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The biology and functional importance of MAIT cells

Dale I. Godfrey[1,2*], Hui-Fern Koay[1,2], James McCluskey[1] and Nicholas A. Gherardin[1,2]

In recent years, a population of unconventional T cells called 'mucosal-associated invariant T cells' (MAIT cells) has captured the attention of immunologists and clinicians due to their abundance in humans, their involvement in a broad range of infectious and non-infectious diseases and their unusual specificity for microbial riboflavin-derivative antigens presented by the major histocompatibility complex (MHC) class I–like protein MR1. MAIT cells use a limited T cell antigen receptor (TCR) repertoire with public antigen specificities that are conserved across species. They can be activated by TCR-dependent and TCR-independent mechanisms and exhibit rapid, innate-like effector responses. Here we review evidence showing that MAIT cells are a key component of the immune system and discuss their basic biology, development, role in disease and immunotherapeutic potential.

T cells detect antigens presented by antigen-presenting molecules. Most T cell studies are focused on 'conventional' $CD4^+$ T cells and $CD8^+$ T cells that recognize peptide antigens presented by MHC class II or MHC class I, respectively. However, several prominent populations of T cells, sometimes referred to as 'unconventional' T cells, recognize non-peptide antigens presented by specialized MHC class I–like molecules[1,2]. Unlike the highly polymorphic MHC class I molecules that present antigen to a diverse population of T cells, these MHC class I–like molecules are monomorphic, and the T cells that recognize them have unique and conserved TCR repertoires, often consisting of an invariant TCR α-chain paired with a restricted TCR β-chain repertoire. Furthermore, recognition of these MHC class I–like targets during intrathymic development confers on the cells developmental pathways that diverge from those of their peptide–MHC–restricted counterparts, which imbues these cells with unique effector functions. Thus, their distinct TCRs and antigenic targets are central to the biology of these cells. The expression of publicly conserved, invariant TCR α-chains in humans was first described in 1993, when a study of human $CD4^-CD8^-$ T cells revealed two distinct TCRα sequences[3] (Fig. 1). One was the α-chain variable region 24 and α-chain joining region 18 ($V_\alpha24J_\alpha18$) that defines what is now known to be type I natural killer T cells (NKT cells) restricted to the antigen-presenting molecule CD1d[1,2], while the other comprised $V_\alpha7.2$ (TRAV1-2) joined to $J_\alpha33$ (TRAJ33). The importance of the $TRAV1\text{-}2^+TRAJ33^+$ cells remained unexplored until Lantz and colleagues identified a population of T cells in mice and humans carrying the same TCR α-chain[4]. In mice, these T cells expressed the orthologous $V_\alpha19J_\alpha33$ (TRAV1 TRAJ33), paired with a limited array of TCR β-chains, mainly $V_\beta6$ (TRBV19) and $V_\beta8$ (TRBV13), or $V_\beta2$ (TRBV20) and $V_\beta13$ (TRBV6) in humans[4] (Fig. 2). Subsequent studies demonstrated that mucosal locations such as gut show enrichment for these T cells, which led to the term 'mucosal-associated invariant T cells' (MAIT cells)[5]. Moreover, this landmark study showed that MAIT cells are restricted to the non-polymorphic MHC class I–like protein MR1[5], a β_2-microglobulin-associated antigen-presenting molecule[6]. The biological relevance of this interaction is emphasized by the fact that MR1 and TRAV1 are highly conserved throughout mammalian evolution and have coevolved, with species that lack MR1 also selectively lacking TRAV1[7–9]. MAIT cells are very abundant in humans, including in non-mucosal tissues, in which they represent up to 10% of blood T cells[10,11] and 45% of liver T cells[12]. Despite their abundance and unique specificity, the role of MAIT cells in immunity remains unclear, although this is a rapidly advancing field, with many studies now hinting at the importance of these cells and therapeutic opportunities if they can be targeted. This Review will cover various aspects of MAIT cells, including their history (Fig. 1), basic biology (Fig. 2), antigen reactivity and activation (Fig. 3) and development (Fig. 4), as well as their involvement in microbial diseases (Tables 1 and 2) and non-microbial diseases (Tables 3 and 4).

Antigens detected by MAIT cells

For many years after the discovery of MAIT cells, the type of antigens they detect in association with MR1 was unknown, which was a major obstacle to understanding the biology of these cells. In 2010, two studies demonstrated that MAIT cells respond to a surprisingly broad range of microbial organisms, including many bacteria and yeast (Fig. 1), yet they fail to respond to three bacterial strains and five different viruses[10,13], which indicates that they are capable of sensing antigens common to a diverse range of, but not all, microbes.

In 2012, a breakthrough was made revealing that MR1 binds to metabolites of vitamin B[14]. These include 6-FP (6-formylpterin), a metabolite of vitamin B9 (folic acid), and several ribityllumazines[14] and pyrimidine-based intermediates[15] of the microbial biosynthesis of vitamin B2 (riboflavin). While 6-FP and its synthetic analog acetyl-6-FP bind to MR1 and increase its cell-surface expression, they generally do not activate MAIT cells[14,16], whereas the riboflavin-derivatives promote potent activation of MAIT cells. The importance of the riboflavin pathway is highlighted by the observation that the genes encoding components of this pathway are intact in the microbes previously shown to stimulate a MAIT cell response and are missing from bacterial strains that did not[15]. Similarly,

[1]Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Parkville, Victoria, Australia. [2]Australian Research Council Centre of Excellence for Advanced Molecular Imaging, University of Melbourne, Parkville, Victoria, Australia.
*e-mail: godfrey@unimelb.edu.au

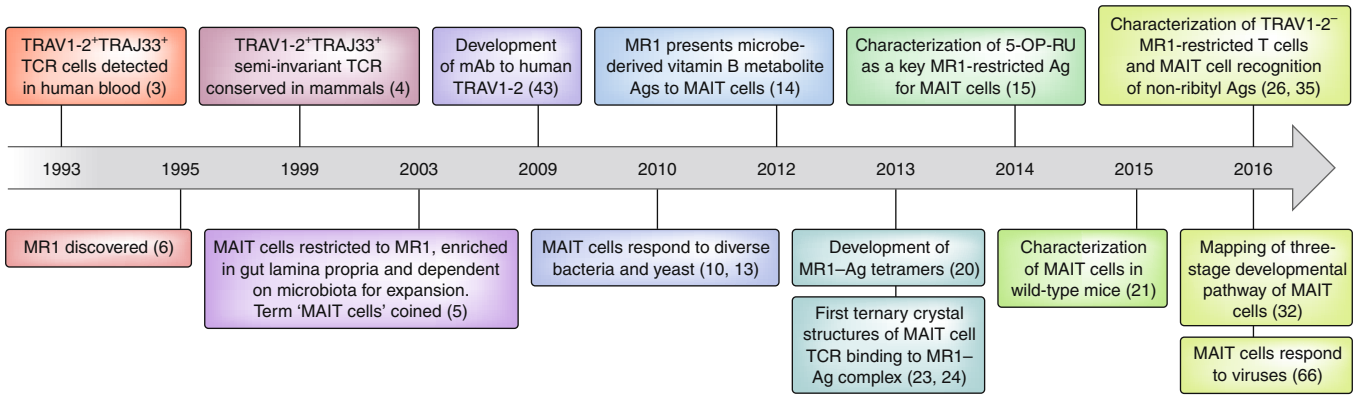


Fig. 1 | A timeline highlighting some of the key events in the field of MAIT cell biology. Ag, antigen.

MR1-dependent reactivity of MAIT cells to *Streptococcus pneumoniae* correlates with the presence of the riboflavin operon and riboflavin production[17,18]. Genetic experiments have verified that deletion of genes encoding key enzymes in the riboflavin pathway abolishes an otherwise productive MAIT cell response to *Lactococcus lactis*, *Salmonella enterica* serovar Typhimurium[14,15] or *Escherichia coli*[19]. Likewise, inhibition of the riboflavin operon in *L. lactis* also abolishes the activation of MAIT cells[15]. These studies[15,19] have isolated the production of an intermediate in the riboflavin-biosynthesis pathway, 5-A-RU (5-amino-6-D-ribitylaminouracil), as being necessary for the production of lumazine- and pyrimidine-based antigens. Indeed, the pyrimidine antigens are derived from the non-enzymatic condensation of 5-A-RU with one of two common cellular metabolites, methylglyoxal or glyoxal, to form the antigens 5-OP-RU (5-(2-oxopropylideneamino)-6-D-ribitylaminouracil) or 5-OE-RU (5-(2-oxoethylideneamino)-6-D-ribitylaminouracil), respectively[15]. Thus, microbial riboflavin synthesis is intimately linked to the activation of MAIT cells, with 5-A-RU representing a molecular signature of microbial activity, derivatives of which are detected by the MAIT cell TCR.

Most of the focus since the studies noted above has been on 5-OP-RU, which is loaded into MR1 tetramers to identify MAIT cells and is also used as an antigen to activate MAIT cells in vivo and in vitro[15,20–22] (Fig. 3). Cellular, molecular and structural studies have demonstrated precisely how metabolites of vitamin B bind to MR1 and are recognized by MAIT cell TCRs[14–16,23–26]. Intriguingly, while peptides bind to MHC molecules non-covalently, vitamin B–derivative antigens bind to MR1 via a covalent Schiff-base bond[14], which is necessary for the translocation of MR1 to the cell surface[27]. In turn, the conserved ribityl tail, contributed by 5-A-RU, is directly detected by the germline-encoded TRAV1-TRAJ33 CDR3α junctional loop of the MAIT TCR (extensively reviewed elsewhere[28,29]). While the mode by which the TCR recognizes ribityllumazine antigens is similar to the mode used to recognize pyrimidine antigens, the pyrimidine antigens are the most potent. The reasons for this remain unclear and may reflect variation in their stability within the microenvironment, the cell and/or the MR1 antigen-binding cleft. Likewise, their relative contributions to antigenicity during infection is unclear, and these represent important future questions for the field.

A growing list of ligands have been found to bind to MR1, which is permitted by the plasticity of the antigen-binding cleft, together with its propensity to bind small cyclic molecules. These ligands include some pharmacological agents and their derivatives, such as diclofenac, a widely used non-steroidal anti-inflammatory drug[30]; the aspirin analog 3-FSA (3-formylsalicylic acid); and 2,4-DA-6-FP (2,4-diamino-6-formylpteridine), a derivative of the immunomodulatory drug methotrexate (Fig. 3). This flags the possibility that the MR1–MAIT cell axis may contribute to certain drug-hypersensitivity reactions, although only some of these ligands, such as diclofenac, are able to stimulate MAIT cells, and they do so with relatively weak activity compared with that of 5-OP-RU. Conversely, several of these compounds, such as 3-FSA and 2,4-DA-6-FP[30], like 6-FP[16], can actively compete with agonist ligands such as 5-OP-RU, which suggests that they might inhibit the activation of MAIT cells. Recently, other MR1-binding antigens have been described, including riboflavin-derived photolumazine I (PLI) and PLIII; the riboflavin analog FO (7,8-didemethyl-8-hydroxy-5-deazariboflavin); riboflavin itself; and the non-riboflavin-derived hesperidin[31]. Of these, only PLI and PLIII are able to activate MAIT cells, whereas FO and riboflavin seem to be inhibitory. Further characterization of these antigens is needed to understand their relation to the well-defined ribityl antigens.

There is great interest in identifying other MR1-binding antigens, both natural and synthetic, especially mammalian antigens that may link MAIT cells to self-reactivity and tumor immunity. As a key example, intrathymic MAIT cell selection is MR1 dependent, and this also happens in germ-free mice, so the selecting antigen is probably not of microbial origin[32]. Some cells, including some human B cells and some tumor cell lines, express cell-surface MR1 in the apparent absence of microbial antigens[27,33,34]. There is also evidence that non–riboflavin-based antigens, including microbial molecules[35] and tumor cell–derived molecules[34], can bind to MR1 and activate some MR1-restricted T cells, although the identity of these antigens remains to be defined. Given that the antigen-binding groove of MR1 is not fully occupied by the currently recognized antigens[14,15,23], it seems likely that MR1 ligands will be even more diverse than is presently appreciated. Collectively, the studies discussed here have paved the way for a new arm of immunological research: metabolite antigen–reactive T cell immunity.

Tools for studying MAIT cells

Until recently, the study of MAIT cells relied on antibodies specific for combinations of cell-surface markers, such as CD3, TRAV1-2 and CD161. In healthy human blood, cells expressing these marker combinations are highly enriched for MAIT cells, although it is unclear how well these surrogate markers define these cells in other tissues or in the context of disease. The development of MR1 tetramers loaded with 5-OP-RU[15,20] has marked a key advance in the study of MAIT cells, enabling new investigations and direct assessment of the effectiveness of surrogate phenotypes for the analysis of MAIT cells in humans[11,20,36]. Populations of blood-derived CD8+TRAV1-2+ T cells that express CD161, the dipeptidyl peptidase CD26 or the cytokine receptor CD218 in humans show considerable enrichment for MAIT cells, but not all of these are MAIT cells, as defined on the basis of MR1 tetramer staining, and not all MAIT cells are

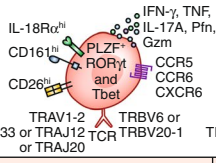
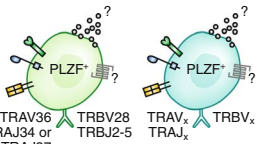
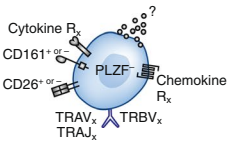
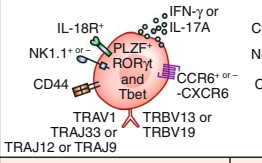
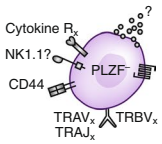
	Human			Mouse	
	TRAV1-2$^+$	TRAV1-2$^-$		TRAV1-2$^+$	TRAV1-2$^-$
	Classical MAIT cells	Non-classical MAIT cells	Atypical MR1-rest'd T cells	Classical MAIT cells	Atypical MR1-rest'd T cells
					
Frequency (% of T cells)	Blood, ~1–10%; liver, up to 50%; present in other organs (GIT, lungs, thymus, LNs, spleen, skin, kidneys)	Blood, ~0.001–0.01%	Blood, ~0.01–0.05%	Blood, ~0.1%; thymus, ~0.01%; spleen, ~0.1%; LNs, ~0.3%; liver, ~0.6%; lungs, ~3%; LP, ~2%; skin, ~3%	Thymus, ~0.0002%; other tissues, unknown
Antigens	All 5-OP-RU; subset-specific recognition of other Ags	All 5-OP-RU; subset-specific recognition of other Ags	Variable	All 5-OP-RU	Variable
Co-receptors	CD8αβ$^+$, CD8αα$^+$; DN, CD4$^+$ and DP less frequent	CD8$^+$; DN, CD4$^+$and DP less frequent	Mostly CD8$^+$; some CD4$^+$ or DN	Mostly DN; some CD8αβ$^+$, CD8αα$^+$, CD4$^+$	Mostly DN; some CD4$^+$ and CD8$^+$
Memory markers	CD45RO$^+$	Unknown	CD45RA$^{+\text{ or }-}$, CD45RO$^{+\text{ or }-}$	CD44$^+$	CD44$^+$
Homing receptors	CCR4$^+$, CCR5$^+$, CCR6$^+$, CCR7$^-$, CCR9$^-$, CXCR3$^-$, CXCR4$^+$, CXCR6$^+$, CD62L$^-$, CD49d$^+$	Unknown	Unknown	CCR6$^{+\text{ or }-}$, CCR7$^-$, CCR8$^{+\text{ or }-}$, CCR9$^{+\text{ or }-}$, CXCR3$^+$, CXCR6$^+$, CCRL2$^{+\text{ or }-}$, CD49a$^-$, CD49e$^{+\text{ or }-}$, CD61$^+$, CD62L$^{+\text{ or }-}$	Unknown
Cytokine receptors	IL-1R$^+$, IL-7R$^+$, IL-12R$^+$, IL-15R$^+$, IL-18R$^+$, IL-23R$^+$	IL-18R$^+$	Unknown	IL-2Rβ$^+$, IL-7R$^+$, IL-12Rβ$^+$, IL-18R$^+$	Unknown
Co-stimulatory receptors	CD28$^+$, CD27$^{+\text{ or }-}$, ICOS$^-$	Unknown	Unknown	ICOS$^+$	Unknown
NK cell-related markers	CD161^{hi}, 2B4$^+$, CD56$^{+\text{ or }-}$, NKG2D$^{+\text{ or }-}$, NKG2A$^{+\text{ or }-}$, NKp80$^{+\text{ or }-}$, SLAMF1$^+$, SLAMF5$^{+\text{ or }-}$, SLAMF7$^{+\text{ or }-}$, DNAM-1$^{+\text{ or }-}$, KIR2DL1$^-$, KIR2DL2$^-$3$^-$, KIR2DL/S5$^-$, NKp30$^-$, NKp40$^-$, NKp44$^-$	CD161^{hi}	Unknown	NK1.1$^{+\text{ or }-}$, NKG2D$^{+\text{ or }-}$	Unknown
Transcription factors	PLZF$^+$, RORγt$^+$, T-bet$^+$, Eomes$^+$, Helios$^+$	PLZF$^+$	PLZF$^-$	PLZF$^+$ and either RORγt$^+$ or T-bet$^+$	Unknown
Cytokine profiles	IFN-γ, TNF, IL-2, IL-17A$^{+\text{ or }-}$, IL-22$^{+\text{ or }-}$	Unknown	Unknown	IFN-γ$^{+\text{ or }-}$, TNF, IL-2, IL-17A$^{+\text{ or }-}$	Unknown

Fig. 2 | MR1-restricted T cell characteristics in humans and mice. Four groups of human MR1-restricted T cells and two groups of mouse MR1-restricted T cells (top rows) and key characteristics of these cells (below). Co-stim, costimulatory; rest'd, restricted.

captured by this surrogate phenotype[11]. Furthermore, surrogate markers such as CD161 are not present on immature MAIT cells[32] and may be downregulated on MAIT cells following activation[37–39], which complicates interpretation of how these cells act in disease states. Finally, it is unclear how well CD161 works as a surrogate marker of MAIT cells in tissues and disease lesions in which these cells may be activated and other CD161$^+$ T cells may be more abundant. As the majority of MAIT cell studies were carried out before MR1 tetramer became available, there was little choice but to rely on surrogate markers. However, problems arising from the use of surrogate markers for MAIT cells may explain some of the conflicting reports in this field.

MR1 tetramers have also instigated rapid advances in the study of mouse MAIT cells. For example, mouse MR1 tetramers enabled the first comprehensive study of the phenotype and function of MAIT cells in 'normal' laboratory mice (i.e., without transgenic TCR expression)[21], which was previously impossible due to a lack of antibodies specific for the V_α19 (TRAV1) TCR α-chain, and furthermore, MAIT cells are 10- to 100-fold less frequent in mice than in humans[4,21,40]. Other tools used to study mouse MAIT cells include mice with transgenic expression of an invariant TRAV1$^+$TRAJ33$^+$ TCR and MR1-knockout mice[41–43]. As expected, those TCR-transgenic mice have large numbers of MAIT cells and have provided valuable insight into the development and function of these cells. However, a caveat is that the development and function of those cells may differ from that of non-transgenic MAIT cells. For example, the TCR-transgenic MAIT cells[43] mostly have a naive phenotype and do not express the transcription factor PLZF (promyelocytic leukemia zinc finger), in contrast to MAIT cells in non-transgenic mice[21,40]. Moreover, TRAV1$^+$TRAJ33$^+$ TCR-transgenic × TCR α-chain constant region (C_α)-knockout mice on an MR1-knockout background still develop a sizeable population of MAIT-like cells[20,44] that are probably not MR1 restricted. More recently, after the discovery that the castaneus mouse strain has a higher frequency of MAIT cells than does the C57BL/6 mouse strain, a C57BL/6.CAST-congenic strain was generated that produces about ten times more MAIT cells than does the non-congenic C57BL/6 mouse strain[40]. The MAIT cells in C57BL/6.CAST-congenic mice are PLZF$^+$ and MR1 dependent[40] and will be a valuable resource for the study of MAIT cells. Another study has described TRAJ33-knockout mice[45]. These have a major (albeit incomplete) deficiency in MAIT cells yet retain MR1 expression, which suggests that they will be useful for adoptive-transfer studies in which transferred MAIT cells will be in an MR1-intact environment.

MAIT cell development

Like most T cells, MAIT cells develop in a thymus-dependent manner[4,43]. This is thought to begin following random rearrangements in TCR-encoding genes, whereby cells that generate a TCR that interacts with MR1 expressed on CD4$^+$CD8$^+$ cortical thymocytes

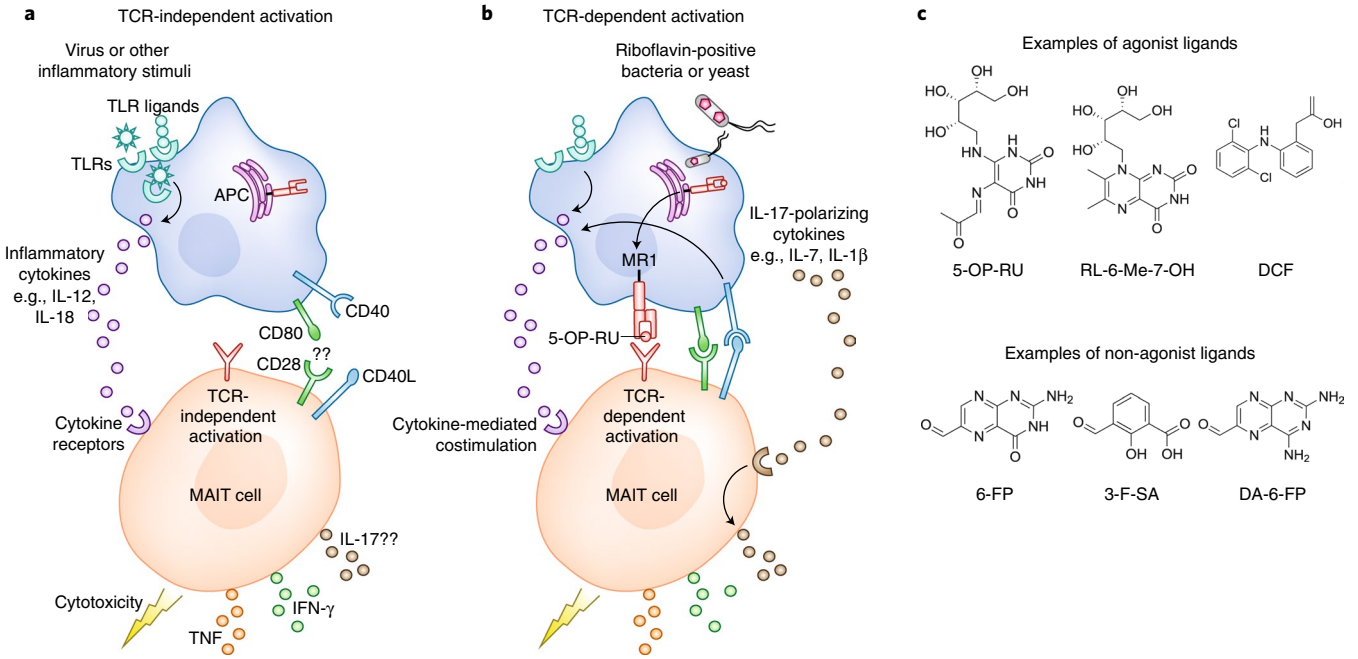


Fig. 3 | MAIT cell activation. Left, TCR-independent MAIT cell activation involving inflammatory cytokines and TLR ligands such as viral DNA and lipopolysaccharide. Middle, TCR-dependent MAIT cell activation involving MR1-mediated presentation of riboflavin-derivative antigen. Right, examples of MR1-ligands that are agonists (top) or non-agonists (bottom) for MAIT cells. 3-F-SA, 3-formylsalicylic acid; APC, antigen-presenting cell; DCF, diclofenac; RL-6-Me-7-OH, 7-hydoxy-6-methyl-8-D-ribityllumazine.

are then selected into the MAIT cell lineage[4,43,46] (Fig. 4). This is similar to CD1d-restricted type I NKT cells that also develop after interacting with $CD4^+CD8^+$ thymocytes and contrasts with conventional T cell development, during which positive selection requires interactions of the TCR with MHC molecules on thymic epithelial cells. This also suggests that MAIT cells may undergo developmental programming similar to that of type I NKT cells, and indeed, MAIT cells and type I NKT cells share many transcription factors and functions[47], as highlighted by transcriptomics comparisons of these cell types[48,49]. However, despite their similarities, there are some striking differences between MAIT cells and type I NKT cells; for example, most mouse MAIT cells produce the cytokine IL-17A, and only a small subset of these cells produce the cytokine IFN-γ, while the opposite is true for type I NKT cells. Furthermore, in mice, type I NKT cells outnumber MAIT cells by 10- to 100-fold in most tissues, whereas the opposite applies in humans. One common characteristic is that in contrast to conventional T cells, the number of MAIT cells and type I NKT cells varies widely between individual humans, yet the number of MAIT cells correlates with the number of type I NKT cells[11], for reasons that remain unclear, and with uncertain consequences for human immunity.

Better understanding of what regulates the number and function of MAIT cells will require a clearer picture of the development and homeostasis of MAIT cells. The use of MR1 tetramers to assess MAIT cells in the thymus led to the identification of immature MAIT cells and the mapping of MAIT cell development to a three-stage sequence in both mice and humans[32] (Fig. 4). In mice, the earliest cells (at stage 1) are defined as $CD3^+$, MR1 tetramer positive (MR1-tet^+), $CD24^+$ and $CD44^-$ ($CD3^+$MR1-$tet^+CD24^+CD44^-$) cells. These cells are only found in the thymus and are the dominant population in very young (2-week-old) mice. Stage 2 MAIT cells are defined as $CD3^+$MR1-$tet^+CD24^-CD44^-$ cells. The progression to stage 2 depends on MR1 and the microRNA miR181a/b-1[32,50] and is less efficient in germ-free mice, suggestive of a role for microbial antigens in the transition, survival and/or expansion of MAIT cells beyond stage 1. The next maturation step sees the emergence of stage 3 MAIT cells, defined as $CD3^+$MR1-$tet^+CD24^-CD44^+$ cells, which more closely resemble mature MAIT cells in the periphery. This is the first time at which they begin to express classic markers of MAIT cells, such as CD218 (IL-18 receptor (IL-18R)), CD44 and PLZF. The transition from stage 2 to stage 3 is regulated by multiple factors, including PLZF, MR1, IL-18, miR181a/b-1 and undefined microbial factors[32,50]. PLZF in other T cells is associated with tissue homing and residency and with rapid responses to antigen and to TCR-independent stimuli via cytokines[51], which are characteristics of MAIT cells that are probably controlled by this transcription factor. Stage 3 also sees the functional bifurcation of MAIT cells into the IFN-γ-producing T-bet^+ (MAIT-1) sub-lineage or the IL-17A-producing $ROR\gamma t^+$ (MAIT-17) sub-lineage[21,32]. Essentially nothing is known about the factors that regulate this polarization event in the thymus, and given their functional distinctiveness, this is an important area for future studies.

In humans, three similar stages of MAIT cell development can be identified, albeit through the use of different cell-surface markers (Fig. 4). Stage 1 is defined as $CD3^+$MR1-$tet^+CD27^-CD161^-$, stage 2 is $CD3^+$MR1-$tet^+CD27^+CD161^-$ and stage 3 is $CD3^+$MR1-$tet^+CD27^+CD161^+$ (ref. [32]). Despite the different markers used, there are close parallels in development of mouse MAIT cells and that of human MAIT cells: stage 1 cells are present only in thymus, stage 2 cells are present at low frequency in periphery, and the transition from stage 2 to stage 3 involves upregulation of PLZF and IL-18R, and the acquisition of functional potential[32]. An important distinction between mice and humans is the lack of a functional bifurcation into either MAIT-1 cells or MAIT-17 cells during the intrathymic development of MAIT cells in humans[32].

After leaving the thymus, MAIT cells undergo further maturation and expansion. Indeed, the high frequency of MAIT cells commonly observed in human blood is not observed in the human thymus at any age[32]. It seems that MAIT cells expand gradually after leaving the thymus, reaching a peak at approximately age 25, after which time they gradually begin to decrease in numbers such that by age 70, they usually represent less than 1% of T cells[11,52,53].

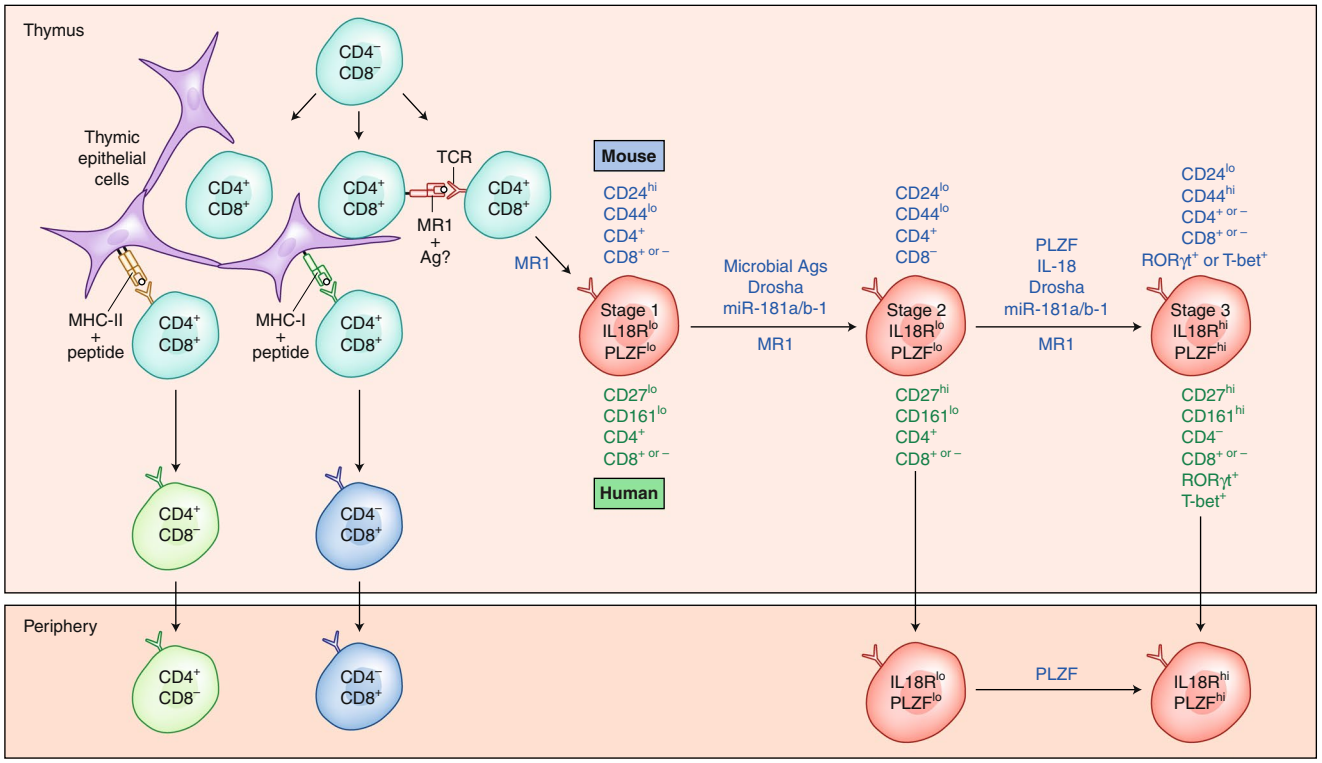


Fig. 4 | Development of MAIT cells in mice and humans. Conventional thymocyte development (top left), three stages of MAIT cell development in the thymus (top right), and thymic emigrants in peripheral tissues (bottom) in mice (blue text) and humans (green text). MHC-I, MHC class I; MHC-II, MHC class II.

Peripheral maturation of MAIT cells also involves the transition from expression of CD8αβ to that of CD8αα and a marked increase in cytokine-producing potential[32,54]. The drivers of the peripheral maturation, expansion and homeostasis of MAIT cells are unknown. Given the absence of these cells in the periphery of germ-free mice, and their dramatic and long-term expansion in microbe-challenged mice[22], it seems likely that exposure to microbes serves an important role in regulating the number of MAIT cells in the periphery, and that this is independent of their production in the thymus.

MAIT cell activation and effector function

After TCR-mediated activation, MAIT cells can become activated (Fig. 3), which leads to cytokine production, cytotoxic effector function, migration and proliferative expansion[10,13,14,20–22,55,56]. Following in vivo antigen-driven activation and expansion in mice, IL-17A-producing MAIT cells predominate, as they do in unchallenged mice, although following activation, many co-express the transcription factors RORγt and T-bet[22,57]. This is somewhat similar to human blood MAIT cells that also co-express RORγt and T-bet. However, activated human blood MAIT cells secrete predominantly IFN-γ and TNF, and only a minor population produces IL-17A[11,12,58,59]. IL-17A production by human MAIT cells can be enhanced by the presence of IL-7[59], and MAIT cells from human tissues such as the liver and female reproductive tract make large amounts of IL-17A and IL-22 after activation[59,60]. Whether MAIT cells are an important source of cytokines of the T_H2 subset of helper T cells or anti-inflammatory cytokines, such as IL-4, IL-5, IL-10 and IL-13, is unclear. These can be detected at low concentrations in the supernatants of activated mouse MAIT cells[21] and from some cultured human MAIT cell clones[61]. However, these cytokines were below detection limits in short-term ex vivo–stimulated human MAIT cell subsets defined by an MR1 tetramer[11].

Given that MAIT cells are probably constantly exposed to microbial riboflavin-derivative antigens from gut bacteria, this raises the question of why they are not chronically activated. The answer may lie in a need for threshold levels of riboflavin synthesis by actively replicating bacteria and the need for additional inflammatory signals in the form of cytokines and/or Toll-like receptor (TLR) ligands[22,62–64] (Fig. 3). Indeed, MAIT cells can even be activated by inflammatory stimuli in the absence of TCR-mediated antigen recognition. Thus, ligands for TLR2, TLR3, TLR4, TLR5, TLR8 and TLR9 have all been shown to promote the activation of MAIT cells, as measured by upregulation of IFN-γ or granzyme B[22,65]. This is mediated at least in part by cytokines such as IL-12 and IL-18 that are produced by monocytes following TLR ligation or viral infection[66]. MAIT cells express several cytokine receptors, including IL-1R, IL-7R, IL-12R, IL-15R, IL-18R and IL-23R, and these cytokines can all stimulate MAIT cells. Efficient cytokine-dependent activation of MAIT cells seems to require a combination of at least two cytokines; for example, IL-12 and IL-18 together promote strong MAIT cell production of IFN-γ, TNF and granzyme B in a TCR-independent manner, but either alone does not[65,66]. IL-15 can activate MAIT cell production of IFN-γ, granzyme B and perforin, but only in the presence of monocytes that produce IL-18 in response to IL-15[67]. Similarly, IL-15 can act in synergy with either IL-12 or IL-18 to drive IFN-γ production by MAIT cells[66]. The type I interferons IFN-α or IFN-β can also promote MAIT cell activation (IFN-γ and granzyme B) in conjunction with IL-12 and IL-18, independently of TCR signaling[66]. IL-1β[63] and IL-7[59,68,69] can preferentially promote IL-17A production by MAIT cells. IL-7 (in conjunction with TCR signals) also strongly enhances the cytotoxic effector function of MAIT cells, including expression of granzyme A, granzyme B, perforin and the degranulation marker CD107a[68]. While MAIT cells express costimulatory receptors such as CD27 and CD28, the influence of these on MAIT cell activation is unclear,

although costimulation with CD28 can enhance the activation of MAIT cell–like ($CD161^{hi}CD8^+$) cells[63].

In addition to their potential role as direct effector cells, MAIT cells also promote bystander activation of other cells[70]. Antigen-activated human MAIT cells upregulate the B cell–stimulatory molecule CD40L and promote the maturation of dendritic cells (DCs) and their IL-12 production in an MR1- and CD40L-dependent manner, and this can be enhanced by TLR ligands[70] (Fig. 3). That in turn leads to the activation of NK cells and, while it was not assessed in that study[70], should also promote the activation of conventional T cells that interact with antigen presented by MAIT cell–activated DCs. Thus, the effect of the activation of MAIT cells may be amplified through other cell types, precipitating an army of downstream effector cells.

Many questions remain about how MAIT cells are optimally activated for different settings. For example, does TCR-independent signaling via cytokines induce more-potent activation than TCR-dependent signaling does[62], and if so, how important is the role of antigen in MAIT cell–dependent immune responses? Do microbes that elicit distinct antigen-presenting cell–activation pathways via different TLRs induce different MAIT cell responses? Would an IL-12- or IL-18-dominated response differ from an IL-1β or IL-23 response, and what is the degree of plasticity between IL-17A-producing MAIT cell subsets and their IFN-γ-producing counterparts? These are key questions for future investigation.

MAIT cell subsets

On the basis of expression of the co-receptors CD4 and CD8, MAIT cells can be categorized into five subsets ($CD4^+CD8^-$, $CD4^+CD8^+$, $CD4^-CD8^-$, $CD4^-CD8\alpha\alpha^+$ and $CD4^-CD8\alpha\beta^+$)[11]. In human blood, the majority of MAIT cells are either $CD4^-CD8\alpha\alpha^+$ or $CD4^-CD8\alpha\beta^+$, subsets that collectively constitute roughly 80% of MAIT cells; $CD4^-CD8^-$ MAIT cells represent about 15%, whereas the $CD4^+CD8^-$ and $CD4^+CD8^+$ subsets usually constitute less than 5% of MAIT cells. The role of CD4 and CD8 in MAIT cell biology is unclear, although some evidence suggests that CD8 has a role in the recognition of MR1-presented antigen[58,71]. Generally, these five subsets produce similar amounts of cytokines (IFN-γ, TNF, IL-2 and IL-17A) after being activated[11,36,58], although $CD8^+$ MAIT cells may produce slightly more IFN-γ and TNF than do $CD4^-CD8^-$ cells[36,72]. One study suggested that $CD4^-CD8^-$ MAIT cells are more mature than are $CD8^+$ MAIT cells[36]. The authors found that $CD4^-CD8^-$ MAIT cells accumulate later than $CD8^+$ MAIT cells in fetal human tissue, that many $CD8^+$ MAIT cells became $CD8^-$ in vitro and that $CD4^-CD8^-$ MAIT cells exhibit a more-restricted TCR repertoire and a pro-apoptotic phenotype following activation[36]. While $CD4^+CD8^-$ MAIT cells are often ignored, these may be developmentally and functionally distinct from other MAIT cells. In one study, these cells (defined as $CD4^+CD161^+TRAV1\text{-}2^+$) produced IL-4 and IL-13[58]; however, this was not seen for $CD4^+CD8^-$ MAIT cells isolated through the use of an MR1 tetramer[11], which may be because many $CD4^+CD161^+TRAV1\text{-}2^+$ T cells are not MAIT cells, on the basis of MR1 tetramer staining[11,36,58]. $CD4^+$MR1-tet$^+$ MAIT cells produce more IL-2 than do other MAIT cell populations and also do not show the same age-related rise-and-fall kinetics that other MAIT cells show, so they may have a distinct role in the immune system[11]. Indeed, apical periodontitis lesions show considerable enrichment for $CD4^+$ MAIT cells[73]. MAIT cells in mice also include $CD4^+CD8^-$, $CD4^-CD8^-$, $CD8\alpha^+CD8\beta^-$ and $CD8\alpha^+CD8\beta^+$ subsets, and in C57BL/6 mice, $CD4^-CD8^-$ MAIT cells are the main population in peripheral lymphoid organs, while in BALB/c mice, there is a higher frequency of $CD4^-CD8^+$ MAIT cells[21]. There have not been any studies comparing the function of mouse subpopulations defined by expression of CD4 and/or CD8, although these molecules are differentially distributed, with $CD4^+$ MAIT cells being far more abundant in lymph nodes than in other tissues[21], suggestive of distinct homing for these cells.

MAIT cells can also be categorized into subsets on the basis of other aspects of their biology. One study categorized them into subsets on the basis of distinct TCR β-chain use with differential responses to microbial challenge[74], and a subset with higher expression of NK cell–associated receptors showed increased responsiveness to IL-12 and IL-18[74]. They can also be categorized into MAIT-1 and MAIT-17 subsets[21,32], as mentioned above. Tissue-resident MAIT cells generally have a more-activated phenotype than that of circulating MAIT cells[39,62] with more IL-17A production[39] than that of their blood-derived counterparts, although at least some seem to recirculate between blood and tissues[75], expressing a range of chemokine receptors (such as CCR2, CCR5 and CCR6) that facilitate this[12,76]. The developmental relationships and degree of plasticity between these subsets represents an important area of future study.

MAIT cells are now typically defined by their expression of the invariant $TRAV1\text{-}2^+TRAJ33^+$ TCR α-chain, MR1 restriction and ability to bind an MR1–5-OP-RU tetramer[77]. TCR sequencing of human cells positive for the MR1–5-OP-RU tetramer revealed the use of two alternative TRAJ genes (*TRAJ12* and *TRAJ20*) by some MAIT cells[20], and similarly, rare MR1-tet$^+$ cells in TRAJ33-knockout mice expressed alternative TRAJ genes (*Traj6*, *Traj9*, *Traj12*, *Traj30* and *Traj40*)[45]. As the proteins encoded by these alternative TRAJ sequences maintain a tyrosine at position 95, previously shown to be a critical residue for antigen binding by the $TRAJ33^+$ TCR, and exhibit a conserved CDR3α length, these are conservative substitutions. It is unclear whether these alternate TRAJ segments change the function or antigen specificity of MAIT cells, but some human tissues have been found to show enrichment for $TRAJ12^+$ MAIT cells relative to $TRAJ33^+$ MAIT cells[61]. A more diverse collection of MR1-restricted T cells has also been described in humans and mice[26,31,34,78]. These cells are typically less frequent than MAIT cells and utilize a range of TRAV and TRAJ genes that affect the types of antigens they detect. Indeed, many $TRAV1\text{-}2^-$ MR1-restricted T cells, and a minor subset of $TRAV1\text{-}2^+$ MAIT cells, can bind 6-FP and/or acetyl-6-FP[26,45]. Moreover, some $TRAV1\text{-}2^-$ cells bind to undefined tumor-derived molecules[34] and microbial antigens[35]. Alternative TCR α-chains can also change the hierarchy of riboflavin-metabolite-antigen-mediated activation of these cells[31]. This has been extensively reviewed elsewhere[77]. Some $TRAV1^-$ MR1-restricted T cells phenotypically resemble MAIT cells with high expression of CD161, CD218, CD26 and PLZF, including a subset that expresses invariant $TRAV36^+TRBV28^+$ TCRs[45], while others lack these markers, which suggests that at least two distinct developmental pathways can generate $TRAV1^-$ MR1-restricted T cells. While there is much to learn about these atypical MR1-restricted T cells, it seems that MR1 can present a range of antigens to a broad array of T cells. It will be important to understand the full scope of these MR1-restricted T cells and the antigens that they recognize. Humans also have a population of $CD161^+$ T cells that includes $TRAV1\text{-}2^+$ and $TRAV1\text{-}2^-$ subsets that do not bind MR1 tetramers[11,79]. These cells outnumber MAIT cells in early human life and share a cytokine-receptor profile and PLZF expression similar to that of MAIT cells, suggestive of similar developmental programming[79]. The specificity of these cells is unknown, and further investigation of these cells is required.

As the family of MR1-restricted T cells grows, an increasingly pertinent question is how these cells should be defined. While the original term 'mucosal-associated invariant T cells' implies an invariant TCR, this fails to encompass even conservative TRAJ substitutions or TCRβ diversity. We recently proposed some definitions that group these cells on the basis of similar phenotypic features[77]. Thus, MR1-restricted T cells with conservative TRAJ substitutions could be included under the 'MAIT cell' umbrella and could be collectively defined as 'classical' MAIT cells (Fig. 2). For MR1-restricted T cells with non-conservative TRAV and/or TRAJ

substitutions, those that are phenotypically similar to MAIT cells (on the basis of their expression of CD161, CD218, CD26 and PLZF), including the TRAV36$^+$ TRBV28$^+$ population in humans, could be defined as 'non-classical' MAIT cells, while those that are phenotypically distinct from MAIT cells can be broadly defined as 'atypical MR1-restricted T cells' (Fig. 2). These are broad definitions, but they should be helpful in understanding and explaining this increasingly diverse family of cells.

The role of MAIT cells in infection

As outlined above, MAIT cells have the ability to respond to a range of bacteria and yeasts, on the basis of whether these organisms have an intact riboflavin-biosynthesis pathway. Furthermore, studies have supported the proposal of a unique and non-redundant role for MAIT cells in immunity to infection. Initial investigations into the role of MAIT cells showed that MR1-deficient mice clear infection with *Mycobacterium abscessus* with an efficiency similar to that of wild-type mice[10]. This may reflect the fact that MAIT cells are quite rare in laboratory mice, because a comparison of MAIT cell TCR–transgenic mice (with a greater abundance of MAIT cells) and MR1-deficient TCR-transgenic mice showed that the MR1-deficient group had impaired ability to respond to infection with *E. coli* or *M. abscessus*[10]. Notwithstanding caveats with the use of TCR-transgenic mice, this study[10] provided the first demonstration of the potential of MAIT cells to provide protection against bacterial infection in vivo.

Subsequent studies in mice have demonstrated important roles for MAIT cells directed against a range of bacterial and fungal models (Tables 1 and 2). Some key examples are described below. MR1-deficient mice were less able to control early stages of infection with *K. pneumonia* than were wild-type mice, but, interestingly, no such differences were observed for infection with three related Gram-negative bacteria from the same Enterobacteriaceae family: *E. coli*, *Shigella dysenteriea* and *Yersinia enterocolitica*[80]. MR1-deficient mice showed impaired T cell responses at an early stage (10 days) following infection with *Mycobacterium bovis* bacillus Calmette-Guérin (BCG), but not later (30 days) following inoculation[81], which may indicate an important role for MAIT cells in protection before the full induction of adaptive immunity. That study also showed that TRAV1$^+$TRAJ33$^+$ TCR–transgenic MAIT cells responded to BCG-infected macrophages in vitro by producing IFN-γ and IL-17A and effectively controlled BCG growth[81]. Notably, that response was blocked by antibody to IL-12p40, but not by antibody to MR1[81], suggestive of a TCR-independent role for MAIT cells in this setting. MAIT cells expanded in the lungs of mice infected with the pathogen *Francisella tularensis*[82]. They also produced IFN-γ, TNF and IL-17A during the course of infection, and this response required both MR1 and IL-12p40-dependent signals. Moreover, in a model of chronic infection with *F. tularensis* in which mice that had been depleted of CD4$^+$ T cells and CD8$^+$ T cells were able to survive despite an ongoing bacterial burden, MR1-knockout mice depleted of CD4$^+$ T cells and CD8$^+$ T cells died, which indicated that MAIT cells were necessary for ongoing control of this chronic infection. A follow-up study demonstrated that in *F. tularensis*–infected mice, MAIT cells promoted the differentiation of monocytes into monocyte-derived DCs in a manner dependent on the cytokine GM-CSF[83].

In an in vivo challenge model involving intranasal infection with *Salmonella enterica* serovar Typhimurium, MAIT cells expanded dramatically to constitute roughly 50% of lung T cells within a week of infection[22]. This response was MR1 dependent and required antigen from the bacterial riboflavin-synthesis pathway. However, 5-OP-RU antigen alone was unable to drive a similar response, but simultaneous signaling through TLR2, TLR3 and TLR9 was able to emulate the bacteria-driven expansion of MAIT cells. Notably, while the expansion of MAIT cells in mouse lungs peaked at day 7, they remained at high levels for 10 weeks[22]. Similarly, MAIT cells are important for optimal immunity to lung infection with *Legionella longbeachae* that leads to activation and long-term expansion of these cells in the lungs and a greater bacterial burden in MR1-deficient mice than in wild-type mice[57]. These mouse-based studies raise the possibility that the higher frequency of MAIT cells in humans than in mice reflects their infectious disease history, which normally would not affect appropriately housed, 'clean' laboratory mice. It is also noteworthy that MAIT cells are much less frequent in very young humans (<2 years old) than in older humans[11,32,52,79], similar to their frequency in mice, but they accumulate gradually over the first two to three decades of life, a timespan that does not apply to mice. The mouse infection experiments also reveal the extent to which MAIT cell immunity in mice is masked by conventional T cell immunity. Thus, adoptive transfer of MAIT cells into hosts with variable degrees of immunodeficiency (for example, *Rag2*$^{-/-}$*Il2rg*$^{-/-}$ mice, which are deficient in T cells, B cells and NK cells, or mice that lack CD4$^+$ T cells) rescued these mice from lethal infection with *L. longbeachae* in a manner that was substantially MR1 dependent[57]. Collectively, these studies highlight the important role that MAIT cells can have in immunity to infection. The findings suggest that protection by MAIT cells supplements conventional adaptive immunity but may be critical when the host is immunocompromised or during overwhelming infection, when eliciting every host-protective mechanism becomes a matter of life and death. Indeed, a low frequency of MAIT cells in the blood of patients in the intensive-care unit correlates with the severity of acquired infections[84]. Likewise, patients with cystic fibrosis who have secondary infections have an exceptionally low number of MAIT cells in the circulation[85,86].

While most evidence suggests a protective role for MAIT cells in infection, the opposite may apply in some settings. In mice infected with *Helicobacter pylori*, MAIT cells were expanded in the gastric mucosa and adopted an IL-17A- and IFN-γ-producing phenotype[87]. However, in contrast to the studies described above, this response was pathogenic, because MR1-deficient mice showed less gastric pathology than that in wild-type mice, whereas mice in which MAIT cells had been previously expanded showed increased pathology compared with that of mice without MAIT cell expansion[87]. As human MAIT cells respond to *H. pylori*[88], it will be important to investigate whether they also have a pathogenic role in this or other human infections, as blocking MAIT cells may represent a novel approach to immunotherapy for such diseases.

Many studies of humans have demonstrated a reduced number of MAIT cells in the peripheral blood, combined with diminished function, and signs of prior activation, in subjects with various bacterial infections, relative to the number and characteristics of such cells in healthy, uninfected subjects (Table 1). This may reflect the migration of MAIT cells from the blood to the site of infection, a proposal supported by in vivo studies in mouse models[22,82] and longitudinal studies showing depletion of blood MAIT cells in controlled experiments of humans infected with *S. enterica* serovar Typhi[89], *S. enterica* serovar Paratyphi A[90] or *Shigella dysenteriae*[55]. These animal and human studies highlight the potential that MAIT cells offer as a new target for vaccines and immunotherapy directed against bacterial infections, which is increasingly important with the alarming spread of multi-drug-resistant pathogens.

Early studies suggested that viruses do not induce the activation of MAIT cells, at least in vitro[10,13], which made sense when it was determined that MAIT cells respond to riboflavin metabolites[14,15], as viruses do not synthesize riboflavin. However, as described above, MAIT cells are also capable of responding to cytokines in a TCR- and/or antigen-independent manner. It is therefore perhaps unsurprising that MAIT cells can indeed respond to, or be modulated by, many different viruses in in vitro infection models and/or in vivo, including dengue virus[66], influenza virus[66,91,92], hepatitis B virus[93–95], hepatitis C virus[66,96–102] and human immunodeficiency virus (reviewed in ref. [103]) (Table 2). In general, the response of MAIT cells

Table 1 | Studies of MAIT cells in bacterial, fungal and parasitic diseases

Pathogen	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
General	H & M		↑			MR1-dependent response to diverse (but not all) bacteria and yeast, but not viruses	10,13,17,168
	H & M		↑			Microbial MAIT cell–activating capacity correlates with presence of riboflavin operon	14,17–19,22,169
Clostridium difficile	H		↑			Hypervirulent strains correlate with ↑ MAIT cell activation, associated with ↑ IL-12 and IL-18 production	169
E. coli	M		↑	↑	↑	MAIT cell TCR–transgenic mice better protected than *Mr1*$^{-/-}$ MAIT cell TCR–transgenic mice	10
F. tularensis	M		↑	↑	↑	Early expansion and accumulation in lungs; impaired protection in T cell–depleted *Mr1*$^{-/-}$ mice	82
	M					MAIT cell–dependent GM-CSF promotes differentiation of monocytes into DCs = ↑ $CD4^+$ T response	83
	M		↑			IL-18 is critical for MAIT cell IFN-γ production in vitro but not in vivo in lungs of infected mice	170
Haemophilus influenzae	H		↑			Infection of lung explants activates MAIT cells in antigen- and IL-12- and IL-7-dependent manner	171
H. pylori	H	↓	↑	↑		↓ MAIT cell frequency in blood, present in gastric mucosa; MAIT cells recognize infected cells	87,88
	M		↑	↑	↓	↑ MAIT cells in infected mucosa, produce inflammatory cytokines; ↑ gastritis	87
	H					In patients with ITP (low frequency of MAIT cells), no change in blood MAIT cells with or without *H. pylori* infection	172
Klebsiella pneumoniae	M				↑	More-severe infection in *Mr1*$^{-/-}$ mice	80
L. longbeachae	M		↑	↑	↑	Activation and accumulation in lungs; impaired protection in *Mr1*$^{-/-}$ mice; protection with MAIT cell transfer	57
M. abscessus	M		↑	↑	↑	MAIT cell TCR–transgenic mice better protected than *Mr1*$^{-/-}$ MAIT cell TCR–transgenic mice	10
Mycobacterium tuberculosis or *M. bovis* BCG	H				↑	MR1 polymorphism associated with susceptibility	173
	H		↑			MAIT cells respond to M.tb or BCG-infected cells	13,81
	H	↓	↓			↓ MAIT cells in blood in patients with active M.tb infection[10,13,174–176] and NTM[174] and M.tb or HIV co-infection[177,178]. Blood MAIT cells produce ↓ IFN-γ[174,179], TNF, IL-17F, granulysin, GzB[179]; ↑ PD-1[174]	10,13,174–178,180
	H	↓				↓ MAIT cells in blood in children (>5 years old) with active M.tb; no accumulation in lungs	181
	H		↑			Pleural effusions: ↑ IFN-γ, IL-17F, GzB, γ_c-receptor; partially MR1 dependent	180
	H					Distinct phenotypes of MAIT cell subsets defined by CD4 and CD8 during early infection	182
	H	↑	↑			↑ MAIT cells in blood after M.tb and IAV co-infection than after M.tb mono-infection; MAIT cells produce ↑ IFN-γ and IL-17	183
	M				↑	↑ bacterial loads at early, but not later, time points in *Mr1*$^{-/-}$ mice infected with BCG	81
	NHP		↑			MAIT cells activated, not decreased, in blood after BCG inoculation; ↑ MAIT cell response after re-challenge	184
	NHP			↑		Variable and/or late accumulation of MAIT cells in airways; little evidence of activation in granulomas	185
Orientia tsutsugamushi	H	↓	↑↓			↓ MAIT cells in blood, residual MAIT cells activated, ↓ TNF production but normal IFN-γ production	186
Pseudomonas aeruginosa	H	↓				Blood MAIT cells in CF lowest in patients infected with *P. aeruginosa*; correlates with infection severity	86

Continued

Table 1 | Studies of MAIT cells in bacterial, fungal and parasitic diseases (continued)

Pathogen	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
Shigella flexneri	H		↑			MAIT cells lyse infected epithelial cells. In vivo activation in recipients of *S. flexineri* vaccine	55
S. enterica Paratyphi A	H	↓				↓ MAIT cells in blood, residual activated, recovered and/or increased after antibiotics; TCR repertoire reshaped during infection	90
S. enterica Typhimurium	M		↑	↑	-	Lungs of infected mice enriched for MAIT cells (MR1, antigen, TLR dependent); long-term accumulation in lungs, draining lymph nodes and spleen; bacterial clearance MAIT cell independent	22
S. pneumoniae	H		↑			MAIT cells respond to infected cells; MR1 dependent with macrophages, MR1 independent with monocytes	18
Vibrio cholerae	H	↓	↑	•		Blood MAIT cells activated early after infection; ↓ MAIT cells in blood of children but that of not adults	187
Commensals	H		↑			Respond to rib-gene$^+$ strains; activation correlates with riboflavin production: high, Bacteroidetes and Proteobacteria; low or none, Actinobacteria and Firmicutes	17
	H					Number and function of blood MAIT cells correlates with specific gut microbes that are influenced by exposure to M.tb	182
Severe or opportunistic infection	H	↓			↑	↓ MAIT cells in blood in patients in the ICU with infection; ↑ incidence of infection with persistent ↓ number of MAIT cells	84
	H		↑	↑		MAIT cells accumulate in infected peritoneum; produce IFN-γ and/or TNF in response to bacteria (MR1 dependent)	188
	H	↓				Very low number of blood MAIT cells in patients with CF with uncontrolled bacterial infection	85
Aspergillus spp.	H		↑			MAIT cells respond to three different *Aspergillus* species; requires APCs, cell contact, MR1	189
Plasmodium falciparum	H	↓				↓ MAIT cells in blood during parasitemia in controlled malaria infection, then rebound and ↑ long term	190
Bacterial superantigen	H		↑			MAIT cells are major source of pro-inflammatory cytokines after exposure to bacterial superantigen	191

↓ decreased; ↑ increased; ↑↓ mixed response; •, detected; H, human; M, mouse; NHP, non-human primate; ITP, idiopathic thrombocytopenic purpura; M.tb, *M. tuberculosis*; NTM, non-tuberculous mycobacteria; HIV, human immunodeficiency virus; GzB, granzyme B; PD-1, programmed cell death protein 1; γ_c, common γ-chain; IAV influenza A virus; CF, cystic fibrosis; ICU, intensive care unit.

to viruses seems to depend on the induction of cytokines (especially IL-18 and IL-12, but sometimes also IL-15 and type I interferons) in myeloid cells in response to the virus and is not inhibited by blockade of MR1, which would indicate TCR-independent stimulation. This literature has been extensively reviewed elsewhere[104].

Despite the clear ability of MAIT cells to respond to viral infection, the key question is whether this is important to the disease outcome or MAIT cells are simply activated as bystanders. At least in the case of infection with influenza virus, there is good evidence that MAIT cells serve a non-redundant role in overcoming this infection. First, the number of MAIT cells is moderately lower in the blood of patients with influenza than in that of healthy subjects[66]. Furthermore, in patients hospitalized with severe infection with influenza virus, there was a correlation between a lower number of MAIT cells in blood and later patient death, in support of the proposal of an important role for these cells in disease resolution[91]. Direct evidence for the importance of MAIT cells during infection with influenza virus derives from a mouse-based study in which MR1-deficient mice exhibited a higher mortality rate than that of MAIT cell–sufficient mice, most of which survived the infection[92]. Adoptive transfer of MAIT cells into MR1-deficient mice before infection reduced weight loss and extended survival, although not to the same extent as in MAIT cell–sufficient mice[92]. Such partial protection in MR1-deficient mice supports the concept that the transferred MAIT cells can respond in an antigen-independent manner, but the absence of MR1 may also explain why the transfer of MAIT cells did not fully restore protection in this model.

The role of MAIT cells in autoimmunity and inflammation

While many studies have focused on the role of MAIT cells in infection, it is increasingly clear that they are also modulated in non-microbial diseases (Tables 3 and 4). This may reflect the possibility that MR1 is presenting non-microbial, possibly self antigens to MAIT cells, or that MAIT cells are responding to inflammatory cytokines in the autoimmune environment, in the absence of TCR ligation. In most cases, studies have detected alterations in the number or function of MAIT cells in the blood or disease lesions of patient cohorts; whether these changes are a cause or an effect remains to be established. A selection of diseases in which MAIT cells have been studied more extensively are discussed below.

Despite several studies of the role of MAIT cells in multiple sclerosis (MS), their role in this disease remains very unclear. MAIT cells are present within autoimmune lesions of patients with MS[105–109]. Some reports have also shown a lower abundance of MAIT cells (defined as CD8$^+$CD161$^+$ (ref. [107]) or CD8$^+$CD161$^+$TRAV1-2$^+$ (ref. [110])) in the blood of patients with MS, but this has not been

Table 2 | Studies of MAIT cells in viral diseases

Pathogen	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
Dengue virus	H	↑	↑			↑ MAIT cells in blood, number and activation, normalized after resolution; correlates with disease severity	66
Hepatitis B virus	H	↓?	↑↓			MAIT cells normal in number but activated; normalized with therapy[93], or MAIT cells ↓ in number and functionally impaired with ↑ PD-1[94,95,192]	93–95,192
Hepatitis C virus	H	↓	↓	↓		↓ MAIT cells in blood[66,97–102] and liver[98,99]; residual blood MAIT cells activated and/or exhausted[66,97,100,101]; worsened with HIV co-infection[97,99,102]; antiviral therapy does not restore MAIT cells[98–100,102,193]	66,97–102, 193
Hepatitis D virus	H	↓	↓	↓		↓ MAIT cells in blood and liver; blood MAIT cells activated and/or exhausted, ↓ functional responsiveness in vitro	192
HIV	H	↓	↓?	↓		↓ MAIT cells in blood, colon in early and chronic infection with HIV[37,97,102,177,178,194–200] exacerbated by co-infection with HCV[196] or TB[177]. Residual MAIT cells activated or dysfunctional[37,68,178] or with normal function[197]; ART does not restore MAIT cells in adults[37,177,178,194–196,200,201], but does in children[199] and adult colon[195]	37,97,102,177, 178,194–201
	NHP	↓?		↓		Systemic depletion of MAIT cells in SIV-infected rhesus macaques[202]; cells in pigtail macaques proliferate and home to the rectum after infection with SIV or sHIV; ↓T-bet, but not depleted[203]	202,203
HTLV-1	H	↓	↓?			↓ MAIT cells in blood, residual activated and functionally impaired	204
Influenza A virus	H	↓	↑?		↑?	↓ MAIT cells in blood with acute infection and residual MAIT cells activated[66,91] normalized after resolution[91]; fatal infections associated with lowest number of MAIT cells[91]; infected cells activate MAIT cells, IL-18 dependent[91]	66,91
	M		↑	↑	↑	MAIT cells ↑ in lungs, activated early, cytokine-dependent function; *Mr1*$^{-/-}$ mice more susceptible to disease; protection restored by MAIT cell transfer	92

?, unclear; HTLV-1, human T cell leukemia virus type I; HCV, hepatitis C virus; TB, tuberculosis; ART, anti-retroviral therapy; SIV, simian immunodeficiency virus; sHIV, simian–human immunodeficiency virus.

not seen in other studies[109,111–113]. Interestingly, reduced CD8$^+$ MAIT cells in the blood of patients with MS was reported, but this was offset by an increase in CD4$^-$CD8$^-$ MAIT cells, which resulted in no net change in the total frequency of MAIT cells[112]. Regardless of whether MAIT cells are altered in blood, their presence in MS lesions suggests a possible role for these cells in this disease. If MAIT cells are activated in these lesions, they may exacerbate disease by producing IL-17A, which is enhanced in MAIT cells in blood samples from patients with MS[114]. On the other hand, MAIT cells were shown to inhibit responses of the T_H1 subset of helper T cells in samples from patients with MS as well as in those of healthy subjects, suggestive of a protective role for these cells in MS[110]. The hypothesis of a protective role for MAIT cells was also supported by a study of experimental autoimmune encephalitis (EAE), a mouse model of MS[41]. Over-representation of MAIT cells in TRAV1$^+$TRAJ33$^+$ TCR–transgenic mice inhibits disease induction and progression, whereas the absence of MAIT cells in TRAV1$^+$TRAJ33$^+$ TCR–transgenic × *Mr1*$^{-/-}$ mice exacerbates EAE disease[41].

It is generally agreed that MAIT cells (defined as CD3$^+$CD161$^+$ TRAV1-2$^+$) are less frequent in the blood of patients with gastrointestinal inflammatory disorders, including celiac disease and inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis)[115–119]. The possibility that MAIT cells migrate from the blood to inflamed mucosal tissue was investigated in IBD studies, three of which reported an increase in mucosal tissue relative to blood[116–118], while one reported a decrease[115]. Furthermore, the remaining MAIT cells in the blood of patients with IBD showed signs of activation and altered cytokine production, although there were variations in what was observed among the studies and disease types. Most prominently, increased IL-17A production[116–118] and/or IL-22 production[115,117] was detected after activation of blood MAIT cells from patients with IBD. Given the important yet potentially opposing effects of IL-17 and IL-22 on IBD[120], it is difficult to predict whether MAIT cells producing these cytokines would have a pathogenic or protective role.

The number of MAIT cells (CD3$^+$CD161$^+$TRAV1-2$^+$) has been reported to be diminished in the blood and relatively increased in the synovial fluid of patients with two forms of autoimmune arthritic disease (rheumatoid arthritis and ankylosing spondylitis)[69,121–124]. Furthermore, residual MAIT cells in the blood of patients with ankylosing spondylitis produce higher levels of IL-17 and IL-22 than did those from healthy control subjects[69,122,124], suggestive of their potential to contribute to disease pathology, given the pathogenic role of IL-17 in these diseases[125]. Evidence from two mouse models of autoimmune arthritis (collagen-induced arthritis and collagen antibody–induced arthritis) supports this possibility[126]. MR1-deficient mice develop less-severe disease than that of control MAIT cell–sufficient mice, and transfer of MAIT cells into MR1-deficient mice restores disease severity. The fact that this works in MR1-deficient recipient mice also suggests that MAIT cells contribute to these diseases in an antigen-independent manner. However, other studies have failed to detect a decrease in the number of MAIT cells in humans with these diseases relative to that in healthy

Table 3 | Studies of MAIT cells in autoimmune, allergic or inflammatory disorders

Disease	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
Autoimmune hepatitis	H	↓	↑↓	↑		↓ MAIT cells in blood; residual MAIT cells ↑ GzB, ↓ IFN-γ; ↑ MAIT cells in liver	205
ANCA vasculitis	H	↓	↑			↓ MAIT cells in blood; residual MAIT cells activated; ↑ CD69, IFN-γ	206
Ankylosing spondylitis	H	↓?	↑	↑		↓ MAIT cells in blood[69,122,124] or not[121]; residual MAIT cells ↑ IL-17[69,122,124]; IL-22, IFN-γ[124]; MAIT cell number and IL-17 ↑ in synovial fluid[69]	69,121,122,124
Ankylosing spondylitis	H	–				No change in MAIT cells by MR1 tetramer, but decreased CD161 and CD8 on MAIT cells	38
Asthma	H	↓?	↑?	↓	↑↓?	↓ MAIT cells in blood associated with severe asthma[136]; high MAIT cell IL-17 but not IFN-γ or MAIT cell number associated with asthma exacerbation[138,139]; ↑ MAIT cells in 1-year-old subjects associated with later protection[137], but no association with MAIT cell production of IFN-γ or IL-17 in 1-year-old subjects and later asthma[137,140]	136–140
CAIA	M				↓	Absence of MAIT cells ameliorated disease; transfer of MAIT cells enhanced disease	126
CIA	M				↓	Absence of MAIT cells ameliorated disease; transfer of MAIT cells enhanced disease	126
Celiac disease	H	↓?				↓ MAIT cell frequency, but not number, in blood	119
COPD	H	↓		↓		↓ MAIT cells in blood and lungs[141,142], probably due to steroid therapy[142]	141,142
Crohn's disease	H	↓	↑	↑↓		↓ MAIT cells in blood[115,117,118]; residual MAIT cells activated; ↑ IL-17[117,118]; number of MAIT cells ↑[117,118] or ↓[115] in inflamed mucosa.	115,117,118
Dermatitis herpetiform	H			↑		↑ MAIT cells in skin lesions	207
EAE	M				↑	MAIT cell TCR-transgenic mice protected; *Mr1*$^{-/-}$ MAIT cell TCR-transgenic mice have exacerbated disease	41
ITP	H	↓				More-severe depletion in prednisolone-unresponsive patients	172
Liver fibrosis	H	↓	↑	↓		↓ MAIT cells in blood and liver; residual MAIT cells in blood and liver activated; ↑IL-17, GzB	208
Liver fibrosis	M				↓	Liver fibrosis in mouse model; more severe in MAIT cell TCR-transgenic mice and less severe in *Mr1*$^{-/-}$ mice	208
MS	H	↓?	↑	↑		MAIT cells in lesions[105–109,113]; ↓ MAIT cells in blood[107,110] or not[105,109,111]; Blood MAIT cells ↑ IL-17, IL-7R, RORγt, CCR6[114]; stem cell transplantation therapy depletes MAIT cells for at least 2 years[106]	105–111,113,114
Obesity	H	↑↓	↑	↓?		↓ MAIT cells in blood in adults[133–135] but ↑ in obese children[134]; residual blood MAIT cells ↑ IFN-γ, IL-2, IL-17, GzB, PD-1[133,134]; MAIT cell frequency in adipose tissue unaltered[133] or ↓[134] with obesity	133–135
PBC	H	↓	↑	↑		↓ MAIT cells in blood; residual MAIT cells activated↑ GzB; ↑ MAIT cells in liver	209
Pre-eclampsia	H	↓	↑			↓ MAIT cells in blood; residual MAIT cells ↑ CD69, perforin, ↓ PD-1	210
Psoriasis	H	↓	↑	↑		↓ MAIT cells in blood; residual MAIT cells ↑ IL-17; IL-17-producing MAIT cells in lesions	211,212
Rheumatoid arthritis	H	↓	↑	↑		↓ MAIT cells in blood, ↑ MAIT cells in synovial fluid and activated	69,121,123

Continued

Table 3 | Studies of MAIT cells in autoimmune, allergic or inflammatory disorders (continued)

Disease	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
Sjögren's syndrome	H	↓	↑	•		↓ MAIT cells in blood, present in salivary glands	213,214
SLE	H	↓	↑			↓ MAIT cells in blood[121,215]; residual MAIT cells ↓ IFN-γ, ↑ PD-1[121], ↑ CD69[215]	121,215
Systemic sclerosis	H	↓				↓ MAIT cells in blood	216
T1D	H	↓	↑			MAIT cells in blood ↓[129] or not[128] in pre-diabetic sero-converted subjects; MAIT cells in blood ↓[128] or not[129,130] in patients with T1D; residual MAIT cells activated ↑ CD25, PD-1, TNF, IL-4, IL-17, GzB, ↓ IFNγ[128]; no MAIT cells detected in insulitic lesions of newly diagnosed patients[131]	128–131
T1D	M	↓	↑	↑	↑	MAIT cell TCR–transgenic NOD mice have less disease[132]; *Mr1*$^{-/-}$ NOD mice have exacerbated disease[128]	128,132
T2D	H	↓	↑	↑		↓ MAIT cells in blood; residual MAIT cells activated ↑ IFN-γ, IL-2, IL-17, GzB	133
Ulcerative colitis	H	↓	↑	↑↓		↓ MAIT cells in blood; residual MAIT cells activated[116–118]; ↑IL-17[116–118]; ↑IL-22[115,117]; MAIT cells ↑[116–118] or ↓[115] in inflamed mucosa	115–118

CAIA, collagen-antibody-induced arthritis; CIA, collagen-induced arthritis; COPD, chronic obstructive pulmonary disease; PBC, primary biliary cholangitis; SLE, systemic lupus erythematosus.

control subjects[38,127]. One of those studies used MR1 tetramers to define MAIT cells, and no difference was detected in the number of MAIT cells in the blood of patients with early-stage rheumatoid arthritis or spondyloarthritis relative to that in healthy control subjects[38]. This discrepancy may be explained by the findings that the MR1 tetramer–defined MAIT cells in patients with rheumatoid arthritis had lower surface expression of CD161, and the ratio of CD4$^+$ MAIT cells to CD8$^+$ MAIT cells was higher[38]. This highlights the potential risks of using surrogate markers such as CD161 and CD8 to identify MAIT cells, because it is not known whether these markers remain stable on MAIT cells in disease states.

A reduced number of MAIT cells (CD3$^+$CD4$^-$CD8$^+$CD161$^+$TRAV1-2$^+$ or CD3$^+$CD4$^-$CD8$^-$CD161$^+$TRAV1-2$^+$) has been detected in the blood of children with type 1 diabetes (T1D), relative to the number in healthy subjects, but not before disease onset, as assessed in a small cohort of seroconverted at-risk subjects who expressed anti-islet antibodies[128]. Conversely, a different team reported fewer MAIT cells in seroconverted at-risk subjects than in healthy control subjects[129] but not in children who progressed to T1D[129,130]. MAIT cells in patients with recent-onset T1D produced less IFN-γ, more TNF and slightly more IL-4 and IL-17A than did those from healthy control subjects[128], although other non-MAIT cells in the MAIT cell–diminished CD161$^+$TRAV1-2$^+$ population might have contributed to some of these effects. The MAIT cells also had high expression of granzyme B and were able to kill pancreatic β-cells in vitro, suggestive of pathogenic potential in this disease[128]. However, no increase in MAIT cells was detected in insulitis lesions from patients with early-onset T1D, as assessed by immunohistochemistry or quantitative PCR for the MAIT cell TCR α-chain[131]. In T1D-susceptible mice of the non-obese diabetic (NOD) strain compared with C57BL/6 mice, MAIT cells (defined by the MR1 tetramer) were numerically diminished in peripheral lymphoid tissues, including pancreatic lymph nodes, but they were elevated and activated in the pancreatic islets, where they were capable of producing IFN-γ, TNF, IL-17A and granzyme B[128]. Adoptively transferred TRAV1$^+$TRAJ33$^+$ TCR–transgenic NOD MAIT cells showed heightened migration to pancreas but decreased migration to the ileum around the time of disease onset[128]. While that might have suggested a destructive role for MAIT cells in the mouse disease, it was countered by the fact that MAIT cell–deficient (*Mr1*$^{-/-}$) NOD mice develop exacerbated diabetes[128], and an earlier study showed that a different line of TRAV1$^+$TRAJ33$^+$ TCR–transgenic NOD mice had delayed disease onset[132]. Similar findings were obtained in another model of T1D in which streptozotocin-treated MR1-deficient C57BL/6.CAST mice were more susceptible to T1D development than were their control (MR1-sufficient C57BL/6.CAST) littermates[128]. Thus, mouse-based studies indicate a protective role for MAIT cells in T1D development. Despite the very different underlying causes of T1D versus T2D, patients with T2D also exhibit a major decrease in circulating blood MAIT cells (defined by the MR1 tetramer) compared with such cells in healthy subjects, and the residual cells show enhanced production of IFN-γ, IL-2, IL-17A and granzyme B after stimulation[133]. A similar MAIT cell profile has been observed in obese children[134] and adults[133,135] regardless of whether they had T2D. As a direct measure of relationship between disease and MAIT cells, obese patients that had undergone bariatric surgery exhibited a partial restoration in the number of MAIT cells in blood and of their functional potential within 3–6 months[133].

MAIT cells have also been linked to allergies and asthma. A low number of MAIT cells (CD3$^+$CD161$^+$TRAV1-2$^+$) in the blood and lungs was associated with severe asthma[136], and a higher frequency of MAIT cells in 1-year-old children was associated with a lower risk of asthma at 7 years of age[137]. These studies suggest a protective role for MAIT cells in asthma. However, a larger number of IL-17A-producing MAIT cells, but not of IFN-γ$^+$ or total MAIT cells, was associated with recent exacerbations in asthmatic children at 11 years of age[138,139]. While no correlation in MAIT cell cytokine profile and asthma was detected in a study of 1-year-old children[140], this apparent discrepancy may be simply due to the different ages of the subjects when the cells were sampled (1-year-old pre-asthmatic subjects versus 11-year-old asthmatic subjects). MAIT cells are also diminished in patients with chronic obstructive pulmonary disease[141], although this may be mainly due to the use of steroid-based therapy in these patients[142].

Collectively, there is considerable evidence to suggest a role for MAIT cells in autoimmune and allergic diseases, and further investigations, ideally using MR1 tetramers to capture all MAIT cell populations, and mouse-based studies in which MAIT cells can be manipulated, will be very valuable.

Table 4 | Studies of MAIT cells in cancer and GVHD

Disease	Host species	MAIT cells in blood	MAIT cell activity	MAIT cells at disease site	Effect on health	Comments	Refs
Brain	H			•		MAIT cells and MR1 detected in lesions	147
Breast	H		↑			MAIT cells from breast duct produce ↑ IL-17 with bacteria-exposed breast carcinoma cells	156
Cervical	H	↓				↓ MAIT cells in blood	154
Colorectal	H	↓	↑↓	•	↓?	↓ MAIT cells in blood[152,153], present in lesions[151–153]; blood MAIT cells ↓ IFN-γ ↑ IL-17[152] or normal cytokine production[153]; blood MAIT cells arrest growth of tumor lines[152]; MAIT cells from tumor site ↓ IFN-γ[150] but contact tumor cells in situ and strong cytotoxic potential[217]; ↑ MAIT cells in tumor = poor prognosis[151]	150–153,217
Gastric	H	↓				↓ MAIT cells in blood, normal cytokine profile	153
GVHD	H	↓		•	↑↓?	↓ MAIT cells in blood[161]; ↓ MAIT cell number correlates with ↑ disease[160] or no correlation of MAIT cell number with disease, but ↑CD8$^+$ MAIT cell frequency correlates with ↑ disease[162]	160–162
GVHD	M			•	↑	MAIT cells serve protective role via IL-17; absence of MAIT cells (*Mr1*$^{-/-}$) exacerbates disease	159
HCC	H			↓	↓?	↓ MAIT cells in blood and tumor lesions; residual MAIT cells activated; intratumoral MAIT cells produce pro-tumor cytokines (IL-8); ↑ MAIT cells in infiltrates = poor prognosis	163
HCC	H			•	↑?	Abundant MAIT cells in infiltrates = good prognosis	164
Kidney	H	↓		•		MAIT cells and MR1 detected in lesions	147
LCC	H	↓		•		↓ MAIT cells in blood, detected in lesions	158
Lung	H	↓				↓ MAIT cells in blood, normal cytokine profile	153
MM	H	↓?	↓	↓?		↓ MAIT cells in blood and bone marrow[33,157] (due to greater age of patients?[33]). ↓ MAIT cell IFN-γ, TNF	33,157

ANCA, anti-neutrophil cytoplasmic autoantibodies; HCC, hepatocellular carcinoma; LCC, Langerhans cell histiocytosis.

The role of MAIT cells in cancer

Several studies point to a possible role for MAIT cells in tumor immunity, although evidence of a direct and critical role for these cells in cancer is limited. In a large investigation of diverse tumor samples, *KLRB1* (encoding CD161) was the gene most significantly associated with a good prognosis, and this correlated with tumor-infiltrating CD8$^+$ T cells[143], which hints that tumor-infiltrating MAIT cells may be a positive prognostic factor. The first papers to suggest a role for MAIT cells in the context of cancer demonstrated that the gene encoding $V_\alpha 7$ (*TRAV1-2*) was one of only a few genes encoding TCR V_α regions that was consistently detected in tumor-infiltrating lymphocytes from patients with uveal melanoma and patients with glioma[144,145]. However, as those were published before MAIT cells were a recognized entity, the importance of this $V_\alpha 7$ usage was unclear. Subsequently, transcripts encoding TRAV1-2 TRAJ33, TRAV1-2 TRAJ12, and MR1 were detected in brain and kidney tumor lesions, strongly suggestive of the presence of MAIT cells with a possible role in tumor immunity[146,147]. Other studies have provided intriguing data showing that CD8$^+$ T cells with a MAIT cell–like phenotype (CD161^{hi}CD218^{hi}) can efflux chemotherapeutic drugs and therefore are more resistant to chemotherapy[148], while another study showed that enrichment for CD161^{hi}CD218^{hi}CD26^{hi} CD8$^+$ T cells in autografted apheresis products correlated inversely with progression-free survival in hematological malignancies[149].

Subsequent studies specifically focusing on MAIT cells have begun to shed light on the potential role of these cells in a variety of solid tumors. Studies of patients with colorectal cancer showed that MAIT cells were diminished in the blood and present or enriched in the tumor lesions[150–153]. Analysis of diverse cancer types provided the interesting suggestion of depletion of MAIT cells (CD3$^+$CD161$^+$TRAV1-2$^+$) in the blood of patients with mucosal tumors (gastric, colon or lung)[153] or cervical cancer[154] but not in that of patients with non-mucosal tumors (breast, liver or thyroid)[153]. It has been demonstrated that MAIT cells were present within metastatic colorectal cancer infiltrates in the liver, but that they were impaired in their ability to produce IFN-γ within the tumor mass, and at the tumor margin, relative to the ability of those in the healthy region of the liver[155]. Furthermore, MAIT cells (defined as CD3$^+$CD161$^+$TRAV1-2$^+$ and also by the MR1 tetramer) have been observed in human breast ductal tissue and responded with IL-17A production to bacterial antigen–exposed human breast carcinoma cell lines in an MR1-dependent manner[156]. Given the potential pro-tumor effects of IL-17A, this suggests that activated MAIT cells in breast tumors may generate an undesirable response in breast cancer.

MAIT cells have also been investigated in the context of hematological malignancies: there are fewer MAIT cells (MR1-tet$^+$ (ref. [33]) or CD3$^+$TRAV1-2$^+$CD161$^+$ (ref. [157])) in the blood and bone marrow of patients with multiple myeloma (MM)[33,157] than in that of healthy subjects. The residual cells in newly diagnosed patients exhibit impaired ability to produce IFN-γ and TNF[33,157], but this is restored in samples from refractory or relapsed patients[33]. As patients with MM are generally elderly (>50 years of age), the reduced number of MAIT cells may simply reflect the natural age-related decrease in MAIT cells[33]. Nonetheless, reduced function of MAIT cells may affect tumor immunity. Indeed, healthy donor–derived MAIT cells were capable of killing MM cell lines pulsed with 5-OP-RU, in an

MR1-dependent manner, which shows that MAIT cells can directly kill human tumor cells[33]. The number of MAIT cells is also reduced in the blood of people with Langerhans cell histiocytosis, and MAIT cells are present in the tumor lesions[158]. These cells retain the ability to produce cytokines IFN-γ and TNF after stimulation in vitro.

Transplantation of allogeneic bone marrow or hematopoietic stem cells is a life-saving therapy for certain hematological malignancies that balances the risk of potentially lethal graft-versus-host disease (GVHD) with beneficial graft-versus-leukemia effects. In mice that received allogeneic bone marrow transplantation, recipient MAIT cells ($CD3^+MR1\text{-}tet^+$) were detected in organs such as the colon, a frequent target of GVHD[159]. Furthermore, MAIT cell–deficient *Mr1*$^{-/-}$ mice that received allogeneic bone marrow transplantation developed severe GVHD at a higher incidence than that of MAIT cell–sufficient mice[159]. This study suggested that MAIT cells have a regulatory role via IL-17A production, along with favorable gut microbiota, helping maintain gastrointestinal barrier function and limiting the activation of pathogenic donor-derived T cells[159]. Those findings align with two clinical studies in which a low number of MAIT cells ($CD3^+CD161^+CD8^+TRAV1\text{-}2^+$) correlated with a higher risk of delayed acute GVHD and reduced overall survival[160,161]. However, that contrasted with an earlier study showing no correlation between the total number of MAIT cells ($CD3^+CD161^+TRAV1\text{-}2^+$) and susceptibility to acute GVHD, although a higher proportion of MAIT cells that were $CD8^+$ was linked to disease[162].

The important question of whether MAIT cells actively influence tumor immunity remains to be answered. In one study, an increased number of MAIT cells ($CD3^+CD26^+TRAV1\text{-}2^+$) in colorectal cancer infiltrates correlated with a poor prognosis[151]. Similarly, a larger number of MAIT cells in hepatocellular carcinoma infiltrates was also linked to a poor prognosis, because the MAIT cells adopted a pro-tumor cytokine profile, producing factors such as IL-8[163]. Those two reports raise the possibility that MAIT cells suppress anti-tumor immunity. In contrast, however, in another study of patients with hepatocellular carcinoma, a larger number of MAIT cells (defined as a separate $CD8^+$ T cell cluster in a transcriptomics study) in infiltrates correlated with a better prognosis[164]. Given the link between MAIT cells and exacerbated *H. pylori* pathology[87], MAIT cells may have an indirect role in gastric cancer induced by this pathogen, which would offer a potential immunological link between microbiota and cancer development. Finally, MAIT cells themselves can become lymphomas[165], and given their unique biology and specificity, this may offer novel means by which these could be treated, such as antibody-mediated MR1 blockade or treatment with 6-FP.

Whether tumor antigens exist that can be presented to MAIT cells via MR1 is an important question in this field. Some MM cell lines constitutively express MR1, indicative of the presence of an unknown antigen[33], and some $TRAV1\text{-}2^-$ MR1-restricted T cells seem to respond to tumor cell line–derived, but undefined, antigens in an MR1-dependent manner[34], so there is some basis for searching for these antigens. However, given the ability of MAIT cells to respond to inflammatory cytokines in the absence of TCR signaling, they may be present and activated in tumor lesions, even without defined MR1-presented antigens. Tumor-growth studies in MR1-deficient mice are eagerly awaited and should help to shed light on these important problems.

Summary and future directions

Although they were discovered over 25 years ago, it has only been in recent years that MAIT cells have started to broadly capture the attention of researchers in the field of immunology. The key reasons are advances in the understanding of these cells and the antigens and other stimuli that activate them, as well as the development of tools such as MR1 tetramers that facilitate their accurate identification. The striking observation that MAIT cells are such an abundant population of human T cells, with potent cytokine-producing potential, is both intriguing and a reminder that they should not be ignored. It is known that the abundance of MAIT cells varies widely among people and is particularly low in people at high risk of disease, including the very young, the elderly and the immunocompromised. As mouse models frequently demonstrate that deficiency in MAIT cells affects disease susceptibility, the consequences of a diminished number of MAIT cells in humans warrants further investigation. As has been flagged in this Review, while many studies have suggested a role for MAIT cells in various diseases, there is also considerable disagreement about how they are affected and/or what role they have. This is probably in part due to differences among studies in how they are identified, particularly when imprecise surrogate markers such as CD161 are used to define these cells. To avoid such uncertainty, future studies should use MR1 tetramers where possible (available from the US National Institutes of Health tetramer facility: http://tetramer.yerkes.emory.edu/reagents/mr1) to identify and isolate MAIT cells. New techniques for expanding MAIT cells with antigen in vitro and in vivo[21,22] should help with such investigations, and an important challenge will be to determine whether antigens such as 5-OP-RU and analogs can be used as MAIT cell–based adjuvants to enhance adaptive immunity, in much the same way that glycolipid antigens such as α-GalCer can mediate potent type I NKT cell–based adjuvant-like effects[166]. Conversely, the use of non-agonist MR1 ligands such as 6-FP[16] may offer the potential to block MAIT cell function, which may be advantageous in situations in which the cells have a TCR-dependent pathogenic role. The potential for pharmaceutical products to inhibit or stimulate MAIT cell function[30] is also worthy of further study. MAIT cells represent excellent candidates for engineering with chimeric antigen receptors, because they have cytotoxic function, they readily infiltrate tissue spaces including solid tumors and they are unlikely to cause GVHD after transfer into allogeneic recipients[167]. These are exciting times in the field of immunology and immunotherapy, and it is likely that MAIT cells will have an important role in future approaches to a range of diseases.

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Competing interests

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Correspondence should be addressed to D.I.G.

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