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$\gamma\delta$ T cells: an important source of IL-17

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Summary

IL-17 is a cytokine that plays an important role in orchestrating innate immune function. In addition, IL-17 has been shown to exacerbate autoimmune diseases. CD4⁺ $\alpha\beta$ T cells, $\gamma\delta$ T cells, and NK cells all produce IL-17. Th17 cells are a newly defined $\alpha\beta$ ⁺ T cell lineage characterized by IL-17 production. However, $\gamma\delta$ T cells are often the major source of this cytokine. Their response can be very rapid during bacterial infections and has been shown to be protective, but IL-17 producing $\gamma\delta$ T cells have also been found to exacerbate collagen-induced arthritis. Interestingly, some $\gamma\delta$ T cells produce IL-17 in response to IL-23 alone, even in naïve animals, suggesting they are already differentiated and may develop differently than CD4⁺ $\alpha\beta$ Th17 cells.

Introduction

Effector CD4⁺ $\alpha\beta$ T cells can be divided into 3 separate lineages: Th1, Th2, and the more recently identified Th17 lineage. Th1 cells are characterized by production of IL-2 and IFN γ . These cells develop when local antigen presenting cells secrete IL-12, especially in the presence of IFN γ , and are important in promoting a cell-mediated immune response to intracellular pathogens [1,2]. Th2 cells produce IL-4, IL-5, and IL-13 and develop when IL-4 is present. These cells promote the humoral response to extracellular pathogens [3,4]. Th17 cells are characterized by production of IL-17 (or IL-17A) and IL-17F. They also can produce IL-21, IL-22, tumor necrosis factor (TNF α), IL-6, and granulocyte-macrophage colony stimulating factor (GM-CSF), but usually not IFN γ or IL-4 [5–13]. Th17 cells are thought to increase inflammation by recruiting cells, particularly neutrophils, to the peripheral tissues for pathogen clearance. In addition, Th17 cells have been associated with pathology in autoimmune disease.

The IL-17 family

There are six members in the IL-17 family: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25), and IL-17F. Most studies have focused on IL-17A and IL-17F and these 2 family members are the most closely related [14]. Multiple cell types including CD4⁺ $\alpha\beta$ T cells, $\gamma\delta$ T cells, NK cells, and neutrophils have been shown to produce IL-17A and IL-17F. Among CD4⁺ T cells, co-expression of IL-17 A and IL-17 F has been noted, suggesting that these related cytokines may work together to mediate a distinct function. In fact, these two family members have been shown to form a heterodimeric protein that induces airway neutrophil recruitment [15]. IL-17A

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has been found to play a central role in autoimmune inflammation (reviewed in [16]). Similarly, other IL-17 family members may also play a role in autoimmune diseases, such as collagen-induced arthritis (CIA). Recently, IL-17B and IL-17C were found associated with TNF- α production, and adoptive transfer of IL-17B and IL-17C transduced CD4⁺ T cells exacerbated arthritis in mice [17].

Th17 cell differentiation

Many reviews have focused on how Th17 cells differentiate [18–20]. Briefly, TGF β and IL-6 are necessary for the differentiation of naïve CD4⁺ $\alpha\beta$ T cells into Th17 cells [21–23]. When IL-6 is not available, IL-21, in combination with TGF β , can also induce Th17 cells using an IL-6 independent pathway. IL-21 is also highly expressed by Th17 cells, and the IL-21 production creates a positive feedback loop to further amplify Th17 responses in vivo (reviewed in [19]). IL-21 signaling additionally upregulates expression of ROR γ t, a key transcription factor in the differentiation program of Th17 cells [24]. In addition, IL-21 activates expression of IL-23R and this process is also dependent on ROR γ t and STAT3 [8, 25]. Once the IL-23R is expressed in T cells, IL-23 can bind to this receptor and bypass the requirement for IL-6 and TGF β , to induce IL-17 on its own [8]. IL-23, which is produced by activated dendritic cells, is necessary for the maintenance of the Th17 response and induces previously differentiated Th17 cells to expand [21].

IL-17 producing $\gamma\delta$ T cells

The development of IL-17 producing $\gamma\delta$ T cells is less well understood. In ROR γ t deficient animals, $\gamma\delta$ T cells that express IL-17 in the intestinal lamina propria were absent suggesting that $\gamma\delta$ T cells also require ROR γ t for their development [24]. Similarly, in IL-21^{-/-} animals, lamina propria and splenic $\gamma\delta$ T cells showed a ten-fold decrease in IL-17 expressing cells compared to wild type mice, indicating a role for IL-21 in the differentiation of IL-17 producing $\gamma\delta$ T cells as well [26]. In IL-6^{-/-} animals, the mRNA levels of ROR γ t, IL-23R, IL-17, and IL-17F from sorted lamina propria CD4⁺ $\alpha\beta$ T cells were greatly diminished as compared to wild type mice and there was a 10-fold decrease in the percent of IL-17⁺ CD4⁺ $\alpha\beta$ ⁺ lamina propria cells. However, the percent of non-CD4⁺ IL-17⁺ cells, which includes IL-17 producing $\gamma\delta$ T cells, was only decreased 2 fold [24]. This may indicate that when IL-6 is absent, IL-21 in combination with TGF- β is largely sufficient to differentiate non-CD4⁺ cells into IL-17 producing cells.

$\gamma\delta$ T cells can dominate the IL-17 response

While the focus of most studies on IL-17 production has been on CD4⁺ $\alpha\beta$ T cells, $\gamma\delta$ T cells have also been shown to be a potent source of IL-17, and in some cases, more dominant than Th17 $\alpha\beta$ T cells. For example, in a model of Fas-ligand induced inflammation, Umemura, et al. found that injection of a FasL-expressing tumor cell line into the peritoneum of mice induced a marked increase in proinflammatory cytokines, including IL-17. CD4⁻CD8⁻ cells were identified as the major producers of IL-17 in this system. Many of these cells were $\gamma\delta$ TCR⁺, and IL-17 producing $\gamma\delta$ T cells represented a much higher proportion of the total $\gamma\delta$ T cell population than IL-17 producing $\alpha\beta$ T cells did of total $\alpha\beta$ T cells [27]. In *Mycobacterium tuberculosis* (*M. tb.*) infection, T cells isolated from the lung were found to produce IL-17 when stimulated in vitro with *M. tb.*-infected dendritic cells. Again, $\gamma\delta$ T cells and other non-CD4⁺ or non-CD8⁺ cells were found to be the main producers of IL-17 [28]. Moreover, $\gamma\delta$ T cells from the lung and spleen of *M. tb.*-infected mice produced more IL-17 than did CD4⁺ T cells as measured by ELISPOT. In addition, $\gamma\delta$ T cells were found to be the main producers of IL-17 after *Escherichia coli* (*E. coli*) infection, and antibody depletion of $\gamma\delta$ T cells during the infection led to decreased IL-17 production and less neutrophil infiltration into the peritoneum [29]. Similarly, in pulmonary *Mycobacterium bovis* Bacille Calmette-Guerin infection, $\gamma\delta$ T

cells in the lung were identified as the main source of IL-17, rather than CD4⁺ αβ T cells [30]. We have recently found that in a mouse model of hypersensitivity pneumonitis, Vγ6⁺ cells dominate the response to *Bacillus subtilis*, and a large proportion of those Vγ6⁺ γδ T cells produce IL-17 (P. Simonian, et al. in preparation). Finally, in a model of experimental sepsis, γδ T cells, but not αβ T cells, were identified as the source of elevated plasma IL-17A that is induced after cecal ligation and puncture [31].

Some γδ T cells appear to have an inherent ability to produce IL-17

In bacterial infections, γδ T cells can be the dominant source of IL-17, and rapid production of IL-17 was observed in many of the models described above. Interestingly, unlike naïve CD4⁺ αβ⁺ cells, which must be induced, γδ T cells from naïve animals often also produce IL-17. This was discovered by Stark, et al. while investigating neutrophil homeostasis in mice with various defects in leukocyte adhesion molecules. IL-17 is important in regulating granulopoiesis through G-CSF induction. In mice that lack leukocyte adhesion molecules, neutrophilia in the blood is observed and trafficking by neutrophils is disturbed. αβ and γδ T cells were identified as the cellular sources of IL-17 in these mice and surprisingly, in wild type naïve C57BL/6 (B6) mice, splenic γδ T cells, stimulated with PMA/ionomycin, accounted for 63% of all the IL-17 producing cells [32]. Moreover, the IL-17 producing cells were shown to have characteristics of effector memory cells: CD44 high, CD45RB low, and CD62L low. Similarly, Romani et al. have shown that γδ T cells from naïve wild type B6 animals produce IL-17, after overnight stimulation with anti-CD3 antibody and lipopolysaccharide [33]. Moreover, naïve γδ T cells have been shown to produce IL-17 in response to IL-23 alone, a cytokine known to expand and/or stabilize Th17 cells [28,29]. These findings suggest that some γδ T cells may be already differentiated in the periphery, poised to produce IL-17 in a rapid manner. For example, IL-17 production peaked in the peritoneum of *E. coli* infected animals 6 hours post-infection and was found to be produced by Vγ1⁺ γδ T cells in response to IL-23 [29]. In contrast, when these γδ T cells were stimulated in vitro with TGFβ and IL-6, no IL-17 was produced, suggesting γδ T cells behave like IL-17 producing memory αβ T cells.

We find that γδ T cells taken from the lymph nodes, spleen, and even thymus of naïve mice can produce IL-17 after in vitro stimulation with PMA/ionomycin. We have compared Vγ1⁺ and Vγ4⁺ subsets in the thymus and found this potential occurs within a proportion of the Vγ4⁺ cells, while the Vγ1⁺ cells essentially do not produce IL-17. Similarly, in the spleen of naïve C57BL/6 mice, 10% of the Vγ4⁺ cells produce IL-17 in response to PMA/ionomycin (C. Roark, unpublished observation). This observation was not limited to C57BL/6 mice, for in studies on collagen-induced arthritis (CIA), a mouse model of rheumatoid arthritis that requires the DBA/1 mouse strain, 20% of the naïve Vγ4⁺ cells in the lymph nodes were also capable of producing IL-17. Again, the Vγ1⁺ population produced virtually no IL-17 [34]. In contrast, Romani, et al. found that in the lungs of uninfected wild type C57BL/6 mice, Vγ1⁺ cells produced IL-17 after overnight stimulation with anti-CD3 and bacterial lipopolysaccharide, whereas the Vγ4⁺ cells produced IL-10 [33]. This may indicate that the cytokine bias of particular γδ T cell subsets can be altered by subsequent stimuli.

IL-17 producing γδ T cells can exacerbate autoimmune disease

In addition to infections, Th17 cells and/or IL-17 have been shown to play a very important role in the induction and propagation of autoimmune disease. Studies in CIA have shown that the disease is markedly suppressed in IL-17 deficient animals and IL-17 has been shown to be responsible for priming collagen-specific T cells and for collagen-specific IgG2a autoantibody production [35]. We have recently shown that during CIA, the Vγ4/Vδ4⁺ subset of γδ T cells is expanded and produces IL-17 [34]. These cells are a potent source of IL-17 and appear to be present in numbers similar to those of the CD4⁺ αβ⁺ Th-17 cells. Sequence analysis of this

expanded V γ 4/V δ 4⁺ cell population suggested that these cells are selected, because most also expressed a particular motif for both the TCR- γ and the TCR- δ junction. Antibody depletion of the V γ 4⁺ subset in mice with CIA resulted in lower disease incidence as well as less severe disease, revealing a pathogenic role for this subset of $\gamma\delta$ T cells. However, neither collagen nor arthritis was necessary to induce this specific V γ 4/V δ 4⁺ T cell expansion. Instead, the $\gamma\delta$ T cell response was due to the adjuvant used in the system to break tolerance to collagen. Therefore, the V γ 4/V δ 4 IL-17 producing $\gamma\delta$ T cells appear to be driven by self-molecules that arise during inflammation.

Are V γ 6/V δ 1⁺ invariant T cells specialized to produce IL-17 rapidly?

V γ 6/V δ 1⁺ $\gamma\delta$ T cells are a subset of $\gamma\delta$ T cells that reside primarily in mucosal areas in the mouse [36]. These cells are produced during fetal development and they express an invariant TCR [37]. V γ 6/V δ 1⁺ cells are often expanded during bacterial infection, but also can be induced in other inflammatory conditions [38–43]. Some evidence suggests that V γ 6/V δ 1⁺ cells are specially primed for IL-17 production. Though very low in number in a normal mouse, within 6 hours after *E. coli* infection, this subset appeared to be responsible for most of the IL-17 measured in the peritoneum [29]. Days later, the V γ 6/V δ 1⁺ cells were still present in expanded numbers, and continued to produce IL-17. Similarly, Hamada, et al. found that during *Listeria* infection, V γ 4 and V γ 6 cells in the liver produce IL-17, and the peak mRNA expression of IL-17 occurred on day 1 of the infection. In addition, this early IL-17 response was found to be protective (Hamada, et al., submitted). In our studies on mice infected with *Listeria* intraperitoneally, we also found that V γ 6/V δ 1⁺ cells are increased in the peritoneum, and by day 6, the majority of the V γ 6/V δ 1⁺ cells produce IL-17. Interestingly, an overlapping population of these cells produces IFN γ suggesting that dual expression of these two cytokines occurs in at least some of the cells (Roark, et al. in preparation). Despite our finding, most studies describing IL-17 production by $\gamma\delta$ T cells report that similar to CD4⁺ $\alpha\beta$ Th17, IL-17 producing $\gamma\delta$ T cells do not express both of these cytokines [27,28,34]. Our finding of dual production was unexpected because both Th1 and Th2 cytokines, including IFN γ , have been shown to antagonize the development of Th17 cells [5,6].

In conclusion, several lines of evidence suggest that IL-17 producing $\gamma\delta$ T cells probably develop differently from CD4⁺ $\alpha\beta$ Th17 cells. They may require the same developmental pathways when differentiating from naïve cells to cells committed to IL-17 production, but in the periphery, many $\gamma\delta$ T cells already seem to exist as effector memory cells, ready to produce IL-17 quickly, and possibly other Th17 cytokines such as IL-21 and IL-22. For instance, when $\gamma\delta$ T cells were stimulated in vitro with anti-CD3 and anti-CD28, they did not produce IL-17, but IL-17 was readily produced in response to PMA/ionomycin or IL-23 [28]. Therefore, Th17 like $\gamma\delta$ T cells may differentiate early in the life of the mouse in response to environmental, inflammatory, or stress-related stimuli and position themselves in the peripheral tissues in order to mount a quick response, when triggered by IL-23 produced by dendritic cells, following activation by external pathogens (Fig. 1). Rapid production of IL-17 can then quickly activate and recruit neutrophils to the site of inflammation. In addition, IL-17 and/or other Th17 cell products may influence the subsequent $\alpha\beta$ T cell response. Umemura, et al. found that IFN γ production by mycobacterial Ag-specific T cells was impaired in IL-17 deficient mice infected with *M. bovis* BCG, suggesting that IL-17 is important for an optimal Th1 response [30]. Further studies will help elucidate the functional roles of IL-17 producing $\gamma\delta$ T cells.

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Figure 1.

$\gamma\delta$ T cells appear to be the dominant early source of IL-17. During an immune response, $\gamma\delta$ T cells rapidly produce IL-17 in response to IL-23 and/or other dendritic cell products. Later, antigen-specific $CD4^{+}\alpha\beta^{+}$ Th17 cells may also develop and contribute to the response.