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Review

Role of gamma-delta ($\gamma\delta$) T cells in autoimmunity

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ABSTRACT

$\gamma\delta$ T cells represent a small population of overall T lymphocytes (0.5–5%) and have variable tissue distribution in the body. $\gamma\delta$ T cells can perform complex functions, such as immune surveillance, immunoregulation, and effector function, without undergoing clonal expansion. Heterogeneous distribution and anatomic localization of $\gamma\delta$ T cells in the normal and inflamed tissues play an important role in alloimmunity, autoimmunity, or immunity. The cross-talk between $\gamma\delta$ T cells and other immune cells and phenotypic and functional plasticity of $\gamma\delta$ T cells have been given recent attention in the field of immunology. In this review, we discussed the cellular and molecular interaction of $\gamma\delta$ T cells with other immune cells and its mechanism in the pathogenesis of various autoimmune diseases.
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Introduction

$\gamma\delta$ T cells represent a subset of T lymphocytes that comprise <5% of the peripheral lymphocyte population. In mice, $\gamma\delta$ T cells comprised of 0.1–1% of cells in d 12–13 fetal liver, and it can increase up to 1–8% at birth and reduce dramatically within 3 d of birth in the liver [1]. $\gamma\delta$ T cells are also present in the fetal livers of humans [2, 3]. With the use of athymic mice, it has been shown that during the embryonic stage, $\gamma\delta$ T cells develop within the fetal liver and the gut and do not require the thymic education for their differentiation [1]. In murine fetal thymus, $\gamma\delta$ T cell-surface proteins were detected as early as d 14 of gestation [1, 4]. In the thymus, genes for the TCR-β, TCR-γ, and TCR-δ chains rearrange in DN2 and DN3 stages, and development of $\gamma\delta$ thymocytes branches off from the DN3 to DN4 stage from $\alpha\beta$ thymocytes [5]. TCR signaling strength and Notch signaling have been proposed to control the decisionmaking to differentiate into $\gamma\delta$ versus $\alpha\beta$ lineages [6]. In contrast to $\alpha\beta$ T cells, development of $\gamma\delta$ T cells is not affected in the absence of MHC class II or β2 microglobulin, suggesting that they do not require classic MHC restriction for development and function [7, 8]. $\gamma\delta$ T cells come out of the thymus as mature $\gamma\delta$ T cells and do not require TCR signaling for their differentiation and function [9–11]. However, a recent report has shown that TCR-mediated activation is critical for IL-17A production in DETCs during the wound-healing response [12]. $\gamma\delta$ T cells are mostly enriched in various epithelial and intestinal tissues, as well as in the skin [13–16]. Most tissue-specific $\gamma\delta$ T cells express restricted TCR [17]. $\gamma\delta$ T cells expressing invariant Vγ5Vδ1 TCR are distributed mostly in skin epidermis [18], whereas Vγ6Vδ1 TCR-bearing $\gamma\delta$ T cells reside mostly in the tongue, lung, peritoneum, and reproductive organ [19]. It has been reported that V$\gamma1^+$ and V$\gamma2^+$ T cells preferentially home to secondary lymphoid organs, and V$\gamma4^+$ $\gamma\delta$ T cells migrate into the lung [20]. $\gamma\delta$ T cells recognize nonprotein phosphoantigens, isoprenoid pyrophosphates, alkylamines, nonclassic MHC class I molecules, MICA, and MICB molecules, as well as hsp-derived peptides without requiring antigen processing and MHC presentation [21–23]. These cells produce a wide array of cytokines and chemokines and can lyse directly the target tumor cells or viral-infected cells through production of cytolytic molecules [24–26]. They display a memory phenotype and modulate the function of other innate and adaptive immune cells and can also function as APCs [27–30]. $\gamma\delta$ T cells function as a primary defense against invading pathogens, especially during early life. They secrete various chemokines that attract neutrophils at the site of inflammation and help in pathogen clearance [31]. Depending on its anatomic localization and inflammatory and tolerogenic signals present in the tissue microenvironment, $\gamma\delta$ T cells show phenotypic and functional plasticity [30]. Like $\alpha\beta$ T cells, $\gamma\delta$ T cells also show a Th1-, Th2-, Th17-, and T_{reg}-like phenotype and play an important role in inflammation and tolerance [30]. Distinct subsets of $\gamma\delta$ T cell have the ability to secrete IFN-γ and IL-4 in a way similar to Th1 and Th2 cells in response to various pathogens, respectively [32]. The expression of type of MHC

Abbreviations: $^{-/-}$ = deficient, AHR = airway hyper-responsiveness, AIH = autoimmune hepatitis, *aly/aly* = alymphoplastic mutation, BTLA = B- and T-lymphocyte attenuator, CD30L = cluster of differentiation 30 ligand, CIA = collagen-induced arthritis, CSF = cerebrospinal fluid, DC = dendritic cell, DETC = dendritic epidermal T cell, DN = double-negative, DSS = dextran sodium sulfate, EAE = experimental autoimmune encephalomyelitis, FasL = Fas ligand, Foxp3 = forkhead box p3, GD = Graves' disease, hsp60/65/90 = heat shock protein of 60/65/90 kDa, IA2 = insulinoma antigen 2, IBD = inflammatory bowel disease, Id3 = inhibitor of DNA-binding 3 , IEC = intestinal

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class II antigen can influence the development and function of γδ T cells. C57BL/6 mice express MHC class II IA but not IE antigen and have ~50% Vγ1 and ~20% Vγ4 T cells in spleen [33]. Bl.Tg.Eα (C57BL/6 transgenic for IE antigen) has ~35% Vγ1 and ~40% Vγ4 cells in the spleen. During Coxsackievirus B3 infection in C57BL/6, $V\gamma1^+$ γδ T cells modulate CD4 T cells toward a Th2 response and suppress myocarditis [33], whereas in Bl.Tg.Eα mice, $V\gamma4^+$ γδ T cells promotes the Th1 response and myocarditis [33]. Consistent with these observations—repeated airway exposure to OVA—$V\gamma1^+$ γδ T cell enhanced AHR by increasing Th2 cytokines (IL-5, IL-13) and promoting eosinophilic infiltration in the lung, whereas the $V\gamma4^+$ γδ T cell subset suppressed AHR [34]. $V\gamma1^+$ γδ T cells also promoted AHR induced by ozone exposure in a TNF-α-dependent manner [35]. These studies clearly suggest that γδ T cells can have an inflammatory and anti-inflammatory phenotype and modulate the pathogenesis of the disease.

Apart from Th1- and Th2-like γδ T cells, IL-17-producing γδ T cells, also known as Tγδ17, have gained much attention recently and are known to play an important role in the infection, autoimmunity, and antitumor responses. IL-17 production by γδ T cells appears to be more important than IL-17 production by αβ T cells in early immune responses, as it is strong and rapid and does not require antigen-specific priming or clonal expansion. Tγδ17 cells express high levels of IL-23R, Scavenger receptor 2 (SCART2), CD44, and CCR6 and low levels of CD122 and CD27 molecules [9, 36–38]. IL-17-producing γδ T cells express an IL-2Rα chain (CD25) and require IL-2 for their maintenance (but not IFN-γ^+ γδ T cells), and IL-17-producing γδ T cells are severely affected in $IL\text{-}2^{-/-}$ and $CD25^{-/-}$ mice [36, 39]. Signaling through lymphotoxin-βR [40], B lymphoid kinase [41], Notch/hairy and enhancer of Split-1 (HES1) pathway [42], IL-23 [43, 44], IL-1β [44, 45], and to some extent, IL-6, TGF-β [46, 47] is also required for IL-17 production by γδ T cells. Gene expression required for IL-17 production was enriched in $V\gamma2^+$ and $V\gamma4^+$ γδ T cells [48]. More recently, Tγδ17 cells have been classified as natural and inducible [49]. Natural Tγδ17 cells produce IL-17 within 24 h after infection and are mostly tissue resident and derived from fetal thymocytes. Inducible Tγδ17 cells reside in secondary lymphoid organs and differentiate to reduce IL-17 in response to microbial or foreign antigen, such as PE. These Tγδ17 cells produce IL-17 with 60 h after immunization and require signaling through an inflammatory cytokine, as well as TCR stimulation, for a sustained IL-17 response [49].

γδ T cells are known to mobilize very early during the immune response and produce inflammatory cytokine IFN-γ, TNF-α [50], and IL-17 [9, 11, 44, 53], and anti-inflammatory cytokine IL-10 [51, 52] in various infection and autoimmunity models.

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epithelial cell, IEL = intraepithelial lymphocyte, JIA = juvenile idiopathic arthritis, KGF = keratinocyte growth factor, MBP = myelin basic protein, MICA/B = MHC class I polypeptide-related sequence A/B, miRNA = micro RNA, MMP = matrix metalloproteinase, MOG = myelin oligodendrocyte peptide, MS = multiple sclerosis, PB = peripheral blood, PDK1 = phosphoinositide-dependent protein kinase 1 gene, RA = rheumatoid athritis, RANKL = receptor activator for NF-κB ligand, RegIII = regenerating islet-derived protein 3, RORγt = retinoid-related orphan receptor γt, SLE = systemic lupus erythematosus, SS = Sjögren's syndrome, sTRAIL = soluble TRAIL, T1D = type 1 diabetes, T_{reg} = regulatory CD4 T cell, WT = wild-type

Recently, there were various reviews published on γδ T cells that discuss their role in the infection and immunity [30, 54]. In the present review, we focus on the role of γδ T cells in the development and progression of autoimmunity and discuss the beneficial and detrimental influence of γδ T cells in various autoimmune diseases.

MECHANISM OF γδ T CELL FUNCTION

γδ T cell express a variety of activation and inhibitory molecules and secrete several cytokines that play an important role in the pathogenesis of various diseases (**Table 1** and **Fig. 1**). Several of these signaling molecules dictates the outcome of γδ T cell effector function. CD30L (CD153) is a TNF superfamily member expressed on activated and memory CD4 T cells. CD30L–CD30 interaction plays an important role in the context of T–T cell interaction, and signaling from this receptor-ligand interaction affects the differentiation of Th1 and Th17 cells [68–70]. $CD30L^{-/-}$ and $CD30^{-/-}$ mice have normal γδ T cells in fetal thymus; however, adult mice mucosal-associated tissues have reduced Vγ6/Vδ1 T cells [71]. CD30/CD30L are preferentially expressed in Vγ6/Vδ1 T cells of mucosal-associated tissues. CD30/CD30L signaling promotes production of IL-17 by this subset in the mucosal tissues and plays an important role in host defense during infection. The impaired response of Vγ6/Vδ1 T cells in $CD30^{-/-}$/$CD30L^{-/-}$ mice was not a result of their defective response to IL-23/IL-1β signaling, as IL-23-induced IL-17A expression in γδ T cells was not affected in $CD30L^{-/-}$ or $CD30^{-/-}$ γδ T cells [71]. This suggests that CD30 and CD30L signals might use different molecular mechanism to control the IL-17 expression [71]. CD27 is another TNFR superfamily member, and known to regulate the effector function of γδ T cells, $CD27^+$ γδ T cells secrete IFN-γ, whereas $CD27^-$ γδ T cells produce IL-17 [9]. Genome-wide epigenetic analysis showed that $CD27^+$ γδ T cells were committed to produce IFN-γ but not IL-17, whereas $CD27^-$ γδ T cells showed a permissive chromatin configuration and can be differentiated to produce IFN-γ and IL-17 [72]. IL-17A- and IFN-γ-producing cells have a protective role in the bacterial infection, in which IL-17 helps in the recruitment of neutrophils, whereas IFN-γ helps in the early innate response [58, 73]. 4-1BB is another TNFR superfamily molecule expressed on activated γδ T cells and stimulates the activation, expansion, and effector function of γδ T cells [74]. These studies suggest that TNF superfamily members play an important role in the development and function of γδ T cells. The inhibitory receptor BTLA negatively regulates IL-7-mediated expansion of $CD27^-$ γδ T cells and inhibits IL-17 and TNF-α production [65]. BTLA expression is suppressed by RORγt, while up-regulated by IL-7, thereby allowing RORγt and IL-7 to balance the activating and inhibitory stimuli [65]. Interaction of BTLA on Vγ9/Vδ2 cells with its ligand herpes virus entry mediator has been shown to inhibit proliferation of Vγ9/Vδ2 cells in response to lymphoma cells by inducing partial cell-cycle arrest in S-phase, thereby allowing an immune escape mechanism for tumor cells [66]. BTLA expression has been shown to regulate homeostasis of γδ T cells [65] and negatively regulates the proliferation of γδ T cells [66].

Recently, Notch signaling has been shown to regulate proliferation and effector function of γδ T cells [75]. γδ T cells

TABLE 1. Expression of effector and regulatory molecules on γδ T cells

Function	γδ T cell subset	Molecules	Experimental condition/model	References
Activation/effector	Murine γδ T cells	CD73	In thymic development, $CD73^-$ γδ TCR^+ progenitors adopt the αβ fate, whereas the $CD73^+$ population remains $CD4^-CD8^-$ and gives rise to γδ T cells.	[55]
	Human γδ T cells	TRAIL and NKG2D	NKG2D regulates production of sTRAIL and induces apoptosis in lung cancer cells.	[56]
	Human Vγ2Vδ2 T cells	TNF-α and IFN-γ	Showed cytotoxic activity in nasopharyngeal carcinoma patients	[57]
	Murine γδ T cells	IL-1β and IL-23	Activates γδ T cells leading to production of IL-17 and IL-21 and an amplifying Th17 response in EAE	[44]
	Murine TCR Vγ4 or Vγ6 T cells	IL-17	γδ T cells express IL-17 in a very early stage of *Listeria monocytogenes* infection and control the infection.	[58]
	MurineVγ4/$Vδ4^+$ γδ T	IL-17	Aggravate CIA	[59]
	Human γδ T cells	NKp44	Cytotoxicity against myeloma cells	[60]
	Murine skin-associated $NKG2D^+$ γδ T cells	NKG2D	In vitro killing of skin carcinoma cells	[61]
Suppression/ tolerogenic/ inhibitory	Murine γδ T cells	FasL	Fas-mediated killing of Coxsackievirus B3-infected cardiac myocytes	[62]
	Murine γδ T cells	IL-10	Generation of anterior chamber-associated immune deviation T_{regs}	[51]
	Murine γδ T_{regs}	CD39	Immunosuppressive	[63]
	TCR-$γδ^+$/$CD56^+$ cells	IL-10 and TGF-β	Promotes immunotolerance to fetus during normal pregnancies	[64]
	Murine γδ T cells	BTLA	Limits γδ T cell number by restricting IL-7 responsiveness; also negatively regulates IL-17 and TNF-α production by limiting the expansion of $CD27^-$ γδ T cells	[65, 66]
	Murine Vγ1 T cells	IL-4	Vγ1 γδ T cell produces IL-4, which reduces NKG2D expression on Vγ4 γδ T cells, and also reduces the percentage of IFN-γ-producing $NKG2D^+$ Vγ4 γδ T cells.	[67]

predominantly expressed Notch 2 and a low level of Notch 1, whereas expression of Notch 3 and 4 was not reported. Notch signaling is required for anti-CD3/IL-2, as well as phosphoantigen-dependent activation and proliferation [75]. Inhibition of Notch signaling in γδ T cells also reduced degranulation and cytotoxic function of γδ T cells and inhibited the secretion of TNF-α, IFN-γ, and IL-17 [75]. Interestingly, γδ T cells can be activated by activation receptor NKG2D, leading to production of sTRAIL, which promotes the killing of lung cancer cells expressing TRAILR [56]. γδ T_{regs} were shown to express membrane-bound ectonucleoside triphosphate diphosphohydralase 1 (also known as CD39), which converts ATP into AMP (Fig. 1). $CD39^+$ γδ T cells express significantly higher levels of IL-10 and suppressed T cell proliferation [63]. Otsuka et al. [63] showed that suppressive $CD39^+$ γδ T cells can be in vitro induced from $CD39^-$ γδ T cells after stimulation with IL-2 and anti-CD3ε mAb, and these γδ T_{regs} were able to suppress an effector immune response in vitro and in vivo [63]. γδ T Cells are 1 of the major T_{regs} in the bovine PB [76]. These γδ T_{regs} suppress CD4 and CD8 T cell proliferation in an IL-10-dependent manner [76]. These studies suggest the regulatory function of γδ T cells can help to control autoimmune inflammation.

In addition to activation/inhibitory molecules, cytokines play an important role in shaping the effector function of γδ T cells. It has been reported that γδ T cells have the ability to secrete IL-17 in an IL-1βR-dependent manner that attracts neutrophils further at the site of surgical and lung infections [77–79]. Interestingly, IL-17-producing γδ T cells share several features of Th17 cells, such as expression of CCR6, RORγt, aryl hydrocarbon receptor, and IL-23R [53]. The cytokine IL-23 acts as a maturation factor for the pathogenic Th17 cells [80]. IL-23, along with IL-1β, also plays a critical role in IL-17A production by γδ T cells through up-regulation of RORγt and IL-23R, and this is independent of TCR stimulation and APCs [44]. γδ T cells in naive mice have very low IL-23R expression. However, activated γδ T cells express a very high level of IL-23R during

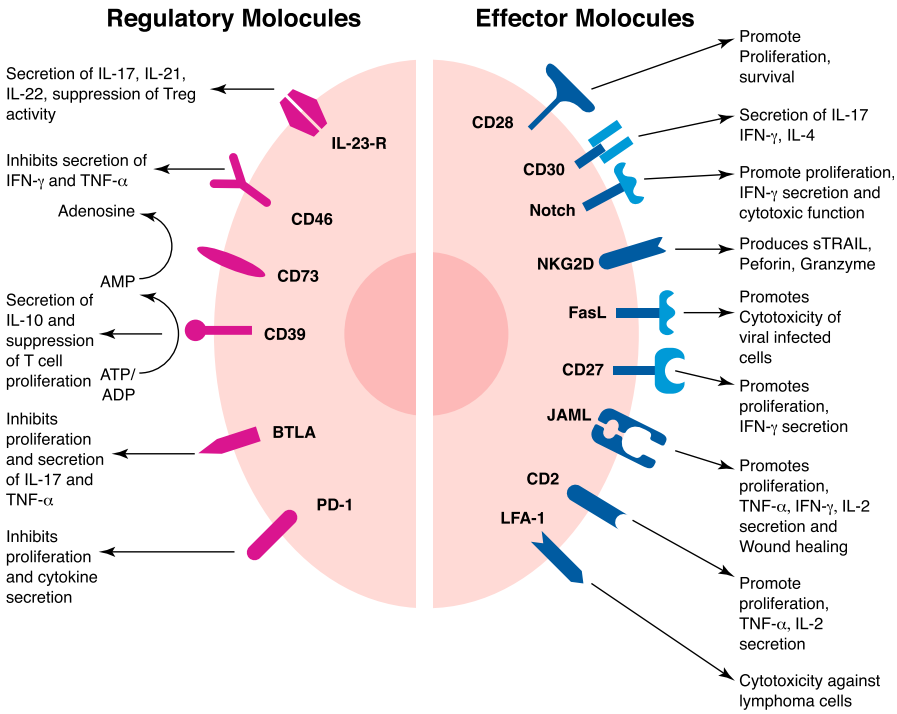

Figure 1. Control of γδ T cell function by effector and regulatory molecules. Regulatory molecules and effector molecule expression are depicted; arrows from each molecule indicate the function of these receptors in γδ T cells. Activation of γδ T cells through CD27, CD2, junctional adhesion molecule-like protein (JAML), and Notch induces proliferation as well as cytokine secretion by γδ T cells. Signaling through CD28 induces proliferation and expression of antiapoptotic genes, whereas CD30 signaling affects cytokine secretion. Activation of NKG2D, FasL, LFA-1, and Notch triggers cytotoxic function of γδ T cells against tumor cells and virally infected cells. Other receptors, such as BTLA, CD46, and programmed death 1 (PD-1), act as negative regulators and inhibit proliferation and cytokine secretion of γδ T cells. CD39 expression by γδ T cells is associated with the regulatory function of γδ T cells.

autoimmune disease [81, 82]. It has been shown that IL-23R$^+$ γδ T cells express more IL-17, whereas IL-23R$^-$ γδ T cells express more IFN-γ [81]. During the progression of EAE, IL-23R$^+$ γδ T cells accumulate in the CNS and inhibit the suppressor activity of Foxp3$^+$ T_{regs} [81]. TCR-δ$^{-/-}$ mice have been reported to have significantly more Foxp3$^+$ CD4 T_{regs} in secondary lymphoid tissues compared with WT mice [81], suggesting that γδ T cells may be controlling the generation and expansion of T_{regs}. Culture of IL-23R$^+$ γδ T cells in the presence of IL-23 induces a very high level of IL-17, IL-21, and IL-22 and perturbs the balance between regulatory and effector function of T cells [81]. Although IL-23R$^+$ γδ T cells produce IL-17, IL-21, and IL-22, these cytokines are not known to inhibit the suppressor function of Foxp3$^+$ T_{regs}, suggesting that the IL-23R$^+$ γδ T cells use some other secondary pathways to inhibit T_{reg} function. The detailed mechanism of how IL-23R$^+$ γδ T cells suppress in vitro and in vivo needs better investigation. Interestingly, IL-23p19$^{-/-}$ mice and IL-23R$^{-/-}$ mice are completely resistant to MOG peptide-induced EAE [83, 84]. As these mice have a genetic defect of IL-23 and IL-23R expression in all cell types, that might be the reason for the resistance to EAE. How the deficiency of IL-23 or IL-23R expression, specifically on γδ T cells, contributes to the pathogenesis of the disease needs to be evaluated further. Anatomic localization of γδ T cells at the epithelial barrier and production of IL-17 and IL-22 in the autoimmune inflammation by IL-23R$^+$ γδ T cells may have a profound effect on the pathogenesis of disease [85, 86]. It is interesting to note that once γδ T cells exit the thymus, they are preprogrammed to produce cytokines and no longer require TCR stimulation to produce IL-17, and they can produce IL-17 in response to IL-1 and IL-23 alone [79]. In contrast to these observations, IL-23 and IL-1β did not induce IL-17A production directly in Vγ3$^+$ DETCs but could only enhance TCR-induced IL-17A production, suggesting that DETC might behave differently from IL-17-committed peripheral γδ T cells [12]. Th17 cell-associated cytokines (IL-17, IL-21, and IL-22) play an important role in the pathogenesis of neuronal autoimmune diseases. However, it has been reported that IL-17A$^{-/-}$, IL-17F$^{-/-}$, IL-21$^{-/-}$, and IL-22$^{-/-}$ mice are not protected from autoimmunity, such as EAE [87–89]. Most of these studies primarily focused on Th17 cells in EAE. How specific deletion of these cytokines in γδ T cells affects the disease progression is not well characterized. These studies also suggest that the pathogenesis of the disease requires a combinatorial effect of cytokines and different cell types, and an individual cytokine or cell type is not sufficient to induce disease.

The details of molecular mechanisms of γδ T cell function in specific autoimmune diseases are discussed below.

γδ T CELLS IN AUTOIMMUNE DISEASES

γδ T cells play an important role in the regulation of various autoimmune diseases [90–92] and are known to have a strong clinical association with many autoimmune diseases, such as RA [93], autoimmune thyroid disease [94], and autoimmune liver disease [95]. Activated γδ T cells were shown to be capable of producing predominant Th1 or Th2 cytokine [32] and provide help to B cells and control development of germinal center and autoreactive IgG formation [96].

IBD

Lymphocytes present in the epithelial layer of mucosal lining are known as IELs and play an important role in host defense against pathogen (**Fig. 2**). γδ T cells comprise a minor subset of T cells in the secondary lymphoid organ but represent a major subset of IEL. γδ T cell$^{-/-}$ mice showed reduced turnover of epithelial cells and down-regulation of MHC class II molecules, which were not observed in αβ T cell$^{-/-}$ mice [97], suggesting that intraepithelial γδ T cells regulate the regeneration of IECs. In DSS-induced colitis,

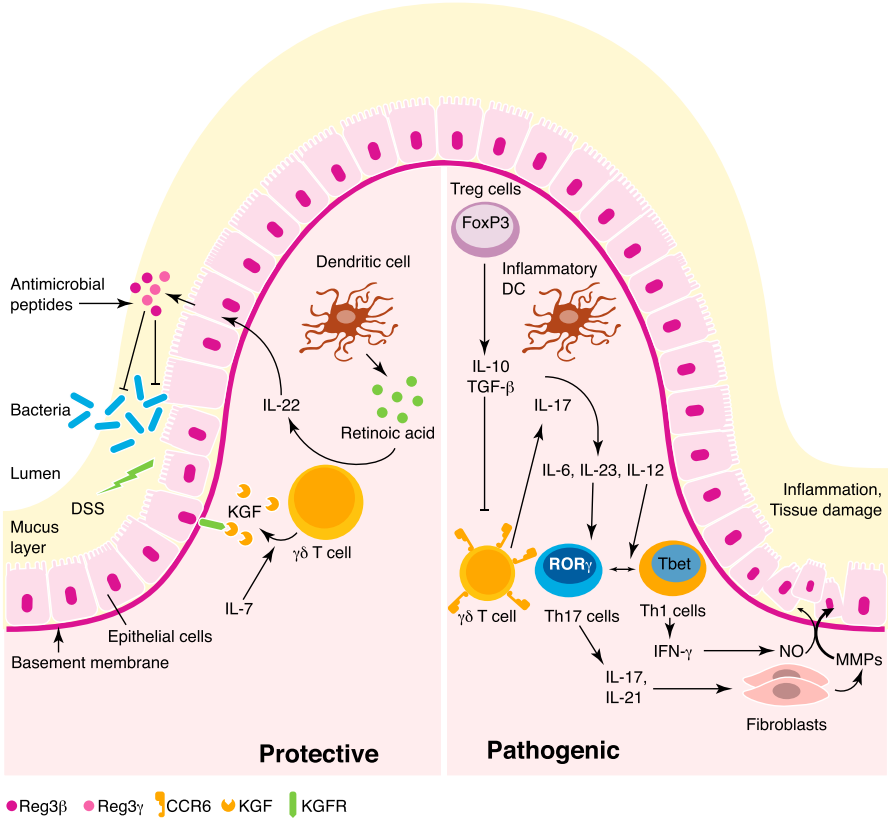

Figure 2. γδ T cells in IBD. Protective γδ T cells accumulate during intestinal inflammation induced by DSS or microbial pathogen and produce KGF, which promotes tissue repair and epithelial cell healing. Inflammatory stimuli promote production of retinoic acid by DCs, which induce IL-22 secretion by γδ T cells. IL-22 enhances epithelial cell-mediated production of antimicrobial peptides, which subsides inflammation by promoting tissue repair. Pathogenic IL-17-producing γδ T cells induce Th17 differentiation through the inflammatory DC-mediated production of IL-6 and IL-23. DC-induced IL-12 and IL-23 also promote differentiation of Th17 cells to IFN-γ-secreting Th1 cells. Th17 cell-derived IL-17 and IL-21 promote MMP production by tissue resident fibroblast, whereas IFN-γ promotes NO production. NO and MMP induce inflammation and epithelial cell basement membrane degradation, leading to the development of colitis. Tbet, T box expressed in T cells.

γδ T cells have been shown to accumulate in large numbers at the site of epithelial damage and express IEC mitogen, KGF [98]. The severity of DSS-induced mucosal injuries in TCR-$\delta^{-/-}$ mice and $KGF^{-/-}$ mice [99] were increased compared with αβ TCR-$\alpha^{-/-}$ mice, and after removal of DSS, these mice showed delayed recovery from the colitis [98]. Administration of IL-7 was shown to increase KGF expression significantly on γδ T cells [100]. Furthermore, reconstitution of γδ T cells into TCR-$\delta^{-/-}$ mice showed a protective effect from colitis through induction of TGF-β production [101]. A recent study has shown that vitamin A metabolite retinoic acid promotes IL-22 secretion by γδ T cells and innate lymphoid cells, leading to tissue repair in the intestine and attenuation of intestinal inflammation [102]. DCs are the major source of retinoic acid in gut, skin, lung, and associated lymph nodes [103]. Retinoic acid is known to promote the induction of $CD4^+Foxp3^+$ T_{reg} [104, 105] and inhibits the differentiation of Th17 cells [106, 107]. In the gut, IL-22 induces epithelial cell repair and secretion of antimicrobial peptides RegIIIγ and RegIIIβ from epithelial cells that limit bacterial growth and prevent intestinal inflammation [108]. Crohn's disease or ulcerative colitis patients have increased production of IL-22 in intestine [109], and deficiency of IL-22 in mice showed development of severe colitis [110]. Retinoic acid induced the binding of retinoic acid receptor γ on the IL-22 promoter and acts as a switch between IL-17 and IL-22 production in γδ T cells after stimulation with IL-1β and IL-23 [102]. These studies suggest that γδ T cells play an important role in the regulation of immunosuppressive function of IECs and contribute to the development of tolerance.

TCR-$\delta^{-/-}$ and TCR-$\beta^{-/-}$ mice were shown to develop equally severe colitis. However, TCR-$\delta^{-/-}$ mice showed increased intestinal infiltrates of $Mac1^+Gr1^-$ monocytes, whereas TCR-$\beta^{-/-}$ mice have $Mac1^+Gr1^+$ granulocyte infiltration [111]. In spontaneous colitis models, cytokine imbalance, as a result of expansion of γδ T cells, leads to B cell expansion, production, and switching of autoantibodies to the IgG2 subclass and the development of IBD [112]. It is important to note that TCR-$\alpha^{-/-}$ mice develop spontaneous colitis under a conventional condition, but they are protected under a germ-free condition. TCR-$\alpha^{-/-}$ mice, together with the *aly/aly* (*aly/aly* TCR-$\alpha^{-/-}$ mice) that lack Peyer's patches and peripheral lymph nodes, do not develop colitis. Adoptive transfer of γδ T cells from TCR-$\alpha^{-/-}$ mice into *scid* or *aly/aly* TCR-$\delta^{-/-}$ mice did not induce colitis [113]. Furthermore, depletion of γδ T cells in TCR-$\alpha^{-/-}$ mice also prevented the development of colitis [113]. This suggests that activation of resident intestinal γδ T cells in the secondary lymphoid organs is required for induction of colitis. PDK1$^{-/-}$ mice showed an increased number of IL-17-producing γδ T cells and a reduced number of $Foxp3^+$ T_{regs}. Deletion of the TCR-δ gene in PDK1$^{-/-}$ mice or adoptive transfer of WT T_{regs} into PDK1$^{-/-}$ mice protects from the development of colitis [114]. This suggests that suppression of γδ T cell activation by $Foxp3^+$ T_{regs} is required for maintaining intestinal homeostasis [114]. It has also been reported that IL-17$^+$ γδ T cells promote Th17 cell differentiation and development of T cell-mediated colitis [115]. Thus, interaction of γδ T cells with intestinal microbes, as well as with IECs and other immune cells, shapes the inflammatory response in the colon (Fig. 2). Future studies should address in detail how these interactions

dictate the cytokine production by γδ T cells, leading to intestinal inflammation and tissue damage. In-depth knowledge of how γδ T cells cross-talk with Th17 and T_{regs} in the gut microenvironment needs detail investigation.

Autoimmune diabetes

T1D is an organ-specific autoimmune disease, where activated, autoreactive T cells damage insulin-secreting β cells in the pancreas. T1D is characterized by infiltration of innate and adaptive immune cells in the pancreatic islets called insulitis. The major autoantigens involved in T1D include proinsulin, glutamic decarboxylase 65, zinc transporter ZnT8, IA2, IA2β (Phogrin), and islet-cell autoantigen 69 [116, 117]. Administration of oral insulin or intranasal proinsulin peptides into NOD mice was shown to control diabetes [118]. It has been reported that delivery of intact insulin as an inhaled aerosol or intranasally induces CD8 γδ T_{regs} [119]. Adoptive transfer of CD8 γδ T cells from aerosol insulin-treated mice prevents diabetogenic effector T cell-induced diabetes. IL-10 produced by CD8 γδ T cells and its migration into pancreatic lymph nodes were required for its suppressive function [119]. IL-17-producing γδ T cells were reported as one of the major sources of IL-17 in NOD mice [120], and IL-17-producing γδ T cells suppressed the development of diabetes in NOD mice in a TGF-β-dependent manner in an adoptive transfer model [120]. As IL-17-secreting γδ T cells are known to have a proinflammatory phenotype and exacerbate the disease progression in various other autoimmune models, it is currently not well understood how these cells act as protective in a diabetes model. Although TGF-β- and IL-10-secreting T_{reg}-like γδ T cells have been suggested to act in the tumor microenvironment [121], they have not been well characterized in autoimmune disease and need to be explored further in autoimmunity. In contrast to the observation mentioned above, Markle et al. [122] showed that IL-17-producing $CD27^{-}CD44^{+}$ γδ T cells mediate the pathogenesis of T1D in the NOD mouse model and suggested that IL-17-secreting γδ T cells play an effector role rather than protective. Thus, these studies suggest that γδ T cells play an important role in the pathogenesis of autoimmune diabetes, and a better understanding of their molecular mechanism will help in designing a better strategy to control autoimmunity.

RA

RA is a chronic autoimmune disease that affects joints and is known to be caused by accumulation of inflammation-induced, self-reactive T cells in synovial fluid and joint tissue. It has been reported that PB and synovial joints of RA and JIA patients have an increased number of γδ T cells [123, 124]. An increased number of γδ T cells were reported in CIA, a murine model of RA [125]. Depletion of total γδ T cells before induction of CIA resulted in a significant delay in onset and severity of CIA, whereas absence of γδ T cells after development of CIA expedites the onset and severity of arthritis [125]. This study suggests that γδ T cells might behave differently during a different phase of the disease. Interaction of γδ T cells with different immune cells during early and late phases of CIA might result in protection or pathogenesis of the disease. Mice lacking γδ T cells (TCR-$\delta^{-/-}$ mice) had no significant difference in CIA incidence, onset, development, and arthritic score compared with littermate control. In another study, it has been shown that after the 1st dose of injection of collagen antigen in mice, $V\gamma1^{+}$ and $V\gamma4^{+}$ γδ T cell numbers increased and subsequently boosting with the same antigen, led to a rapid increase in $V\gamma4^{+}$ cells compared with $V\gamma1^{+}$ cells [59]. These $V\gamma4^{+}$ γδ T cells produced proinflammatory cytokine IL-17 in the draining lymph node and inflamed joint [59]. Depletion of $V\gamma4^{+}$ γδ T cells and not $V\gamma1^{+}$ cells before the 2nd dose of collagen antigen injection lowered the disease incidence and reduced severity, suggesting that these cells play a pathogenic role in the development of CIA [59]. It is possible that these different subsets of γδ T cells might have a different cytokine-secretion pattern or altered interaction with other proinflammatory cells, which results in different disease outcome. Thus, a specific subset of γδ T cells might have a different response during different phases of the disease. Furthermore, Ito et al. [126] showed that γδ T cells were the predominant source of IL-17 in the inflamed joints in CIA but not in RA patients. The majority of γδ T cells in the synovial fluid of patients with JIA and juvenile RA expresses Vδ1 [127]. $V\delta1^{+}$ and $V\delta2^{+}$ γδ T cells in synovial fluid showed significantly higher levels of activation antigen CD69 compared with those in PB [127]. $V\delta1^{+}$ γδ T cells also predominate in the synovial fluid and PB of RA patients [93, 128]. Pollinger et al. [129] showed that proinflammatory $IL\text{-}17^{+}$ γδ and CD4 T cells accumulate in the same frequency in the inflamed synovium of RA patients. However, with the use of the CIA model, they showed that only $IL\text{-}17^{+}$ CD4 T cells and not γδ T cells are responsible for disease development [129]. The cellular and molecular interaction of γδ T cells with other immune cells in an RA patient's joint is depicted in **Fig. 3**. These studies clearly suggest that a specific subset of γδ T cell migrates into the inflamed tissue and contributes to the progression and severity of RA. Apart from γδ T cells, other cells in the synovium, particularly osteoblast and synovial fibroblast, play an important role through secretion of RANKL, MMPs that ultimately lead to bone loss and development of RA [130]. How γδ T cells interact with these synovial cells and influence their response, directly or indirectly, is not well studied and needs to be addressed in the future. Thus, the subset of γδ T cells acting during different phases of RA, cytokines produced by them, their localization, and interaction with other immune cells, such as CD4 T cells, NK cells, as well as nonimmune cells, might influence the disease pathogenesis and needs to be investigated better.

MS

MS is a chronic autoimmune disease of the CNS, characterized by demyelination of neuronal axons. Infiltration of self-reactive immune cells from peripheral circulation to the brain and spinal cord plays a critical role in the development of inflammation in MS. EAE is an animal model to study the pathogenesis of MS. EAE is induced by immunization of mice with MOG_{35-55} peptide in the presence of adjuvant or by adoptive transfer of MBP-sensitized CD4 T cells into syngeneic animals [131, 132]. Although neuronal antigen-specific $CD4^{+}$ T cells are considered to be the prime mediators of EAE, a number of studies have shown that γδ T cells are present in increased frequency in the PB and CSF of MS patients [133–135], as well as in the brain of EAE [136, 137].

LFA-1 and VLA-4 on γδ T cells interact with their cognate ligand present on brain endothelial cells and control the trafficking of γδ T cells into the CNS [138]. However, the β2

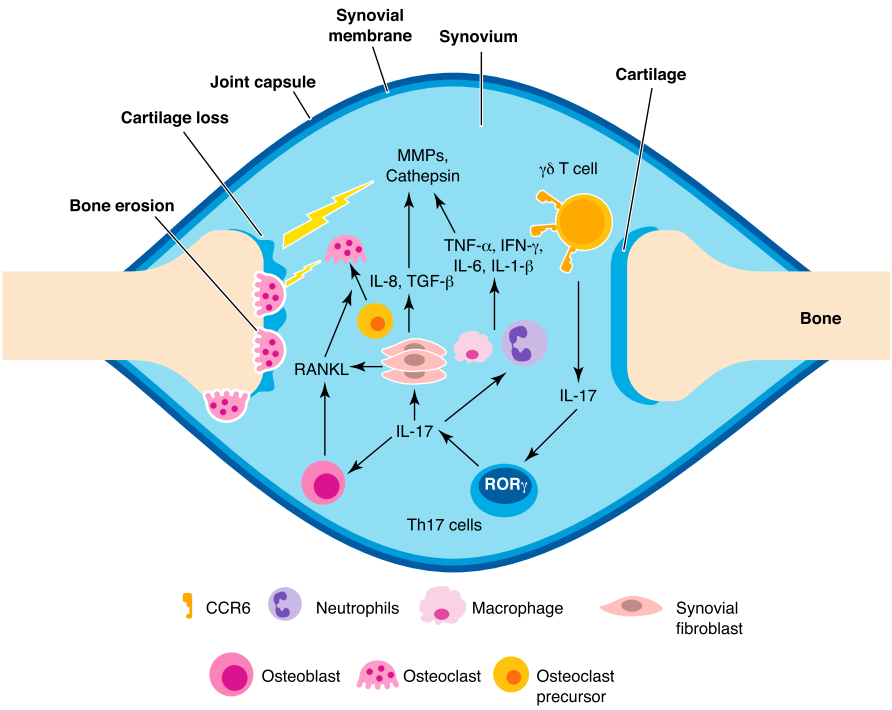

Figure 3. γδ T cells in RA. IL-17-producing γδ T cells accumulate into the inflamed synovium and produce IL-17, which in an inflamed synovium, induces production of inflammatory cytokines from macrophage, neutrophils, and synovial fibroblast and RANKL from osteoblast and synovial fibroblast. Inflammatory cytokines produced in the microenvironment induce production of MMPs and cathepsins; RANKL promotes conversion of osteoclast precursors into osteoclast. MMPs and cathepsin cause loss of cartilage, and osteoclast induces bone erosion, leading to the development of RA.

family of adhesion molecules, such as CD11a, CD11b, and CD11c, has been shown to be dispensable for γδ T cell trafficking, as CD11a$^{-/-}$, CD11b$^{-/-}$, and CD11c$^{-/-}$ γδ T cells were able to induce EAE when reconstituted in γδ T cell$^{-/-}$ mice in a manner similar to WT γδ T cells [138]. The interaction and function of γδ T cells in the brain tissue during EAE are depicted in **Fig. 4**. It has been shown that restricted populations of γδ T cells (cells expressing Vγ1–3, Vγ6, Vδ1, Vδ4, and Vδ5 transcripts) infiltrated the brain during the initial phase of EAE, but as the disease progressed, expression of different Vγ and Vδ TCR transcripts into the brain was dominant [137]. Vδ1, Vδ2, and Vγ9 TCRs expressing γδ T cells have been reported to infiltrate acute, demyelinating MS plaques in patients [133]. hsp60 and -90 have been shown to be overexpressed in MS plaques compared with normal CNS tissues [133]. Selmaj et al. [139] reported the colocalization of hsp65 and γδ T cells on immature oligodendrocyte into MS lesions. The majority of the γδ T cell clones (43%) obtained from PB and CSF of MS patients proliferates in response to hsp70 but not to hsp65 [135], suggesting that hsps might be the antigen responsible for stimulating expansion of autoreactive γδ T cells in MS patients.

Adoptive transfer of MBP-activated lymph node cells in mice resulted in increased infiltration of γδ T cells in the CNS during the peak of the acute phase and decreased during remission, followed by increased infiltration during the relapse phase of EAE [140]. Depletion of γδ T cells during acute and chronic phases of EAE resulted in reduced severity of the disease, suggesting that γδ T cells play an important role in EAE, and its mobilization into the inflamed tissue is associated with the pathogenesis of neuronal autoimmunity [140]. γδ T cells are also known to modulate the function of inflammatory cells in the CNS [141]. Immunization of TCR-δ$^{-/-}$ mice with MOG$_{35-55}$ peptide/CFA resulted in reduced severity of disease and decreased expression of IFN-γ, IL-2, IL-5, and IL-10 compared with WT animals [142]. γδ T cell$^{-/-}$ mice reconstituted with IFN-γ$^{-/-}$ and TNF-α$^{-/-}$ γδ T cells failed to develop severe EAE, suggesting that IFN-γ and TNF-α production by γδ T cells is required for development of severe EAE [143]. γδ T cells activated by IL-1β and IL-23 promote IL-17 production by the CD4 T cell, which leads to exacerbation of EAE [44]. With the use of a fate-tracking system, it has been reported that 5–10% of IL-17-producing γδ T cells in the CNS also express IFN-γ, suggesting that IFN-γ^{+}IL-17^{+} γδ T cells might be an important intermediate in the pathogenesis of EAE [144]. However, the mechanism by which γδ T cells regulate the inflammatory cytokine and chemokine expression in CNS-infiltrating cells and the heterogeneity of infiltrating cells involved in autoimmunity needs detailed investigation.

In contrast to the above observations, it has also been reported that γδ T cells have a protective role in EAE [145, 146]. Depletion of γδ T cells with γδ TCR-specific mAb (clone UC7-13D5) in B10PL mice, 3 d before spinal cord homogenate injections, augmented the severity and recurrence of EAE and resulted in increased expression of IFN-γ in the spleen during onset and prerelapse [145]. Ponomarev and Dittel [146] showed that reconstitution of γδ T cell$^{-/-}$ mice with WT γδ T cells but not FasL dysfunctional γδ T cell resulted in the resolution of inflammation and recovery from EAE. This suggests that the γδ T cell mediated Fas/FasL-induced apoptosis of encephalitogenic T cells regulates inflammation in the CNS and facilitates recovery from EAE. A recent study by Blink et al. [147] showed that IL-17-producing Vγ4^{+} γδ T cells exacerbate EAE, whereas Vγ1^{+} γδ T cells act as regulatory cells and protect from disease development. The pathogenic nature of Vγ4^{+} γδ T cells in EAE development was attributed to their ability to produce several Th17-associated factors, such as IL-17A, IL-17F, IL-22, IL-1β, RORγt, IL-1R, and IL-23R, and their ability to interact with

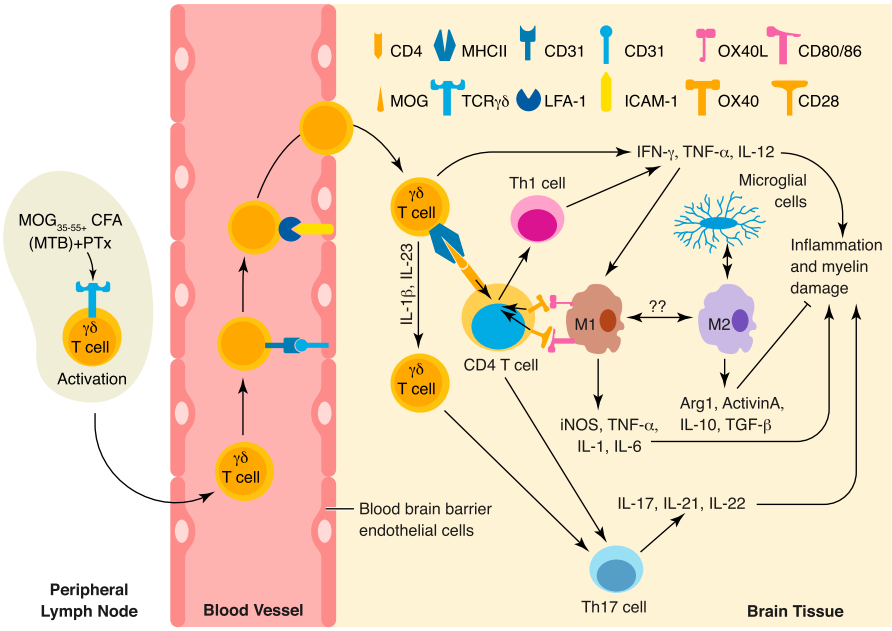

Figure 4. γδ T cells in EAE. During EAE, immunization with the MOG peptide in CFA and pertussis toxin (PTx) promotes activation of γδ T cells in peripheral lymph nodes. Activated γδ T cells enter the bloodstream and migrate through the compromised blood-brain barrier endothelium into CNS tissue. Infiltrating γδ T cells produce IFN-γ and TNF-α, which exacerbates inflammation. γδ T cells can act as APCs and present MOG peptide to CD4 T cells to induce differentiation of antigen-specific Th1 and/or Th17 cells. Inflammatory cytokines in brain parenchyma, such as IL-1β and IL-23, further activate infiltrating γδ T cells and induce IL-17 production by CD4 T cells. These antigen-specific Th17 cells promote destruction of myelin and increase the severity of the disease. During early stages of disease development, the CNS resident M1-type macrophage also promotes differentiation of myelin-reactive Th1 cells, which produce proinflammatory cytokines, such as IFN-γ, IL-12, and TNF-α, and promote demyelination. These inflammatory cytokines further accelerate the activation of the M1 macrophage to release other inflammatory cytokines that also contribute to myelin damage. However, during the relapse phase of the disease, M2 macrophages are generated by differentiation from the M1 macrophage or through the proliferation of microglial cells. These M2 macrophages produce anti-inflammatory cytokines that drive the immune response toward a Th2/T_{reg} response, promote apoptosis of autoreactive T cells, and also participate in remyelination, leading to recovery from the disease. Arg1, arginase 1; MTB, *Mycobacterium tuberculosis*; OX40L, OX40 ligand.

oligodendrocyte to mediate their destruction. In contrast, Vγ1$^+$ γδ T cells secrete a higher amount of chemokines, such as CCL3, CCL4, and CCL5, which play an important role in balancing the Th17-T_{reg} [147]. In most of the studies in EAE, the mechanism by which γδ T cells regulate the inflammatory cytokine and chemokine expression in CNS-infiltrating cells and the heterogeneity of infiltrating γδ T cells involved have not been addressed in detail and need thorough investigation.

Other autoimmune diseases

SLE. SLE is an autoimmune disease characterized by the production of autoantibodies against a variety of nuclear and cytoplasmic antigens [148] and affects multiple organs, such as skin, joints, kidney, and neuronal tissues. Several studies reported that γδ T cells (Vδ1 and Vδ2 subtypes) were present in significantly lower numbers in the PB of SLE patients compared with healthy controls [149–151]. The sequencing of the junctional region of Vδ1 and Vδ2 TCRs containing γδ T cells of SLE patients and controls indicated the oligoclonal nature of the γδ T cells in SLE [152]. Reduced Vδ2$^+$ γδ T cells [149, 150] and increased Vδ3$^+$ γδ T cells were reported in SLE patients [150]. Interestingly, γδ T cells in SLE patients were shown to secrete IFN-γ, IL-4, IL-10, and TGF-β but not IL-17 [153]. However, the specific inflammatory or anti-inflammatory cytokines produced by specific subsets of γδ T cells are not known. It can be hypothesized that Vδ2$^+$ T cells might have anti-inflammatory phenotypes, and Vδ3$^+$ T cells may have a more effector function to play in SLE patients. SLE patients also showed decreased inhibitory receptor NKG2A and increased activating receptors CD69 and HLA-DR on γδ T cells [151]. Thus, γδ T cell$^{-/-}$ coupled with their hyperactivated nature may contribute to the pathogenesis in SLE.

SS. SS is a systemic autoimmune disease characterized by destruction of salivary and lacrimal glands, resulting in oral and ocular dryness. Patients with primary SS were shown to have increased PB γδ T cells [154, 155] and poor proliferation in response to anti-CD3ε mAb stimulation and secreted low levels of IL-2 but showed increased production of Igs in B cells [154]. Activated (HLA-DR$^+$) and CD16$^+$ γδ T cells were also found in a higher proportion in SS patients compared with controls [156, 157]. Id3$^{-/-}$ mice have autoimmune lesions only in exocrine glands and were used as a mouse model for human SS [158]. Although these mice showed infiltration of CD4 and CD8 T cells into the affected exocrine gland, the presence of γδ T cells and their phenotype remains to be identified [158]. Id3 limits the proliferation and survival of a small subset of innate-like γδ T cells coexpressing Vγ1.1 and Vδ6.3 [159]. Id3$^{-/-}$ mice have an increased percentage of TNF-α-, IFN-γ-, and IL-4-producing Vγ1.1$^+$Vδ6.3$^+$ T cells [160]. However, the role of this subset of γδ T cells in the pathogenesis of SS by use of the Id3$^{-/-}$ mouse model can be explored in the future.

AIH, myositis, and GD. Hepatitis is a liver inflammation caused by various factors, such as chemicals, drugs, alcohol. Primary sclerosing cholangitis and AIH were shown to have an increased percentage, as well as the absolute number of γδ T cells [95, 161]. γδ T cells in the PB of both group of patients display a higher expression of activation markers HLA-DR, IL-2R, and CD45RO [95]. In myositis, muscle fibers were damaged by monoclonal γδ T cells [162–164]. γδ T cell clone M88 (Vγ1.3Vδ2), isolated from muscle lesions of autoimmune myositis, responds to antigen derived from muscle, other mammalian cells, and bacteria. Furthermore, it has been shown that tRNA synthetases and translation molecules are exposed during diseased conditions, and these patients develop

autoantibodies against nuclear and cytoplasmic antigens [165]. GD is an autoimmune disease caused by binding of autoantibodies to the thyroid-stimulating hormone receptor and leading to overproduce thyroid hormones by thyroid cells. It has been reported that γδ T cells expand within the thyroid gland of patients with GD compared with healthy controls [94]. Catalfamo et al. [166] developed a cytotoxic γδ T cell line from thyroid glands of GD patients and showed that it recognizes a ligand expressed on thyroid epithelial cells and cell lines of endocrine epithelial origins. However, a detailed investigation on subsets of γδ T cells in each of these autoimmune diseases, type of cytokines and chemokines secreted by them, and their interaction with other immune cells during development of hepatitis, GD, and myositis is warranted in the future.

Psoriasis. Psoriasis is a chronic inflammatory skin disease characterized by expansion of pathogenic, autoreactive T cells. In addition to the contribution of adaptive immune T cells, such as Th1, Th17, and T_{reg}, in disease development, innate immune cells, such as γδ T cells, also play an important role in disease progression. Dermal γδ T cells have been shown to express constitutively IL-23R and RORγt and produce significant levels of IL-17 in response to IL-23 stimulation that promotes development and progression of psoriasis [167, 168]. Intradermal injection of IL-23 leads to accumulation of $CCR6^+$ γδ T cells in the epidermis and expresses an increased amount of IL-17A and IL-22, leading to severe psoriasiform dermatitis [168]. Similar to other autoimmune disease, murine $V\gamma4^+$ γδ T cells express elevated levels of IL-17A and are associated with the progression of psoriasis [162]. Consistent with a murine model of psoriasis, a high frequency and number of IL-17-producing γδ T cells were observed in skin lesions of psoriasis patients [167]. Additionally, a novel skin-homing Vγ9Vδ2 T cell subset, expressing cutaneous lymphocyte antigen and CCR6, has been identified in humans that plays a role in psoriasis. This population of γδ T cells was found to be increased in the skin lesions of psoriasis patients but decreased in the blood [169], suggesting that the γδ T cell mobilization in inflamed skin and its effector function contribute to the pathogenesis of psoriasis.

CONCLUDING REMARKS

Apart from secreting cytokines, such as TNF-α, IL−17, IL-22, and IFN-γ, γδ T cells also secrete chemokines [170], which influence recruitment of other immune cells at the site of inflammation and modulate the function of other innate and adaptive immune cells. γδ T cells interact with other innate and adaptive immune cells and modulate their function. Some of these immune cells in the inflamed tissue microenvironment display immunosuppressive activity. Therefore, cross-talk between γδ T cells and regulatory cells in the inflamed microenvironment should be investigated in more detail. The pathogenesis of autoimmune disease results from an abnormal immune response, leading to production of autoreactive T cells and/or autoantibodies. γδ T cells, through the production of proinflammatory cytokines, help B cells to produce autoantibody and contribute in the pathogenesis of autoimmunity. γδ T cells showed protective effects against DSS-induced colitis [98, 101], whereas they promote development of colitis in $PDK1^{-/-}$ mice [114]. However, it is not known whether different subsets of γδ T cells in different microenvironments might have differential function—protective versus pathogenic—and warrant further investigation. In fact, $IL\text{-}17^+$ γδ T cells promoted the development of colitis, RA, and psoriasis [59, 115, 167, 168], whereas they suppressed development of diabetes in NOD mice [120]. Based on existing literature, we hypothesize that the opposing role of γδ T cells in different disease might be a result of the fact that different γδ T cell subsets are involved in different disease and their potential to localize to a specific tissue. For example, IL-17 produced by $V\gamma4^+$ γδ T cells promotes pathogenesis of EAE, RA, and psoriasis [59, 147], whereas this cell type is protective in an AHR model [34, 171]. Likewise, $V\gamma1^+$ γδ T cells play a pathogenic role in airway inflammation [172] and show a protective phenotype in EAE [147]. Distinct gene expression programs might be induced in different γδ T cell subsets exposed to different cytokine and chemokine microenvironments in the inflamed tissues, resulting in an opposing outcome. In fact, global gene expression-profiling studies also suggest that different γδ T cell subsets in human and mice have a differential gene-expression pattern [48, 173]. Alternatively, the interaction of different γδ T cell subsets with other innate or adaptive immune cells during different phases of the disease might also result in different outcomes. Thus, future studies investigating the molecular mechanism of γδ T cell function and their cross-talk during different phases of autoimmune diseases will help in the development of novel therapeutics required for γδ T cell-based immunotherapy. Recent studies showed that miRNAs control the phenotypic and functional plasticity of αβ T cells [174]. Several miRNAs are known to play an important role in the development of various autoimmune diseases. How miRNAs control the effector and suppressive function of γδ T cells in autoimmunity forms an active area of research in γδ T cell biology.

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DISCLOSURES

The authors declare no conflict of interest.

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