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REVIEW

Mucosal-associated invariant T cells: new players in CF lung disease?

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Abstract

The past decade has witnessed a surge in research centered around exploring the role of the enigmatic innate immune-like lymphocyte MAIT cell in human disease. Recent evidence has led to the elucidation of its role as a potent defender at mucosal surfaces including lungs due to its capacity to mount a formidable immediate response to bacterial pathogens. MAIT cells have a unique attribute of recognizing microbial ligands in conjunction with non-classical MHC-related protein MR1. Recent studies have demonstrated their contribution in the pathogenesis of chronic pulmonary disorders including asthma and chronic obstructive pulmonary disease. Several cellular players including innate immune cells are active contributors in the immune imbalance present in cystic fibrosis(CF) lung. This immune dysregulation serves as a central pivot in disease pathogenesis, responsible for causing immense structural damage in the CF lung. The present review focuses on understanding the role of MAIT cells in CF lung disease. Future studies directed at understanding the possible relationship between MAIT cells and regulatory T cells (Tregs) in CF lung disease could unravel a holistic picture where a combination of antimicrobial effects of MAIT cells and anti-inflammatory effects of Tregs could be exploited in synergy to alleviate the rapid deterioration of lung function in CF lung disease due to the underlying complex interplay between persistent infection and inflammation.

Keywords Cystic fibrosis · Pulmonary inflammation · MAIT cells

Introduction

Cystic fibrosis (CF) lung disease is characterized by a complex interplay between airway infection and inflammation. Pulmonary inflammation in CF in spite of being self-perpetuating and excessive is incapable and ineffective in clearing CF lung infection arising from several bacteria species colonizing the CF lung including *Psuedomonas aeruginosa, Staphylococcus aureus, and Hemophilus influenzae*. This Vicious cycle of infection and inflammation results in causing tremendous structural damage in CF lung eventually leading to respiratory failure [1, 2]. Several cellular players including lymphocytes are known to play an important role in orchestrating the immune imbalance in CF airways [3, 4]. Recent reports have elucidated the role of Th17 and Tregs in perpetuating immune imbalance in CF airways [5, 6]. The past decade has witnessed a surge in research exploring the role of innate-like lymphoid cells as active contributors in the disease pathogenesis of several chronic airway disorders [5, 6].

One such promising candidate is mucosal-associated invariant T (MAIT) cell. MAIT cell belongs to a subset of innate-like T lymphocytes, highly abundant in human blood and mucosal tissues including lung and intestine [7, 8]. Increasing evidence suggests that MAIT cells serve as important innate immune effectors in response to pathogens due to their ability to rapidly recognize microbial metabolites upon restriction by non-classical MHC molecules MR1. Upon activation, MAIT cells are capable of secreting high levels of IFN-γ, IL-17 and TNF-α [9, 10]. Recent reports have elucidated their contribution as early innate immune responders crucial in lung defense against incoming pathogenic insult. The present review focuses on understanding their role in CF lung disease. Future studies directed at understanding the possible relationship between MAIT cells and regulatory T cells (Tregs) in CF lung disease could unravel a holistic picture where a combination of antimicrobial effects of MAIT cells and anti-inflammatory effects of

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Tregs could be exploited in synergy to alleviate the rapid deterioration of lung function in CF lung disease.

MAIT cell and its ligands

MAIT T Cells belong to a class of innate immune-like lymphocytes and express a semi-variant T cell receptor (TCR), comprising of invariant TCR α chain mainly TRAV1-2 TRAJ33 or TRAV1-2 TRAJ20, TRAJ12 in humans [11, 12], which is associated with TCR β chain TRBV20 or TRBV6 in humans. MAIT T cells undergo TCR rearrangement in the thymus. A unique feature that separates MAIT T cells from the conventional T cells is their ability to exhibit effector function prior to their exiting the thymus, suggestive of a prominent role played by these cells in host defense [13, 14] Their relative abundance in peripheral blood and mucosal tissues in humans and limited diversity of MAIT TCR is indicative of their high relevance in the early phase of immune responses as compared to their conventional counterparts [15].

Recent studies have reported that MAIT cells are restricted by a non-classical antigen-presenting molecule MHC-related protein 1 (MR1) [16, 17]. Study by Kjer-Neilsen et al. [18] and several other studies demonstrated that MAIT cells recognize a Vitamin B and folic acid derivatives produced during the highly conserved biosynthetic pathways in wide range of microorganisms including bacteria and yeast [19–21]. The two prominent ligands which are recognized by MAIT cells include 6 formylpterin (6-FP) and reduced from hydroxymethyl 8-D-ribityllumazine (rRL-6-CH_2OH); the second one is putatively believed to be a secondary metabolite of riboflavin synthesis. Recent reports have identified several newer ligands for MAIT Cells including 5-(2 oxoethylideneamino)-6-D ribitylaminouracil (5-OE-RU), glyoxal and 5-(2 oxopropylideneamino) 6-D ribitylaminouracil (5-OP-RU) [18, 19]. MAIT cell activation occurs either through TCR-dependent signaling or through TCR-independent cytokine signaling [22–25].

MAIT cells in chronic respiratory disorders and in response to corticosteroids

Until recently, the role of MAIT cells in human diseases was not well characterized. Several recent research reports have thrown light on the role of MAIT cells in disease pathogenesis of chronic respiratory disorders including asthma and chronic obstructive pulmonary disease (COPD). Asthma is long been characterized by an inflammatory disease driven by dysregulated production of Th2 mediators. However, this concept is increasingly being challenged in light of available evidence supporting that there exists a considerable heterogeneity in asthma mechanisms attributable to distinct patient phenotypes. Several new players including Th17 cells, Tregs and innate immune-like lymphocytes including MAIT cells have also been shown to contribute to the pathogenesis of asthma [26, 27].

Hinks et al. [28] reported a reduced frequency of MAIT cells in blood, sputum as well of biopsy of patients with asthma as compared to controls; furthermore, this reduced frequency of MAIT cells was related with the disease severity. Furthermore, the study observed that patients treated with inhaled corticosteroids were associated with a pronounced deficiency in MAIT cells in peripheral blood. MAIT cells have been shown to be activated indirectly by pro-inflammatory cytokines IL-23, IL-1β present in lungs of patients with asthma; upon activation, MAIT cells secrete IL-17, IFN-γ both of which are increasingly recognized as mediators in steroid-resistant asthma [29]. Another study in children with asthma [30] reported similar frequency of circulating MAIT cells in patients with or without exacerbation. Furthermore, the study observed a positive correlation between frequency of IL-17-producing MAIT cells with exacerbation and negatively correlated with asthma control test score.

A recent study [31] reported an association between a high frequency of MAIT cells and lower risk of asthma in children with increasing age from 1 to 7 years. Observations from the study indicate that a higher MAIT cell frequency in 1 year old children with asthma confer protection to asthma as they grow older. Holistically, these studies point out that MAIT cells producing IL-17 are linked with asthma pathophysiology; conversely, pro-Th1 MAIT cells confer protection from the disease.

Several reports have elucidated the role of MAIT cells in patients with chronic obstructive pulmonary disease (COPD). A study reported reduced numbers of MAIT cells in airways of patients with COPD being administered inhaled corticosteroids. However, no significant difference in peripheral blood MAIT cell frequency in steroid-naive patient group was reported as compared to controls. Furthermore, the study reported that *Hemophilus influenzae* infection induced surface expression of MR1 on pulmonary macrophages, which resulted in secretion of IFN-γ by MAIT cells. However, this IFN-γ response was found to be significantly impaired in the presence of steroids, thereby reaffirming the suppressive effect of corticosteroids on MAIT cell frequency in patients with COPD [32]. Another study reported a deficiency of circulating MAIT cells in patients with COPD. Moreover, an inverse association between elevated C-reactive protein levels and reduced MAIT cell numbers was observed [33]. A recent study by Szabo et al. [34] reported decreased MAIT cell numbers in the peripheral blood of COPD patients. However, no significant difference in sputum MAIT cell frequency in patients with COPD and controls was reported [34].

MAIT cells in pulmonary infections

The past decade has witnessed a surge in the interest pertaining to research centered around the role of innate immune-like lymphoid MAIT cells in microbial infections [35–37]. Several in vitro studies have demonstrated the ability of peripheral blood MAIT cells exposed to bacteria including *E. Coli* and *Mycobacterium tuberculosis* to produce a variety of pro-inflammatory cytokines including IFN-γ and TNF-α, and exhibit cytotoxicity through the secretion of perforin and granzymes. Furthermore, the production of these cytokines by MAIT cells in these experiments was dependent on TCR signaling triggered by the ligand presented in conjunction with MR1 [36]. A recent study by Le-Bourhis et al. [38], using an in vivo model system for pulmonary infection utilizing iVα19 transgenic MR1-sufficient or -deficient mice, reported lower bacterial burden in the former mice in comparison with latter, thereby suggestive of a protective role for MAIT cells in antibacterial defense.

Another study [39] reported that the addition of MAIT cells to macrophages which were experimentally infected with *Mycobacterium bovis* resulted in inhibiting the bacterial growth. This protective effect was restricted to early days of exposure to pathogen. The observations from this study demonstrated higher burden of pulmonary infection in MR1 knock-out mice 10 days post aerosol infection with *M. bovis* as compared to control mice. However, the bacterial burden did not differ significantly in both the groups 30 days post infection. There exists increasing evidence supported by several studies [40, 41] about the protective role MAIT cells in case of tuberculosis infection. One study reported a reduced MAIT frequency in circulating blood in patients with active tuberculosis. Furthermore, the MAIT cells present in circulation during active pulmonary tuberculosis had diminished functional capacity and were producing less IFN-γ, TNF α upon stimulation. However, an increased percentage MAIT cells was observed in lungs of these patients with active tuberculosis as compared to healthy individuals (pleural effusion). Also MAIT cells in pleural effusions had an enhanced IFN-γ and granzyme B response, suggestive of that these cells migrate to the mucosa of the lung from the periphery upon infection and thereby play a protective role during tuberculosis infection [40]. In another recent study, in pediatric patients with tuberculosis, a reduced level of MAIT cells in both peripheral blood and lungs was observed [41].

A study by Georgel et al. [42], reported a protective role played by MAIT cells in *Klebsiella pneumoniae* infection using MR1 knock-out mice. A recent report [43] elucidated the important role of MAIT cells in protecting against Gram-negative bacterium *Francisella tularensis* causing pulmonary infection. Holistically, evidence from several recent studies highlights the protective role played by MAIT cells in pulmonary infections [44].

MAIT cells in cystic fibrosis

Persistent airway inflammation coupled with chronic bacterial infection is a hallmark of CF lung disease. Several cellular players including lymphocytes serve as active contributors to the immune imbalance in CF airways [3]. Over the last decade, several elegant studies have unraveled the contribution of unconventional innate immune cells in perpetuating the immune imbalance in CF lung. Recent studies have put the spotlight on innate immune-like MAIT cell as an active contributor in disease pathogenesis of several chronic inflammatory disorders. Furthermore, research pertaining to their role in pulmonary disorders have garnered considerable attention in last couple of years due to their unique attributes namely their relative abundance at the mucosal surfaces including lungs and their ability to mount a formidable immediate immune response to pathogens. Evidence from several recent reports has demonstrated a deficiency of circulating MAIT cells in patients with asthma, COPD and tuberculosis. Furthermore this deficiency correlated inversely with disease severity [28, 33, 40].

A study by Smith et al. [45] reported a reduced frequency of MAIT cells in peripheral blood of patients with CF. Furthermore, the reduced MAIT cell numbers correlated with *Pseudomonas aeruginosa* infection and patients with CF infected with *P. aeruginosa* had lowest MAIT cell percentage. Deficiency of MAIT cells in these patients was associated with pulmonary exacerbation and increased severity lung disease. These observations were further corroborated by a recent case report [46], in a patient with CF where a striking deficiency of circulating MAIT cells was reported along with severely impaired clearance of bacterial infection. The circulating MAIT cells were strikingly deficient in this patient; whereas normal levels of natural killer cells, B cells were detected. Furthermore, the observations from this study indicated that the deficiency of MAIT cells was not related to MR1. Taken together, these findings led to a trail unravelling the potential protective role played MAIT cells against respiratory infections, possibly contributing towards modifying the clinical phenotype in patients with CF (Table 1).

CF airway inflammation remains at the center stage for several directed therapeutic interventions aiming to reduce and curtail the damage caused due to excessive proinflammatory mediator release [6]. The use of inhaled corticosteroids seems a logical choice in patients with CF, since inhaled corticosteroids (ICS) are known to reduce inflammation and prevent pulmonary exacerbations in patients with CF. However, it remains to be ascertained what would be the effect of ICS treatment on MAIT cell numbers both at the circulating level and in the lung in patients with CF. In this regard, a recent study [33] in patients with COPD reported an impaired frequency and

Table 1 MAIT cells in Cystic Fibrosis

Author(s)	Year of study	Type of study	Conclusions
Smith et al. [45]	2014	Case Control	Reduced MAIT cell numbers in peripheral blood of patients with CF. Furthermore, reduced MAIT cell frequency was associated with Pseudomonas aeruginosa infection and more severe lung disease
Pincikova et al. [46]	2018	Case report	Pronounced near complete deficiency of circulating MAIT cells in a patient with CF, resulting in severely impaired control of bacterial infections. Findings gave credence to the view that MAIT cells are key players in mucosal defense
Pincikova et al. [47]	2017	Pilot study	Reduced MAIT cell frequency upon vitamin D treatment in patients with CF. Furthermore, change in free-s25OHD negatively correlated with PD-1 expression on MAIT cells

function of MAIT cells upon ICS treatment, making them more susceptible to future bacterial infections. A study by Pincikova et al. [47] reported a decreased peripheral blood MAIT cell frequency in patients receiving vitamin D, a structurally related steroid in patients with CF. In these patients, at the baseline free-s25OHD was positively associated with CD38 expression and HLA-DR expression on MAIT cells. Furthermore, change in free-s25OHD was correlated negatively with change in PD-1 expression on MAIT cells at the end of vitamin D treatment. In light of these observations, vitamin D may exert an influence on the activation state of MAIT cells in patients with CF, causing a decrease in both their numbers and exhaustion markers in circulation, possibly promoting the migration of activated MAIT cells to the lungs.

Immune imbalance in CF airways partially stems from a deficiency of regulatory subset of T cells known (Tregs), which serves to control the hyperinflammatory Th2/Th17 responses a hallmark in patients with CF [48]. A previous report by us [49], and Hector et al. [50] demonstrated a characteristic deficiency in Tregs in patients with CF and this deficiency of Tregs was correlated with lung function. Experimental evidence from study by Hector and colleagues [50] elucidated the role of *P. aeruginosa* in contributing towards Treg deficiency in patients with CF. Given these facts, it becomes pertinent to explore the crosstalk between MAIT cells and Tregs in patients with CF in the presence of bacterial infections namely *P. aeruginosa.* Future studies directed at understanding the possible relationship between MAIT cells and regulatory T cells (Tregs) in CF lung disease could unravel a holistic picture where a combination of antimicrobial effects of MAIT cells and anti -inflammatory effects of Tregs could be exploited in synergy to alleviate the rapid deterioration of lung function in CF lung disease. Also, studies directed at evaluating their expression in CF lung could serve useful in pinpointing the role of these MAIT cells in disease pathogenesis of CF. MAIT cells could be used as potential surrogate biomarker for infections in CF lung, for which extensive longitudinal studies in CF patients are warranted in future.

Conclusion

Increasing evidence suggests a deficiency of peripheral MAIT cells in patients with CF in response to bacterial infections. Future studies directed towards understanding whether this deficiency occurs at the circulating level only or is this also witnessed at pulmonary level could unravel holistic outlook towards pinpointing its role in pathogenesis of CF lung disease. Future studies directed towards exploring the role played by lung microbiome in CF patients and its interaction MAIT cells are warranted at the pulmonary level. Finally, it is pertinent to evaluate the relationship of MAIT cells with Tregs since the antimicrobial effects of MAIT cells and anti-inflammatory of Tregs could be exploited in synergy in the future to alleviate the rapid deterioration of lung function in patients with CF lung disease.

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