



$\gamma\delta$ T17/ $\gamma\delta$ Treg cell subsets: a new paradigm for asthma treatment

Yi-En Yao, Cai-Cheng Qin, Chao-Mian Yang & Tlan-Xia Huang

To cite this article: Yi-En Yao, Cai-Cheng Qin, Chao-Mian Yang & Tlan-Xia Huang (2021): $\gamma\delta$ T17/ $\gamma\delta$ Treg cell subsets: a new paradigm for asthma treatment, Journal of Asthma, DOI: [10.1080/02770903.2021.1980585](https://doi.org/10.1080/02770903.2021.1980585)

To link to this article: <https://doi.org/10.1080/02770903.2021.1980585>



© 2021 The Author(s). Published with license by Taylor and Francis Group, LLC



Accepted author version posted online: 11 Oct 2021.



Submit your article to this journal [↗](#)



Article views: 51



View related articles [↗](#)



View Crossmark data [↗](#)

$\gamma\delta$ T17/ $\gamma\delta$ Treg cell subsets: a new paradigm for asthma treatment

Yi-En Yao[#], Cai-Cheng Qin, Chao-Mian Yang^{*}, and Tian-Xia Huang^{*}

Department of Respiratory Medicine, The Fifth Affiliated Hospital of Guangxi Medical University, Nanning, China

***CONTACT** Chao-Mian Yang 450932217@qq.com; Tian-Xia Huang 770928176@qq.com
Department of Respiratory Medicine, The Fifth Affiliated Hospital of Guangxi Medical University, Nanning, China.

[#]First author.

Abstract

Bronchial asthma (abbreviated as asthma), is a heterogeneous disease characterized by chronic airway inflammation and airway hyperresponsiveness. The main characteristics of asthma include variable reversible airflow limitation and airway remodeling. The pathogenesis of asthma is still unclear. Th1/Th2 imbalance, Th1 deficiency and Th2 hyperfunction are classic pathophysiological mechanisms of asthma. Some studies have shown that the imbalance of the Th1/Th2 cellular immune model and Th17/Treg imbalance play a key role in the occurrence and development of asthma; however, these imbalances do not fully explain the disease. In recent years, studies have shown that $\gamma\delta$ T and $\gamma\delta$ T17 cells are involved in the pathogenesis of asthma. $\gamma\delta$ Treg has a potential immunosuppressive function, but its regulatory mechanisms have not been fully elucidated. In this paper, we reviewed the role of $\gamma\delta$ T17/ $\gamma\delta$ Treg cells in bronchial asthma, including the mechanisms of their development and activation. Here we propose that $\gamma\delta$ T17/Treg cell subsets contribute to the occurrence and development of asthma, constituting a novel potential target for asthma treatment.

Keywords Asthma; $\gamma\delta$ T17/ $\gamma\delta$ Treg; Mechanism

Introduction

As a subgroup of T cells, $\gamma\delta$ T cells are immune cells composed of T cell antigen receptor (TCR)- γ and TCR- δ ^[1] that plays an important role in innate and specific immunity. There is evidence that V γ 1⁺ $\gamma\delta$ T cells can induce eosinophilic inflammation^[2], while Th2 and eosinophilic T cells can induce airway inflammation and airway hyper reactivity (AHR) by secreting a large number of inflammatory cytokines^[3]. As an important source of IL-17 production, $\gamma\delta$ T cells can recruit concentrated granulocytes and participate in a variety of inflammatory diseases^[4,5]. Indeed, IL-17 is associated with airway inflammation, hyper reactivity and remodeling in asthma^[6–10]. The production of IL-17 by $\gamma\delta$ T cells is performed by $\gamma\delta$ T17 cells^[11] and compared with other T lymphocytes, the expression of IL-17 in $\gamma\delta$ T cells is reportedly higher^[12]. Studies have shown that

$\gamma\delta$ T17 is involved in the pathogenesis of asthma^[13] and that upon the inhibition of IL-23R, the inactivated *Mycoplasma sputum* attenuated the immune response mediated by $\gamma\delta$ T17 cells, and alleviated the airway inflammation and AHR in asthmatic mice^[3]. Regulatory $\gamma\delta$ T cells ($\gamma\delta$ Tregs) are a newly reported subset of $\gamma\delta$ T cells, which are characterized by the potential immunosuppressive function of TCR $\gamma\delta$ and Foxp3^[14].

1. $\gamma\delta$ T cell

1.1. Composition, structure and activation pathway of $\gamma\delta$ T cells

According to the TCR receptor, T cells can be divided into α - β T and γ - δ T cells. The arrangement of $\gamma\delta$ T cells is composed of TCR- γ and TCR- δ . Major histocompatibility complexes do not restrict TCR $\gamma\delta$, thus their antigen recognition is independent of CD4 or CD8 co-receptors. Unlike $\alpha\beta$ T cells, $\gamma\delta$ T cells constitute only a small proportion (1–5%) of the lymphocytes that circulate in the blood and peripheral organs of most adult animals. $\gamma\delta$ T cells are, however, more widespread within epithelial-rich tissues, such as the skin, intestine and reproductive tract, where they can comprise up to 50% of T cells^[15]. The percentage of $\gamma\delta$ T cells in lymphoid tissue, intestinal tract and skin-related lymphoid system is similar.

Human $\gamma\delta$ T cells can be divided into V δ 1 and V δ 2 according to the V δ chain. V δ 1⁺ T cells are mainly distributed in the epithelium and mucosa and V δ 2⁺ T cells, which usually express V19, are mainly in the peripheral blood and lymphatic system. Mouse $\gamma\delta$ T cells can be divided into two groups according to the V δ chain: V γ 2, V γ 3, V γ 5, V γ 6 and V γ 7 being mainly expressed in peripheral lymphoid organs, while V γ 1 and V γ 4 are preferentially expressed in the respiratory system. In recent years, mouse and human $\gamma\delta$ T cells were shown to play an important role in maintaining the immune homeostasis of the local microenvironment and in autoimmunity, cancer and other related diseases^[16]. The production of IL-17 ($\gamma\delta$ T17) by $\gamma\delta$ T cells is not induced by antigen, while IFN- γ ($\gamma\delta$ T1) can be induced by antigen. By activating TLR, $\gamma\delta$ T cells activate IL-17, which is involved in the expression of cytokines, chemokines and pattern recognition receptors, such as IL-1, IL-6, IL-18, IL-23 and TGF- β 1. TGF- β 1 activates toll-like receptor 2 and the aromatic hydrocarbon receptor^[17]. It has been found that IL-1 β and IL-23 can stimulate the production of IL-17 by $\gamma\delta$ T cells^[18] and the release of IL-1 β and IL-18 via the inflammasome-triggered pathway is an important source of IL-17 secretion by $\gamma\delta$ T cells^[19].

1.2 $\gamma\delta$ T cells and asthma

In ovalbumin (OVA)-induced asthmatic mice, the expression of OVA-specific IgE and IgG1 decreased in mice lacking $\gamma\delta$ T cells compared with those of wild-type mice^[20]. Meanwhile, IL-5, eosinophils and T lymphocytes were also decreased in the lungs of mice lacking $\gamma\delta$ T cells^[20]. Therefore, $\gamma\delta$ T cells can promote allergic airway diseases mediated by Th2 cells and secrete OVA-specific IgE by B cells. However, some studies have found that the level of OVA-specific IgE in serum of mice with OVA-induced asthma was increased after treatment with anti- $\gamma\delta$ TCR^[21]. These data show that $\gamma\delta$ T cells can regulate humoral immunity and exert a double regulatory effect.

Indeed, it was found that $V\gamma 1^+$ $\gamma\delta$ T cells could increase OVA-specific IgE, but $v\gamma 4^+$ $\gamma\delta$ T cells had the opposite effect^[22].

In OVA-sensitized and -challenged asthmatic mice, $V\gamma 1^+$ $\gamma\delta$ T cells increase AHR by inhibiting the production of IL-10 by $CD4^+$ $CD25^+$ T cells^[23]. Many studies have confirmed that $\gamma\delta$ T cells can inhibit AHR. In OVA-sensitized mice, the number of $V\gamma 4^+$ $\gamma\delta$ T cells in the lung increased after airway stimulation, while the airway responsiveness increased after injection of $V\gamma 4^+$ $\gamma\delta$ T cells. Adoptive transfer of $V\gamma 4^+$ $\gamma\delta$ T cells into mice can therefore inhibit AHR^[24]. Nevertheless, the effect of $\gamma\delta$ T cells on AHR is complex and depends on the dominance of specific subpopulations. After treatment with an anti- $\gamma\delta$ TCR antibody, the staining of collagen around the airway was increased. The quantitative analysis of collagen around the bronchus showed an increased deposition of collagen fibers and TGF- β ^[25]. Of note, TGF- β can promote pulmonary fibrosis and lead to airway remodeling, thus the absence of $\gamma\delta$ T cells further aggravates airway remodeling. It was shown that $\gamma\delta$ T cells could inhibit AHR and inflammation in asthmatic mice; however, whether this is related to its subgroup still needs further clarification.

The function of $\gamma\delta$ T cells in clinical asthma is still controversial. Clinical studies have found that the human IL-4 production phenotype $V\gamma 1^+$ $V\delta 1$ subgroup can increase allergic inflammation, while the IFN- γ production phenotype $V\gamma 2^+$ $V\delta 2$ subgroup can regulate allergen-specific immune shift to Th2^[26]. A previous study has found an increasing trend in the proportion of $\gamma\delta$ T cells in patients with asthma compared with that of healthy people^[27], however another study observed that the proportion of $\gamma\delta$ T cells in patients with asthma was similar to that of healthy people^[28]. We speculate that in the process of asthma the number and function of $\gamma\delta$ T cells as well as the proportion of $\gamma\delta$ T cell subsets is changed. The underlying mechanism of the effect of $\gamma\delta$ T cells on asthma is still unclear. Further investigation of the mechanism pertaining the occurrence and development of allergic diseases can provide novel targets for the treatment of asthma in the future.

2. $\Gamma\delta$ t17/ $\gamma\delta$ Treg cell

2.1 $\Gamma\delta$ t17 cell

IL-17 was originally thought to be produced by α - and β -T lymphocytes, but further studies have found that several immune cells secrete this cytokine, including $\gamma\delta$ T cells, cytotoxic T cells, naive natural killer T (NKT) cells, innate lymphoid CEUS (ILC) and lymphoid tissue-inducing cells^[29]. IL-17 and its closely related cytokine IL-17F can activate the mitogen-activated kinase (MAPK) pathway, classic NF-KB and C/EBP β pathways through IL-17RA/RC. In various models of infection, cancer and autoimmune diseases, $\gamma\delta$ T cells were shown to be the main source of pro-inflammatory cytokines IL-17 and INF- γ .

$\gamma\delta$ T lymphocytes are produced by common progenitor cells in the thymus and are directly involved in the occurrence and development of asthma. The majority of $\alpha\beta$ $CD4^+$ T cells leave the thymus as "immature" cells. These cells differentiate after the activation of peripheral cells, while $\gamma\delta$ T cells play a role in the development of the thymus^[30]. Therefore, mouse $\gamma\delta$ thymocytes contain subsets that are fully committed to IFN- γ or IL-17 production. These subsets can be distinguished according to the expression of co-stimulatory receptors CD27 and chemokine receptor CCR6^[31–33].

Studies have shown that the potential mechanisms of the fate difference of $\gamma\delta$ thymocytes include the controversial role of signaling through TCR^[30]. The variable region of the gamma chain ($V\gamma$)^[15] is also related to the bias of effectors^[34]. In particular, the production of IL-17 is mainly limited by $V\gamma 4^+$ or $V\gamma 6^+$ $\gamma\delta$ T cell subsets, although there are some exceptions with regards to $V\gamma 1^+$ $\gamma\delta$ T cells^[35,36]. In fact, high-resolution transcriptome analysis of $\gamma\delta$ thymocyte subsets showed that $V\gamma 4^+$ and $V\gamma 6^+$ $\gamma\delta$ T cells clustered together and were isolated from $V\gamma 5^+$, $V\gamma 1^+$ and $V\gamma 7^+$ subsets^[37]. The main differences between these cells are two high-mobility family box transcription factors Sox4 and Sox13, which are essential for the development of $V\gamma 4^+$ and $V\gamma 6^+$ $\gamma\delta$ T17 thymocytes^[38]. However, mature peripheral blood $V\gamma 6^+$ $\gamma\delta$ T17 cells bypass the need for Sox4 and Sox13, while there are no $V\gamma 4^+$ $\gamma\delta$ T17 cells in Sox4^{-/-} and Sox13^{-/-} mice^[38].

Regarding the mechanism, Sox13 induces the expression of BLK, which is a crucial signal transducer for the development of $\gamma\delta$ T17 cells^[37]. Together with Sox4, it controls the expression of ROR γ t20, which is the main "Type 17" transcription factor of $\gamma\delta$ T and similar cells^[39-41]. Interestingly, the locus encoding ROR γ t is controlled by epigenetic mechanisms in $\gamma\delta$ T cells, which accumulates positive modifications of histone H3 related to gene transcription in CD27-CCR6⁺ subpopulations that produce $\gamma\delta$ T17 cells. Therefore, there is a complex regulatory mechanism of differentiation and transcription in $\gamma\delta$ T17 cells^[30,40,42]. For "pre-programmed" mouse $\gamma\delta$ T cells, their peripheral activation is usually faster and simpler than other lymphocytic cells carrying rearranged antigen receptors. In fact, even in the absence of TCR stimulation, IL-1 β and IL-23 stimulation were sufficient to trigger IL-17 secretion by CD27-CCR6⁺ $\gamma\delta$ T cells *in vitro*, however stimulations with TGF- β or IL-6 alone led to no effect^[17,32,41,43]. The innate pattern activated by mouse $\gamma\delta$ T17 cells is highlighted by its rapid response to pathogen-related molecules such as lipopolysaccharide or lipoproteins (ligands of receptor TLR4 and TLR2, respectively). Such rapid response is mediated by IL-1 β and IL-23 derived from bone marrow cells, such as macrophages^[43-45]. In addition, IL-1 β and IL-23 could also induce the production of IFN- γ by $\gamma\delta$ T17 cells^[40,41]. This peripheral plasticity of $\gamma\delta$ T17 cells is shown by the permissive chromatin configuration of the IFN- γ locus in CD27-CCR6⁺ $\gamma\delta$ T cells^[40], which occurs when considerable inflammation occurs in the body^[46-48].

For T cell subsets, the TCR reactivity of $\gamma\delta$ T17 cells remains controversial. TCR and CD3 agonists do not phosphorylate TCR-dependent kinases (such as ERK) nor do they induce rapid mobilization of calcium, in spite of causing extensive cell death^[44,49]. In an *in vivo* model with clear TCR specificity, a discrete population of $\gamma\delta$ T cells (approximately 0.4%) could recognize phyco-erythrodin and differentiate into IL-17 producing cells^[50]. T cells expressing the $\gamma\delta$ T cell receptor (TCR) are an important innate source of the proinflammatory cytokines interleukin-17(IL-17A) and IL-17F^[51-53]. Compared with CD4⁺ Th17 cells, $\gamma\delta$ T17 cells can respond to various stimuli immediately, including IL-23, IL-1 and their TCR triggering^[32,52,54,55]. Study shows that $\gamma\delta$ T17 cells are involved in the defense against mucocutaneous infections, and other microbial infections^[31,56-59]. IL-17 production by $\gamma\delta$ T cells has been shown to play important roles anticancer in immune responses, in the pathology of autoimmune encephalomyelitis, and in the inflammatory processes associated with brain injury^[60-64]. Furthermore, the IL-17A and IL-17F absence or mutations in their signaling pathway lead to chronic mucocutaneous candidiasis, and they are particularly important for control of mucocutaneous infections in humans^[65,66]. There is some evidence that two distinct TCR-defined IL-17-producing $\gamma\delta$ T cell subsets also exist in humans, but unlike the mouse $\gamma\delta$ T-17 cells, these cells are probably not imprinted with an IL-17 bias during thymic development, but rather acquire an IL-17 bias in the periphery^[67]. Although it was shown that there is little study about the production of $\gamma\delta$ T cells on human IL-17^[68, 69], but studies found

that Human $\gamma\delta$ T17 cells appear to be crucial for immune responses in young individuals^[70–73]. TCR engagement favors the development of $\gamma\delta$ T cells precommitted to make interferon- γ (IFN- γ)^[33], but, it is unclear whether development of $\gamma\delta$ T17 cells is at all dependent on positive selection via TCR signaling. There are reports that development of $\gamma\delta$ T17 cells occurs either TCR independently^[33,74], or requires a weak TCR signal^[75]. Study shows that $\gamma\delta$ T17 cells appear in the embryonic thymus, and their number progressively decreases in adult mice with age^[31,76]. $\gamma\delta$ T17 cells comprise semi-invariant V γ 6+ $\gamma\delta$ T cells as well as more polyclonal V γ 1+ and V γ 4+ cells in lung, peritoneal cavity, and secondary lymphoid organs^[35,58,77]. It has been showed that the receptor proximal tyrosine kinase Syk is essential for $\gamma\delta$ TCR signal transduction and development of $\gamma\delta$ T17 in the mouse thymus, Syk induced the activation of the PI3K/Akt pathway upon $\gamma\delta$ TCR stimulation, mice deficient in PI3K signaling exhibited a complete loss of $\gamma\delta$ T17, without impaired development of IFN- γ -producing $\gamma\delta$ T cells; Moreover, $\gamma\delta$ T17-dependent skin inflammation was ameliorated in mice deficient in RhoH^[78]. Study demonstrate that IL-1 β and IL-23 together are able to promote the development of bona fide $\gamma\delta$ T17 cells from peripheral CD122-IL-23R- $\gamma\delta$ T cells, whereas CD122+ $\gamma\delta$ T cells fail to convert into $\gamma\delta$ T17 cells and remain stable IFN- γ producers ($\gamma\delta$ T1 cells), IL-23 is instrumental in expanding extrathymically generated $\gamma\delta$ T17 cells, In particular, TCR-V γ 4+ chain-expressing CD122-IL-23R- $\gamma\delta$ T cells are induced to express IL-23R and IL-17 outside the thymus during skin inflammation; In contrast, TCR-V γ 1+ $\gamma\delta$ T cells largely resist this process because prior TCR engagement in the thymus has initiated their commitment to the $\gamma\delta$ T1 lineage^[18]. It has found that TCR δ -deficient mice had a more severe dextran sodium sulfate (DSS)-induced colitis that was reduced upon reconstitution of $\gamma\delta$ T17 cells but not IFN γ -producing $\gamma\delta$ T cells^[3]. For $\gamma\delta$ T17 cells, TCR ligand interaction has a low affinity, while a strong TCR signal can easily trigger activation-induced cell death. Under the condition of homologous interaction with proteins, in addition to experiencing proliferation and developing a CD44^{hi}CD62L^{lo} phenotype, the expression of IL-23R and IL-1R1 is up-regulated in $\gamma\delta$ T17 cells. Studies have shown that CD28, BTLA and PD-1 are important regulators of the $\gamma\delta$ T17 cell subsets. The data showed that the number of $\gamma\delta$ T17 cells in mice infected with CD28 deficiency of *Plasmodium falciparum* increased, while BTLA and PD-1 produced IL-17 by negatively regulating skin cd27- $\gamma\delta$ T cells, which affected psoriasis-like skin inflammation^[79,80]. Thus, the activation of $\gamma\delta$ T17 cells relies mainly on innate cytokines but is regulated and fine-tuned by various accessory receptors.

2.2 $\Gamma\delta$ treg cells

Treg are a kind of T cell subsets that control autoimmunity *in vivo*. Regulatory T cells can be divided into natural regulatory T cells (nTreg) and induced adaptive regulatory T cells (iTreg or iTreg), such as Th3 and Tr1. In addition, CD8 Treg and NKT cells are closely related to the occurrence of autoimmune diseases since their abnormal expression can lead to autoimmune diseases. Tr1 cells secrete IL-10 and Th3 cells secrete TGF- β , while in 1995, Sakaguchi found that nearly 10% of the peripheral CD4⁺ T cells in adult mice expressed the IL-2 receptor α chain CD25. Removal of these cells leads to a variety of autoimmune diseases in mice, and reinfusion of these cells can prevent the occurrence of such diseases. In addition, Treg cell activity is affected by many cytokine interactions in the thymus, which is essential for maintaining self-tolerance^[81]. Therefore we herein refer to these cells as CD4⁺ CD25⁺ Treg

Studies have shown that Treg cells play a key role in the occurrence and development of immune diseases. Treg cells can inhibit the proliferation of T cells and the production of cytokines,

and play an important role in the prevention of autoimmunity. In the presence of IL-10 and TGF- β , repeated stimulation of TCR can induce Treg production. IL-2 is also essential for Treg cell homeostasis, function and development since in the absence of IL-2, Treg cells are unable to proliferate and survive^[82–84].

There are similarities and differences between iTreg and nTreg cells. iTreg is similar to nTreg in phenotype and function, but there are differences in their epigenetic state and stability^[85]. It is known that Treg can inhibit effector T lymphocytes by three mechanisms. First, through direct contact inhibition, Treg cells can produce IL-10, IL-35, TGF- β , galectin-1 and other inhibitory cytokines, as well as cytotoxic factors and perforin release^[86]. Second, through the release of granular enzymes, such as a serine protease family called granzyme. Finally, through the interference of the metabolism of target cells mainly through IL-2, CD39 and CD73 pathways^[87].

Treg cells play an important role in inhibiting infection, maintaining autoimmune tolerance and tumor induced-immune responses. Forkhead box protein-3 (Foxp3) is a transcription factor for Treg cell differentiation. TGF- β is also involved in Treg cell differentiation. Treg cells play a protective role in the tissue damage of infectious diseases by producing immune tolerance to autoantigen and inhibiting autoimmune reaction. From mature T cells in the thymus to peripheral tissues, natural Treg cells inhibit the activated T cells, while adaptive Treg cells inhibit initial T cells in peripheral lymphoid tissues after antigen activation.

It was reported that TGF- β 1 and IL-15 can induce Foxp3⁺ $\gamma\delta$ Treg cells, thus inhibiting the proliferation of PBMC-stimulated cells by anti-CD3 and anti-CD28 antibodies^[88]. Indeed, anti-human TCRV δ 1 antibody and TGF- β 1 *in vitro* expanded V δ 1 T cells that mainly expressed Foxp3, CD25, glucocorticoid-induced TNFR family-related proteins and CTLA4, all of which inhibit the proliferation of CD4⁺ T cells^[89]. IP-10 secreted by breast cancer cells can induce the infiltration of $\gamma\delta$ Treg cells, thereby inhibiting T cell response and DC maturation^[90]. These regulated $\gamma\delta$ T cells lack the expression of Foxp3, girt and CD25, and their inhibitory activity does not produce TGF- β 1 or IL-10. These studies identified a new subtype of $\gamma\delta$ Treg, whose CD39 expression accounted for 60% of $\gamma\delta$ T17 cells and were polarized by TGF- β 1. Therefore, this subset has a stronger immunosuppressive effect than that of CD4⁺ Treg cells in colorectal cancer. These CD39⁺ $\gamma\delta$ Treg cells inhibited the activity of human CD3⁺ T cells in an adenosine-dependent manner^[91].

In the presence of TGF- β 1 and IL-2, $\gamma\delta$ Treg cells can be produced by anti TCR $\gamma\delta$ stimulation *in vitro*. Similar to CD4⁺ Foxp3⁺ Tregs, $\gamma\delta$ Tregs also express Foxp3. In addition, Foxp3⁺ $\gamma\delta$ T cells mainly belong to the V δ 1 subset with a CD25⁺ CD27⁺ CD45RA2 phenotype. These cells show effective immunosuppressive function at least *in vitro* through an intercellular contact mechanism^[92]. As a recently reported subset of $\gamma\delta$ T cells, $\gamma\delta$ Treg cells are characterized by simultaneous expression of TCR $\gamma\delta$ and Foxp3 and have a potential immunosuppressive function. A previous report shows that Foxp3⁺ $\gamma\delta$ Tregs are involved in some diseases, which may inhibit the activation and function of T cells involved in antigen-specific immune responses^[93]. Moreover, Treg cells can be recruited into the tumor microenvironment through immunosuppressive and metabolic factors^[94].

The immunosuppressive activity of Tregs is one of the mechanisms that promote carcinogenesis^[95]. The frequency of Foxp3⁺ Tregs and CD8⁺ T cells and the density ratio of A2AR⁺/CD8⁺ T cells, CD39⁺/Foxp3⁺ Treg and CD73⁺/Foxp3⁺ Treg were detected by a multiplex immunofluorescence method. Tregs in gastric cancer metabolizes ATP into adenosine through

A2AR pathway, while it induces apoptosis, inhibits the proliferation of CD8⁺ T cells, and leads to the immune escape of gastric cancer^[96]. Data indicate that the IL6-adenosine loop between CD73⁺γδTregs and CAFs is important to promote immunosuppression and tumor progression in human breast cancer, which may be critical for tumor immunotherapy^[97]. Consequently, modulating CD73 or cancer-derived adenosine in the tumor microenvironment emerges as an attractive novel therapeutic strategy to limit tumor progression, improve antitumor immune responses, avoid therapy-induced immune deviation, and potentially limit normal tissue toxicity^[98]. In addition, it was the first description that IL-23R-expressing γδT cells can inhibit regulatory T cells from two pathways after being activated by IL-23. First by inhibiting the differentiation of Treg and second through directly inhibiting the function of Treg^[63]. However, the full mechanism of IL-23-activated γδ T cells inhibiting regulatory T cells is still unclear. The discovery of specific active molecules that inhibit Treg can lead to novel clinical therapeutic targets. It may also be a new therapeutic strategy to use Treg-mediated immune regulation and immunosuppression mechanisms in the treatment of asthma.

Regulatory cells include regulatory T cells (Tregs) and regulatory B cells (Bregs), which play important roles in immune modulation^[99–101]. There are importances of Bregs in the pathobiology of different diseases, including graft rejection and tolerance mechanisms^[102]. Flores-Borja, F. et al. proposed a dual capacity of CD19⁺CD24^{hi}CD38^{hi} Bregs in maintaining the pool of Tregs and Th1/Th17 populations through controlling over-production of proinflammatory cytokines, preventing engagement of CD4 with Th1 and Th17 and participating in converting effector T cells into Tregs^[103]. Studies have shown that, healthy CD19⁽⁺⁾CD24^(hi)CD38^(hi) B cells inhibited naïve T cell differentiation into T helper 1 (T(H)1) and T(H)17 cells and converted CD4⁽⁺⁾CD25⁽⁻⁾ T cells into regulatory T cells (T(regs)), in part through the production of IL-10. However, in patients with Active rheumatoid arthritis, CD19⁽⁺⁾CD24^(hi)CD38^(hi) B cells with regulatory function may fail to prevent the development of autoreactive responses and inflammation, leading to autoimmunity^[103]. Tregs, Th17 cells and their balance are considered central for the homeostasis of immune responses and tolerance^[104 105]. An imbalance of these cells is closely linked to the pathogenesis of various diseases and conditions, including autoimmunity, transplant rejection and carcinogenesis^[106 107]. A correlation between decreased Tregs and the incidence of bronchiolitis obliterans syndrome (BOS) has been reported in lung transplantation recipients^[108]. In addition to Tregs being decreased or suppressed post transplantation, such as acute rejection may suppress the regulatory activity of Tregs. Patients in the acute rejection showed a predominance of Th17 cells, both in BAL and peripheral blood, and simultaneous impairment of Tregs resulting in a depressed Treg/Th17 ratio^[109]. The role of Tregs and Th17 cells in lung rejection has been widely investigated and the networks involving them have been proposed in a new immunological approach to transplantation^[110 111].

3. Role of γδT17/γδTreg cells in asthma

Previous studies show that the key pathogenic basis of asthma is the imbalance between different T cell populations, especially that of the Th1/Th2 and Th17/Treg cells^[112 113]. However, these imbalances cannot fully explain the phenomena of asthma. In parallel, it was shown that γδT cells play a key role in the pathogenesis of asthma^[92 114]. The airway inflammation and AHR induced by γδ T cells are due to the secretion of a large number of inflammatory cytokines that stimulate Th2 type cells to produce eosinophilic inflammation^[3]. As an important source of IL-17 production, γδT can recruit concentrated granulocytes and participate in the occurrence and development of a variety

of inflammatory diseases^[4,5]. IL-17 is associated with airway inflammation, AHR and airway remodeling in asthma^[6-10]. It was found that there was a high concentration of IL-17 in the blood and BALF of asthmatic patients, and it was confirmed that the concentration of IL-17 was positively correlated with the severity of asthma^[115]. Another study has shown that IL-17 may be a target factor for gene-targeted therapy of hormone-resistant asthma^[116]. $\gamma\delta$ T cell subsets were shown to drive the pathogenesis of asthma by increasing the production and release of inflammatory cytokines, and eventually lead to airway remodeling^[114,117]. High levels of IL-17 are associated with airway inflammation, responsiveness and remodeling in asthma^[6,9,10].

There is evidence that Treg cells can improve airway remodeling and restore Th1/Th2 balance through the Dll4/Notch signaling pathway^[118]. TLR3 is highly expressed in mesenchymal stem cells and can increase Treg production through the Notch pathway after activation^[119], while Treg cells can produce IL-10, inhibit Th2 type immune response factors such as IL-4, IL-5, IL-13, and prevent Th cells from secreting IL-17^[120]. TLR3 can induce the differentiation of IL-17-producing T cells under the activation of the TLR3 ligand^[121]. TLR3 can also inhibit food allergy in mice by inducing IFN- γ Foxp3 Treg cells^[122]. IFN- γ Foxp3 Treg cells also play an important role in the occurrence and development of asthma, and TLR3 is also significantly expressed in the lungs. TLR3 may also regulate asthma through this mechanism, which needs further experiments to confirm.

Therefore, the pathogenesis of asthma is very complex, mainly involving the imbalance of Th1/Th2 of $\gamma\delta$ T cells^[25]. In addition, in allergic and autoimmune diseases, the Treg subsets of $\gamma\delta$ T cells are also dysregulated^[23]. There is also the involvement of $\gamma\delta$ T17/ $\gamma\delta$ Treg cells in the occurrence and development of asthma^[123], as shown in OVA-induced asthmatic mice^[13]. Therefore, $\gamma\delta$ Tregs are a newly identified immunosuppressive $\gamma\delta$ T cell subgroup, which is characterized by the expression of TCR and Foxp3^[124].

4. Regulatory role of $\gamma\delta$ T cells in the treatment of asthma

This review attempts to comprehensively cover the influence of $\gamma\delta$ T cells on the occurrence and development of asthma. Therefore, it is important to use this new understanding to develop new methods for the diagnosis and treatment of asthma. Although $\gamma\delta$ T17/ $\gamma\delta$ Treg cells are a subset of T cells, they play a key role in the process of asthma, as discussed above. In order to utilize the intrinsic activity of $\gamma\delta$ T17/ $\gamma\delta$ Treg cells for asthma immunotherapy, it is essential to better characterize the human $\gamma\delta$ T cell subsets and the mechanisms involved in various types of asthma. It is also necessary to understand the differentiation stage, activation status and central paradigm of immune checkpoint receptor expression of $\gamma\delta$ T cells, so that these can be activated persistently with effective anti-asthma medications. In asthma, $\gamma\delta$ T cells proliferate and activate, and the proportion of $\gamma\delta$ T cells change, showing a dominant response of $\gamma\delta$ T17. Through the activated $\gamma\delta$ T cells, the airway inflammatory response is regulated, and the specific mechanism needs to be studied.

Important questions should be addressed. First, whether the inhibition of $\gamma\delta$ T17 cells is beneficial to asthma patients. Second, if $\gamma\delta$ Treg can inhibit the Notch signaling pathway, regulate Th1/Th2 differentiation in asthma. Third, if it is possible to increase the immunosuppressive function of Tregs by inhibiting active molecules of $\gamma\delta$ T cells expressing IL-23R. Finally, if TLR3 can activate the immune response of Tregs through the overexpression of IFN- γ Foxp3 Treg cells.

Altogether, we are now in a favorable position to study asthma from the perspective of developmental biology and immune mechanisms, which will continue to provide valuable insights into the underlying role of $\gamma\delta$ T cells. The role of $\gamma\delta$ T cells in asthma is therefore a novel field of research. Since $\gamma\delta$ T cells are heterogeneous, it is necessary to thoroughly study the pro- and anti-asthmatic properties of different subpopulations of $\gamma\delta$ T cells, and use these to maximize the efficacy of immunotherapy.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

References

- [1] Cheng M, Hu S. Lung-resident $\gamma\delta$ T cells and their roles in lung diseases [J]. Immunology, 2017, 151(4): 375.
- [2] Yang L Y, Li X, Li W T, et al. Vgamma1(+) gammadeltaT Cells Are Correlated With Increasing Expression of Eosinophil Cationic Protein and Metalloproteinase-7 in Chronic Rhinosinusitis With Nasal Polyps Inducing the Formation of Edema [J]. Allergy, asthma & immunology research, 2017, 9(2): 142-51.
- [3] Sun X, Cai Y, Fleming C, et al. Innate $\gamma\delta$ T17 cells play a protective role in DSS-induced colitis via recruitment of Gr-1(+)CD11b(+) myeloid suppressor cells [J]. Oncoimmunology, 2017, 6(5): e1313369.
- [4] Nakada E M, Shan J, Kinyanjui M W, et al. Adjuvant-dependent regulation of interleukin-17 expressing $\gamma\delta$ T cells and inhibition of Th2 responses in allergic airways disease [J]. Respiratory Research, 2014, 15(1): 1-14.
- [5] Fengyun Z, Dawei C, Hong T, et al. IL-17A-producing T cells and associated cytokines are involved in the progression of gastric cancer [J]. Oncology Reports, 2015, 34(5): 2365-74.
- [6] Silva M D J, Santana M B R D, Tosta B R, et al. Variants in the IL17 pathway genes are associated with atopic asthma and atopy makers in a South American population [J]. Allergy Asthma and Clinical Immunology, 2019, 15(1): 1-14.
- [7] Kinyanjui M W, Jichuan S, Nakada E M, et al. Dose-dependent effects of IL-17 on IL-13-induced airway inflammatory responses and airway hyperresponsiveness [J]. Journal of Immunology, 2013, 190(8): 3859-68.
- [8] Hisako H, Akiko K, Shintaro O, et al. IL-17A/F modulates fibrocyte functions in cooperation with CD40-mediated signaling [J]. Inflammation, 2013, 36(4): 830-8.
- [9] Chiba Y, Tanoue G, Suto R, et al. Interleukin-17A directly acts on bronchial smooth muscle cells and augments the contractility [J]. Pharmacological Reports, 2016, 69(3): 377-85.
- [10] Whitehead G S, Kang H S, Thomas S Y, et al. Therapeutic suppression of pulmonary neutrophilia and allergic airway hyperresponsiveness by a RORgamma inverse agonist [J]. JCI insight, 2019, 5(1): 1-14.
- [11] Wu P, Dang W, Chao N, et al. $\gamma\delta$ T17 Cells Promote the Accumulation and Expansion of Myeloid-Derived Suppressor Cells in Human Colorectal Cancer [J]. Immunity, 2014, 40(5): 785-800.
- [12] Papotto P H, Ribot J C, Silva-Santos B. IL-17+ $\gamma\delta$ T cells as kick-starters of inflammation [J]. Nature Immunology, 2017, 18(6): 604.
- [13] Liao Y, Wu Q, Kelly B C, et al. Effectiveness of a text-messaging-based smoking cessation intervention ("Happy Quit") for smoking cessation in China: A randomized controlled trial [J]. PLoS medicine, 2018, 15(12): e1002713.
- [14] Ning K, Long T, Xiaoyan L, et al. Identification and characterization of Foxp3(+) gammadelta T cells in mouse and human [J]. Immunology Letters, 2009, 125(2): 105-13.
- [15] Carding S R, Egan P J. Gammadelta T cells: functional plasticity and heterogeneity [J]. Nature reviews. Immunology, 2002, 2(5): 336-45.
- [16] Lu H, Li D J, Jin L P. $\gamma\delta$ T Cells and Related Diseases [J]. American journal of reproductive immunology (New York, N.Y. : 1989), 2016, 75(6): 609-18.

- [17] Martin B, Hirota K, Cua D J, et al. Interleukin-17-producing gammadelta T cells selectively expand in response to pathogen products and environmental signals [J]. *Immunity*, 2009, 31(2): 321-30.
- [18] Muschaweckh A, Petermann F, Korn T. IL-1 β and IL-23 Promote Extrathymic Commitment of CD27(+)CD122(-) $\gamma\delta$ T Cells to $\gamma\delta$ T17 Cells [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2017, 199(8): 2668-79.
- [19] Huang H, Saravia J, You D, et al. Impaired gamma delta T cell-derived IL-17A and inflammasome activation during early respiratory syncytial virus infection in infants [J]. *Immunology and cell biology*, 2015, 93(2): 126-35.
- [20] Zuany-Amorim C, Ruffié C, Hailé S, et al. Requirement for gammadelta T cells in allergic airway inflammation [J]. *Science* (New York, N.Y.), 1998, 280(5367): 1265-7.
- [21] Newcomb D C, Boswell M G, Sherrill T P, et al. IL-17A induces signal transducers and activators of transcription-6-independent airway mucous cell metaplasia [J]. *American journal of respiratory cell and molecular biology*, 2013, 48(6): 711-6.
- [22] Huang Y, Jin N, Roark C L, et al. The influence of IgE-enhancing and IgE-suppressive gammadelta T cells changes with exposure to inhaled ovalbumin [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2009, 183(2): 849-55.
- [23] Roark C L, Simonian P L, Fontenot A P, et al. gammadelta T cells: an important source of IL-17 [J]. *Curr Opin Immunol*, 2008, 20(3): 353-7.
- [24] Hahn Y S, Taube C, Jin N, et al. V gamma 4+ gamma delta T cells regulate airway hyperreactivity to methacholine in ovalbumin-sensitized and challenged mice [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2003, 171(6): 3170-8.
- [25] Murdoch J R, Gregory L G, Lloyd C M. $\gamma\delta$ T cells regulate chronic airway inflammation and development of airway remodelling [J]. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*, 2014, 44(11): 1386-98.
- [26] Korematsu S, Tanaka Y, Nagakura T, et al. Human gammadelta T cells modulate the mite allergen-specific T-helper type 2-skewed immunity [J]. *Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology*, 2007, 37(11): 1681-7.
- [27] Zheng R, Yang Q. The role of the $\gamma\delta$ T cell in allergic diseases [J]. *Journal of immunology research*, 2014, 2014(963484).
- [28] Urboniene D, Babusyte A, Lötval J, et al. Distribution of $\gamma\delta$ and other T-lymphocyte subsets in patients with chronic obstructive pulmonary disease and asthma [J]. *Respiratory medicine*, 2013, 107(3): 413-23.
- [29] Das S, Khader S. Yin and yang of interleukin-17 in host immunity to infection [J]. *F1000Research*, 2017, 6(741).
- [30] Muñoz-Ruiz M, Sumaria N, Pennington D J, et al. Thymic Determinants of $\gamma\delta$ T Cell Differentiation [J]. *Trends in immunology*, 2017, 38(5): 336-44.
- [31] Ribot J C, Debarros A, Pang D J, et al. CD27 is a thymic determinant of the balance between interferon-gamma- and interleukin 17-producing gammadelta T cell subsets [J]. *Nature immunology*, 2009, 10(4): 427-36.
- [32] Haas J D, González F H, Schmitz S, et al. CCR6 and NK1.1 distinguish between IL-17A and IFN-gamma-producing gammadelta effector T cells [J]. *European journal of immunology*, 2009, 39(12): 3488-97.
- [33] Jensen K D, Su X, Shin S, et al. Thymic selection determines gammadelta T cell effector fate: antigen-naïve cells make interleukin-17 and antigen-experienced cells make interferon gamma [J]. *Immunity*, 2008, 29(1): 90-100.
- [34] O'brien R L, Born W K. gammadelta T cell subsets: a link between TCR and function? [J]. *Seminars in immunology*, 2010, 22(4): 193-8.
- [35] Romani L, Fallarino F, De Luca A, et al. Defective tryptophan catabolism underlies inflammation in mouse chronic granulomatous disease [J]. *Nature*, 2008, 451(7175): 211-5.
- [36] Heilig J S, Tonegawa S. Diversity of murine gamma genes and expression in fetal and adult T lymphocytes [J]. *Nature*, 1986, 322(6082): 836-40.
- [37] Narayan K, Sylvia K E, Malhotra N, et al. Intrathymic programming of effector fates in three molecularly distinct $\gamma\delta$ T cell subtypes [J]. *Nature immunology*, 2012, 13(5): 511-8.
- [38] Malhotra N, Narayan K, Cho O H, et al. A network of high-mobility group box transcription factors programs innate interleukin-17 production [J]. *Immunity*, 2013, 38(4): 681-93.

- [39] Lochner M, Peduto L, Cherrier M, et al. In vivo equilibrium of proinflammatory IL-17+ and regulatory IL-10+ Foxp3+ RORgamma t+ T cells [J]. *The Journal of experimental medicine*, 2008, 205(6): 1381-93.
- [40] Schmolka N, Serre K, Grosso A R, et al. Epigenetic and transcriptional signatures of stable versus plastic differentiation of proinflammatory $\gamma\delta$ T cell subsets [J]. *Nature immunology*, 2013, 14(10): 1093-100.
- [41] Barros-Martins J, Schmolka N, Fontinha D, et al. Effector $\gamma\delta$ T Cell Differentiation Relies on Master but Not Auxiliary Th Cell Transcription Factors [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2016, 196(9): 3642-52.
- [42] Schmolka N, Wencker M, Hayday A C, et al. Epigenetic and transcriptional regulation of $\gamma\delta$ T cell differentiation: Programming cells for responses in time and space [J]. *Seminars in immunology*, 2015, 27(1): 19-25.
- [43] Sutton C E, Lallor S J, Sweeney C M, et al. Interleukin-1 and IL-23 induce innate IL-17 production from gammadelta T cells, amplifying Th17 responses and autoimmunity [J]. *Immunity*, 2009, 31(2): 331-41.
- [44] Ribot J C, Chaves-Ferreira M, D'orey F, et al. Cutting edge: adaptive versus innate receptor signals selectively control the pool sizes of murine IFN- γ - or IL-17-producing $\gamma\delta$ T cells upon infection [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2010, 185(11): 6421-5.
- [45] Li F, Hao X, Chen Y, et al. The microbiota maintain homeostasis of liver-resident $\gamma\delta$ T-17 cells in a lipid antigen/CD1d-dependent manner [J]. *Nature communications*, 2017, 7(13839).
- [46] Reynolds J M, Martinez G J, Chung Y, et al. Toll-like receptor 4 signaling in T cells promotes autoimmune inflammation [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2012, 109(32): 13064-9.
- [47] Sheridan B S, Romagnoli P A, Pham Q M, et al. $\gamma\delta$ T cells exhibit multifunctional and protective memory in intestinal tissues [J]. *Immunity*, 2013, 39(1): 184-95.
- [48] Rei M, Gonçalves-Sousa N, Lança T, et al. Murine CD27(-) V γ 6(+) $\gamma\delta$ T cells producing IL-17A promote ovarian cancer growth via mobilization of protumor small peritoneal macrophages [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2014, 111(34): E3562-70.
- [49] Wencker M, Turchinovich G, Di Marco Barros R, et al. Innate-like T cells straddle innate and adaptive immunity by altering antigen-receptor responsiveness [J]. *Nature immunology*, 2014, 15(1): 80-7.
- [50] Zeng X, Wei Y L, Huang J, et al. $\gamma\delta$ T cells recognize a microbial encoded B cell antigen to initiate a rapid antigen-specific interleukin-17 response [J]. *Immunity*, 2012, 37(3): 524-34.
- [51] Bonneville M, O'brien R L, Born W K. Gammadelta T cell effector functions: a blend of innate programming and acquired plasticity [J]. *Nature reviews. Immunology*, 2010, 10(7): 467-78.
- [52] Cua D J, Tato C M. Innate IL-17-producing cells: the sentinels of the immune system [J]. *Nature reviews. Immunology*, 2010, 10(7): 479-89.
- [53] O'brien R L, Roark C L, Born W K. IL-17-producing gammadelta T cells [J]. *European journal of immunology*, 2009, 39(3): 662-6.
- [54] Lallor S J, Dungan L S, Sutton C E, et al. Caspase-1-processed cytokines IL-1 β and IL-18 promote IL-17 production by gammadelta and CD4 T cells that mediate autoimmunity [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2011, 186(10): 5738-48.
- [55] Mills K H. Induction, function and regulation of IL-17-producing T cells [J]. *European journal of immunology*, 2008, 38(10): 2636-49.
- [56] Hamada S, Umemura M, Shiono T, et al. IL-17A produced by gammadelta T cells plays a critical role in innate immunity against listeria monocytogenes infection in the liver [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2008, 181(5): 3456-63.
- [57] Lockhart E, Green A M, Flynn J L. IL-17 production is dominated by gammadelta T cells rather than CD4 T cells during Mycobacterium tuberculosis infection [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2006, 177(7): 4662-9.
- [58] Shibata K, Yamada H, Hara H, et al. Resident V δ 1+ gammadelta T cells control early infiltration of neutrophils after Escherichia coli infection via IL-17 production [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2007, 178(7): 4466-72.

- [59] Cho J S, Pietras E M, Garcia N C, et al. IL-17 is essential for host defense against cutaneous *Staphylococcus aureus* infection in mice [J]. *J Clin Invest*, 2010, 120(5): 1762-73.
- [60] Hayday A C. Gammadelta T cells and the lymphoid stress-surveillance response [J]. *Immunity*, 2009, 31(2): 184-96.
- [61] Ma Y, Aymeric L, Locher C, et al. Contribution of IL-17-producing gamma delta T cells to the efficacy of anticancer chemotherapy [J]. *The Journal of experimental medicine*, 2011, 208(3): 491-503.
- [62] Hirota K, Duarte J H, Veldhoen M, et al. Fate mapping of IL-17-producing T cells in inflammatory responses [J]. *Nature immunology*, 2011, 12(3): 255-63.
- [63] Petermann F, Rothhammer V, Claussen M C, et al. $\gamma\delta$ T cells enhance autoimmunity by restraining regulatory T cell responses via an interleukin-23-dependent mechanism [J]. *Immunity*, 2010, 33(3): 351-63.
- [64] Shichita T, Sugiyama Y, Ooboshi H, et al. Pivotal role of cerebral interleukin-17-producing gammadeltaT cells in the delayed phase of ischemic brain injury [J]. *Nature medicine*, 2009, 15(8): 946-50.
- [65] Puel A, Cypowyj S, Bustamante J, et al. Chronic mucocutaneous candidiasis in humans with inborn errors of interleukin-17 immunity [J]. *Science (New York, N.Y.)*, 2011, 332(6025): 65-8.
- [66] Van De Veerdonk F L, Plantinga T S, Hoischen A, et al. STAT1 mutations in autosomal dominant chronic mucocutaneous candidiasis [J]. *The New England journal of medicine*, 2011, 365(1): 54-61.
- [67] O'brien R L, Born W K. Two functionally distinct subsets of IL-17 producing $\gamma\delta$ T cells [J]. *Immunological reviews*, 2020, 298(1): 10-24.
- [68] Caccamo N, La Mendola C, Orlando V, et al. Differentiation, phenotype, and function of interleukin-17-producing human V γ 9V δ 2 T cells [J]. *Blood*, 2011, 118(1): 129-38.
- [69] Moens E, Brouwer M, Dimova T, et al. IL-23R and TCR signaling drives the generation of neonatal Vgamma9Vdelta2 T cells expressing high levels of cytotoxic mediators and producing IFN-gamma and IL-17 [J]. *Journal of leukocyte biology*, 2011, 89(5): 743-52.
- [70] Debarros A, Chaves-Ferreira M, D'orey F, et al. CD70-CD27 interactions provide survival and proliferative signals that regulate T cell receptor-driven activation of human $\gamma\delta$ peripheral blood lymphocytes [J]. *European journal of immunology*, 2011, 41(1): 195-201.
- [71] Deknuydt F, Scotet E, Bonneville M. Modulation of inflammation through IL-17 production by gammadelta T cells: mandatory in the mouse, dispensable in humans? [J]. *Immunology letters*, 2009, 127(1): 8-12.
- [72] Ness-Schwickerath K J, Jin C, Morita C T. Cytokine requirements for the differentiation and expansion of IL-17A- and IL-22-producing human Vgamma2Vdelta2 T cells [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2010, 184(12): 7268-80.
- [73] Peng M Y, Wang Z H, Yao C Y, et al. Interleukin 17-producing gamma delta T cells increased in patients with active pulmonary tuberculosis [J]. *Cellular & molecular immunology*, 2008, 5(3): 203-8.
- [74] Jensen K D, Chien Y H. Thymic maturation determines gammadelta T cell function, but not their antigen specificities [J]. *Current opinion in immunology*, 2009, 21(2): 140-5.
- [75] Turchinovich G, Hayday A C. Skint-1 identifies a common molecular mechanism for the development of interferon- γ -secreting versus interleukin-17-secreting $\gamma\delta$ T cells [J]. *Immunity*, 2011, 35(1): 59-68.
- [76] Shibata K, Yamada H, Nakamura R, et al. Identification of CD25+ gamma delta T cells as fetal thymus-derived naturally occurring IL-17 producers [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2008, 181(9): 5940-7.
- [77] Simonian P L, Roark C L, Wehrmann F, et al. IL-17A-expressing T cells are essential for bacterial clearance in a murine model of hypersensitivity pneumonitis [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2009, 182(10): 6540-9.
- [78] Muro R, Nitta T, Nakano K, et al. $\gamma\delta$ TCR recruits the Syk/PI3K axis to drive proinflammatory differentiation program [J]. *The Journal of clinical investigation*, 2018, 128(1): 415-26.
- [79] Bekiaris V, Šedý J R, Macauley M G, et al. The inhibitory receptor BTLA controls $\gamma\delta$ T cell homeostasis and inflammatory responses [J]. *Immunity*, 2013, 39(6): 1082-94.
- [80] Imai Y, Ayithan N, Wu X, et al. Cutting Edge: PD-1 Regulates Imiquimod-Induced Psoriasiform Dermatitis through

- Inhibition of IL-17A Expression by Innate $\gamma\delta$ -Low T Cells [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2015, 195(2): 421-5.
- [81] Sakaguchi S, Sakaguchi N, Asano M, et al. Immunologic self-tolerance maintained by activated T cells expressing IL-2 receptor alpha-chains (CD25). Breakdown of a single mechanism of self-tolerance causes various autoimmune diseases [J]. *Journal of immunology* (Baltimore, Md. : 1950), 1995, 155(3): 1151-64.
- [82] Kondělková K, Vokurková D, Krejsek J, et al. Regulatory T cells (TREG) and their roles in immune system with respect to immunopathological disorders [J]. *Acta medica (Hradec Kralove)*, 2010, 53(2): 73-7.
- [83] Zheng S G, Wang J, Wang P, et al. IL-2 is essential for TGF-beta to convert naive CD4+CD25- cells to CD25+Foxp3+ regulatory T cells and for expansion of these cells [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2007, 178(4): 2018-27.
- [84] Zhang S Y, Jouanguy E, Ugolini S, et al. TLR3 deficiency in patients with herpes simplex encephalitis [J]. *Science (New York, N.Y.)*, 2007, 317(5844): 1522-7.
- [85] Owczarczyk-Saczonek A, Czerwińska J, Placek W. The role of regulatory T cells and anti-inflammatory cytokines in psoriasis [J]. *Acta dermatovenerologica Alpina, Pannonica, et Adriatica*, 2018, 27(1): 17-23.
- [86] Kondelková K, Vokurková D, Krejsek J, et al. The number of immunoregulatory T cells is increased in patients with psoriasis after Goeckerman therapy [J]. *Acta medica (Hradec Kralove)*, 2012, 55(2): 91-5.
- [87] Amin H Z, Sasaki N, Hirata K I. Regulatory T Cell Immunity in Atherosclerosis [J]. *Acta medica Indonesiana*, 2017, 49(1): 63-8.
- [88] Casetti R, Agrati C, Wallace M, et al. Cutting edge: TGF-beta1 and IL-15 Induce FOXP3+ gammadelta regulatory T cells in the presence of antigen stimulation [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2009, 183(6): 3574-7.
- [89] Hua F, Kang N, Gao Y A, et al. Potential regulatory role of in vitro-expanded V δ 1 T cells from human peripheral blood [J]. *Immunologic research*, 2013, 56(1): 172-80.
- [90] Ye J, Ma C, Wang F, et al. Specific recruitment of $\gamma\delta$ regulatory T cells in human breast cancer [J]. *Cancer research*, 2013, 73(20): 6137-48.
- [91] Hu G, Wu P, Cheng P, et al. Tumor-infiltrating CD39(+) $\gamma\delta$ Tregs are novel immunosuppressive T cells in human colorectal cancer [J]. *Oncoimmunology*, 2017, 6(2): e1277305.
- [92] Li X, Kang N, Zhang X, et al. Generation of human regulatory gammadelta T cells by TCRgammadelta stimulation in the presence of TGF-beta and their involvement in the pathogenesis of systemic lupus erythematosus [J]. *Journal of immunology* (Baltimore, Md. : 1950), 2011, 186(12): 6693-700.
- [93] Wu Q, Gupta P K, Suzuki H, et al. CD4 T Cells but Not Th17 Cells Are Required for Mouse Lung Transplant Obliterative Bronchiolitis [J]. *American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons*, 2015, 15(7): 1793-804.
- [94] Mantovani A, Allavena P, Sica A, et al. Cancer-related inflammation [J]. *Nature*, 2008, 454(7203): 436-44.
- [95] Churov A, Zhulai G. Targeting adenosine and regulatory T cells in cancer immunotherapy [J]. *Human immunology*, 2021,
- [96] Shi L, Feng M, Du S, et al. Adenosine Generated by Regulatory T Cells Induces CD8(+) T Cell Exhaustion in Gastric Cancer through A2aR Pathway [J]. *BioMed research international*, 2019, 2019(4093214).
- [97] Hu G, Cheng P, Pan J, et al. An IL6-Adenosine Positive Feedback Loop between CD73(+) $\gamma\delta$ Tregs and CAFs Promotes Tumor Progression in Human Breast Cancer [J]. *Cancer immunology research*, 2020, 8(10): 1273-86.
- [98] De Leve S, Wirsdörfer F, Jendrossek V. Targeting the Immunomodulatory CD73/Adenosine System to Improve the Therapeutic Gain of Radiotherapy [J]. *Frontiers in immunology*, 2019, 10(698).
- [99] Gregson A L, Hoji A, Saggarr R, et al. Bronchoalveolar immunologic profile of acute human lung transplant allograft rejection [J]. *Transplantation*, 2008, 85(7): 1056-9.
- [100] Bergantini L, D'alessandro M, Cameli P, et al. Regulatory T cell monitoring in severe eosinophilic asthma patients treated with mepolizumab [J]. *Scandinavian journal of immunology*, 2021, 94(1): e13031.
- [101] Bergantini L, Cameli P, D'alessandro M, et al. Regulatory T Cells in Severe Persistent Asthma in the Era of

- Monoclonal Antibodies Target Therapies [J]. *Inflammation*, 2020, 43(2): 393-400.
- [102] Rosser E C, Mauri C. Regulatory B cells: origin, phenotype, and function [J]. *Immunity*, 2015, 42(4): 607-12.
- [103] Flores-Borja F, Bosma A, Ng D, et al. CD19+CD24hiCD38hi B cells maintain regulatory T cells while limiting TH1 and TH17 differentiation [J]. *Science translational medicine*, 2013, 5(173): 173ra23.
- [104] Diller M L, Kudchadkar R R, Delman K A, et al. Balancing Inflammation: The Link between Th17 and Regulatory T Cells [J]. *Mediators of inflammation*, 2016, 2016(6309219).
- [105] Bargagli E, Madioni C, Bianchi N, et al. Serum analysis of coagulation factors in IPF and NSIP [J]. *Inflammation*, 2014, 37(1): 10-6.
- [106] Lee G R. The Balance of Th17 versus Treg Cells in Autoimmunity [J]. *International journal of molecular sciences*, 2018, 19(3):
- [107] Knochelmann H M, Dwyer C J, Bailey S R, et al. When worlds collide: Th17 and Treg cells in cancer and autoimmunity [J]. *Cellular & molecular immunology*, 2018, 15(5): 458-69.
- [108] Mamessier E, Lorec A M, Thomas P, et al. T regulatory cells in stable posttransplant bronchiolitis obliterans syndrome [J]. *Transplantation*, 2007, 84(7): 908-16.
- [109] Bergantini L, D'alessandro M, De Vita E, et al. Regulatory and Effector Cell Disequilibrium in Patients with Acute Cellular Rejection and Chronic Lung Allograft Dysfunction after Lung Transplantation: Comparison of Peripheral and Alveolar Distribution [J]. *Cells*, 2021, 10(4):
- [110] Nakagiri T, Inoue M, Minami M, et al. Immunology mini-review: the basics of T(H)17 and interleukin-6 in transplantation [J]. *Transplantation proceedings*, 2012, 44(4): 1035-40.
- [111] Neujahr D C, Larsen C P. Regulatory T cells in lung transplantation--an emerging concept [J]. *Seminars in immunopathology*, 2011, 33(2): 117-27.
- [112] Ming M, Luo Z, Lv S, et al. Inhalation of inactivated-*Mycobacterium phlei* prevents asthma-mediated airway hyperresponsiveness and airway eosinophilia in mice by reducing IL-5 and IL-13 levels [J]. *Molecular medicine reports*, 2016, 14(6): 5343-9.
- [113] Yang X, Zhang J H, Deng W S, et al. Imbalance of $\gamma\delta$ T17/ $\gamma\delta$ Treg cells in the pathogenesis of allergic asthma induced by ovalbumin [J]. *Brazilian journal of medical and biological research = Revista brasileira de pesquisas medicas e biologicas*, 2018, 51(9): e7127.
- [114] Hahn Y S, Taube C, Jin N, et al. Different potentials of gamma delta T cell subsets in regulating airway responsiveness: V gamma 1+ cells, but not V gamma 4+ cells, promote airway hyperreactivity, Th2 cytokines, and airway inflammation [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2004, 172(5): 2894-902.
- [115] Chesné J, Braza F, Mahay G, et al. IL-17 in Severe Asthma. Where Do We Stand? [J]. *American Journal of Respiratory & Critical Care Medicine*, 2014, 190(10): 1094-101.
- [116] Choy D F, Hart K M, Borthwick L A, et al. TH2 and TH17 inflammatory pathways are reciprocally regulated in asthma [J]. *Science translational medicine*, 2015, 7(301): 301ra129.
- [117] Glanville N, Message S D, Walton R P, et al. $\gamma\delta$ T cells suppress inflammation and disease during rhinovirus-induced asthma exacerbations [J]. *Mucosal immunology*, 2013, 6(6): 1091-100.
- [118] Huang M T, Dai Y S, Chou Y B, et al. Regulatory T cells negatively regulate neovasculature of airway remodeling via DLL4-Notch signaling [J]. *Journal of immunology (Baltimore, Md. : 1950)*, 2009, 183(7): 4745-54.
- [119] Rashedi I, Gómez-Aristizábal A, Wang X H, et al. TLR3 or TLR4 Activation Enhances Mesenchymal Stromal Cell-Mediated Treg Induction via Notch Signaling [J]. *Stem cells (Dayton, Ohio)*, 2017, 35(1): 265-75.
- [120] Boonpiyathad T, Satitsuksanoa P, Akdis M, et al. IL-10 producing T and B cells in allergy [J]. *Seminars in immunology*, 2019, 44(101326).
- [121] Veldhoen M, Hocking R J, Atkins C J, et al. TGFbeta in the context of an inflammatory cytokine milieu supports de novo differentiation of IL-17-producing T cells [J]. *Immunity*, 2006, 24(2): 179-89.
- [122] Hong J Y, Li S S, Hu T Y, et al. Frontline Science: TLR3 activation inhibits food allergy in mice by inducing IFN- γ (+)

Foxp3(+) regulatory T cells [J]. *Journal of leukocyte biology*, 2019, 106(6): 1201-9.

[123] Zhao J, Lloyd C M, Noble A. Th17 responses in chronic allergic airway inflammation abrogate regulatory T-cell-mediated tolerance and contribute to airway remodeling [J]. *Mucosal immunology*, 2013, 6(2): 335-46.

[124] Kang N, Tang L, Li X, et al. Identification and characterization of Foxp3(+) gammadelta T cells in mouse and human [J]. *Immunology letters*, 2009, 125(2): 105-13.

Accepted Manuscript