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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 effector molecules 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.

## 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 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 mice, 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-

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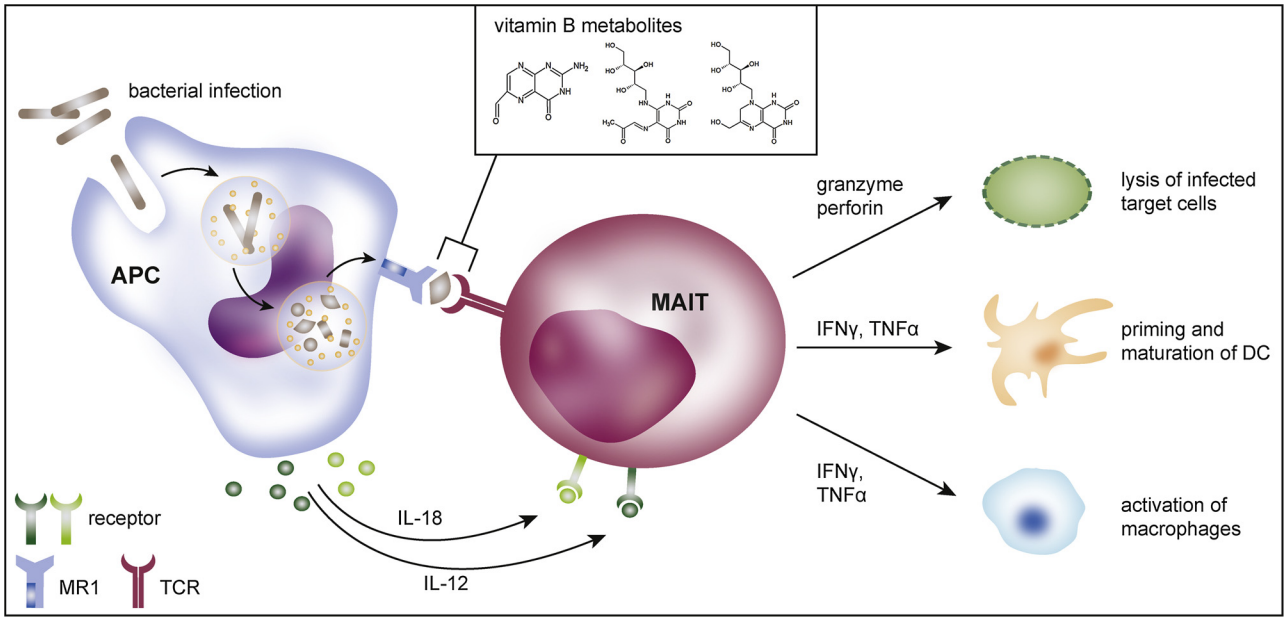


**Fig. 1.** Scheme for activation of MAIT cells during bacterial infections. Upon bacterial infection, bacteria or fragments of bacteria are taken up by antigen-presenting cells (APC). Mucosal-associated invariant T (MAIT) cells recognize complexes of vitamin B metabolites and MR1 that form in endocytic 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-$CH_2OH$. 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.

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-$CH_2OH$). The former ligand is derived from breakdown 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., 2013a, 2013b). rRL-6-$CH_2OH$ 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-$CH_2OH$ is thought to be a secondary metabolite from riboflavin synthesis because of its structural similarity to riboflavin precursors. Unlike 6-FP, rRL-6-$CH_2OH$ strongly activated TRAV1-2$^+$ MAIT cells 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., 2013a, 2013b).

Since the initial identification of the 6-FP and rRL-6-$CH_2OH$, 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 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