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Role of MAIT cells in pulmonary bacterial infection

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Abstract

Mucosal-associated invariant T (MAIT) cells represent a population of innate T cells that is highly abundant in humans. MAIT cells recognize metabolites of the microbial vitamin B pathway that are presented by the major histocompatibility complex (MHC) class I-related protein MR1. Upon bacterial infection, activated MAIT cells produce diverse cytokines and cytotoxic effectors and accumulate at the site of infection, thus, MAIT cells have been shown to be protective against various bacterial infections. Here, we summarize the current knowledge of the role of MAIT cells in bacterial pulmonary infection models.

Keywords

MAIT cells; MR1; innate immunity; pulmonary infection

1. Introduction

Pneumonia remains a frequent cause of morbidity and mortality worldwide and is the leading cause of death among children 5 years and younger (O'Brien et al. 2009). It can be caused by certain viruses and fungi; however, the most common cause of pneumonia is *Streptococcus pneumoniae*, a Gram-positive bacterium that transiently colonizes the healthy

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human respiratory tract, but that can become invasive resulting in pulmonary disease. Innate and adaptive immune responses play a pivotal role in host defense against bacterial pneumonia. In the early stages, natural killer (NK), natural killer T (NKT) and γδ T cells are protective during pneumococcal infection of mice and are involved in the recruitment and activation of macrophages and neutrophils to control bacterial colonization. Antibodies specific to capsular polysaccharides protect against individual capsular serotypes.

In recent years, a conserved subset of innate-like T lymphocytes called mucosal-associated invariant T (MAIT) cells have sparked interest as potentially important players in the protective immune response during bacterial and viral infections. MAIT cells are highly abundant in human peripheral blood as well as liver, lung and other sites, whereas their numbers are relatively infrequent in conventional, inbred mouse strains. MAIT cells express a semi-invariant TCR α chain, TRAV1–2–TRAJ33, TRAJ20 or TRAJ12 in humans and TRAV1-TRAJ33 in mouse, combined with a restricted set of TCR β chains, predominantly TRBV20 or 6 in humans and TRBV19 and 13 in mice. This TCR recognizes bacterial antigens presented by MR1, a highly conserved major histocompatibility complex (MHC) class I-related protein (Fig. 1). MR1 has been shown to bind to a new and surprising class of antigens, microbial vitamin B derivatives originating from riboflavin metabolism or folic acid degradation (Kjer-Nielsen et al. 2012). Potential effectors of MAIT cell antimicrobial activity include the secretion of TNF, IFNγ, IL-17A and IL-22 as well as granzyme B and perforin, however, how the antibacterial activity is orchestrated *in vivo* remains unknown. Here, we describe the recent progress and understanding of the role of MAIT cells in pulmonary bacterial infection models.

2. MR1 antigen presentation

MR1, like the MHC-encoded class I molecules, is a membrane anchored, tri-molecular complex consisting of an α chain, β2-microglobulin (β2m) and a bound ligand. Unlike most classical class I MHC molecules (HLA-A, B, C), the α chain encoded at the MR1 locus is relatively monomorphic, with the human allele having greater than 95% nucleotide identity with other primates (Greene et al. 2017). Also, the ligand bound to MR1 distinctly differs from other MHC molecules in that it is a small molecule metabolite instead of a peptide or lipid, as in the case of HLA and CD1 proteins, respectively.

The breath and structural identity of the small molecule ligands bound to MR1 are just beginning to be characterized. The first study to describe a ligand bound to MR1 was by Kjer-Nielsen L. et al. (Kjer-Nielsen et al. 2012). In this report, two ligands were identified: 6-formylpterin (6-FP) and a reduced form of 6-(hydroxymethyl)-8-D-ribityllumazine (rRL-6-CH2OH). The former ligand is derived from break-down products of folic acid that were found in the cell media. While crystallographic data showed 6-FP is bound covalently to Lys 43 in the groove of MR1, it does not activate TRAV1-2$^+$ MAIT cells (Kjer-Nielsen et al. 2012, López-Sagaseta et al. 2013). rRL-6-CH2OH was identified as an MR1 ligand when purified MR1 complexes that were refolded in cell supernatants from *Salmonella* Typhimurium were analyzed by mass spectrometry. rRL-6-CH2OH is thought to be a secondary metabolite from riboflavin synthesis because of its structural similarity to riboflavin precursors. Unlike 6-FP, rRL-6-CH2OH strongly activated TRAV1-2$^+$ MAIT cells

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and later was shown to be bound in the groove of MR1 by structural analysis of material from *Escherichia coli* supernatants (Kjer-Nielsen et al. 2012, López-Sagaseta et al. 2013).

Since the initial identification of the 6-FP and rRL-6-CH2OH, several other MR1 ligands have been discovered from intermediates or secondary metabolites of bacterial riboflavin synthesis. Of note are the two MAIT cell activating ligands 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU) and 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) (Corbett et al. 2014, Greene et al. 2017). Both molecules are products of a reaction between the lumazine precursor 5-amino-6-D-ribitylaminouracil (5-A-RU) and glyoxal and methylglyoxal, respectively. These normally unstable compounds are stabilized by covalently binding to Lys 43 in the MR1 groove in the same manner as 6-FP (Corbett et al. 2014). In addition to these uracil-based compounds, lumazines such as 7-hydroxy-6-methyl-8-D-ribityllumazine and 6,7-dimethyl-8-D-ribityllumazine (the direct precursor for riboflavin), have been shown to both bind to MR1 and activate MAIT cells (Meermeier et al. 2016, Patel et al. 2013).

While ligands from the bacterial riboflavin synthesis pathway activate MAIT cells, there is evidence for activating MR1 ligands from other non-riboflavin pathways. For example, a study by Meermeier et al. showed TRAV12-2^{+} MR1-restricted T cell recognition of microbial ligands from a bacterial strain unable to synthesize riboflavin: *Streptococcus pyogenes* (Meermeier et al. 2016). Furthermore, a recent report identified MR1-restricted T cells in human blood, called MR1 T cells by the authors, which have diverse TCRs and are not reactive to microbial antigens, but are activated in an MR1-dependent manner, suggesting the presence of a stimulatory self-ligand(s) presented by MR1 (Lepore et al. 2017). Indeed, the groove of MR1 can accommodate ligands derived from synthetic drugs with much more structural diversity than just lumazine and uracil-based compounds (Keller et al. 2017). Together these studies indicate the repertoire of MR1 ligands is not restricted to riboflavin and folic acid metabolites.

3. Antibacterial reactivity of MAIT cells after lung infections

3.1 Klebsiella pneumoniae

The Gram-negative bacterium *Klebsiella pneumoniae* colonizes mucosal surfaces in the nasal cavity and intestines and is the leading cause of infections, including pneumonia, in hospitalized patients. The global emergence of multi-drug resistant *Klebsiella* strains makes it a public health issue world-wide and requires the need for a greater understanding of its disease-causing mechanism and alternative treatments. Using a mouse model of systemic *Klebsiella* infection, Cogen and Moore discovered in 2009 that β2m-deficient or knockout (KO) mice are highly susceptible compared to their wildtype counterparts (Cogen and Moore 2009). A possible role for iNKT cells and CD8^{+} T cells was ruled out using *Cd1d*$^{-/-}$ and *Tap*-deficient mice. As MR1 has been shown to be associated with β2m, it was a possible candidate for the identified phenotype. Indeed, MR1-deficient mice showed high susceptibility and a low survival rate during *Klebsiella* infection (Georgel et al. 2011). Serum analyses of *Klebsiella*-infected mice demonstrated reduced cytokines, including TNF and IL-17, the latter cytokine having been described to be important for bacterial clearance and survival during *Klebsiella* infection (Aujla et al. 2008, Ye et al. 2001). Even though the

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data suggested that the IL-17-producing cells were MR1-restricted, the authors did not clearly identify the cell population due to the lack of an MR1-antigen tetramer in 2009. Later, it was shown that DCs infected with *K. pneumoniae* can trigger an *in vitro* response in MAIT cells from transgenic mice expressing the canonical MAIT TCR α chain *in vitro*, although only an increase in CD69 was reported and there was no direct evidence for cytokine release by MAIT cells (Le Bourhis et al. 2010). The *K. pneumoniae* genome contains genes encoding enzymes of the riboflavin pathway, however, and thus, *Klebsiella* is possibly capable of producing the required vitamin B metabolites for MAIT cell activation.

3.2 Francisella tularensis

Another Gram-negative bacterium, *Francisella tularensis*, is highly infectious and is usually transmitted to humans by handling infected animals. This intracellular pathogen is the causative agent of tularemia, and is studied in pulmonary infection models. In 2013, Meierovics and colleagues analyzed the role of MAIT cells during mucosal lung infection. Although the MR1-antigen tetramer was not available, they distinguished MAIT cells from other T cells by purifying the double-negative and TCR β-positive population and analyzing it for TRAV1-2 expression (Meierovics et al. 2013). After intranasal infection with the live vaccine strain of *F. tularensis*, MAIT cells expanded primarily in the lungs, and to a lesser extent in the liver, and produced protective cytokines including IL-17A, IFNγ and TNF in an MR1-dependent fashion. The secretion of the latter two cytokines depended on IL-12 signaling and was required for the ability of MAIT cells to control the intracellular growth of *F. tularensis* in macrophages *in vitro*. In contrast, IL-17A production was IL-12-independent and its blocking did not influence bacterial growth in macrophages. In addition to their antimicrobial activity, MAIT cells have been shown to be involved in the timely recruitment of $CD4^+$ and $CD8^+$ T cells, which are also crucial for final bacterial clearance.

Interestingly, in 2016 the same group reported on how MAIT cells influence the recruitment of conventional T cells after infection (Meierovics and Cowley 2016). As monocyte-derived dendritic cells (Mo-DC) have been implicated in stimulating $CD4^+$ and $CD8^+$ T cells, the authors analyzed Mo-DCs during *F. tularensis* infection. They could indeed show that MAIT cell-deficient mice accumulated significantly fewer CCR2-dependent $CD11b^+$ DCs in their lungs. Furthermore, Mo-DCs purified from wild-type mice and adoptively transferred into MR1-deficient mice rescued the number of $CD4^+$ T cells after infection, suggesting that the impaired recruitment of conventional T cells in $Mr1^{-/-}$ mice resulted from a reduced number of Mo-DCs. However, $Mr1^{-/-}$ mice did not have a diminished egress of $CD11b^+$ DC precursors from the bone marrow, thus, the lack of accumulation of Mo-DCs in infected lungs was suggested to result from impaired differentiation, which requires IFNγ and GM-CSF. When precursor monocytes from bone marrow obtained from wild-type and $Mr1^{-/-}$ mice were cultured in the presence of IFNγ and GM-CSF, the cells increased expression of MHC II and CD11c, showing that $Mr1^{-/-}$ mice have functional Mo-DC precursors, but are impaired in Mo-DC differentiation. The authors analyzed the direct effect of MAIT cells on monocyte differentiation *in vitro* and showed that $Ly6C^{hi}$ $CD11b^+$ monocytes upregulated MHC II and CD11c when co-cultured with MAIT cells and macrophages from *F. tularensis*-infected wild-type mice. Neutralizing antibodies for GM-CSF, but not for IFNγ, significantly reduced monocyte differentiation. In agreement with these *in vitro* data, the

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authors could show that *Mr1*$^{-/-}$ mice displayed strongly reduced GM-CSF levels in their lungs during the very early stage of infection when compared to their wild-type counterparts. GM-CSF-neutralizing antibodies also reduced the number of differentiated Mo-DCs co-expressing MHC II and CD11c.

Together, these data indicate that MAIT cells are required for early GM-CSF production which in turn induces the differentiation of recently recruited monocytes into Mo-DCs, cells that are able to take up and present *F. tularensis* antigens. It remains to be determined if those Mo-DCs are capable of migrating into the draining lymph nodes for CD4 and CD8 T cell activation. Thus, in this regard MAIT cells show similar features to iNKT cells, which stimulate the differentiation of DCs, dependent on GM-CSF, IL-13 and CD1d (Hegde et al. 2007). However, at least *in vitro*, MAIT cells did not require MR1 to induce monocyte differentiation, although it needs to be determined if this is also observed *in vivo* during infection. Additionally, MAIT cells produce cytotoxic molecules that can target *E. coli*-infected cells *in vitro* (Kurioka et al. 2015). Although the authors showed an early impact of MAIT cells during *F. tularensis* infection control, it is still not certain if their role only involves differentiation of monocytes and thus recruitment of other T cells, or if they also exhibit a direct antibacterial effect through cytotoxicity.

3.3 Streptococcus pneumoniae

The most common cause of community-acquired pneumonia is the gram-positive bacterium *Streptococcus pneumoniae*. There are over 90 serotypes of *S. pneumoniae*, all of which differ in their ability to cause disease. Although antibiotics and vaccines are available, they are not sufficiently effective for children and the elderly, and do not cover all disease-causing serotypes and strains. A greater understanding of the immune mechanisms that result in the progression of *S. pneumoniae* from an innocuous colonizer of the nasopharynx to lower respiratory pathogen is required for the development of improved therapeutics. Although CD8^{+} T cells are known for their role in controlling viral infections, results from mouse models demonstrate that CD8^{+} T cells also play a role in limiting bacterial dissemination and lung inflammation following infection with *S. pneumoniae* (Weber et al. 2011).

It has been suggested that MAIT cells could play a role in the early recognition and response to *S. pneumoniae*, as the bacteria encode enzymes required for riboflavin metabolism (Ivanov et al. 2014), however this was not tested until recently. Kurioka et al. examined the sequenced genomes of nearly 600 *S. pneumoniae* isolates from nearly all serotypes and found that over 98% of the isolates contained the riboflavin operon (Kurioka et al. 2017). Monocytes cultured with fixed reference strains stimulated CD69 expression and IFN-γ production by PBMC-derived MAIT cells from most donors. Interestingly, in assays with monocytes, the response was cytokine-dependent but MR1-independent, thus the importance of ligands from the riboflavin pathway was not proven in this context. In contrast, MAIT cell activation in the context of monocyte-derived macrophages incubated with fixed bacteria was dependent to some extent on both MR1 and cytokines.

We also examined MAIT cell responses to clinical *S. pneumoniae* isolates from the same serotype (19A), a serotype linked to invasive disease in some human subjects. MAIT cells

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were cultured with infected human Mo-DCs and airway epithelial cells (Hartmann et al. 2018). For many of the isolates, MAIT cells had MR1-dependent responses to cells infected with live bacteria, however, there was variability in the magnitude of the responses, and there were also isolates which elicited no MAIT cell responses. Although the strain with the highest antigenic activity was isolated from pleural fluid, there was no positive or negative correlation of invasive infection with antigenic activity for MAIT cells. Instead, we could demonstrate that the variation in MAIT cell responses was due to different bacterial expression levels of the enzymes in the riboflavin metabolic pathway, which were correlated to the genetics-based classification for *S. pneumoniae* isolates, Multilocus Sequence Type (MLST) groups. Similar to Kurioka et al., we further demonstrated that riboflavin availability could influence the expression of these bacterial enzymes and thus is likely to affect the synthesis of vitamin B metabolite ligands, which would change the ability of MAIT cells to recognize infected cells. The differences in expression of the riboflavin biosynthesis pathway that we observed could be important for early MAIT cell control of *S. pneumoniae* infection, as isolates that did not elicit MAIT cell responses were not well controlled *in vitro* by MAIT cells, and did not elicit the same level of cytokine production by mouse MAIT cells *in vivo*. Serotype 19A is not highly virulent in mice, and therefore clinical isolates with differences in riboflavin metabolism that are also pathogenic in mice will need to be tested, such that the role of these differences on bacterial control *in vivo* can be studied. Additionally, because MAIT cells can be activated by cytokines, such as IL-12 and IL-18, even in the absence of TCR stimulation, how cytokine-dependent and MR1-dependent mechanisms of MAIT cell activation function together *in vivo* in defense from extracellular pathogens, such as *S. pneumoniae*, remains to be explored.

3.4 *Salmonella* Typhimurium

The Gram-negative bacterium *Salmonella enterica* serovar Typhimurium causes gastrointestinal disease after foodborne or animal-to-animal transmission, and the emergence of multi-drug resistant *Salmonella* strains is a global health concern (Glynn et al. 1998).

S. Typhimurium has been shown stimulate MAIT cells *in vitro*, which was dependent on the microbial riboflavin pathway (Corbett et al. 2014, Kjer-Nielsen et al. 2012). Even though *S.* Typhimurium is not a lung pathogen, Chen et al. used the live-attenuated vaccine strain *S.* Typhimurium BRD509 for intranasal infection in mice to study MAIT cell activation *in vivo* after bacterial infection (Chen et al. 2017). Interestingly, the authors could show a drastic MR1-dependent accumulation of MAIT cells in lungs from infected wild-type mice, with MAIT cells representing up to 50% of T cells. Moreover, the response was sustained long-term post infection, with a peak at day 7. While intranasal administration of a riboflavin-deficient mutant or synthetic 5-OP-RU antigen alone could not stimulate MAIT cell enrichment, their co-administration rescued the MAIT cell accumulation effect. After infection, MAIT cells produced the pro-inflammatory cytokines IL-17A, TNF and IFNγ, which was sustained in a small percentage of the cells when analyzed directly *ex vivo* even 120 days post infection. During that time, the expression of RORγt in MAIT cells declined slightly and T-bet expression levels increased while long-term cells co-expressed both transcription factors. The T cell memory marker CD62L was low on MAIT cells before and after infection indicating an effector/memory phenotype.

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Despite the strong and sustained response of MAIT cells after *S.* Typhimurium infection, the authors did not detect any difference in bacterial clearance comparing wild-type and MR1-deficient mice, suggesting a T cell redundancy using this particular disease model. The most striking finding using *Salmonella* in a respiratory infection model was the persistence of an increased MAIT cell population long after the infection was cleared. This finding raises the question as to whether the high frequency of MAIT cells in humans might be due to consistent exposure to microbes, and furthermore, if this newly described strong response can be harnessed for fighting bacterial infections.

4. Concluding remarks

The addition of MR1 tetramers and synthetic antigens for MAIT cells to the immunologists' toolbox has significantly increased our understanding of MAIT cell protective function in the context of bacterial infections, but critical questions regarding their role during infections remain unanswered. MAIT cells initiate early immune responses, exhibit antimicrobial activity and are protective in various mouse models of pulmonary infections. In contrast, the role of MAIT cells in protection from infection in humans is not as well understood, and most studies are limited to PBMC-derived MAIT cells. Despite this limitation, MAIT cells have been studied in patients infected with various pathogens including *Mycobacterium tuberculosis*, *Helicobacter pylori*, *Pseudomonas aeruginosa* and *Vibrio cholerae* and the frequency of circulating MAIT cells in the blood from infected individuals was decreased in most cases (Booth et al. 2015, Gold et al. 2010, Leung et al. 2014, Smith et al. 2014). MAIT cell frequency in the blood was also decreased in a variety of viral and autoimmune diseases (Hinks 2016, Leeansyah et al. 2013, Serriari et al. 2014), suggesting that MAIT cells are involved in diverse types of immune responses. As MAIT cells are abundant in healthy human individuals, and they are capable of immediate secretion of Th1 and Th17 cytokines, they could be potential targets for enhancing vaccines or other immune therapeutics.

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HIGHLIGHTS

- activated MAIT cells accumulate in infected tissues and provide protection against various pulmonary bacterial infections
- synthesis of MAIT cell antigen is decreased in the presence of riboflavin
- clinical *Streptococcus pneumoniae* isolates differ greatly in their content of activating antigens for MAIT cells, suggesting the protective role of these cells could vary greatly

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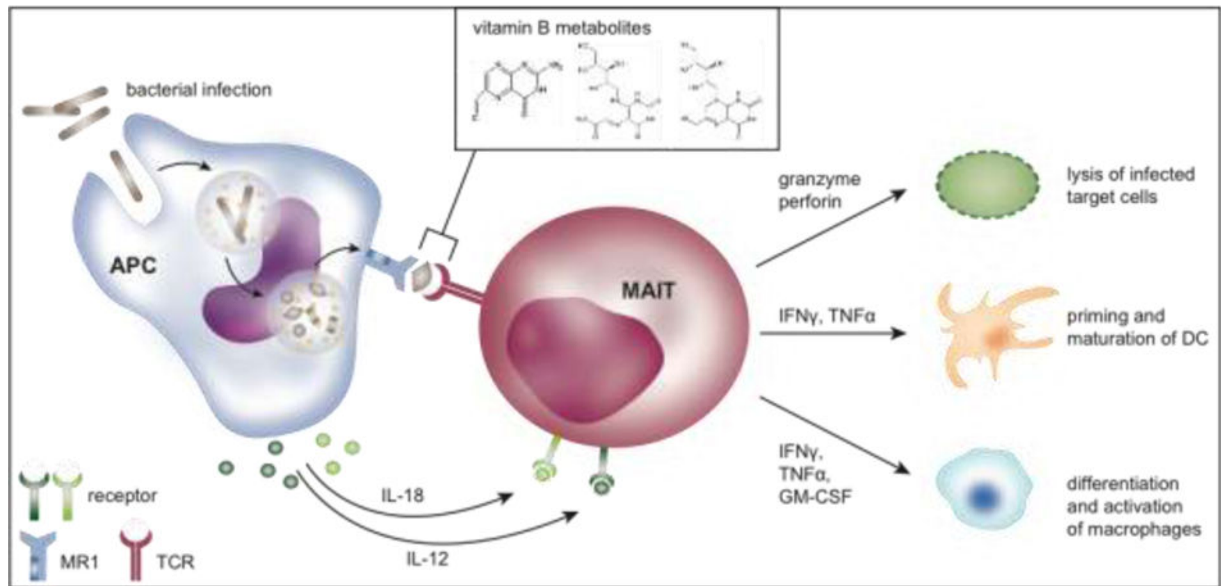

Fig. 1. Scheme for activation of MAIT cells during bacterial infections

Upon bacterial infection, bacteria or fragments of bacteria are taken up by antigen presenting cells (APC). Mucosal-associated invariant T (MAIT) cells recognize complexes of vitamin B metabolites and MR1 that form in endocytic compartments. The inset box shows some of these derivatives including (left to right): 6-FP which binds MR-1 but is not antigenic, antigenic compounds 5-OP-RU, and rRL-6-CH2OH. MAIT cell responses also can be driven by cytokines such as IL-12 and IL-18 from APC. Activated MAIT cells release a variety of cytotoxic molecules and cytokines.