Published in final edited form as:

Clin Immunol. 2005 September ; 116(3): 202–207. doi:10.1016/j.clim.2005.04.005.

Immune regulation of $\gamma\delta$ T cell responses in mycobacterial infections

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Abstract

Antigen-specific $\gamma\delta$ T cells may play a role in anti-mycobacterial immunity. Studies done in humans and animal models have demonstrated complex patterns of $\gamma\delta$ T cell immune responses during early mycobacterial infections and chronic tuberculosis. Recent studies have also shown a clinical correlation between major recall expansion of antigen-specific $\gamma\delta$ T cells and immunity against fatal early mycobacterial diseases. Multiple host and microbial factors can regulate diverse immune responses of phosphoantigen-specific $\gamma\delta$ T cells during mycobacterial infections.

Keywords

$\gamma\delta$ T cells; HIV/AIDS; Tuberculosis; Immune regulation

Introduction

While CD4 T cells have been shown to be important for immunity against tuberculosis, the role of $\gamma\delta$ T cells in anti-mycobacterial immune responses remains poorly characterized. $\gamma\delta$ T cells have long been considered innate-like immune cells. However, adaptive immune responses of antigen-specific $\gamma\delta$ T cells during mycobacterial infections have recently been demonstrated in humans and monkey models. It is important to note that phosphoantigen remains the sole mycobacterial antigen recognized by a primate $\gamma\delta$ T cell subset that expresses V γ 2 and V δ 2 TCR (V γ 2V δ 2 T cells), and that rodent $\gamma\delta$ T cells have not been shown to recognize phosphoantigen or other mycobacterial antigens. Phosphoantigen-specific V γ 2V δ 2 T cells constitute 60–95% of total circulating human $\gamma\delta$ T cells, implicating important and broad function of these $\gamma\delta$ T cells in the development of immune responses against mycobacterial infections. This article reviews recent human and animal studies of $\gamma\delta$ T cell immune responses during mycobacterial infections.

Early infection and $\gamma\delta$ T cell expansions

Mycobacterial infections may regulate both innate and adaptive $\gamma\delta$ T cell immune responses. Such regulated responses of $\gamma\delta$ T cells may be particularly evident during the early infection due to a burst of bacterial replication. While adaptive $\gamma\delta$ T cell immune responses are regulated by TCR-dependent clonal expansion and immune memory in response to specific antigen stimulation, regulatory factors driving TCR-independent activation/expansion of $\gamma\delta$ T cells remains poorly characterized. Interestingly, despite the absence of defined microbial antigens recognized by murine $\gamma\delta$ TCR, mouse $\gamma\delta$ T cells can expand during early infection with mycobacteria and other pathogens [3,6,7] (Table 1). The expansion usually peaks a week after

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infection and lasts for a short time. Similarly, early *Mycobacterium bovis* infection in ruminants can drive an increase in numbers of activated $\gamma\delta$ T cells in both the lung and blood, although there is no apparent expansion of total circulating $\gamma\delta$ T cells [9]. Whether an activation/expansion of murine and bovine $\gamma\delta$ T cells represents antigen-specific or innate-like responses remain to be determined [11] (Table 1). Recent identification of mycolylarabinogalactan peptidoglycan recognized by bovine $\gamma\delta$ T cells suggests that ruminant $\gamma\delta$ T cell responses may be induced by specific antigens in early *M. bovis* infection [10], although bovine TCR–phosphoantigen interaction has not been defined. It might also be possible that the activation of murine and bovine $\gamma\delta$ T cells in early infection occurs as a result of TCR-independent stimulation events driven by inflammatory cytokines and other regulatory factors. This presumption is indeed supported by a recent observation that human V δ 1 T cells, which do not recognize mycobacterial phosphoantigen, can be nonspecifically activated by inflammatory cytokines in the context of the V δ 1 TCR. Other factors such as dendritic cells, adhesion (LFA3/CD2, LFA1/ICAM1), and costimulatory (MHC class I-related chain B molecule/NK-activating receptor G2D) molecules also contribute to this antigen-nonspecific activation of human V δ 1 T cells [11].

Adaptive immune responses of $\gamma\delta$ T cells during mycobacterial infections have been demonstrated in macaque animal models (Table 1). While V γ 2V δ 2 T cells recognize mycobacterial phosphoantigen, V γ 2V δ 2 TCR in these $\gamma\delta$ T cells clearly plays a role in driving clonal expansion and adaptive immune responses during mycobacterial infections. Primary *M. bovis* BCG infection induces major clonal expansion of phosphoantigen-specific V γ 2V δ 2 T cells [14,15]. Surprisingly, these antigen-specific $\gamma\delta$ T cells can have immune memory and mount rapid, prolonged and high-magnitude recall expansion of V γ 2V δ 2 T cell subpopulation after BCG re-infection or *Mycobacterium tuberculosis* infection in monkeys previously exposed to BCG [14,15]. The memory immune responses of antigen-specific V γ 2V δ 2 T cells are also seen in human studies [17,18]. The memory-type responses can be detected in BCG-vaccinated humans, whereas tea antigen recognized by $\gamma\delta$ T cells mediate both the innate-like and memory responses of V γ 2V δ 2 T cells in tea-drinking humans [17,18].

Adaptive immune responses of mycobacterial phosphoantigen-specific $\gamma\delta$ T cells may contribute to immune control of bacterial burdens in early mycobacterial infections. Major expansions of V γ 2V δ 2 T cells are associated with the decline of bacterial burdens and resolution of active BCG infection in monkeys [14,15]. In addition, a rapid recall expansion of V γ 2V δ 2 T cells in the pulmonary compartment is associated with low levels of bacterial burdens and immunity against acutely fatal tuberculosis after *M. tuberculosis* challenge of BCG-vaccinated monkeys by aerosol [15]. The association of V γ 2V δ 2 T cells with anti-mycobacterial immunity is also seen in the macaque models of AIDS-related tuberculosis-like disease [22]. Nevertheless, a role of murine $\gamma\delta$ T cells in immunity against mycobacterial infections is controversial [21,23–25]. It is argued that an absence of $\gamma\delta$ T cell-mediated immunity in mice may be attributed to the fact that murine $\gamma\delta$ T cells do not recognize phosphoantigen or other mycobacterial antigens.

Infection and memory/effector phenotypes of antigen-specific $\gamma\delta$ T cells

The capacity of antigen-specific V γ 2V δ 2 T cells to mount adaptive immune response is consistent with what is found in the studies of memory/effector phenotypes of these cells in humans. It has been shown that the surface expression of CD45RA and CD27 antigens defines four subsets of V δ 2 T cells: naïve CD45RA+CD27+; memory CD45RA–CD27+; effector memory CD45RA–CD27– and terminally differentiated CD45RA+CD27– cells [26]. Naïve CD45RA+CD27+ and memory CD45RA–CD27+ V δ 2 T cells express lymph node-homing receptors and predominate in lymph nodes; whereas effector memory CD45RA–CD27– and terminally differentiated CD45RA+CD27– V δ 2 T cells are mainly present in the circulation

and inflamed tissues, respectively [26]. Interestingly, within effector memory subset, V δ 2 T cells can be functionally grouped into IFN γ /TNF α -producing effectors and cytotoxic effectors. The IFN γ /TNF α -producing effectors do not express CD16 but express high levels of chemokine receptors and produce large amounts of IFN γ /TNF α in response to phosphoantigens. In contrast, cytotoxic effectors are CD16⁺ with NK-like phenotypes and highly active against tumor cell lines, but they are refractory to phosphoantigen-mediated production of IFN γ and TNF α [27]. Consistently, macaque V γ 2V δ 2 T cells that do not express CD45RA or CD27 are predominated in the blood circulation and spleen but not in the lymph nodes after mycobacterial infection (data not shown). Clonotypic TCR analyses indicate that the $\gamma\delta$ T cells with those memory phenotypes have undergone recall expansion after mycobacterial infections (data not shown and [15]). The data suggest that mycobacterial infection regulates both memory/effector phenotypes and adaptive immune function of phosphoantigen-specific V γ 2V δ 2 T cells.

Infection dose/route and the extent of initial $\gamma\delta$ T cell responses

While virulence or pathogenicity of mycobacterial strains can impact on the immune system and consequences of infection, infection dose and route have not been assessed for their capacity to regulate immune responses of antigen-specific $\gamma\delta$ T cells in humans. Recent studies in monkey models of mycobacterial infections provide evidence that mycobacterial infection dose and route play a role in regulating $\gamma\delta$ T cell immune responses. It has been shown that the systemic BCG infection introduced by intravenous inoculation with 10⁸ BCG organisms results in up to 5-fold expansion of V γ 2V δ 2 T cells in the blood [14]. In contrast, a systemic BCG infection generated by 10³ BCG organisms or a pulmonary infection by bronchoscope-guided inoculation induces only subtle changes in numbers of circulating V γ 2V δ 2 T cells. On the other hand, pulmonary exposure to BCG through the bronchial route induces detectable expansions of CD4⁺, CD8⁺, and V γ 2V δ 2 T cells only in the lung but not in the blood. Similarly, a progressive increase in pulmonary *M. tuberculosis* burden drives a linear expansion of V γ 2V δ 2 T cells in the lung but not in the blood of naïve monkeys after *M. tuberculosis* infection by aerosol (data not shown and [15]). In humans, systemic infections, which may represent high microbial burdens, clearly drive major clonal expansions of V γ 2V δ 2 T cells. Disseminated *M. avium* infection can stimulate V γ 2V δ 2 T cell expansion to the extent of 40% of total circulating T cells [28]. Systemic infections with other phosphoantigen-producing pathogens such as Malaria, *H. influenzae*, *N. meningitidis*, *S. pneumoniae*, and *F. tularensis* also coincide with a profound expansion of V γ 2V δ 2 T cells [20]. The infection dose- and route-dependent responses of V γ 2V δ 2 T cells may help to explain why some individuals with pulmonary tuberculosis exhibit no detectable expansion of V γ 2V δ 2 T cells in the blood circulation [15, 29].

Tuberculosis and down-regulation of V γ 2V δ 2 T cells

Chronically active tuberculosis appears to down-regulate V γ 2V δ 2 T cell responses rather than drive major expansion of these cells. While an expansion of antigen-specific V γ 2V δ 2 T cells is seen in the lung of monkeys after *M. tuberculosis* infection by aerosol [15], $\gamma\delta$ T cell responses in humans during early *M. tuberculosis* infection remains largely inconclusive [20]. The absence of definitive information regarding an early human V γ 2V δ 2 T cell expansion may be attributed to a clinical difficulty for early sampling, since tuberculous patients would not visit clinics until they had onset of tuberculosis after infection. Studies done at a chronic phase of tuberculosis have reported a decrease in percentage of V γ 2V δ 2⁺ T cells in both the blood and BAL fluid of patients with pulmonary tuberculosis when compared with normal individuals [30,31]. It has also been shown that patients with active pulmonary tuberculosis exhibit an impaired ability of V γ 2V δ 2⁺ T cells to produce cytokines or proliferate in response to in vitro stimulation with phosphoantigens [30,32]. The down-regulation or impaired function

of V γ 2V δ 2 T cells appear to be consistent with an absence or anergy of CD4⁺ T cell responses and PPD skin test reactivity identified in patients with active tuberculosis [33,34].

The reduced number and function of V γ 2V δ 2 T cells seen in tuberculous patients may be regulated through complex immune mechanisms (Fig. 1). Irreversible one-way pulmonary migration of activated V γ 2V δ 2 T cells may occur in tuberculosis and contribute to reduced numbers of these cells in the circulation. In fact, it has been shown that pulmonary *M. tuberculosis* leads to an increase in numbers of macaque V γ 2V δ 2 T cells in the lung and an associated decrease in circulating V γ 2V δ 2 T cells (Dan et al., data not shown and [15]). Since activated V γ 2V δ 2 T cells express high levels of chemokine receptors [20,35,36], the chemokine/receptor-mediated chemostasis may facilitate the pulmonary migration of V γ 2V δ 2 T cells. Given the possibility that adult pulmonary tuberculosis usually occurs as a result of a loss of immunity against latent infection or re-infection, there may be a fundamental immune suppression or defect of immune cells including V γ 2V δ 2 T cells in patients with tuberculosis. Such an immune suppression or defect may help to explain the reduced level of V γ 2V δ 2 T cell proliferation in response to in vitro antigen stimulation [32,37]. Changes in cytokine environments during tuberculosis may also contribute to the down-regulation of V γ 2V δ 2 T cells. Furthermore, the defect in effector function of V γ 2V δ 2 T cells in tuberculous patients may result from chronic activation and exhaustion of these cells. This possibility is supported by a recent finding that patients with active tuberculosis display a decrease in numbers of CD45RA–CD27– V γ 2V δ 2 T cells and a loss of in vitro effector function in responses to phosphoantigens, suggesting that these cells are pre-terminally activated $\gamma\delta$ T cells [32,37]. Further studies are needed to elucidate the precise mechanisms by which tuberculosis induces down-regulation or defect of V γ 2V δ 2 T cells.

CD4 T helper function and the restorable inhibition of V γ 2V δ 2 T cell responses during active HIV-mycobacterial coinfection

The possibility that CD4 T effector cells and HIV can function as important host and microbial factors for immune regulation of antigen-specific V γ 2V δ 2 T cell responses during active *M. tuberculosis* infection has not been studied in humans. Since the hallmark of HIV infection is CD4 T cell depletion and global immune suppression, it is important to determine the extent to which HIV inhibits adaptive immune responses of V γ 2V δ 2 T cells during active mycobacterial coinfection of HIV-infected humans. It is also important to determine whether immune reconstitution during anti-retroviral treatment can restore potentially inhibited responses of antigen-specific V γ 2V δ 2 T cell responses during active mycobacterial coinfection of HIV-infected individuals. SIVmac-infected monkeys provide a good system in which to address these questions. While SIVmac-infected macaques with high viral loads exhibit inhibited responses of V γ 2V δ 2 T cells in the blood and lungs after BCG infection and reinfection, CD4 T cells are needed for the in vitro restoration of the ability of V γ 2V δ 2 T cells to proliferate in response to phosphoantigen [38]. Tenofovir or tenofovir + indinavir antiretroviral treatment of SIVmac-infected monkeys can restore the capacity of V γ 2V δ 2 T cells to undergo major expansions and pulmonary migration in active BCG re-infection. Importantly, the restored expansion of V γ 2V δ 2 T cells coincides with increases in numbers of PPD-specific IFN γ -producing CD4 T cells and increases in the magnitude of their proliferative responses (Fig. 2 and [22]). Such a restored V γ 2V δ 2 T cell response during antiretroviral treatment of SIVmac-infected monkeys is mounted on a polyclonal $\gamma\delta$ T cell repertoire background. These results suggest that the development of adaptive immune responses of phosphoantigen-specific V γ 2V δ 2 T cells in AIDS requires control of viral infection and immune competence of peptide-specific CD4 T cells during early mycobacterial infection. The findings in SIV-infected monkeys are indeed supported by in vitro studies in HIV-infected humans who received antiretroviral drugs. Effective antiretroviral treatment in HIV-infected humans has been shown to restore the TCR repertoire [39] and the ability of V γ 2V δ 2⁺ T cells

to produce IFN- γ in response to in vitro stimulation with phosphoantigen [40,41]. The monkey and human studies suggest that CD4 T helper function and HIV coinfection are important host or microbial factors that impact on the development of V γ 2V δ 2⁺ T cell immune responses during active mycobacterial infections.

Given the possibility that effective T cell immune responses during early mycobacterial infection impact on initial bacterial burdens and subsequent disease outcomes, restored immune responses of T cells including $\gamma\delta$ T cells may contribute to immunity against AIDS-related tuberculosis after mycobacterial coinfection or re-infection. Interestingly, restored immune responses of antigen-specific V γ 2V δ 2 T cells and CD4 T cells during antiretroviral treatment of SIV/BCG-coinfected monkeys are associated with immunity against fatal SIV-related tuberculosis-like diseases (Shen et al., data not shown). In contrast, inhibited responses of V γ 2V δ 2 T cells and CD4 T cells during active BCG coinfection coincide with the development of the fatal SIV-related tuberculosis-like disease in early SIVmac-infected monkeys or in naïve monkeys simultaneously coinfecting with SIV and BCG [38,42]. The finding that AIDS-related inhibition of V γ 2V δ 2 T cell responses in active mycobacterial coinfection is restorable during antiretroviral treatment may have potential clinical implications. V γ 2V δ 2 T cells may emerge as important anti-microbial effector cells in AIDS patients whose CD4 T cell counts remain low during HAART. Since many microbes produce phosphoantigen, V γ 2V δ 2 T cells may confer broad immunity against opportunistic infections in AIDS patients.

Conclusion

Progress has been made about the nature and regulation of antigen-specific $\gamma\delta$ T cell responses in mycobacterial infections. The unique ability of V γ 2V δ 2 T cells to mount both innate-like and adaptive immune responses may allow these $\gamma\delta$ T cells to respond rapidly to phosphoantigen-producing mycobacteria and other pathogens. Further studies are clearly needed to define a precise role of V γ 2V δ 2 T cells in immunity to mycobacterial infections as well as understand immuno-pathogenesis of these antigen-specific $\gamma\delta$ T cells in tuberculosis.

Acknowledgments

The author would like to thank members at the Chen's laboratory for discussions and suggestions. The studies in nonhuman primates were supported by NIH RO1 grants RR13601 (to ZWC) and HL64560 (to ZWC) and by the Pittsfield Anti-Tuberculosis Association (to ZWC).

Abbreviations

SIVmac	Simian immunodeficiency virus of macaques
BCG	<i>Mycobacterium bovis</i> bacille Calmette–Guerin
TCR	T cell receptor

References

1. Griffin JP, Harshan KV, Born WK, Orme IM. Kinetics of accumulation of gamma delta receptor-bearing T lymphocytes in mice infected with live mycobacteria. *Infect Immun* 1991;59(11):4263. [PubMed: 1834574]
2. Fulton SA, Martin TD, Redline RW, Henry Boom W. Pulmonary immune responses during primary *Mycobacterium bovis* –Calmette–Guerin bacillus infection in C57Bl/6 mice. *Am J Respir Cell Mol Biol* 2000;22(3):333. [PubMed: 10696070]

3. Dieli F, Ivanyi J, Marsh P, Williams A, Naylor I, Sireci G, Caccamo N, Di Sano C, Salerno A. Characterization of lung gamma delta T cells following intranasal infection with *Mycobacterium bovis* bacillus Calmette–Guerin. *J Immunol* 2003;170(1):463. [PubMed: 12496432]
4. Xiong X, Morita CT, Bukowski JF, Brenner MB, Dascher CC. Identification of guinea pig gammadelta T cells and characterization during pulmonary tuberculosis. *Vet Immunol Immunopathol* 2004;102(1–2):33. [PubMed: 15451613]
5. Beard PM, Rhind SM, Sinclair MC, Wildblood LA, Stevenson K, McKendrick IJ, Sharp JM, Jones DG. Modulation of gammadelta T cells and CD1 in *Mycobacterium avium* subsp. paratuberculosis infection. *Vet Immunol Immunopathol* 2000;77(3–4):311. [PubMed: 11137128]
6. Carding SR, Egan PJ. Gammadelta T cells: functional plasticity and heterogeneity. *Nat Rev, Immunol* 2002;2(5):336. [PubMed: 12033739]
7. Matsuzaki G, Yamada H, Kishihara K, Yoshikai Y, Nomoto K. Mechanism of murine Vgamma1+ gamma delta T cell-mediated innate immune response against *Listeria monocytogenes* infection. *Eur J Immunol* 2002;32(4):928. [PubMed: 11920558]
8. Lee J, Choi K, Olin MR, Cho SN, Molitor TW. Gammadelta T cells in immunity induced by *Mycobacterium bovis* bacillus Calmette–Guerin vaccination. *Infect Immun* 2004;72(3):1504. [PubMed: 14977956]
9. Kennedy HE, Welsh MD, Bryson DG, Cassidy JP, Forster FI, Howard CJ, Collins RA, Pollock JM. Modulation of immune responses to *Mycobacterium bovis* in cattle depleted of WC1(+) gamma delta T cells. *Infect Immun* 2002;70(3):1488. [PubMed: 11854237]
10. Vesosky B, Turner OC, Turner J, Orme IM. Gamma interferon production by bovine gamma delta T cells following stimulation with mycobacterial mycolylarabinogalactan peptidoglycan. *Infect Immun* 2004;72(8):4612. [PubMed: 15271921]
11. Das H, Sugita M, Brenner MB. Mechanisms of Vdelta1 gammadelta T cell activation by microbial components. *J Immunol* 2004;172(11):6578. [PubMed: 15153472]
12. Cassidy JP, Bryson DG, Gutierrez Cancela MM, Forster F, Pollock JM, Neill SD. Lymphocyte subtypes in experimentally induced early-stage bovine tuberculous lesions. *J Comp Pathol* 2001;124(1):46. [PubMed: 11428188]
13. Rhodes SG, Hewinson RG, Vordermeier HM. Antigen recognition and immunomodulation by gamma delta T cells in bovine tuberculosis. *J Immunol* 2001;166(9):5604. [PubMed: 11313400]
14. Lai X, Shen Y, Zhou D, Sehgal P, Shen L, Simon M, Qiu L, Letvin NL, Chen ZW. Immune biology of macaque lymphocyte populations during mycobacterial infection. *Clin Exp Immunol* 2003;133(2):182. [PubMed: 12869023]
15. Shen Y, Zhou D, Qiu L, Lai X, Simon M, Shen L, Kou Z, Wang Q, Jiang L, Estep J, Hunt R, Claggett M, Sehgal PK, Li Y, Zeng X, Morita CT, Brenner MB, Letvin NL, Chen ZW. Adaptive immune response of Vgamma2Vdelta2+ T cells during mycobacterial infections. *Science* 2002;295(5563):2255. [PubMed: 11910108]
16. Wang H, Lee HK, Bukowski JF, Li H, Mariuzza RA, Chen ZW, Nam KH, Morita CT. Conservation of nonpeptide antigen recognition by rhesus monkey V gamma 2V delta 2 T cells. *J Immunol* 2003;170(7):3696. [PubMed: 12646635]
17. Hoft DF, Brown RM, Roodman ST. Bacille Calmette–Guerin vaccination enhances human gamma delta T cell responsiveness to mycobacteria suggestive of a memory-like phenotype. *J Immunol* 1998;161(2):1045. [PubMed: 9670986]
18. Kamath AB, Wang L, Das H, Li L, Reinhold VN, Bukowski JF. Antigens in tea-beverage prime human Vgamma 2Vdelta 2 T cells in vitro and in vivo for memory and nonmemory antibacterial cytokine responses. *Proc Natl Acad Sci U S A* 2003;100(10):6009. [PubMed: 12719524]
19. Morita CT, Mariuzza RA, Brenner MB. Antigen recognition by human gamma delta T cells: pattern recognition by the adaptive immune system. *Springer Semin Immunopathol* 2000;22(3):191. [PubMed: 11116953]
20. Chen ZW, Letvin NL. Adaptive immune response of Vgamma2V-delta2 T cells: a new paradigm. *Trends Immunol* 2003;24(4):213. [PubMed: 12697454]
21. Worku S, Gorse GJ, Belshe RB, Hoft DF. Canarypox vaccines induce antigen-specific human gammadelta T cells capable of interferon-gamma production. *J Infect Dis* 2001;184(5):525. [PubMed: 11474428]

22. Shen L, Shen Y, Huang D, Qiu L, Sehgal P, Du GZ, Miller MD, Letvin NL, Chen ZW. Development of V gamma 2V delta 2+ T Cell Responses during active mycobacterial coinfection of simian immunodeficiency virus-infected macaques requires control of viral infection and immune competence of CD4+ T Cells. *J Infect Dis* 2004;190(8):1438. [PubMed: 15378436]
23. Ladel CH, Blum C, Dreher A, Reifenberg K, Kaufmann SH. Protective role of gamma/delta T cells and alpha/beta T cells in tuberculosis. *Eur J Immunol* 1995;25(10):2877. [PubMed: 7589086]
24. Mogues T, Goodrich ME, Ryan L, LaCourse R, North RJ. The relative importance of T cell subsets in immunity and immunopathology of airborne *Mycobacterium tuberculosis* infection in mice. *J Exp Med* 2001;193(3):271. [PubMed: 11157048]
25. D'Souza CD, Cooper AM, Frank AA, Mazzaccaro RJ, Bloom BR, Orme IM. An anti-inflammatory role for gamma delta T lymphocytes in acquired immunity to *Mycobacterium tuberculosis*. *J Immunol* 1997;158(3):1217. [PubMed: 9013962]
26. Dieli F, Poccia F, Lipp M, Sireci G, Caccamo N, Di Sano C, Salerno A. Differentiation of effector/memory Vdelta2 T cells and migratory routes in lymph nodes or inflammatory sites. *J Exp Med* 2003;18(3):391. [PubMed: 12900516]
27. Angelini DF, Borsellino G, Poupot M, Diamantini A, Poupot R, Bernardi G, Poccia F, Fournie JJ, Battistini L: FcgammaRIII discriminates between 2 subsets of Vgamma9Vdelta2 effector cells with different responses and activation pathways. *Blood* 2004;104(6):1801. [PubMed: 15178578]
28. Wendland T, Herren S, Yawalkar N, Cerny A, Pichler WJ. Strong alpha beta and gamma delta TCR response in a patient with disseminated *Mycobacterium avium* infection and lack of NK cells and monocytopenia. *Immunol Lett* 2000;72(2):75. [PubMed: 10841941]
29. Langermans JA, Andersen P, van Soolingen D, Vervenne RA, Frost PA, van der Laan T, van Pinxteren LA, van den Hombergh J, Kroon S, Peekel I, Florquin S, Thomas AW. Divergent effect of bacillus Calmette–Guerin (BCG) vaccination on *Mycobacterium tuberculosis* infection in highly related macaque species: implications for primate models in tuberculosis vaccine research. *Proc Natl Acad Sci U S A* 2001;98(20):11497. [PubMed: 11562492]
30. Li B, Rossman MD, Imir T, Oner-Eyuboglu AF, Lee CW, Biancaniello R, Carding SR. Disease-specific changes in gammadelta T cell repertoire and function in patients with pulmonary tuberculosis. *J Immunol* 1996;157(9):4222. [PubMed: 8892660]
31. Carvalho AC, Matteelli A, Airo P, Tedoldi S, Casalini C, Imberti L, Cadeo GP, Beltrame A, Carosi G. gammadelta T lymphocytes in the peripheral blood of patients with tuberculosis with and without HIV co-infection. *Thorax* 2002;57(4):357. [PubMed: 11923557]
32. Gioia C, Agrati C, Casetti R, Cairo C, Borsellino G, Battistini L, Mancino G, Goletti D, Colizzi V, Pucillo LP, Poccia F. Lack of CD27-CD45RA-V gamma 9V delta 2+ T cell effectors in immunocompromised hosts and during active pulmonary tuberculosis. *J Immunol* 2002;168(3):1484. [PubMed: 11801693]
33. Toossi Z, Ellner JJ. Mechanisms of anergy in tuberculosis. *Curr Top Microbiol Immunol* 1996;215:221. [PubMed: 8791716]
34. Delgado JC, Tsai EY, Thim S, Baena A, Boussiotis VA, Reynes JM, Sath S, Grosjean P, Yunis EJ, Goldfeld AE. Antigen-specific and persistent tuberculin anergy in a cohort of pulmonary tuberculosis patients from rural Cambodia. *Proc Natl Acad Sci U S A* 2002;99(11):7576. [PubMed: 12032325]
35. Cipriani B, Borsellino G, Poccia F, Placido R, Tramonti D, Bach S, Battistini L, Brosnan CF. Activation of C–C beta-chemokines in human peripheral blood gammadelta T cells by isopentenyl pyrophosphate and regulation by cytokines. *Blood* 2000;95(1):39. [PubMed: 10607682]
36. Glatzel A, Wesch D, Schiemann F, Brandt E, Janssen O, Kabelitz D. Patterns of chemokine receptor expression on peripheral blood gamma delta T lymphocytes: strong expression of CCR5 is a selective feature of V delta 2/V gamma 9 gamma delta T cells. *J Immunol* 2002;168(10):4920. [PubMed: 11994442]
37. Gioia C, Agrati C, Goletti D, Vincenti D, Carrara S, Amicosante M, Casarini M, Giosue S, Puglisi G, Rossi A, Colizzi V, Pucillo LP, Poccia F. Different cytokine production and effector/memory dynamics of alpha beta+ or gamma delta+ T-cell subsets in the peripheral blood of patients with active pulmonary tuberculosis. *Int J Immunopathol Pharmacol* 2003;16(3):247. [PubMed: 14611728]

38. Zhou D, Lai X, Shen Y, Sehgal P, Shen L, Simon M, Qiu L, Huang D, Du G, Wang Q, Letvin NL, Chen ZW. Absence of adaptive Vgamma2Vdelta2 T cell responses during active mycobacterial coinfection of SIVmac-infected monkeys. *J Virol.* (in press).
39. Bordon J, Evans PS, Propp N, Davis CE Jr, Redfield RR, Pauza CD. Association between longer duration of HIV-suppressive therapy and partial recovery of the V gamma 2 T cell receptor repertoire. *J Infect Dis* 2004;189(8):1482. [PubMed: 15073686]
40. Martini F, Urso R, Gioia C, De Felici A, Narciso P, Amendola A, Paglia MG, Colizzi V, Poccia F. gammadelta T-cell anergy in human immunodeficiency virus-infected persons with opportunistic infections and recovery after highly active antiretroviral therapy. *Immunology* 2000;100(4):481. [PubMed: 10929075]
41. Martini F, Poccia F, Goletti D, Carrara S, Vincenti D, D'Offizi G, Agrati C, Ippolito G, Colizzi V, Pucillo LP, Montesano C. Acute human immunodeficiency virus replication causes a rapid and persistent impairment of Vgamma9Vdelta2 T cells in chronically infected patients undergoing structured treatment interruption. *J Infect Dis* 2002;186(6):847. [PubMed: 12198622]
42. Shen Y, Zhou D, Chalifoux L, Shen L, Simon M, Zeng X, Lai X, Li Y, Sehgal P, Letvin NL, Chen ZW. Induction of an AIDS virus-related tuberculosis-like disease in macaques: a model of simian immunodeficiency virus-mycobacterium coinfection. *Infect Immun* 2002;70(2):869. [PubMed: 11796622]

Fig. 1.

Proposed mechanisms for decreases in numbers and Ag-specific effector function (proliferation and IFN γ production) of circulating V γ 2V δ 2 T cells during tuberculosis. Shown is expansion, downregulation, or migration of the circulating V γ 2V δ 2 T cells during early mycobacterial infection/re-infection and chronic tuberculosis.

Fig. 2.

Restored capacity of $V\gamma 2V\delta 2$ T cells to expand during anti-retroviral treatment coincides with effector function ($IFN\gamma$ production and proliferation) of peptide-specific CD4 T cells in active BCG co-infection. Top panel shows the correlation between restored expansion of phosphoantigen-specific $V\gamma 2V\delta 2$ T cells and PPD-specific $IFN\gamma$ -specific CD4 T cells in four SIV-infected monkeys that simultaneously receive tenofovir treatment and BCG re-infection. The bottom panel displays kinetics of the restoration of $V\gamma 2V\delta 2$ T cell expansion and PPD-specific CD4 T cell proliferation during BCG re-infection of three SIV-infected monkeys that receive delayed antiretroviral treatment with tenofovir and indinavir.

Table 1 $\gamma\delta$ T cell immune responses during mycobacterial infections in different species

Species	Mycobacterium-specific $\gamma\delta$ T cell subset	Defined mycobacterial Ag recognized by $\gamma\delta$ T cells	In vivo $\gamma\delta$ T cell responses	References
Mouse	?	?	Increases in numbers of pulmonary $\gamma\delta$ T cells during early BCG infections	[1–3]
Guinea pig	?	?	No expansion of blood $\gamma\delta$ T cells after <i>M. tuberculosis</i> challenge by aerosol	[4]
Sheep	?	?	Increase in numbers of $\gamma\delta$ T cells in Peyer's patches during <i>M. avium</i> infection	[5]
Pig	?	?	Enhanced $\gamma\delta$ T cell response after BCG infection	[8]
Bovine	?	Mycolylarabinogalactan peptidoglycan	Increases in numbers of $\gamma\delta$ T cells in the lung and blood after <i>M. bovis</i> infection	[9,10,12–14]
Monkey	V γ 2V δ 2 T cells	Phosphoantigen	Major clonal expansion and adaptive immune responses in BCG and <i>M. tuberculosis</i> infections	[14–16]
Human	V γ 2V δ 2 T cells	Phosphoantigen	Memory-type response in BCG infection; expanded in healthy professionals exposed to TB patients; down-regulated in TB	[17,19–21]