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Forum in immunology

Antiviral reactivities of γδ T cells

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Abstract

The complex antiviral immune mechanisms involve both adaptive and innate reactions mediated by γδ T lymphocytes, whose unique immunosurveillance contributions are analyzed here in different clinical and experimental settings. It is beyond any doubt that the fast, potent, cytotoxic as well as non-cytolytic antiviral activities of γδ T cells are critical in protecting the host against diverse viral pathogens.
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1. The γδ T-cell function

Murine γδ T cells are the first lineage of T lymphocytes that appear in the mouse thymus, and later, predominate in epithelia. Intestinal, lymphoid and dendritic epidermal γδ T cells develop normally in both athymic and MHC class I/II-deficient mice. The expression of distinct V-gene segments not only marks different subsets, but is often associated with a more-or-less specific preponderance — for example, Vγ3Vδ1 in the epidermis, Vγ2Vδ5/6 in the lungs, Vγ4Vδ1 in the tongue and uterus/vagina, and Vγ5Vδ4/2/5/6 or Vγ1Vδ5/6 in the intestinal epithelium (reviewed in [1]). Circulating murine γδ T cells mainly express the Vγ1Vδ5/6 or Vγ2Vδ5 T-cell receptor (TCR) chains. Structures recognized by murine γδ T cells include I-E^k (Vγ2Vδ5), heat-shock protein 65 (HSP65) (Vγ1Vδ4/6), T10/22 (Vγ2Vδ5), HSV-gI (Vγ2Vδ8) and stressed epithelial cells (Vγ3Vδ1). However, γδ T-cell stimulatory activities of murine γδ ligands have not been examined in vivo, and there is no rodent model for assessing the therapeutic potential of activated γδ T cells, with the exception of human γδ T-cell testing in SCID mice [2].

Similarly to the mouse, the expression of human γδ TCR variable segments is associated with tissue prevalence—for instance, the Vδ1 T-cell subset appears to have largely resident characteristics, whereas Vγ9Vδ2 T lymphocytes frequent the adult peripheral blood. Human Vδ1 T cells form a large subpopulation of gut, skin and lung lymphocytes. Some Vδ1 T cells seem to recognize CD1c through the TCR and/or MIC-A/B stress-molecules through the NKG2D receptor [3]. In contrast, human Vγ9Vδ2 T cells are the main blood/lymphoid organ γδ T-cell subpopulation and typically recognize phosphomonoester molecules synthesized in the mevalonate and DOXP metabolic pathways [4]. Since γδ T cells display potent antiviral activities against many different viruses, it may be possible to design novel antiviral therapies utilizing activated γδ T cells.

2. Retroviruses

The involvement of γδ T cells in antiviral immunosurveillance has been extensively analyzed (Table 1). A large number of studies indicate that γδ T cells participate in immune responses against the human immunodeficiency virus (HIV) (reviewed in [5]) and other retrovirus such as the human T-cell leukemia virus (HTLV) type 1 [6,7], the simian immunodeficiency virus (SIV) [8] and the murine leukemia virus (MuLV) [9,10]. An extrathymic expansion of a TCR-δ clonotype among Vδ5 T cells was found to correlate with the presence of an endogenous MuLV in inbred mice [10]. A genotype-independent extrathymic expansion of a γδ T-cell subset (Vγ9Vδ2) has also been reported in human and non-human primates [11,12]. Upon SIV infection of rhesus monkeys (*Macaca mulatta*), transient increases in the percentage

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Table 1
γδ T cells in RNA virus infections

Virus	Host[a]	γδ subset	Reference
Retroviridae			
MuLV	Mouse	pan-γδ	[9,10]
HTLV	Human	pan-γδ	[6,7]
HIV	Human	Vδ1/Vδ2	[23,24,27,30,31,43,105–115]
		Vδ1	[25,26,29,116–121]
		Vδ2	[5,16,17,22,32,33,38–40,122–133]
SIV	Macaque	Vδ1/Vδ2	[14,15,134,135]
		Vδ2	[8,13,136]
Flaviviridae			
HCV	Human	Vδ1/Vδ2	[45–47,51,137]
GBV-C		Vδ1	[28,52]
		Vδ2	[48]
		pan-γδ	[49,54]
WNV	Mouse	pan-γδ	[50]
Paramyxoviridae			
RSV	Mouse	pan-γδ	[58,138–140]
	Human	pan-γδ	[55,141]
Sendai virus	Mouse	Vγ1/2 Vγ4	[59,142]
Measles virus	Human	Vδ2	[60]
Orthomyxoviridae			
Influenza virus	Mouse	pan-γδ	[56,57,61–69]
		Vγ2/Vγ1	[57,63]
		Vγ4	
Picornaviridae			
Coxsackieviruses	Mouse	pan-γδ	[70–77,143]
		Vγ1/Vγ4	
Coronaviridae			
MHV	Mouse	pan-γδ	[78]
Rhabdoviridae			
VSV	Mouse	pan-γδ	[80]

[a] Natural or experimental.

of Vγ9Vδ2 T cells were observed [13]. γδ T cells from SIV-infected macaques appear to express more activation markers, such as CD69, CD44 and the memory marker CD45RO, differently from uninfected animals. The simian γδ T cells were also able to suppress SIV replication in vitro, assessed by p27 antigenemia [8]. Significant increases in γδ T cells eluted from the rectal mucosa were observed in 'protected' versus SIV-infected macaques [14]. After vaccination with attenuated SIV, the protection against pathogenic virus at the mucosal challenge site was accompanied by an expansion of γδ T cells concomitantly with dendritic cells [15]. Investigations of the mechanism of protection have revealed that simian γδ T cells can generate antiviral factors RANTES, MIP-1α and MIP-1β, which prevent SIV infection by competing for the CCR5 co-receptors. Similarly, in *Homo sapiens*, several studies suggest a potent antiviral activity of Vγ9Vδ2 T cells against HIV. Human Vγ9Vδ2 T cells exert both cytolytic [16,17] and non-cytolytic (through the induction of β-chemokines such as MIP-1α/β and RANTES) antiviral activity. The efficacy of inhibition is comparable to that of CD8+ T lymphocytes [17,18–20]. Moreover, human Vγ9Vδ2 T cells have been shown to release α-defensin [21] and other, yet unidentified, non-cytolytic antiviral factors [22].

Increases in relative and absolute numbers of γδ T cells have been described in the peripheral blood of HIV-1-seropositive persons, including those free of opportunistic pathogens [23–25]. These increases are due to the Vδ1 T-cell subset, resulting in an inversion of the adult peripheral blood Vδ2 to Vδ1 ratio (>2 in HIV-seronegative controls) [25,26]. Augmented representation of the Vδ1 T-cell subset in the peripheral blood of HIV-seropositive persons is independent of particular γ-chain expression, not correlated with a CDR3-dependent Vδ1 selection [26], not associated with any particular junctional motifs [26], and not correlated with high levels of HIV-1 antigenemia [25]. Moreover, the comparison between mucosal and blood γδ T cells revealed a similar increase in Vδ1 T cells [27]. In both compartments, antiretroviral treatments were not able to restore Vδ1 T cells to normal levels [27,28], indicating that factors other than HIV replication are responsible for the Vδ1 T-cell expansion. An increased expression of 'natural killer receptors' was found on Vδ1 T cells from HIV patients [29]. This may be due to chronic activation of Vδ1 T cells in HIV-1-infected persons. These cells are able to lyse uninfected bystander CD4+ T cells during HIV infection [30], indicating that the Vδ1 T-cell subset may directly contribute to the HIV-associated immunopathogenesis.

The HIV-associated Vδ1 T-cell increase is accompanied by a polyclonal Vγ9Vδ2 T-cell decrease, in both the peripheral blood and the mucosal tissues. This situation is even more

evident in HIV patients with opportunistic and other co-infections [26,27,31,32]. The low numbers of Vγ9Vδ2 T cells remaining after HIV infections are frequently anergic [32]. Although influencing the cytokine production of normal Vγ9Vδ2 T cells, neither interleukin-12 (IL-12) nor IL-15 were able to reverse the Vδ2 T-cell anergy observed in HIV-infected patients [33]. Although the spectrotype analysis of Vδ2 and Vδ1 did not reveal significant differences in HIV+ individuals compared to uninfected controls [26,32], significant changes have been observed in the Vγ9 (Vγ2 in an alternate nomenclature) chain repertoire. Among all possible combinations of Vγ9 with any of the four known Jγ segments, healthy adults preferentially express the Vγ9 and JγP chain combination [34,35]. This pairing is also associated with the strongest responses to nonpeptidic antigens (NpAgs), even though the response is still polyclonal [36]. Typically, Vγ9Vδ2 T cells stimulated with NpAgs mainly exhibit JγP rearrangements (alternatively known as Jγ1.2) [36]. Also, gene transfer studies have shown that the Vγ9-JγP combination is associated with the strong NpAg responsiveness, whereas Vγ9Vδ2 TCRs containing the other Vγ9-Jγ combinations appear to be somewhat less responsive. The lysine residues within the JγP segment are unique and absent in other human Jγ segments. Mutations of these lysine residues completely abrogated the responsiveness to NpAgs without affecting the response to anti-CD3 monoclonal antibodies (mAb) [37]. This suggests that the positively charged lysine residues in the TCRγ CDR3 region encoded by the germline JγP segment play a key role in the response to NpAgs. HIV-infected individuals have substantially reduced numbers of Vγ9 cells with the Vγ9-JγP rearrangement [38]. This alteration and the reduced T-cell reactivities were shown to be partially reversed towards 'normal levels' during highly active antiretroviral therapy (HAART) treatment [31,39]. The depletion of Vγ9Vδ2 T cells is the earliest known TCR-specific cell deletion associated with HIV infection. Importantly, the loss of Vγ9Vδ2 T cells may be a contributing factor in the establishment of viral persistence in AIDS by reducing the level of type 1 cytokines [38]. In HIV-infected persons undergoing structured treatment interruption (STI) [40], a loss in circulating Vγ9Vδ2 T cells has been observed, suggesting that acute HIV replication may influence Vγ9Vδ2 homeostasis. Specifically, the reduction in γδ T-cell numbers was evident in the effector CD45RA-CD27-Vγ9Vδ2 T-cell subset. In addition, NpAg-driven interferon-γ (IFN-γ) production was substantially decreased during the STI. After HAART resumption and the ensuing inhibition of HIV replication, the Vγ9Vδ2 T-cell reactivities were restored. Altogether, these observations indicate that Vγ9Vδ2 T cells are activated soon after the initiation of active HIV replication, but are rapidly lost in HIV-infected persons who fail to control viremia. In this context, it is noteworthy that the Vγ9Vδ2 T-cell loss observed after the STI-induced increase in plasma HIV-RNA could mimic the status found in the very early phases of HIV infection. In summary, these data indicate that soon after plasma HIV-RNA rebound, the Vγ9Vδ2 T-cell subset becomes rapidly anergic and subsequently depleted. The mechanism of this loss may involve activation-induced cell death of reactive clones triggered by Fas/FasL interactions [41] or by NpAgs [42]. Thus, the antiviral potential of Vγ9Vδ2 T cells is rapidly diminished by HIV replication. Furthermore, the increase in the Vδ1 subset may not result from a clonal expansion in response to HIV—rather it may be a bystander effect induced by cytokine changes occurring during the HIV disease progression. In addition, HIV-related molecules may interfere with γδ T-cell homeostasis, since HIV-1 Tat seems to compete for chemokine binding to CXCR3 and CXCR4 receptors expressed on γδ T cells [43].

3. Flaviviruses

Expansion and activations of γδ T-cell subsets were observed in hepatitis C virus (HCV) patients [44–48] and in other flavivirus infections such as GB virus C [49] and West Nile virus (WNV) [50]. Intrahepatic T lymphocytes from patients with chronic hepatitis C with a high histology activity index score in the liver carried mostly γδ TCR [51]. Liver γδ T-cell lines from HCV-infected individuals exhibit high levels of MHC-unrestricted cytotoxic activity against different targets, including primary hepatocytes, and produce IFN-γ, tumor necrosis factor-α (TNF-α) and IL-8 following activation by anti-CD3. These liver γδ T-cell lines do not recognize any of the structural or nonstructural proteins of HCV and have no cytotoxic activity against cells infected with recombinant vaccinia viruses expressing different HCV proteins. However, the cross-linking of CD81 (which binds HCV particles and E2) results in significant IFN-γ and TNF-α production by liver γδ T cells. Moreover, the Vδ1 T-cell subset is polyclonally activated and recruited in the liver of chronic HCV-infected patients [52]. During chronic HCV infection, this T-cell subset may release Th1 cytokines and thus contribute to the inflammatory and necrotic processes in the liver. HIV/HCV co-infected patients show an increased frequency of both peripheral and intrahepatic Vδ1 natural T lymphocytes. This may result in a higher degree of hepatic inflammation in comparison with patients with other liver diseases [28]. Altogether, these findings suggest that Vδ1 T cells may play a role in the HCV-associated liver pathology [46]. In contrast, the Vγ9Vδ2 T-cell decrease may contribute to the impaired cellular immune response and the persistent nature of HCV disease [48]. In chronic HCV infection, similarly to the HIV infection, a Vδ2/Vδ1 T-cell impairment (e.g. intrahepatic Vδ1 T cells are expanded in the course of disease) is also observed. The Vδ2 T-cell deficit may be associated with persistent viral infections in humans [53].

Infections with GB virus-type C (GBV-C), which is genetically similar to HCV, are relatively common worldwide. There is no convincing evidence that GBV-C infection causes any human pathology. Nevertheless, the current interest in GBV-C has been fuelled by reports indicating that HIV-infected patients co-infected with GBV-C have a slower disease pro-

gression. A recent study among HIV-infected mothers from South Africa shows that mothers co-infected with GBV-C have a higher percentage of circulating γδ T cells than HIV-infected mothers without GBV-C infection [49,54]. However, in our cohort of HIV-infected patients, we have found no correlation between Vδ2 T-cell exhaustion/Vδ1 T-cell increase and GBV-C co-infection (Martini et al., Clin. Infect. Dis. 40 (2005) 326–328). Perhaps future studies that investigate the association between circulating γδ T-cell frequencies and GBV-C load in particular clinical settings may elucidate whether or not the γδ T-cell increases are directly related to GBV-C infection.

West Nile virus (WNV) is a flavivirus transmitted by mosquitoes (it recently emerged in the New York City metropolitan area and then spread to central parts of the US), with clinical manifestations ranging from asymptomatic seroconversion to fatal meningoencephalitis. WNV also causes fatal meningoencephalitis in laboratory mice. Using this model, it has been shown that mice deficient in T cells are more susceptible to WNV infection. TCRδ–/– mice have elevated viral loads and a greater viral dissemination in the central nervous system [50]. Adoptive transfer of γδ T cells to TCRδ–/– mice reduced the susceptibility of these mice to WNV, and this effect was primarily due to IFN-γ-producing T cells. These data demonstrate a distinct antiviral role of γδ T cells in the control of WNV infection.

4. Myxoviruses

Mouse γδ T cells are activated and home to the site of viral replication during paramyxo- and orthomyxovirus infections [55–57]. In the mouse model, the epithelial T-cell response to respiratory syncytial virus (RSV) infection is dominated by αβ T cells, with very few γδ T cells being present [58]. In *H. sapiens*, mitogen-stimulated γδ T cells from the peripheral blood of infants with acute RSV infection produce significantly less IFN-γ and more IL-4 than γδ T cells from infants with acute reovirus infection [55]. During convalescence, the percentage of γδ T cells producing IFN-γ increases in children who recovered fully, but not in children who developed post-bronchiolitic wheezing. This suggests that cytokine production by γδ T cells during acute RSV infection may play a role in the development of recurrent wheeze after RSV infection. γδ T cells form a minority of lung-infiltrating lymphocytes in mice infected by Sendai virus [59], a paramyxovirus that causes nonfatal pneumonia. The Vγ1/2 phenotype is prevalent throughout the course of Sendai virus infection, with a transition to the Vγ4 phenotype preponderance occurring very late in the resolution of inflammation. In measles paramyxovirus infection, the expansion of human Vγ9Vδ2 T cells in vitro is negatively regulated by the measles virus glycoproteins [60], and this viral immunomodulation depends on the interaction of virus glycoproteins with surface molecules present on γδ T cells and monocytes.

Most of the studies on γδ T-cell involvement in orthomyxovirus infections were performed in mice, since bronchoalveolar lavage (BAL) populations from influenza A virus-infected mice express high frequencies of γδ TCR chain mRNA [61,62]. After 1 week of influenza A infection, the inflammatory exudate in the lungs consisted largely of macrophages and γδ T cells, with an early increase in Vγ4 T cells and a late increase in Vγ2/Vγ1 T cells. Since increasing numbers of macrophages expressing heat-shock protein (HSP) mRNA were found, the increase in Vγ2/Vγ1 T cells is consistent with the possibility that at least some of these lymphocytes are responding to the HSP-positive cells during the resolution of inflammatory process [56,63]. A γδ T-cell hybridoma established from influenza virus-infected mice responded both to influenza virus-infected stimulators and to recombinant HSP60. Interestingly, an HSP60-reactive hybridoma obtained from an uninfected mouse also responded to influenza virus-infected cells, indicating that HSP60 could indeed be the target antigen [64]. The TCR variable γ-gene usage in the buccal epithelium of normal mice and that of mice challenged locally with influenza virus infection are different. In the control mice, there is a restricted use of Vγ genes by buccal γδ T cells (consisting primarily of Vγ1.2, Vγ3, and Vγ5). Expression of the Vγ2 and Vγ5 genes is diminished in influenza-infected mice, but expression of other Vγ genes does not appear to be altered by the infection. A local challenge with BSA is followed by a decreased expression of Vγ1.2, Vγ3, and Vγ5 genes, and to a lesser extent, Vγ2 gene, whereas Vγ4 gene expression is increased. It is possible to speculate that the immunomodulating effect of oral antigen exposure on buccal γδ T cells suggests that these cells are functionally involved in the local immune response to replicating and non-replicating antigens in oral mucosal surfaces [57].

When the ligand-dependent lytic function was studied in mice with influenza pneumonia, γδ T cells were not constitutively cytotoxic when recovered directly from the site of virus-induced damage in the respiratory tract. However, they could display cytotoxic activities when stimulated in the presence of anti-CD3 mAb and low concentrations of rIL-2 [65]. Activated γδ T cells showed profound cytotoxicity against the target cells expressing HA of either the H1 or H3 subtype, in an MHC-unrestricted manner [66].

Substantial numbers of lung γδ T cells constitutively express mRNA for a variety of cytokines and are replicating vigorously [67]. Cells that express mRNA for IL-2, IL-4, and IFN-γ predominate among γδ T cells recovered from inflammatory exudates [65,68]. The frequency of cytokine mRNA+ lymphocytes is much higher than the expected frequency of virus-specific cells, which may suggest their involvement in innate immune reactions [65].

Predictably, the immunosuppressive drug cyclosporin A diminishes the resistance of mice to influenza virus infection. Mice inoculated intravenously with trehalose-6,6′-dimycolate (TDM, a glycolipid component of the mycobacterial cell wall) regain resistance to influenza virus infection impaired by cyclosporin A. It is likely that the better outcome

of TDM-treated mice can be due to the activation of T, and especially of γδ T, lymphocytes, since this T-cell subpopulation increases markedly in the lung of TDM-treated mice [69].

5. Other RNA viruses

γδ T cells have been studied in the immune response to other RNA viruses such as coxsackieviruses, murine coronaviruses, and vesicular stomatitis virus. A role of γδ T cells has been demonstrated in coxsackievirus-induced myocarditis [70,71]. Cells expressing the γδ TCR accounted for 5–13% of lymphocytes infiltrating the hearts of coxsackievirus H3 (CVB3)-infected mice, and adoptive transfer of γδ T cells produces IFN-γ-induced myocarditis by apoptosis [72]. The pathogenic γδ T-cell response is linked to MHC class II haplotype, since animals lacking the MHC class II IE antigen develop minimal cardiac lesions subsequent to infection, despite high concentrations of virus in the heart. The susceptibility to myocarditis correlates with a Th1 (IFN-γ-positive) cell response in the spleen, whereas disease resistance is associated with the Th2 (IL-4 positive) phenotype. γδ T-cell analysis indicates that distinct cell subpopulations are activated after CVB3 infection in resistant and susceptible mice. Depletion of γδ T cells abrogates myocarditis susceptibility in IE+ animals and results in a Th1 versus Th2 phenotype shift [73]. It appears that γδ T cells modulate T-cell responses by selectively lysing CD4+ Th2 cells. Lysis requires direct cell-to-cell interaction between the γδ T-cell and the CD4+ Th2 target, and is most likely mediated through Fas/FasL interaction [74]. The heart infiltrate in CVB3-infected myocarditis-susceptible mice contains abundant Vγ1 T cells, whereas heart-infiltrating Vγ4 T cells are plentiful in myocarditis-resistant mice. Interestingly, the mAb-induced depletion of Vγ1 T cells potentiates myocarditis, whereas the mAb-induced depletion of Vγ4 T cells leads to suppression of myocarditis. Vγ4-cell transfer experiments in myocarditis-resistant mice show that the Vγ4 subset promotes myocarditis. Th subset analyses suggest that Vγ1 T cells induce a dominant Th2-cell response, whereas Vγ4 T cells bring on a dominant Th1-cell response [75]. Infection with a myocarditis-inducing strain (H3) of CVB3 preferentially activates Vγ4Vδ4 cells, which are strongly positive for IFN-γ, whereas Vγ1Vδ4 cells are increased in both myocarditis-inducing strain (H3)- and myocarditis-non-inducing strain (H310A1)-infected animals [76]. In this model system, the CD1 molecule is required for stimulation of Vδ4 cells. The activated Vδ4 cells initiate myocarditis through a IFN-γ-mediated induction of Th1 cells that in turn activate autoimmune CD8+ αβ T effector response. The activated Vδ4 cells can adoptively transfer myocarditis to animals infected with a non-myocarditic variant, but not to either uninfected or CD1(–/–) recipients. This demonstrates that the Vδ4 myocarditic function requires both infection and CD1 expression. In contrast, CD8+ αβ T cells transfer myocarditis into either infected CD1(–/–) or uninfected recipients, showing that the function of these activated CD8 effectors is both virus- and CD1-independent. Thus, Vδ4 cells influence CVB3 pathogenicity by their ability to manipulate both the CD4 and CD8 adaptive immune response [77].

In a murine model of coronavirus infection induced by mouse hepatitis virus (MHV), γδ T cells are the major T-cell effectors found predominantly in areas of virus antigen [78]. Infection of mice with MHV results in acute and chronic demyelination, with many similarities to multiple sclerosis in *H. sapiens*. Also, the fact that this pathological process is mediated by γδ T cells is compatible with possible involvement of γδ T cells in the pathogenesis of multiple sclerosis [79]. In MHV-infected mice, γδ T cells may function by both lysing infected target cells and secreting proinflammatory cytokines. This is likely to contribute to the activation of macrophages/microglial cells that are the final effectors in the disease process.

A possible antiviral role of γδ T lymphocytes may be related to their ability to promote B-cell help. Specifically, γδ T cells are able to provide signals that are required for immunoglobulin isotype switching during vesicular stomatitis virus infection of immunocompetent mice [80]. The different immunoregulatory function mediated by γδ T lymphocytes on CD4, CD8, B and/or DC cells may vary, depending on the viral agent and the γδ T-cell subset involved in the antiviral response.

6. DNA viruses

The involvement of γδ T cells in natural immunity against infections caused by DNA viruses is well established (Table 2). In particular, many studies describe a protective role of γδ T lymphocytes in the immunosurveillance against herpesviruses in both rodents and people. In the murine model of herpes simplex virus (HSV) infection, a γδ T-cell clone recognizing glycoprotein I of HSV type 1 without the requirement of expression of MHC class I or class II gene products has been isolated [81–83]. Studies of HSV disease course in TCR-γδ- or TCR-αβ-deficient mice have shown that γδ T cells limit severe HSV-1-induced epithelial lesions and greatly reduce mortality by preventing the development of lethal viral encephalitis. This protection is due to a γδ T cell-mediated arrest of both viral replication and neurovirulence [84]. After corneal HSV infection in mice, γδ T lymphocytes are able to infiltrate the trigeminal ganglion. These cells produce IFN-γ, suggesting a direct role of γδ T cells in the control of virus replication through the production of such antiviral molecules [85].

HSV-specific γδ T cells can be isolated from infected persons and are able to express HSV-specific cytotoxic activity. To mediate the lytic activity, these virus-specific CTLs require the expression of HLA class I molecules on the surface of target cells [86]. However, the response itself appears to be HLA-unrestricted, suggesting the possible involvement of NK receptors expressed by human γδ T cells [87–90]. Specifi-

Table 2
γδ T cells in DNA virus infections

Virus	Host[a]	γδ subset	Reference
Herpesviridae			
HSV	Mouse	pan-γδ	[81,83–85,144–146]
		Vγ2	[146]
	Human	pan-γδ	[86,91,92]
		Vγ9Vδ2	
EBV	Human	pan-γδ	[93]
		Vδ1	[94,95]
m-CMV	Mouse/rat	pan-γδ	[96–98]
h-CMV	Human	Vδ1/Vδ2	[99,100]
Hepadnaviridae			
HBV	Human	pan-γδ	[101]
Orthopoxviridae			
Vaccinia virus	Mouse	pan-γδ	[102]
Canarypox virus	Human	Vδ2	[103]

[a] Natural or experimental.

cally, PBMC from HSV-seropositive individuals stimulated with autologous HSV-infected PHA blasts show an expansion of Vγ9Vδ2 T cells, and are able to lyse HSV-infected, but not mock-infected targets. Also, Vγ9Vδ2 T cells obtained after PHA or mycobacterial stimulation are able to lyse HSV-infected as well as unrelated vaccinia-infected targets, but not mock-infected targets [91]. Similarly to the mouse models, human γδ T cell-mediated cytotoxic activity is not restricted by classical HLA class I or class II molecules, and can be blocked by mAbs to CD3 and the γδ TCR. Interestingly, γδ T cells have been shown to be susceptible to human herpes virus (HHV)-6 infection, and display cytolytic activities against both autologous and heterologous target cells infected with HHV-6. HHV-6 infection induces CD4 expression in γδ T lymphocytes, rendering them susceptible to HIV [92]. Thus, HHV-6 has evolved strategies to interfere with γδ T-cell antiviral activities, exploiting the activation of these cells to expand the pool of target cells susceptible to productive infection. Lymphocytes bearing γδ TCRs are expanded during other herpesvirus infections, such as the acute phase of Epstein–Barr virus (EBV)-induced infectious mononucleosis. These γδ T cells express activation antigens, such as HLA-DR and CD38, and persist during the convalescent phase of infectious mononucleosis, suggesting a possible role of γδ T cells in the control of primary EBV infection [93]. A large proportion of human sinovial tissue- and peripheral blood-derived Vδ1 T-cell clones can proliferate in response to stimulation with autologous and allogeneic EBV-transformed B-lymphoblastoid cell lines (LCL). This proliferative response is dependent on contact between responder and stimulator cells, and can be blocked by a mAb to LFA-1 and by antibodies to the γδ TCR/CD3 complex [94]. In subsequent studies, the nature of the stimulatory ligand was found to be of cellular rather than of viral origin, and its expression was upregulated upon activation of B cells. Moreover, the expression of B7 and CD39 molecules on the surface of activated B cells appears to be crucial, since antibodies to these structures can block the induction of Vδ1 T-cell proliferation. Finally, no predominant V–D–J sequences have been found among the LCL-responsive Vδ1 T-cell clones, arguing strongly against a mono- or oligoclonal Vδ1 T-cell response to LCL [95].

In a murine model of cytomegalovirus (M-CMV) infection, the number of γδ T cells increases in the liver and peritoneal cavity from day 3, and reaches a peak on day 5 after intraperitoneal infection. The γδ T cells show an activated T-cell phenotype, largely expressed Vγ1, and may recognize the HSP65. M-CMV-induced γδ T cells express IFN-γ and TNF-α, but not IL-4, and are able to produce IFN-γ in vitro in response to HSP65. Moreover, depletion of γδ T cells by anti-TCR γδ mAb treatment results in a significant increase in virus titer and a parallel decrease in IFN-γ in the liver on day 3 after M-CMV infection. This further supports the importance of γδ T cells in early protection against infection [96]. In another study, the phenotypic and functional characteristics of leukocytes infiltrating the submaxillary gland (SMG) were analyzed in CMV-infected BALB/c mice. A robust innate immune response comprising CD11c+ MHC II+ CD11b– CD8α+ dendritic cells and γδ T cells was prominent through at least 28 days post-infection. The expression of IFN-γ, IL-10 and CC chemokines was extraordinarily high in the SMG in response to M-CMV infection, indicating that innate and acquired immune responses are quite vigorous in the SMG of CMV-infected mice [97]. In a rat model, the accumulation of γδ T cells in regional popliteal lymph nodes (PLN) starts 2 days after inoculation of CMV into the footpad. PLN γδ T cells inhibit the plaque development and the spread of CMV infection, are negative for CD4 and CD8 receptors, proliferate in response to IL-2, and contain high levels of IFN-γ. The IFN-γ positivity correlates with the curing of fibroblasts from virus infection [98].

A dramatic expansion of γδ T cells in the peripheral blood has been noted during post-transplant human cytomegalovirus (H-CMV) infections. This increase is associated with the activation of γδ T cells expressing mainly the Vδ1 or Vδ3 TCR chains. Analyses of TCR junctional diversity revealed that H-CMV infection is accompanied by a selective expansion of Vδ1 T cells bearing recurrent junctional amino acid motifs, suggesting an in vivo antigen-driven selection of γδ T-cell

subsets during the course of H-CMV infection [99]. Both Vδ1 and Vδ3 T cells from H-CMV-infected kidney recipients are able to proliferate in vitro in the presence of free CMV virions or CMV-infected fibroblast lysates, but not in the presence of uninfected or other herpesvirus-infected fibroblast lysates. This suggests that a population of γδ T cells may play an important role in immune responses to H-CMV infections. The relationship between the evolution of CMV infection and the kinetics of γδ T-cell amplification has been followed up to 10 months after transplantation. Patients with late γδ T-cell expansions (≥45 days) have significantly longer ($P < 0.0001$) and higher ($P < 0.0003$) pp65 antigenemia and are more symptomatic than patients with early expansions. Moreover, single patient analyses have shown that γδ T-cell expansions parallel the resolution of CMV infection, strongly supporting the idea of a protective role of γδ T cells in H-CMV infections [100].

An increase in γδ T cells during hepatitis B virus (HBV) seroconversion has been described. It is conceivable that these cells may be involved in HBV immunosurveillance and maintaining low virus levels during seroconversion [101].

The role of γδ T cells in innate resistance to vaccinia virus (VV) infection has been studied using normal, αβ- and γδ-TCR-deficient mice. Mice deficient in γδ T cells have significantly higher VV titers and increased mortality in comparison with normal mice. There is a rapid and profound VV-induced increase in IFN-γ-producing γδ T cells in the peritoneal cavity and spleen of αβ-TCR-deficient VV-infected mice. This rapid response occurs in the absence of priming, and there are substantial numbers of VV-specific γδ T cells present in uninfected mice. These cells express a constitutive cytolytic activity, which is increased after VV infection. VV-infected αβ-deficient mice show a transient control of VV replication on the day of the γδ T-cell response peak, but thereafter γδ T-cell numbers decline, and the virus infection recrudesces. Thus, γδ T cells can be mediators of innate immunity to viruses, having a significant impact on virus replication in the presence or absence of adaptive immune responses [102].

In *H. sapiens*, the role of γδ T cells has been assessed in vaccinated subjects who received live recombinant canarypox virus expressing HIV proteins or soluble MN rgp120. Canarypox virus vaccination induces increased γδ T-cell responses detectable after secondary in vitro expansions. These augmented γδ T-cell responses are specific for canarypox virus, but not for HIV antigens, and are mediated primarily by IFN-γ-producing Vγ9 T cells. γδ T-cell lines generated from canarypox vaccinees respond to canarypox antigens but not to mycobacterial antigens. Increased IFN-γ production by γδ T cells may boost the induction of protective type 1 memory immunity and augment the effectiveness of live vaccines [103].

7. Conclusions

Clearly, γδ T cells play an important role in innate and adaptive immune responses to viral infections. The molecules recognized by γδ T cells during viral infections are probably of cellular rather than viral origin and appear to be metabolites of altered cellular pathways, in particular the products of the mevalonate pathway. Moreover, virus-exposed γδ T cells can be rapidly activated by type I interferons (IFN-α, IFN-β), a phenomenon that is likely to contribute to the effective antiviral response [104]. The antiviral role of γδ T cells has been intensively studied in mice and correlated with the production of IFN-γ by distinct γδ T-cell subsets. In *H. sapiens*, Vδ1 T cells are systemically or locally expanded in some chronic viral infections and are probably involved in the accompanying inflammatory processes. Vγ9Vδ2 T cells are activated early during the acute phase of most viral infections and can display potent antiviral responses. Moreover, a plethora of soluble factors with antiviral characteristics induced by Vγ9Vδ2-stimulatory molecules can influence the outcome of viral infections. In addition to their direct antiviral properties, many of these molecules play crucial immunoregulatory roles and are decisive in controlling the complex antiviral immunosurveillance function as well as in establishing the correct immunological memory environment in vivo.

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