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Regulation and pro-inflammatory function of interleukin-17 family cytokines

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Summary

The interleukin-17 (IL-17) family consists of six cytokines in mammals. Among them, IL-17 and IL-17F are expressed by a novel subset of CD4⁺ helper T cells and play critical function in inflammation and autoimmunity. IL-17E, also called IL-25, has been associated with allergic responses. Here I summarize recent work by my laboratory as well as other investigators in understanding the regulation and function of these three cytokines. From these studies, IL-17 family cytokines may serve as novel targets for pharmaceutical intervention of immune and inflammatory diseases.

Keywords

IL-17; IL-17F; IL-25; inflammation; helper T cells; autoimmune diseases

Introduction

Inflammation is a process in which immune cells are mobilized to infectious or wound tissues. Chronic inflammation plays an important role in the pathogenesis of autoimmune and allergic diseases and cancers. Interleukin-17 (IL-17) is the founding member of a new cytokine family that has recently gained prominence due to its involvement in autoimmune diseases in both human and mouse. The IL-17 family consists of six members including IL-17 (also called IL-17A), IL-17B, IL-17C, IL-17D, IL-17E (also called IL-25), and IL-17F (1–4). Among these cytokines, IL-17, IL-25, and IL-17F have been investigated most thoroughly. IL-17 and IL-17F share the greatest similarity with 50% identity at the amino acid level, whereas IL-25 is most divergent in the family (5). In this review, I discuss about the regulation and biological actions of these cytokines.

IL-17 and IL-17F: expression, receptor signaling, and biological functions

IL-17

IL-17 has long been implicated in several autoimmune diseases (6–8). It was reported initially that cytotoxic T-lymphocyte antigen-8 (CTLA-8) and Herpesvirus saimiri virus gene 13 product, named as IL-17 and vIL-17, respectively, induced nuclear factor- κ B (NF- κ B) activity and IL-6 production in human fibroblasts (9,10). Later, it was shown that the proliferation of hematopoietic progenitor cells and maturation of neutrophils was sustained in the presence of fibroblasts treated with human IL-17, which stimulated the production of IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor (GM-CSF) (11). These results suggest a broad role for IL-17 as a potent inducer of other inflammatory mediators. Moreover, IL-17 also synergizes with tumor necrosis factor- α (TNF- α) in inflammatory regulation (12).

We have performed extensive analysis of IL-17-induced genes by a microarray analysis and found that several chemokines such as CXCL1 (Gro1), CXCL10, CCL2, CCL7, CCL20, and matrix metalloproteinase-3 (MMP3), and MMP13 were upregulated upon IL-17 treatment (13). Similarly, using transgenic mice overexpressing IL-17 in the lung, we found that these transgenic mice exhibited spontaneous airway inflammation and mucus hyperplasia, associated with increased expression of several chemokines and MMPs (13). Conversely, blocking IL-17 reduced disease severity and the expression of several chemokines in experimental autoimmune encephalomyelitis (EAE). IL-17 is thus an important mediator of tissue inflammation.

IL-17F

Since IL-17 and IL-17F share strongest homology, there is considerable overlap in the biological functions of these cytokines (14–16). IL-17F also stimulates the production of IP-10 [interferon- γ (IFN- γ)-inducible protein 10] in human bronchial epithelial cells, which was enhanced by IFN- γ , IL-1 β , and TNF- α (17). We, as well as others, have shown that IL-17 and IL-17F form a biologically active heterodimer with intermediate potency when compared with homodimers in inducing inflammatory genes (18,19).

We have recently analyzed the biological function of IL-17F *in vivo* (20). Transgenic overexpression of IL-17F in lung epithelial cells resulted in airway inflammation and mucus hyperplasia, similar to what was reported for IL-17-overexpressing transgenic mice (13), suggesting that these two cytokines may have similar function. Our comparison of IL-17- and IL-17F-deficient mice revealed that IL-17 is more important in the initiation of EAE disease (20). However, allergen-induced acute neutrophilia was found to be dependent on IL-17F but not IL-17. In an airway hyperresponsiveness model, IL-17 was required for proper T-helper 2 cell (Th2) cytokine expression, while lack of IL-17F resulted in greater Th2 response. Furthermore, in the dextran sulfate sodium (DSS)-induced colitis model, we found IL-17-deficient mice had worsened epithelium damage in the colon tissues while IL-17F-deficient mice exhibited greatly improved pathology. These unexpected results pointed out the differential effects and perhaps antagonism of IL-17 and IL-17F *in vivo*.

Signaling mechanisms of IL-17 and IL-17F

Signaling of IL-17 family cytokines is mediated by the IL-17 receptor family, currently consisting of five individual members (21). The IL-17 receptor (IL-17R) (also called IL-17RA) is a type 1 transmembrane protein (10). IL-17R is ubiquitously expressed in tissues (21). It was shown that IL-17R forms multimeric complexes even in the absence of ligand binding, and the receptors may undergo considerable conformational changes upon ligation by IL-17 (22). Furthermore, IL-17R has been shown to associate with IL-17RC and acts as primary signal transducer of IL-17 and IL-17F (23,24). Recently, we showed that IL-17F, just like IL-17, depends on IL-17R for its signaling *in vitro* and *in vivo* (20).

How IL-17R signals has not been very clear. It was first shown that IL-6 induction by IL-17 in mouse embryonic fibroblasts (MEFs) is dependent on TNF receptor-associated factor 6 (TRAF6) (25). It was reported that TRAF6 is recruited to IL-17R upon IL-17F binding and ubiquitinates the receptor, whereas IL-17-mediated ubiquitination does not require TRAF6 (26). These results indicate that despite using same receptor, mechanisms of signal transduction by IL-17 and IL-17F may use different intracellular signaling pathways. Both IL-17R and IL-17RC possess cytoplasmic domains containing conserved SEFIR (similar expression to fibroblast growth factor, IL-17 receptor, and Toll-IL1R family) motifs which mediate homophilic interactions (27). However, our recent analysis indicated that myeloid differentiation factor 88 (MyD88) or IL-1R-associated kinase 4 (IRAK4), essential components of Toll-like receptor (TLR) and IL-1R signaling, are not required for IL-17-

induced IL-6 expression (28). Furthermore, the intracellular domain of IL-17R contains a novel Toll-IL-1R domain (TIR)-like loop, which is required for the activation of NF- κ B and mitogen-activated protein kinases (MAPKs) and for upregulation of CCAAT/enhancer binding protein β (C/EBP β) and C/EBP δ (29).

Studies in our laboratory demonstrated that the SEFIR domain in IL-17R directly interacts with an NF- κ B activator protein 1 (Act1) (28). Act1 physically associates with the intracellular domain of IL-17R through homotypic interactions, and knocking down Act1 expression abrogated IL-17-induced inflammatory gene expression and NF- κ B activation (28). It was further confirmed by another group using Act1-deficient mice that IL-17-mediated inflammatory responses were indeed severely impaired in these mice (30). Act1 but not IL-17R contains a TRAF6-binding motif, raising the possibility of Act1-dependent recruitment of TRAF6 into the IL-17R signalosome. Recently, we also found that IL-17F signaling was impaired in the absence of Act1 and TRAF6 (20).

Regulation of IL-17 and IL-17F expression

Th17 as a new effector Th subset

Expression of IL-17 was first detected in memory CD4⁺ T cells from peripheral blood in humans (9,31). In addition to CD4⁺ T cells, IL-17 is expressed by CD8⁺ T cells, natural killer (NK) T cells, $\gamma\delta$ T cells, and neutrophils under certain conditions (32–34). Recent studies from various groups have focused on the murine Th cells that produce IL-17 and have indicated that IL-17 is predominantly expressed by a Th cell subset that is distinct from Th1 and Th2 cells (35).

For many years, Th1 and Th2 cells represented two mutually exclusive differentiation programs undertaken by naive CD4⁺ T cells during immune responses (36). IFN- γ is the signature cytokine produced by Th1 cells and is responsible for immunity against intracellular pathogens. IL-4, IL-5, and IL-13 are secreted by Th2 cells, which provide immunity against extracellular pathogens and play an important role in allergic responses.

Th1 cells have been implicated historically in autoimmune diseases such as murine EAE and collagen-induced arthritis (CIA) models. However, mice deficient in IFN- γ or signal transducer and activator of transcription 1 (STAT1), an important intracellular signaling component of IFN γ signaling pathway, were more susceptible to EAE and CIA (37–40), suggesting that an additional Th cell type other than Th1 cells plays a more important pathogenic role. Our previous study revealed that mice deficient in inducible costimulator (ICOS) were protected against CIA, which was associated with normal Th1 response but greatly reduced production of IL-17 (41), suggesting that IL-17, regulated differently from IFN γ , may be more important in CIA. Moreover, it was demonstrated that IL-23 rather than IL-12 is critical for the development of CIA and EAE (42–45). In a series of experiments, IL-23 was found important for IL-17 production and could function to expand antigen-primed IL-17-expressing T cells. Thus, the IL-17-producing Th cells appear to have distinct regulatory roles from Th1 cells.

The subsequent studies by my laboratory as well as the Weaver group on the differentiation of IL-17-producing cells *in vitro* and *in vivo* indicated that the generation of these cells was independent of cytokines and transcription factors involved in Th1 or Th2 differentiation. These results thus provided direct evidence for IL-17-expressing cells as a novel lineage of Th cells, which has since been referred as Th17 cells (13,46).

Cytokine regulation of Th17 cell differentiation

Although IL-23 is an important factor in regulation of Th17 cells *in vivo*, it does not appear to have a direct effect on naïve T cells to induce Th17 differentiation. It has been shown by several groups that transforming growth factor- β (TGF β) and IL-6 together potently instruct T cells to differentiate into Th17 cells (47–49). Both TGF β and IL-6 were found necessary in Th17 differentiation *in vivo* (47,50,51).

Thus, TGF β not only regulates the generation of forkhead box protein 3 (Foxp3)⁺ Treg cells but also together with IL-6 initiates Th17 differentiation. To understand the decision of Treg versus Th17 cell lineage specification, we recently developed and utilized a Th17 reporter mouse in which a red fluorescent protein (RFP) sequence was placed into the IL-17F gene (52). RFP sensitively and faithfully marked Th17 cells *in vitro* and *in vivo*. Using IL-17F-RFP together with a Foxp3 reporter, we found that the development of Th17 and Foxp3⁺ Treg cells were strongly associated in immune responses. This result is consistent with a recent report showing that Foxp3 sometimes was co-expressed with retinoid-related orphan receptor γ t (ROR γ t), a Th17-specific transcription factor (53). In keeping with data from this report (53), we found that Foxp3, induced by TGF β , inhibited Th17 differentiation by antagonizing ROR γ t and ROR α function, possibly by blocking their binding of a co-activator (52). In contrast, IL-6 could overcome this suppressive effect of Foxp3 and together with IL-1, induce genetic re-programming in Foxp3⁺ Treg cells. Treg and Th17 cells thus are reciprocally regulated *in vitro* and *in vivo* and also exhibit molecular antagonism and, unexpectedly, plasticity.

Th1 and Th2 differentiation is mediated not only by cytokines produced by the innate immune system, but also IFN γ and IL-4, respectively, as autocrine factors. Studies by us and others (54–56) have recently shown that IL-21 is an important cytokine produced by Th17 cells and functions in promoting Th17 differentiation. IL-6 induces the production of IL-21 via STAT3. In the presence of TGF β , IL-21 promotes Th17 differentiation and inhibits generation of Foxp3⁺ regulatory T cells. IL-21- and IL-21R-deficient mice exhibit deficiency of Th17 cells *in vivo*.

After differentiation, Th17 cells are regulated by selective cytokine stimuli. For instance, Th17 cells highly express IL-23R and can be expanded by this cytokine (44). Recently, we found that Th17 cells additionally express a member of TNF receptor family, DR3, and can be expanded by its ligand, TL1A, even in the absence of T-cell receptor stimulation (57). *In vivo*, TL1A regulates Th17 cell differentiation and the autoimmune function of these cells.

Transcriptional regulation of Th17 cells

During Th1 and Th2 differentiation, innate cytokines signal through particular STAT family members to establish lineage-specific transcriptional programs. Initial characterization of Th17 cells have shown that their differentiation is not dependent on STAT1, STAT4, or STAT6, and they do not express any conventional transcriptional factors such as T-bet, HLX, and GATA3, which are involved in Th1 and Th2 differentiation (13,46). Deficiency in suppressor of cytokine signaling 3 (SOCS3), a negative regulator STAT3 phosphorylation, was reported to result in great enhancement in IL-17 expression, and SOCS3 conditional knockout mice develop systemic autoimmune disease, similar to the phenotype observed in IL-17 and IL-23p19 transgenic mice (58). Subsequently, we provided direct evidence that STAT3 deficiency resulted in impaired differentiation of Th17 cells (51). Furthermore, a hyperactive form of STAT3 can induce differentiation of Th17 cells and enhance the expression of Th17-associated genes. More importantly, STAT3 is involved in the expression of ROR γ t, a critical transcription factor required for Th17 differentiation. STAT3-mediated signals also repress Th1-associated transcription factor T-bet and FoxP3

that are required for Treg cell differentiation, and these results are further confirmed by another independent study (59).

ROR γ t was identified as the first transcription factor specifically expressed in Th17 cells (60). T cells from *lamina propria* that expresses ROR γ t are IL-17⁺, and these IL-17-expressing cells are greatly reduced in ROR γ t-deficient mice (60). These results suggest that ROR γ t is required for the generation of Th17 cells in *lamina propria*. Consistent with this notion, retroviral overexpression of ROR γ t in the activated CD4⁺ T cells drove the differentiation of naïve CD4⁺ T cells into Th17 lineage of cells and induced the expression of IL-17A and IL-17F (60). Furthermore, ROR γ t deficiency greatly reduced the differentiation of Th17 cells even in the presence of TGF β and IL-6, establishing ROR γ t as a master transcriptional regulator of Th17 differentiation.

Compared with STAT3-deficient cells, residual Th17 cells are still present in the absence of ROR γ t, and mice lacking T-cell expression of ROR γ t can still develop EAE, which indicates that other factors are also involved. We reported recently that ROR α is also expressed by Th17 cells, induced by TGF β and IL-6 in a STAT3-dependent manner (61). Similar to ROR γ t, ROR α overexpression promoted Th17 cell differentiation when Th1 and Th2 cell differentiation was inhibited, which could occur independently of ROR γ . However, ROR α deficiency in T cells only resulted in a selective decrease in IL-17 and IL-23R expression and had a very moderate inhibitory effect on EAE (61).

Compared with ROR γ t, ROR α seems to be a minor player in Th17 cell differentiation. To understand the collective function of these two factors, we showed that overexpression of ROR α and ROR γ t had a synergistic effect in promoting Th17 cell differentiation, especially when T cells were cultured under polarized differentiation conditions for Th1 cells or Treg cells (61). In addition, compound mutations in both factors completely inhibited Th17-cell differentiation *in vitro* and *in vivo* and entirely suppressed the development of EAE (61). Thus, ROR α and ROR γ t have similar and redundant functions. As there is no evidence for their cross-regulation, their combined concentrations might be important in determining Th17 cell differentiation, especially in the presence of negative regulators.

In addition to ROR family members, the IFN regulatory factor-4 (IRF4) was identified as an important transcription factor necessary for Th17 lineage differentiation. IRF4 deficiency resulted in decreased ROR γ t expression and increased Foxp3 expression that may negatively impact Th17 differentiation (62). Moreover, the aryl hydrocarbon receptor (AHR), a type I nuclear receptor that interacts with Hsp90 upon ligand binding, has been recently reported by two groups. Both regulatory T cells and Th17 cells express AHR (63,64), although the expression of this receptor is significantly higher in Th17 cells compared to regulatory T cells or any other Th subset (63). Interestingly, both regulatory T cell and Th17 cell differentiation is not impaired in AHR-deficient mice. However, Th17 cells from AHR-deficient mice do not express IL-22 (63).

How mechanistically the above transcription factors function to regulate Th17 gene expression programs remain unknown. We found that IL-17 and IL-17F gene promoters undergo lineage-specific chromatin remodeling, providing an insight into the regulation of Th17 differentiation at the epigenetic level (65). Moreover, several non-coding conserved sites were identified in the IL-17-IL-17F locus and shown to undergo coordinated chromatin modifications such as histone acetylation in differentiating Th17 cells. One of them, named as CNS2, was found to respond to ROR α or ROR γ t regulation, which could be inhibited by Foxp3 (52,61).

IL-25 (IL-17E): regulation of allergic inflammation

IL-25 was originally identified on the basis of sequence homology search of other IL-17 family members (66,67). However, unlike other IL-17 family member, IL-25 had unique function in promoting type 2 immune responses. The biological activity of this cytokine was initially described *in vivo* by exogenous administration of IL-25 protein (66,68) or using IL-25 transgenic mice (69,70). These mice showed upregulation of Th2 cytokine transcripts, including IL-4, IL-5, and IL-13 in several tissues, eosinophilia, mucus hyperplasia and epithelial cells hyperplasia, implicating this particular IL-17 family cytokine as a new player in regulating type 2 immunity.

The source of IL-25 and its cellular targets

IL-25 was described initially as a Th2 derived cytokine since its transcript expression was found in highly polarized Th2 cells *in vitro* (66). However, we found that IL-25 can also be produced by lung epithelial cells and alveolar macrophages upon allergen stimulation (71), suggesting that IL-25 may be involved in the innate responses to allergens.

The receptor for IL-25, IL-17BR also called EVI27 or IL17 receptor homolog 1 (IL-17Rh1) is also used by IL-17B, but with a higher affinity of binding for IL-25 (67,72,73). Unlike the broad expression of IL-25, its receptor has been shown to be more restricted in expression. Previously, a population of non-T/non-B cells (NBNT), characterized as lineage (Lin)⁻, major histocompatibility complex (MHC) class II^{high} and CD11c^{dull}, was found to respond to IL-25 and produce Th2 cytokines (66). This population was further described to be important for the initiation of *N. brasiliensis* worm clearance *in vivo* (74). More recently, we found that IL-17BR was also expressed in naive T cells, which was downregulated during Th1 and Th17 differentiation but sustained in Th2 cells (71). Our collaborators also found greatly increased IL-17BR expression in human memory Th2 cells (75).

The role of IL-25 in allergic asthma disease

Allergic asthma disease is characterized by mucus hyperplasia, airway hyperresponsiveness, airway infiltration of Th2 cells, and eosinophils (76). Systemic overexpression or administration of IL-25 or instillation of IL-25 into the lung consistently resulted in eosinophilia, an increase in serum IgE and IgG1, upregulation of tissue expression of IL-4, IL-5, and IL-13, and lung pathological changes, including epithelial cell hypertrophy and mucus hypersecretion (66,68–70), implicating that IL-25 might play a role in regulating allergic asthma disease.

Using a novel anti-IL-25 antibody, we found that blockade of IL-25 in an allergen-induced allergic inflammation resulted in decreased antigen-specific Th2 cells and eosinophil infiltration in lung (71). Conversely, transgenic overexpression of IL-25 by lung epithelial cells led to a pro-allergic type 2 phenotype, including mucus hypersecretion, increased infiltration of eosinophils and macrophages. Interestingly, eosinophilia in IL-25 transgenic mice was not found in IL-17 or IL-17F transgenic mice (13,20).

Regulation of Th2 differentiation and expansion by IL-25

We found that IL-25 treatment during CD4⁺ T-cell differentiation enhanced Th2 cytokine production, including IL-4, IL-5, and IL-13 and inhibited IFN- γ production (71). This effect was greatly potentiated in the presence of anti-IFN γ antibody. These data indicate a novel role of IL-25 in regulating Th2 differentiation. IL-25 upregulated the expression of IL-4 gene transcript on day 2 after activation of naive T cells and further enhanced its production by day 3 after activation (71). These data indicate that IL-25 may induce Th2 differentiation by regulating early IL-4 gene expression. Moreover, we observed that IL-25 treatment

increased early IL-4 expression by upregulating the expression of transcription factor nuclear factor of activated T cells c1 (NFATc1) and JunB, which then possibly activate GATA-3 and STAT6 through the IL-4 signaling pathway. IL-25 thus serves as an innate signal induced in response to allergen and parasitic infections to promote Th2 differentiation.

IL-25 not only plays a role during Th2 differentiation but also is involved in functional regulation of effector and memory Th2 cells. IL-25 acts on *in vitro* differentiated effector Th2 cells by further enhancing their Th2 cytokine production (75). Unlike the early Th2 differentiation, it was found that IL-25-mediated regulation of CCR4⁺ memory Th2 cells was independent of IL-4 (75). Moreover, it was found that IL-25 prevented the downregulation of GATA-3, c-maf, and JunB in memory Th2 cells during T-cell receptor triggering (75). Therefore, compared to IL-17 and IL-17F, IL-25 has a unique function in promoting pro-allergic inflammatory responses. Further understanding on the source as well as function of IL-25 will be important.

Conclusions

Studies on IL-17 cytokines, especially on IL-17, IL-17F, and IL-25, have substantially advanced our knowledge of immune responses, especially in revealing novel pathways of T-cell differentiation and regulation. IL-17 family cytokines have come to the center stage of immunology and play essential roles in various types of inflammation. Future work on these cytokines, especially on their regulation and signal transduction, will further benefit our understanding of the immune responses and may help to develop new treatments of immune diseases. In addition, other IL-17 cytokines await exploration. So far, these cytokines have not been shown to be expressed in T cells and perhaps are involved in the innate inflammatory responses. The proteins in IL-17R family are also poorly studied, and understanding of their expression, regulation, and cell type-specific signaling may reveal complexity in orchestration of the inflammation symphony.

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