Published in final edited form as:

Microbes Infect. 2003 May ; 5(6): 491–498.

V γ 2V δ 2⁺ T cells and anti-microbial immune responses

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Abstract

V γ 2V δ 2⁺ T cells exist only in primates and constitute the majority of circulating human $\gamma\delta$ T cells. Recent studies have demonstrated that this unique $\gamma\delta$ T cell subpopulation can be a component of adaptive immune responses and contribute to anti-microbial immunity to infections.

Keywords

$\gamma\delta$ T cells; TCR; Memory responses; Immunity; Infections; Primates

1. Introduction

The majority of circulating $\gamma\delta$ T cells in humans expresses T cell receptor (TCR) heterodimers comprised of V γ 2 and V δ 2 segments. The dominance of these V γ 2V δ 2⁺ T cells in the circulation is likely due to exposure to antigens from microbes or environmental sources in childhood [1]. Human V γ 2V δ 2⁺ T cells recognize small organic phosphate antigens from microbes and other nonpeptide molecules such as alkyl-amines and aminobisphosphonates [2]. The recognition of these nonpeptide antigens does not require antigen processing or MHC presentation, although cell–cell contact is needed for this to occur [2]. While the definition of these nonpeptide antigens has been important, the role of human $\gamma\delta$ T cells in immune responses remains poorly understood. Studies of the immune responses of V γ 2V δ 2⁺ T cells have been hindered by an absence of relevant animal models.

Mice do not express a homolog of V γ 2V δ 2 TCR, and there is no functional equivalent of these cells in small laboratory animals. Nonhuman primates can serve as good animal models for studying human immune biology and diseases, since they are genetically and biologically close to humans. Macaques express human TCR homologs including $\gamma\delta$ TCR [3]. The macaque V γ or V δ elements can share up to 91% similarity in amino acid sequences to their human counterparts. More importantly, macaque V γ 2V δ 2⁺ T cells can recognize nonpeptide phosphoantigens as efficiently as their human counterparts [4]. Recent studies in humans and macaque animal models have increased our understanding of the immune biology and function of V γ 2V δ 2⁺ T cells. This article reviews recent findings concerning immune responses of V γ 2V δ 2⁺ T cells in the setting of microbial infections.

2. Potent immune responses of V γ 2V δ 2⁺ T cells during microbial infections

The development of potent responses of immune cells following exposure to certain microbes may indicate that the responding cells participate in immune regulation and protection against those microbial infections. Since phospholipids recognized by V γ 2V δ 2⁺ T cells are widely distributed in a variety of bacteria and protozoal parasites, infections with those microbes are likely to induce potent immune responses of this $\gamma\delta$ T cell subset. In fact, major expansions of V γ 2V δ 2⁺ T cells have been reported in individuals with various microbial infections (Table 1). Most of those studies have focused on changes in $\gamma\delta$ T cells in the blood of patients with infections. In humans with tularemia, salmonellosis, brucellosis and ehrlichiosis, $\gamma\delta$ T cells expanded up to 48–97% of total T cells [5–8]. In the patients with bacterial meningitis resulting from systemic infections with *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus pneumoniae*, the circulating $\gamma\delta$ T cells expanded up to 37–46% of total T cells, although the representation of these cells in cerebral spinal fluid was not described [9]. As many as 15–46% of total circulating T cells could be $\gamma\delta$ T cells or V γ 2V δ 2⁺ T cells in patients with protozoal parasite infections such as malaria, toxoplasmosis and leishmaniasis [10–14]. Furthermore, expansions of V γ 2V δ 2⁺ T cells were also seen in humans with mycobacterial infections.

Increases in total $\gamma\delta$ T cells or the V δ 2/V γ 2 subset were detected in the blood of humans with active *Mycobacterium avium* and *Mycobacterium tuberculosis* infections as well as healthy hospital professionals recently exposed to patients with tuberculosis [15–19], although some studies reported no significant increases in these cells in tuberculous patients (see discussion below). The expansion of $\gamma\delta$ T cells can occur as early as 7 d after the onset of the disease caused by those microbes, and can persist for up to 1 year after infection. Interestingly, expansions of V γ 2V δ 2⁺ T cells have also been identified in the lesions associated with those infections. Earlier studies showed a five- to eightfold increase in $\gamma\delta$ T cells in the granulomatous reaction of leprosy and localized leishmaniasis [20]. A predominance of V γ 2V δ 2⁺ T cells in cerebral spinal fluid was also reported in patients with tuberculous meningitis [21]. Marked increases in numbers of V γ 2V δ 2⁺ T cells are detected in the bronchoalveolar lavage (BAL) fluid of some patients with psittacosis caused by *Chlamydia psittaci* infection [22].

Although V γ 2V δ 2⁺ T cell expansions have been described in association with microbial infections, the nature of these potent immune responses has not been characterized in humans. Particularly, the fundamental question of whether V γ 2V δ 2⁺ T cells possess immunological memory has not been addressed. Recent studies in nonhuman primate models provide detailed information regarding immunological features of V γ 2V δ 2⁺ T cells that expand in response to microbial infections. The V γ 2V δ 2⁺ T cells of macaques inoculated with *M. bovis* BCG develop a primary immune response that is detected 2–3 weeks after infection. A memory-type recall response of V γ 2V δ 2⁺ T cells can be detected as early as 4–6 d after BCG reinfection. The magnitude of the recall expansion of V γ 2V δ 2⁺ T cells is 2–9 times greater than that observed during primary BCG infection, and the expansion persists as long as 7 months, even after the resolution of the BCG infection [4]. Such adaptive immune responses of V γ 2V δ 2⁺ T cells are also detected in monkeys challenged with *M. tuberculosis* by aerosol administration [4]. Interestingly, predominant expansions of V γ 2V δ 2⁺ T cells are detected in pulmonary and intestinal mucosal sites but not in lymphoid organs [4]. These major expansions of V γ 2V δ 2⁺ T cells in humans and monkeys suggest that this phosphoantigen-specific $\gamma\delta$ T cell subset may be involved in anti-microbial immune responses during infections.

3. Contribution of V γ 2V δ 2⁺ T cells to immunity against microbial infections

In a macaque model of *M. bovis* BCG infection, a primary expansion of V γ 2V δ 2⁺ T cells is associated with the clearance of BCG organisms from the blood [4] and lymphoid tissues

[23] as well as the resolution of active BCG infection. The correlation between the recall expansion of $V\gamma 2V\delta 2^+$ T cells and the down-regulation of BCG reinfection is also evident following the second BCG inoculation of monkeys that have immune control of primary BCG infection [23]. The contribution of $V\gamma 2V\delta 2^+$ T cells to anti-microbial immune responses is also seen in the rhesus model of *M. tuberculosis* infection. It has been shown that a rapid recall expansion of pulmonary $V\gamma 2V\delta 2^+$ T cells after an aerosol challenge with *M. tuberculosis* is associated with low bacterial burdens in BAL fluid and immune protection against acutely fatal tuberculosis in BCG-vaccinated animals [23]. In contrast, aerosol challenge of naïve monkeys with *M. tuberculosis* aerosol results in slow increases in numbers of $V\gamma 2V\delta 2^+$ T cells in BAL fluid and subsequent development of acutely fatal tuberculosis characterized by wasting, *M. tuberculosis* dissemination and milliary tuberculosis. Consistent with the anti-microbial responses seen in nonhuman primates, the anti-bacterial effect of human $V\gamma 2V\delta 2^+$ T cells has been demonstrated in a chimeric severe combined immunodeficiency (SCID) mouse (hu-SCID) model. Human $V\gamma 2V\delta 2^+$ T cells have been shown to mediate resistance to acutely lethal infections with *Staphylococcus aureus* and *Escherichia coli*/*Morganella morganii* in hu-SCID mice [24]. Surprisingly, this anti-bacterial effect mediated by $V\gamma 2V\delta 2^+$ T cells is observed as early as 1 d after infection, a time before the expansion of these cells is seen. Moreover, in vivo administration of nonpeptide phospholigand can enhance $V\gamma 2V\delta 2^+$ T cell-mediated anti-bacterial effect in hu-SCID mice [24].

The immune functions of microbe-specific $V\gamma 2V\delta 2^+$ T cells may be diverse. Activated and expanded $V\gamma 2V\delta 2^+$ T cells may directly participate in anti-microbial immune responses. $V\gamma 2V\delta 2^+$ T cells have been shown to kill bacteria-infected cells and bacteria [25,26]. However, this effector function detected in vitro may not reflect the in vivo function of these cells. Upon activation, $V\gamma 2V\delta 2^+$ T cells can produce a large amount of IFN- γ and TNF- α [27–29], cytokines important for controlling mycobacterial infection in mice. Through production of those Th1 cytokines, $V\gamma 2V\delta 2^+$ T cells may function as a link connecting innate and adaptive immune systems and facilitate the development of adaptive immune responses of antigen-specific $\alpha\beta$ T cells. The impact of $\gamma\delta$ T cells on naïve immune cells such as macrophages and NK cells has also been reported in murine models [30]. Mice deficient in $\gamma\delta$ T cells develop enhanced inflammation characterized by disruption of macrophage homeostasis and liver necrosis [30]. In the absence of $\gamma\delta$ T cells, IFN- γ production by NK cells is reduced, which leads to a delay in the formation of granulomas and an increase in bacterial growth [31]. $V\gamma 2V\delta 2^+$ T cells may also regulate immune functions of other lymphocytes [32,33], given their ability to produce various cytokines. Furthermore, nonpeptide antigen-specific $\gamma\delta$ T cells may contribute to anti-inflammatory function or tissue repair during infection and disease. This potential role has been suggested by the recent novel observation that resident $\gamma\delta$ T cells can have a unique role in epithelium or tissue repair after the damage [34]. Finally, it is important to realize that $V\gamma 2V\delta 2^+$ T cells express NK receptors such as NKG2D [35,36], and mediate antigen-independent cytotoxic activity against target cells infected with various viruses including human herpes-6, herpes simplex virus, and human or simian immunodeficiency virus (SIV) [37,38]. Engagement of NKG2D by various ligands including MICA during infections may enhance effector function of $V\gamma 2V\delta 2^+$ T cells [36].

4. Immune compromise of $V\gamma 2V\delta 2^+$ T cell responses in HIV infection

Although there is no evidence that HIV encodes peptide antigens recognized by $V\gamma 2V\delta 2^+$ T cells, efforts have been made to explore $\gamma\delta$ T cell immune responses in HIV-1 infection. Studies of HIV-1-infected humans suggest that HIV infection can impact on repertoire and effector function of $V\gamma 2V\delta 2^+$ T cells. While $V\gamma 2V\delta 2^+$ T cells comprise the majority of the circulating $\gamma\delta$ T cell population in normal individuals, the frequency of $V\delta 2^+$ T cells is markedly reduced in the blood of HIV-1-infected humans [39–41]. Interestingly, the contracted numbers of $V\gamma 2V\delta 2^+$ T cells are associated with an increase in $V\delta 1^+$ T cells in HIV-1-infected individuals

[42–44]. Changes in $\gamma\delta$ T cell repertoires are also seen in monkeys acutely infected with SIV [45,46]. In vitro studies have shown that HIV infection can inhibit the ability of $V\gamma 2V\delta 2^+$ T cells to proliferate in response to the in vitro stimulation with *M. tuberculosis* or nonpeptide antigens [40,47,48]. Consistently, $V\gamma 2V\delta 2^+$ T cells from HIV-1-infected humans exhibit a reduced capacity to produce Th1 cytokines following stimulation with *M. tuberculosis* or nonpeptide antigens, and this defect in cytokine production cannot be restored by the addition of IL-12 and IL-15 to the culture [41,48–51]. The cytolytic function of $V\gamma 2V\delta 2^+$ T cells is also impaired during HIV-1 infection [52]. Recent studies that have assessed phenotypes of human $\gamma\delta$ T cells also suggest that immune compromise of $V\gamma 2V\delta 2^+$ T cells during HIV-1 infection and pulmonary tuberculosis is restricted to the effector cells of $V\gamma 2V\delta 2^+$ T cell subset. It has been shown that the central memory $V\gamma 2V\delta 2^+$ T cells are $CD45RA^-CD27^+$, whereas effector memory cells have lost the expression of CD27 costimulatory molecules and lack the proliferative potential of central memory cells [27,41]. The frequency of effector $V\gamma 2V\delta 2^+$ T cells is decreased in peripheral blood mononuclear cells of humans with HIV-1 infection and pulmonary tuberculosis [27]. The impaired function of $V\gamma 2V\delta 2^+$ T cells appears to be related to the immune competence of $CD4^+$ T cells, since co-culture of $V\gamma 2V\delta 2^+$ T cells with allogeneic $CD4^+$ peripheral blood lymphocytes (PBLs) from uninfected individuals can restore some levels of depressed capacity of these cells to expand in vitro in response to phosphoantigens [47,53].

The pathogenic consequences of $V\gamma 2V\delta 2^+$ T cell abnormalities in HIV-1 infection remain uncertain. It is important to note that $V\gamma 2V\delta 2^+$ T cells can mediate anti-viral activity in vitro. The $V\gamma 2V\delta 2^+$ T cell clones generated from PBLs of HIV-negative humans have been shown to lyse HIV-infected cells [38]. The cytotoxic effect mediated by $V\gamma 2V\delta 2^+$ T cells does not appear to be $\gamma\delta$ TCR-dependent, since those cytotoxic clones also recognize Daudi lymphoma cells. In addition, such an effector function does not require prior exposure of $V\gamma 2V\delta 2^+$ T cells to HIV. On the other hand, $V\gamma 2V\delta 2^+$ T cells can inhibit HIV replication in vitro following stimulation with nonpeptide phosphoantigens [54]. The suppression of HIV replication by activated $V\gamma 2V\delta 2^+$ T cells is linked to the ability of these cells to produce the β chemokines, MIP1- α , MIP1- β and RANTES, which have been shown to block HIV-1 entry to cells through binding to CC chemokine receptors [54]. Recognition of HIV and resulting production of anti-viral cytokine by $V\gamma 2V\delta 2^+$ T cells may also occur in vivo during acute and chronic HIV-1 infection. Thus, a decreased number and impaired function of $V\gamma 2V\delta 2^+$ T cells during HIV infection may result in a loss of $\gamma\delta$ T cell-related anti-HIV immune responses as well as adaptive $\gamma\delta$ T cell immunity against opportunistic pathogens.

5. Immune biology of $V\gamma 2V\delta 2^+$ T cells in mycobacterial infections

Patients with *M. tuberculosis* infection have been assessed for changes in the number and function of their $\gamma\delta$ T cells. Studies of total $\gamma\delta$ T cells or $V\gamma 2V\delta 2^+$ T cells in tuberculous patients without HIV infection have yielded conflicting results. Some studies have reported increased numbers of $V\gamma 2V\delta 2^+$ T cells in the blood of both *M. tuberculosis* infected humans and healthy hospital professionals recently exposed to patients with tuberculosis [15–17]. Other cross-sectional studies have found a decrease in numbers of $V\gamma 2V\delta 2^+$ T cells in the blood of patients with pulmonary tuberculosis when compared with normal individuals [55,56]. Studies of pulmonary $\gamma\delta$ T cells have shown an increase in absolute numbers of $V\gamma 2V\delta 2^+$ T cells in BAL fluid of patients with active pulmonary tuberculosis, although the percentage of these cells is reduced or similar to those of normal controls [55,57]. The reduced numbers of $V\gamma 2V\delta 2^+$ T cells in some tuberculous patients may be related to the increased apoptosis of $V\gamma 2V\delta 2^+$ T cells involving a Fas/Fas ligand pathway, since in vitro stimulation with mycobacterial antigens up-regulates the expression of Fas/Fas ligand on $V\gamma 2V\delta 2^+$ T cells and predisposes these cells to activation-induced death [58]. The conflicting reports of representation of circulating $\gamma\delta$ T cells in *M. tuberculosis* infected humans may be due to the differences in sampling times after

infections as well as microbial and host factors that might differ among those infected individuals in the various study populations.

The potency of $\gamma\delta$ T cell immune responses appears to be influenced by the timing and route of infection, bacterial burdens, degree of inflammation, and the immune status of the host. We have found that an *M. tuberculosis* pulmonary aerosol challenge of monkeys results in increased numbers of $V\gamma 2V\delta 2^+$ T cells in BAL fluid but not PBL of the infected monkeys [4]. In monkeys intravenously inoculated with BCG, a major expansion of these cells is seen in the pulmonary compartment, blood and intestinal mucosae but not in lymph nodes. This increased number of $V\gamma 2V\delta 2^+$ T cells is particularly marked in the lung, despite the fact that BCG loads in the lung are extremely low after systemic BCG infection. Surprisingly, there are larger increases in numbers of $V\gamma 2V\delta 2^+$ T cells than $\alpha\beta$ T cells in the lung of the monkeys intravenously inoculated with BCG. These results suggest that there may be a preferential migration of activated $V\gamma 2V\delta 2^+$ T cells to the lung from the circulation or lymphoid tissues after mycobacterial infection. In fact, in murine models of infectious diseases, the involved $\gamma\delta$ T cells have been identified at local sites of infections but not in draining lymph nodes and spleen [30]. Recent studies suggest that the chemokine receptor-mediated trafficking $V\gamma 2V\delta 2^+$ T cells may be responsible for transendothelial migration of immune cells to the lung from the circulation and/or lymphoid tissues. It has been shown that human $V\delta 2^+$, but not $V\delta 1^+$ or $\alpha\beta$ TCR⁺ T cells express high levels of CCR5 and CXCR3 [59,60]. MIP-1 α , MIP-1 β and RANTES, the ligands for CCR5, have been shown to facilitate $\gamma\delta$ T cell migration in an in vitro migration system [61]. Since inflammation after mycobacterial infections is inevitably associated with an increased production of chemokines, these chemokines may have roles in transendothelial chemotaxis of $V\gamma 2V\delta 2^+$ T cells into the lung or other organs. On the other hand, the expansion of $V\gamma 2V\delta 2^+$ T cells during mycobacterial infection appears to be dependent upon the inoculum size of mycobacteria, since the primary expansion of these cells is detected only in monkeys inoculated with a large but not a small inoculum of BCG (unpublished data). The inoculum size-dependent expansion of circulating $V\gamma 2V\delta 2^+$ T cells in monkeys is reminiscent of the increased number of circulating $\gamma\delta$ T cells seen in patients with substantial mycobacterial burdens due to the dissemination of *M. avium* [19]. Other studies have also demonstrated that mycobacteremia is associated with a higher proportion of $\gamma\delta$ T cells in the blood of infected humans [62]. Interestingly, marked expansions of liver $\gamma\delta$ T cells are seen in disseminated infections with *M. tuberculosis* or *M. avium* complex [63].

Although various immunological factors defined in studies in animal models may contribute to variation seen in $\gamma\delta$ T cell responses in patients with tuberculosis, the immune responses of $V\gamma 2V\delta 2^+$ T cells in human tuberculosis are likely different from those seen in animal models. Experimental mycobacterial infections in monkeys or small laboratory animals cannot precisely mimic the natural infection of *M. tuberculosis* in humans. While a relatively large mycobacterial inoculum is used to initiate infections in animal models, the natural *M. tuberculosis* infection in humans usually occurs as a result of aerosol transmission of small inocula of mycobacteria from actively infected patients. Pulmonary tuberculosis in adults without HIV infection often results from endogenous reactivation of latent infection, although primary infection and reinfection also can lead to the development of tuberculosis. Reactivation tuberculosis due to a functional defect of established immunity may be distinct from primary infection and reinfection from both microbial and immunological standpoints. In fact, some patients with active pulmonary tuberculosis appear to share certain features of immune dysfunction with those infected with HIV-1. An absence or anergy of CD4⁺ T cell responses and PPD skin test reactivity have been reported in patients with active tuberculosis [64,65]. It has also been shown that patients with active pulmonary tuberculosis exhibit an impaired ability of $V\gamma 2V\delta 2^+$ T cells to produce cytokines or proliferate in response to in vitro stimulation with phosphoantigens [27,55]. Further studies of functional immune defects in tuberculosis may help to clarify immunopathogenesis of $\gamma\delta$ T cell responses in *M. tuberculosis* infection.

6. V γ 2V δ 2⁺ T cell immune responses during coinfection with AIDS virus and mycobacterium

Little is known about whether HIV-infected humans are able to mount phosphoantigen-specific V γ 2V δ 2⁺ T cell immune responses during acute *M. tuberculosis* infection. The paucity of information regarding the development of V γ 2V δ 2⁺ T cell responses in HIV/*M. tuberculosis*-coinfected persons can be attributed, at least in part, to the difficulty in recruiting coinfecting patients for obtaining tissue samples at the right times during acute *M. tuberculosis* infection. Relevant animal models should facilitate the careful study of $\gamma\delta$ T cell responses during the active mycobacterial coinfection of AIDS virus-infected individuals. We have recently developed a macaque model of SIVmac and BCG coinfection to study immune biology and disease consequences of AIDS virus and mycobacterial coinfection [23]. We have made use of SIVmac/BCG-coinfected macaques to determine the extent to which adaptive immune responses of V γ 2V δ 2⁺ T cells are compromised during coinfection. SIVmac-negative macaques develop primary and recall expansions of phosphoantigen-specific V γ 2V δ 2⁺ T cells after both BCG infection and BCG reinfection introduced by intravenous inoculation, respectively. In contrast, SIVmac-infected macaques with profound CD4⁺ T cell deficiency did not exhibit primary and recall expansions of V γ 2V δ 2⁺ T cells in the blood or pulmonary alveoli following BCG infection and reinfection [53]. These coinfecting monkeys developed an SIVmac-related tuberculosis-like disease, characterized clinically by diarrhea and weight loss, and pathologically by disseminated granulomas in multiple organs [23,53]. These results are consistent with those reported in cross-sectional studies of $\gamma\delta$ T cell responses in HIV-infected humans with pulmonary tuberculosis [55,56]. It has been shown that there is a reduced number of circulating V γ 2V δ 2⁺ T cells in HIV-infected humans who also have pulmonary tuberculosis, when compared with the values of these cells in normal individuals.

The absence of V γ 2V δ 2⁺ T cells during active mycobacterial coinfection of HIV-infected humans and SIV-infected monkeys raises questions as to whether AIDS virus directly affects V γ 2V δ 2⁺ T cells or simply mediates an immune suppression of V γ 2V δ 2⁺ T cell responses. Naïve monkeys simultaneously inoculated with SIVmac and BCG provide a good setting in which to address this issue, since V γ 2V δ 2⁺ T cell responses can be evaluated during the initial burst viral replication that occurs during an acute SIVmac infection. Although some naïve monkeys inoculated simultaneously with SIVmac and BCG can develop a detectable expansion of V γ 2V δ 2⁺ T cells, these animals are unable to sustain this expansion of V γ 2V δ 2⁺ T cells as they develop lymphoid depletion, BCG dissemination and a fatal tuberculosis-like disease [53]. This contrasts with the linear V γ 2V δ 2⁺ T cell expansion seen during mycobacterial dissemination of normal monkeys without SIVmac infection [4]. In normal monkeys not infected with SIVmac, uncontrolled infection that progresses to mycobacterial dissemination after primary infection was associated with a sustained/prolonged expansion of V γ 2V δ 2⁺ T cells [4]. The demonstration that burst viral replication during an acute SIVmac infection fails to abrogate the expansion of V γ 2V δ 2⁺ T cells in previously naïve monkeys simultaneously inoculated with SIVmac and BCG suggests that SIVmac itself may not directly interfere with V γ 2V δ 2⁺ T cell function. Furthermore, no deletion in the V δ 2 TCR repertoire has been identified in SIVmac/BCG-coinfected macaques, implicating an SIVmac-induced down-regulation rather than a clonal exhaustion of these cells. Thus, an SIVmac-induced compromise of the adaptive V γ 2V δ 2⁺ T cell responses may contribute to the immunopathogenesis of the SIVmac-related tuberculosis-like disease in macaques.

The fact that functional defect of $\gamma\delta$ T cells is at least in part due to the generalized immune dysfunction in HIV/SIV-infected individuals suggests that control of viral infection by highly active antiretroviral therapy (HAART) may improve the immune responses of V γ 2V δ 2⁺ T cells. In fact, HAART has been shown to reverse the defect of V γ 2V δ 2⁺ T cell production of IFN- γ in HIV-1-infected humans, and such an immune reconstitution is associated with a

sustained recovery of CD45RA T helper function [48]. Structured treatment interruption in HIV-1-infected persons receiving HAART results in a rapid loss of CD45RA-CD27-V γ 2V δ 2⁺ T cell effectors and reduction of their ability to produce cytokines in response to the in vitro stimulation with phosphoantigens. Interestingly, the resumption of HAART and control of HIV-1 infection in these infected humans can restore the number and impaired function of V γ 2V δ 2⁺ T cells [41]. The results in these in vitro studies are similar to those found in vivo in SIVmac-infected monkeys that receive both BCG inoculation and antiretroviral treatment. A 2–3-log reduction of SIVmac plasma viral RNA during antiretroviral drug treatment was associated with the expansion of V γ 2V δ 2⁺ T cells during active BCG coinfection of SIVmac-infected monkeys. The restoration of V γ 2V δ 2⁺ T cell responses coincided with the immune reconstitution of CD4⁺ T cells (unpublished data). The results in humans and nonhuman primates suggest that the development of adaptive immune responses of V γ 2V δ 2⁺ T cells during active mycobacterial coinfection of AIDS virus-infected individuals may require the control of AIDS virus infection and functional CD4⁺ T cells.

7. Conclusion

V γ 2V δ 2⁺ T cells represent a unique $\gamma\delta$ T cell subpopulation in primates. V γ 2V δ 2⁺ T cells appear to differ from $\gamma\delta$ T cells that reside in epithelial mucosae. V γ 2V δ 2⁺ T cells, like $\alpha\beta$ T cells, can mount potent immune responses during microbial infections. The capacity of V γ 2V δ 2⁺ T cells to expand rapidly to large numbers and produce Th1 cytokines during infections suggests that it is beneficial to explore vaccine-induced immune responses of these cells for protection against microbial infections. The effective anti-microbial functions of V γ 2V δ 2⁺ T cells remain uncertain. Immune mechanisms underlying the dysfunction or anergy of V γ 2V δ 2⁺ T cells in some pathogenic conditions such as HIV infection and active tuberculosis in humans are poorly characterized. Further studies should allow an elucidation of the diverse roles of V γ 2V δ 2⁺ T cells in immune regulation and protection against infections.

Acknowledgments

The authors acknowledge the financial support of the National Institutes of Health (HL64560 and RR13601, to ZWC), and technical assistance from members at the Chen laboratory.

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Table 1Reported infections that induce in vivo expansions of total $\gamma\delta$ T cells or V γ 2V δ 2⁺ T cells

Infections/diseases	Anatomic sites tested	Mean % of T cells	References
Humans			
Tularemia	Blood	~33	[5,66]
Salmonellosis	Blood	18	[6]
Brucellosis	Blood	29	[7]
Legionellosis	Blood	15	[67]
Listeriosis	Blood	12	[68]
<i>H. influenzae</i> /meningitis	Blood	27	[9]
<i>N. meningitidis</i> /meningitis	Blood	25	[9]
<i>S. pneumoniae</i> /meningitis	Blood	35	[9]
Ehrlichiosis	Blood	57	[8]
<i>Coxiella burnetii</i> /Q-fever	Blood	16	[69]
<i>Chlamydia psittaci</i>	BAL fluid	25–66	[22]
Malaria	Blood	16–18	[10–12,70]
Toxoplasmosis	Blood	9	[13]
Leishmaniasis	Blood	13	[14]
<i>M. tuberculosis</i>	Blood, increased	6–14	[15–17]
	Blood, declined	1.5	[55,56]
	BAL fluid	Increased total cells	[57]
	BAL fluid	Decreased percentage	[55]
	Liver	15.5	[63]
<i>M. avium</i>	Blood	Up to 40	[18,19]
	Liver	26	[63]
Leprosy	Skin lesions	29	[20]
Sarcoidosis	Blood	9.2	[17]
Monkeys			
<i>M. bovis</i> BCG or <i>M. tuberculosis</i>	Blood, BAL fluid, intestine, lymph nodes	Up to 30	[4]