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# Regulation and function of IL-17A- and IL-22-producing *γδ* T cells

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## Abstract

The regulation of IL-17A and IL-22 production differs between human and murine *γδ* T cells. We find that human *γδ* T cells expressing V*γ*2V*δ*2 T cell receptors are peripherally polarized to produce IL-17A or IL-22, much like CD4 *αβ* Th17 T cells. This requires IL-6, IL-1*β*, and TGF-*β*, whereas expansion and maintenance requires IL-23, IL-1*β*, and TGF-*β*. In contrast, IL-17A and IL-22 production by murine *γδ* T cells is innately programmed during thymic ontogeny but requires IL-23 and IL-1*β* for maintenance. Murine *γδ* cells producing IL-17A and IL-22 play important roles in microbial, autoimmune, and inflammatory responses. However, the roles played by human IL-17A- and IL-22-producing *γδ* T cells are less clear but are also likely to be important. These observations highlight differences between humans and murine *γδ* T cells and underscore the importance of IL-17A- and IL-22-producing *γδ* T cells.

### Keywords

Interleukin-17A; Interleukin-22; *γδ* T cell; V*γ*2V*δ*2 T cells; Isoprenoid metabolism

## Introduction

*γδ* T cells have properties of both innate and adaptive immune cells. Although expressing adaptive T cell antigen receptors (TCRs) by rearranging V, D (for the *δ* chain), and J gene segments, human and mouse *γδ* T cells utilize a limited set of V*γ* and V*δ* genes. In cases where the *γδ* ligands and/or presenting molecules have been identified, they have been found to be ubiquitous nonpeptide compounds [such as lipids or (*E*)-4-hydroxy-3-methyl-but-2-enyl pyrophosphate (HMBPP)] presented by major histocompatibility complex (MHC) class Ib molecules such as CD1 or by an unknown presenting molecule (for phosphoantigens). In other cases, the *γδ* T cells do not recognize an exogenous or endogenous antigen at all—instead they directly recognize an MHC class Ib molecule, such as H-2T or MICA/MICB. In these ways, recognition by *γδ* TCRs more resembles recognition of nonpeptide compounds by pattern recognition receptors than the recognition by conventional *αβ* TCRs of peptide antigens presented by MHC class I or II molecules.

Despite the identification of *γδ* T cells in 1986 [1], major questions still remain unanswered about their functional roles. Although normally constituting a small proportion of total T cells in humans and mice, certain infections or other stimuli can expand *γδ* T cells to high

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levels. Also, in many cases $\gamma\delta$ T cells express invariant TCRs or TCRs with restricted V gene diversity, resulting in high frequencies of T cells with a defined specificity (although largely unknown for murine $\gamma\delta$ T cells). Moreover, these invariant $\gamma\delta$ T cells can be highly enriched at specific anatomic locations. From the study of other unconventional T cells, such as invariant natural killer $\alpha\beta$ T (iNKT) cells that recognize lipids presented by CD1d [2, 3], it is clear that small populations of T cells that respond early during immune responses can greatly influence the eventual outcome.

Discoveries over the last decade have now defined a new lineage of T cells—the Th17 lineage—that produces IL-17A, IL-17F, and IL-22. Through studies of the role of IL-23 in autoimmune diseases, it became clear that deletion of the shared IL-12$\beta$ chain ameliorated disease because of the loss of IL-23 function, not IL-12 function, and that, in most cases, traditional Th1 cells producing IFN-$\gamma$ did not cause autoimmune pathology. This rapidly led to the delineation of the Th17 differentiation schema with identification of the cytokines and transcription factors involved (detailed below). Members of the IL-17 cytokine family (IL-17A through IL-17F) are proinflammatory cytokines that possess a diverse array of functions ranging from neutrophil recruitment to induction of wound repair and tissue remodeling that begin to function early in responses. Similarly, IL-22 can also mediate inflammation and stimulate the production of antimicrobial peptides, and plays a prominent role in skin inflammation and repair.

Although initial studies focused on Th17 and Th22 CD4 $\alpha\beta$ T cells, Th17 $\alpha\beta$ cells require time to develop and, therefore, would not be available during the crucial early phases of immune responses (within hours) where IL-17A plays critical roles in recruiting neutrophils to sites of infection and in initiating inflammatory responses. In these situations, $\gamma\delta$ T cells, other innate lymphocytes (such as iNKT cells and lymphoid tissue inducer cells), Paneth cells, and neutrophils play sentinel functions by releasing IL-17A [4]. $\gamma\delta$ T cells are important sources of IL-17A and IL-22 during infections and autoimmune diseases, and secrete IL-17A earlier in disease than conventional CD4 or CD8 $\alpha\beta$ T cells. For example, in murine tuberculosis, $\gamma\delta$ T cell production of IL-17A actually exceeds that of Th17 cells [5]. Furthermore, murine $\gamma\delta$ T cells can produce IL-17A, IL-22, and IL-21 in response to IL-23 and IL-1$\beta$ without exposure to exogenous antigens [6] or with exposure only to toll-like receptor (TLR) and dectin-1 ligands [7, 8].

From a therapeutic perspective, it is essential to determine the role played by these cells in disease as well as the mechanisms regulating their development. Moreover, although it is clear that IL-17A-producing $\gamma\delta$ T cells are important in mice and that they exist in humans [9], little is known about the roles of human IL-17A-producing $\gamma\delta$ T cells in infections and autoimmune diseases. In this review, we first cover the basic differentiation scheme of conventional T cells, including recently described Th17 T cells, then discuss the regulation and function of IL-17A and IL-22 production by unconventional $\gamma\delta$ T cells in humans and in mice.

## Biology of IL-17A and IL-22

IL-17A is a multifactorial cytokine, which promotes inflammation. It does this by increasing production of inflammatory cytokines, chemokines, matrix remodeling proteins, adhesion molecules, antimicrobials, and acute phase reactants. The major consequence of IL-17A signaling is the recruitment of neutrophils to areas of inflammation.

Because the IL-17A receptor (IL-17RA) is expressed ubiquitously throughout the body, virtually every cell in the body can participate in IL-17A-mediated inflammation. The principle effect of IL-17A is propagation of proinflammatory cytokines; for example, fibroblasts and epithelial cells respond to IL-17A by producing IL-6 and G-CSF [10] as well

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as the chemokines IL-8/CXCL8, CXCL1, CXCL2, CCL20, CCL2, and CCL7 [11–14]. IL-17A signaling also induces the expression of matrix metalloproteinases (MMP) such as MMP-1 [15], -3 [16, 17], -9 [18], and -13 [17, 19], and aggrecanase-1 [17]. MMPs are involved in tissue remodeling, and can contribute to tissue repair or tissue destruction. IL-17A also stimulates the production of receptor activator of nuclear factor kappa-B ligand (RANKL, also known as TNFSF11), a key stimulator of osteoclast differentiation and activation for bone resorption [20].

IL-17A also induces endothelial cells to upregulate the adhesion molecules E-selectin, VCAM-1 and ICAM-1, which enable neutrophils and other cells responding to the proinflammatory cytokines to exit the vasculature [21]. IL-17A also boosts mucosal immunity by induction of antimicrobials, such as the *β*-defensins and mucins, which are rapidly produced by airway epithelial cells in response to IL-17A [22, 23]. Lastly, IL-17A boosts systemic innate immunity through the induction of acute phase reactants, produced by the liver. One such reactant, C-reactive protein [24], is directly released by hepatocytes treated with IL-17A and functions to activate the complement system.

IL-17A signaling also acts at the molecular level to stabilize mRNA transcripts within target cells. This is achieved through activation of the MAPK pathway and targets mRNA transcripts containing Au-rich elements in myeloid cells. Examples of such transcripts include *Cxcl-1* [25], *Il-6* [26, 27], *Il-8* [28], and *G-csf* [29]. IL-22 is often produced alongside IL-17A. IL-22 acts on non-immune cells, specifically epithelial cells and other cells of the skin, gut, lungs, and kidneys. Similar to IL-17A, IL-22 induces antimicrobial peptides, acute phase reactants, and MMPs, but uniquely mediates re-epithelialization and inhibition of keratinocyte differentiation [30–32].

## Lineage commitment and differentiation of conventional *αβ* T cells: what lessons can we learn for *γδ* T cells?

To differentiate conventional naive *αβ* T cells from memory T cells, naive CD4 *αβ* T cells must be exposed to their peptide antigens bound to MHC class II molecules while naive CD8 *αβ* T cells must be exposed to their peptide antigens bound to MHC class I molecules. This process is generally initiated by professional antigen-presenting cells (APC) that express not only the MHC molecules with bound peptide antigens, but also costimulatory ligands such as CD80 (B7-1) and CD86 (B7-2). Engagement of other receptors expressed on T cells such as the CD4 and CD8 accessory molecules, costimulatory and inhibitory receptors (such as CD28, CTLA-4, and JCAM), CD2 and SLAM family receptors, TNF-family receptors (such as CD27), and integrins (such as LFA-1), to their ligands also enhances or are required for naive T cell activation. The binding of the *αβ* TCR to its cognate MHC-peptide antigen along with the other receptor interactions activates the T cell and converts it to a memory (educated) T cell. The affinity of the MHC–peptide complex for the TCR and the length of time that the TCR is bound also affect T cell differentiation and function.

While converting to memory T cells, naive T cells commit to different functional lineages. There is a strong contribution to function that is determined by the expression, or lack of expression (in the case of *γδ* and innate *αβ* T cells), of CD4 and CD8 accessory receptors on the naive T cells. Thus, expression of the CD4, CD8*αβ* heterodimer, CD8*αα* homodimer, or the lack of expression of $CD4^{-}CD8^{-}$ in both *αβ* and *γδ* T cells delineates (or is a marker for) some of the functional capabilities of the cells, principally cytotoxicity versus helper activity.

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During peripheral conversion of naive to memory, the types of cytokines produced by the memory T cell (Th1, Th2, Th9, Th17, Th22, $T_{FH}$, etc.) depend on the type of APC, the cytokines present during activation, and the receptors/ligands expressed by the APC. In turn, the types of APC and surrounding cytokines are strongly dependent on the triggering of innate receptors [TLRs, nucleotide-binding oligomerization domain-containing proteins (NODs), nucleotide-binding domain leucine-rich repeat containing NOD-like receptors, mannose receptors, etc.] by pathogen-associated molecular patterns associated with the antigen source (e.g. viral, bacterial, or parasitic infections). These innate sensors direct T cell differentiation by engaging innate receptors on APC and surrounding cells which, in turn, stimulates the expression of specific cellular ligands and cytokines. Innate signals can also direct T cell differentiation by engaging innate receptors expressed by the T cells themselves. Therefore, the types of innate receptors engaged by the pathogen-associated molecular patterns play a major role in determining the downstream lineage commitment of T cells.

The cytokines and receptor–ligand interactions signal naive T cells to increase production or activity of various transcriptional activators/suppressors that then turn on and off genes to commit the T cells to different functional lineages. Then epigenetic changes serve to firmly commit the T cells to a particular functional lineage in many but not all cases. Depending on the number of times the T cells are activated through their TCRs, the number of cell divisions they undergo, and the conditions under which they are activated (i.e. surrounding cytokines and receptor ligand interactions), the memory T cells then undergo progressive differentiation to a more effector/terminally differentiated state with the associated loss or gain of various surface receptors and effector molecules.

The challenge of studying memory and lineage commitment of $\gamma\delta$ T cells and unconventional $\alpha\beta$ T cells is that, in many cases, the TCRs of these cells function more like pattern recognition receptors than foreign antigen receptors. That is, the antigens recognized by $\gamma\delta$ T cells so far have been either nonpeptide conserved molecules, such as prenyl pyrophosphate isoprenoid metabolites and lipids, that are expressed by a variety of pathogens and have mammalian homologs, or endogenous self proteins (such as MICA/MICB, CD1, or H-2T MHC class Ib molecules). The presence of these self-ligands or ubiquitous nonpeptide antigens can rapidly convert naive $\gamma\delta$ T cells into memory cells. Exposure to self-ligands may explain why many murine T cell V gene subsets acquire "memory" T cell phenotypes and commit to a functional lineage in the thymus. In contrast, although acquisition of a "memory" phenotype can take place in the thymus, many human neonatal V$\gamma$2V$\delta$2 T cells exhibit naive phenotypes. In this case, commitment by human V$\gamma$2V$\delta$2 T cells to T$\gamma\delta$17 or other lineages can take place in the periphery, as for most $\alpha\beta$ T cells.

## Differentiation of Th17 CD4 *αβ* T cells

When considering the commitment of $\gamma\delta$ T cells to the Th17 lineage, it is useful to consider the requirements for the differentiation of naive CD4 $\alpha\beta$ T cells to Th17 cells that has been extensively studied in both humans and mice [33].

Th17 differentiation begins with the ligation of the TCR in the presence of IL-6 and/or IL-21. This activates STAT3, which induces and increases expression of the master transcription factor, retinoid-related orphan receptor $\gamma$t (ROR$\gamma$t, produced from the *RORC* gene) [34], and/or ROR$\alpha$ (produced from the *RORA* gene) [35]. ROR$\gamma$t and ROR$\alpha$ are key transcription factors required for IL-17A and IL-17F production. STAT3, in the presence of ROR$\gamma$t, binds to the *IL17A* and *IL17F* promoters [36], initiating IL-17A and IL-17AF mRNA production. IL-1$\beta$, through induction of IRF4, appears to stabilize the Th17

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phenotype [37, 38]. Additionally, the *RUNX1* transcription factor may further promote the differentiation of Th17 cells since it upregulates RORγt expression and *IL17A* transcription [39]. Within these developing Th17 T cells, IL-6 also induces expression of IL-23R [40]. This enables further STAT3 signaling through the binding of IL-23 to the IL-23R. Continued IL-23/IL-23R signaling through STAT3 is required by committed Th17 precursors for terminal differentiation of these cells into effector Th17 cells and maintenance of their phenotype in vivo [41]. In mice, TGF-*β* appears to be required to maximally differentiate naive cells into Th17 cells [42]. TGF-*β* has been suggested to indirectly suppress Th1 and Th2 differentiation through inhibition of STAT4 and GATA-3 transcription factors, respectively [43]. Human Th17 CD4 *αβ* T cells also require TGF-*β* for maximal differentiation of Th17 cells [44–46] probably through a similar mechanism [47]. Thus, triggering naive CD4 *αβ* T cells with MHC/peptide antigens in the presence of IL-6 and/or IL-21, IL-1*β*, and TGF-*β* directs their differentiation to the Th17 lineage. IL-23 serves to reinforce and maintain this lineage commitment.

## Human IL-17A-producing *γδ* T cells

### Human *γδ* V gene subsets: expansion of V*γ*2V*δ*2 T cells in infancy driven by microbial expression of HMBPP and other phosphoantigens

Humans express six functional V*γ* gene segments and three major V*δ* gene segments. Five of the V*γ* gene segments (V*γ*1.2, V*γ*1.3, V*γ*1.4, V*γ*1.5, and V*γ*1.8; also termed V*γ*2, V*γ*3, V*γ*4, V*γ*5, and V*γ*8) belong to a single family showing 71–91% amino acid homology. The V*γ*1 family also shows 42–48% amino acid homology with murine V*γ*5 (using the Tonegawa nomenclature). The sixth functional V*γ* gene segment, V*γ*2 (also termed V*γ*9), is distinct from all murine V*γ* gene segments. In adults, the V*γ*2 gene segment is commonly found paired with the V*δ*2 gene segment (also distinct from all known murine V*γ* gene segments). The V*γ*2 gene segment can also pair with the V*δ*1 gene segment (showing 58% amino acid homology with murine V*δ*6), although V*δ*1 is most commonly paired with a V*γ*1 family member. The V*δ*3 gene segment is the third most common segment in adults and shows 66% amino acid homology with murine V*δ*5. Although V*α* gene segments can recombine with the C*δ* constant region and pair with V*γ* gene segments, these TCRs constitute only a small fraction of total *γδ* T cells in most individuals.

Unlike mice, humans do not exhibit a predominance of *γδ* T cells at epithelial surfaces, nor are invariant TCRs commonly found at localized anatomic sites. There is evidence, however, for an early wave of *γδ* T cells, from fetal thymus and liver, expressing invariant V*γ*2 gene segments [48] paired with oligoclonal V*δ*2 gene segments [49–51]. However, by birth, the thymus has switched to V*δ*1 and the V*γ*1V*δ*1 subset predominates [49, 52]. At birth, the repertoire of *γδ* TCR pairs is quite diverse with significant fractions of neonatal *γδ* T cells expressing V*γ*1V*δ*2 and V*γ*2V*δ*1 TCRs that are seldom seen in adults [52].

Between the ages of 1 and 10 years, however, the V*γ*2V*δ*2 T cell population expands to predominate among adult *γδ* T cells [53]. This expansion is independent of genetic background, since identical twins can have different V gene repertoires and there is no evidence for inheritance of V gene expression in families [53]. Instead, environmental exposure to microbes is likely responsible for this expansion. This expansion is limited to T cells expressing V*γ*2 paired with V*δ*2 and to a lesser extent, V*γ*1 paired with V*δ*1; other combinations that are present in neonates become almost non-existent in adults [52].

Because of this extensive activation and expansion, V*γ*2V*δ*2 T cells become the major subset in adult peripheral blood *γδ* T cells [53] with almost all exhibiting memory phenotypes (data not shown; [53, 54]). The V*γ*2V*δ*2 TCR (also termed V*γ*9V*δ*2) specifically recognizes HMBPP [55], an essential metabolite in isoprenoid biosynthesis pathways of

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many bacteria and all Apicomplexan parasites. Activation of V$\gamma$2V$\delta$2 T cells in vivo is dependent on the production of this essential metabolite [56]. A related prenyl pyrophosphate, isopentenyl pyrophosphate (IPP), is similarly recognized by V$\gamma$2V$\delta$2 T cells [57]. However, unlike HMBPP, IPP is present in both microbial and human isoprenoid biosynthesis. IPP is normally sequestered inside host cells, and does not activate V$\gamma$2V$\delta$2 T cells unless the cells have been treated with bisphosphonates [58] or alkylamines [59] to block farnesyl diphosphate synthase, thereby increasing IPP levels.

Although never the predominant T cell population, V$\gamma$1V$\delta$1 T cells (and rarely V$\gamma$2V$\delta$2 T cells) are enriched in intraepithelial (but not lamina propria) tissues in the gut, constituting up to 37% of total T cells [60, 61]. They are also found in the skin, constituting about 5% of total T cells [61, 62]. A significant fraction of V$\gamma$1V$\delta$1 and V$\gamma$2V$\delta$1 T cells (up to 66% of duodenal $\gamma\delta$ T cells) respond to self and foreign lipids presented by CD1 molecules [63–66]. Antigens identified include pollen-derived phosphatidyl ethanolamine [67] and lipid A [68]. Thus, a significant proportion of V$\delta$1 T cells recognize self and foreign lipids presented by CD1. Members of the V$\gamma$1V$\delta$1 T cell subset also recognize the MHC class I-related molecules, MICA and MICB [69, 70]. Such recognition is TCR-dependent [71, 72] but is independent of antigen processing, presentation, and $\beta_2$M [72]. In addition, V$\delta$1 and V$\gamma$2V$\delta$2 T cells also express NKG2D. This C-type lectin also binds MICA, MICB, and UL16-binding proteins, and, together with TCR ligation, provides T cell costimulation [71, 73]. In response to activation, V$\gamma$1V$\delta$1 and V$\gamma$2V$\delta$2 T cells similarly produce IFN-$\gamma$ and TNF$\alpha$, and mediate cytolysis.

Finally, human $\gamma\delta$ T cells expressing V$\delta$1, V$\delta$3, and V$\delta$5 have been found to expand in response to cytomegalovirus (CMV) infection after in utero infection [74] in normal adults [75], and in adults after kidney transplantation [76, 77]. In patients with in utero infection, an invariant V$\gamma$1.8V$\delta$1 TCR is greatly enriched. $\gamma\delta$ clones expressing this V$\gamma$1.8V$\delta$1 TCR secrete IFN-$\gamma$ in response to CMV-infected fibroblasts and kill CMV-infected target cells [74]. Similarly, V$\delta$1 and V$\delta$3 T cells expand greatly (up to 15–42% of total T cells in some cases) after renal transplantation in patients who develop a CMV infection. These $\gamma\delta$ T cells may be further expanded in vitro when exposed to lysates of CMV-infected cells [76] and $\gamma\delta$ clones derived from these cells specifically lyse CMV-infected target cells [78]. Thus, although the CMV-associated ligand(s) and the restricting molecules have not been defined, there is evidence for specific recognition of a CMV-associated compound.

## Peripheral differentiation of neonatal V$\gamma$2V$\delta$2 T cells into T$\gamma\delta$17 and T$\gamma\delta$1/17 cells requires antigen stimulation and IL-6, IL-1$\beta$, and TGF-$\beta$

In our studies on neonatal V$\gamma$2V$\delta$2 T cells [9], we found that V$\gamma$2V$\delta$2 T cells behave much like naive $\alpha\beta$ T cells since they can be polarized into Th17-like lineage cells, which we term T$\gamma\delta$17. Approximately 50% of neonatal V$\gamma$2V$\delta$2 T cells are phenotypically naive (based on the expression of CD27 and CD28 without expression of CD45RO). Polarization of neonatal V$\gamma$2V$\delta$2 T cells to produce IL-17A (termed T$\gamma\delta$17 T cells) requires IL-6, IL-1$\beta$, and TGF-$\beta$ coupled with TCR stimulation by the antigen, HMBPP. Neutralization of IL-6 or the absence of exogenous TGF-$\beta$ or IL-1$\beta$, greatly reduces generation of T$\gamma\delta$17 cells. Neutralization of IL-23, in contrast, increases the numbers of T$\gamma\delta$17 T cells. Costaining for IFN-$\gamma$ revealed that IL-23, in conjunction with IL-6, IL-1$\beta$, and TGF-$\beta$, induces T$\gamma\delta$17 T cells to produce IFN-$\gamma$ in addition to IL-17A (termed T$\gamma\delta$1/17). A similar phenomenon was observed with Th17 CD4 T cell clones, where IL-23 and/or IL-12 induces IFN-$\gamma$ production [79]. These results suggest that under these conditions, IL-23 may function to drive production of IFN-$\gamma$.

Our results suggest the following model (Fig. 1). In naive V$\gamma$2V$\delta$2 T cells, IL-6 binding to the IL-6R activates STAT3 which in turn binds and activates the *IL-23R*, *RORC/A*, and

*IL-17A/F* genes. IL-1$\beta$ stabilizes the T$\gamma\delta$17 phenotype by inducing IRF4 [37, 38]. TGF-$\beta$ inhibits IL-12-mediated STAT4 signaling, thereby inhibiting differentiation into Th1-like cells (termed T$\gamma\delta$1) that produce IFN-$\gamma$. Using intranuclear staining, we verified that neonatal V$\gamma$2V$\delta$2 T cells producing IL-17A have increased levels of ROR$\gamma$t, consistent with the hypothesis that it is also a master regulator of T$\gamma\delta$17. Studies examining RUNX1 levels in T$\gamma\delta$17V$\gamma$2V$\delta$2 T cells are planned to determine whether this transcription factor also plays a role.

In the presence of IL-23, the IL-17A-producing T$\gamma\delta$17 T cells (which now express the IL-23R) acquire the ability to produce IFN-$\gamma$ via an uncharacterized mechanism [9]. This acquisition of the ability to produce IFN-$\gamma$ by T$\gamma\delta$17V$\gamma$2V$\delta$2 T cells is not unique to $\gamma\delta$ T cells. Both human Tc17 [80, 81] and human Th17 [82, 83] $\alpha\beta$ T cells show some level of instability/plasticity, and over time, many of these cells begin to produce IFN-$\gamma$ and lose the ability to produce IL-17A. Similar to Tc17 $\alpha\beta$ T cells, IL-17A production by T$\gamma\delta$17 and T$\gamma\delta$1/17V$\gamma$2V$\delta$2 T cells is unstable in vitro and most of the cells eventually lose the ability to make IL-17A and, instead, produce IFN-$\gamma$ (Ness-Schwickerath and Morita, unpublished observations). Future studies with sorted T$\gamma\delta$17 populations are needed to confirm the role of IL-23 in the conversion to T$\gamma\delta$1.

## IL-23 with IL-1$\beta$ and TGF-$\beta$ helps maintain adult T$\gamma\delta$17 cells but there is significant conversion into T$\gamma\delta$1/17 and T$\gamma\delta$1, IFN-$\gamma$-producing cells

In contrast to neonatal V$\gamma$2V$\delta$2 T cells, adult V$\gamma$2V$\delta$2 T cells are almost exclusively memory cells (about 98% of blood V$\gamma$2V$\delta$2 T cells; Jin et al., unpublished observations). Consistent with this difference, the cytokine requirements for IL-17A production by adult V$\gamma$2V$\delta$2 T cells is significantly different from those for neonatal V$\gamma$2V$\delta$2 T cells [9]. In adults, optimal expansion of IL-17A-producing V$\gamma$2V$\delta$2 T cells requires IL-1$\beta$, TGF-$\beta$, and IL-23, but does not require IL-6 (Fig. 1). Although the small population of naive V$\gamma$2V$\delta$2 T cells in adults hypothetically could be polarized to T$\gamma\delta$17 under these conditions, the lack of a requirement for IL-6 suggests that the majority of IL-17A-producing cells are memory V$\gamma$2V$\delta$2 T cells already committed to the T$\gamma\delta$17 and T$\gamma\delta$1/17 lineages.

Given the plasticity of the Th17 lineage, it is likely that some fraction of IFN-$\gamma$-producing V$\gamma$2V$\delta$2 T cells are actually T$\gamma\delta$17 lineage cells that have failed to maintain IL-17A production. These former T$\gamma\delta$17V$\gamma$2V$\delta$2 T cells, however, may maintain permissive histone modifications at the *IL-17A/F*, *RORC*, or *RORA* loci, such that signaling by IL-1$\beta$, IL-23, and TGF-$\beta$ could restore IL-17A production. They may also have other differences in chemokine receptor expression, cytotoxicity, or accessory molecule expression that confer specialized functional roles on these cells when compared with true T$\gamma\delta$1 cells. Consistent with this possibility, CD4 Th17 $\alpha\beta$ T cells producing IFN-$\gamma$ but not IL-17A, that were stimulated under polarizing conditions for Th17 cells produce the Th17-lineage IL-22 cytokine and CCL20 (MIP-3A/LARC) chemokine [83].

In contrast to neonatal V$\gamma$2V$\delta$2 T cells, adult T$\gamma\delta$17 cells (IFN-$\gamma^{-}$) are less frequent and were observed in only four out of ten donors [9]. Thus, most V$\gamma$2V$\delta$2 T cells that produce IL-17A also produce IFN-$\gamma$. However, within the four donors with expandable T$\gamma\delta$17 T cells, these cells could be detected ex vivo prior to expansion. The cytokines required for T$\gamma\delta$17 expansion in adult blood were similar to those expanding T$\gamma\delta$1/17 cells. This suggests that T$\gamma\delta$17V$\gamma$2V$\delta$2 T cells can persist in humans, as do $\alpha\beta$ T cells. Because captive, specific pathogen-free rhesus macaques have much higher frequencies of T$\gamma\delta$17 cells than human donors, it is likely that the type and number of infections may determine whether these cells persist in vivo. It is likely that frequent Th1 immune responses (involving ample IL-12) cause many human T$\gamma\delta$17V$\gamma$2V$\delta$2 T cells to transition to T$\gamma\delta$1/17 cells, and then ultimately to T$\gamma\delta$1-like cells.



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## Regulation of IL-22 production by human Vγ2Vδ2 T cells

Generation of neonatal IL-22-producing (Tγδ22) Vγ2Vδ2 T cells require conditions very similar to those required to generate IL-17A-producing Vγ2Vδ2 T cells, namely, IL-1β, IL-6, and TGF-β [9]. Adult Tγδ22Vγ2Vδ2 T cells, much like adult Tγδ1/17, require IL-23, IL-1β, and TGF-β, and are independent of IL-6 [9]. However, under these conditions, fewer Vγ2Vδ2 T cells converted to the Tγδ22 lineage than to the Tγδ17 (or Tγδ1/17) lineage. This may reflect the requirement for TNF-α (not included in our study) and inhibition by TGF-β (since the 1 ng/ml concentration we used inhibited Th22 priming in the study by Duhen et al.) [84]. Additionally, the lack of ligands for the aryl hydrocarbon receptor (AHR; discussed below for IL-22-producing murine γδ T cells) might have inhibited Th22 development since we did not include AHR ligands, nor did we use Iscove's DMEM which has high levels of aromatic amino acids and favors Th17/Th22 differentiation [85]. Unlike murine CD4 αβ T cells, very few if any Vγ2Vδ2 T cells stimulated ex vivo produce both IL-17A and IL-22 cytokines [9]. Similarly, very few in vitro-polarized IL-17A-producing Vγ2Vδ2 T cells coproduce IL-22. This suggests that the Tγδ17 (and Tγδ1/17) lineage is distinct from the Tγδ22 lineage. As with Tγδ17 cells, IL-23 reduces the number of neonatal Tγδ22Vγ2Vδ2 T cells. Again we believe this is because under some conditions or at high concentrations, IL-23 can drive Tγδ22 cells to transition into Tγδ1 cells (perhaps by stimulating IL-12 production or by direct action). The Tγδ22 population, like the Tγδ1/17 population, consists of mixed populations of IFN-$\gamma^+$ and IFN-$\gamma^-$ cells. Future studies examining polarization to Tγδ22 in the presence of AHR ligands or additional cytokines such as IL-6 and TNF-α [84] are in progress.

## Role of IL-17A-producing Vγ2Vδ2 T cells in human microbial immunity

Relatively few studies have examined the role of human γδ T cells producing IL-17A and IL-22 in human immunity and autoimmunity. In our samples from ten healthy adult donors, an average of 1.1% of Vγ2Vδ2 T cells produced IL-17A. A similar, non-overlapping proportion of Vγ2Vδ2 T cells produced IL-22 (1.2%). Since Vγ2Vδ2 T cells constitute 5.25 ± 2.1% of total $CD3^+$ T cells, IL-17A- and IL-22-producing Vγ2Vδ2 T cells occur at frequencies of 1 in 2,762 and 1 in 1,864 T cells, respectively. Moreover, several donors showed increased frequencies of IL-$17^+$ Vγ2Vδ2 T cells (up to 1 in 906 T cells). Furthermore, in specific pathogen-free rhesus macaques, there was a five-fold increased baseline frequency of IL-17-producing Vδ2 T cells (5.6 ± 1.3%, ranging from 1.1 to 13.4%). This suggests that continued bacterial infections in humans may drive Tγδ17 cells to lose the ability to produce IL-17A.

Although the frequencies appear low, adult Vγ2Vδ2 T cells recognize most bacterial and Apicomplexan protozoan pathogens by virtue of their recognition of essential prenyl pyrophosphates, such as HMBPP, and a phospho-antigen produced by Gram-positive cocci (data not shown). Numerous bacterial and protozoan infections in humans (detailed in Table 1) are associated with major expansions of Vγ2Vδ2 T cells such that in some individuals, Vγ2Vδ2 T cells can constitute up to 50% of circulating T cells (one in two T cells) with increases to 10–25% commonly found (Table 1).

Essentially all adult Vγ2Vδ2 T cells recognize prenyl pyrophosphate antigens due to the extensive use of germ-line encoded regions of the Vγ2Vδ2 TCR for prenyl pyrophosphate recognition [86] and the selection for Jγ1.2 and a hydrophobic Vδ2 CDR3 residue that occurs during infancy [52, 87–90]. For example, 91 out of 94 adult Vγ2Vδ2 T cell clones (97%) were antigen-responsive [88, 91, 92]. Thus, the frequency of Vγ2Vδ2 T cells is actually the antigen-specific frequency and, therefore, is very high at 1 in 19 T cells [9]. In contrast, the frequency of αβ T cells specific for a particular peptide/MHC complex among naive cells is usually very low: 1:158,000–1:1,875,000 for CD4 [93] and 1:33,000–

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1:164,000 (four of six were >1:142,000) for CD8 [94]. Since essentially all IL-17A- and IL-22-producing Vγ2Vδ2 T cells are antigen-specific, during primary infections, Vγ2Vδ2 T cells and other unconventional T cells are likely to be important sources of early IL-17A and IL-22 until naive CD4 and CD8 *αβ* T cells can be expanded and differentiated into memory Th17/Tc17 and Th22/Tc22 cells.

Thus far, IL-17A production by *γδ* T cells has only been described in two human diseases, active tuberculosis and HIV infection. In response to active tuberculosis infection, Peng et al. [95] demonstrated increases in the proportion of peripheral blood *γδ* cells producing IL-17A, and decreases in the proportion producing IFN-*γ*. Similarly, exposure of peripheral blood mononuclear cells from either tuberculosis patients or healthy controls to *M. tuberculosis* antigens for 7 days dramatically expanded IL-17A$^+$ *γδ* T cells [95]. These results suggest that *M. tuberculosis* infection in vivo may expand blood IL-17A$^+$ *γδ* T cells. Although the role of *γδ* production of IL-17A in granuloma formation cannot be easily addressed in humans, murine studies would suggest an important role. Additional studies in this patient population are needed to define the *γδ* subsets producing IL-17A and the mechanism by which the *γδ* T cells become activated. Based on our results, we would hypothesize that *M. tuberculosis* infection stimulates IL-23 and IL-1*β* cytokine production by lung APCs, which together with TLR ligands and HMBPP, activate and expand IL-17A$^+$ Vγ2Vδ2 T cells.

To model human tuberculosis infections, Yao et al. [96] infected cynomolgus and rhesus macaques with *M. tuberculosis* and monitored cytokine production by T cells at various time points. After 4 weeks, statistically significant increases were observed in the percent of circulating T cells producing IL-22, but not IL-17A. However, in contrast to the work by Peng et al., they did not detect differences among the Vγ2Vδ2 T cells. There are several potential explanations for these differences. First and most significantly, Yao et al. stimulated Vγ2Vδ2 T cells only with HMBPP ex vivo, whereas Peng et al. restimulated Vγ2Vδ2 T cells with PMA and ionomycin (which allows maximal determination of IL-17A-producing cells). Second, Peng et al. study, examined cytokine production during reactivation of tuberculosis in chronically infected patients, whereas Yao et al. examined cytokine production at late time points in primary tuberculosis. And lastly, Yao et al. injected *M. tuberculosis* directly into the lung parenchyma via bronchoscopy, whereas Peng et al. examined patients who had acquired TB through a natural infection.

In a second human study, Fenoglio et al. [97] examined *γδ* T cells from healthy and HIV$^+$ individuals and found increased frequencies of circulating *γδ* T cells (mostly Vδ1) and a higher propensity for IL-17 and IFN-*γ* production by both Vδ1 and Vγ2Vδ2 T cells. More than one-third of Vδ1 and approximately one-half of Vγ2Vδ2 T cells isolated ex vivo contained intracellular IL-17A [97]. However, the ability to produce IL-17A was rapidly lost in vitro unless *Candida albicans* extract or *M. tuberculosis* purified protein derivative was included in the cultures for Vδ1 or Vγ2Vδ2 T cells, respectively. In the absence of the bacterial products, the ability to produce IL-17 by either subset was lost. This suggests that the bacterial products stimulate the correct cytokines to retain the ability to produce IL-17A and that in their absence, IL-17-producing *γδ* T cells convert to Tγδ1 T cells. Consistent with this possibility, IL-17A-producing Vδ1 and Vγ2Vδ2 T cells also produced IFN-*γ*, were CD161$^+$, and expressed RORγt and T-bet [97]. These results are similar to our findings. Unfortunately, their analysis did not extend to IL-22 production, nor did it address the specific factors present within the bacterial products that were required to retain IL-17A production. However, human memory CD4 *αβ* T cells specific for *C. albicans* include many Th17 cells [82] and IL-17A is essential for the control of *C. albicans* infections in mice [98]. Stimulation by *C. albicans* induces strong IL-17 responses due to the production of *β*-glucans and mannans that engage dectin-1 and mannose receptors, respectively, on APC

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[99]. This stimulates production of prostaglandin E2, which in turn, stimulates IL-6 and IL-23 production, thus favoring development of Th17 cells [99–101]. Similarly, *M. tuberculosis* infection stimulates both murine Th17 $\alpha\beta$ T cells and T$\gamma\delta$17 $\gamma\delta$ T cells [5] through production of ligands for TLR4 and dectin-1 [102]. Thus, rather than being specific for antigens in *C. albicans* extracts or purified protein derivative, these microbial products likely stimulate cytokine production to favor the maintenance and/or differentiation of T$\gamma\delta$17 cells.

There is evidence to suggest that IL-17 production by V$\gamma$2V$\delta$2 T cells in neonates and infants will be highly relevant to their resistance to infections. Newborns have intrinsic defects in both APC and conventional T cells resulting in poor adaptive immune responses to infection [103, 104]. Defective IL-12 production by neonatal APC is in part responsible for poor Th1 $\alpha\beta$ immunity. Instead of producing the Th1 cytokine, IL-12, neonatal APC produce IL-23, IL-1$\beta$, and IL-6 [105–108]. Because $\gamma\delta$ T cells are the first T cells to develop, do not require professional antigen processing or presentation, and respond to shared microbial isoprenoid antigens, they are uniquely poised to mount protective immune responses in neonates [109]. In fact, nearly every V$\gamma$2V$\delta$2 T cell will become activated prior to the age of 1 year by self or environmental antigens [53, 54]. From our studies on neonatal V$\gamma$2V$\delta$2 T cells, we know that the IL-1$\beta$, IL-6, and IL-23 cytokines promote the differentiation of T$\gamma\delta$1/17 T cells in vitro, and we propose that the same process occurs in vivo.

We speculate that neonatal V$\gamma$2V$\delta$2 T cells activated in response to a broad range of HMBPP-producing microbes, are polarized by the high levels of IL-23, IL-1$\beta$, and IL-6 into T$\gamma\delta$17 or T$\gamma\delta$1/17 T cells which, in the absence of strong Th1 immunity, function to immediately upregulate protective innate immune mechanisms. Because of repeated infections, most of these T$\gamma\delta$17 and T$\gamma\delta$1/17 T cells lose their ability to produce IL-17A and only produce IFN-$\gamma$ in adults. However, they are likely to retain some of the functional characteristics of T$\gamma\delta$17 cells. A method to determine the proportion of adult V$\gamma$2V$\delta$2 T cells derived from T$\gamma\delta$17 awaits the identification of markers for T$\gamma\delta$17 cells that have lost IL-17A production, but the proportion could be substantial.

## Role of IL-17A-producing V$\gamma$2V$\delta$2 T cells in human autoimmunity

The role of IL-17-producing V$\gamma$2V$\delta$2 T cells in human autoimmunity is also poorly studied. Human $\gamma\delta$ T cells coproducing IL-17A and IFN-$\gamma$ have been found in the synovial fluid and synovium of patients with rheumatoid arthritis [110]. Pollinger et al. found that all of the patients with rheumatoid arthritis examined had IL-17-and IFN-$\gamma$-coproducing $\gamma\delta$ T cells in the inflamed synovium. Moreover, in synovial fluid, the IL-17$^+$, IFN-$\gamma^+$ $\gamma\delta$ T cells occur at a frequency equal to that of the IL-17$^+$, IFN-$\gamma^+$ CD4 T cells. The authors attempted to translate the results seen in their murine collagen-induced arthritis (CIA) model of human rheumatoid arthritis, and concluded that IL-17-producing $\gamma\delta$ T cells do not drive bone destruction [110]. However, only three patients were examined in this study, and all were undergoing cortisone treatment. Thus, more patients will need to be studied before firm conclusions can be drawn. Moreover, human and murine $\gamma\delta$ T cells have quite different antigen specificities, anatomic localization, and cytokine potentials, and, therefore, are unlikely to function similarly in most diseases. Finally, these findings do not preclude a contribution by $\gamma\delta$ T cells to joint inflammation. Further studies in rheumatoid arthritis and other autoimmune diseases are needed to assess the pathogenic potential of IL-17-producing $\gamma\delta$ T cells, especially during the initiation of autoimmunity, where a small population of T cells can direct the subsequent development of specific T lineages.

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## IL-17A-producing murine γδ T cells

### Murine γδ T cells develop in thymic waves with poorly defined TCR specificity

Murine *γδ* T cells begin to develop prior to *αβ* T cells in thymic waves characterized by specific V gene combinations. The first waves produce invariant V*γ*5V*δ*1 and V*γ*6V*δ*1 TCRs that lack significant junctional diversity and exhibit tropism to the skin (dendritic epidermal T cells, DETC) and epithelial tissues, respectively [111] (in the nomenclature of Heilig and Tonegawa [112]). Postnatally, the thymus then switches to the production of highly diversified V gene segments (such as V*γ*4, V*γ*1, and V*δ*1) on *γδ* T cells that localize to secondary lymphoid organs [113]. A subset of these *γδ* T cells, expressing a variety of V*γ* and V*δ* regions, recognize the nonclassical MHC class I molecules, T10 and T22, through their expression of a CDR3*δ* motif of nine amino acids primarily encoded by D*δ*2 and containing six invariant residues [114]. T22 and T10 molecules are upregulated on activated immune cells, suggesting a role for these T10-/T22-specific *γδ* T cells during microbial responses [115]. Besides the H-2T molecules, a subpopulation of murine V*γ*4 T cells are restricted to lipid-presenting CD1d molecule in coxsackievirus-induced myocarditis [116]. The relationship between these V*γ*4 T cells and V*γ*4V*δ*4 T cells exhibiting limited diversity that are found in CIA [117] is unknown. Additionally, a ligand for the invariant skin V*γ*5V*δ*1 TCR is expressed by stressed keratinocytes, although the exact identity of the molecule is unknown. There have also been examples of murine *γδ* T cells specific for the herpes protein, gI [118], and H-2 MHC class II proteins (although this recognition does not involve peptides) [119]. Beyond these examples, most of the natural murine *γδ* antigens/ligands remain unknown. To date, IL-17A production has been documented for V*γ*1 [120], V*γ*4 [117, 120], V*γ*6V*δ*1 [8], and V*γ*5V*δ*1 DETC [121] *γδ* subsets.

### Regulation of IL-17A-producing murine γδ T cells: thymic imprinting of distinct γδ T cell subsets for IL-17A production

Unlike *αβ* T cells, murine *γδ* T cells can be developmentally imprinted to produce IFN-*γ* or IL-17A. Utilizing a T22 tetramer to identify H-2T-specific cells, Jensen et al. [122] found that tetramer-positive antigen-inexperienced *γδ* T cells that lack CD122 (IL-2R*β*) produce IL-17A, whereas antigen-experienced *γδ* T cells expressing CD122 produce IFN-*γ*. Similarly, IL-17A-producing peritoneal V*γ*6V*δ*1 T cells lack CD122 but express CD25 (IL-2R*α*) and originate from IL-17A-producing thymic precursors [123]. The appearance of IL-17A-producing thymic *γδ* T cells peaks at embryonic day 19, arguing against a role for exogenous antigen(s).

CD27 plays a critical role in determining whether *γδ* T cells produce IFN-*γ* or IL-17A (Fig. 2). CD27 expressed on thymic *γδ* T cells engages its ligand, CD70 (presumably expressed on thymic epithelial cells), while the *γδ* TCR likely binds to endogenous antigens resulting in trans-conditioning of thymic *γδ* T cells to produce IFN-*γ* [120]. CD27 ligation induces expression of the lymphotoxin-*β* receptor and other trans-conditioning genes, including *Crem*, *N24a2*, *Rgs2*, and *Rgs1*, in thymic V*γ*4 and V*γ*1 *γδ* T cells [120]. Thymic *γδ* T cells have high baseline expression of *Rorc* (which encodes ROR-*γ*t) and *Runx1*, but require CD27 signaling to upregulate *Tbx21* (which encodes T-bet) expression and to derepress the IFN-*γ* locus, which then enables them to produce IFN-*γ* [120] like CD4 *αβ* T cells [124]. In agreement with the other studies, the majority of CD27-negative, IL-17A-producing thymic *γδ* T cells did not express CD122 [122, 123].

Further characterization of adult thymic *γδ* T cells has revealed two distinct subsets, one being $CD27^-$, $CD122^-$, $CCR6^+$, and $NK1.1^-$ producing IL-17A, and the other being $CD27^+$, $CD122^+$, $CCR6^-$, and $NK1.1^+$ producing IFN-*γ*. Unlike human CD4 *αβ* and V*γ*2V*δ*2 T cells producing IL-17A, the segregation between IL-17A and IFN-*γ* production in

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the thymus appears stable and irreversible. No IL-17A$^+$, IFN-$\gamma^+$ dual-positive $\gamma\delta$ cells were observed [120]. Moreover, culturing IL-17A-producing CCR6$^+$ $\gamma\delta$ T cells with polarizing cytokines for the Th1 lineage (IL-12 and IL-18), or culturing IFN-$\gamma$-producing, NK1.1$^+$ $\gamma\delta$ cells with polarizing cytokines for the Th17 lineage (IL-23), fails to alter the cytokines produced [125]. Thus, unlike human $\alpha\beta$ and $\gamma\delta$ T cells, there appears to be little plasticity in thymic derived murine $\gamma\delta$ T cells producing IL-17A.

In addition to CD27, SCART2 scavenger receptors (related to CD5 and CD6 in humans and WC1.1 in cattle and sheep) are predominantly expressed on murine $\gamma\delta$ T cells and also identify $\gamma\delta$ T cells producing IL-17A [126]. SCART2$^{hi}$ $\gamma\delta$ T cells were found in peripheral lymph nodes and nearly all were V$\gamma$4$^+$, constituting about 25% of total V$\gamma$4$^+$ cells [126]. SCART2$^{hi}$ $\gamma\delta$ T cells were also found in the dermis but did not express V$\gamma$5V$\delta$1 DETC TCRs.

As discussed above for human $\alpha\beta$ and V$\gamma$2V$\delta$2 T cells, polarizing cytokines play a vital role in the differentiation of T cells into Th17/IL-17A-producing cells. In contrast to $\alpha\beta$ and neonatal V$\gamma$2V$\delta$2 T cells, neutralization of IL-6 has little effect on innate production of IL-17A by murine fetal thymic $\gamma\delta$ T cells [7, 123, 127]. Furthermore, IFN-$\gamma$ does not interfere with innate IL-17A production by thymic $\gamma\delta$ T cells [120]. IL-6 is required at some point for optimal IL-17A production since about 75% fewer peripheral IL-17A$^+$ $\gamma\delta$ T cells were noted in IL-6$^{-/-}$ mice [128].

Conflicting reports exist concerning the requirement for TGF-$\beta$ in the innate programming of IL-17A-producing thymic $\gamma\delta$ T cells. In fetal thymic organ cultures, neutralization of TGF-$\beta$ had no effect on the development of $\gamma\delta$ T cells producing IL-17A [123]. In contrast, in $\gamma\delta$ T cells from very young TGF-$\beta$-deficient mice prior to the development of lymphoproliferative disease, TGF-$\beta$ is required for the innate programming of IL-17A production by thymic and peripheral $\gamma\delta$ T cells [129]. One explanation for the different conclusions is that TGF-$\beta$ exerts its effects indirectly by inhibiting STAT4 and GATA-3 in $\gamma\delta$ T cells but has no effects on the expression of ROR-$\gamma$t. This has been observed for $\alpha\beta$ Th17 T cell differentiation where if the ability of $\alpha\beta$ T cells to differentiate into Th1 and Th2 lineages is blocked, then TGF-$\beta$ is not required for their differentiation into Th17 cells [43].

In contrast to the differing results on thymic innate programming, IL-23 clearly appears to have significant effects on IL-17A production by peripheral $\gamma\delta$ T cells [7, 120, 130]. IL-1 has also been shown to play a critical role in IL-17A production by mature peripheral $\gamma\delta$ T cells because IL-1R$^{-/-}$ mice show reduced production of IL-17A [6, 130]. Within mature splenic $\gamma\delta$ T cells, IL-23 functions with IL-1$\beta$ to further upregulate the constitutive expression of *Rorc* (ROR$\gamma$t) and *Il23r* [6]. This production of IL-17A in response to IL-23 is dependent on Tyk-2 [131], a member of the JAK family whose absence decreases phosphorylation of STAT3 [132]. Signals following IL-23R binding to IL-23 activate STAT3, which then binds and activates the *Il-17a* and *Il-17f* promoters [36]. IL-1R signaling appears to be required for maintenance of IL-23R expression in differentiated Th17 cells, and we assume that such signaling would be true of innately programmed $\gamma\delta$ T cells [133]. Together, these results suggest a mechanism, distinct from that of $\alpha\beta$ T cells, where $\gamma\delta$ T cells acquire IL-17A-producing capacity and differentiate into "memory"-type T cells in the thymus, perhaps by responding to endogenous TCR ligands. Although these IL-17-producing $\gamma\delta$ T cells respond to the normal cytokines that upregulate Th17 $\alpha\beta$ T cell function (such as IL-23 and IL-1$\beta$), they are firmly committed to producing only IL-17A and do not exhibit the plasticity of human $\alpha\beta$ and $\gamma\delta$ T cells which can acquire the ability to produce IFN-$\gamma$ and lose the ability to make IL-17A.

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## Regulation of IL-22-producing murine *γδ* T cells: requirement of the AHR

The development of murine *γδ* T cells producing IL-22 is less well understood. Thymic populations producing IL-22 have yet to be described. Therefore the bulk of knowledge comes from studies on peripheral *γδ* T cells and the development of IL-22-producing CD4 *αβ* T cells. The differentiation of *αβ* T cells into IL-22-producing cells (Th22 cells) requires engagement of the AHR (also known as the dioxin receptor). AHR is a ligand-dependent transcription factor that, upon engaging one of its ligands, binds the promoter region within dioxin-response genes and activates their transcription [134]. Ligands for AHR include numerous polycyclic aromatic hydrocarbons, both synthetic and naturally occurring. It is not known if there is a single, primary endogenous physiological ligand. Known ligands include 2,3,7,8-tetrachlorodibenzo-*p*-dioxin and the photoproduct of tryptophan, 6-formylindolo[3,2-*b*]carbazole (FICZ). AHR is upregulated in developing Th17 T cells [135] in response to the Th17 polarizing cytokines, TGF-*β* and IL-6, and in Tr1 regulatory cells in response to IL-27 [136]. AHR enhances naive T cell differentiation into Th17 cells by decreasing STAT1 activation, thereby enabling Th17 development [135]. The presence of AHR is required for production of IL-22 but not IL-17A or IL-17AF [85, 137].

Consistent with the reported effects of AHR activation on *αβ* T cells, injection the AHR ligand, FICZ, with heat-killed mycobacteria induces expansion of peritoneal *γδ* cells that produce both IL-17A and IL-22. IL-22 production is highly dependent upon the presence of the AHR because *γδ* T cells from $AHR^{-/-}$ mice do not produce IL-22 but do produce IL-17A [7]. V*γ*6V*δ*1 T cells in the lung are another peripheral IL-22-producing population that produce IL-22 in response to repeated stimulation by *Bacillus subtilis* in a lung fibrosis model [138]. This production of IL-22 by V*γ*6V*δ*1 T cells has been found to be critical to avoiding lung fibrosis in this model. Although some CD4 *αβ* T cells are reported to produce both IL-17A and IL-22, there were two distinct subsets of V*γ*6V*δ*1 T cells in the lung setting, those producing IL-22 and those producing IL-17A [138]. Very few V*γ*6V*δ*1 cells produced both cytokines, which is identical to what we observed with V*γ*2V*δ*2 T cells [9]. $AHR^{d/d}$ mice, that express an AHR with lower affinity, produce reduced amounts of IL-22 compared to wild-type mice. However, the levels of IL-17A and IL-17F are similar [138]. These results point to similarities between IL-22 production by Th17 *αβ* T cells and innately programmed *γδ* T cells since both require AHR.

## Functions of IL-17A-/IL-22-producing murine *γδ* T cells in microbial immunity

IL-17A-producing murine *γδ* T cells are protective during many bacterial and fungal infections. An early indication of the importance of IL-17A production by *γδ* T cells is the ability of *γδ* and *αβ* NKT cells to control neutrophil levels in adhesion molecule-deficient mice [139]. The rapid production of IL-17A is an important property of *γδ* and unconventional *αβ* T cells and helps protect against microbial infections. This ability is critically dependent on their expression of the IL-23R [128].

*γδ* T cells can rapidly produce IL-17A, independent of foreign antigens, upon TLR and/or cytokine stimulation. This early production of IL-17A occurs in *Escherichia coli* infections where peritoneal IL-17A can be found as early as 1 h after infection and peaks at 6 h with neutrophil levels peaking at 24 h [8]. The IL-17A is produced by V*δ*1 *γδ* T cell since production is significantly impaired in V*δ*1-deficient mice [8]. Furthermore, IL-23 is sufficient to induce IL-17A production from *γδ* T cells purified from the infected peritoneum [8]. Similarly, IL-17A production by peritoneal *γδ* T cells rapidly reaches a peak 12 h after injection of heat-killed mycobacteria [7] or after sepsis due to cecal puncture [140]. IL-17A production requires TLR2 signaling and is amplified by IL-23 signaling, although it is not clear whether the *γδ* T cells were directly responding to the TLR stimulus [7].

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In another study, lipopolysaccharide TLR4 and $PAM_3CysSerLys_4$ TLR2 ligands were directly injected into the peritoneal cavity where they stimulated the expansion of IL-17A$^+$ $\gamma\delta$ T cells [141]. Production of IL-23 and IL-1$\beta$ by activated myeloid cells in the peritoneum stimulates CD27$^-$ $\gamma\delta$ T cells to expand and produce IL-17A [141]. No direct response to TLR ligands is observed with purified $\gamma\delta$ T cells in vitro. However, they do expand and produce IL-17A when cultured with exogenous IL-23 and IL-1$\beta$ [141]. In contrast, infection with murine herpesvirus 4 or malaria parasites stimulates the expansion of CD27$^+$ IL-17A$^-$ $\gamma\delta$ T cells that produce IFN-$\gamma$ [141].

Taken together, these results indicate that CD27 expression divides peritoneal $\gamma\delta$ T cells into a CD27$^+$ IFN-$\gamma$-producing subset that requires CD27 signaling and a CD27$^-$ IL-17A-producing subset that responds to IL-23 and IL-1$\beta$ cytokines released by myeloid cells in response to innate immune signals [141]. All of these findings, however, do not preclude the requirement for recognition by the $\gamma\delta$ TCR of self ligands since there is evidence that such self ligands are constitutively expressed on murine cells when detected by soluble multimeric $\gamma\delta$ TCR [142, 143].

In addition to increasing neutrophil numbers and recruiting them to the sites of infection, IL-17A-producing $\gamma\delta$ T cells can also promote the formation of abscesses and granulomas to help mediate containment of microbial infections. In cutaneous *Staphylococcus aureus* infections, IL-17A-producing skin V$\gamma$5V$\delta$1 T cells play a critical role in immunity. Their production of IL-17A helps to recruit neutrophils into skin abscesses and limits the size of abscesses and the number of *S. aureus* bacteria that they contain [121].

In *Listeria monocytogenes* infections, IL-17A-producing V$\gamma$6 paired with V$\delta$1 [144] and V$\gamma$4 $\gamma\delta$ T cells contribute to bacterial clearance by containing the bacteria within granulomas in the liver [145] and recruiting neutrophils and other myeloid cells. Without $\gamma\delta$ T cells or IL-17A, bacterial numbers are more than 100-fold higher. Moreover, *L. monocytogenes* infections in $\gamma\delta$ T cell-deficient mice are associated with large inflammatory lesions in the liver with necrotic hepatocytes [146, 147] that are indistinguishable from those seen in IL-17A-deficient mice [145]. IL-23 and IL-17R signaling are required to control *L. monocytogenes* systemic infections and $\gamma\delta$ T cells are the principal source of IL-17A early in infection [148] although CD4$^-$8$^-$ $\alpha\beta$ T cells also produce IL-17A in the peritoneum [128].

The formation of lung granulomas during mycobacterial infections is critical to containing these infections. Here again, IL-17A production by murine lung $\gamma\delta$ T cells, expressing V$\gamma$4 and V$\gamma$6 [149] paired with V$\delta$1 TCRs [144], are critical for the recruitment of granulocytes and monocytes into pulmonary granulomas in *M. bovis* BCG-infected mice [149, 150]. In fact, during *M. tuberculosis* infections in mice, IL-17A production is primarily from $\gamma\delta$ and other unconventional T cells, rather than from CD4 and CD8 $\alpha\beta$ T cells [5]. Both IL-23 and IL-17A are essential for protective vaccine responses to subsequent *M. tuberculosis* challenge [151], and mice unable to produce IL-17A have impaired maturation of BCG-induced granulomas with low numbers of $\gamma\delta$ T cells [149]. An identical phenotype has been noted in mice lacking V$\gamma$4 and V$\gamma$6 T cells [149]. IL-17A is critical in *M. tuberculosis* infections since mice lacking IL-17A have 30-fold higher bacterial counts associated with poor granuloma formation [149].

Additional mechanisms for protection by IL-17A- or IL-22-producing $\gamma\delta$ T cells include the induction of antimicrobial peptides and the remodeling of the extracellular matrix. Individually, IL-17A and IL-22 can upregulate expression of the antimicrobial peptides, $\beta$-defensin-2, S100A7, S100A8, and S100A9 by keratinocytes [32]. The combination of IL-17A and IL-22 is synergistic for induction of antimicrobials [152]. Such antimicrobials are especially important to mucosal immunity since they are broadly active and rapidly

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microbicidal. IL-17A also induces tissue remodeling proteins such as MMP-1, -3, -9 and -13, and aggrecanase-1 (see above). IL-22 also induces MMP-1 and MMP-3. MMP-9 and MMP-13 are important in bone homeostasis and repair, whereas MMP-1 is important in collagen remodeling and keratinocyte migration [32, 153]. MMP-3 is normally induced in response to skin injury and contributes to wound contraction [154].

## Functions of IL-17A-/IL-22-producing murine $\gamma\delta$ T cells in autoimmunity

IL-17A-producing $\gamma\delta$ T cells can also prove pathogenic. Several autoimmune disease models have identified IL-17A-producing $\gamma\delta$ T cells as being important in disease progression. As with any T cell population, inappropriate or sustained production of a proinflammatory cytokine can have devastating consequences. For example, in a model of CIA, oligoclonal IL-17A-producing V$\gamma$4 $\gamma\delta$ T cells accumulate in the lymph nodes and joints of collagen-injected mice [117]. Depletion of V$\gamma$4 $\gamma\delta$ T cells greatly reduces disease severity consistent with a significant reduction in pathogenic anticollagen IgG2a [117]. IL-17A production by the joint-infiltrating $\gamma\delta$ T cells is regulated by IL-23 and IL-1$\beta$ but not by collagen itself [155]. This study, however, found a heterogeneous population of $\gamma\delta$ T cells that produce IL-17A expressing V$\gamma$1, V$\gamma$2, V$\gamma$4, or V$\gamma$6 paired with either V$\delta$1 or V$\delta$5. IL-17A production by $\gamma\delta$ T cells is also observed in the methylated bovine serum albumin antigen-induced arthritis model—another model that uses complete Freund's adjuvant (containing *M. tuberculosis*) with antigen to induce arthritis [156].

IL-17A induces the production of MMPs by synoviocyte and inhibits new matrix synthesis by chondrocytes, which together results in cartilage destruction of the joints [15, 157–159]. IL-17A also affects the delicate balance between bone formation by osteoblasts and bone resorption by osteoclasts. IL-17A favors osteoclast differentiation through the induction of RANKL. This results in unbalanced bone resorption and loss of bone mass [20]. Although equal numbers of $\alpha\beta$ and $\gamma\delta$ T cells produce IL-17A in joints with CIA, CD4 $\alpha\beta$ T cells localize to bone and their deletion abrogates bone destruction. This suggests that CD4 $\alpha\beta$ T cells help mediate bone destruction while $\gamma\delta$ T cells increase overall joint inflammation [110].

In two different models of neuroinflammation, $\gamma\delta$ T cells play an important role in early activation and recruitment of cells through the release of IL-17A. In a mouse model of multiple sclerosis, experimental autoimmune encephalomyelitis (EAE), $\gamma\delta$ T cells producing IL-17A accumulate in the brain [6, 122, 160]. Like the CIA model, IL-17A production by these cells requires IL-1$\beta$ and IL-23 [6]. Although $\gamma\delta$ cells alone are not sufficient to reconstitute disease ($\alpha\beta$ T cells are also required), $\gamma\delta$-deficient mice have reduced EAE severity [6]. In addition to producing IL-17A, $\gamma\delta$ T cells also inhibit CD4 Treg responses in EAE and reverse Treg suppression of $\alpha\beta$ T cells in vitro [161].

IL-17A-mediated neuroinflammation also plays a major role in the pathogenesis of ischemia–reperfusion brain injury. In a mouse model of middle cerebral artery occlusion followed by reperfusion, Shichita et al. [162] identified IL-17A-producing $\gamma\delta$ T cells within the infarct areas. In IL-17A-, IL-23- or $\gamma\delta$ T cell-deficient mice, the infarct volume is reduced. IL-17A is especially neurotoxic in that it induces blood–brain barrier disruption and mediates recruitment of cells into the CNS [162–164]. From these studies a common mechanism emerges in which neuroinflammation resulting in local IL-23 and IL-1$\beta$ induces infiltrating $\gamma\delta$ T cell production of IL-17A, independently of a defined $\gamma\delta$ TCR antigen.

Besides classic autoimmune diseases, $\gamma\delta$ T cells producing IL-17A and IL-22 also play important roles in the development of inflammatory responses during infections/ environmental exposures that cause tissue damage. Thus, in hypersensitivity pneumonitis induced by repeated inhalation of the nonpathogenic *B. subtilis* bacteria, V$\gamma$6V$\delta$1 T cells

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accumulate in the lung and produce IL-17A [165]. This accumulation requires live bacteria, whereas CD4 $\alpha\beta$ T cell recruitment does not [166]. In the absence of IL-17A signaling, bacteria persist longer in the lung and the mice develop increased lung inflammation and fibrosis [165]. The absence of V$\gamma$6V$\delta$1 T cells also leads to increased lung inflammation and fibrosis [166]. Besides IL-17A, V$\gamma$6V$\delta$1 T cells also produce IL-22 [138]. V$\gamma$6V$\delta$1 production of IL-22 requires the AHR and protects against lung fibrosis, whereas treatment with anti-IL-22 monoclonal antibodies increases fibrosis [138]. Similarly, the presence of IL-17A-producing $\gamma\delta$ T cells shorten the recovery period in bleomycin-induced lung injury [167]. In contrast, in experimental silicosis both $\gamma\delta$ and CD4 $\alpha\beta$ T cells mediate inflammation and the mice go on to develop fibrosis even in the absence of IL-17A (or IL-22) and even when treated with IL-22 [168]. Finally, in another murine model of "Farmer's lung" caused by *Saccharopolyspora rectivirgula*, V$\gamma$6V$\delta$1 T cells again accumulate (albeit in lesser numbers) but there is no attenuation of lung fibrosis by $\gamma\delta$ T cells although fibrosis does require IL-17A [169]. Thus, $\gamma\delta$ T cells can mediate inflammation and can aid healing of lungs without fibrosis by producing IL-22, but their function varies according to the initiating stimuli.

IL-17A-producing $\gamma\delta$ T cells also likely promote myocarditis in murine coxsackievirus B3-induced myocarditis [170, 171]. Murine V$\gamma$4$^+$ $\gamma\delta$ T cells in infected mice are the earliest T cells infiltrating the myocardium where they are activated by CD1d and promote myocarditis [172]. A second population of $\gamma\delta$ T cells expressing V$\gamma$1 receptors suppresses the development of myocarditis [170]. V$\gamma$4$^+$ T cells can transfer myocarditis and kill infected cardiocytes [173], and their deletion decreases myocarditis [174]. Anti-IL-17A antibody treatment ameliorates disease and improves survival [171], suggesting that these V$\gamma$4$^+$ $\gamma\delta$ T cells produce IL-17A as in other diseases.

## Concluding remarks

Unlike murine $\gamma\delta$ T cells, human V$\gamma$2V$\delta$2 T cells acquire IL-17A production post-thymically through a mechanism similar to Th17 polarization of $\alpha\beta$ T cells (Fig. 1). Naive V$\gamma$2V$\delta$2 in the presence of HMBPP-producing microbes and the cytokines IL-6, IL-1$\beta$, and TGF-$\beta$ upregulate expression of ROR$\gamma$t and become IL-17A-secreting T$\gamma\delta$17 cells. In the absence of these cytokines, V$\gamma$2V$\delta$2 T cells upregulate T-bet expression leading to the generation of T$\gamma\delta$1 which have high levels of IL-12R$\beta$2 and respond to IL-12. T$\gamma\delta$17 cells likely express both IL-12R$\beta$2 and IL-23R, enabling them to become T$\gamma\delta$1/17 (through IL-23 signaling) or functionally T$\gamma\delta$1 (through IL-12 signaling), or to maintain the T$\gamma\delta$17 phenotype (through IL-23, IL-1$\beta$, and TGF-$\beta$ signaling).

Murine thymic $\gamma\delta$ T cells have basal expression of ROR$\gamma$t and Runx1 (Fig. 2), which in the absence of antigen and through thymic trans-conditioning, yield IL-17A-producing $\gamma\delta$ T cells. Alternatively, $\gamma\delta$ T cells, which possibly encounter antigen in the thymus, upregulate T-bet and become IFN-$\gamma$ producing T$\gamma\delta$1 cells. Phenotypically, the IL-17A-producing $\gamma\delta$ cells express IL-23R, CD25, and CCR6 whereas IFN-$\gamma$-producing $\gamma\delta$ cells express NK1.1, CD27, and CD122. The IL-17A-producing $\gamma\delta$ T cells require IL-23 and IL-1 in the periphery to maintain and reinforce expression of ROR$\gamma$t and production of IL-17A, whereas T$\gamma\delta$1 cells require IL-12. Ligation of the AHR and its association with c-MAF, mediates acquisition of IL-22 production by the T$\gamma\delta$17 cells.

The involvement of IL-17A- and IL-22-producing $\gamma\delta$ T cells in many diverse models of microbial, autoimmune, and inflammatory diseases underscores their importance in the initiation and resolution of acute inflammatory responses in a variety of settings. Despite their small numbers, $\gamma\delta$ T cells can have large effects on the type of immune response and the disease outcome.

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## Abbreviations

| | |
|---|---|
| **APC** | Antigen-presenting cell |
| **AHR** | Aryl hydrocarbon receptor |
| **CIA** | Collagen-induced arthritis |
| **DETC** | Dendritic epidermal T cells |
| **EAE** | Experimental autoimmune encephalomyelitis |
| **FICZ** | 6-Formylindolo[3,2-*b*]carbazole |
| **HMBPP** | (*E*)-4-Hydroxy-3-methyl-but-2-enyl pyrophosphate |
| **IL** | Interleukin |
| **IPP** | Isopentenyl pyrophosphate |
| **MHC** | Major histocompatibility complex |
| **MMP** | Matrix metalloproteinase |
| **NKT** | Natural killer T |
| **ROR** | Retinoid-related orphan receptor |
| **STAT** | Signal transducer and activator of transcription |
| **TCR** | T cell antigen receptor |
| **TLR** | Toll-like receptor |

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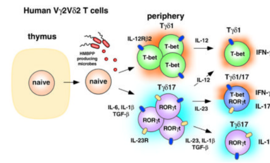


**Fig. 1.**

Regulation of IL-17A-producing human $\gamma\delta$ T cells. Human V$\gamma$2V$\delta$2 T cells are peripherally programmed to become T$\gamma\delta$17 through the effects of IL-6, IL-1$\beta$, and TGF-$\beta$ in the presence of HMBPP. These cells can then be maintained as T$\gamma\delta$17 through the action of IL-23, IL-1$\beta$, and TGF-$\beta$, or they can acquire IFN-$\gamma$ potential through IL-23 signaling. T$\gamma\delta$1/17 T cells commonly lose the ability to produce IL-17A altogether and revert functionally to T$\gamma\delta$1-like cells through IL-12 signaling

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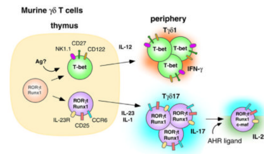


**Fig. 2.**

Murine *γδ* T cells are thymically programmed to produce IL-17A in the absence of exogenous antigen. IL-23 and IL-1 are required by peripheral T*γδ*17 T cells to maintain IL-17A production. Ligation of the AHR by these cells leads to the coproduction of IL-17A and IL-22. Murine *γδ* cells appear to show firm commitment to the T*γδ*17 lineage and most do not acquire the ability to produce IFN-*γ*

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**Table 1**

Expansion of human $\gamma\delta$/V$\gamma$2V$\delta$2 T cells in response to infection

| Infection | $\gamma\delta$ T cells, mean (max) % of T cells | | Reference |
|---|---|---|---|
| | **Normal subjects** | **Patients** | |
| Bacterial | | | |
| Tuberculosis | 6 | 14 (35) | [175] |
| | 2 | 6 (17) | [176] |
| TB contacts | 5 | 10 (18) | [177] |
| TB meningitis | 3 | 4 (80% V$\gamma$2V$\delta$2) | [178] |
| Leprosy reversal reaction | 5 | 29[a] | [179] |
| Tularemia | 3 | 33 | [180] |
| | 7 | 31 (48) | [181] |
| | 5 | 25 (50) | [182] |
| Salmonellosis | 5 | 18 (48) | [183] |
| Legionellosis | 5 | 15 (42) | [184] |
| Brucellosis | 4 | 29 (48) | [185] |
| Q-fever (*Coxiella burnetii*) | 4 | 16 (30) | [186] |
| Ehrlichiosis | 5 | 57 (97) | [187] |
| Meningitis (*H. influenzae*) | 7 | 27 (37) | [188] |
| Meningitis (*N. meningitidis*) | 7 | 25 (42) | [188] |
| Meningitis (*S. pneumoniae*) | 7 | 35 (46) | [188] |
| Listeriosis | 2 | 12 (33) | [189] |
| Protozoal parasites | | | |
| Acute malaria (non-endemic) | 4 | 16 (26) | [190] |
| | 5 | 16 (27) | [191] |
| | 3 | 18 (46) | [192] |
| Malarial paroxysm | 4 | 11 (27) | [193] |
| Toxoplasmosis | 4 | 9 (15) | [194] |
| Leishmaniasis, visceral | 8 | 44 | [195] |
| Leishmaniasis | 3 | 13 (18) | [196] |
| Leishmaniasis, localized | 4 | 20[a] | [179] |

[a] % $\gamma\delta$ T cells among $CD3^{+}$ T cells in skin lesions.