. 2009). Although the production of IL-21 and the expression of ROR $\gamma$ t was found to be reduced in BATF-deficient mice, addition of IL-21 and overexpression of ROR $\gamma$ t failed to fully restore T<sub>H</sub>17 development in BATF<sup>-/-</sup> T cells, suggesting that BATF may possess distinct interaction with T<sub>H</sub>17 specific factors in regulating IL-17 production. Several genes were identified to regulate T<sub>H</sub>17 development in a BATF-dependent manner, including ROR $\gamma$ t, ROR $\alpha$ , the aryl hydrocarbon receptor, IL-22, and IL-17A (Schraml et al. 2009). BATF binds conserved intergenic elements in the IL-17A/F locus and to the IL-17, IL-21, and IL-22 promoters (Schraml et al. 2009). Analysis of the composition of the BATF-containing complex using supershift analysis indicated that BATF preferentially heterodimerized with JunB during T<sub>H</sub>17 differentiation (Schraml et al. 2009).

Numerous transcription factors have been identified to regulate the expression of IL-17 and IL-17F, but the mechanisms by which these factors function to establish T<sub>H</sub>17 gene expression programs remain unclear. In our study, IL-17 and IL-17F gene promoters undergo lineage-specific chromatin remodeling, providing insights into the regulation of T<sub>H</sub>17 differentiation at epigenetic level (Akimzhanov et al. 2007). Several non-coding conserved sites are identified in the IL-17-IL-17F locus and can undergo coordinated chromatin modifications such as histone acetylation and methylation in differentiating T<sub>H</sub>17 cells (Akimzhanov et al. 2007). Further analysis of epigenetic changes in the IL-17 and IL-17F locus and the DNA binding specificity will provide better understanding in the regulation of T<sub>H</sub>17 lineage differentiation.

### ***3.3 Biological Function of IL-17 and IL-17F and Its Receptors***

IL-17 and IL-17F are associated with several immune regulatory functions. Most notably, they are involved in the inflammatory process during infection and in auto-immune diseases. Non-immune cells such as fibroblasts and epithelial cells or hematopoietic cells such as macrophages are known targets for IL-17, which upregulate the expression of many pro-inflammatory cytokines and chemokines in response to IL-17 treatment. As a result, IL-17 mediates the recruitment of neutrophils and macrophages into non-lymphoid tissues. In a microarray analysis on IL-17-treated fibroblasts, we found upregulation of several cytokines including CXCL1 (Gro1), CCL2, CCL7, CCL20, and matrix metalloproteinases (MMP) 3 and 13 (Park et al. 2005). Treatment with IL-17 in lung epithelial cell line resulted in similar up-regulation of above genes (Park et al. 2005). IL-17 blockade led to the reduced severity of EAE associated with decreased expression of several chemokines, while overexpression of IL-17 in the lung epithelial cells caused airway inflammation with the induction of several chemokine genes (Park et al. 2005).

Besides infection, auto-immune diseases, and asthma, IL-17 also participates in tumor immunity. IL-17 was found to be over-expressed in several types of tumors (Kato et al. 2001; Numasaki et al. 2003; Sfanos et al. 2008). Whether this cytokine functions in promoting or inhibiting tumor progression remains controversial. In lymphopenic environment, T<sub>H</sub>17 cells were found to mediate protection against skin melanoma after conversion to T<sub>H</sub>1 cells (Muranski et al. 2008). By using IL-17-deficient mice, we found that IL-17 is involved in tumor protection (Martin-Orozco et al. 2009). IL-17-deficient mice were more susceptible to B16-F10 melanoma development in the lung that was associated with reduction of CCL20 and CCL2 expression in lungs (Martin-Orozco et al. 2009). Transferring T<sub>H</sub>17 cells into tumor-bearing mice elicited the greatest infiltration of granulocytes, macrophages, and DC, whereas T<sub>H</sub>1 cell treatment showed slightly increased DC but reduced macrophage numbers. T<sub>H</sub>17 cells but not T<sub>H</sub>1 cells can induce lung cells to produce CCL2 and CCL20, resulting in DC and activated T cell recruitment, associated with more effective anti-tumor responses (Martin-Orozco et al. 2009). In addition, T<sub>H</sub>17 cells can promote



CD8<sup>+</sup> T cell proliferation, sustain their cytokine expression, and activate the endogenous anti-tumor CD8<sup>+</sup> cells at the tumor sites (Martin-Orozco et al. 2009).

Because IL-17 and IL-17F share the strongest homology, there is a considerable overlap in their biological functions. IL-17F also can induce the production of anti-microbial peptides (defensins), cytokines (IL-6, G-CSF, GM-CSF), and chemokines (CXCL1, CXCL2, CXCL5), as well as enhance granulopoiesis and neutrophil recruitment (Kawaguchi et al. 2004; Kolls and Linden 2004), although its activity seem to be less potent than that of IL-17. Overexpression of IL-17F in the lungs resulted in increased pro-inflammatory cytokine and chemokine expression, and airway inflammation predominantly infiltrated with neutrophil and macrophage (Oda et al. 2005; Yang et al. 2008a). Similar to IL-17, IL-17F had a synergistic effect with TNF- $\alpha$  on enhancing the expression of pro-inflammatory cytokines (Fossiez et al. 1996). As previously mentioned, IL-17 and IL-17F can be secreted as homodimeric protein (IL-17A/A, IL-17F/F) and heterodimeric protein (IL-17A/F). Fully differentiated T<sub>H</sub>17 cells secreted IL-17A/F and homodimeric IL-17A and IL-17F (Chang and Dong 2007). However, the potency of heterodimeric cytokine on IL-6 expression was shown to be intermediate (Chang and Dong 2007).

Although IL-17 and IL-17F share the strongest homology and overlap functions, several reports suggest their distinct function in certain cases (Ishigame et al. 2009; Yang et al. 2008a). We generated IL-17- and IL-17F-deficient mice to compare their biological functions. They seem to have distinct functions in the development of inflammatory responses in EAE and asthma. IL-17, but not IL-17F, was required for the initiation of EAE, and while IL-17 contributed positively, IL-17F had a negative effect in allergic asthma (Chang et al. 2008). IL-17F<sup>-/-</sup> mice showed greater T<sub>H</sub>2 cytokine expression and enhanced eosinophil function (Yang et al. 2008a). In a mouse model of dextran sulfurate sodium (DSS)-induced acute colitis, IL-17 was shown to play protective role while IL-17F exacerbated inflammation (Yang et al. 2008a). Studies by Ishigame et al. using a similar approach suggest that both cytokines play distinct functions in immune responses against bacterial infection (Ishigame et al. 2009). They showed that IL-17 played a major role in T cell-dependent auto-immune, but IL-17F only marginally contributed to these responses. Both IL-17A and IL-17F are critically important to protect the mice against mucocutaneous *S. aureus* infections, even though cellular source of both cytokines seem to be different (Ishigame et al. 2009). IL-17A was produced mainly in T cells, whereas IL-17F was produced in T cells, innate immune cells, and epithelial cells (Ishigame et al. 2009).

The reason why IL-17 and IL-17F possess different functions may be explained by their receptors. Both cytokines function through the receptors that belong to the IL-17 receptor family. The IL-17R family consists of 5 members, IL-17 receptor A (IL-17RA or IL-17R), IL-17 receptor B (IL-17RB or IL-17BR), IL-17 receptor C (IL-17RC), IL-17 receptor D (IL-17RD), and IL-17 receptor E (IL-17RE) (Haudenschild et al. 2002; Moseley et al. 2003; Shi et al. 2000; Tian et al. 2000; Yao et al. 1995a, 1997). IL-17, IL-17F and IL-17A/F heterodimer mediates their function through a heterodimeric complex of IL-17RA and IL-17RC (Kuestner et al. 2007; Toy et al. 2006; Wright et al. 2008). Lack of either IL-17RA or IL-17RC



completely abrogates the inflammatory function of IL-17 and IL-17F. However, the binding affinities of IL-17A and IL-17F for these receptors are different (Kuestner et al. 2007; Toy et al. 2006; Wright et al. 2008) and different activities may affect cytokine activities. In humans, IL-17 activity can be inhibited by IL-17RA, while IL-17F is inhibited by IL-17RC, and a combination of soluble IL-17RA/IL-17RC receptors is required for inhibition of the IL-17F/IL-17A activity (Wright et al. 2008). In our study, several isoforms of these receptors were detected, suggesting a large number of splice variants in transcripts encoding receptors. Additionally, the distribution of IL-17RA and IL-17RC in tissues seems to be different. IL-17RA mRNA was highly expressed in lymphoid tissues, while IL-17RC mRNA was expressed at high amounts in non-hematopoietic tissues as the colon, small intestine, and lung (Ishigame et al. 2009). T cells expressed IL-17RA but not IL-17RC (Ishigame et al. 2009). Thus, the differential expression and their alternative splices may contribute to different roles of IL-17 and IL-17F.

Early studies showed that IL-17 and IL-17F induced inflammatory cytokines in mouse embryonic fibroblasts (MEFs) through the activation of NF- $\kappa$ B and MAP kinase pathways (Awane et al. 1999; Shalom-Barak et al. 1998). Further studies showed that a tumor necrosis factor receptor-associated factor (TRAF6), an E3 ubiquitin ligase, was required for this activity (Schwandner et al. 2000). Because no TRAF6 binding domain was found in IL-17 receptor, the existence of other adaptors was proposed. All members of the IL-17 receptor family contain a conserved sequence segment that shares similar residues to the conserved motifs of Toll-like receptors (TIR)/IL-1R domain. This domain was named as STIR SEFIR (similar expression to fibroblast growth factor genes and IL-17Rs) and TIR (Novatchkova et al. 2003). The SEFIR domain is also observed in one cytoplasmic protein named Act1 (known as CIKS) with a connection to I $\kappa$ B kinase and stress-activated kinase (Leonardi et al. 2000; Li et al. 2000a, b). Further characterization by our group showed that Act1 physically associates with IL-17RA through the SEFIR domain (Chang et al. 2006). The deficiency of Act1 resulted in the defect of IL-17-mediated function in fibroblast (Chang et al. 2006). IL-17 does not utilize MyD88 and IRAK4 for cytokine induction (Chang et al. 2006). A follow-up study confirmed that Act1 is essential in IL-17-dependent signaling in auto-immune and inflammatory disease (Qian et al. 2007). Because both IL-17RA and IL-17RC are required for IL-17 function, it remains elusive whether Act1 and TRAF6 were recruited through IL-17RA or IL-17RC or both in mediating IL-17 and IL-17F function.

## 4 Conclusion

In summary, extensive analyses of the IL-17 cytokine family have revealed crucial roles of individual IL-17 family members in immune regulation of infectious and inflammatory diseases. A novel identified T<sub>H</sub>17 effector subset of T cells that expresses both IL-17 and IL-17F appears as a central regulator for auto-immune diseases and host defenses to bacterial and fungal infection. These two cytokines

may function as homodimeric or heterodimeric secreted proteins, which exert similar activities. Recent characterizations of mice lacking either IL-17 or IL-17F reveal distinct function of individual cytokines. They utilize similar downstream signals but cell-specific receptors and isoforms of their receptors may contribute to distinct function. Further studies on the regulation and function of this important cytokine family may provide better understanding on the roles of the IL-17 family in immune-mediated diseases and such knowledge may lead to the development of immunotherapeutic strategies for treatment of several inflammatory diseases.

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