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The natural and the inducible: IL-17 producing gamma delta T cells

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Abstract

$\gamma\delta$ T cells are the major initial IL-17 producers in acute infections. Recent studies indicate that some $\gamma\delta$ T cells have IL-17 producing capabilities without explicit induction of an immune response. They are preferentially localized in barrier tissues and are likely to originate from fetal $\gamma\delta$ thymocytes. In addition, $\gamma\delta$ T cells present in the secondary lymphoid organs will mature and differentiate to produce IL-17 after antigen encounter in an immune response. Based on these studies we propose that there are two different sets of IL-17 producing $\gamma\delta$ T cells (T $\gamma\delta$ 17) referred to as the “natural” and the “inducible” T $\gamma\delta$ 17 cells. This review focuses on recent publications leading to the delineation of these two types of cells and their implied roles in host immune defense.

Introduction

The inflammatory response is an essential host response to infection and injury. Although it is largely within the confines of the innate immune system, vertebrates integrate the adaptive and innate responses in the inflammatory response by requiring IL-17, a cytokine made mostly by T cells, to induce the maturation and release of neutrophils from the bone marrow ¹. Neutrophil influx focuses the immune response at the infection/injury site to reduce the pathogen load, initiate the resolution program and prime the antigen-specific $\alpha\beta$ T cell and B cell response. Although both $\alpha\beta$ T cells and $\gamma\delta$ T cells can make IL-17, $\alpha\beta$ T cells that produce IL-17 (Th17 cells) require antigen-specific priming and an inflammatory environment in order to develop ². In an acute infection, the host must mount a rapid IL-17 response without prior antigen exposure. $\gamma\delta$ T cells are found to be the major initial IL-17 producers after immunization and in animal models of infection ³⁻⁴. However, it is unclear what triggers $\gamma\delta$ T cells to act in any of these situations. Nevertheless, because the $\gamma\delta$ T cell IL-17 response is strong and rapid, it has been argued that this response is triggered through the engagement of pathogen pattern recognition receptors (PRRs) and/or by inflammatory cytokine receptors, but not through the antigen receptor ⁵⁻⁷. In this scenario, $\gamma\delta$ T cells function as innate immune lymphocytes to provide an innate source of IL-17, and the ability of $\gamma\delta$ T cells to respond to antigens is irrelevant to their function. Recent publications have shed new light on this issue.

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The natural and the inducible IL-17 producing $\gamma\delta$ T cells

It has been reported that substantial numbers of $\gamma\delta$ T cells in the peripheral mucosal tissues, such as the dermal layer of the skin, and possibly in the lung and the peritoneal cavity in mice, have effector IL-17 producing capabilities without explicit induction of an immune response^{4, 8-11}. We classified these cells as the “natural” IL-17 producing $\gamma\delta$ T cells. $\gamma\delta$ T cells that are found to make IL-17 within 24 hours after infection^{3, 4} are likely to be in this category. Re-constitution studies indicate that these tissue localizing, fast IL-17 producing cells are derived from fetal thymocytes⁸⁻¹¹ (Figure 1).

In contrast, recent studies indicate that in secondary lymphoid organs such as the lymph nodes, $\gamma\delta$ T cells mature and differentiate to produce IL-17 after antigen encounter in an immune response¹²; we classified these cells as the “inducible” IL-17 producing $\gamma\delta$ T cells. Notably, antigen-specific naïve $\gamma\delta$ T cells do not require extensive clonal expansion to gain IL-17 effector function. These cells make IL-17 within 60 hours after the initial antigen encounter. Moreover, antigen stimulation induces the expression of inflammatory cytokine receptors that enable $\gamma\delta$ T cells to respond to inflammatory cytokine signals that perpetuate IL-17 production¹² (Figure 2). IL-17-producing $\gamma\delta$ T cells developed in a mouse model of collagen-induced arthritis are likely to fall within this category¹³.

There have been an increasing number of reports linking human IL-17 producing $\gamma\delta$ T cells with various pathological situations, but the regulation of IL-17 production by human $\gamma\delta$ T cells is not well understood. It would be interesting to test whether the models we propose here are also applicable to the development of human IL-17 producing $\gamma\delta$ T cells.

Subsets of $\gamma\delta$ thymocytes expressing genes associated with IL-17 effector functions

It has been demonstrated in *in vitro* assays that populations of $\gamma\delta$ thymocytes can be activated to make IL-17 with kinetics similar to those of the natural IL-17 producing $\gamma\delta$ T cells in the periphery¹⁴⁻¹⁶. In fact, the ability to make IL-17 appears to be a “default” property of uncommitted early thymocytes⁸. In Rag1-deficient thymi, IL-17A-producing cells can be found in the double-negative DN1 cells that express intracellular CD3¹⁷. Moreover, strong TCR signaling appears to divert $\gamma\delta$ thymocytes from IL-17 producing to IFN- γ ¹⁸⁻¹⁹ or IL-4²⁰⁻²² producing fates.

The observation that $\gamma\delta$ thymocytes have an effector-like property is somewhat surprising, as $\alpha\beta$ T cells gain effector capability in the periphery. There has been intense effort aimed at identifying the signaling pathways necessary for the development of these IL-17 making $\gamma\delta$ thymocytes. It was reported that signaling through transforming growth factor beta (TGF- β receptor)²³, Lymphotoxin-b receptor/RelB²⁴, B lymphoid kinase (Blk)²⁵ and the Notch/Hes1 pathway²⁶ (but not through Stat3, IL-6 or IRF-4^{24, 26-29}) is important. Although the signaling pathways that drive the development of thymic IL-17 effectors are not fully understood²⁸, it is clear that they are not the same as those required for the Th17 cells.

IL-17 producing $\gamma\delta$ thymocytes have also been analyzed extensively in terms of their cell-surface markers and gene expression patterns. These cells are mostly CD44^{hi} and express IL23R, SCART2, and CCR6 but have low/no level expression of the common β chain of IL-2 and IL-15 receptor CD122, or the TNF-receptor CD27^{14-16, 18, 30}. Recently, Narayan *et al.*, together with the Immunological Genome Project Consortium, carried out a comprehensive gene expression analysis of adult $\gamma\delta$ thymocytes³¹. They reported that the IL-17 producing potential segregates largely with V γ gene expression of the $\gamma\delta$ thymocytes. In particular, transcription patterns associated with IL-17 producing capacity, such as

elevated expression of *Rorc* and the cytokine receptors IL-1R1, IL-7R, IL-17RA, and IL-23R, as well as CCR6, are preferentially found in V γ 2⁺, but not V γ 1⁺ $\gamma\delta$ thymocytes (Note: in the Narayan et al., the nomenclature of V γ gene usage is according to that of Raulet and Garman³². They associated IL-17 production with the expression of V γ 2+ TCRs. Nonetheless, V γ 2 corresponds to V γ 4, according to the nomenclature of Heilig and Tonegawa³³ and this will be used in the present review, as most studies that describe V γ gene usage of IL-17 producing cells use the Heilig and Tonegawa nomenclature). In general, the pool of peripheral natural T $\gamma\delta$ 17 cells and IL-17 effector-like $\gamma\delta$ thymocytes are similar in the expression of these markers.

The embryonic thymocytes are the source of natural IL-17 producing effector cells in the periphery

Although it is commonly assumed that in adult animals, IL-17 effector-like $\gamma\delta$ thymocytes contribute directly to the pool of peripheral T $\gamma\delta$ 17 cells, recent studies indicate that after lethal irradiation, neonate thymocytes, but not adult bone marrow cells, reconstitute dermal T $\gamma\delta$ 17 cells⁸. In addition, Haas and colleagues analyzed *Indu-Rag1* mice³⁴ and showed that deficient *Rag1* expression could be induced in adult mice by Tamoxifen gavage. They also showed that at multiple sites, including the thymus, lymph nodes, spleen, lung and liver, natural T $\gamma\delta$ 17 cells were not regenerated when T cell receptor rearrangement was initiated only in adult mice. Instead, natural T $\gamma\delta$ 17 cells were generated from E15.5 fetal thymi transplanted under the renal capsule, but not from the thymus of *Indu-Rag1* mice⁶. Consistent with these observations, V γ 6⁺ cells, which are prominent in fetal, but not adult thymocytes, constitute up to 50% of all natural IL-17 producing $\gamma\delta$ T cells in the peripheral organs of C57BL/6 mice, and play a critical role in host immune responses to bacterial infections, particularly in the lung³⁵.

$\gamma\delta$ T cells respond to microbial/foreign antigen challenges to generate inducible IL-17 effector cells

Although $\gamma\delta$ T cells, like $\alpha\beta$ T cells, develop in the thymus before entering the periphery, past studies indicate that this process does little to constrain the antigen specificity of the $\gamma\delta$ T cells, but largely determines their effector fate. In particular, $\gamma\delta$ T cells that do not have antigen specificities for thymic ligands make IL-17 preferentially¹⁸. These results suggest that those $\gamma\delta$ T cells specific for microbial/foreign antigens will make IL-17. Recently, Zeng *et al.* confirmed these observations by identifying an algae protein, phycoerythrin (PE), as an antigen for mouse and human $\gamma\delta$ T cells. Using PE to track and analyze specific $\gamma\delta$ T cells in mice, they demonstrated that before immunization, most of the PE-specific $\gamma\delta$ T cells have naïve phenotype. These cells are activated (e.g. becoming CD44^{hi} CD62L^{lo}) within 24 hours after PE/alum immunization. Activated PE-specific $\gamma\delta$ T cells start to express ROR γ t after another 24 hours. Sixty hours after PE/alum immunization, PE specific $\gamma\delta$ T cells make IL-17. Importantly, immunization with ovalbumin/alum does not activate PE specific $\gamma\delta$ T cells and neither PE/alum nor ovalbumin/alum immunization induces general $\gamma\delta$ T cell activation.

Strikingly, naïve PE-specific $\gamma\delta$ T cells gained the ability to produce IL-17 without the requirement of extensive clonal expansion, unlike the development of $\alpha\beta$ effector cells. Nonetheless, it has been noted that the initial antigen specific $\gamma\delta$ T cell frequency (~0.02-1% of total $\gamma\delta$ T cells in naïve animals) is much higher than that of antigen specific $\alpha\beta$ T cells before clonal expansion (0.0001% to 0.001% of total $\alpha\beta$ T cells)^{12, 36-39}. These two attributes would allow $\gamma\delta$ T cells to mount a swift and substantial response when they encounter antigen for the first time.

It was noted that the receptors for IL-1 and IL-23 are only expressed on $\gamma\delta$ T cells that have been activated through the TCR^{12,40}. Indeed, only activated $\gamma\delta$ T cells can respond to either IL-1 and IL-23 or to IL-23 together with agonists of toll-like receptors (TLRs) such as Pam₃Csk₄ to produce IL-17 without explicitly triggering the TCR. Even then, the response is inhibited by compounds such as cyclosporine A (CsA) and FK506¹². Both compounds reduce/disrupt the calcineurin-NFAT (nuclear factor of activated T-cells) signaling circuit that is activated by signaling through the antigen receptor⁴¹. These observations indicate that signaling through the TCR is necessary for the production of IL-17. However, neither the inflammatory cytokines alone, nor the engagement of TCR alone induces sustained IL-17 response that can match the magnitude of that induced by TCR stimulation in the presence of inflammatory cytokines^{12,42}. This suggests that the cytokine receptor signaling provides a “second signal” to TCR engagement to perpetuate the IL-17 response in inflammation, and also to prevent the development of a prolonged and robust IL-17 response without inflammation.

Concluding remarks

The presence of natural $\gamma\delta$ T cells in naïve mice that are ROR γ t⁺ and make IL-17 rapidly after infection and/or *in vitro* stimulation, has led to the branding of $\gamma\delta$ T cells as innate immune lymphocytes. It has been assumed that these cells, similar to the semi-invariant natural killer (NK) T cells, are exported from the thymus as ‘pre-wired’ memory-like cells, displaying cell-surface markers associated with cellular activation. However, the observations discussed in this review raise the possibility that $\gamma\delta$ T cell emigrants expand, differentiate into natural IL-17 effector cells in the lymphopenic environment during the neonate period and take residence in tissues where they persist throughout adult life. Naïve $\alpha\beta$ T cells undergo homeostasis-driven proliferation and display phenotypic and functional characteristics of tissue seeking memory/activated cells. This process is dependent on signaling both through cytokine receptors such as IL-7 and IL-15 and through the TCR⁴³. Thus, the observations that fetal but not adult $\gamma\delta$ T cell precursors generate natural IL-17 producing $\gamma\delta$ T cells in adult animals in reconstitution experiments after induced lymphopenic conditions suggest that these two types of precursor cells may differ in antigen specificity and/or the expression of cytokine receptors and their signaling network. Whether the natural T $\gamma\delta$ 17 cells in adult un-manipulated animals are indeed derived from fetal thymocytes will require further analysis.

A clear dissection of what is required for activation of inducible IL-17 producing $\gamma\delta$ T cells stems from the analysis of the antigen specific $\gamma\delta$ T cell response using PE as a model antigen. PE happens to be a classic B cell antigen that is used extensively for the analysis of the $\alpha\beta$ T cell dependent antibody response⁴⁴⁻⁴⁶. These observations indicate that $\gamma\delta$ T cells, B cells and $\alpha\beta$ T cells can recognize the same antigen. While the diversity in antigen receptor specificity is the hallmark of the adaptive immune response, not all antigenic responses produce results. In fact, effective adaptive immune responses are focused in antigen specificity. This is best illustrated in the T-dependent antibody response, where the participating $\alpha\beta$ T cells and B cells must respond to the same antigen. Such a tight coupling of antigen specificity ensures a highly focused response. The observation that PE, which induces a robust B cell response, also triggers $\gamma\delta$ T cells at the onset of the inflammatory response suggests that a focused adaptive immune response includes the participation of $\gamma\delta$ T cells. Whether this observation can be generalized requires the identification of additional $\gamma\delta$ T cell antigens. Regardless, these recent advancements extend and clarify our understanding of IL-17 producing $\gamma\delta$ T cells and their roles in host immune defense.

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Figure 1.

Model for development of natural Tγδ17 (nTγδ17) cells according to Haas et al. [REF]. Commitment and differentiation of nTγδ17 cells is restricted to the fetal thymus. It requires the absence of specific TCR ligation and depends on signaling via lymphotoxin-β-receptor (LTβR), Transforming growth factor-beta (TGF-β), B lymphoid kinase (Blk), and the Notch-Hes1 pathway. nTγδ17 cells exit the thymus as CCR6⁺CD27⁻CD44^{hi}IL-23R⁺ effector cells and persist as a self-renewing pool in peripheral tissues. There, specific TCR triggering and/or IL-23 and IL-1 induce IL-17 production of nTγδ17 cells.

Induction of T $\gamma\delta$ 17 cells **Figure 2.**

Model for induction of T $\gamma\delta$ 17 (iT $\gamma\delta$ 17) cells according to Zeng et al. [REF]. Specific microbial antigen such as phycoerythrin (PE) can activate uncommitted naive $CD62L^{hi}CD44^{lo}$ $\gamma\delta$ T cells in secondary lymphoid tissues via their TCR. This TCR-ligation stimulates their rapid acquisition of effector phenotype and effector functions including IL-17 production, without extensive clonal expansion. Concurrently induced responsiveness to IL-23 and IL-1 further perpetuates pro-inflammatory IL-17 production by iT $\gamma\delta$ 17 cells.