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REVIEW

γδ 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. γδ T cells are non-conventional lymphocytes, which express T cell receptor (TCR) γδ chains on their surface and straddle between innate and adaptive immunity. Recent advances in of γδ T cell biology have allowed us to expand our understanding of γδ T cell in the dysregulation of immune responses and the development of autoimmune diseases. In this review, we summarize current knowledge on γδ T cells and their roles in skin and joint inflammation as commonly observed in rheumatic diseases.

Keywords γδ 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 αβT and γδ T cells, which express αβTCRs and γδTCRs, respectively [1]. αβ T cells are usually found in peripheral tissues and circulatory system whereas γδ 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 γδ T cells only comprise a small portion of all T lymphocytes (0.55%), they represent a larger proportion of T cells in certain tissues, such as the murine skin and lymph nodes [2, 3]. γδ 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, γδ T cells are able to produce the effector cytokines of Th1, Th2, and Th17 cells, such as IFN-γ, IL-4 and IL-13, and IL-22 and IL-17, respectively, as well as chemokines including CCL5/RANTES, CXCL10/IP-10, and 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 γδ T cells may also express FOXP3, a master regulator in the development and function of regulatory T cells, thereby assuming regulatory roles [10]. Moreover, γδ T cells can influence specific antibody responses, and as consequence serum antibody levels including IgG1, IgG2b, and IgE are reduced in γδ T cell–deficient (TCRδ$^{-/-}$) mice [11].

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γδ17 T cells have similar features with Th17 cells, which express CC-chemokine receptor 6 (CCR6), IL-23 receptor, retinoic acid receptor-related orphan receptor-γt (RORγt), and aryl hydrocarbon receptor (AhR), as well as the secretion of IL-17 and IL-22 [12]. Since γδ 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 γδ 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 γδ T cell subtypes are of primary importance. As the role of T cell receptor signaling in γδ T cell development was recently reviewed [17], this review will focus on the human and murine γδ T cell subtypes in the pathogenesis of skin and joint inflammation.

Human and murine γδ T cell subtypes in innate and adaptive immunity

Human γδ T cells

In humans, γδ T cells can be categorized into two major subtypes based on the expression of TCR δ chain: Vδ1 and Vδ2 T cells [18]. The diversity and complexity of γδ T cells are results of specific Vδ/Vγ pairing. Preferentially, the Vδ1 chain is paired with different VγI family members (Vγ2/3/4/5/8) whereas Vδ2 is typically (but not exclusively) paired with the Vγ9 chain [19, 20] (Table 1). Although not common, there are descriptions of Vγ9Vδ1 in the literature associated with viral infection and cancer [23]. In addition to these major populations, non-Vδ1 and non-Vδ2 γδ T cells are also found in healthy humans. $Vδ3^+$ T cells are often paired with Vγ2 or Vγ3 and can be found in peripheral blood and liver [24]. $Vδ4^+$, $Vδ6^+$, $Vδ7^+$, and $Vδ8^+$ T cells are detected in the peripheral blood of lymphoma patients, but these subtypes have not been well characterized [25]. $Vγ9^+Vδ2^+$ γδ T cells are the dominant population in the peripheral blood [26]. Among human γδ T cell subtypes, $Vγ9^+Vδ2^+$ γδ 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 [26]. While the antigen specificity of the vast majority of γδ T cells remains elusive [27], the TCR of a $Vγ4^+Vδ5^+$ clone directly binds endothelial protein C receptor (EPCR), a major histocompatibility complex-like molecule [28]. Moreover, the recognition of target cells by γδ T cells required a multi-molecular stress signature composed of EPCR and costimulatory ligand(s) demonstrating that γδ TCR mediates recognition of broadly stressed human cells by engaging a stress-regulated self-antigen [28]. While the specificity of most human γδ T cell receptors remains elusive, the breadth of possible ligands appears to span MHC and MHC-related molecules, and surface-expressed and soluble proteins as well as small peptides and lipids [27].

Human γδ T cells play essential roles in the innate immunity response. $Vγ9^+Vδ2^+$ T cells induce monocyte differentiation into antigen presenting cells through release of IFN-γ, TNF-α, GM-CSF, and IL-4, as well as recruitment, activation, and differentiation of neutrophils [29–32]. Freshly isolated human peripheral blood γδ T ($Vγ9^+Vδ2^+$) cells can function as professional phagocytes via antibody opsonization and CD16 (FcγRIII), leading to antigen processing and presentation on MHC class II [33]. $Vγ9^+Vδ2^+$ T cells also efficiently process and display antigens and provide co-stimulatory signals sufficient for strong induction of naïve αβ T cell proliferation and differentiation [34]. The adaptive immune responses of γδ T cells are demonstrated by memory-like $Vγ9^+Vδ2^+$ T cells in vaccinated humans which persist for as long as 7 months post the secondary vaccination [35]. Besides the memory function, γδ T cells also regulate adaptive

Table 1 Subsets of human and murine γδ T cells [21, 22]

Vγ gene	Paired Vδ gene	Tissue resident
Human		
$Vγ2^+$, $Vγ3^+$, $Vγ4^+$, $Vγ5^+$, $Vγ8^+$, $Vγ9^+$	$Vδ1^+$	Peripheral blood, skin, gut, spleen, liver
$Vγ9^-/Vγ9^+$	$Vδ2^+$	Peripheral blood and solid tissues
$Vγ2^+$, $Vγ3^+$, $Vγ4^+$	$Vδ3^+$	Peripheral blood, liver
Murine		
$Vγ1^+$	$Vδ5^+$, $Vδ6.3^+$	Lung, colon
$Vγ4^+$	$Vδ4^+$	Skin, brain, lung, colon, joint
$Vγ5^+$	$Vδ1^+$	Skin
$Vγ6^+$	$Vδ1^+$	Lung, reproductive tract and oral mucosa

immune through interaction with B cells. Vγ9$^+$Vδ2$^+$ 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 [36–38]. Human Vδ2$^+$ and Vδ3$^+$ γδ T cells both induce expression of maturation markers (CD40, CD86) and secretion of antibodies by B cells [38, 39]. Activated Vγ9$^+$Vδ2$^+$ 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, 40, 41]. Consequently, CXCR5 identifies a unique subset of Vγ9Vδ2 T cells which secrete IL-2, IL-4, and IL-10 and help B cells for antibody production [42]. Collectively, human γδ T cells display a broad array of functional activities as summarized in Fig. 1 [5, 43].

Murine γδ T cells

The murine γδ literature can be confusing due to the various nomenclatures that have been used to number the individual γ and δ 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 γδ T cell subtypes are only partially understood, at least 2 major functionally distinct γδ T cell subsets have been identified including Vγ1$^+$ and Vγ4$^+$ γδ T cells which have similar features with human peripheral blood γδ T cells [21] (Table 1 and Fig. 1). Murine Vγ1$^+$ and Vγ4$^+$ γδ T cells require direct interaction with CD8$^+$ dendritic cells (DCs) in lymphoid tissues for their functional development [44]. IL-23 drives differentiation of peripheral γδ17 T cells from adult bone marrow–derived precursors [45]. Moreover, different populations of γδ T have different levels of IL-23R expression as Vγ1$^+$ and Vγ4$^+$ γδ T cells express IL-23R differently in vivo and in vitro [46]. For example, when compared with their IL-23R expression in naïve mice, Vγ4$^+$ γδ T cells express high levels of IL-23R in immunized mice whereas Vγ1$^+$ γδ T cells from either naïve or immunized mice only expressed IL-23R at low or very low levels [46]. In addition, Vγ4$^+$Vδ4$^+$ T cells are found in joints and joint-draining lymph nodes in experimental models of skin and joint inflammation. The vast majority produces IL-

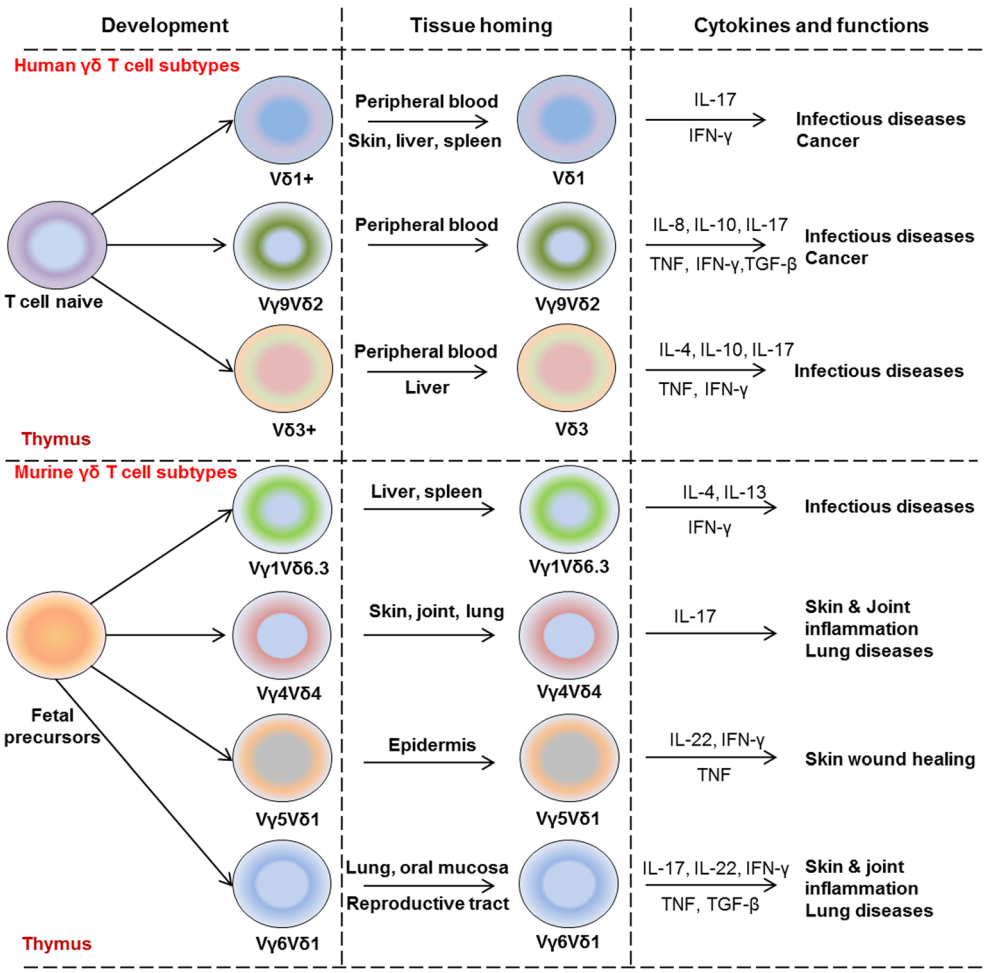

Fig. 1 Overview of γδ T cell functional programing in human and mouse. Schematic illustration of γδ T cell development from naïve fetal precursors in human (upper panel) and mouse (lower panel) thymus. Human naïve γδ T cells differentiate into **Vδ1**$^+$ γδ T subtypes found in peripheral blood, skin, liver, and spleen and produce IL-17 and IFN-γ; **Vγ9**$^+$**Vδ2**$^+$ γδ T cells found in the peripheral blood and produce predominantly TNF and IFN-γ as well as IL-8, IL-10, IL-17; **Vδ3**$^+$ found in peripheral blood and liver and produce several cytokines such as IL-4, IL-10, IL-17, TNF, and IFN-γ. In mouse, **Vγ1**$^+$**Vδ6.3**$^+$ γδ T cells normally resident in lymphoid tissues including spleen and liver and produce IL-4, IL-13, and IFN-γ. **Vγ4**$^+$**Vδ4**$^+$ γδ T cells are found in the skin, joint, and lung and known as IL-17-producing γδ T cells. **Vγ5**$^+$**Vδ1**$^+$ are residents in epidermis, produce IL-17, TNF, IFN-γ whereas **Vγ6**$^+$**Vδ1**$^+$ have been found in the female reproductive tract and oral mucosa and produce IL-17, IL-22, TNF, IFN-γ and TGF-β

17, which contributes to the development of collagen-induced arthritis (CIA) and imiquimod-induced skin inflammation (a model of psoriasis) [47–51].

Dendritic epidermal γδ T cells (DETCs) characteristically express $V\gamma5^+V\delta1^+$ TCRs and normally reside in the mouse skin (nomenclature according to Heilig and Tonegawa) [52, 53]. $V\gamma6^+V\delta4^+$ T cells (most commonly referred to as $V\gamma6^+V\delta1^+$ T cells) share the exact same CDR3 a.a sequence (CACWDSSGFHKVF) [54] as the $V\gamma5^+V\delta1^+$ cells, but these cells reside predominantly at mucosal sites. Both subtypes express identical δ1 chains encoding the same CDR3 a.a. sequence (CGSDIGGSSWDTRQMFF). Skin epidermal $V\gamma5^+V1^+$ DETCs were originally thought to be the only resident γδ T cell population in the skin, although now other γδ T cell populations have also been detected. In addition, $V\gamma5^+$ T cells with the same CDR3 sequence have now been detected at very low frequencies in the lymph nodes. However, in general the $V\gamma5^+V\delta1^+$ DETCs appear to be the major non-circulating skin-resident γδ T cell population in the skin. Skint-1, a thymic epithelial cell determinant, selectively determines the functional phenotype of $V\gamma5^+V\delta1^+$ fetal thymocytes by inducing an Egr3-mediated pathway, provoking differentiation and IFN-γ production while suppressing the γδ T cell lineage factor, Sox13, and a RORγt transcription factor-associated IL-17-producing capacity [52]. Moreover, Skint-1 is essential for the development in the thymus and the establishment of the DETC population in the skin [55, 56]. A recent study showed that signaling via the NF-κB-inducing kinase (NIK) is important for the full development of functional $V\gamma5^+$ dendritic epidermal T cells (DETCs) [57]. $V\gamma6^+V\delta1^+$ T cells are rare in most normal tissues but are the dominant γδ T cell population in the female reproductive tract, oral mucosa, and lung [58–60]. $V\gamma6^+V\delta4^+$ T cells preferentially expand in skin-draining lymph nodes following *S. aureus* skin infection and mediate long-term immunity to *S. aureus* [54].

γδ T cells can act as both positive and/or negative regulators of innate immune responses via myeloid cell activation. RNA-Seq analysis of γδ T cells from infected mice demonstrates that γδ 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*, *Ccrl2*) [61]. 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 [62], which are critical for neutrophil migration [63] (Fig. 2). Consistently, Jiang et al. demonstrated that dermal γδ T cells are required for recruitment of $Gr\text{-}1^+CD11b^+$ neutrophils into skin during skin inflammation [64]. In keeping with these observations, we recently demonstrated that γδ T cell 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 [65]. Negative regulatory roles of γδ T cells in myeloid cell activity have also been described during wound healing [66]. Specifically, γδ T cells suppress the infiltration of macrophages ($F4/80^+CD11b^+$) and myeloid derived suppressor cells ($CD11b^+Gr1^+$) during skin wound healing [66]. In addition, Toll-Like receptor 2 (TLR), which has critical roles in early innate immunity and initiate immune responses, is expressed in freshly isolated γδ T cells although its exact role in γδ T cells is not completely understood [67]. Activated γδ 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 [68]. Collectively, murine γδ 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 [69]. Although specific antigens for murine γδ T cells have not been well characterized, γδ T cells have the ability to recognize and are specifically stimulated by a different repertoire of antigens derived from bacteria [70], small peptides [68], and tumor cells [27]. Interestingly, a memory feature is observed in murine γδ T cells where memory-like $V\gamma4^+$ γδT17 cells are detected, respond more rapidly, and produce more IL-17 leading to a faster skin inflammatory response in a murine skin inflammation model [48]. IL-17-producing memory γδ T cells promote inflammation in both involved and uninvolved psoriatic-like lesions in a murine model of psoriasis [71, 72]. In addition, γδ 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 [73]. Moreover, intraepithelial-resident γδ T cells have a unique role in initiating and regulating IgE production, driving an early innate-like response, which directs a subsequent adaptive response [74]. High-throughput antibody sequencing revealed that γδ T cells shape the IgE repertoire by supporting specific variable-diversity-joining (VDJ) rearrangements [74]. Also, γδ T cells control humoral immune response by inducing T follicular helper (Tfh) cell differentiation [75]. In summary, γδ T cells can regulate a plethora of innate and adaptive immune responses (Fig. 2).

Pathophysiology of γδ T cells in autoimmunity

γδ T cell subsets contribute to tissue damage and development of experimental autoimmune diseases including psoriasis-like disease [13], collagen-induced arthritis [47], colitis [76], autoimmune uveitis [77], and experimental autoimmune encephalomyelitis (EAE) [78]. Inflammatory functions of γδ T cells are defined by their cytokine production, including IL-17, IFN-γ, and TNF-α, which are commonly involved in

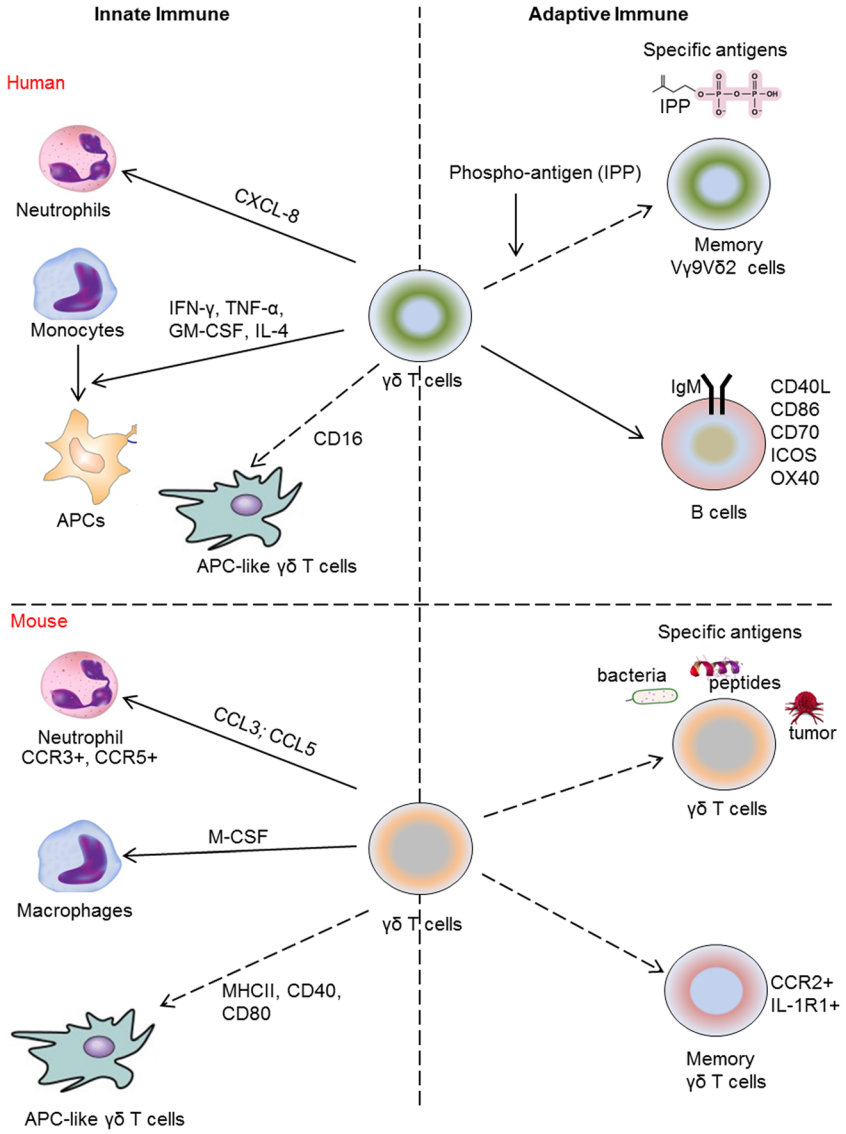

Fig. 2 Functional roles of human/murine γδ T cells in immune responses. The figure illustrates the roles of human (upper panel) and mouse (lower panel) γδ T cells in innate and adaptive immune responses. In human, γδ T cells induce neutrophil migration through regulation of CXCL8 production, monocyte differentiation into antigen presenting cells (APCs) through release of IFN-γ, TNF-α, GM-CSF, and IL-4 and function as a professional phagocyte via antibody opsonization and CD16 (FcγRIII), leading to antigen processing and presentation on MHC class II. For adaptive immune responses, non-peptide phospho-antigens are specific antigens for $Vγ9^+Vδ2^+$ γδ T and also induce robust expansion of memory $Vγ9^+Vδ2^+$. γδ 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, γδ T cells regulate macrophages and neutrophils through release of M-CSF (responsible for macrophages polarization), CCL3 and CCL5 (chemokines for neutrophil migration). Activated γδ 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, γδ 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 γδ T cells ($CCR2^+$ and $IL\text{-}1R^+$)

autoimmunity (Table 2). Different subsets of γδ 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 γδ T cells in psoriasis, which is well established [86, 87], several studies suggest that γδ T cells are involved in the pathogenesis of rheumatoid arthritis (RA) [88–90]. In RA patients, peripheral $Vγ9^+Vδ2^+$ T cells, which express high levels of chemokine receptors CCR5 and CXCR3, migrate into the synovium and secrete IFN-γ and IL-17 [89]. Also in juvenile idiopathic arthritis (JIA), $Vγ9^+Vδ2^+$ 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 [91]. $Vγ9^+Vδ2^+$ T cells could play a critical negative-feedback role in ameliorating disease in JIA patients by inducing apoptosis of rheumatoid synovial fibroblasts [91]. The specific subtypes and tissues involved in these pathologies are considered below.

Table 2 Functions of murine γδ T cell subsets in some inflammatory diseases

γδT subsets	Functions	References
$V\gamma1^+$	Pathogenesis of airway hyper responsiveness	[79]
$V\gamma4^+$	Development of collagen-induced arthritis	[47]
	Pathogenesis of autoimmune uveitis	[77]
	Disruption of intestinal homeostasis (colitis)	[80]
	Development of psoriasis induced by IL-17, IL-22	[81]
$V\gamma5^+$	Protective roles in skin wound healing ($V\gamma5^+V\delta1^{+)}$	[82]
$V\gamma6^+$	IL-17-mediated inflammation of joint (arthritis)	[83]
	Pathogenic roles in psoriasis ($V\gamma6^+V\delta1^+$)	[84]
	Protective roles in pulmonary fibrosis ($V\gamma6^+$ $V\delta1^+$)	[85]

Inflammatory arthritis and bone remodeling

In collagen-induced arthritis (CIA), IL-17-producing γδ T cells are detected in the joint, and their numbers are significant higher than Th17 cells suggesting that γδ 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 $V\gamma1^+$ and $V\gamma4^+$ T cells in the joints but only the $V\gamma4^+$ cells were activated and produced IL-17 during CIA [47]. Moreover, depletion of $V\gamma4^+$ T cells showed a significant reduction in disease incidence and severity that correlated with a reduction of total IgG and IgG2a anti-collagen antibodies [47]. $V\gamma4^+$ γδ T cells increase rapidly and appear to be specifically responsive to the collagen/CFA injections, whereas the $V\gamma1^+$ subset does not, suggesting that antigen-driven clonal and/or memory response is predominantly via the $V\gamma4^+$ γδ T cell subset [47]. In the CIA model, treatment with IL-28A dramatically reduces numbers of pro-inflammatory IL-17-producing γδ T cells in the joints and inguinal lymph nodes, to exert an anti-inflammatory effect further highlighting the importance of the γδ T cells in joint inflammation and inflammatory arthritis [92]. Apart from the CIA model, γδ 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 $V\gamma6^+$ and $V\gamma4^+$ γδ T cells were observed to the joints, but only the $V\gamma6^+$ subset efficiently produced IL-17 [83] whereas functional depletion of γδ 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 [65]. Collectively, these results suggest functional specific roles of each murine γδ T cell subtype in the different disease models.

A common denominator between γδ T cell subtypes is IL-17 expression, and IL-17^+γδ 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 [93, 94]. Recent studies have also shown that IL-17 can induce osteogenic activity in vitro in both murine and human cells [95, 96]. 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 [97]. Another study demonstrated that the IL-$17A^+V\gamma6^+$ 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 [98].

Although the human and murine data are in agreement regarding IL-17 actions, there are other cytokines produced by γδ T cells that affect bone remodeling and need to be considered. In humans, the effects of γδ T cells on osteoclastogenesis differ between "activated" and "freshly isolated" γδ T cells [99]. Specifically, "activated" γδ T cells inhibit osteoclastogenesis through secretion of high levels of IFN-γ (anti-osteoclastogenic) whereas "freshly isolated" γδ T cells enhance osteoclast differentiation by production of high levels of IL-6 [99]. In addition, human $V\gamma9^+V\delta2^+$ T cells inhibit immature dendritic cells (DCs) trans-differentiation into osteoclasts [100]. 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 γδ T cells, indicating that γδ T cells inhibited osteoclastogenesis through the RANK/c-Fos/ATP6V0D2 signaling pathway [100].

Skin inflammation

In the murine skin, there are distinct populations of γδ T cells including $V\gamma5^+V\delta1^+$ T cell subsets which localize in the epidermis [82] whereas $V\gamma4^+$ and $V\gamma6^+$ T cell subsets are resident in the dermis [101]. $V\gamma5^+V\delta1^+$ DETCs are responsible for wound healing by secreting keratinocyte growth factors and inflammatory cytokines (IFN-γ, TNF, and IL-13) [82, 102] whereas the $V\gamma4^+$ and $V\gamma6^+$ T cell subsets contribute to the development of skin inflammatory disease by production of IL-17 [13, 84]. A spontaneous mutation in *Sox13*, a developmental transcription factor, causes defect in development of dermal $V\gamma4^+$ γδ17 T cells in mice and protects the mice from psoriasis-like skin inflammation, suggesting that

dermal Vγ4$^+$ γδ17 T cells mature in the neonatal thymus in a *Sox13*-dependent manner [103]. In the imiquimod (IQM)–induced skin inflammation model, Vγ4$^+$Vδ4$^+$ T cells are long-lived and persist in the skin long after the initial inflammation; thus, memory Vγ4$^+$Vδ4$^+$ T cells mediate the severity of IQM secondary challenge [72]. Follow-up studies demonstrated that Vγ4$^+$ T cells predominantly induce skin inflammation and are the major IL-17 producers [104]. Specifically, adiponectin, a mediator of insulin metabolism, inhibits production of IL-17 by murine dermal Vγ4$^+$ γδ T cells through binding of AdipoR1, and adiponectin-deficient mice showed severe skin inflammation with elevated infiltration of Vγ4$^+$ γδ17 T cells in the epidermis [104]. In addition, dermal γδ 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 [87]. In humans, dermal Vγ9$^+$Vδ2$^+$ T cells express CCR6 and produce inflammatory mediators including IL-17A, TNF-α, IFN-γ, CXCL8, and CCL4 upon activation with specific antigen [86]. Collectively, these results show that dermal γδ17 T cells are regulators of skin inflammation, and their modulation could prevent skin inflammation.

Enthesitis

Vγ6$^+$ γδ T cells have been detected in the murine enthesis [105], 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 γδ T cells [106]. 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 enthesis detected the presence of γδ T cells (on the basis of TCR expression) and constituted a very small fraction of the total lymphocyte population [107, 108].

Concluding remarks

In different conditions, γδ 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 γδ T cells which are highly expressed in murine skin are relatively rare in human skin, and the ratio of γδ T cells to αβ T cells increases only modestly in the setting of psoriasis [109]. These data partly reflect the differences of various γδ T cell subtypes between mouse and human as there is no equivalent of mouse DETCs (Vγ5$^+$Vδ1$^+$) in healthy human epidermis and only around 4% of dermal leukocytes expresses γδ TCR as reviewed previously [110]. Similar observations may be possible for other tissues implicated in the pathogenesis of rheumatic diseases given the multi-functionality of γδ T cell subsets and/or clonal plasticity combined with the plethora of effector functions exhibited by γδ T cells that govern autoimmunity. Nevertheless as our imaging and genetic tools increase [111], we are moving closer to a detailed understanding of individual γδ T cell subtypes and/or their cytokines that could be a promising therapy for modulation of immune responses in multiple autoimmune diseases.

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Compliance with ethical standards

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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