Int J Clin Exp Med 2019;12(8):9597-9606
www.ijcem.com /ISSN:1940-5901/IJCEM0094762

Review Article

Research progress on the mechanism of γδT cells in pathogenic microbial infection

Yiren Wang[1], Yashu Wang[2], Keqiang Wang[3]

[1]Medical Laboratory Class, Grade 2016, Medical College, Qingdao University, Qingdao, Shandong Province, China; [2]Department of Clinical Laboratory, Tai'an Central Hospital, Shandong Province, China; [3]Department of Clinical Laboratory, The Second Affiliated Hospital of Shandong First Medical University, Tai'an, Shandong Province, China

Received April 2, 2019; Accepted June 25, 2019; Epub August 15, 2019; Published August 30, 2019

Abstract: Depend on the difference of T cell receptor, the T cells are divided into two categories: the αβT and the γδT cells. γδT cells belong to small number of subgroup, and for the recognition of antigen, the antigen do not need the processing and presenting progress and do not have the MHC restriction, showing the different characteristics from αβT cells. The number of γδT cells is small, but they play an important role in the anti-infection of organism, anti-tumor and immune regulation. In this review, research progress of γδT cells about the biological characteristics, the antigen recognition characteristics and their mechanisms in pathogenic microbial infections are summarized.

Keywords: γδT cells, pathogenic microorganisms, research progress

Introduction

According to the differences among the types of T cell receptors (TCR), T cells can be divided into αβT cells and γδT cells. αβT cells play an important role in the adaptive immune response; γδT cells play a unique role in innate immunity due to their distribution characteristics and non-MHC (major histocompatibility complex) restriction of immune response. As the research progresses, its role in the adaptive immune response is gradually revealed. Recent studies have shown that, γδT cells not only directly recognize and kill target cells, but also participate in early anti-HIV natural immunity, and the various cell factors secreted by them can help induce an adaptive immune response, γδT cells play an important role in anti-tumor, anti-infection and immune regulation [1-3]. In this review, the research progress on the biological characteristics of γδT cells and the mechanism of action in viral infectious diseases are summarized as follows.

Overview of γδT cells

Production, development and distribution of γδT cells

Human γδT cells occur in the thymus medulla of normal fetus at 7-8 weeks, and their development is similar to that of αβT cells, successively undergo the functional TCR expression and negative selection, then obtain autoimmune tolerance. The process of studying its development and function found that the formation of various functional characteristics of γδT cells began in the thymus and matured in the peripheral circulation. The formation and development of its function can be divided into three stages: 1) In the thymus, γδT cells are regulated by TCR signaling pathway to complete the differentiation of thymocyte progenitor to γδT cells. At this time, γδT cells preliminarily have a certain function. After induction, they can secrete some cytokines such as TNF-α and IFN-γ [4, 5]. 2) γδ TCR+ thymocytes leave the thymus and become γδT cells in the peripheral circulation [6]. At this stage, γδT cells can express MHC II molecules and possess the antigen-presenting functions [7], thus having an ability to function rapidly in the innate immune response and beginning to serve as a bridge for acquired immune responses. 3) After γδT cells have undergone the first two stages, the immune function of the subtype cells has been basically improved, but different subtype of cells experess different functional characteristics under the same incentive, and in the third stage γδT cells can be differentiated into a single oligoclo-

nal cell subtype via the induction of TCR ligand's related molecules [8]. Depending on the difference of their δ-chain, γδT cells can be divided into two sub-populations, Vδ1 and Vδ2. The Vδ1 sub-population is mainly distributed in mucosa and subcutaneous tissues, such as 10-18% in human-intestinal epithelial lymphocytes (IEL), and accounts for 25~37% of IEL in the human large intestine. The Vδ2 subgroup is mainly present in the peripheral blood, and the Vγ2Vδ2 subtype (also called Vγ9Vδ2) is the main form of circulating cell and accounted for 0.5 to 5% in the peripheral blood of adults. Mucosa and epithelial tissue are the first line of defense against pathogen invasion and often is the site of tumor development. The high proportion of γδT cells in mucosa and epithelial tissues suggests that γδT cells play an important role in anti-microbial, parasitic and tumor immunity [1-3].

Genetic characteristics of γδT cells

The TCRγδ gene is composed of four groups of V, D, J, and C genes; the V region is a functional region of the TCR recognition antigen peptide-MHV (mouse hepatitis virus) complex. The γ chain and the δ chain have 10 and 7 V gene fragments, 2 and 0 D gene accounted for 0.5 to 5%, 2 and 2 J gene fragments respectively, and these genefragments can be combined to form 500 types of TCRγδ genes, thereby providing TCRγδ a possibility of diversity. However, due to the use of specific VγVδ and junction (J region) sequences in the γδT cell subset, the TCRγδ structure lacks diversity [9]. Therefore, in adult peripheral blood, more than 90% of γδT cells belong to the Vγ9Vδ2 subtype [10]. As a result, the γδT gene diversity is less than that of αβT cells, and the gene rearrangement is limited compared with αβT cells, and the recognized antigens are different. The antigen reaction is often MHC-independent [11], and has the activity of natural killer cells (NK) and lymphokine activated killer cells (LAK). Because of its similar function to innate immune-related cells, γδT cells were originally thought to be an important part of the body's natural immunity.

Antigen recognition characteristics of γδT cells

Since γδT cells have partial functions of αβT cells and can also function as immunoglobulins, they are the main cell group involved in the innate immune response and are the key components of non-specific immunity. Its antigen recognition characteristics are as follows: 1) Compared with αβT cells, the molecular structure and antigen binding properties of γδT cells are more similar to those of immunoglobulins, and can directly recognize antigens. 2) The antigen recognition of γδT cell is MHC-independent, and the polypeptide does not need to be processed into small peptide fragments, which can be recognized in the intact form to make a rapid immune response to the antigen. 3) γδT cells do not recognize the polypeptide-MHC molecular complex, but can respond to antigens presented by some MHC-I molecules, and have a special affinity for heat shock proteins. 4) Different tissues of γδT cells can express different TCRs and recognize antigens with different properties, while γδT cells in the same tissue express the same TCR and recognize antigens of the same nature [12].

Biological and immunological functions of γδT cells

γδT cells are mostly CD4- and CD8- cells, a few are CD4+ or CD8+ cells. CD4+ γδT cells secrete cytokines and participate in immune regulation. CD8+ γδT cells are mainly involved in immune response. Activated γδT cells have a variety of biological and immunological functions: 1) Non-specific immune response: no need for APC (antigen-presenting cells) presentation, can be directly activated by its TCR recognition of a variety of bacterial, viral and other antigenic components, and play a significant role in non-specific immune responses. 2) Antigen presentation: partially activated γδT cells can differentiate into APC, which surface can highly express MHC class II molecules and CD80, CD86 and CCR7 (chemokine receptors), processing antigens, cross-presenting to αβT cell to stimulate specific immune response [13]. 3) Stabilize the body's immune environment: γδT cells have the effect of inhibiting the excessive activation of αβT cells, which in turn regulates the relative balance of αβT cells and γδT cells [14]. 4) By immunizing, inhibiting or recruiting other immune cells to play an immune role. For example, dendritic cells, granulocytes, macrophages, Langerhans cells, αβT cells and B cells are closely related to the anti-infective function of γδT cells [15]. 5) Immune surveillance: memory γδT cell surface can prevent the spread of the virus, resist opportunistic infections, and play an immune surveillance role through high

expression of CCR7, CD161, etc. [16]. 6) Immunomodulatory function of γδT cells: activated γδT cells can inhibit the proliferation of Foxp3+ Tregs (regulatory T cells) [17], and can also produce IL-10 and TGF-β (transforming growth factor-β) to play an immunomodulatory role [18]. 7) By directly acting on B cells, most γδT cells are directly stimulated by antigen and produce IL-4, stimulating B cell proliferation and secreting immunoglobulin (Ig). Also, some subgroups' γδT cells can inhibit B cells to produce Ig. 8) Direct lysis of target cells: activated γδT cells can directly lyse target cells through the granzyme-perforin pathway, and can also induce target cell apoptosis via Fas-FasL (transmembrane protein/transmembrane protein cytokine) and IFN-γ [19, 20]. 9) Antibody-dependent cytotoxicity: γδT cells exert ADCC (antibody-dependent cell-mediated cytotoxicity) via certain membrane surface receptors such as Fcγ R (IgG Fc-segment receptor) and enhance its cytotoxicity by secreting IL-2 [21]. 10) Production of cytokines [22-24]: in intracellular bacterial infection, γδT cells produce interleukin 2 (IL-2) and interferon-gamma (IFN-γ), showing Th1 (helper lymphocyte type 1 cells) -like effects. In the case of extracellular parasite infection, γδT cells produce IL-4, IL-5 and IL-10, which stimulate B cells and exhibit Th2 (helper lymphocyte type 2 cell)-like effects. In addition, the IL-10 produced in the above process can also inhibit the proliferation of γδT cells and the secretion of the cytokine IFN-γ [25]. 11) Promote wound healing: γδT cells can respond quickly to skin damage. γδT cell aggregation can be detected at the wound site in 4 hours [26], and produce a small amount of vascular endothelial growth factor and fibroblast growth factor 2 [27]. Activated γδT cells promote epidermal cell proliferation and re-epithelialization of wounds by expressing KGFs and IGF-1 [28], as well as the ability to repair intestinal damage tissue [29]. 12) Identification and killing of tumor cells: γδT cells can recognize the stress-inducing molecules MICA, MICB, ULBP and RAET1 as well as apolipoprotein A1, Toll-like receptors such as ectopic expression on the surface of the tumor [30]. MICA/B and ULBPs are expressed in different types of tumor epithelial cells. γδT cells recognize tumor cells in a non-limiting manner similar to NK cells by MHC2D receptors, suggesting that γδT cells still have the ability to clear target cells in the absence of human leukocyte antigens or tumor antigens [31]. In addition, γδT cells are similar to αβT cells, and bind to specific receptor molecules on endothelial cells by molecules such as CD44, CD11a (LFA21) and MEL-14 (mouse CD62L APC-labeled fluorescent monoclonal antibody), so that γδT cells adhere to endothelial cells, which mediate their recycling and homing.

γδT cells and viral infectious diseases

Coxsackie virus

Coxsackie virus is an enterovirus. It is a common type of virus that infects the human body through the respiratory tract and alimentary canal. It can cause infectious myocarditis after infection. The mouse experiment of myocarditis induced by the virus showed that the occurrence of myocarditis depends on the expression of γδTCR by T cells, and only the mice in which the myocardium accumulates γδT cells show the apoptosis of cardiomyocytes, which indicates that the occurrence of Coxsackie myocarditis is closely related to γδT cells [32, 33]. In the past, Coxsackie myocarditis was thought to be mediated by CD4+ IFN-γ+ cells, but studies have found that [34], antibody blocking γδT cell response can inhibit the occurrence of Coxsackie myocarditis. At this time, in the spleen as well as the heart, CD4+ IFN-γ+ cells decreased, while CD4+ and Foxp3 (regulatory T cell factor 3) (+) cells increased significantly. The γδT cell-deficient mice infected with Coxsackie virus and the CD4+ T cells of normal mice were adoptively transferred to normal mice, and one month later, the Coxsackie virus was used for challenge. The former caused more serious myocarditis. At the same time, CD4+ IFN-γ+ cells were reduced. Thus, γδT cells may contribute to the development of myocarditis by promoting CD4+ IFN-γ+ cell responses through inhibiting CD4+ Foxp3+ cells. It can be seen that γδT cells play a role in regulating the acquired immune response and may be an initiating factor in Coxsackie infection.

Rotavirus

Rotavirus is one of the main pathogens causing diarrhea in infants. It mainly infects intestinal epithelial cells, causing cell damage and diarrhea. Studies have found that CD2+ CD4- and CD4-CD8-γδT cells can directly secrete IFN-γ or promote CD4+ αβT cell proliferation and secrete IFN-γ to regulate T cell expression; while CD2+ CD4+ γδT cells mainly secrete IL-10

and TGF- directly, or promote CD4+ αβT cell proliferation and secrete IL-10, TGF-β and express Foxp3+ to regulate T cell expression [35]. It has also been reported that γδT cells resist and suppress rotavirus by increasing the expression of TLR2 (Toll-like type 2 receptor), TLR4 and TLR9, and secreting and releasing IFN-γ, TGF-β [36].

Influenza virus

Influenza virus is an RNA virus that causes influenza in humans, dogs, horses, pigs and poultry, etc. Proliferating and activating human Vγ9Vδ2T cells by IPP (isopentenyl pyrophosphate) in vitro can kill macrophages infected influenza through NKG2D, direct contact between cells, Fas-FasL and perforin-granzyme, thereby inhibiting viral replication. Vγ9Vδ2T cells can also be used as APC to present antigens of cells infected influenza or virus particles themselves to CD4+ or CD8+ T cells, inducing a specific immune response [37]. During the infection, Vγ9Vδ2 T cells can rapidly produce IFN-γ, mediating cytotoxic effects on cells infected with the virus. In the later stages of infection, γδT cells can recognize HSP (heat shock protein) expressed by viral infection, produce a regulatory immune response, and secrete regulatory cytokines to attenuate the intensity of the immune response [12]. In addition, γδT17 cells may be activated by γδTCR-independent action mode, and participate in the early inflammatory injury process of lung tissue in mice infected with severe H1N1 by releasing IL-17A [38].

Cytomegalovirus

Cytomegalovirus (HCMV), also known as cell inclusion virus, is a herpesvirus DNA virus. Both humans and animals can be infected, mainly causing genitourinary infections. There is an imbalance in the expression of γδT cells and Treg cells in HCMV-infected infants [39]. Studies have found that γδT cells recognize HSP65 and other antigens through the TCR/CD3 pathway, activate and express high levels of IFN-γ, TNF-α, TGF-β, natural killer cell receptors and cytotoxic regulators to clear infected cells [40, 41].

Herpes simplex virus

Herpes simplex virus can cause human corneal conjunctivitis, gingivitis, encephalitis, and inflammation of the genitourinary system. Studies have found that γδT cells can recognize stress molecules (such as HSP) or phosphorylated antigens produced by infected cells, rapidly activate and highly express Th2 cytokines such as IFN-γ, TNF-α, IL-8, MIP-Iα and CCL5, and then act as a cytotoxic agent to clear the virus. When the skin is infected with the virus, γδT cells can induce apoptosis and block E-cadherin down-regulation, preventing the Langerhans cells that have been infected with the virus from moving, thereby inhibiting the further spread of infection [42].

Human immunodeficiency virus (HIV)

Human immunodeficiency virus (HIV) is a lentivirus that infects cells of the human immune system and is a type of retrovirus. 1) The role of γδT cells in anti-HIV infection: During HIV infection, Vγ9Vδ2T cells exert antiviral function directly or indirectly through non-specific recognition of HIV; activated Vγ9Vδ2T cells can secrete Th1 cytokines (such as TNF-α, IFN-γ). IPP-stimulated Vγ9Vδ2T cells produce macrophage inflammatory protein 1α (MIP-1α), MIP-1β and lymphotactin [43], and can also express multiple β-chemokines receptors (e.g., CCR1, CCR5 and CCR8) [44]. In addition, γδT cells are similar to NK cells, and under the "missing self" mechanism, they can secrete perforin, granzyme or play a cytotoxic effect through the Fas/FasL apoptotic pathway, directly killing cells infected with HIV [45]. Second, activated Vγ9Vδ2T cells compete with HIV for CCR5 costimulatory molecules or release antiviral factors, thereby inhibiting HIV replication [46]. 2) The effect of HIV infection on γδT cells: compared with normal people, the ratio of Vδ2T cells/Vδ1T cells in peripheral blood was significantly reversed in HIV-infected patients, which was caused by the loss of Vδ2T cells and the increase of Vδ1T cells in peripheral blood. Loss of Vγ9Vδ2T cells is associated with viral load. By sexually transmitted with HIV, the Vγ9Vδ2T cell loss in circulation increases with increasing HIV load, which may be due to the induction of Fas/FasL on the cell surface after HIV invasion, and causes apoptosis in Vγ9Vδ2T cells [47]. Thus, HIV infection leads to a decrease in the number of γδT cells and inhibits the function of γδT cells [48, 49], resulting in immune escape. In this regard, the cytotoxicity and ADCC effect of the activation of γδT cells may be eliminated by means of adop-

tive treatment, which deserves further study. In addition, in the study of chimpanzees infected with HIV [50], it was found that the ratio of Vδ2T cells/Vδ1T cells in peripheral blood did not reverse, and chimpanzees could control the progression of the virus so that no disease occurred. The chimpanzee's γδT cells subset is similar to human γδT cells, and studying chimpanzee's immune system compared to humans will help improve the human immune system and thus controlling the occurrence of HIV disease. γδT cells also have the ability to clear the HIV-1 reservoir, and autologous or allogeneic adoptive immunotherapy based on γδT cells is expected to be a new strategy to clear the reservoir and cure HIV-1 infection [51].

West Nile virus

West Nile virus is an infectious disease caused by West Nile virus (WNV), a mosquito-borne single-stranded RNA virus. In recent years, West Nile virus disease has appeared in temperate regions of Europe and North America, posing a threat to the health of humans and animals. The serious harm of this disease is that humans and horses are suffering from deadly encephalitis and death of birds and chickens. The researchers used a mouse model to demonstrate that mice deficient in γδT cells were more susceptible to WNV than wild-type mice. After TCRδ-/- mice were infected with WNV, the number of viruses that transmit to the central nervous system will increase significantly. When γδT cells were transplanted into TCRδ-/- mice, the susceptibility of mice to WNV was significantly reduced. γδT cells produce these effects by producing IFN-γ and directly or indirectly regulating cytotoxicity [52].

Vaccinia virus

Some scholars used Cowpox virus to infect normal C57BL/6 mice and βTCR knockout mice, demonstrating that γδT cells produce a rapid antiviral innate immune response [53]. Compared with normal mice, γδT cell-deficient mice have significantly higher virus titers and a significant increase in mortality. After the virus infects the body, the number of γδT cells that can produce IFN-γ in the peritoneal cavity and spleen of normal mice is rapidly increased, and the changes in amount is caused by vaccinia virus infection.

γδT cells and bacterial infectious diseases

Escherichia coli

It was found that when γδT cells were deleted, the resistance of mice to Escherichia coli was significantly decreased [54]. γδT cells activated after Escherichia coli infection further activate macrophages by producing IFN-γ and release IL-15 to induce γδT cells to gather at the site of infection and participate in local anti-inflammatory. Neutrophils were also recruited through self-released IL-17 to play an anti-infective function. When blocked with anti-IL-15 monoclonal antibody, the number of γδT cells decreased significantly, and mice were more susceptible to Escherichia coli. It can be seen that γδT cells mediate the accumulation of γδT cells by activating macrophages to release IL-15, thus participating in its protective effect. In addition, some scholars have used confocal microscopy, transmission electron microscopy and functional antigen presentation analysis to find that γδT cells in human peripheral blood can recognize and capture Escherichia coli mediated by antibody modulin and CD16 molecules. Then the expressed MHC-II accumulator played the role of antigen presentation [55, 56]. Therefore, γδT cells can be used as an effector cell, activated by antigen, through the secretion of cytokines.

Mycobacterium tuberculosis

Mycobacterium tuberculosis is an intracellular parasite. After mice are infected with Mycobacterium tuberculosis, γδT cells accumulate in the lungs. These cells secrete IFN-γ and have cytotoxicity, which can kill macrophages phagocytosis of Mycobacterium tuberculosis [57]. Alveolar macrophages of Mycobacterium tuberculosis infection can secrete chemokines to aggregate γδT cells and play their anti-inflammatory effects [58].

Salmonella typhimurium

In 2011, Pieper found that γδT cells expressing CD8 α in the blood and spleen of chicks infected with Salmonella typhimurium proliferated rapidly and increased the transcription of Fas, IL-2R α (human interleukin 2 receptor α) and IFN-γ [59]. In 2012, Li studied the intestinal infection model of Salmonella typhimurium,

and found that the γδT cell subtypes of intestinal epithelial lymphoid tissue could play the role of immune monitoring and clearance of infected epithelial cells by expressing NKG2D (activated receptor of NK cells), CD8 α, FasL and IFN-γ [60]. It is also related to the secretion of keratinocyte growth factor by epithelial cells, which can promote the regeneration of epithelial cells and limit the further invasion of pathogenic bacteria.

Helicobacter pylori

Gastric mucosa was the main site of Helicobacter pylori invasion and colonization. In peripheral blood of patients with Helicobacter pylori infection, the number of αβT cells was not significantly different from that of uninfected patients, but the number of γδT cells was significantly increased [61]. IL-7 and IL-1β were also significantly increased [62]. The number of γδT cells was also closely related to the severity of gastritis, and the number of γδT cells decreased significantly after clearance of Helicobacter pylori [63]. Whether this phenomenon is related to anti-inflammatory factors secreted by γδT cells or Toll-like receptors (Toll-like receptors, TLR) on the surface needs to be further studied.

Brucella

Brucella is a kind of intracellular parasitic glomerular bacilli, which can infect human beings and animals, and has a high degree of infectivity. When infected, Vδ2T cells can directly dissolve macrophages phagocytic with Brucella, and reduce the number of bacteria through Fas-Fas ligands, thus limiting the spread of infection [64].

Leptospirosis

Leptospira can be divided into pathogenic and non-pathogenic categories, and pathogenic Leptospira can cause human and animal leptospirosis. Some researchers have found that scavenger receptors interfering with the surface of γδT cells can significantly reduce the ability of Leptospira to stimulate the proliferation of γδT cells and secrete IFN-γ by RNA interference technique. Whether this is related to Toll receptor needs to be further explored [65].

Chlamydia trachomatis

In 2015, Wang Yue established a model of Chlamydia trachomatis pneumonia using Chlamydia mu-ridarum (Cm), and used flow cytometry to detect the percentage of CD3+ TCRγδ+ T cells in mice. Intracellular cytokine staining technique detects the production of IFN-γ and IL-17 in γδT cells [66]. It was found that a certain dose of Cm respiratory infection could induce the accumulation and activation of γδT cells in mice. During the whole infection process, αβT cells and γδT cells secreted IFN-γ and IL-17, but γδT cells activated and secreted IFN. IFN-γ and IL-17 are earlier than αβT cells, which are the main cell types secreting IFN-γ and IL-17 early in the host anti-Chlamydia immune response. Whether there is also an interaction between αβT cells and γδT cells, and whether γδT cells have an effect on the adaptive immune response induced by Chlamydia trachomatis infection remains to be further studied.

Conclusion and outlook

γδT cells differ in their expression of TCR, and their subpopulations have different distributions and functions. Vδ2T cells present in peripheral blood can produce a large amount of IFN-γ and TNF-α, which have cytotoxic effects, while Vδ1T cells present in tissues have less cytotoxic effects, mainly producing cytokines such as IL-4, IL-17 and etc. When stimulated by antigens such as pathogenic microorganisms, two cell populations of γδT cells can express chemotactic receptors associated with their respective functions and metastasize to the site of inflammation of extracellular tissues to exert an anti-infective effect. As a type of T cells which have unique composition and function, γδT cells have received more and more attention from researchers in recent years. The academic community has reached a consensus on the antigen recognition mode and MHC-free restriction of γδT cells, but the infection immune mechanism mediated by them is still not fully understood. Therefore, it is worthy of further in-depth study to determine the function and mechanism of γδT cells in viral infectious diseases and whether they can be used as a means of adoptive treatment for immunodeficiency diseases. On the basis of clear mechanisms, γδT cells will have wider application prospects in immunologically related diseases.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (No. 814-73687), and Shandong Provincial Natural Sci-

ence Foundation, China (No. ZR2009CM039 and No. ZR2013HM038), and Shandong provincial medical and health science and technology development plan (No. 2015WS0095), and Tai'an Science and Technology plan (No. 201440774; No. 2018NS0116).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Keqiang Wang, Department of Clinical Laboratory, The Second Affiliated Hospital of Shandong First Medical University, Tai'an 271000, Shandong Province, China. Tel: +86-538-6236422; Fax: +86-538-8420042; E-mail: wkqsd@163.com

References

[1] Wang KQ, Hou YQ, Li QH, Zhao DP, Duan YC, Ran ZS, Li XQ. Inhibitory effect of LY294002 on CD3mAb-activated T cells and Mtb-Ag-activated γδT cells via TCR signal transduction pathway. Int J Clin Exp Pathol 2017; 10: 5538-5544.

[2] Wang KQ, Hou YQ, Gu CX, Zhao DP, Duan YC, Ran ZS, Li QH, Li XQ. Inhibitory effect of the mitogen activated protein kinase specific inhibitor PD98059 on Mtb-Ag-activated γδT cells. Int J Clin Exp Pathol 2017; 10: 9644-9648.

[3] Wei L, Wang KQ, Ran ZS, Liu QH, Chen YY, Ji B, Meng L, Cao WW, An X. Auxiliary diagnostic value of γδT cell, IL-17, and IFN-γ levels in peripheral blood and bronchoalveolar lavage fluid for lung cancer complicated with chronic obstructive pulmonary disease. Int J Clin Exp Med 2018; 11: 7183-7191.

[4] Shekhar S, Milling S, Yang X. Migration of γδT cells in steady-state conditions. Vet Immunol Immunopathol 2012; 147: 1-5.

[5] Narayan K, Sylvia KE, Malhotra N, Yin CC, Martens G, Vallerskog T, Kornfeld H, Xiong N, Cohen NR, Brenner MB, Berg LJ, Kang J. The immunological genome project consortium. Intrathymic programming of effector fates in three molecularly distinct γδT cell sub-types. Nat Immunol 2012; 13: 511-518.

[6] Cook L, Miyahara N, Jin N, Cook L, Miyahara N, Jin N, Wands JM, Taube C, Roark CL, Potter TA, Gelfand EW, O'Brien RL, Born WK. Evidence that CD8+ dendritic cells enable the development of γδT cells that modulate airway hyperresponsiveness. J Immunol 2008; 181: 309-319.

[7] Cheng L, Cui Y, Shao H, Han GC, Zhu L, Huang YF, O'Brien RL, Born WK, Kaplan HJ, Sun DM. Mouse γδT cells are capable of expressing MHC class II molecules, and of functioning as antigen-presenting cells. J Neuroimmunol 2008; 203: 3-11.

[8] Roark CL, French JD, Taylor MA, Bendele AM, Born WK, O'Brien RL. Exacerbation of collagen-induced arthritis by oligoclonal, IL-17-producing γδT cells. J Immunol 2007; 179: 5576-5583.

[9] Chen H, Bernstein H, Ranganathan P, Schluter SF. Somatic hypermutation of TCRγ V genes in the sandbar shark. Dev Comp Immunol 2012; 37: 176-183.

[10] Yang QT, Huang XK, Li P, Chen YL, Zheng GH. Distribution and clonality of T cell receptor Vγ and Vδ subfamily in peripheral blood of patients with allergic rhinitis before and after immunotherapy. Chin J Otorhinolaryngol Head Neck Surg 2011; 46: 992-997.

[11] Li HM, Lebedeva MI, Llera AS, Fields BA, Brenner MB, Mariuzza RA. Mariuzza RA. Structure of the Vδ domain of a human γδ T-cell antigen receptor. Nature 1998; 391: 502-506.

[12] Khatri M, Dwivedi V, Krakowka S, Manickam C, Ali A, Wang LY, Qin ZM, Renukaradhya GJ, L CW. Swine influenza H1N1 virus induces acute inflammatory responses in pig lung: a potential animal model fot human H1N1influenza virus. J Virol 2010; 84: 11210-11218.

[13] Wu Y, Wu W, Wong WM, Ward E, Thrasher AJ, Goldblatt D, Osman M, Digard P, Canaday DH, Gustafsson K. Human γδT cells: a lymphoid lineage cell capable of professional phagocytosis. J Immunol 2009; 183: 5622-5629.

[14] Kaufmann SH. Gamma/delta and other unconventional T lymphocytes: what do they see and what do they do. Proc Natl Acad Sci U S A 1996; 93: 2272-9.

[15] Puttur FK, Fernandez MA, White R, Roediger B, Cunningham AL, Weninger W, Jones CA. Herpes simplex virus infects skin γδT cells before Langerhans cells and impedes migration of infected Langerhans cells by inducing apoptosis and blocking E-cadherin downregulation. J Immunol 2010; 185: 477-487.

[16] Chodaczek G, Papanna V, Zal MA, Zal T. Erratum: body-barrier surveillance by epidermal γδ TCRs. Nat Immunol 2012; 13: 272-282.

[17] Gong G, Shao L, Wang Y, Chen CY, Huang D, Yao S, Zhan X, Sicard H, Wang R, Chen ZW. Phosphoantigen-activated V gamma 2V delta 2 T cells antagonize IL-2-induced CD4+ CD25+ Foxp3+ T regulatory cells in mycobacterial infection. Blood 2009; 113: 837-845.

[18] Kühl AA, Pawlowski NN, Grollich K, Loddenkemper C, Pawlowski NN, Blessenohl M, Westermann J, Zeitz M, Hoffmann JC. Human peripheral γδT cells possess regulatory potential. Immunology 2009; 128: 580-588.

[19] Qin G, Mao H, Zheng J, Sia SF, Liu YP, Chan PL, Lam KT, Peiris JSM, Lau YL, Tu WW. Phosphoantigen- expanded human γδT cells display potent cytotoxicity against monocyte- derived macrophages infected with human and avian influenza viruses. J Infect Dis 2009; 200: 858-865.

[20] Kubota K. Innate IFN-γ production by subsets of natural killer cells, natural killer T cells and γδT cells in response to dying bacterial-infected macrophages. Scand J Immunol 2010; 71: 199-209.

[21] Poonia B, Pauza CD. Gamma delta T cells from HIV+ donors can be expanded in vitro by zoledronate/interleukin-2 to become cytotoxic effectors for antibody-dependent cellular cytotoxicity. Cytotherapy 2012; 14: 173-181.

[22] Szczepanik M, Nowak B, Askenase P, Ptak W. Cross-talk between γδT lymphocytes and immune cells in humoral response. Immunology 1998; 95: 612-617.

[23] Wang KQ, Hou YQ, Duan YC, Wang YR, Li XQ. A method for detecting intracellular IL-2 in γδT cells. Biomedical Research 2018; 29: 3144-3148.

[24] Wang KQ, Hou YQ, Gu CX, Zhao DP, Duan YC, Wang YR, Ran ZS, Li XQ. Western blotting was used to detect ZAP-70 molecule from γδT cells in peripheral blood. Int J Clin Exp Med 2019; 11: 1785-1790.

[25] Rojas RE, Balaji KN, Subramanian A, Boom WH. Regulation of human CD4 (+) alphabeta T-cell-receptor- positive TCR (+) and gammadelta TCR (+) T-cell responses to Mycobacterium tuberculosis by interleukin-10 and transforming growth factor betab. Infect Immun 1999; 67: 6461-6472.

[26] Havran WL, Jameson JM. Epidermal T cells and wound healing. J Immunol 2010; 184: 5423-5428.

[27] Laggner U, Di Meglio P, Perera GK, Hundhausen C, Lacy KE, Ali N, Smith CH, Hayday AC, Nickoloff BJ, Nestle FO. Identification of a novel proinflammatory human skin-homing Vγ9-Vδ2T cell subset with a potential role in psoriasis. J Immunol 2011; 187: 2783-2793.

[28] Jameson J, Havran WL. Skin γδT - cell functions in homeostasis and wound healing. Immunol Rev 2007; 215: 114-122.

[29] Li CC, Mannoor K, Inafuku M, Taniguchi T, Inamine Y, Miyazaki T, Watanabe H. Protective function of an unconventional gammadelta T cell subset against malaria infection in apoptosis inhibitor deficient mice. Cell Immunol 2012; 279: 151-159.

[30] Caccamo N, Dieli F, Meraviglia S, Guggino G, Salerno A. Gamma delta T cell modulation in anticancer treatment. Curr Cancer Drug Targets 2010; 10: 27-36.

[31] Xiang D, Sharma VR, Freter CE, Yan J. Anti-tumor monoclonal antibodies in conjunction with beta-glucans: a novel anti-cancer immunotherapy. Curr Med Chem 2012; 19: 4298-4305.

[32] Li ZX. Potential of human γδT cells for immunotherapy of osteosarcoma. Mol Biol Rep 2013; 1: 132-140.

[33] Hanagiri T, MShigematsu Y, Kuroda K, Baba T, Shiota H, Ichiki Y, Nagata Y, Yasuda M, So T, Takenoyama M, Tanaka F. Antitumor activity of human γδT cells transducted with CD8 and with T-cell receptors of tumor-specific cytotoxic T lymphocytes. Cancer Sci 2012; 8: 232-239.

[34] Nakajima J, Murakawa T, Fukami T, Goto S, Kaneko T, Yoshida Y, Takamoto S, Kakimi K. A phase I study of adoptive immunotherapy for recurrent non-small-cell lung cancer patients with autologous γδT cells. European J Cardio-Thoracic Surg 2010; 5: 92-103.

[35] Benjamin H, Beck, Kim HG, Kim H, Samuel SL, Liu ZY, Shrestha R, Haines H, Zinn K, Lopez RD. Adoptively transferred ex vivo expanded γδT cells mediate in vivo antitumor activity in preclinical mouse models of breast cancer. Breast Cancer Res Treat 2010; 19: 320-329.

[36] Wen K, Castellucci T, Li GH, Liu FN, Li YR, Kocher J, Yuan LJ. Characterization of immune modulating functions of γδT cell subsets in a gnotobiotic pig model of human rotavirus infection. Comp Immunol Microb 2012; 35: 289-301.

[37] Nedellec S, Sabourin C, Bonneville M, Scotyt E. NKG2D costimulates human V gamma 9V delta 2 T cell antitumor cytotoxicity through protein kinase C theta-dependent modulation of early TCR-induced calcium and transduction signals. J Immunol 2010; 185: 55-63.

[38] Wen MJ, Liu M, Zhang XL, Cao B. Distribution of γδT17/Th17/Tc17 cells in lung of H1N1 infected mice and their relationship with immunologic injury of lung. Chin J Immunology 2017; 33: 563-568.

[39] Xu L, Zhu LL, Ye LL, Meng LJ, Liu WQ, Wang J. Percentages of peripheral blood γδT cells and regulatory T cells and expression of associated cytokines in infants with human cytomegalovirus infection. Chin J Contemporary Pediatrics 2018; 20: 204-208.

[40] Couzi L, Lafarge X, Pitard V, Neau-Cransac M, Dromer C, Billes MA, Lacaille F, Moreau JF, Merville P, Déchanet-Merville J. Gamma-delta T cell expansion is closely associated with cytomegalovirus infection in all solid organ transplant recipients. Transpl Int 2011; 24: e40-42.

[41] Daguzan C, Moulin M, Kulyk-Barbier H, Davrinche C, Peyrottes S, Champagne E. Aminobisphosphonates synergize with human cytomegalovirus to activate the antiviral activity of

Vγ9Vδ2 cells. J Immunol 2016; 196: 2219-2229.
[42] Puttur FK, Fernandez MA, White R, Roediger B, Cunningham AL, Weninger W, Jones CA. Herpes simplex virus infects skin γδT cells before Langerhans cells and impedes migration of infected Langerhans cells by inducing apoptosis and blocking E-cadherin downregulation. J Immunol 2010; 185: 477-487.
[43] Poccia F, Gougeon ML, Agrati C, Montesano C, Martini F, Pauza CD, Fisch P, Wallace M, Malkovsky M. Innate T-cell immunity in HIV infection: the role of Vγ9Vδ2T lymphocytes. Curr Mol Med 2002; 2: 769-781.
[44] Agrati C, D' Offizi G, Gougeon ML, Malkovsky M, Sacchi A, Casetti R, Bordoni V, Cimini E, Martini F. Innate γδT-cells during HIV infection: Terra relatively incognita in novel vaccination strategies. AIDS Rev 2011; 13: 3-12.
[45] Halary F, Peyrat MA, Champagne E, Lopez-Botet M, Moretta A, Moretta L, Vié H, Fournie JJ, Bonneville M. Control of self-reactive cytotoxic T lymphocytes expressing γδT cell receptors by natural killer inhibitory receptors. Eur J Immunol 1997; 27: 2812-2821.
[46] Biswas P, Ferrarini M, Mantelli B, Fortis C, Poli G, Lazzarin A, Manfredi AA. Double-edged effect of Vγ9/Vδ2T lymphocytes on viral expression in an in vitro model of HIV-1/mycobacteria co-infection. Eur J Immunol 2003; 33: 252-263.
[47] 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 Vγ9Vδ2T cells in chronically infected patients undergoing structured treatment interruption. J Infect Dis 2002; 186: 847-850.
[48] Silva-santos B, Serre K, Norell H. gammadelta T ceus in cancer. Nat Rev Immunol 2015; 15: 683-691.
[49] Li Z, Jiao YM, Hu Y, Cui LX, Chen DX, Wu H, Zhang JM, He W. Distortion of memory Vγ2 γδT cells contributes to immune dysfunction in chmnic HIV infection. Cell Mol Immunol 2015; 12: 604-614.
[50] Hodara VL, Parodi LM, Chavez D, Smith LM, Lanford R, Giavedoni L. Characterization of γδT cells in naïve and HIV-infected chimpanzees and their responses to T- cell activators in vitro. J Med Primatol 2014; 43: 258-271.
[51] Li Z, Lu XF, Sun JP, SU B, Wu H, Zhang YH, Zhang T. Cytotoxic role of γδT cells to latency cells in patients with early human immunodeficiency virus-1 infection. Basic Clinical Medicine 2017; 37: 953-958.
[52] Wang T, Scully E, Yin Z, Kim JH, Wang S, Yan J, Mamula M, Anderson JF, Craft J, Fikrig E. IFN-γ-producing γδT cells help eontml murine West Nile virus infection. J Immunol 2003; 171: 2524-2531.
[53] Sclin LK, Santolucito PA, Pinto AK, Szomolanyi-Tsuda E, Welsh RM. Innate immunity to viruses: control of vaccinia virus infection by γδT cells. J Immunol 2001; 166: 6784-6794.
[54] Cheng L, Cui Y, Shao H, Han G, Zhu L, Huang Y, O'Brien RL, Born WK, Kaplan HJ, Sun D. Mouse γδT cells are capable of expressing MHC class II molecules, and of func-tioning as antigen-presenting cells. J Neuroimmunol 2008; 203: 3-11.
[55] Heine H, Ulmer AJ. Recognition of bacterial products by toll-like receptors. Chem Immunol Allergy 2015; 38: 565-574.
[56] Moser B, Eberl M. Gamma delta T cells, novel initiators of adaptive immunity. Immunol Rev 2007; 215: 89-102.
[57] Dieli F, Ivany J, Marsh P, Williams A, Naylor I, Sireci G, Caccamo N, Caterina Di Sano, Salerno A. Characterization of lung gamma delta T cells follow ing intranasal infectionw ithM ycobacterium bovis bacillus Calmette-Guerin. J Immuno 2003; 170: 463-469.
[58] Ferrero E, Biswas P, Vettoretto K, Ferrarini M, Uguccioni M, Piali L, Leone BE, Moser B, Rugarli C, Pard R. Macrophages exposed to Mycobacterium tuberculosis release che mokines able to recruit selected leucocyte subpopulations: focus on γδ cells. Immunology 2003; 108: 365-374.
[59] Pieper J, Methner U, Berndt A. Characterization of avian γδT- cell subsets after salmonella enterica serovar typhimurium infection of chicks. Infect Immun 2011; 79: 822-829.
[60] Li ZY, Zhang C, Zhou ZX, Zhang JH, Zhang J, Tian ZG. Small intestinal intraepithelial lymphocytes expressing CD8 and T cell receptor γδ are involved in bacterial clearance during salmonella enterica serovar typhimurium infection. Infect Immun 2012; 80: 565-574.
[61] Hayday AC. Gammadelta T cells and the lympho id stress surveillance response. Immunity 2009; 31: 184-96.
[62] Futagami S, Hiratsuka T, Suzuki K, Kusunoki M, Wada K, Miyake K, Ohashi K, Shimizu M, Takahashi H, Gudis K, Kato S, Tsukui T, Sakamoto C. Gammadelta T cells increase with gastric mucosal interleukin (IL)-7, IL-1beta, and H elicobacter py lori urease specific i mmunoglobulin levels via CCR2 up regulation in H elicobacter py lori gastritis. J Gastroenterol Hepato 2006; 21: 32-40.
[63] Hayday AC. γδT cells and the lymphoid stress-surveillance response. Immunity 2009; 31: 184-196.
[64] Skyberg JA, Thornburg T, Rollins M, Huarte E, Jutila MA, Pascual DW. Murine and bovine γδT

cells enhance innate immunity against brucella abortus infections. PLoS One 2011; 6: e21978.

[65] Wang F, Herzig CT, Chen C, Hsu H, Baldwin CL, Telfer JC. Scavenger receptor WC1 contributes to the γδT cell response to Leptospira. Mol Immunol 2011; 48: 801-809.

[66] Wang Y, Tang YY, Qiao S, Zhao HL, Liu TL, Liang JY, Zheng YB, Tan L, Zhang YC, Zhang H, Bai H. Chlam ydia mu ridra um respiratory tract infection induces the proliferation ofγδT cells and the secre-t ion of IFN-γand IL-17. Chin J Microbiol Immunol 2015; 35: 793-798.