Immunology
The Journal of cells, molecules, systems and technologies

British Society for immunology

doi:10.1111/imm.12673

IMMUNOLOGY REVIEW ARTICLE

REVIEW SERIES: MAIT CELLS-LIGANDS AND FUNCTIONS
Series Editor: Chris Willberg

The role of mucosal-associated invariant T cells in infectious diseases

Emily B. Wong,[1,2,3] Thumbi Ndung'u[1,4,5,6] and Victoria O. Kasprowicz[1,4,5]

[1]*African Health Research Institute, Durban, South Africa,* [2]*Division of Infectious Diseases, Massachusetts General Hospital, Boston, MA,* [3]*Harvard Medical School, Boston, MA, USA,* [4]*HIV Pathogenesis Programme, Doris Duke Medical Research Institute, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa,* [5]*The Ragon Institute of MGH, MIT, and Harvard, Harvard Medical School, Cambridge, MA, USA and* [6]*Max Planck Institute for Infection Biology, Berlin, Germany*

doi:10.1111/imm.12673
Received 29 June 2016; revised 19 August 2016; accepted 5 September 2016.
Correspondence: Emily B. Wong, African Health Research Institute, Nelson R. Mandela School of Medicine, 719 Umbilo Rd, Congella, Durban, 4001, South Africa.
Emails: ebwong@mgh.harvard.edu, emily.wong@k-rith.org
Senior author: Victoria Kasprowicz

Summary

Mucosal-associated invariant T (MAIT) cells are donor-unrestricted lymphocytes that are surprisingly abundant in humans, representing 1–10% of circulating T cells and further enriched in mucosal tissues. MAIT cells recognize and are activated by small molecule ligands produced by microbes and presented by MR1, a highly conserved MHC-related antigen-presenting protein that is ubiquitously expressed in human cells. Increasing evidence suggests that MAIT cells play a protective role in anti-bacterial immunity at mucosal interfaces. Some fungi are known to produce MAIT-activating ligands, but the role of MAIT cells in fungal infections has not yet been investigated. In viral infections, specifically HIV, which has received the most study, MAIT cell biology is clearly altered, but the mechanisms explaining these alterations and their clinical significance are not yet understood. Many questions remain unanswered about the potential of MAIT cells for protection or pathogenesis in infectious diseases. Because they interact with the universal, donor-unrestricted ligand-presenting MR1 molecule, MAIT cells may be attractive immunotherapy or vaccine targets. New tools, including the development of MR1-ligand tetramers and next-generation T-cell receptor sequencing, have the potential to accelerate MAIT cell research and lead to new insights into the role of this unique set of lymphocytes in infectious diseases.

Keywords: bacterial; cytotoxic T lymphocytes; mucosa; viral.

Introduction

What are MAIT cells and what is known about their phenotype and function?

Mucosal associated invariant T (MAIT) cells are $\alpha\beta$ T cells with a limited T-cell receptor (TCR) repertoire that uses mostly TRAV1-2 recombined with a biased set of TRAJ genes (primarily TRAJ 33, TRAJ 12 and TRAJ 20) and TCR-β chains.[1–4] MAIT cells are uniquely activated by small molecule vitamin B metabolites presented by the ubiquitously expressed and non-polymorphic MHC-class 1-like molecule, MR1.[5–9] Circulating MAIT cells express certain phenotypic markers that have been used in varying combinations to identify them in human specimens: TRAV1-2, IL-18Ra, IL-23/12Ra, and high expression of both CD26 and CD161.[10,11] Use of different phenotypic definitions of MAIT cells has limited comparability of findings in the field. The recent development of ligand-loaded MR1 tetramers promises to aid in consistent definitions.[12] At this point it appears that MR1 tetramers loaded with 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) stain the vast majority of MR1-reactive cells in the peripheral blood of healthy humans, though whether additional classes of MAIT cell activating MR1 ligands exist is a topic of ongoing active investigation.[13]

MAIT cells comprise 1–10% of circulating $CD3^+$ T cells in healthy adults.[14,15] Although their distribution in tissues has not been thoroughly investigated, they have been found to be enriched in the gastrointestinal tract, liver and airway.[10,16–19] MAIT cell activation can result from either TCR-dependent signalling (triggered by ligand presented on MR1 by antigen-presenting cells) or from TCR-independent cytokine signalling.[20–23] Like other 'innate-like' lymphocytes including invariant natural killer T

cells and natural killer cells, MAIT cells respond rapidly to activation by producing cytokines and cytolytic products. Upon TCR-dependent or TCR-independent activation, MAIT cells produce interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α), cytolytic products (perforin, granulysin and granzymes) and degranulate (exposing CD107a to the cell surface).[10,11,24–26] Interleukin-12 (IL-12) and IL-18 have been shown to induce MAIT cell production of IFN-γ in the absence of TCR signalling.[22] Both IL-15 and IL-7 have each been shown to license MAIT cells for enhanced production of TCR-activated pro-inflammatory cytokines and cytolytic products.[23,26,27] MAIT cells express the transcription factors promyelocytic leukaemia zinc finger protein (PLZF) and RAR-related orphan receptor (ROR$\gamma\tau$) and do not develop in *Rorc*$^{-/-}$ mice.[26,28] Multiple groups have noted that circulating MAIT cells produce IL-17 upon PMA/ionomycin stimulation but not TCR-triggered stimulation.[10,17,26,29] A recent study found that compared with peripheral blood MAIT cells, MAIT cells from the female genital tract produced significantly more IL-17 and IL-22 and significantly less IFN-γ or TNF-α when stimulated with either bacteria or PMA/ionomycin.[30] The significance of IL-17 production by MAIT cells *in vivo* requires further investigation.

The MAIT cell biology field is still in its early stages. Despite recent increased interest and increasing numbers of papers that examine MAIT cells in human diseases and animal models of diseases, many questions remain unanswered about the function of this immune subset in the healthy and perturbed immune system. Here we review the rapidly evolving literature concerning the role of MAIT cells in infectious diseases and highlight areas of evolving consensus and remaining gaps in knowledge.

MAIT cells in infectious diseases

In their structure and function MAIT cells appear to bridge the innate and adaptive immune system. They are $\alpha\beta$ T cells whose TCRs have restricted diversity and recognize small molecule microbial metabolites. In the process of synthesizing riboflavin, many bacterial and fungal organisms, both pathogens and commensals, produce small molecule intermediates that have the capacity to directly activate MAIT cells.[9,31,32] It has been hypothesized that these small molecule metabolites may comprise a novel class of microbial 'danger' signals that alert the host's immune system – via MAIT cells – to the presence of non-host products. However, the exact role that this class of unique T cells plays in the detection of and response to these organisms in human disease is unknown. Data from *in vitro* experiments, animal models of disease and observational human cohorts provide some indication of the role that MAIT cells may play in infections with MR1-ligand producing organisms (bacteria and fungi) and in infections with non MR1-ligand producing organisms (viruses). The role that MAIT cells play in other classes of human infectious disease – including parasitic infections – is completely unknown.

The role of MAIT cells in bacterial and mycobacterial infections

Insights from *in vitro* experiments

Upon exposure to bacteria that produce MR1 ligands, MAIT cell clones cultured from human peripheral blood and polyclonal MAIT cell populations isolated from human peripheral blood (TRAV1-2^{+} CD161^{++}) produce pro-inflammatory cytokines (TNF-α, IFN-γ) and cytolytic products (granzymes, granulysin, perforin).[11,20,21,24–26] This is true when MAIT cells are exposed to bacterial preparations directly (fixed *Escherichia coli*, *Mycobacterium tuberculosis* lysate) or when MAIT cells are added to cultured cells that have been experimentally infected (with *E. coli*, *Salmonella typhimurium*, *Mycobacterium smegmatis*, *M. tuberculosis*).[13,20,33] The production of cytokines and cytolytic products by MAIT cells in these experiments appears to largely depend on TCR signalling triggered by MR1-presented ligand and can be augmented by pre-conditioning with a number of cytokines including IL-12, IL-23, IL-15 and IL-7.[22,23,26,27] Adding MAIT cells to infected cells can result in lysis or apoptosis of the infected cells.[1,25,26] Moreover, MAIT cells have the ability to decrease mycobacterial burden when added to experimentally infected cell cultures. Chua *et al.*[34] showed that the addition of polyclonal MAIT cells to macrophages experimentally infected with *Mycobacterium bovis* BCG inhibited bacterial growth. Lepore *et al.*[1] demonstrated that MAIT cell clones with typical (TRAV1-2/TRAJ33) and atypical (TRAV1-2/TRAJ12) TCRs decreased *M. bovis* BCG load in infected macrophages. In sum, these *in vitro* experiments show that bacterially produced MR1 ligand activates MAIT cells and triggers the secretion of pro-inflammatory cytokines and cytolytic products that can directly lyse and/or cause apoptosis of the infected host cells. In models of mycobacterial infection MAIT cells enhance the ability of macrophages to inhibit the growth of intracellular organisms. Whether the primary mechanism of control is through enhancing the ability of macrophages to control infection or by killing infected cells is unknown. The effector functions of MAIT cells in the context of bacterial and mycobacterial infection appear to rely in part on bacterially produced ligand being presented by MR1, with cytokines produced in the context of infection potentiating MAIT cell effector functions (Figure 1).

Insights from animal experiments

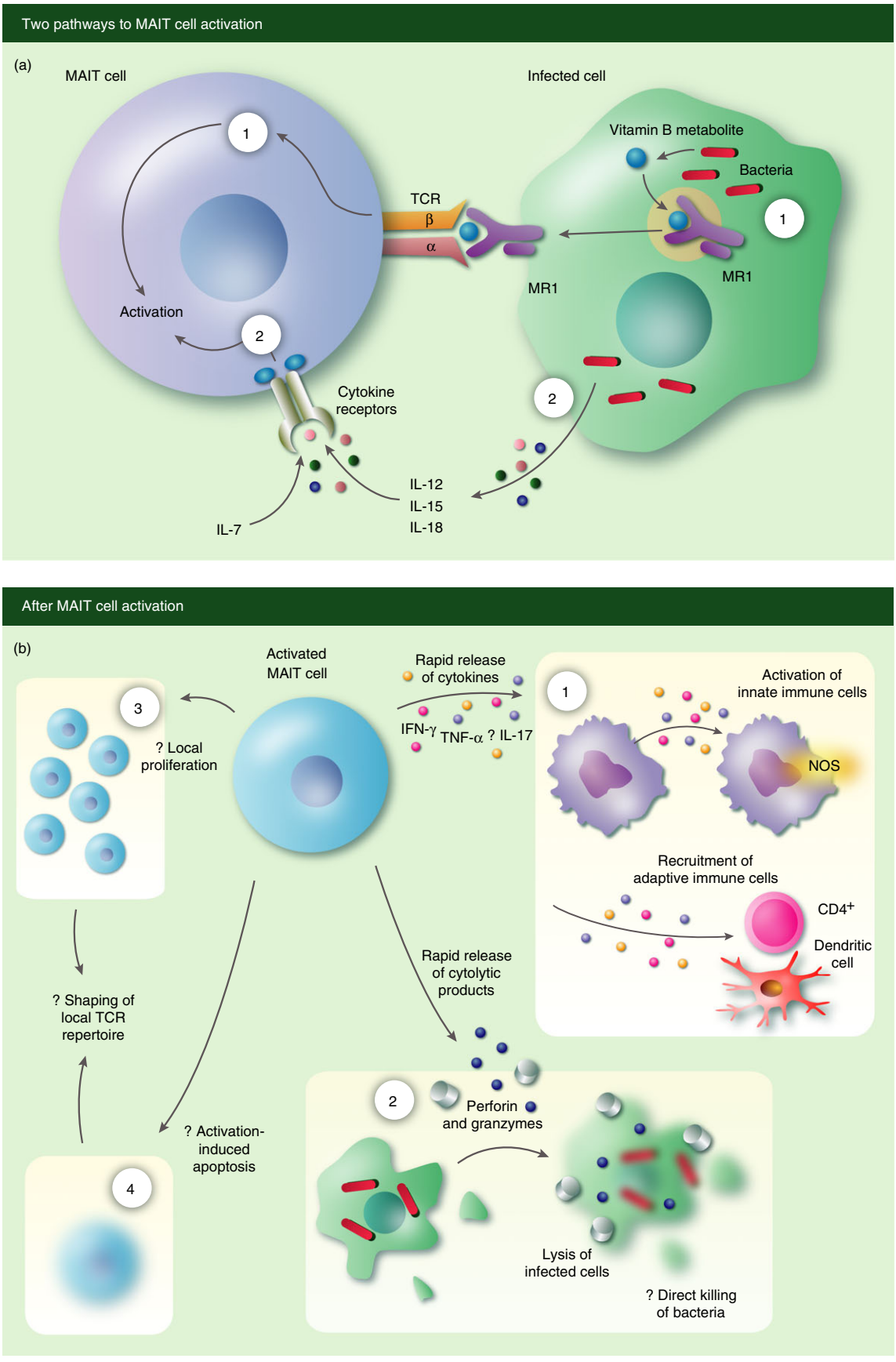
MR1 is highly conserved among mammals, and although mice have considerably lower levels of MAIT cells than

humans, experiments using mice have provided some insights into the role that MAIT cells may play in the immune response to infections with MR1-ligand producing bacteria.[3,4,35] These experiments make use of transgenic mouse strains that over-express MAIT cells (Vα19i-Tg and Vβ6-Tg), MR1 knock-outs (MR1-KO) of the transgenic strains and wild-type C57BL/6 mice. These models have allowed comparisons of the outcome of experimental infection in mice with enhanced, intact or disrupted MR1–MAIT cell axes. When exposed to the same initial intraperitoneal inoculum, C57BL/6 MR1-KO mice developed higher burdens of systemic infection with *Klebsiella pneumoniae* and had decreased survival compared with wild-type animals.[36] This suggests that MR1 (and presumably MAIT cells) play a protective role and aid in the containment of *K. pneumoniae* infection. Interestingly, these findings were not replicated in similar infections with three other Gram-negative organisms that are known to produce MR1-ligands: *E. coli*, *Shigella dysenteriae* and *Yersinia enterocolitica.* Another group making use of the transgenic over-expressing MAIT cell mice (both Vα19i-Tg and Vβ6T), found that MR1-KO mice had higher bacterial burdens of both *E. coli* and *Mycobacterium abscessus* than those with intact MR1.[21] Sakala *et al.*[37] recently compared outcomes in the Vα19i-Tg stain (and its MR1-KO) and C57BL/6 (and its MR1-KO) after nasal aerosolized *M. tuberculosis* infection and found that the MAIT over-expressing mice had the lowest burden of infection and the MR1 KO mice had the highest. This growing body of evidence suggests that an intact MAIT cell–MR1 axis may be protective against some (but not all) bacterial infections with MR1-ligand producing organisms.

Additional data suggest that the protective role of MAIT cells in these infections probably occurs in the early days after exposure to pathogen. Chua *et al.*[34] demonstrated that MR1 KO mice had higher burdens of pulmonary infection 10 days after aerosolized infection with *M. bovis*, but that after 30 days there was no difference in the bacterial burden between the two groups. Using intranasal infection with the live vaccine strain of *Francisella tularensis* (LVS) in BL/6 wild-type and MR1-KO mice, Meierovics *et al.*[38] demonstrated that MAIT cells appear to have a direct, early antibacterial effect in the lungs and a sustained impact on the establishment of an effective adaptive mucosal immune response. Specifically, they demonstrated that upon exposure to LVS *F. tularensis*, MAIT cells, here defined as double-negative T cells that were enriched for the canonical MAIT cell TCR Va19-Ja33, accumulated in the lungs and were associated with brisk production of IFN-γ, TNF-α, IL-17A and iNOS as well as significantly faster clearance of the bacteria from the lungs. The authors explored the relative contribution of MAIT cells and classical $CD4^+$ and $CD8^+$ T cells to bacterial control and investigated the impact of MAIT cells on the classical adaptive immune response. In mice depleted of classical $CD4^+$ and $CD8^+$ T cells but with intact MR1, MAIT cells were able to control LVS *F. tularensis* infection and establish a state of chronic non-lethal infection for up to 2 months. In contrast, mice depleted of both classical T cells and MR1/MAIT cells died rapidly, suggesting that MAIT cells have the ability to control infection for prolonged periods of time even in the absence of conventional T cells. Importantly, in this study the adaptive immune system was incapable of optimal function in the absence of MR1 and MAIT cells. In the MR1-KO mice, recruitment to the lungs of activated IFN-γ producing classical $CD4^+$ and $CD8^+$ T cells was significantly delayed and attenuated with 60–80% fewer conventional T cells recruited to the lungs at Day 8 following infectious challenge. Taken together these findings suggest that MAIT cells are poised in the mucosal surface of the airways and lungs, where they provide early control of bacterial infection through production of pro-inflammatory cytokines and antimicrobial products (Fig. 2). Additionally, during this period of early infection they are required for the establishment of optimal adaptive immune response. The mechanisms by which MAIT cells lay the ground work for later adaptive immunity is unknown.

Insights from study of human cohorts

In one of the first studies of MAIT cells in human disease, Gold *et al.*[20] demonstrated that *M. tuberculosis*-reactive MR1-restricted T cells were found in the peripheral circulation of all the people that they assessed, including those who had no evidence of previous exposure to *M. tuberculosis.* Interestingly, these innately *M. tuberculosis*-reactive T cells were found at much lower levels in those individuals with active tuberculosis (compared with those with no history of exposure, or those with evidence of latent infection). Other studies have confirmed that MAIT cell frequencies are decreased during active tuberculosis (and non-tuberculosis mycobacterial lung disease) in diverse geographic settings.[11,21,33,39] Peripheral depletion of MAIT cells is not, however, disease specific, with low levels of peripheral MAIT cells found in individuals with cystic fibrosis experiencing pulmonary exacerbations due to *Pseudomonas aeruginosa*,[40] non-streptococcal sepsis[41] and cholera.[42] There is evidence that the degree of peripheral MAIT depletion may correlate with disease severity and may be reversed with antibiotic treatment during recovery from illness.[11,39–41] Interestingly, in a study of peripheral MAIT cells in intensive care unit patients with sepsis, failure of peripheral MAIT cells to rise during the intensive care unit stay was correlated with the subsequent acquisition of secondary infections.[41] Depletion of MAIT cells in the peripheral blood is not specific to bacterial infection and is also observed in



infections due to non MR1-ligand producing organisms (i.e. viral infections, discussed below) and non-infectious states of disease including autoimmunity, asthma, obesity and diabetes (beyond the scope of this article).[43–46]

The mechanism for depletion of peripheral MAIT cells during active bacterial infections is unknown. Although MAIT cells are named for their enrichment in the gut mucosa, there are very few human data about mucosal MAIT cells during bacterial infections that would allow assessment of the hypothesis that peripheral depletion is due to redistribution of MAIT cells to the site of disease. *Mycobacterium tuberculosis*-reactive MAIT cells were found in healthy uninfected lung tissue by Gold *et al.*[20] and MAIT cells were found to be present in two *M. tuberculosis*-infected lungs by LeBourhis *et al.*[21] without control tissue or paired peripheral sample available for comparison. LeBourhis *et al.*[21] reported enrichment of MAIT cells in the ascites fluid from a single patient with tuberculosis peritonitis, but in a larger series, Jiang *et al.*[33] found diminished frequencies of MAIT cells in pleural fluid from patients with tuberculosis pleuritis and non-enriched levels of MAIT cells in the peritoneal fluid of patients with tuberculosis peritonitis. Hence, it is not clear whether MAIT cell depletions in bacterial infections are due to redistribution to mucosal sites.

The few MAIT cells that remain in circulation during active pulmonary tuberculosis have diminished functional capacity, producing less IFN-γ upon stimulation and decreased transcription of effector genes (IFN-γ, TNF-α, IL-17F, granulysin and granzyme B).[33,39] These functionally impaired MAIT cells express higher levels of pro-apoptotic markers and higher levels of the inhibitory co-stimulating molecule programmed death-1 (PD-1) than MAIT cells from non-tuberculous patients.[33,39,47] *In vitro* blockade of PD-1 can increase IFN-γ production in circulating MAIT cells from patients with tuberculosis.[33]

In summary, human data provide little indication about the role that MAIT cells are playing in bacterial infectious disease, but do demonstrate that during active bacterial infections MAIT cells become depleted from the peripheral blood and those that remain display a dysfunctional phenotype. Using the mouse model, Sakala *et al.*[37] found that peripheral MAIT cells up-regulate integrins and cell trafficking molecules to migrate to the lungs soon after aerosolized mycobacterial infection. Given that the animal data suggest migration of peripheral MAIT cells to the lung upon respiratory exposure and protective activity of MAIT cells in the lungs, the lack of human data about the role of MAIT cells at mucosal sites during bacterial infection is a considerable gap in the field.

Fungal infections

Candida albicans and *Candida glabrata* both have intact riboflavin synthesis pathways and have both been shown to activate MAIT cells *in vitro*.[21] Other fungal pathogens have not been evaluated. Gold *et al.*[13] compared the T-cell receptor repertoire of *C. albicans*-reactive MAIT cells to *M. smegmatis*-reactive or *S. typhimurium*-reactive MAIT cells and found that the *C. albicans*-reactive MAIT TCR repertoire appeared to be less diverse than the repertoires of cells reactive to the other two pathogens. The authors hypothesize that this might be due to previous expansion of *C. albicans*-reactive MAIT cell clonotypes in response to specific MR1-restricted ligands from this relatively ubiquitous commensal. The clinical significance of MAIT cells in commensal fungal colonization or in pathogenic fungal infection has not been investigated in either animal models or human cohorts. Whether other pathogenic fungi have the capacity to activate MAIT cells *in vitro* or engage MAIT cells *in vivo* is also unknown.

Viral infections

In contrast to many bacterial and fungal pathogens, viruses lack the metabolic pathways to synthesize riboflavin and therefore do not produce MAIT cell activating MR1 ligands. Indeed, *in vitro* infection of antigen-presenting cells with a panel of viruses (including encephalomyocarditis virus, Sendai virus, Newcastle disease virus, herpes simplex virus and parainfluenza 3 virus) failed to activate MAIT cells directly.[21] Recently, however, a report by van Wilgenburg *et al.*[48] has demonstrated that MAIT cells can be activated in an MR1-independent cytokine-driven manner by dengue virus, hepatitis C virus and influenza virus. Interleukin-18 signalling is most central to MAIT activation in these settings, though the effects of other virally driven cytokines

Figure 1. Mucosal-associated invariant T (MAIT) cell activation and activities in the setting of infection. (a) Infected cells activate MAIT cells by two independent pathways. (1) Bacteria produce small molecule vitamin B metabolites that are loaded onto MR1 and presented on the surface of the infected cell. The semi-invariant MAIT cell T-cell receptor $\alpha\beta$ (TCR-$\alpha\beta$) binds the MR1–ligand complex resulting in TCR-dependent MAIT cell activation. (2) Alternatively, or additionally, cytokines produced by infected cells, including interleukin-12 (IL-12), IL-15, IL-18 and IL-7 can activate MAIT cells through cytokine receptors. (b) Upon activation, MAIT cells perform anti-bacterial effector functions. Rapidly, they release effector molecules including (1) cytokines [including interferon-γ (IFN-γ), tumour necrosis factor-α (TNF-α) and possibly IL-17] and (2) cytolytic products (including granzymes and perforin). In the tissue environment these may result in the activation of innate immune cells, lysis of infected cells, direct killing of bacteria, and recruitment of other immune cells to the site of infection. (3) MAIT cell activation may result in local proliferation and/or (4) apoptosis of individual MAIT cell clones both of which may potentially shape the tissue-resident TCR repertoire.

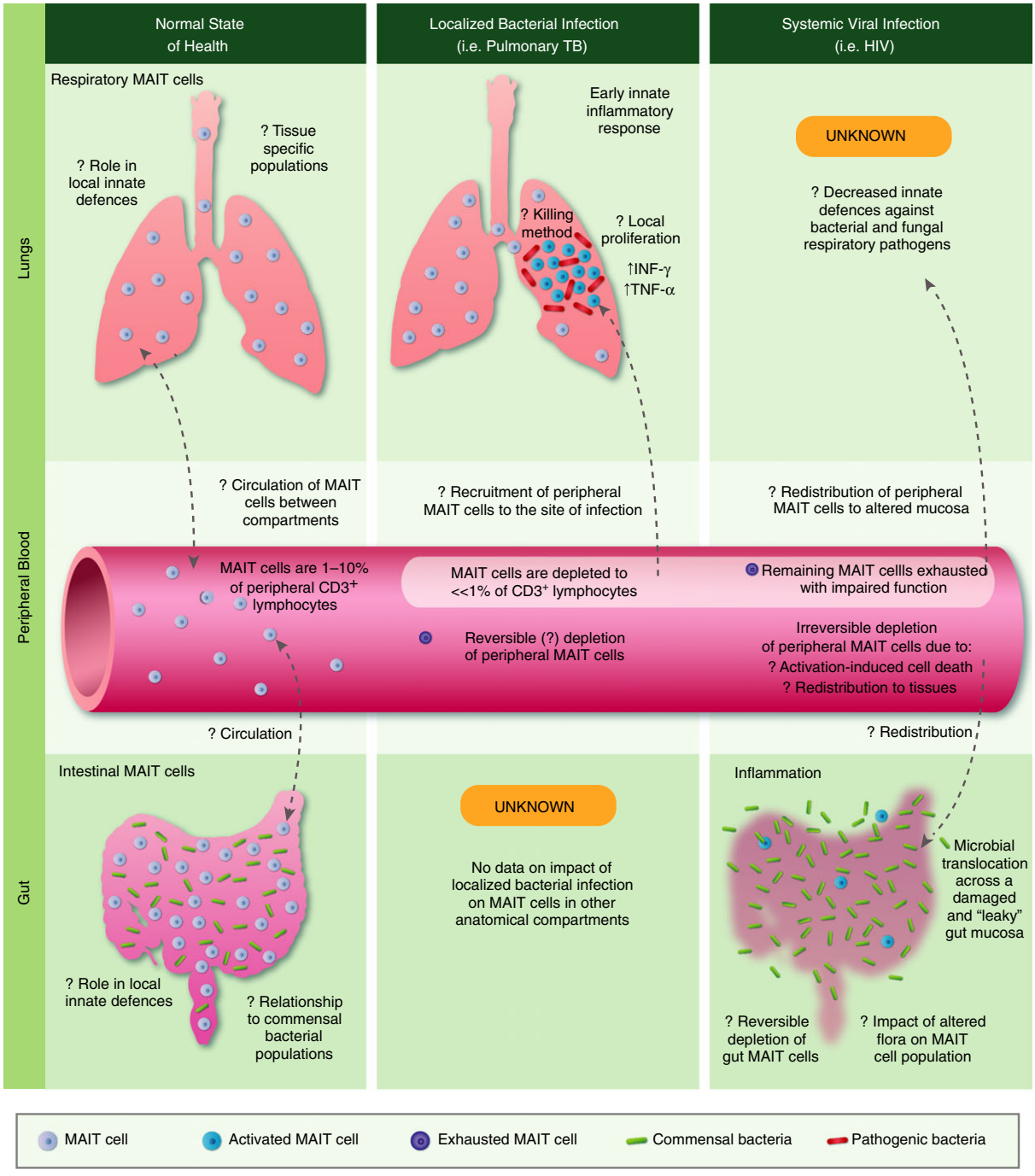


Figure 2. Mucosal-associated invariant T (MAIT) cells during bacterial and viral infection. In a state of health (left panel), MAIT cells are abundant in the circulation, comprising 1–10% of $CD3^+$ lymphocytes and are present in both respiratory and gut mucosa. The relationship of MAIT cells to commensal microbial populations in the gut and upper airway and the extent to which MAIT cell populations are tissue-specific is not well understood, but they are likely to contribute to innate anti-bacterial defences at both sites. During local bacterial infection (i.e. pulmonary tuberculosis, middle panel) MAIT cells may become enriched at the site of infection and possibly contribute to the early anti-bacterial immune response. Circulating MAIT cells become depleted and the remaining population is activated, exhausted and dysfunctional. There is some evidence that this may be reversible after the infection resolves. It is unknown what impact infection at one mucosal surface has on MAIT cells at a distant site, i.e. the impact of pulmonary infection on gut MAIT cells or vice versa. During systemic viral infection [i.e. human immunodeficiency virus (HIV) infection, right panel], MAIT cells in the peripheral circulation are irreversibly depleted and those remaining in circulation are activated, exhausted and dysfunctional. It is hypothesized that this may be driven by microbial translocation across a damaged gut epithelium leading to activation-induced death of MAIT cells systemically. Alternatively, MAIT cells may redistribute to other mucosal surfaces. The impact of altered microbial populations in the gut is unknown. To date there are no data on the impact of HIV on MAIT cells in the human lung.

including IL-12, IL-15 and IFN-α/β also contributes. It has long been apparent that chronic viral infections, especially human immunodeficiency virus (HIV) and hepatitis C virus (HCV), appear to alter human MAIT cells significantly by unclear mechanisms, so these new results may shed light on the altered role of MAIT cells during viral infections.

HIV

Investigations of MAIT cells from several cohorts of HIV-infected people from around the world (USA, Europe, South Africa and Australia) have shown that people with chronic HIV infection have significantly lower levels of peripheral MAIT cells than comparable healthy controls.[49–54] Interestingly, the degree of MAIT cell depletion does not correlate to the usual markers of HIV disease progression, including the degree of peripheral $CD4^+$ T-cell depletion or the level of viral replication in the blood (HIV viral load).[51,54] Even individuals who appear to have a natural ability to control HIV infection (long-term non-progressors and elite controllers) have been found to experience similar levels of MAIT cell depletion to those observed in people with chronic progressive HIV infection.[50] Leeansyah *et al.*[26,53] have found that the MAIT cells that remain in the peripheral circulation of patients with HIV are functionally impaired compared with MAIT cells from healthy people. Upon bacterial stimulation, they have found that MAIT cells from people with untreated chronic HIV produce lower levels of effector cytokines (IFN-γ, TNF-α, IL-17) and cytolytic products (granzyme A, granzyme B, CD107a and perforin) upon stimulation with bacterial MR1 ligand.[26,53] Interestingly, these authors have found that *in vitro* treatment with IL-7 has the capacity to restore the cytolytic response to bacterial exposure in MAIT cells from HIV-infected people.[26] In contrast, Fernandez *et al.*[55]found that MAIT cells from individuals with chronic untreated HIV retained comparable levels of IFN-γ and TNF-α production upon stimulation with purified MR1 ligand. The contrasting findings about the functionality of residual MAIT cell populations may be due to differences in the functional assays used by each group. Fernandez *et al.* stimulated MAIT cells from HIV-positive patients with an hMR1 over-expressing cell line that had been pulsed with purified synthetic MAIT cell activating antigen. In contrast, Leeansyah *et al.*[26,53] stimulated peripheral blood mononuclear cells with paraformaldehyde-fixed whole *E. coli*. Differences in the strength of stimulation and cytokine co-stimulation or inhibition may explain the discrepant findings. At this point, therefore, there is consensus in the finding of MAIT cell depletion but lack of consensus on the functional capacity of those MAIT cells that remain in circulation in patients with chronic HIV (Figure 2).

MAIT cell depletion appears to occur very early (within the first few weeks) after HIV infection.[49,54,55] To date there have been no animal or human studies following individuals longitudinally before and after HIV infection to address the possibility that individuals with pre-existing low levels of peripheral MAIT cells are more likely to become HIV infected. Nonetheless, the leading hypothesis in the field is that events surrounding acute HIV infection result in peripheral MAIT cell depletion. Circulating MAIT cells express high levels of CCR5, which is the co-receptor that facilitates HIV entry into $CD4^+$ T cells. However, Cosgrove *et al.*[49] performed *in vitro* infections with a CCR5-trophic HIV strain and found that peripheral MAIT cells are no more likely to be directly infected by HIV than other T cells. Finding that *E. coli* exposure induced caspase-3-mediated apoptosis in MAIT cells, they proposed that translocation of microbial products due to injury to the intestinal mucosa during acute HIV infection could result in uncontrolled activation and activation-induced MAIT cell death.[49] In support of this hypothesis, which was also put forth by Leeansyah *et al.*[53], activation markers (CD38 and HLA-DR) are elevated on MAIT cells from HIV-infected individuals compared with healthy controls and levels of MAIT cell activation inversely correlate with MAIT cell frequency.[50,51,56] Despite the fact that multiple groups have put forward the hypothesis that MAIT cell depletion is due to microbial translocation, no study to date has directly linked plasma markers of microbial translocation to MAIT cell loss or dysfunction. An alternative, and perhaps related, hypothesis to explain the absence of peripheral MAIT cells in HIV is that they redistribute to mucosal sites and become sequestered there. The human data on non-peripheral MAIT cells in HIV are very limited. Eberhard *et al.*[50] found that MAIT cells were reduced in the lymph nodes of HIV patients compared with uninfected controls. MAIT cell levels in the colon have been assessed by three groups and were also found to be lower in HIV-infected compared with uninfected people during chronic infection.[49,52,53] Recently, human MR1-5-OP-RU tetramers were used to evaluate MAIT cell distribution in simian immunodeficiency virus-infected rhesus macaques. Although limited by lack of species-specific reagents, this study found low frequencies of MAIT cells in all examined tissue sites (peripheral blood, liver, mesenteric lymph nodes, jejunum and bronchoalveolar lavage) of simian immunodeficiency virus-infected animals.[57] There are therefore currently no data to support the redistribution hypothesis; however, with only two non-blood sites having been investigated to date human data are limited.

Studies suggest that otherwise effective antiretroviral therapy that suppresses HIV viral load and restores peripheral $CD4^+$ T cells does not appear to restore circulating MAIT cell frequencies.[49,50,53,54,58,59] Greathead

et al.[52] have reported that colonic MAIT cells were restored to levels comparable to those of healthy controls after long term ART. Although there is no consensus about the effect of HIV on residual MAIT cell function, the group that reported that cytokine and cytolytic function decreased during chronic untreated HIV infection has found that antiretroviral therapy partially restores functional capacity.[53] Importantly there has been a single report of a patient who received antiretroviral therapy very early after HIV infection (Fiebig Stage III) who had relatively preserved MAIT frequencies.[50]

In summary, HIV infection is associated with early and largely irreversible depletion of MAIT cells from the peripheral circulation. The mechanism for this depletion is currently unknown and does not appear to be direct viral infection. Whether or not this peripheral depletion is reflective of universal MAIT cell depletion or whether it may be due to redistribution to mucosal sites has not been definitively addressed, although there is some intriguing data indicating that mucosal MAIT cells may be more responsive to antiretroviral therapy than circulating MAIT cells. The impact that HIV-induced MAIT cell alterations have on overall immune function is unknown. Gaardbo *et al.*[60] have found that low MAIT cells are associated with a constellation of immunological and metabolic derangements that are linked to immune activation and poor outcomes, but the specific role of MAIT cells in this is unclear. Based on the previous discussion of the role of MAIT cells as pre-armed mucosal effectors that respond to bacterial and fungal infections early and contribute to the eventual quality of the adaptive immune response, it is hypothesized that derangements of normal MAIT cell frequencies, function and distribution in HIV may play a role in the increased vulnerability to mucosal bacterial and fungal infections that is seen both early in and throughout the course of HIV disease. Assessing this hypothesis and determining mechanisms and potential strategies for intervention are critical next steps for the field.

MAIT cells and viral hepatitis

MAIT cells are significantly enriched in the liver, where they have been found to comprise up to 50% of liver-resident lymphocytes. They are found primarily in the biliary tract and in the context of liver infection can be activated by MR1-presented bacterial ligand or indirectly via IL-12 and IL-18 produced by antigen-presenting cells in response to Toll-like receptor 8 signalling triggered by viral RNA.[18,61] Jo *et al.*[18]found that MAIT cells were enriched in normal and chronically hepatitis B virus-infected livers but were relatively depleted in end-stage liver disease. Billerbeck *et al.*[17] found that $CD161^{++}$ $CD8^{+}$ cells (probably MAIT cells) had higher capacity for IL-17 and IL-22 production in the liver compared with the peripheral blood and that dual functionality (ability to co-express IL-17 and IFN-γ upon stimulation) of these cells was inversely correlated with clinical disease score in chronic untreated hepatitis C. In the peripheral compartment, Barathan *et al.*[62] found that patients with chronic HCV had lower MAIT cells frequencies compared with healthy controls. Likely reflecting a state of chronic inflammation and infection, MAIT cells in these patients had higher levels of markers of activation and exhaustion (HLA-DR, CD38, PD-1, TIM-3 and CTLA-4) compared with healthy controls. van Wilgenburg *et al.*[48] confirmed the finding that people with chronic HCV infection have depleted and activated peripheral MAIT cell populations; and interestingly demonstrated that MAIT cells have the ability to inhibit HCV replication in an IFN-γ-dependent manner. As discussed above, in patients with HIV infection, peripheral MAIT cell depletions are not improved by otherwise effective antiretroviral therapy. Two recent studies in HCV-infected patients have similarly found that the MAIT cell depletion and dysfunction observed in chronic HCV is not reversible even after successful interferon therapy or interferon-free therapy.[63,64] The role of MAIT cells in liver inflammation and the impact of MAIT cell perturbations on the general state of mucosal immunity in patients with these infections require further investigation.

What we know and what remains unknown

Before the discovery of the nature of the MAIT cell antigen, it was a mystery how and why individual MAIT cell clones could respond to cells infected with multiple different bacterial and fungal organisms (*E. coli*, *Klebsiella*, *M. tuberculosis* and *C. albicans*) but not react at all to cells infected with other bacterial species (*Streptococcus pyogenes* and *Enterococcus faecalis*) or viruses. The discovery that organisms that synthesize riboflavin produce metabolic intermediates that activate MAIT cells has significantly advanced our understanding of this abundant class of unconventional T cells. At this stage, however, many critical questions about the role of MAIT cells in the response to infection and in the pathogenesis of infectious disease remain. Increasing *in vitro* and mouse model evidence suggests that MAIT cells play a protective role against bacterial and mycobacterial infections. They appear to act as pre-armed pro-inflammatory and cytolytic effectors that have the capacity to lyse infected cells and control bacterial growth in the early days after infection.[65–70] They may also, like other tissue-resident unconventional cells including natural killer T and innate lymphoid cells, play an important role in setting the stage for the establishment of a coordinated adaptive immune response to infection.

As has been discussed, human data on MAIT cells in infectious diseases is currently very limited. The distribution of MAIT cells in human mucosal sites and the impact of healthy and diseased microbiota on human MAIT cells are unknown. The role of MAIT cells in respiratory and gastrointestinal viral infections, all human fungal infections, and parasitic infections is also unknown. To date, when MAIT cells have been studied outside the peripheral circulation, attention has mostly focused on respiratory or gut-resident MAIT cells. Recently, however, MAIT cells have been shown to have a distinct functional profile in the female genital mucosa.[30] It is likely that MAIT cells are also present in the urinary and male genital tracts, although these have not yet been explored. MAIT cells have been found in the central nervous system in the setting of neoplasm as well as multiple sclerosis.[71–73] The potential role of MAIT cells in immunoprotection or immunopathology of infections of these various anatomical sites is not currently known but is important to understand. Even in the human diseases that have been most studied to date – HIV and mycobacterial infections – there is little understanding of the reasons for or the immunological consequences of the widely observed peripheral MAIT cell depletions. New tools, including synthetic MAIT ligands, MR1 tetramers and next-generation TCR sequencing have recently been added to the toolbox available to MAIT cell immunologists and will hopefully accelerate research into these fundamental questions. As the most abundant class of donor-unrestricted T cells in humans, MAIT cells represent a potentially attractive target for immunotherapy or T-cell vaccines.[74–76] To advance towards this exciting possibility, however, the field will first need to answer the fundamental questions about the role that MAIT cells play in the protection against and the pathogenesis of infectious diseases.

Acknowledgements

The authors are supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health (NIAID/NIH) grant K08 AI118538, the Burroughs Wellcome Fund/ASTMH Postdoctoral Fellowship in Tropical Infectious Diseases, the Advancing Care & Treatment for TB/HIV (ACT4TB/HIV) funded by the South African Medical Research Council, the South African Research Chairs Initiative, the Victor Daitz Foundation and the Howard Hughes Medical Institute.

Disclosure

The authors declare no competing interests relevant to this article.

References

1 Lepore M, Kalinicenko A, Colone A, Paleja B, Singhal A, Tschumi A, *et al.* Parallel T-cell cloning and deep sequencing of human MAIT cells reveal stable oligoclonal TCRβ repertoire. *Nat Commun* 2014; **5**:3866.
2 Tilloy F, Treiner E, Park SH, Garcia C, Lemonnier F, de la Salle H, *et al.* An invariant T cell receptor α chain defines a novel TAP-independent major histocompatibility complex class Ib-restricted α/β T cell subpopulation in mammals. *J Exp Med* 1999; **189**:1907–21.
3 Treiner E, Duban L, Bahram S, Radosavljevic M, Wanner V, Tilloy F, *et al.* Selection of evolutionarily conserved mucosal-associated invariant T cells by MR1. *Nature* 2003; **422**:164–9.
4 Treiner E, Duban L, Moura IC, Hansen T, Gilfillan S, Lantz O. Mucosal-associated invariant T (MAIT) cells: an evolutionarily conserved T cell subset. *Microbes Infect* 2005; **7**:552–9.
5 Kjer-Nielsen L, Patel O, Corbett AJ, Le Nours J, Meehan B, Liu L, *et al.* MR1 presents microbial vitamin B metabolites to MAIT cells. *Nature* 2012; **491**:717–23.
6 Reantragoon R, Kjer-Nielsen L, Patel O, Chen Z, Illing PT, Bhati M, *et al.* Structural insight into MR1-mediated recognition of the mucosal associated invariant T cell receptor. *J Exp Med* 2012; **209**:761–74.
7 Lopez-Sagaseta J, Dulberger CL, Crooks JE, Parks CD, Luoma AM, McFedries A, *et al.* The molecular basis for Mucosal-Associated Invariant T cell recognition of MR1 proteins. *Proc Natl Acad Sci USA* 2013; **110**:E1771–8.
8 Lopez-Sagaseta J, Dulberger CL, McFedries A, Cushman M, Saghatelian A, Adams EJ. MAIT recognition of a stimulatory bacterial antigen bound to MR1. *J Immunol* 2013; **191**:5268–77.
9 Corbett AJ, Eckle SB, Birkinshaw RW, Liu L, Patel O, Mahony J, *et al.* T-cell activation by transitory neo-antigens derived from distinct microbial pathways. *Nature* 2014; **509**:361–5.
10 Dusseaux M, Martin E, Serriari N, Peguillet I, Premel V, Louis D, *et al.* Human MAIT cells are xenobiotic-resistant, tissue-targeted, CD161^{hi} IL-17-secreting T cells. *Blood* 2011; **117**:1250–9.
11 Sharma PK, Wong EB, Napier RJ, Bishai WR, Ndung'u T, Kasprowicz VO, *et al.* High expression of CD26 accurately identifies human bacteria-reactive MR1-restricted MAIT cells. *Immunology* 2015; **145**:443–53.
12 Reantragoon R, Corbett AJ, Sakala IG, Gherardin NA, Furness JB, Chen Z, *et al.* Antigen-loaded MR1 tetramers define T cell receptor heterogeneity in mucosal-associated invariant T cells. *J Exp Med* 2013; **210**:2305–20.
13 Gold MC, McLaren JE, Reistetter JA, Smyk-Pearson S, Ladell K, Swarbrick GM, *et al.* MR1-restricted MAIT cells display ligand discrimination and pathogen selectivity through distinct T cell receptor usage. *J Exp Med* 2014; **211**:1601–10.
14 Treiner E, Lantz O. CD1d- and MR1-restricted invariant T cells: of mice and men. *Curr Opin Immunol* 2006; **18**:519–26.
15 Lee OJ, Cho YN, Kee SJ, Kim MJ, Jin HM, Lee SJ, *et al.* Circulating mucosal-associated invariant T cell levels and their cytokine levels in healthy adults. *Exp Gerontol* 2014; **49**:47–54.
16 Kawachi I, Maldonado J, Strader C, Gilfillan S. MR1-restricted Vα19i mucosal-associated invariant T cells are innate T cells in the gut lamina propria that provide a rapid and diverse cytokine response. *J Immunol* 2006; **176**:1618–27.
17 Billerbeck E, Kang YH, Walker L, Lockstone H, Grafmueller S, Fleming V, *et al.* Analysis of CD161 expression on human CD8$^+$ T cells defines a distinct functional subset with tissue-homing properties. *Proc Natl Acad Sci USA* 2010; **107**:3006–11.
18 Jo J, Tan AT, Ussher JE, Sandalova E, Tang XZ, Tan-Garcia A, *et al.* Toll-like receptor 8 agonist and bacteria trigger potent activation of innate immune cells in human liver. *PLoS Pathog* 2014; **10**:e1004210.
19 Leeansyah E, Loh L, Nixon DF, Sandberg JK. Acquisition of innate-like microbial reactivity in mucosal tissues during human fetal MAIT-cell development. *Nat Commun* 2014; **5**:3143.
20 Gold MC, Cerri S, Smyk-Pearson S, Cansler ME, Vogt TM, Delepine J, *et al.* Human mucosal associated invariant T cells detect bacterially infected cells. *PLoS Biol* 2010; **8**:e1000407.
21 Le Bourhis L, Martin E, Peguillet I, Guihot A, Froux N, Core M, *et al.* Antimicrobial activity of mucosal-associated invariant T cells. *Nat Immunol* 2010; **11**:701–8.
22 Ussher JE, Bilton M, Attwod E, Shadwell J, Richardson R, de Lara C, *et al.* CD161^{++} CD8$^+$ T cells, including the MAIT cell subset, are specifically activated by IL-12$^+$ IL-18 in a TCR-independent manner. *Eur J Immunol* 2014; **44**:195–203.
23 Sattler A, Dang-Heine C, Reinke P, Babel N. IL-15 dependent induction of IL-18 secretion as a feedback mechanism controlling human MAIT-cell effector functions. *Eur J Immunol* 2015; **45**:2286–98.
24 Kurioka A, Ussher JE, Cosgrove C, Clough C, Fergusson JR, Smith K, *et al.* MAIT cells are licensed through granzyme exchange to kill bacterially sensitized targets. *Mucosal Immunol* 2015; **8**:429–40.

25 Le Bourhis L, Dusseaux M, Bohineust A, Bessoles S, Martin E, Premel V, *et al.* MAIT cells detect and efficiently lyse bacterially-infected epithelial cells. *PLoS Pathog* 2013; **9**: e1003681.

26 Leeansyah E, Svard J, Dias J, Buggert M, Nystrom J, Quigley MF, *et al.* Arming of MAIT cell cytolytic antimicrobial activity is induced by IL-7 and defective in HIV-1 infection. *PLoS Pathog* 2015; **11**:e1005072.

27 Tang XZ, Jo J, Tan AT, Sandalova E, Chia A, Tan KC, *et al.* IL-7 licenses activation of human liver intrasinusoidal mucosal-associated invariant T cells. *J Immunol* 2013; **190**:3142–52.

28 Okada S, Markle JG, Deenick EK, Mele F, Averbuch D, Lagos M, *et al.* Immunodeficiencies. Impairment of immunity to *Candida* and *Mycobacterium* in humans with bi-allelic RORC mutations. *Science* 2015; **349**:606–13.

29 Rahimpour A, Koay HF, Enders A, Clanchy R, Eckle SB, Meehan B, *et al.* Identification of phenotypically and functionally heterogeneous mouse mucosal-associated invariant T cells using MR1 tetramers. *J Exp Med* 2015; **212**:1095–108.

30 Gibbs A, Leeansyah E, Introini A, Paquin-Proulx D, Hasselrot K, Andersson E, *et al.* MAIT cells reside in the female genital mucosa and are biased towards IL-17 and IL-22 production in response to bacterial stimulation. *Mucosal Immunol* 2016; doi: 10.1038/mi.2016.30.

31 Birkinshaw RW, Kjer-Nielsen L, Eckle SB, McCluskey J, Rossjohn J. MAITs, MR1 and vitamin B metabolites. *Curr Opin Immunol* 2014; **26**:7–13.

32 Eckle SB, Birkinshaw RW, Kostenko L, Corbett AJ, McWilliam HE, Reantragoon R, *et al.* A molecular basis underpinning the T cell receptor heterogeneity of mucosal-associated invariant T cells. *J Exp Med* 2014; **211**:1585–600.

33 Jiang J, Wang X, An H, Yang B, Cao Z, Liu Y, *et al.* Mucosal-associated invariant T-cell function is modulated by programmed death-1 signaling in patients with active tuberculosis. *Am J Respir Crit Care Med* 2014; **190**:329–39.

34 Chua WJ, Truscott SM, Eickhoff CS, Blazevic A, Hoft DF, Hansen TH. Polyclonal mucosa-associated invariant T cells have unique innate functions in bacterial infection. *Infect Immun* 2012; **80**:3256–67.

35 Tsukamoto K, Deakin JE, Graves JA, Hashimoto K. Exceptionally high conservation of the MHC class I-related gene, MR1, among mammals. *Immunogenetics* 2013; **65**:115–24.

36 Georgel P, Radosavljevic M, Macquin C, Bahram S. The non-conventional MHC class I MR1 molecule controls infection by *Klebsiella pneumoniae* in mice. *Mol Immunol* 2011; **48**:769–75.

37 Sakala IG, Kjer-Nielsen L, Eickhoff CS, Wang X, Blazevic A, Liu L, *et al.* Functional heterogeneity and antimycobacterial effects of mouse mucosal-associated invariant T cells specific for riboflavin metabolites. *J Immunol* 2015; **195**:587–601.

38 Meierovics A, Yankelevich WJ, Cowley SC. MAIT cells are critical for optimal mucosal immune responses during *in vivo* pulmonary bacterial infection. *Proc Natl Acad Sci USA* 2013; **110**:E3119–28.

39 Kwon YS, Cho YN, Kim MJ, Jin HM, Jung HJ, Kang JH, *et al.* Mucosal-associated invariant T cells are numerically and functionally deficient in patients with mycobacterial infection and reflect disease activity. *Tuberculosis* 2015; **95**:267–74.

40 Smith DJ, Hill GR, Bell SC, Reid DW. Reduced mucosal associated invariant T-cells are associated with increased disease severity and *Pseudomonas aeruginosa* infection in cystic fibrosis. *PLoS One* 2014; **9**:e109891.

41 Grimaldi D, Le Bourhis L, Sauneuf B, Dechartres A, Rousseau C, Ouaaz F, *et al.* Specific MAIT cell behaviour among innate-like T lymphocytes in critically ill patients with severe infections. *Intensive Care Med* 2014; **40**:192–201.

42 Leung DT, Bhuiyan TR, Nishat NS, Hoq MR, Aktar A, Rahman MA, *et al.* Circulating mucosal associated invariant T cells are activated in *Vibrio cholerae* O1 infection and associated with lipopolysaccharide antibody responses. *PLoS Negl Trop Dis* 2014; **8**: e3076.

43 Cho YN, Kee SJ, Kim TJ, Jin HM, Kim MJ, Jung HJ, *et al.* Mucosal-associated invariant T cell deficiency in systemic lupus erythematosus. *J Immunol* 2014; **193**:3891–901.

44 Hinks TS, Zhou X, Staples KJ, Dimitrov BD, Manta A, Petrossian T, *et al.* Innate and adaptive T cells in asthmatic patients: relationship to severity and disease mechanisms. *J Allergy Clin Immunol* 2015; **136**:323–33.

45 Magalhaes I, Pingris K, Poitou C, Bessoles S, Venteclef N, Kiaf B, *et al.* Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. *J Clin Investig* 2015; **125**:1752–62.

46 Serriari NE, Eoche M, Lamotte L, Lion J, Fumery M, Marcelo P, *et al.* Innate mucosal-associated invariant T (MAIT) cells are activated in inflammatory bowel diseases. *Clin Exp Immunol* 2014; **176**:266–74.

47 Jiang J, Yang B, An H, Wang X, Liu Y, Cao Z, *et al.* Mucosal-associated invariant T cells from patients with tuberculosis exhibit impaired immune response. *J Infect* 2015; **72**:338–52.

48 van Wilgenburg B, Scherwitzl I, Hutchinson EC, Leng T, Kurioka A, Kulicke C, *et al.* MAIT cells are activated during human viral infections. *Nat Commun* 2016; **7**:11653.

49 Cosgrove C, Ussher JE, Rauch A, Gartner K, Kurioka A, Huhn MH, *et al.* Early and nonreversible decrease of CD161^{++}/MAIT cells in HIV infection. *Blood* 2013; **121**:951–61.

50 Eberhard JM, Hartjen P, Kummer S, Schmidt RE, Bockhorn M, Lehmann C, *et al.* CD161^{+} MAIT cells are severely reduced in peripheral blood and lymph nodes of HIV-infected individuals independently of disease progression. *PLoS One* 2014; **9**:e111323.

51 Fernandez CS, Amarasena T, Kelleher AD, Rossjohn J, McCluskey J, Godfrey DI, *et al.* MAIT cells are depleted early but retain functional cytokine expression in HIV infection. *Immunol Cell Biol* 2014; **93**:177–88.

52 Greathead L, Metcalf R, Gazzard B, Gotch F, Steel A, Kelleher P. CD8^{+}/CD161^{++} mucosal-associated invariant T-cell levels in the colon are restored on long-term antiretroviral therapy and correlate with CD8^{+} T-cell immune activation. *AIDS* 2014; **28**:1690–2.

53 Leeansyah E, Ganesh A, Quigley MF, Sonnerborg A, Andersson J, Hunt PW, *et al.* Activation, exhaustion and persistent decline of the anti-microbial MR1-restricted MAIT cell population in chronic HIV-1 infection. *Blood* 2012; **121**:1124–35.

54 Wong EB, Akilimali NA, Govender P, Sullivan ZA, Cosgrove C, Pillay M, *et al.* Low levels of peripheral CD161^{++}CD8^{+} mucosal associated invariant T (MAIT) cells are found in HIV and HIV/TB co-infection. *PLoS One* 2013; **8**:e83474.

55 Fernandez CS, Amarasena T, Kelleher AD, Rossjohn J, McCluskey J, Godfrey DI, *et al.* MAIT cells are depleted early but retain functional cytokine expression in HIV infection. *Immunol Cell Biol* 2015; **93**:177–88.

56 Leeansyah E, Ganesh A, Quigley MF, Sonnerborg A, Andersson J, Hunt PW, *et al.* Activation, exhaustion, and persistent decline of the antimicrobial MR1-restricted MAIT-cell population in chronic HIV-1 infection. *Blood* 2013; **121**:1124–35.

57 Vinton C, Wu F, Rossjohn J, Matsuda K, McCluskey J, Hirsch V, *et al.* MAIT cells are systemically depleted in SIV-infected rhesus macaques. *J Virol* 2016; **90**:4520–29.

58 Saeidi A, Tien Tien VL, Al-Batran R, Al-Darraji HA, Tan HY, Yong YK, *et al.* Attrition of TCR Vα7.2^{+} CD161^{++} MAIT cells in HIV-tuberculosis co-infection is associated with elevated levels of PD-1 expression. *PLoS One* 2015; **10**:e0124659.

59 Sandberg JK, Dias J, Shacklett BL, Leeansyah E. Will loss of your MAITs weaken your HAART [corrected]? *AIDS* 2013; **27**:2501–4.

60 Gaardbo JC, Trosied M, Stiksrud B, Midttun O, Ueland PM, Ullum H, *et al.* Increased tryptophan catabolism is associated with increased frequency of CD161^{+}Tc17/MAIT cells, and lower CD4^{+} T cell count in HIV-1 infected patients on cART after two years of follow-up. *J Acquir Immune Defic Syndr* 2015; **7**:228–35.

61 Jeffery HC, van Wilgenburg B, Kurioka A, Parekh K, Stirling K, Roberts S, *et al.* bacteria exposed biliary epithelium and liver B cells activate intrahepatic mait cells in an MR1-dependent manner. *J Hepatol* 2015; **64**:1118–27.

62 Barathan M, Mohamed R, Vadivelu J, Chang LY, Saeidi A, Yong YK, *et al.* Peripheral loss of CD8^{+} CD161^{++} TCRVα7.2^{+} mucosal-associated invariant T cells in chronic hepatitis C virus-infected patients. *Eur J Clin Invest* 2016; **46**:170–80.

63 Hengst J, Strunz B, Deterding K, Ljunggren HG, Leeansyah E, Manns MP, *et al.* Nonreversible MAIT cell-dysfunction in chronic hepatitis C virus infection despite successful interferon-free therapy. *Eur J Immunol* 2016; **46**:2204–10.

64 Spaan M, Hullegie SJ, Beudeker BJ, Kreefft K, van Oord GW, Groothuismink ZM, *et al.* Frequencies of circulating MAIT cells are diminished in chronic HCV, HIV and HCV/HIV co-infection and do not recover during therapy. *PLoS One* 2016; **11**: e0159243.

65 Cowley SC. MAIT cells and pathogen defense. *Cell Mol Life Sci* 2014; **71**:4831–40.

66 Gao Y, Williams AP. Role of innate T cells in anti-bacterial immunity. *Front Immunol* 2015; **6**:302.

67 Gapin L. Check MAIT. *J Immunol* 2014; **192**:4475–80.

68 Gold MC, Lewinsohn DM. Mucosal associated invariant T cells and the immune response to infection. *Microbes Infect* 2011; **13**:742–8.

69 Gold MC, Napier RJ, Lewinsohn DM. MR1-restricted mucosal associated invariant T (MAIT) cells in the immune response to *Mycobacterium tuberculosis*. *Immunol Rev* 2015; **264**:154–66.

70 Ussher JE, Klenerman P, Willberg CB. Mucosal-associated invariant T-cells: new players in anti-bacterial immunity. *Front Immunol* 2014; **5**:450.

71 Annibali V, Ristori G, Angelini DF, Serafini B, Mechelli R, Cannoni S, *et al.* CD161^{high}CD8^{+}T cells bear pathogenetic potential in multiple sclerosis. *Brain* 2011; **134**:542–54.

72 Illes Z, Shimamura M, Newcombe J, Oka N, Yamamura T. Accumulation of Vα7.2-Jα33 invariant T cells in human autoimmune inflammatory lesions in the nervous system. *Int Immunol* 2004; **16**:223–30.

73 Willing A, Leach OA, Ufer F, Attfield KE, Steinbach K, Kursawe N, *et al.* CD8^{+} MAIT cells infiltrate into the CNS and alterations in their blood frequencies correlate with IL-18 serum levels in multiple sclerosis. *Eur J Immunol* 2014; **44**:3119–28.

74 Wakao H, Fujita H. Toward the realization of cell therapy: the advent of MAIT cells from iPSCs. *Cell Cycle* 2013; **12**:2341–2.

75 Van Rhijn I, Moody DB. Donor unrestricted T cells: a shared human T cell response. *J Immunol* 2015; **195**:1927–32.

76 Nunes-Alves C, Booty MG, Carpenter SM, Jayaraman P, Rothchild AC, Behar SM. In search of a new paradigm for protective immunity to TB. *Nat Rev Microbiol* 2014; **12**:289–99.