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The Value of γδ T Cells in Lung Infections and Advances in Diagnosis and Treatment

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Abstract

Lung infections are usually caused by pathogenic microorganisms and are a disease with high morbidity and mortality. In clinical practice, the use of broad-spectrum antibiotics has become increasingly common, but this has also led to the problem of antibiotic abuse and irrational use, which in turn has spawned the emergence of multidrug-resistant bacteria, making the treatment of lung infections more complex and difficult. In the human immune system, γδ T cells play a crucial role in defense against foreign pathogens and regulation of autoimmune responses. These cells act as a bridge between innate and adaptive immunity and can be rapidly activated in the early stages of infection to produce inflammatory factors and chemokines that attract other immune cells to the site of infection. Recent advances have shown that γδ T cells not only play a direct role in the innate immunity of pathogen infection, but are also involved in regulating the subsequent adaptive immune response. The aim of this review is to explore the mechanism of γδ T cells in lung infections and to summarize the current progress of clinical research, with the aim of providing new scientific basis and therapeutic strategies for the treatment of lung infections.

Keywords

Lung Infections, γδ T Cells, Immunotherapy, IL-17

1. Introduction

Lung infection is a disease of the lungs caused mostly by infections with pathogenic microorganisms, such as bacteria, viruses, fungi, and chlamydia. As one of the most common infectious diseases, lung infections have high morbidity and

mortality rates, and data from the Global Burden of Disease Study 2019 showed that lower respiratory tract infections, including pneumonia and bronchiectasis, affect 489 million people worldwide [1]. And with the rising incidence of infectious diseases in the lungs, the use of broad-spectrum antibiotics in the clinic is also rising, and the misuse and irrational application of antibiotics have led to the continuous generation of multidrug-resistant bacteria, which has made the treatment of lung infections more and more difficult, so that there is an urgent need for new therapeutic means.

T lymphocytes are a key component of the human immune system and are essential for defense against foreign organisms and regulation of autoimmune dysregulation. T lymphocytes can be classified into $\alpha\beta$ T cells and $\gamma\delta$ T cells based on the different peptide chains of the T cell receptor (TCR). $\gamma\delta$ T cells are a subpopulation of T lymphocytes discovered by Brenner *et al.* in the 1980s [2]. In humans, $\gamma\delta$ T cells express seven different Vγ TCR chains (Vγ2, 3, 4, 5, 8, 9, and 11) with four different Vδ (Vδ1, 2, 3, and 5) chains, and the two chains can be arbitrarily combined [3]. Compared to $\alpha\beta$ T cells, $\gamma\delta$ T cells are characterized by non-restriction of Major histocompatibility complex (MHC) in recognizing antigens as well as the lack of need for antigen processing and presentation. $\gamma\delta$ T cells have a broad spectrum of immunosurveillance functions, and their recognition of antigens, such as heat shock proteins and phosphorylated small molecule substances, is widespread in the $\gamma\delta$ T cells can recognize antigens that cannot be recognized by $\alpha\beta$ T cells. $\gamma\delta$ T cells are a bridge between innate and adaptive immunity, and can be rapidly activated in the early stages of inflammatory response to produce inflammatory factors and chemokines, chemotaxis of other inflammatory cells to reach the site of infection and can regulate the immune response of immune cells such as $\alpha\beta$ T cells, NK cells and macrophages. Modulation of immune response of $\alpha\beta$ T cells, NK cells and macrophages. Before the action of other inflammatory cells, $\gamma\delta$ T cells provide an early immune response to protect the organism from pathogens, and after resisting pathogen invasion, $\gamma\delta$ T cells can down-regulate the antigen-specific adaptive immune response, thus reducing potential immune damage [4] [5]. Although $\gamma\delta$ T cells in the peripheral blood account for only 2% - 7% of mature T lymphocytes, they can play an important role in the lung immune response induced by infections because they are mainly distributed in the lungs [6].

In studies related to infectious diseases, $\gamma\delta$ T cells have been found to be actively involved in the immune response to lung infections, and there are at least four possible mechanisms for their involvement in the immune response to infection: 1) modulation of the innate immunity through the release of cytokines and chemokines cells, such as IFN-γ, TNF-α, IL-17, IL-4, IL-13, etc.; 2) by releasing cytotoxic molecules to lyse pathogens, such as perforin, granzyme A, granzyme B, and Fas ligand, etc.; 3) by inducing CD4 and CD8 T cells; and 4) by increasing the expression of CD80, CD86, and HLA-DR as the initiation of the immune response of the antigen-presenting cells. With further studies, its immune response in lung

infection has been gradually revealed. In this article, we review the value of γδ T cells in lung infections and the progress of diagnosis and treatment.

2. γδ T Cells and Bacterial Infections

Many studies have demonstrated that γδ T cells play an important role in a variety of bacterial infections. In 1989, EMJanis *et al.* showed for the first time that γδ T lymphocytes play a key role in the immune response to *Mycobacterium tuberculosis* (Mtb) [7] [8]. Mtb proteins act as potential ligands that bind to the γδ T receptor and can activate γδ T cell-mediated immunity. γδ T cells recognize a variety of nonpeptide antigens [9]-[11], such as phosphorylated antigens and lipid antigens, and as shown in **Figure 1**, γδ T cells exert their protective effect against *Mycobacterium tuberculosis* in fection by releasing granular lysin to kill extracellular Mtb directly, as well as by releasing granular lysin and perforin to kill intracellular Mtb [12]. It has been shown that a subpopulation of γδ T lymphocytes, the Vγ9Vδ2 T cell population, recognizes *Mycobacterium tuberculosis*-derived phosphoantigens and 6-O-methylglucose-containing lipopolysaccharides, which in turn activate and amplify the Vγ9Vδ2 T cell population [13]-[16]. The Vγ9Vδ2 T cells can secrete INF-γ, TNF-α and IL-17 cytokines to enhance protection against TB [4] [17]-[20]. Vγ9Vδ2 T cells can also produce cytolytic effector molecules such as perforin, granzyme B and granzyme mycolysin to help kill or inhibit intracellular and extracellular *Mycobacterium tuberculosis* [14] [18] [21]-[23]. In a mouse model study, granulocyte-macrophage colony-stimulating factor (GM-CSF) produced by γδ T cells was found to play a protective role, and as shown see **Figure 1**, GM-CSF and IFN-γ could jointly promote macrophage control of intracellular bacterial replication. It has been found that specific Vγ9Vδ2 T cells from tuberculin test-positive individuals produce granzyme A, which acts indirectly on Mtb by stimulating the production of TNF-α by infected macrophages. It has been suggested that isopentenyl pyrophosphate (IPP) binds to the Ig superfamily protein (BTN3A1). BTN3A1 modified by IPP activates subpopulations of γδ T-lymphocytes, such as Vγ2Vδ2 T-lymphocytes, and early differentiation of Vγ2Vδ2 T-lymphocytes increases host immune resistance to TB during Mtb infection [24]. A study on Mtb intracellular mycobacterial model found that γδ T cells could produce a large amount of IL-17 in the early post-infection period, whereas the level of IL-17 secreted by $CD4^+$ T cells was still not significantly elevated, suggesting that γδ T cells were the main source of IL-17 in this Mtb infection model. In contrast, IL-17 knockout mice infected with *Mycobacterium tuberculosis* showed significantly reduced granuloma formation and clearance of pathogenic bacteria [25]. Recently, it has been found that in a macaque model of *Mycobacterium tuberculosis* infection, the over-transfer of autologous Vγ2Vδ2 T cells significantly attenuates histopathological alterations in the lungs and extrapulmonary tissues. Liang's team [26] recruited eight patients with multidrug-resistant tuberculosis in a study on allogeneic Vγ9Vδ2 T-cell therapy, each of whom received 12 cycles of over-transfer cell treatment. According to World Health Organization criteria,

three consecutive negative sputum *Mycobacterium tuberculosis* tests indicate complete clinical control of *Mycobacterium tuberculosis* infection. After these eight patients completed treatment, seven patients had three consecutive negative sputum *Mycobacterium tuberculosis* tests, resulting in a clinical cure rate of 87.5%. According to the World Health Organization's Global TB Report 2020, the global treatment success rate for multidrug-resistant TB patients is 57%. In addition, the team performed a chest CT before and every 2 months after the infusion of Vγ9Vδ2 T cells in these 8 patients and found that all patients had reduced lung lesions. These results suggest that allogeneic Vγ9Vδ2 T cells therapy help to reduce the load of *Mycobacterium tuberculosis* in the body.

In other bacterial infections, such as *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus pertussis*, and *Streptococcus pneumoniae*, $\gamma\delta$ T lymphocytes have been found to be the main source of IL-17 in the early stages of lung infection [27]-[32]. Tesshin *et al.* [33] found in a mouse model of *Klebsiella pneumoniae* infection that IL-17-secreting $\gamma\delta$ T cells could be activated by IL-23-dependent or non-dependent mechanisms were activated to help host defense against *Klebsiella pneumoniae* infection. Previously, it was found that IL-17 could be induced by cytokines IL-1β and IL-23 during *Klebsiella pneumoniae* infection [27]. IL-17 promotes the production of CXC chemokines and granulocyte colony-stimulating factor (G-CSF) in the lung and enhances the lung barrier and anti-injury capacity [34]. In addition to promoting neutrophil recruitment indirectly by inducing chemokine production, IL-17 can also directly activate the bacterial killing function of neutrophils and macrophages. Ye *et al.* [34] showed that defective neutrophil recruitment in *Klebsiella pneumoniae*-infected IL-17 knockout mice was associated with reduced production of macrophage inflammatory protein-2 (MIP2) and G-CSF, leading to compromised host immune responses. Several studies on $\gamma\delta$ T-cell deficient mice have found that the immune function of mice is affected, e.g. Cheng *et al.* [28] found that $\gamma\delta$ T-cell deficient mice exhibited IL-17-induced delayed effects in a *S. aureus* mouse infection model. In mice infected with *S. aureus*, $\gamma\delta$ T cells in the lungs not only facilitated bacterial clearance, but also contributed to the repair of damaged tissues. Liu *et al.* infected the lungs of mice with *Pseudomonas aeruginosa* by intranasal inhalation, and found that compared with the control group, the experimental group of mice with *in vivo* removal of $\gamma\delta$ T lymphocytes showed a significant decrease in the level of IL-17 *in vivo* 8 hours after the infection, and at the same time, IL-17-related chemokines such as G-CSF, Keratinocyte-derived chemokine(KC), Macrophage inflammatory protein-1α (MIP-1α), and MIP-2 also decreased significantly, and the bacterial load of the experimental group of mice was 8-fold higher than that of the control group at 8 hours post-infection and more than 85-fold higher than that of the control group at 16 hours post-infection, and the experimental mice persistently exhibited severe perivascular inflammatory infiltrates that extended to the lung parenchyma, in contrast to the control mice, which showed only mild inflammatory responses and their lung

parenchyma was relatively unaffected [29]. Toka *et al.* [30], in a mouse model of lung infection with *P. aeruginosa*, similarly found that in the absence of gamma-γγ, the bacterial load of the experimental group was significantly lower than that of the control mice [31], in which mice were similarly found to exhibit impaired bacterial clearance and decreased survival in the absence of γδT cells, results that were associated with delayed neutrophil recruitment and impaired recruitment of other immune cells (e.g. macrophages, T cells, NKT cells). It was found that innate Vγ4-γ1-γδT cells provide early IL-17 production after B. pertussis infection, whereas specific Vγ4 γδT cells can be induced as memory cells after infection to rapidly produce IL-17 and help to prevent re-infection [31]. IL-17 is induced by recruitment of highly neutrophilic inflammatory cell death mode activity of neutrophils and inducing antimicrobial peptide production, which plays a key role in B. pertussis infection [35]. A study in a pneumococcal mouse model found that pneumococci induced proliferation and activation of Vγ1$^+$ T and Vγ4$^+$ T cells in mouse lung tissues and that these γδT cells were tissue specific [36]. Recently, it has been noted that human Vγ6Vδ1 γδT cells make a rapid immune response to pneumococcal infection through IL-17 production, indicating that Vγ6Vδ1 γδT cells play an important role in pneumococcal infections [37].

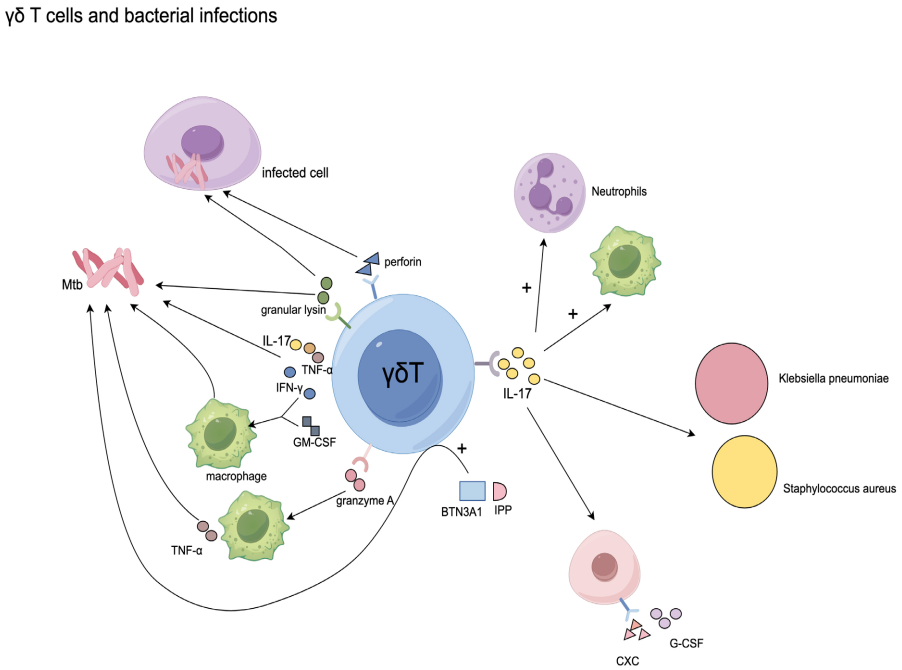

Figure 1. Schematic representation of immunoprotection by γδT cells during bacterial infection. γδT cells kill extracellular *Mycobacterium tuberculosis* (Mtb) directly by releasing granular lysozyme and also intracellular Mtb by releasing granular lysozyme and perforin. γδT cells also secrete INF-γ, TNF-α, and IL-17 against *Mycobacterium tuberculosis*. γδT cells can also directly stimulate or release cytokines to indirectly stimulate macrophages to act against Mtb. γδT cells directly stimulate neutrophils to kill bacteria by secreting IL-17 and also promote the production of CXC chemokines and granulocyte colony-stimulating factor (G-CSF) in the lungs to enhance the lung barrier and resistance to injury. This image was created by Figdraw.

3. γδ T Cells and Viral Infections

In H1N1, H5N1, H9N2 and H3N2 influenza virus infections, IPP, NK cell receptor 2D (NKG2D), or the aminophosphonate pamidronate (PAM) activate Vγ9Vδ2 T cells, in addition, H5N1 and N9N2-related infections, chemokine ligand 5 (CCL5) can act by inducing migration of Vγ9Vδ2 T cells to influenza virus-infected cells [38]. Activated γδT lymphocytes can likewise participate in systemic or local immunomodulation by releasing the cytokines IFN-γ, TNF-α, and IL-17, IL-4, and IL-13, as well as releasing cytotoxic molecules to lysate infecting viruses. Li *et al.* [39], using H1N1 influenza virus to infect human alveolar epithelial cells, found that in vitro PAM-activated Vγ9Vδ2T cells could take a cell contact to kill influenza virus-infected alveolar epithelial cells and inhibit viral replication, as shown in **Figure 2**, Vγ9Vδ2 T cells activated by NKG2D release cytotoxic molecules perforin, granzyme B, tumor necrosis factor-related apoptosis-inducing ligand and Fas ligands thereby cleaving influenza virus. Major histocompatibility complex class I polypeptide-related sequence A and B, as a ligand for NKG2D, was found in the current study to be up-regulated in influenza virus-infected alveolar epithelial cells. Wen *et al.* [40] observed that in vitro PAM-expanded Vγ9Vδ2 T cells could migrate to the lungs and control influenza disease in immunodeficient mice and killed the alveolar epithelial A549 cell line. Tianyu Miao and Xue *et al.* found a gradual increase in the percentage of γδ T cells during the early stage of infection (2 - 3 days), followed by activation of IL-17, which subsequently exerted an important immune role in human observational assays and a mouse model of influenza virus infection with the H1N1 virus in mice [41]. In another neonatal mouse model of influenza virus infection γδ T cell activated IL-17 induced IL-33 production and a type 2 immune response at the site of localized infection, increasing the accumulation of Amphiregulin-producing ILC2 and Treg cells in the lungs, thereby promoting tissue repair and lung integrity after infection [42]. In addition, γδ T cells play an equally important role in pandemic H1N1, human seasonal H1N1, H5N1, H9N2 and H3N2 viruses. A study showed that Vγ9Vδ2 T cells express both type 1 cytokines and chemokine receptors during influenza virus infection. Notably, IPP-activated Vγ9Vδ2T cells were more capable of producing IFN-γ and suppressing seasonal and pandemic H1N1 viruses in a non-cellular cytolytic manner [38]. In a related study of respiratory syncytial virus (RSV), γδ T-cell subtype Vγ4$^+$ T cells attenuated immune injury by releasing cytokines IFN-γ and TNF to promote immune response in the early stage of infection [43]. Among coronaviruses, an earlier study found that the γδ T cell subtype Vδ2T cells could inhibit SARS-CoV replication in vitro through an IFN-γ-dependent process [44]. With the new coronavirus pneumonia pandemic, studies related to SARS-CoV-2 were carried out, and Alyssa *et al.* [45] found a highly significant correlation between the number of Vδ1 T-cells and the viral load in bronchoalveolar lavage (BAL) in a primate model of aerosolized and intratracheal/intranasal (IT/IN) infections with SARS-CoV-2 and that in BAL Many inflammatory factors (including IL-1, TNF-α, GM-CSF, MIP-1β, MIG, IFN-α, and

IL-2β) were increased within 1 week, and the increase of these inflammatory factors was more pronounced after 2 weeks of infection, suggesting that the Vδ1T cells play an effective role in the local antiviral immune response through enhanced cytotoxic effects.

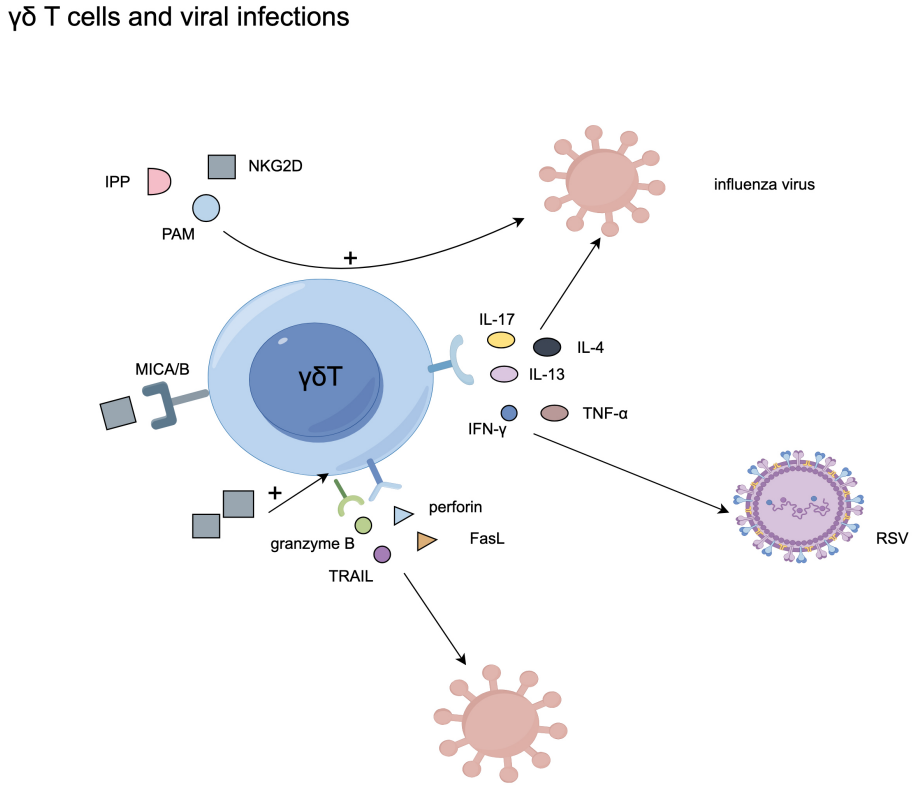

Figure 2. Schematic representation of immunoprotection by $\gamma\delta$ T cells during viral infection. Isopentenyl pyrophosphate (IPP), natural killer group 2, member D (NKG2D), or the aminodiphosphonate pamidronate (PAM) activates $\gamma\delta$ T cells wounding capacity during influenza virus infection. $\gamma\delta$T cells release IFN-γ, TNF-α and IL-17, IL-4, IL-13 against influenza virus infection. Early in respiratory syncytial virus(RSV) infection, $\gamma\delta$T cells contribute to the immune response by releasing IFN-γ, TNF-α. $\gamma\delta$T cells activated by NKG2D release perforin, granzyme B, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and Fas ligand (FasL) thereby lysing influenza virus. Major histocompatibility complex class I polypeptide-related sequence A and B (MICA/B), a ligand for NKG2D, was found to be up-regulated in alveolar epithelial cells after influenza virus infection, suggesting a possible link to the defense against the influenza virus. This image was created by Figdraw.

4. $\gamma\delta$ T Cells and Other Pathogen

In a mouse model of Candida albicans infection, Dejima's team found that most of the IL-17A-secreting cells were present in $\gamma\delta$TCR-positive cells [46]. And then they used mice genetically deficient in $\gamma\delta$ T cells and found that 24 hours after Candida albicans infection, IL-17A production was significantly lower in mice lacking $\gamma\delta$T cells compared to wild-type mice. Neutrophil infiltration and fungal clearance were significantly impaired in mice lacking $\gamma\delta$ T cells 24 hours after

infection, and the results suggest that γδ T cells are mainly involved in early IL-17A production and may play a protective role in the early stages after Candida albicans infection. It has been shown that *Plasmodium* infection induces significant changes in lung γδ T cell content, phenotype and function, and γδ T cells contribute to the T cell immune response in the lungs of *Plasmodium*-infected mice [47]. γδ T cells can secrete a variety of cytokines to mediate the immune response, and Wei *et al.* found in the lungs of *Plasmodium yoelii*-infected mice that more γδ T cells secreted Th2 cytokines (IL-4 IL-5), IL-6, IL-21, IL-1α, and IL-17, while fewer γδ T cells secreted IFN-γ, suggesting that secretion of IL-4 and IL-5 by γδ T cells promotes the Th2 immune response, and this result suggests that γδ T cells can promote T cell recruitment during *Plasmodium yoelii* infection. In Chlamydia trachomatis mouse pneumonia strain (Cm) respiratory infection, γδ T cells producing large amounts of IL-17A promoted neutrophil recruitment in the early stage of infection by inducing the expression of neutrophil chemokines KC and IL-6 at the site of infection. The study of Cha's team showed that γδ T cells secreted more Th2 cytokines (IL-4, IL-10) after *Schistosoma japonicum* infection and less Th1 cytokines (IFN-γ), suggesting that the immune response is promoted by increased expression of Th2-type cytokines by γδ T cells [32]. In addition, the team found that γδ T cells from infected mice expressed higher levels of IL-21, a pleiotropic cytokine that promotes B-cell activation and differentiation, suggesting that γδ T cells can regulate B-cell responses through this pathway. And then, the team infected *Streptococcus japonicus* with Vδ knockout mice and found that the area of granulomas in lung tissues was significantly increased, demonstrating that γδ T cells are likely to inhibit the aggregation of inflammatory cells in the lungs of *Schistosoma japonicum*-infected mice. Cha's team further found that the expression of Major Histocompatibility Complex II (MHC II) and CD80 on γδ T cells was significantly increased after *Schistosoma japonicum* infection. MHC II and the co-stimulatory molecule CD80, which are mainly expressed on the surface of APCs, promote the activation of antigen-specific T lymphocytes [48]. This suggests that γδ T cells may become APCs and mediate immune responses in the lungs of *Schistosoma japonicum*-infected mice.

Several studies have shown that γδ T-cell counts correlate with age. For example, a study by Michishita *et al.* examined the γδ T-cell pool of 120 healthy individuals and found that the absolute number of γδ T cells decreased with age ($R = -0.378$, $P < 0.001$) [49]. Previously, it has been shown that the number of Vγ9Vδ2 T cells varies with age, rising from birth to puberty and gradually decreasing after 30 years of age [50]. Age change not only affects the number of γδ T cells, but can also cause changes in their phenotype and function. It has been shown that γδ T cells in the elderly shift from an early (CD27 CD28 CD45RA CD16) differentiation effector phenotype to a late (CD27 CD28 CD45RA CD16) differentiation effector phenotype, leading to a decline in immune function against pathogens in peripheral blood and lung mucosal tissues [51] [52]. In sepsis, γδ T cell numbers and function are also affected, and it has been shown that γδ T cells are significantly

reduced in septic mice and patients, and that the more severe their depletion, the higher the mortality rate [53] [54]. A prospective study by Andreu *et al.* similarly found that with increasing severity of sepsis, there was a progressive decline in T cells, with the most pronounced decline in $\gamma\delta$ T cells, which was most pronounced in the patients who died. most significantly in patients who died [55]. In another prospective study, 107 patients with sepsis or infectious shock and 45 healthy controls were recruited, and the results showed that compared with healthy controls, sepsis patients had a decreased proportion of $\gamma\delta$ T cells and NKG2D, and an elevated CD69 and cytokines (IFN-γ, IL-17, IL-10, and TGF-β), and that after ex vivo antigenic stimulation, sepsis patients had a decrease in the proportion of $\gamma\delta$ T cells and CD69 and IFN-69 and IFN-β in their T cell population. Both CD69 and IFN-γ expression were significantly lower in sepsis patients than in controls, and the reduction in CD69 and IFN-γ expression was more pronounced in patients who died. Multiple logistic regression analyses showed that reduced IFN-γ expression after stimulation was a risk factor associated with 28-day mortality in sepsis patients (OR: 0.908 [95% CI: 0.853 - 0.966]) [56]. Liao *et al.* similarly found that IFN-γ production in $\gamma\delta$ T cells was significantly impaired in sepsis patients and was strongly associated with mortality [56]. He *et al.* produced a $\gamma\delta$ T cell-deficient mouse model in order to investigate the role of $\gamma\delta$ T in sepsis, and found that $\gamma\delta$ T cell-deficient mice suffered from more severe tissue damage, an increased bacterial load, an increase in intestinal permeability, and a decrease in survival rate [54]. In recent years, the damage of $\gamma\delta$ T cells in early HIV infection has received attention and has been suggested to have an important role in combating HIV infection. Zhao *et al.* [57] examined 39 HIV-infected/AIDS patients and 20 healthy subjects, with the proportion of $\gamma\delta$ T cells being 18.1% ± 10.1% and 15.2 ± 8.9%, respectively, after antiretroviral therapy. and AIDS patients had significantly lower percentages of $\gamma\delta$ T cells. Thus, HIV infection causes an increase in $\gamma\delta$ T cells and exerts their immunocidal, immunomodulatory and cytotoxic effects. It has been found that the inversion of the Vδ2/Vδ1 cell ratio in $\gamma\delta$ T cells in early HIV patients occurs before CD4/CD8 T cells, and that in HIV-infected patients there is an increase in Vδ1 cells and a decrease in Vδ2 cells accompanied by defects in response to phosphorylated antigens or tumor cells [19]. In a model study of HIV-infected non-human primates, dysregulation of $\gamma\delta$ T cells contributes to HIV immune escape and their ability to recognize and kill HIV-infected cells is reduced [58]. Li *et al.* [59] found that early $\gamma\delta$ T cell activation correlates with the CD4/CD8 T cell activation set-point, suggesting that $\gamma\delta$ T cells may be a surrogate marker for acute HIV infection and AIDS progression.

5. Conclusion

With the discovery of the biological functions of $\gamma\delta$ T cells, such as antigen presentation, immunomodulation, and maintenance of immune tolerance, $\gamma\delta$ T cell therapy has made significant progress in the treatment of various human diseases, for example, $\gamma\delta$ T cells have achieved remarkable results in the treatment of various

tumor diseases [3] [60] [61]. In view of the complexity of γδT cell biological properties, antigen recognition activation and related mechanisms of action, further study of the mechanisms of γδT cells in lung infections can provide new ideas for humans to utilize γδT cells in the treatment of infectious lung diseases.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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