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Differentiation and function of pro-inflammatory Th17 cells

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Abstract

After activation, CD4+ helper T (Th) cells differentiate into cytokine-secreting effector subsets. A novel subset of CD4+ helper T (Th) cells that produce two related cytokines IL-17 and IL-17F has been recently identified and shown to play critical function in inflammation and autoimmunity. Here I summarize recent work by us as well as other investigators in understanding the transcriptional regulation of Th17 cell differentiation, their developmental relationship with regulatory T cells and the function of IL-17 and IL-17F in vivo.

Keywords

Helper T cells; cytokines; inflammation; autoimmunity

1. Introduction

For many years, Th1 and Th2 helper T cells represent two mutually exclusive differentiation programs undertaken by naïve CD4+ T cells during immune responses [1]. IFN-γ is the signature cytokine produced by Th1 cells and 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. Expression of IL-17 was first detected in memory CD4+ T cells from peripheral blood in humans [2,3]. In addition to CD4+ T cells, IL-17 is expressed by CD8+ T cells, NK T cells, γδ T cells and neutrophils under certain conditions [4-6]. 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 [7].

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 [8], suggesting that IL-17, regulated differently from IFNγ, 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 [9-12]. 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 regulation than Th1 cells. The subsequent studies by us 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 [13,14].

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 TGFβ and IL-6 together potently instruct T cells to differentiate into Th17 cells [15-17]. Both TGFβ and IL-6 were found necessary in Th17 differentiation in vivo [15,18, 19].

Th1 and Th2 differentiation is mediated not only by cytokines produced by the innate immune system, but also IFNγ and IL-4, respectively, as autocrine factors. Studies by us and others have recently shown that IL-21 is an important cytokine produced by Th17 cells and functions in promoting Th17 differentiation [20-22]. IL-6 induces the production of IL-21 via STAT3. In the presence of TGFβ, 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 [11]. Recently, we found that Th17 cells additionally express a member of TNFR family, DR3 and can be expanded by its ligand, TL1A, even in the absence of TcR stimulation [23]. In vivo, TL1A regulates Th17 cell differentiation and the autoimmune function of these cells.

2. Transcriptional regulation of Th17 cell differentiation

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, 4 or 6 and they do not express any conventional transcriptional factors such as T-bet, HLX and GATA3 which were involved in Th1 and Th2 differentiation [13,14]. Deficiency in Socs3 (suppressor of cytokine signaling 3), a negative regulator STAT3 phosphorylation, was reported to resulted 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 [24]. Subsequently, we provided direct evidence that STAT3-deficiency resulted in impaired differentiation of Th17 cells [19]. Furthermore, a hyper-active 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 RORγt, 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 [25].

RORγt was identified as the first transcription factor specifically expressed in Th17 cells [26]. T cells from lamina propria that expresses RORγt are IL-17+ and these IL-17-expressing cells are greatly reduced in RORγt-deficient mice [26]. These results suggest that RORγt is required for the generation of Th17 cells in lamina propria. Consistent with this notion, retroviral over-expression of RORγt 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 [26]. Furthermore, RORγt deficiency greatly reduced the differentiation of Th17 cells even in the presence of TGFβ and IL-6, establishing RORγt as a master transcriptional regulator of Th17 differentiation.

However, compared with STAT3-deficient cells, residual Th17 cells are still present in the absence of RORγt and mice lacking T-cell expression of RORγt can still develop EAE, which indicates that other factors are also involved. Recently, we reported that RORα is also expressed by Th17 cells, induced by TGFβ and IL-6 in a STAT3-dependent manner [27]. Similar to

RORγt, RORα overexpression promoted Th17-cell differentiation when Th1- and Th2-cell differentiation was inhibited, which could occur independently of RORγ. However, RORα 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 [27].

So, compared with RORγt, RORα seems to be a minor player in Th17-cell differentiation. To understand the collective function of these two factors, we showed that overexpression of RORα and RORγt 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 [27]. In addition, compound mutations in both factors completely inhibited Th17-cell differentiation *in vitro* and *in vivo* and entirely suppressed the development of EAE [27]. Thus, RORα and RORγt 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 interferon regulatory factor-4 (IRF4) was identified as an important transcription factor necessary for Th17 lineage differentiation. IRF4 deficiency resulted in decreased RORγt expression and increased Foxp3 expression that may negatively impact Th17 differentiation [28]. 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 [29,30], although the expression of this receptor is significantly higher in Th17 cells compared to Tregs or any other TH subset [29]. Interestingly, both Treg and Th17 differentiation is not impaired in AHR-deficient mice. However, Th17 cells from AHR-deficient mice do not express IL-22 [29].

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 [31]. 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 RORα or RORγt regulation, which could be inhibited by Foxp3 [27,32].

3. Cross-regulation of TH17 and Treg programs

Thus, TGFβ not only regulates the generation of Foxp3+ Treg cells but also together with IL-6 initiates TH17 differentiation. Upon binding to its tetrameric receptor composed of two subunits of TGF-βRI and two subunits of TGF-βRII, TGF-β induces phosphorylation of Smad2/3 molecules. Phosphorylated Smad2/3 can then bind to the Common-Smad (C-Smad), Smad4, and translocate to the nucleus to induce transcription of target genes [33]. Smad-independent signaling pathways have also been described, involving the activation of MAPK signaling pathways [33]. Although TGF-β receptor signaling is required for both TH17 and iTreg generation, Smad4 was partially required for iTreg generation while it was dispensable for generation of TH17 cells [32]. However, the activation of other Smads or MAPKs by TGF-β for development of TH17 lineage has not been established. Moreover, whether MAPK or Smad proteins crosstalk with STAT3 and regulate the lineage-specific transcription factors, RORα and RORγt needs to be determined.

Since generation of Foxp3+ Treg cells and Th17 cells both requires TGFβ signaling, a reciprocal relationship of the Th17 and Treg development has been proposed [15]. To understand the decision of Treg vs 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 [34]. 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 during their differentiation in vitro. When naïve T cells were treated with TGFβ and IL-6, there was a transient stage when some T cells only expressed Foxp3 but not IL-17F while others expressed both. Moreover, following immunization in vivo, a population of Foxp3- and IL-17F-double positive population was also seen. This result is consistent with a recent report showing that Foxp3 sometimes was co-expressed with RORγt, a Th17-specific transcription factor [35,36]. Indeed, cells co-expressing Foxp3 and RORγt in lamina propria were shown to have lower IL-17 production compared to cells expressing RORγt alone [35]. These data support the close relationship of Treg and Th17 developmental programs.

Although TH17 differentiation requires TGFβ signaling, increasing concentrations of TGF-β can augment Foxp3 levels and reduce IL-23R expression, even in the presence of low concentrations of IL-6, shifting the differentiation of TH cells from TH17 towards regulatory T cells [35]. Several groups have discovered an inhibitory function of Foxp3 in TH17 differentiation [32,35,37]. We found that Foxp3 overexpression under TH17 polarizing conditions inhibited IL-17, IL-17F, IL-21 and IL-22 cytokine expression but did not affect RORα or RORγ mRNA levels [32]. Moreover, Foxp3 inhibited RORα and RORγt transcriptional activity independent of the DNA binding or dimerization of Foxp3. Meanwhile, Foxp3 LxxLL sequence in exon 2 was shown to associate with the newly identified TH17-specific transcription factor RORα [37], suggesting a potential role of Foxp3 in suppression of TH17 development through inhibition of both RORα and RORγt. Furthermore, we found that not only the LxxLL sequence, but also the TIP60/HDAC7 domain of Foxp3 is required for its inhibitory effect on RORγt and RORα [32], suggesting that Foxp3 interacts with RORs and recruits histone deacetylases to TH17-specific genes, thus inhibiting the transcription of those genes.

Although TGFβ-induced Foxp3 strongly inhibits TH17 differentiation, IL-6 could overcome this suppressive effect of Foxp3. We found that IL-6 functions to downregulate Foxp3 expression and together with IL-1, to induce IL-17 expression [32]. This regulation exists for both TGFβ-induced Foxp3+ Treg cells as well as thymus-derived naturally occurring Treg cells. STAT3 was required for Foxp3 downregulation and IL-17 expression, whereas RORα and RORγt were only for the IL-17 expression. These data indicate a possible genetic reprogramming 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.

Our recent work on T follicular helper (Tfh) cell development has suggested a reciprocal relationship of Tfh and Th17 cell development. Tfh development is mediated by IL-6-STAT3-IL-21 axis, similar to Th17 cells, while independent of TGFβ signaling or RORα and RORγt transcription factors [38]. The interaction of Treg, Th17 and Tfh programs will likely be further expanded in the future.

4. Function of IL-17 and IL-17F

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. IL-17 has long been implicated in several autoimmune diseases [39-41]. It was initially reported that CTLA-8 and Herpesvirus saimiri virus gene 13 product, named as IL-17 and vIL-17, respectively, induced NF-κB activity and IL-6 production in human fibroblasts [2,42]. 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 metalloproteinases (MMP) 3 and 13 were upregulated upon IL-17 treatment [14]. Similarly, using transgenic mice over-expressing 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 [14]. 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.

Since IL-17 and IL-17F share strongest homology, there is considerable overlap in the biological functions of these cytokines [43-45]. IL-17F also stimulates the production of IP-10 (interferon-gamma-inducible protein 10) in human bronchial epithelial cells, which was enhanced by IFN-γ, IL-1β and TNF-α [46]. 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 [47,48].

Signaling of IL-17 family cytokines is mediated by the IL-17 receptor family currently consisting of five individual members [49]. Receptor for IL-17, IL-17R (also called IL-17RA), is a type 1 transmembrane protein [42]. IL-17R is ubiquitously expressed in tissues [49]. It was showed 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 [50]. Furthermore, IL-17R has been shown to associate with IL-17RC (Interleukin-17 receptor C) and acts as primary signal transducer of IL-17 and IL-17F [51,52]. Recently, we show that IL-17F, just like IL-17, depends on IL-17R for its signaling in vitro and in vivo [34].

How IL-17R signals has not been very clear. It was first shown that IL-6 induction by IL-17 in mouse embryonic fibroblasts (MEF) is dependent on TRAF6 [53]. 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 [54]. Studies in our laboratory demonstrated that the SEFIR domain in IL-17R directly interacts with an NF-κB activator protein, Act1 [55]. 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 NFκB activation [55]. Recently, we also found that IL-17F signaling was also impaired in the absence of Act1 and TRAF6 [34].

We have recently analyzed the biological function of IL-17F in vivo [34]. 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 [14], 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 [34]. 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 Th2 cytokine expression while lack of IL-17F resulted in greater Th2 response. Furthermore, in 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.

5. Conclusions

Th17 cells are a recently identified effector T cell subset. Extensive analysis in the past several years has revealed that cytokine-mediated Th17 differentiation is mediated by STAT3 and two orphan nuclear receptors RORα and RORγt. Th17 and Treg differentiation programs have a reciprocal relationship and exhibit antagonism as well as plasticity. IL-17 and IL-17F secreted by Th17 cells play important, yet sometimes differential, roles in regulation of inflammatory

responses. This knowledge will likely help us to understand the regulation of immune and inflammatory responses and may lead to novel treatments of chronic disorders.

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