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Review

Title of article: Mucosal-associated invariant T cells in lung diseases

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ABSTRACT

The lungs are directly connected to the external environment, which makes them more vulnerable to infection and injury. They are protected by the respiratory epithelium and immune cells to maintain a dynamic balance. Both innate and adaptive immune cells are involved in the pathogenesis of lung diseases. Mucosal-associated invariant T (MAIT) cells are a subset of unconventional T cells, which have attracted increasing attention in recent years. Although MAIT cells account for a small part of the total immune cells in the lungs, evidence suggests that these cells are activated by T cell receptors and/or cytokine receptors and mediate immune response. They play an important role in immunosurveillance and immunity against microbial infection, and recent studies have shown that subsets of MAIT cells play a role in promoting pulmonary inflammation. Emerging data indicate that MAIT cells are involved in the immune response against SARS-CoV-2 and possible immunopathogenesis in COVID-19. Here, we introduce MAIT cell biology to clarify their role in the immune response. Then we review MAIT cells in human and murine lung diseases, including asthma, chronic obstructive pulmonary disease, pneumonia, pulmonary tuberculosis and lung cancer, and discuss their possible protective and pathological effects. MAIT cells represent an attractive marker and potential therapeutic target for disease progression, thus providing new strategies for the treatment of lung diseases.

1. Introduction

Respiratory diseases are common and mainly involve the lungs, trachea and chest. Most patients with mild lesions have respiratory symptoms such as cough, shortness of breath, and respiratory disturbance. Severe diseases can lead to hypoxia, lung tissue injury and even respiratory failure and death. The lungs are constantly exposed to particulates from the environment. These inhaled substances include uninjurious aeroallergens, airborne pathogens that can result in infection, and noxious substances including smoke, dust, and other environmental pollutants that can induce lung tissue damage. When the body is infected or inflamed, the mucosal barrier and immune cells of the lungs play a defensive role in the development of lung diseases. Recent studies have revealed the existence of a group of immune cells called innate-like lymphocytes in the lungs that act as key sensors of lung insults and direct the pulmonary immune response, including invariant natural killer T (iNKT) cells and mucosal-associated invariant T (MAIT) cells [1,2]. They become participants in pulmonary mucosal

Abbreviations: MAIT, Mucosal-associated invariant T; iNKT, invariant natural killer T; TCR, T cell receptor; MHC, major histocompatibility complex; MR1, MHC-related protein 1; CD, Cluster of Differentiation; 6-FP, 6 formylpterin; 5-OE-RU, 5-(2-oxoethylideneamino)-5-dribitylaminouracil; 5-OP-RU, 5-(2-oxopropylideneamino)-5-dribitylaminouracil; DN, double negative; RORγt, retinoic-acid-related orphan receptor γt; STAT3, signal transducer and activator of transcription 3; PLZF, promyelocytic leukemia zinc finger; CCR, CC receptor; CXCR, chemokine CXC receptor; IL, interleukin; TLR, Toll-like receptor; APC, antigen presenting cell; Th, T helper; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; GM-CSF, granulocyte–macrophage colony-stimulating factor; Gzm, granzyme; SLE, systemic lupus erythematosus; AHR, airway hyper responsiveness; BALF, bronchoalveolar lavage fluid; ILCs, innate lymphoid cells; FEV1, forced expiratory volume in the first second; IL4I1, interleukin-4-induced gene 1; COPD, Chronic obstructive pulmonary disease; CAP, Community-acquired pneumonia; HIF-1α, hypoxia-inducible factor-1α; TCF7, transcription factor 7; COVID-19, coronavirus disease 2019; PD-1, programmed cell death protein 1; TB, tuberculosis; CF, cystic fibrosis; HLA-DR, human leukocyte antigen DR.

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immunity and play a role in pulmonary homeostasis.

These innate T cells are unconventional T cells share the same characteristics as innate and adaptive immunity, recognizing antigens through T cell receptors (TCRs) and being stimulated by cytokines directly [3]. Over the past few decades, the development of gene-targeted mice and tetramers has increased interest in the function and role of unconventional T cells in tissue homeostasis and disease [4-6]. There is increasing evidence to indicate that MAIT cells quickly recognize microbial metabolites antigenic ligands presented by conserved MHC-I-related molecule MR1 [7], they have an important role in innate immunity to pathogens. MAIT cells are found in human blood, lungs, and intestinal mucosa, and they secrete cytokines to exert their effects when they are activated by inflammatory cytokines and microbial antigens [8,9]. Studies have described the related biological functions of MAIT cells as well as harmful and protective effects in autoimmune, inflammatory, metabolic diseases [10,11]. Recent reports have demonstrated the role of MAIT cells as an early innate immune response against pathogenic invasion of the lungs.

This review focuses on the immunoregulation and balance of MAIT cells in lung diseases and discusses the mechanism by which these cells affect disease severity. Although this is a rapidly developing field, many studies have hinted at the importance and treatment opportunities of MAIT cells, suggesting that may be an important target for future immunotherapy.

2. Basic characteristics and performance of MAIT cells

2.1. Characteristics and phenotype of MAIT cells

In 1993, Porcelli et al. [12] discovered $CD4^{-}CD8^{-}\alpha\beta$T cells in peripheral blood of healthy volunteers for the first time, which showed that invariant TCRα chain was preferentially bound to multiple Vβ genes. These genes were remarkably conservative across mammalian species. Later, researchers found that the semi-invariant TCRα chain of iNKT cells mainly expressed Vα24-Jα18 (TRAV10-TRAJ18) in humans and an orthologous Vα14-Jα18 (TRAV11-TRAJ18) in mice. Another called MAIT cells expressed Vα7.2-Jα33 (TRAV1-2-TRAJ33) [12,13] in humans and Vα19-Jα33 (TRAV1-TRAJ33) [13] in mice, while the limited TCRβ chain mainly expressed Vβ2 (TRBV20) and Vβ13 (TRBV6) in humans, and Vβ6 (TRBV19) and Vβ8 (TRBV13) in mice [13,14]. Until 2003, Treiner et al. [15] found that these new T cell subsets were preferentially located in the lamina propria of the gut of humans and mice, and they were named MAIT cells. The interaction of iNKT and MAIT cells suggests that they have important, nonredundant functions in the immune response.

Later, studies have shown that MAIT cells recognize derivatives of vitamin B2 (riboflavin) and vitamin B9 (folic acid) [7,16-20] produced by highly conserved biosynthetic pathways in bacteria and yeast, but not viruses [17,21], as well as drug-like molecules [22]. MAIT cells recognize ligand such as 6 formylpterin (6-FP) as an inhibitor, which was the first MR1 ligand described [23]. Recent studies have reported new ligands such as 5-(2-oxoethylideneamino)-5-dribitylaminouracil (5-OE-RU), and 5-(2-oxopropylideneamino)-5-dribitylaminouracil (5-OP-RU), which are the most potent activating ligands identified to date, but they are unstable, nonenzymatic intermediates of riboflavin biosynthesis [16,20,24].

MAIT cells can be classified as different subsets. In humans, MAIT cells express high levels of type C lectin-like receptor CD161 [14,23,25], which can be used to recognize MAIT cells with Vα7.2TCRα chain, and this is consistent with the recognition of MAIT cells by MR1-tetramer staining [14,20,26,27]. Through antigen-loaded MR1 tetramer detection and co-receptor expression of CD4 and CD8, MAIT cells can be divided into three subtypes: $CD4^{-}CD8^{+}$ (70–90%) and $CD4^{-}CD8^{-}$ (double negative, DN) (10–20%), and a small population of $CD4^{+}CD8^{-}$ [29]. The expression of $CD8^{+}$ MAIT cells in human peripheral blood includes CD8αα homodimer and CD8αβ heterodimer [14,25,28,29]. MAIT cells also consist of the three subsets in wild-type BALB/C mice, with frequencies varying among different tissues and strains [25]. Moreover, MAIT cells also can be divided into MAIT-1 and MAIT-17 according to the production of cytokines [26,30].

The phenotype of MAIT cells is closely related to their function (Fig. 1). In adult blood, MAIT cells show the effector memory phenotype $CD45RO^{+}CD27^{+}CD122^{+}CD95^{hi}CD62L^{lo}CD45RA^{lo}$ [25,30]. In the thymus and cord blood, MAIT cells exhibit a naïve phenotype and are few in number [25]. Besides, tissue-resident markers like CD69 and CD103 can be expressed by MAIT cells in mucosal tissue [31,32]. The function of MAIT cells largely comes from the expression of several key transcription factors: T-bet as the type 1 transcription factor, retinoic-acid-related orphan receptor (ROR)γt and signal transducer and activator of transcription 3 (STAT3) as the type 17 transcription factors, and promyelocytic leukemia zinc finger (PLZF), which endows with innate-like functionality, similar to iNKT cells [25,26,30,33-36]. These transcription factors are all coexpressed in humans [35,36], consequently regulating the quick effector function. In contrast, T-bet and RORγt show mutually exclusive expression in mice, resulting in two populations in which the RORγt expression population is dominant in C57BL/6 mice [26,37].

MAIT cells also express chemokine receptors that mediate tissue homing, such as chemokine CC receptor (CCR)9, chemokine CXC receptor (CXCR)6, and α4β7, which is consistent with its ability to migrate to the liver, skin, lung and intestine [26,38]. MAIT cells also express cytokine receptors, such as interleukin (IL)-12R, IL-18Rα, IL-17Rα and IL-23R [26,39-41], which are important for the response to these cytokines in pathological conditions in the absence of TCR ligation.

2.2. Distribution and frequency of MAIT cells

MAIT cells are abundant in human beings, and are mainly present in mucous tissue, at the lamina propria–environment junction, and circulating in lymph and blood [25,42]. MAIT cells are also found in human and murine lungs, intestines, liver, pancreas, female genital mucosa, spleen and other tissues [26,43,44] (Table 1). Expression frequency is highest in human liver and peripheral blood [25], however, the frequency is low in lymphoid tissue and the spleen. On the contrary, MAIT cells are rarer in mice than in humans and usually account for $< 1\%$ of all T cells [26]. However, MAIT cells can significantly proliferate under the stimulation of antigens *in vivo* [33,45] and *in vitro* [26]. Therefore, microbial antigen exposure is likely to be an important factor affecting the frequency of mature MAIT cells.

2.3. Activation and effector function of MAIT cells

MAIT cells can be activated in two different pathways to perform effector functions, including TCR-dependent and TCR-independent cytokine-mediated activation, resulting in producing related cytokines, cytotoxic effects, migration and proliferation [33,36]. Additionally, these two different pathways can synergize to enhance MAIT cell activation (Fig. 1).

2.3.1. TCR-dependent activation

Like all T cells, MAIT cells recognize antigen-presenting molecules through TCRs and can initiate TCR-mediated MAIT cell activation at the time of primary infection [45]. Microorganisms utilize the riboflavin biosynthesis pathway to activate MAIT cells in an MR1-dependent manner [17,21,33,57,58]. At the same time, the co-stimulation through CD28 can enhance activation of MAIT cells mediated by TCR [41,59]. Human MAIT cells are inefficient when stimulated with soluble ligands in an MR1-dependent manner *in vitro*, and require Toll-like receptor (TLR) and antigen presenting cell (APC) activation [60], which is consistent with the activation of MAIT cells *in vivo* that requires not only riboflavin metabolite-derived antigens but also co-stimulatory signals like TLR stimulators [33]. However, MAIT cells have an unusual

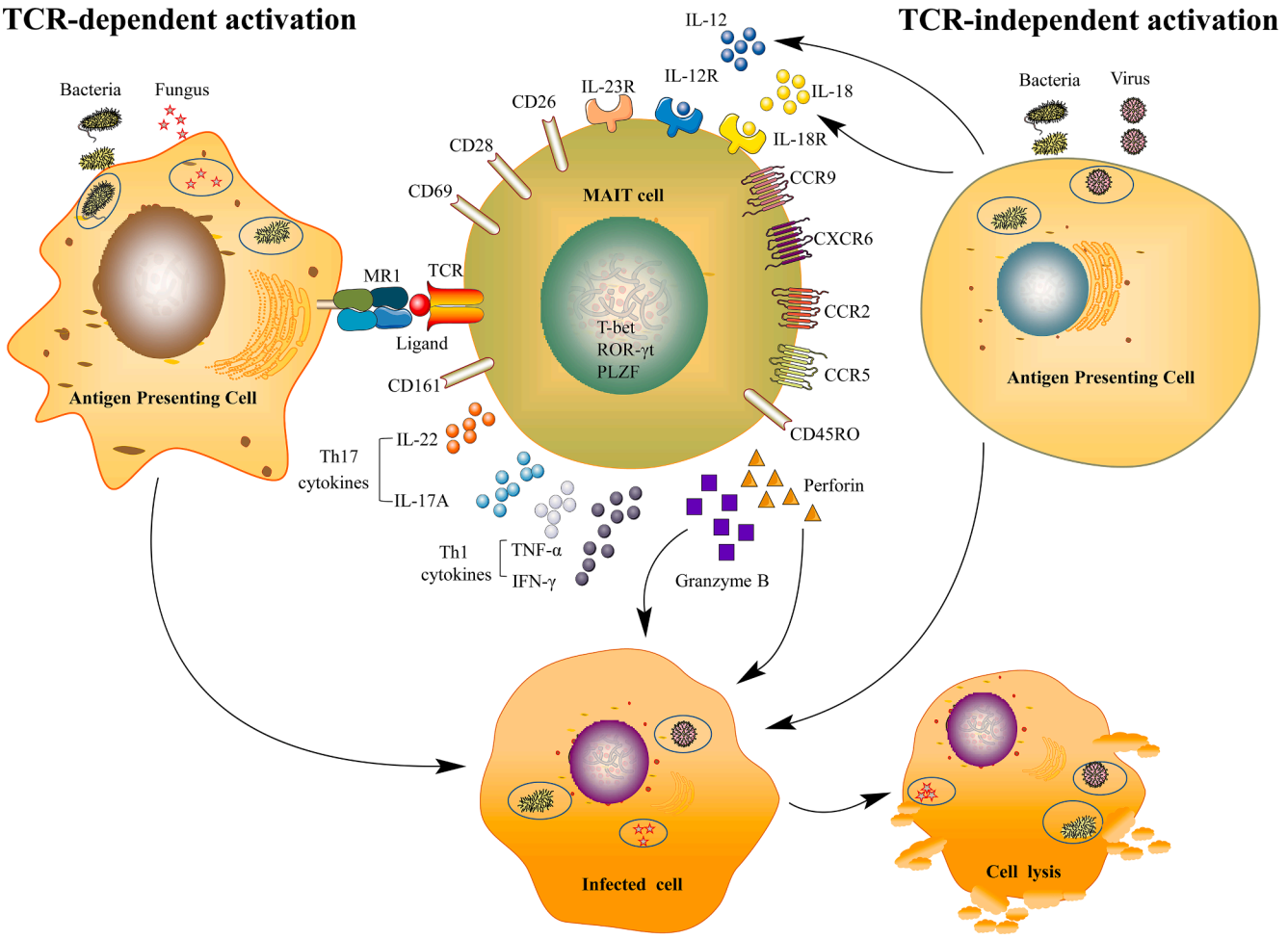

Fig. 1. MAIT cell characteristics, activation and function in immunity. MAIT cells are unconventional cells that express semi-invariant TCRs that recognize antigens presented by MHC-like molecule MR1. MAIT cells exist in the lungs in a stable state. MAIT cells express several key transcription factors such as T-bet, RORγt, PLZF, several tissue-homing cytokines receptors and markers. Upon bacterial, fungal or viral infection, MAIT cells can be activated in a TCR-dependent manner and/or in a TCR-independent cytokine-mediated manner by inflammatory cytokines like IL-12 and IL-18. In response, they secret Th1 type cytokines (IFN-γ, TNF-α) and Th17 type cytokines (IL-17A, IL-22), release granzyme B and perforin to dissolve infected cells. IFN-γ, interferon-γ; IL, interleukin; MAIT cell, mucosal-associated invariant T cell; MR1, MHC-related protein 1; PLZF, promyelocytic leukemia zinc finger; RORγt, retinoic-acid-related orphan receptor γt; TCR, T-cell receptor; TNF-α, tumor necrosis factor-α.

Table 1
Distribution and frequency of MAIT cells in human and mouse tissue.

Tissue distribution	Human MAIT cells/CD3$^+$T cells (%)	Mouse MAIT cells/CD3$^+$T cells (%)
Peripheral Blood	1~10% [9,29,38,46,47]	~0.1% [26,48]
Liver	20~45% [9,46,49,50]	~0.6% [26]
Lung	2~4% [15,17,21,38,51]	~3% [15,26]
Intestine	1~10% [9,14,15,52-55]	~0.7% [26,48]
Lymphoid tissue	<1% [9]	~0.2% [26,48]
Thymus	<0.05% [30]	<0.1% [26,30]
Spleen	not detection	~0.1% [14,26,48]
Adipose tissue	4~14% [47,56]	~2% [48]

characteristic that TCR signals are regulated and prolonged signaling fails to induce continuous cytokine proliferation or generation that is different than in conventional T cells [32,41]. This may due to down regulation of components of the TCR signaling pathway in MAIT cells [41]. Considering the widespread expression of MR1 in cells and tissues [37], and the expression of MR1 ligands in both pathogenic and symbiotic bacteria [24], such regulation might be essential to prevent improper activation of MAIT cells.

When MAIT cells are activated, they upregulate expression of CD25, CD69 and CD161, and secrete T helper (Th)1 type cytokines, such as interferon (IFN)-γ and tumor necrosis factor (TNF)-α, as well as Th17 type cytokines, like IL-17A and IL-22, but do not secrete Th2 cytokines [38,41,53], which is consistent with their transcription factors [9,30,61]. When mouse MAIT cells are activated, they can secrete a high level of IL-17 and low level of IFN-γ, TNF-α, granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-4, IL-10 and IL-13. In addition to secreting proinflammatory cytokines, MAIT cells secrete granzymes (GzmA, GzmB and GzmK) and perforin to dissolve infected cells [36,59]. Therefore, MAIT-cell-mediated killing of bacterially infected cells also needs TCR signaling, which plays an important role in the antibacterial response of MAIT cells.

2.3.2. *TCR-independent cytokine-mediated activation*

The TCR-independent activation of MAIT cells represents their innate function, and similar to iNKT cells or other innate lymphocytes, MAIT cells can be activated in an MR1-independent manner [62]. Thus, viruses such as dengue virus, influenza A virus, hepatitis C virus and hepatitis D virus [8,63-66] or bacteria like *Mycobacterium tuberculosis*, *Mycobacterium bovis BCG vaccine*, *Enterococcus faecalis*, *Francisella tularensis* [67-69], allow MAIT cells to react to microorganisms that do not produce MR1 ligands in this manner and produce IFN-γ, TNF-α and GzmB.

Several studies have shown that activation of MR1-independent MAIT cells depends on the synergistic effect of IL-18 and other inflammatory mediators [8,63,70], which is consistent with the high expression of IL-18R in MAIT cells [8,38,63,70]. Generally speaking, a single cytokine is not enough to induce significant activation. The common combination of cytokines IL-12 and IL-18 had been shown to induce MAIT cells to produce IFN-γ [43,70]. Corresponding to the activation of MAIT cells during virus infection, TLR8 and TLR3 are effective activators of MAIT cells that promote secretion of IL-12 and IL-18 by APCs [8,43,70]. Subsequent studies have confirmed that IL-15, IFN-α/β and TNF-α cooperate with IL-12 or IL-18 to activate MAIT cells [8,32,61,70].

MAIT cells can also be activated in some sterile inflammatory and autoimmune diseases. In patients with systemic lupus erythematosus (SLE), MAIT cells can be activated by IFN-α, IL-15, IL-12 and IL-18 in the absence of exogenous antigens [71]. The plasma concentration of these cytokines is positively correlated with the expression of CD69 on MAIT cells, suggesting that proinflammatory cytokines may activate MAIT cells and play a role in the pathogenesis of SLE and other possible inflammatory processes.

2.3.3. *Synergistic effect of two activation pathways*

Due to the low response of MAIT cells to TCR-mediated stimulation alone, the synergistic effect between TCR-mediated and cytokine signaling may play a key role in activating MAIT cells *in vivo* [32,41,49]. One study has shown that riboflavin metabolites and co-stimulatory signals are necessary for the accumulation of MAIT cells *in vivo* after lung infection [33]. Although there are two pathways to activate MAIT cells in response to bacterial infection, the relative action of these two pathways is still affected by many factors, including the nature of APCs. When THP-1 cells are used as APCs, the activation of MAIT cells induced by *Streptococcus pneumoniae in vitro* is completely driven by cytokines, while in the presence of monocyte-derived macrophages, MAIT cell activation is driven by both MR1-dependent manner and cytokines.

In general, these studies emphasize the role of MAIT cells as a bridge between innate and adaptive immunity. MAIT cells have the ability to sense bacterial and viral infections in patients and mouse models *in vitro*.

3. MAIT cells in lung diseases

MAIT cells have been associated with the pathogenesis of a variety of diseases, including lung diseases, which are increasing in prevalence and have a significant impact on morbidity and mortality [72-74]. The role of MAIT cells in functional change (Table 2) and the development (Fig. 2) of pulmonary disease is summarized and discussed.

3.1. *Asthma*

Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation, mucus overproduction, and airway hyper responsiveness (AHR) and remodeling [75]. A variety of cells is involved in the physiological and pathological process of disease, especially Th2 cells producing cytokines like IL-4, IL-5 and IL-13. A recent study has shown that Th2 cells and MAIT cells contribute to the disease [76]. MAIT cells can be detected in human fetal lungs and are abundant in adult rhesus monkeys [77,78]. Although MAIT cells are ubiquitous in the lungs and are involved in airway infections, little is known about the role of MAIT cells in asthma.

The frequency of MAIT cells in patients is associated with asthma severity and medication. Several studies have shown that the frequency of MAIT cells in blood [76,79-82], sputum [76] and bronchial biopsy specimens [76] of patients with asthma was significantly lower than that in the control groups, while there was no significant difference in the frequency of MAIT cells in bronchoalveolar lavage fluid (BALF) between the two groups. Among them, comparing patients with mild, moderate and severe asthma with healthy controls, the lower frequency of MAIT cells was only significant in peripheral blood and sputum of patients with moderate and severe asthma, which indicated that MAIT cells was negatively correlated with clinical severity [76]. Moreover, it was found

Table 2
MAIT cells in lung diseases.

Disease	Frequency	Phenotype	Function	Reference
Asthma	in blood↓, in sputum↓, in BALF-, in tissue↓	in blood MAIT-17/IL-4R↑ in BALF MAIT-17↑	in blood IL-17A/IL4I1↑ in BALF IL-17A↑	[76-82,84]
COPD	in blood↓	in blood DN/$CD8^+$ MAIT↓	in blood IFN-γ↑	[51,89-91]
Pneumonia				
CAP	in blood↓, in sputum↑, in BALF↑	in blood CD69/CD103↑ in BALF CD69/CD103/CXCR6/CD38/PD-1/DDIT3↑	in blood IL-17A/MCP-1↑,IFN-γ/IL-22↓ in sputum IFN-γ/TNF-α↑ in BALF IL-17A/IFN-γ/IL-22/IL-23/IL-1β/ IL-6/MCP-1/IL-12p70/MCP-1/MIP-1α/ MIP-1β/PLZF↑	[95,96]
COVID-19	in blood↓, in the airways↑	in blood CD69/PD-1/CD38/Ki67/HLA-DR↑, CXCR3↓ in the supernatants of endotracheal aspirates CD69/ PD-1↑	in blood IL-1β/IL-6/IL-1RA/ IL-18/ IL-17A/Granzyme B↑, IFN-γ↓ in the supernatants of endotracheal aspirates IL-1β/IL-6/IL- 1RA/CXCL12/IFN-γ/IL-17A↑	[105,106]
TB				
Activated TB	in blood↓, in pleural effusion↑	in blood CD69↑/↓, CD127/HLA-DR/CCR6/CD25/ γc receptor↑, IL-2Rβ/IL-15Rα- in pleural effusion PD-1/TIM-3/CXCL3/CD38/ CD45RO/CD62L/γC receptor↑	in blood IFN-γ↑/↓, TNF-α/IL-17F/IL-23/granzyme B/ granulysin↓ in pleural effusion IFN-γ/granzyme B/ IL-17F↑	[17,21,68,109,111–113]
Latent TB	in blood↑	ND	in blood IFN-γ↑	[110]
Sarcoidosis	in blood↓, in BALF↑	in blood CD69/PD-1↑ in BALF CD69↑	in blood IL-18↑	[117]
CF	in blood↓	ND	ND	[121,122]
Cancer	in blood↓	in blood CCR6/CXCR6↑, CCR9↓	in blood granzyme B/CD107a↑, IL-17A/IFN-γ/TNF-α-	[124]

COPD, Chronic obstructive pulmonary disease; CAP, Community-acquired pneumonia; COVID-19, coronavirus disease 2019; TB, tuberculosis; CF, cystic fibrosis; BALF, bronchoalveolar lavage fluid; IL, interleukin; CXCR, chemokine CXC receptor; PD-1, programmed death protein 1; DDIT3, DNA damage inducible transcript 3; HLA-DR, human leukocyte antigen DR; CCR, chemokine CC receptor; γc receptor, γ-chain receptor; TIM-3, T cell immunoglobulin domain and mucin domain-containing 3; IL4I1, interleukin-4-induced gene 1; IFN-γ, interferon-γ; TNF-α, tumor necrosis factor-α; MCP-1, monocyte chemotactic protein-1; MIP-1α, macrophage inflammatory protein-1α; PLZF, promyelocytic leukemia zinc finger; MAIT cell, mucosal-associated invariant T cell; ND, not determined; ↑increase; ↓decrease; ↑/↓mix response; –comparable.

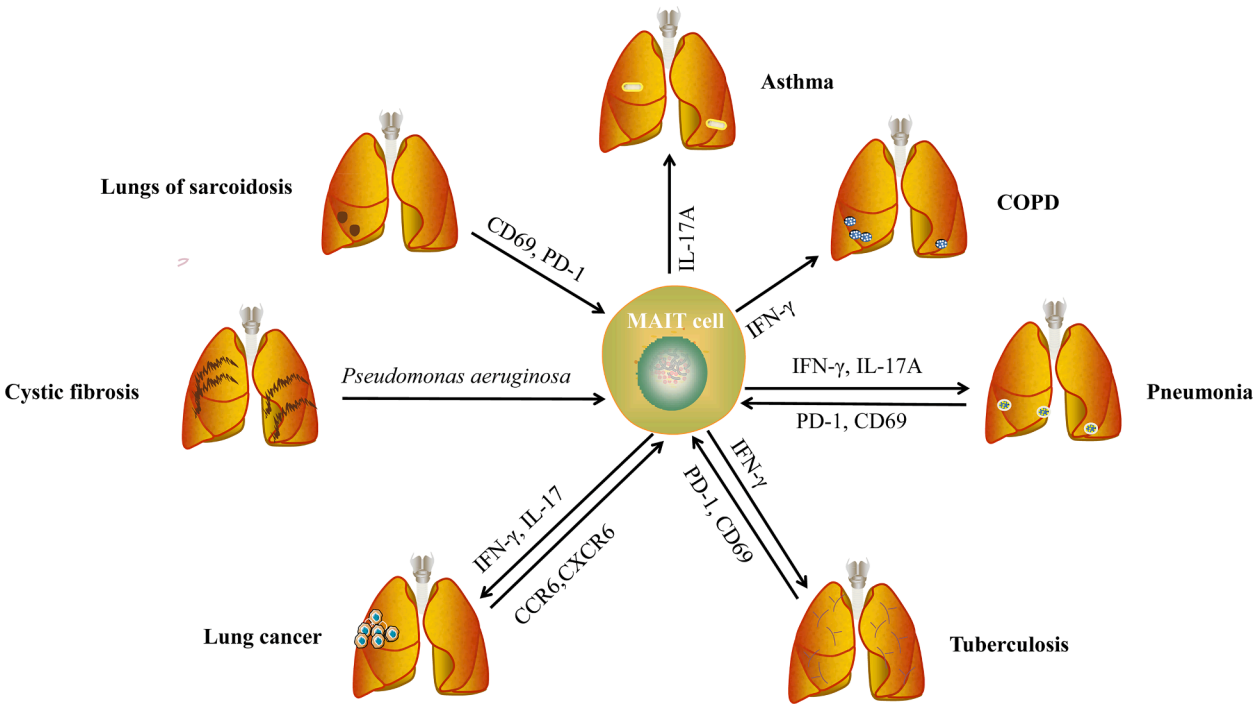

Fig. 2. MAIT cells in lung diseases. In asthma, MAIT cells have a protective effect against chronic inflammation while production of IL-17 is associated with disease severity. In COPD, MAIT cells are associated with disease severity too, and corticosteroid use inhibits MAIT cells in patients with COPD. In pneumonia, inflammatory factors derived from $CD14^+$ monocytes promote the differentiation of MAIT cells producing IL-17 and inflammation. In tuberculosis, MAIT cells are protective against infection and impaired in immune response. In pulmonary sarcoidosis, MAIT cells present as exhaustion and activation phenotype that also reflect disease activity. In cystic fibrosis pulmonary disease, MAIT cells deficiency are related to pulmonary exacerbation and *pseudomonas aeruginosa*. In lung cancer, MAIT cells have potential to kill cancer cells, as well as MAIT cells defects are associated with cancer staging. CCR6, chemokine CC receptor 6; COPD, chronic obstructive pulmonary disease; CXCR6, chemokine CXC receptor 6; IFN-γ, interferon-γ; IL-17, interleukin-17; MAIT cell, mucosal-associated invariant T cell; PD-1, programmed death protein 1.

that the frequency of circulating MAIT cells producing IL-17 (MAIT-17) was positively correlated with asthma severity in children with asthma [81,82]. In contrast, MAIT-17 cells in BALF are associated with the aggravation of symptoms in children with severe asthma [82]. It is worth noting that when MAIT cells are divided into MAIT-17-high and MAIT-17-low phenotypes according to the frequency of IL-17-producing MAIT cells in children with severe asthma, the former shows more severe exacerbation than the latter [82]. Hinks et al. [76] also showed that MAIT cells are associated with serum vitamin D concentration and oral corticosteroids. This provides evidence for the association between corticosteroid use and MAIT cell frequency. The proinflammatory cytokines IL-23 and IL-1β present in the lung tissue of asthmatic patients indirectly activate MAIT cells, which secrete IL-17 and IFN-γ; both of which are considered mediators of steroid-resistant asthma [83]. Whether corticosteroids can alter the expression of MR1 and the effect of MAIT cell activation remain to be elucidated. Some drugs can affect the antigen presentation of MR1 molecules, such as doxofylline, a bronchodilator used for treatment of asthma, which is known to upregulate expression of MR1, but does not act as a MAIT cell agonist [22]. Therefore, these drugs currently used in the treatment of asthma may affect the function of MAIT cells.

Asthma airway inflammation can influence MAIT cell frequency. One study has shown that there is a positive correlation between activated NK cells, innate lymphoid cells (ILCs) and MAIT cells, and a negative correlation with forced expiratory volume in the first second (FEV1), which may be associated with airflow limitation in patients with asthma [79]. However, in an animal model, Ye et al. [84] found that the number of lung-resident MAIT cells was decreased significantly in C57BL/6 mice with repeated intranasal exposure to various common allergens including extracts from *Aspergillus*, *Alternaria*, house dust mite and cockroach, and none of these mice were treated with corticosteroids. $MR1^{-/-}$ mice lacking MAIT cells aggravated ILC2 response, and increased airway inflammation and AHR with inhalation of *Alternaria*, while adoptive transfer of MAIT cells inhibited ILC2 response and reduced airway inflammation and AHR. The researchers also found that human and murine MAIT cells expressed a large number of the anti-inflammatory molecule interleukin-4-induced gene 1 (IL4I1) that inhibits ILC2 activation. MAIT cells decreased after exposure to allergens due to the presence of proinflammatory T cells, suggesting that this feedback may promote persistent airway inflammation. In some patients with asthma, MAIT cell deficiency may lead to increased inflammation in response to allergens and other stimuli. A recent study [80] found that the high frequency of MAIT cells in children's peripheral blood at the age of 1 year is associated with a lower risk of asthma at the age of 7 years; nevertheless, no association was found between MAIT cell frequency and the risk of aeroallergens or wheezing at 3 years old. At the same time, MAIT cells have also been shown to be relevant to the increase of IFN-γ production by traditional $CD4^+$ T cells.

These results also suggest that MAIT cells have a protective effect on chronic inflammation, while MAIT-17 cells are related to the severity of the diseases and linked with pathophysiology. To further understand the mechanism of MAIT cells in local lungs, studies of sputum and BALF should be strengthened. In consideration of the response of MAIT cells to microbial metabolites, it may be necessary for lung microbes to activate MAIT cells to prevent asthma. It can be seen that MAIT cells are involved in the occurrence and development of asthma, while its mechanism needs further study. Since there have been MAIT-cell-deficient mice [85], this study on the function of MAIT cells at the sites of inflammatory infiltration in mouse models may be helpful to provide new insights.

3.2. Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is characterized by persistent airflow limitation and is associated with chronic

inflammation of the airway [86]. The main mechanisms of COPD are emphysema, bronchiolitis and mucus hypersecretion [87]. In the COPD process, chronic inflammation is characterized by infiltration of a large number of activated leukocytes such as neutrophils, macrophages, eosinophils and different lymphocyte subsets into the lungs. Disease exacerbation is the main driving factor for the morbidity and mortality of COPD. It can be driven by bacterial infection, and the activation of MAIT cells is caused by precursors and derivatives of conservative riboflavin biosynthesis pathways in bacteria and yeast that may be involved in the exacerbation of COPD. It has been shown that innate-like T lymphocytes like iNKT cells and MAIT cells are also involved in the pathogenesis of COPD [88].

Similar to asthma, MAIT cells are associated with severity of COPD. It has been found that the frequencies of $CD8^+$ and DN MAIT cells in peripheral blood of patients with COPD are decreased, and the level of circulating MAIT cells in patients with moderate and severe COPD is lower than that in patients with mild COPD [89,90]. Compared with healthy controls, expression of Vα7.2-Jα33TCR mRNA is decreased in COPD patients [89], which is consistent with the decreased frequency of MAIT cells, while no significant difference has been reported in sputum MAIT cell frequency in patients and controls. Another study [90] has shown that there is a negative correlation between circulating MAIT cells and C-reactive protein levels in patients with COPD, suggesting that MAIT cells are involved in enhancing the inflammatory response to harmful particles or gases in the airways in patients with COPD. The defects in MAIT cells reflect inflammatory activity and these findings provide crucial information for predicting the prognosis of COPD.

Defects in the number and function of MAIT cells in the airways of COPD patients are associated with corticosteroid therapy. It has been shown that MAIT cells in blood and bronchial tissues of COPD patients treated with corticosteroids are significantly reduced [51]. It has also been reported that *Haemophilus influenzae* induces expression of MR1 on the surface of pulmonary macrophages, which leads to increased IFN-γ secretion by MAIT cells. However, the IFN-γ secretion is significantly attenuated by treatment with corticosteroids, reflecting the inhibitory effect on MAIT cells in patients with COPD [51]. Eldere et al. [91] showed that MAIT cells respond to *H. influenzae* infected with macrophages in an MR1-dependent manner, suggesting that MAIT cells dysfunction is the reason for a significant increase in *H. influenzae* infection in patients with COPD. These studies provide strong evidence that *H. influenzae* may be a MAIT cell immune target and indicate the antibacterial effects of MAIT cells, and steroid therapy is another factor that can affect MAIT cells.

All these findings provide important information for monitoring the changes in the number of MAIT cells and predicting prognosis, and providing strong evidence for host defense against major respiratory pathogens. These findings also promote study of the pathogenesis of MAIT cells in COPD inflammatory diseases.

3.3. Pneumonia

Community-acquired pneumonia (CAP) is an immune-mediated lung disease caused by a variety of microbial pathogens [92,93]. Severe CAP is associated with acute respiratory and heart failure, multiple organ dysfunction and high mortality [94]. Innate immune defense is important for the prevention and early control of pulmonary infection and guidance of the acquired immune response. Innate immunity and acquired immunity are connected by cells like MAIT cells and γδ T cells.

MAIT cells play an important role in the immune response to CAP. Rachel et al. [95] found that the abundance of MAIT cells in sputum of patients with mild CAP was significantly higher than that of healthy controls, which was determined by quantitative polymerase chain reaction. The length of hospital stay was negatively correlated with the abundance of MAIT cells, and the abundance of MAIT cells in sputum was associated with IFN-α, IFN-γ and sputum neutrophil abundance, but there was no correlation with total bacterial load or the ability of bacteria to produce activating ligands. The production of IL-17 by MAIT cells in BALF of children with severe CAP is significantly increased. At the same time, $PLZF^{hi}CD103^+$MAIT cell subsets in BALF with high expression of hypoxia-inducible factor-1α (HIF-1α), which promote IL-17 production, reflect the hypoxic state of inflammatory tissue [96]. Circulating MAIT cells in CAP patients express a high level of transcription factor 7 (TCF7), which has been confirmed to inhibit differentiation of Th17 cells [97-99]. MAIT cells in BALF also highly express DNA damage inducible transcript 3 (also known as CHOP), which plays an important role in endoplasmic reticulum stress response [100,101]. It is worth noting that tissue-resident MAIT-17 cells are induced in infected respiratory mucosa, which may be promoted by inflammatory cytokines derived from $CD14^+$ monocytes, leading to MAIT-17 differentiation, thus contributing to IL-17-mediated inflammation during CAP [96]. On the one hand, MAIT cells may contribute to improve clinical prognosis, and on the other hand, induced MAIT-17 cells may lead to BALF inflammation and disease severity in children with CAP in the presence of pathogens.

In December 2019, the first case of pneumonia caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2; SARS-CoV-2) was reported in Wuhan, Hubei, China [102,103]. The novel coronavirus, which causes coronavirus disease 2019 (COVID-19), is a new strain related to SARS-CoV-1 and to the Middle East respiratory syndrome coronavirus (MERS-CoV). It can be transmitted from person to person, causing mild or even life-threatening illness [103]. The COVID-19 outbreak has become a global public health emergency [104]. In addition to classic $CD4^+$ and $CD8^+$ T cells, a class of innate T cells like MAIT cells, iNKT cells, have also become participants in mucosal immunity and inflammatory responses during COVID-19 infection [105].

Recent studies showed that the MAIT cells in the peripheral blood of severe COVID-19 patients decreased, while they were higher in the airways compared with blood [105,106]. The expression of $CD69^+$ and PD-1 on MAIT cells is also higher than in blood, suggesting these cells are recruited from the blood and transferred to the lungs. Of importance, a higher $CD69^+$ MAIT cell frequency in peripheral blood on day 1 after admission is associated with reduced hypoxia on day 7 [105]. Although more controlled studies are needed on this issue, this observation supports the beneficial role of MAIT cells in COVID-19. Conversely, IL-17A produced by MAIT cells increased in blood and airways, suggesting MAIT cell pro-inflammatory IL-17A bias [105,106]. Further research is needed to explore the function and mechanism of MAIT cells in COVID-19.

3.4. Pulmonary tuberculosis

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* [107]. The innate immune defense of the host provides early protection against *M. tuberculosis* infection and plays a vital role in initiating adaptive immunity [108].

More and more studies support the protective role of MAIT cells in TB. There is a significant decrease in the frequency and number of circulating MAIT cells in TB patients [17,21,109,110], which may be due to their recruitment at the infected site. MAIT cells can recognize and kill cells infected by *M. tuberculosis*, including dendritic cells and pulmonary epithelial cells [17]. The immune response of MAIT cells in pleural effusion of TB patients to *M. tuberculosis* antigen is significantly enhanced, which is mainly regulated by cytokines produced by innate or adaptive immune cells [68,111,112]. Jiang et al. [111] showed that IL-15 significantly increases the IFN-γ response of MAIT cells to *M. tuberculosis* lysate, while the production of IFN-γ by MAIT cells stimulated by *M. tuberculosis* lysate/IL-15 in patients with active pulmonary TB is significantly lower than that in healthy controls and latent TB infection. This suggests that the control of *M. tuberculosis* infection restores the ability of MAIT cells to respond to *M. tuberculosis*/IL-15 stimulation. There are many differentially expressed genes in MAIT cells of TB patients compared with healthy controls, among which the

expressions of IFN-γ, TNF-α, IL-17F, granulysin and GzmB in TB patients are all downregulated. The expression of γ-chain receptor in MAIT cells of TB patients is significantly lower after stimulation. After blocking γ-chain (γc) receptor and IL-2Rβ receptor, the frequency of IFN-γ produced by MAIT cells decreases significantly [68,111]. Therefore, the cytokine and cytotoxic response of MAIT cells in patients with active pulmonary TB to *M. tuberculosis* antigen is impaired. Another study has shown that the level of MAIT cells expressing PD-1 is related to the degree of TB infection [113]. The ability of PD-1^{+} MAIT cells to produce CXCL13 and IL-21 in pleural effusion of TB patients is enhanced, and the frequency of PD-1^{high}CXCR5^{-} MAIT cells is higher. Collectively, these findings suggest a role for MAIT cells in the immune control of *M. tuberculosis* infection and cytokines are required for MAIT cells to respond to *M. tuberculosis* antigens.

Murine MAIT cells are also important in innate immunity against *M. tuberculosis*. They can effectively inhibit the growth of bovine *Mycobacterium bovis* BCG in macrophages by secreting IFN-γ. However, this protective effect is limited to the early stage of pathogen exposure. The results showed that lung infection of MR$1^{-/-}$ mice was more serious after 10 days of infection compared with the control group, while there was no significant difference in bacterial load between the two groups after 30 days of infection [67]. Another study has shown that intranasal co-stimulation of mice with lipopeptide TLR agonist and synthetic MR1 ligand induces early MAIT cell activation and expansion after *M. tuberculosis* exposure, while MAIT cells are not sufficient to control *M. tuberculosis* bacterial load [5]. MAIT cells produce IL-17, which may help to stimulate an adaptive immune response. MAIT cells not only play a unique role in innate lymphocytes but may also enable adaptive lymphocytes to initiate a protective immune response during infection.

3.5. Lung sarcoidosis

Sarcoidosis is an inflammatory disease and its pathogenesis is not completely understood [114]. Previous studies have shown that the immune response of Th1 cells is involved in sarcoidosis [115,116].

A recent study [117] has proved that the proportion of MAIT cells in peripheral blood of patients with pulmonary sarcoidosis is lower than that of healthy controls, while expression of CD69 and PD-1 is higher, and expression of CD69 is significantly correlated with serum angiotensin-converting enzyme and soluble IL-2R. The ratio and number of MAIT cells in BALF of sarcoidosis patients with pulmonary parenchyma infiltration are significantly higher than those without infiltration, and the expression of CD69 in BALF is higher than that in peripheral blood. The activation of MAIT cells may reflect the disease activity and severity of pulmonary sarcoidosis.

3.6. Lung cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disease characterized by a complex interaction between respiratory infection and inflammation [118]. The vicious cycle of infection and persistent inflammation can lead to severe lung damage in CF, which eventually leads to respiratory failure [119]. It is known that Th17 and regulatory T (Treg) cells have a role in maintaining immune imbalance in CF airways [120]. Recently, there has been an increase in the role of innate lymphocytes in chronic airway diseases.

Several reports have illustrated the role of MAIT cells in patients with CF. Smith et al. [121] reported that the frequency of MAIT cells in peripheral blood of patients with CF is decreased and is associated with *Pseudomonas aeruginosa* infection. MAIT cell deficiency in these patients is related to the deterioration and aggravation of lung disease. In one CF patient, MAIT cells were significantly deficient and infection could not be controlled despite great number use of antibiotics, but the NKT cells, B cells and Treg cells were normal [122]. These findings suggest that MAIT cells are essential for pulmonary immune defense in the case of impaired respiratory mucosa and improve the clinical symptoms of CF.

It is known that inhaled corticosteroids can reduce damage caused by inflammatory mediators and prevent lung deterioration in patients with CF [123]. However, the effects of inhaled corticosteroid treatment on circulatory levels and the number of MAIT cells in the lungs of CF patients remain to be determined. Pincikova et al. [124] pointed out that the circulating MAIT cells were decreased in patients taking vitamin D. Vitamin D is a structure-related steroid that exerts a direct regulatory effect on T cells, inhibiting their proliferation, as well as IFN-γ and IL-17 production. Vitamin D therapy reduces activation and exhaustion markers like CD38, PD-1 and HLA-DR in these patients. Like patients with asthma and COPD, the frequency of MAIT cells tends to drop after vitamin D and free serum 25-hydroxyvitamin (free-s25OHD) treatment. Furthermore, the change in free-s25OHD is correlated negatively with PD-1 on MAIT cells at the end of intervention. It can be seen that vitamin D may affect the activation of MAIT cells in patients with CF, resulting in a decrease in their numbers and exhaustion markers in peripheral blood, which may promote the recruitment of activated MAIT cells to the lungs.

3.7. Lung cancer

Lung cancer is one of the most common types of cancer worldwide and is also the leading cause of cancer mortality among men and women [125]. However, little is known about the role of MAIT cells in cancer.

A recent study [126] has shown that the level of circulating MAIT cells in patients with mucosa-associated cancer like lung, stomach and colon cancer is significantly decreased yet their ability to produce IFN-γ, IL-17 or TFN-α remains unchanged, and their absolute numbers are significantly associated with N staging, carcinoembryonic antigen level, neutrophil count and hemoglobin. The percentage of MAIT cells in cancer tissues is higher than that in peripheral blood, and circulating MAIT cells express high levels of CCR6 and CXCR6. Activated MAIT cells not only have lymphokine-activated killer activity but also have cytotoxic effects on K652 cells through perforin and GzmB. It can be concluded that circulating MAIT cells in patients with mucosa-associated cancer may migrate to cancer tissue and decrease in number, having the potential to kill cancer cells and this absence of circulating MAIT cells is relevant to the degree of cancer progression in mucosal tissue.

4. Discussion

MAIT cells are deficient in peripheral blood in patients with lung diseases, and closely related to inflammation and microbial infection. MAIT cells can play a protective role to effectively resist bacterial and viral infection by secreting IFN-γ, as well as causing infected cell lysis by secreting GzmB and perforin. MAIT cells also play a role in exacerbating lung inflammation by secreting IL-17 and TNF-α. How the body adjusts the balance between protective and proinflammatory effects of MAIT cells is still unclear. So, it remains to be determined whether MAIT cells are “friends or enemies”. Although MAIT cells are involved in the immunology of the above-mentioned lung diseases, especially in aggravation of the diseases, their specific mechanism of action in the case of severe disease is unknown. Animal models of lung disease will provide new insights into the development and regulation of immune responses, but based on the differences in species and the distribution of MAIT cells in human tissues and animals, the research progress will be relatively slow. At present, research on MAIT cells in lung diseases is still in its infancy and most studies are superficial. In order to explain the different roles of MAIT cells in diseases, clinical case analysis and *in vitro* experiments should be increased to study further their molecular mechanisms. Moreover, the immune response is the result of the interaction of various types of immune cells; therefore, MAIT cells are probably connected with other immune cells. Whether these cells regulate each other or perform functions independently remains to be resolved and provides a basis for the study of lung diseases and a direction for the treatment of lung diseases.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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