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### Permalink

<https://escholarship.org/uc/item/6ph392q7>

### Journal

Seminars in Immunopathology, 41(5)

### ISSN

1863-2297

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### Publication Date

2019-09-01

### DOI

10.1007/s00281-019-00752-5

Peer reviewed



Published in final edited form as:

*Semin Immunopathol.* 2019 September ; 41(5): 595–605. doi:10.1007/s00281-019-00752-5.

## $\gamma\delta$ T cells in rheumatic diseases: from fundamental mechanisms to autoimmunity

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### Abstract

The innate and adaptive arms of the immune system tightly regulate immune responses in order to maintain homeostasis and host defense. The interaction between those two systems is critical in the activation and suppression of immune responses which if unchecked may lead to chronic inflammation and autoimmunity.  $\gamma\delta$  T cells are non-conventional lymphocytes, which express T cell receptor (TCR)  $\gamma\delta$  chains on their surface and straddle between innate and adaptive immunity. Recent advances in  $\gamma\delta$  T cell biology have allowed us to expand our understanding of  $\gamma\delta$  T cell in the dysregulation of immune responses and the development of autoimmune diseases. In this review, we summarize current knowledge on  $\gamma\delta$  T cells and their roles in skin and joint inflammation as commonly observed in rheumatic diseases.

### Keywords

$\gamma\delta$  T cells; T cell receptor (TCR); bone remodeling; autoimmune diseases; skin and joint inflammation; psoriatic arthritis

### Introduction

T cells are categorized into distinct types of T cells based on the type of T cell antigen receptors (TCRs) and include  $\alpha\beta$ T and  $\gamma\delta$ T cells, which express  $\alpha\beta$ TCRs and  $\gamma\delta$ TCRs,

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respectively [1].  $\alpha\beta$  T cells are usually found in peripheral tissues and circulatory system whereas  $\gamma\delta$  T cells may reside in blood and lymphoid tissue as well as epithelial environments such as the skin, gastrointestinal tract, or genitourinary tract, where they have important functions in tissue homeostasis and inflammatory response [1]. Although  $\gamma\delta$  T cells only comprise a small portion of all T lymphocytes (0.5–5%), they represent a larger proportion of T cells in certain tissues, such as the murine skin and lymph nodes [2,3].  $\gamma\delta$  T cells have different functions in distinct pathophysiological conditions as driven by their tissue-specific microenvironments and tropism. These non-conventional T cells bridge the innate and adaptive immune systems by sharing functions with antigen presenting cells, pro-inflammatory and cytotoxic effector cells, and immune-regulatory cells [4,5]. Depending on the particular subset, the stimulus and the microenvironment,  $\gamma\delta$  T cells are able to produce the effector cytokines of Th1, Th2, and Th17 cells, such as IFN- $\gamma$ , IL-4 and IL-13, and IL-22 and IL-17, respectively, as well as chemokines including CCL5/RANTES, CXCL10/IP-10, XCL1/lymphotactin [6–9]. They thus have the capacity to regulate both pro-inflammatory and anti-inflammatory responses and orchestrate the specific recruitment of further leukocyte populations. Subsets of  $\gamma\delta$  T cells may also express FOXP3, a master regulator in the development and function of regulatory T cells, thereby assuming regulatory roles [10]. Moreover,  $\gamma\delta$  T cells can influence specific antibody responses, and as consequence serum antibody levels including IgG1, IgG2b, and IgE are reduced in  $\gamma\delta$  T cell deficient (TCR $\delta^{-/-}$ ) mice [11].  $\gamma\delta 17$  T cells have similar features with Th17 cells, which express CC-chemokine receptor 6 (CCR6), IL-23 receptor, retinoic acid receptor-related orphan receptor- $\gamma$ t (ROR $\gamma$ t) and aryl hydrocarbon receptor (AhR), as well as the secretion of IL-17 and IL-22 [12]. Since  $\gamma\delta$  T cells exhibit critical functions in innate and adaptive immunity, their dysregulation has been involved in the pathogenesis of rheumatic diseases [13–16]. The cytokine milieu of the local microenvironment regulates the development and activation of each  $\gamma\delta$  T cell subtype. In succession, the unique characteristics of each subtype subsequently determine the effectiveness of immune regulation in maintaining homeostasis and self-tolerance or its ineffectiveness and rise of pathologic outcomes resulting in chronic inflammation and autoimmunity. Thus, the molecular events that dictate the development and activation of  $\gamma\delta$  T cell subtypes are of primary importance. As the role of T cell receptor signaling in  $\gamma\delta$  T cell development was recently reviewed [17], this review will focus on the human and murine  $\gamma\delta$  T cell subtypes in the pathogenesis of skin and joint inflammation.

## Human and murine $\gamma\delta$ T cell subtypes in innate and adaptive immunity

### Human $\gamma\delta$ T cells

In humans,  $\gamma\delta$  T cells can be categorized into two major subtypes based on the expression of TCR  $\delta$  chain: V $\delta$ 1 and V $\delta$ 2 T cells [18]. The diversity and complexity of  $\gamma\delta$  T cells are results of specific V $\delta$ /V $\gamma$  pairing. Preferentially, the V $\delta$ 1 chain is paired with different V $\gamma$ I family members (V $\gamma$ 2/3/4/5/8) whereas V $\delta$ 2 is typically (but not exclusively) paired with the V $\gamma$ 9 chain [19,20] (Table 1). Although not common, there are descriptions of V $\gamma$ 9V $\delta$ 1 in the literature associated with viral infection and cancer [21]. In addition to these major populations, non-V $\delta$ 1 and non-V $\delta$ 2  $\gamma\delta$ T cells are also found in healthy humans. V $\delta$ 3<sup>+</sup> T cells, are often paired with V $\gamma$ 2 or V $\gamma$ 3, and can be found in peripheral blood and liver [22].

V $\delta$ 4<sup>+</sup>, V $\delta$ 6<sup>+</sup>, V $\delta$ 7<sup>+</sup>, and V $\delta$ 8<sup>+</sup> T cells are detected in the peripheral blood of lymphoma patients but these subtypes have not been well characterized [23]. V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup>  $\gamma\delta$  T cells are the dominant population in the peripheral blood [24]. Among human  $\gamma\delta$  T cell subtypes, V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup>  $\gamma\delta$  T cells have been the most studied, given their abundance in peripheral blood and their ease to be expanded and manipulated in cell culture. These cells possess a 'phosphoantigen'-reactive semi-invariant TCR and are central to protective host immune responses against microbial pathogens producing the corresponding metabolites [24]. While the antigen specificity of the vast majority of  $\gamma\delta$  T cells remains elusive [25], the TCR of a V $\gamma$ 4<sup>+</sup>V $\delta$ 5<sup>+</sup> clone directly binds endothelial protein C receptor (EPCR), a major histocompatibility complex-like molecule [26]. Moreover, the recognition of target cells by  $\gamma\delta$  T cells required a multi-molecular stress signature composed of EPCR and costimulatory ligand(s) demonstrating that  $\gamma\delta$  TCR mediates recognition of broadly stressed human cells by engaging a stress-regulated self-antigen [26]. While the specificity of most human  $\gamma\delta$  T cell receptors remains elusive, the breadth of possible ligands appears to span MHC and MHC-related molecules, surface-expressed and soluble proteins as well as small peptides and lipids [25].

Human  $\gamma\delta$  T cells play essential roles in the innate immunity response. V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells induce monocyte differentiation into antigen presenting cells through release of IFN- $\gamma$ , TNF- $\alpha$ , GM-CSF, and IL-4, as well as recruitment, activation and differentiation of neutrophils [27–30]. Freshly isolated human peripheral blood  $\gamma\delta$  T (V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup>) cells can function as professional phagocytes via antibody opsonization and CD16 (Fc $\gamma$ RIII), leading to antigen processing and presentation on MHC class II [31]. V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells also efficiently process and display antigens and provide co-stimulatory signals sufficient for strong induction of naïve  $\alpha\beta$  T cell proliferation and differentiation [32]. The adaptive immune responses of  $\gamma\delta$  T cells are demonstrated by memory-like V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells in vaccinated humans which persist for as long as 7 months post the secondary vaccination [33]. Besides the memory function,  $\gamma\delta$  T cells also regulate adaptive immune through interaction with B cells. V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells induce the expression of essential B-cell co-stimulatory molecules including CD40L, OX40, CD70, and ICOS, which are important to drive immunoglobulin (Ig) isotype switching in B cells [34–36]. Human V $\delta$ 2<sup>+</sup> and V $\delta$ 3<sup>+</sup>  $\gamma\delta$  T cells both induce expression of maturation markers (CD40, CD86) and secretion of antibodies by B cells [37,36]. Activated V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells can produce CXCL13, a B cell attracting chemokine, which is key in recruiting B cells to secondary lymphoid tissue and establishing germinal centers and the production and affinity maturation of class-switched antibodies [5,38,39]. Consequently, CXCR5 identifies a unique subset of V $\gamma$ 9V $\delta$ 2 T cells which secrete IL-2, IL-4, and IL-10 and help B cells for antibody production [40]. Collectively, human  $\gamma\delta$  T cells display a broad array of functional activities as summarized in Figure 1 [5,41].

### Murine $\gamma\delta$ T cells

The murine  $\gamma\delta$  literature can be confusing due to the various nomenclatures that have been used to number the individual  $\gamma$  and  $\delta$  receptors. The International Immunogenetics Information System (IMGT) is the most up-to-date resource for TCR genes, although their numbering system does not match with how these cells are historically and most commonly

referred to. Although the functions of murine  $\gamma\delta$  T cell subtypes are only partially understood, at least 2 major functionally distinct  $\gamma\delta$  T cell subsets have been identified including  $V\gamma 1^+$  and  $V\gamma 4^+$   $\gamma\delta$  T cells which have similar features with human peripheral blood  $\gamma\delta$  T cells [42] Table 1 and Fig. 1. Murine  $V\gamma 1^+$  and  $V\gamma 4^+$   $\gamma\delta$  T cells require direct interaction with  $CD8^+$  dendritic cells (DCs) in lymphoid tissues for their functional development [43]. IL 23 drives differentiation of peripheral  $\gamma\delta 17$  T cells from adult bone marrow derived precursors [44]. Moreover, different populations of  $\gamma\delta$  T have different levels of IL-23R expression as  $V\gamma 1^+$  and  $V\gamma 4^+$   $\gamma\delta$  T cells express IL-23R differently *in vivo* and *in vitro* [45]. For example, when compared to their IL-23R expression in naïve mice,  $V\gamma 4^+$   $\gamma\delta$  T cells express high levels of IL-23R in immunized mice whereas  $V\gamma 1^+$   $\gamma\delta$  T cells from either naïve or immunized mice only expressed IL-23R at low or very low levels [45]. In addition,  $V\gamma 4^+V\delta 4^+$  T cells are found in joints and joint-draining lymph nodes in experimental models of skin and joint inflammation. The vast majority produces IL-17, which contributes to the development of collagen-induced arthritis (CIA) and imiquimod-induced skin inflammation (a model of psoriasis) [46–50].

Dendritic epidermal  $\gamma\delta$  T cells (DETCs) characteristically express  $V\gamma 5^+V\delta 1^+$  TCRs and normally reside in the mouse skin (nomenclature according to *Heilig and Tonegawa*) [51,52].  $V\gamma 6^+V\delta 4^+$  T cells (most commonly referred to as  $V\gamma 6^+V\delta 1^+$  T cells) share the exact same CDR3 a.a sequence (CACWDSSGFHKVF) [53] as the  $V\gamma 5^+V\delta 1^+$  cells but these cells reside predominantly at mucosal sites. Both subtypes express identical  $\delta 1$  chains encoding the same CDR3 a.a. sequence (CGSDIGGSSWDTRQMFF). Skin epidermal  $V\gamma 5^+V\delta 1^+$  DETCs were originally thought to be the only resident  $\gamma\delta$  T cell population in the skin, although now other  $\gamma\delta$  T cell populations have also been detected. In addition,  $V\gamma 5^+$  T cells with the same CDR3 sequence have now been detected at very low frequencies in the lymph nodes. However, in general the  $V\gamma 5^+V\delta 1^+$  DETCs appear to be the major non-circulating skin-resident  $\gamma\delta$  T cell population in the skin. Skint-1, a thymic epithelial cell determinant, selectively determines the functional phenotype of  $V\gamma 5^+V\delta 1^+$  fetal thymocytes by inducing an *Egr3*-mediated pathway, provoking differentiation and IFN- $\gamma$  production while suppressing the  $\gamma\delta$  T cell lineage factor, *Sox13*, and a ROR $\gamma$ t transcription factor-associated IL-17-producing capacity [51]. Moreover, Skint-1 is essential for the development in the thymus and the establishment of the DETC population in the skin [54,55]. A recent study showed that signaling via the NF- $\kappa$ B-inducing kinase (NIK) is important for the full development of functional  $V\gamma 5^+$  dendritic epidermal T cell (DETCs) [56].  $V\gamma 6^+V\delta 1^+$  T cells are rare in most normal tissues but are the dominant  $\gamma\delta$  T cell population in the female reproductive tract, oral mucosa and lung [57–59].  $V\gamma 6^+V\delta 4^+$  T cells preferentially expand in skin-draining lymph nodes following *S. aureus* skin infection and mediate long-term immunity to *S. aureus* [53].

$\gamma\delta$  T cells can act as both positive and/or negative regulators of innate immune responses via myeloid cell activation. RNA-Seq analysis of  $\gamma\delta$  T cells from infected mice demonstrate that  $\gamma\delta$  T cells highly express several growth factors, chemokines, and other proteins known to control myeloid cell recruitment, activation, and differentiation (*Csf1*, *Ccl3*, *Ccl4*, *Ccl5*, *Ccl6*, *Ccr12*) [60]. M-CSF (encoded by *Csf1*) is known to promote development and polarization of macrophages whereas CCL3 and CCL5 are specific ligands of CCR3 and CCR5 receptors [61], which are critical for neutrophil migration [62] (Fig. 2). Consistently,

Jiang *et al* demonstrated that dermal  $\gamma\delta$  T cells are required for recruitment of Gr-1<sup>+</sup>CD11b<sup>+</sup> neutrophils into skin during skin inflammation [63]. In keeping with these observations, we recently demonstrated that  $\gamma\delta$  T cells blockade inhibited the expansion and recruitment of neutrophils in blood and spleen as well as neutrophil migration into the joint in a murine experimental arthritis model [64]. Negative regulatory roles of  $\gamma\delta$  T cells in myeloid cell activity have also been described during wound healing [65]. Specifically,  $\gamma\delta$  T cells suppress the infiltration of macrophages (F4/80<sup>+</sup>CD11b<sup>+</sup>) and myeloid derived suppressor cells (CD11b<sup>+</sup>Gr1<sup>+</sup>) during skin wound healing [65]. In addition, Toll-Like receptor 2 (TLRs), which has critical roles in early innate immunity and initiate immune responses, is expressed in freshly isolated  $\gamma\delta$  T cells although its exact role in  $\gamma\delta$  T cells is not completely understood [66]. Activated  $\gamma\delta$  T cells are also capable of expressing MHC class II and co-stimulatory molecules (CD40 and CD80) presenting the specific antigen to other adaptive immune cells [67]. Collectively, murine  $\gamma\delta$  T cells regulate innate immune responses via multiple pathways including direct activation of TLR pathways in neutrophil and monocytes, and antigen presentation.

Key features of the adaptive immune system are antigen specificity and generation of immunologic memory which provides a rapid and robust immune response [68]. Although specific antigens for murine  $\gamma\delta$  T cells have not been well characterized,  $\gamma\delta$  T cells have the ability to recognize and are specifically stimulated by a different repertoire of antigens derived from bacteria [69], small peptides [67], and tumor cells [25]. Interestingly, a memory feature is observed in murine  $\gamma\delta$  T cells where memory-like V $\gamma$ 4<sup>+</sup>  $\gamma\delta$ T17 cells are detected, respond more rapidly, and produce more IL-17 which leading to a faster skin inflammatory response in a murine skin inflammation model [47]. IL-17-producing memory  $\gamma\delta$  T cells promote inflammation in both involved and uninvolved psoriatic-like lesions in a murine model of psoriasis [70,71]. In addition,  $\gamma\delta$  T cells modulate systemic antibody levels including all major subclasses and especially IgE antibodies as well as affect IL-4 production, B-cell activation, and B-cell tolerance [72]. Moreover, intraepithelial-resident  $\gamma\delta$  T cells have a unique role in initiating and regulating IgE production, driving an early innate-like response, which directs a subsequent adaptive response [73]. High-throughput antibody sequencing revealed that  $\gamma\delta$  T cells shape the IgE repertoire by supporting specific variable-diversity-joining (VDJ) rearrangements [73]. Also,  $\gamma\delta$  T cells control humoral immune response by inducing T follicular helper (Tfh) cell differentiation [74]. In summary,  $\gamma\delta$  T cells can regulate a plethora of innate and adaptive immune responses (Fig. 2).

## Pathophysiology of $\gamma\delta$ T cells in autoimmunity

$\gamma\delta$  T cell subsets contribute to tissue damage and development of experimental autoimmune diseases including psoriasis-like disease [13], collagen-induced arthritis [46], colitis [75], autoimmune uveitis [76] and experimental autoimmune encephalomyelitis (EAE) [77]. Inflammatory functions of  $\gamma\delta$  T cells are defined by their cytokine production, including IL-17, IFN- $\gamma$ , and TNF- $\alpha$ , which are commonly involved in autoimmunity (Table 2). Different subsets of  $\gamma\delta$  T cells are associated with different autoimmune diseases as depending on their tissue expression, and function may contribute to pathogenicity. Apart from the implication of  $\gamma\delta$  T cells in psoriasis, which is well established [78,79]; several studies suggest that  $\gamma\delta$  T cells are involved in the pathogenesis of rheumatoid arthritis (RA)

[80–82]. In RA patients, peripheral  $V\gamma 9^+V\delta 2^+$  T cells, which express high levels of chemokine receptors CCR5 and CXCR3, migrate into the synovium and secrete IFN- $\gamma$  and IL-17 [81]. Also in juvenile idiopathic arthritis (JIA),  $V\gamma 9^+V\delta 2^+$  T cells are a major synovial fluid T cell population and their proliferation is regulated by  $CD4^+CD25^+FOXP3^+$  T cells, thus controlling synovial inflammation [83].  $V\gamma 9^+V\delta 2^+$  T cells could play a critical negative-feedback role in ameliorating disease in JIA patients by inducing apoptosis of rheumatoid synovial fibroblasts [83]. The specific subtypes and tissues involved in these pathologies are considered below.

### Inflammatory arthritis and bone remodeling

In collagen-induced arthritis (CIA), IL 17–producing  $\gamma\delta$  T cells are detected in the joint, and their numbers are significant higher than Th17 cells suggesting that  $\gamma\delta$  T cells are the major source of IL-17A in the joint [15]. Using the same model, Roark *et al* found an increased number of  $V\gamma 1^+$  and  $V\gamma 4^+$  T cells in the joints but only the  $V\gamma 4^+$  cells were activated and produced IL-17 during CIA [46]. Moreover, depletion of  $V\gamma 4^+$  T cells showed a significant reduction in disease incidence and severity that correlated with a reduction of total IgG and IgG2a anti-collagen antibodies [46].  $V\gamma 4^+$   $\gamma\delta$  T cells increase rapidly and appear to be specifically responsive to the collagen/CFA injections, whereas the  $V\gamma 1^+$  subset does not, suggesting that antigen-driven clonal and/or memory response is predominantly via the  $V\gamma 4^+$   $\gamma\delta$  T cell subset [46]. In the CIA model, treatment with IL-28A dramatically reduces numbers of pro-inflammatory IL-17–producing  $\gamma\delta$  T cells in the joints and inguinal lymph nodes, to exert an anti-inflammatory effect further highlighting the importance of the  $\gamma\delta$  T cells in joint inflammation and inflammatory arthritis [84]. Apart from the CIA model,  $\gamma\delta$  T cells have been important modulators of inflammatory arthritis in the experimental models using IL-1Ra-deficient mice and IL-23 gene transfer. In the IL-1Ra-deficient mice, both  $V\gamma 6^+$  and  $V\gamma 4^+$   $\gamma\delta$  T cells were observed to the joints, but only the  $V\gamma 6^+$  subset efficiently produced IL-17 [85] whereas functional depletion of  $\gamma\delta$  T cells showed protective effects by preventing neutrophil accumulation in the blood, spleen and bone marrow as well as by reducing neutrophil infiltration into the joints of the IL-23 gene transfer mice [64]. Collectively, these results suggest functional specific roles of each murine  $\gamma\delta$  T cell subtypes in the different disease models.

A common denominator between  $\gamma\delta$  T cell subtypes is IL-17 expression, and IL-17 $^+$  $\gamma\delta$  T cell subtypes in both human and mouse affect physiological bone remodeling. IL-17 induces RANKL from stromal cells as well as RANK receptor expression and thus can modulate bone resorption via the osteoclasts [86,87]. Recent studies have also shown that IL-17 can induce osteogenic activity *in vitro* in both murine and human cells [88,89]. A role of IL-17 in bone formation is also supported by recent evidence observed in SpA patient derived human cells and an SpA experimental model [90]. Another study demonstrated that the IL-17A $^+V\gamma 6^+$  T cell subtype modulates bone regeneration and bone fracture healing through stimulating the proliferation and differentiation of osteoblasts in the drill-hole injury murine model [91].

Although the human and murine data are in agreement regarding IL-17 actions, there are other cytokines produced by  $\gamma\delta$  T cells that affect bone remodeling and need to be

considered. In humans, the effects of  $\gamma\delta$  T cells on osteoclastogenesis differ between “activated” and “freshly isolated”  $\gamma\delta$  T cells [92]. Specifically, “activated”  $\gamma\delta$  T cells inhibit osteoclastogenesis through secretion of high levels of IFN- $\gamma$  (anti-osteoclastogenic) whereas “freshly isolated”  $\gamma\delta$  T cells enhance osteoclast differentiation by production of high levels of IL-6 [92]. In addition, human V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells inhibit immature dendritic cells (DCs) trans-differentiation into osteoclasts [93]. Microarray analysis of human immature dendritic cells (iDCs) identified that expression of osteoclast related genes including *c-Fos*, ATPase H + transporting V0 subunit d (ATP6V0D2), RANK and cathepsin K was decreased when iDCs were co-cultured with  $\gamma\delta$  T cells, indicating that  $\gamma\delta$  T cells inhibited osteoclastogenesis through the RANK/*c-Fos*/ATP6V0D2 signaling pathway [93].

### Skin inflammation

In the murine skin, there are distinct populations of  $\gamma\delta$  T cells including V $\gamma$ 5<sup>+</sup>V $\delta$ 1<sup>+</sup> T cell subsets which localize in the epidermis [94] whereas V $\gamma$ 4<sup>+</sup> and V $\gamma$ 6<sup>+</sup> T cell subsets are resident in the dermis [95]. V $\gamma$ 5<sup>+</sup>V $\delta$ 1<sup>+</sup> DETCs are responsible for wound healing by secreting keratinocyte growth factors and inflammatory cytokines (IFN- $\gamma$ , TNF, and IL-13) [94,96] whereas the V $\gamma$ 4<sup>+</sup> and V $\gamma$ 6<sup>+</sup> T cell subsets contribute to the development of skin inflammatory disease by production of IL-17 [13,97]. A spontaneous mutation in *Sox13*, a developmental transcription factor, causes defect in development of dermal V $\gamma$ 4<sup>+</sup>  $\gamma\delta$ 17 T cells in mice and protects the mice from psoriasis-like skin inflammation, suggesting that dermal V $\gamma$ 4<sup>+</sup>  $\gamma\delta$ 17 T cells mature in the neonatal thymus in a *Sox13*-dependent manner [98]. In the imiquimod (IQM)-induced skin inflammation model, V $\gamma$ 4<sup>+</sup>V $\delta$ 4<sup>+</sup> T cells are long lived and persist in the skin long after the initial inflammation, thus memory V $\gamma$ 4<sup>+</sup>V $\delta$ 4<sup>+</sup> T cells mediate the severity of IQM secondary challenge [71]. Follow up studies demonstrated that V $\gamma$ 4<sup>+</sup> T cells predominantly induce skin inflammation and are the major IL-17 producers [99]. Specifically, adiponectin, a mediator of insulin metabolism, inhibits production of IL-17 by murine dermal V $\gamma$ 4<sup>+</sup>  $\gamma\delta$  T cells through binding of AdipoR1, and Adiponectin deficient mice showed severe skin inflammation with elevated infiltration of V $\gamma$ 4<sup>+</sup>  $\gamma\delta$ 17 T cells in the epidermis [99]. In addition, dermal  $\gamma\delta$  T cells are regulated by CD69, an activation marker that regulates secretion of IL-22 through aryl hydrocarbon receptor (AhR). CD69-deficient mice had lower expression of epidermal IL-22 and STAT3 which attenuated skin inflammation, compared with wild-type mice [79]. In humans, dermal V $\gamma$ 9<sup>+</sup>V $\delta$ 2<sup>+</sup> T cells express CCR6 and produce inflammatory mediators including IL-17A, TNF- $\alpha$ , IFN- $\gamma$ , CXCL8, and CCL4 upon activation with specific antigen [78]. Collectively, these results show that dermal  $\gamma\delta$ 17 T cells are regulators of skin inflammation, and their modulation could prevent skin inflammation.

### Enthesitis

V $\gamma$ 6<sup>+</sup>  $\gamma\delta$  T cells have been detected in the murine enthesitis [100], suggesting that they may play a role in the development of enthesitis. However, other groups have previously demonstrated that enthesitis can occur in the absence of  $\gamma\delta$  T cells [101]. Notably, the mice used in these studies were of different backgrounds and thus the difference in MHC complex may account for additional immune activation signals that may be required to induce an inflammatory response. Follow up studies in human enthesitis detected the presence of  $\gamma\delta$  T



cells (on the basis of TCR expression) and constituted a very small fraction of the total lymphocyte population [102,103].

## Concluding remarks

In different conditions,  $\gamma\delta$  T cells have multiple distinct functions and may act as antigen presenting cells, pro-inflammatory and/or immune-regulatory cells. Moreover, translation of murine experimental models to human disease can be challenging. Recent RNA-Seq analysis of healthy murine and human skin transcriptomes demonstrated that  $\gamma\delta$  T cells which are highly expressed in murine skin are relatively rare in human skin, and the ratio of  $\gamma\delta$  T cells to  $\alpha\beta$  T cells increases only modestly in the setting of psoriasis [104]. These data partly reflect the differences of various  $\gamma\delta$  T cell subtypes between mouse and human as there is no equivalent of mouse DETCs ( $V\gamma5^+V\delta1^+$ ) in healthy human epidermis and only around 4% of dermal leukocytes expresses  $\gamma\delta$  TCR as reviewed previously [105]. Similar observations may be possible for other tissues implicated in the pathogenesis of rheumatic diseases given the multifunctionality of  $\gamma\delta$  T cell subsets and/or clonal plasticity combined with the plethora of effector functions exhibited by  $\gamma\delta$  T cells that govern autoimmunity. Nevertheless as our imaging and genetic tools increase [106], we are moving closer to a detailed understanding of individual  $\gamma\delta$  T cell subtypes and/or their cytokines that could be a promising therapy for modulation of immune responses in multiple autoimmune diseases.

## Acknowledgments

Financial support

This work was supported by National Institutes of Health/National Institute of Arthritis and Musculoskeletal and Skin Diseases Grant R01AR062173, and a National Psoriasis Foundation Translational Research grant to IEA. EM was supported by (1DP2OD008752).

Conflict of interest

IEA has received grants, salary, consulting fees from Schering Plough Biopharma/Merck, Novartis, Pfizer and Tanabe Research Labs USA. The authors have no other conflicts of interest to declare.

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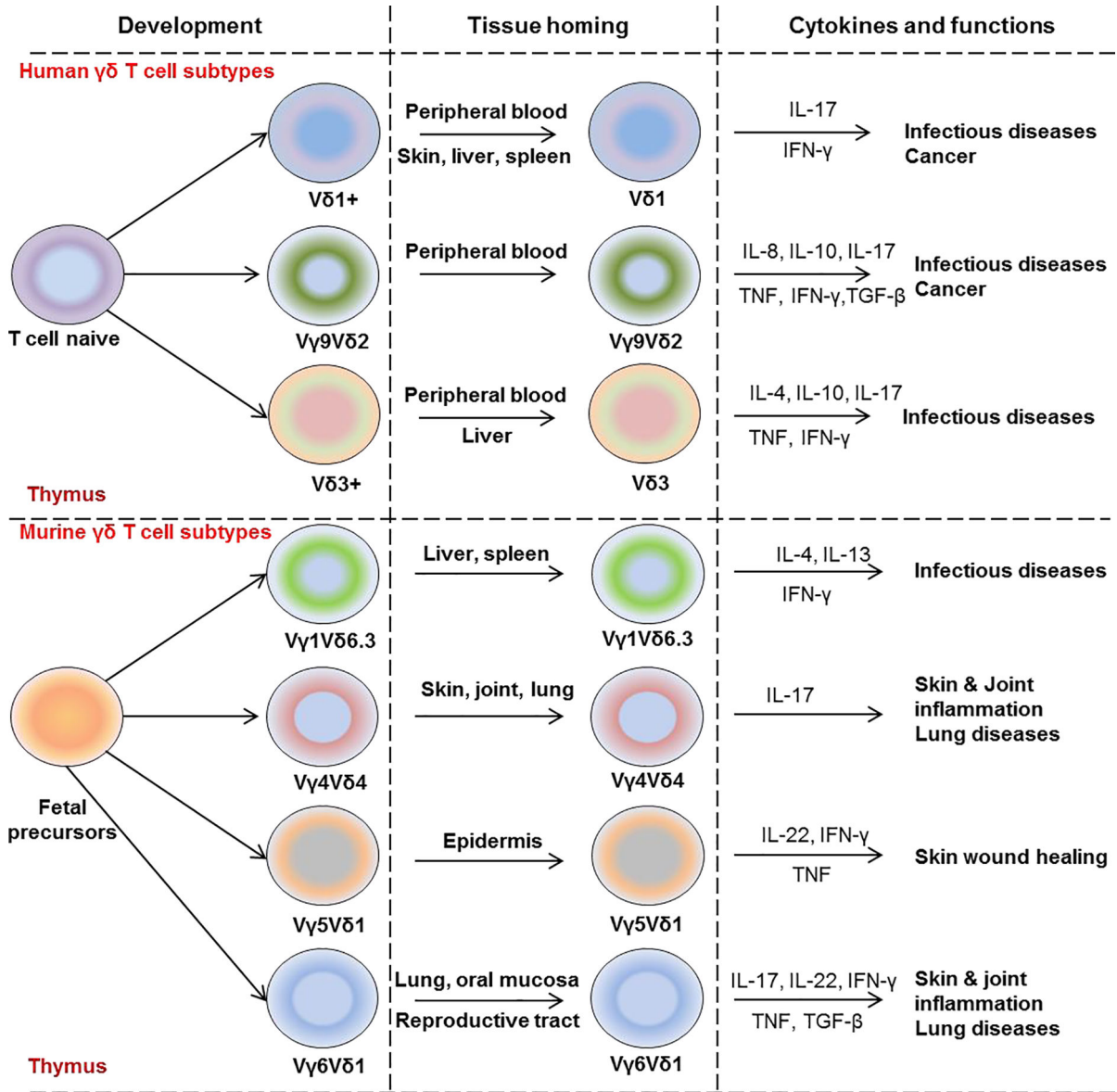
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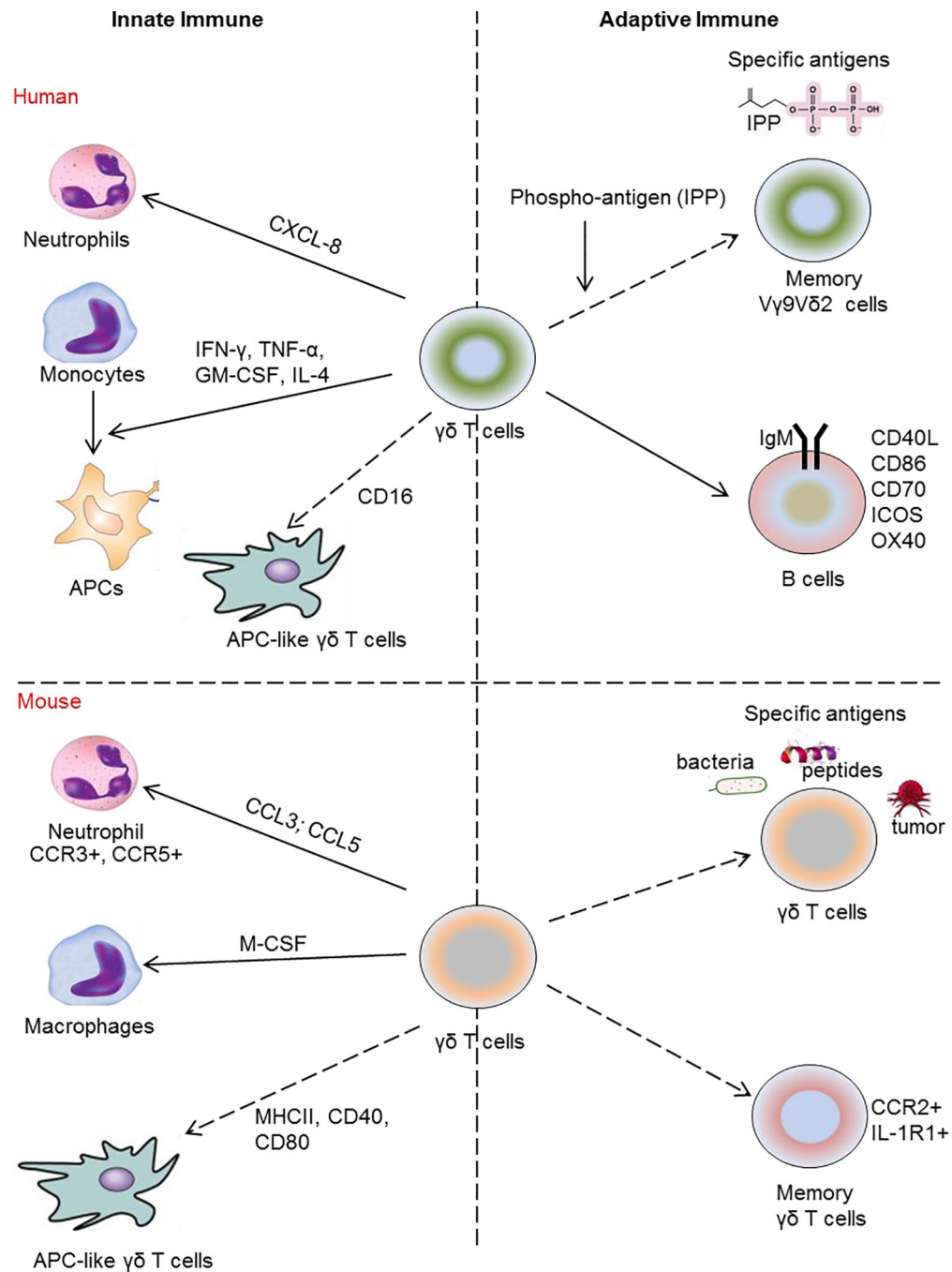
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**Figure 1: Overview of  $\gamma\delta$  T cell functional programming in human and mouse.**

Schematic illustration of  $\gamma\delta$  T cell development from naïve fetal precursors in human (upper panel) and mouse (lower panel) thymus. Human naïve  $\gamma\delta$  T cells differentiate into  $V\delta 1^+$   $\gamma\delta$  T subtypes found in peripheral blood, skin, liver, and spleen and produce IL-17 and IFN- $\gamma$ ;  $V\gamma 9^+V\delta 2^+$   $\gamma\delta$  T cells found in the peripheral blood and produce predominantly TNF and IFN- $\gamma$  as well as IL-8, IL-10, IL-17;  $V\delta 3^+$  found in peripheral blood and liver and produce several cytokines such as IL-4, IL-10, IL-17, TNF, and IFN- $\gamma$ . In mouse,  $V\gamma 1^+V\delta 6.3^+$   $\gamma\delta$  T cells normally resident in lymphoid tissues including spleen and liver and produce IL-4, IL-13, and IFN- $\gamma$ .  $V\gamma 4^+V\delta 4^+$   $\gamma\delta$  T cells are found in the skin, joint, and lung and known as IL-17-producing  $\gamma\delta$  T cells.  $V\gamma 5^+V\delta 1^+$  are residents in epidermis, produce IL-17, TNF, IFN- $\gamma$  whereas  $V\gamma 6^+V\delta 1^+$  have been found in the female reproductive tract and oral mucosa and produce IL-17, IL-22, TNF, IFN- $\gamma$  and TGF- $\beta$ .



**Figure 2: Functional roles of human/murine  $\gamma\delta$  T cells in immune responses.**

The figure illustrates the roles of human (upper panel) and mouse (lower panel)  $\gamma\delta$  T cells in innate and adaptive immune responses. In human,  $\gamma\delta$  T cells induce neutrophil migration through regulation of CXCL8 production, monocyte differentiation into antigen presenting cells (APCs) through release of IFN- $\gamma$ , TNF- $\alpha$ , GM-CSF, and IL-4 and function as a professional phagocyte via antibody opsonization and CD16 (Fc $\gamma$ RIII), leading to antigen processing and presentation on MHC class II. For adaptive immune responses, non-peptide phospho-antigens are specific antigens for  $V\gamma 9^+V\delta 2^+$   $\gamma\delta$  T and also induce robust

expansion of memory  $V\gamma 9^+V\delta 2^+$ .  $\gamma\delta$  T cells induce the expression of essential B-cell co-stimulatory molecules including CD40L, CD86, CD70, OX40, and ICOS as well as secretion of IgM by B cells.

In mouse,  $\gamma\delta$  T cells regulate macrophages and neutrophils through release of M-CSF (responsible for macrophages polarization), CCL3 and CCL5 (chemokines for neutrophil migration). Activated  $\gamma\delta$  T cells are also capable of expressing MHC class II and co-stimulatory molecules (CD40 and CD80) presenting the specific antigen to other immune cells. For adaptive immune responses,  $\gamma\delta$  T cells have the ability to recognize and are specifically stimulated by a different antigens derived from bacteria, small peptides, and tumor cells and function as memory  $\gamma\delta$  T cells ( $CCR2^+$  and  $IL-1R^+$ ).

**Table 1:**

Subsets of human and murine  $\gamma\delta$  T cells [107,42].

V $\gamma$ gene	Paired V $\delta$ gene	Tissue resident
<b>Human</b>		
V $\gamma$ 2 <sup>+</sup> , V $\gamma$ 3 <sup>+</sup> , V $\gamma$ 4 <sup>+</sup> , V $\gamma$ 5 <sup>+</sup> , V $\gamma$ 8 <sup>+</sup> , V $\gamma$ 9 <sup>+</sup>	V $\delta$ 1 <sup>+</sup>	Peripheral blood, skin, gut, spleen, liver.
V $\gamma$ 9 <sup>-</sup> /V $\gamma$ 9 <sup>+</sup>	V $\delta$ 2 <sup>+</sup>	Peripheral blood and solid tissues.
V $\gamma$ 2 <sup>+</sup> , V $\gamma$ 3 <sup>+</sup> , V $\gamma$ 4 <sup>+</sup>	V $\delta$ 3 <sup>+</sup>	Peripheral blood, liver.
<b>Murine</b>		
V $\gamma$ 1 <sup>+</sup>	V $\delta$ 5 <sup>+</sup> , V $\delta$ 6.3 <sup>+</sup>	Lung, colon.
V $\gamma$ 4 <sup>+</sup>	V $\delta$ 4 <sup>+</sup>	Skin, brain, lung, colon, joint.
V $\gamma$ 5 <sup>+</sup>	V $\delta$ 1 <sup>+</sup>	Skin.
V $\gamma$ 6 <sup>+</sup>	V $\delta$ 1 <sup>+</sup>	Lung, reproductive tract and oral mucosa.

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**Table 2:**

Functions of murine  $\gamma\delta$  T cell subsets in some inflammatory diseases.

$\gamma\delta$ T subsets	Functions	References
V $\gamma$ 1 <sup>+</sup>	Pathogenesis of airway hyper responsiveness	[108]
V $\gamma$ 4 <sup>+</sup>	Development of collagen-induced arthritis Pathogenesis of autoimmune uveitis Disruption of intestinal homeostasis (colitis) Development of psoriasis induced by IL-17, IL-22	[46] [76] [109] [110]
V $\gamma$ 5 <sup>+</sup>	Protective roles in skin wound healing (V $\gamma$ 5 <sup>+</sup> V $\delta$ 1 <sup>+</sup> )	[94]
V $\gamma$ 6 <sup>+</sup>	IL-17-mediated inflammation of joint (arthritis) Pathogenic roles in psoriasis (V $\gamma$ 6 <sup>+</sup> V $\delta$ 1 <sup>+</sup> ) Protective roles in pulmonary fibrosis (V $\gamma$ 6 <sup>+</sup> V $\delta$ 1 <sup>+</sup> )	[85] [97] [111]

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