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MAIT cells and MR1-antigen recognition

Andrew N Keller[1,2,*], Alexandra J Corbett[3,*], Jacinta M Wubben[1,2], James McCluskey[3,**] and Jamie Rossjohn[1,2,4,**]

Mucosal-associated invariant T cells (MAIT cells) are innate-like T cells that recognise antigens presented by the monomorphic MHC-I related molecule, MR1. Distinct from the conventional MHC-restricted T cell system, MR1 presents small-molecule precursors, derived from microbial biosynthesis of riboflavin, to activate the innate MAIT cell effector potential. Recent data demonstrates how: vitamin B precursors modulate intracellular trafficking of MR1 and impact on MAIT cell development; variation in the MAIT cell antigen receptor sequence impacts MR1-antigen recognition; and most notably, how MR1 can capture chemical identities distinct from riboflavin precursors, including drugs and drug-like molecules. With mounting evidence demonstrating their roles in immunity and pathology, understanding the MAIT-MR1-antigen axis may have profound implications for human diseases.

Addresses
[1] Infection and Immunity Program and Department of Biochemistry and Molecular Biology, Biomedicine Discovery Institute, Monash University, Clayton, Victoria 3800, Australia
[2] ARC Centre of Excellence in Advanced Molecular Imaging, Monash University, Clayton, Victoria 3800, Australia
[3] Department of Microbiology and Immunology, Peter Doherty Institute for Infection and Immunity, University of Melbourne, Parkville, Victoria 3000, Australia
[4] Institute of Infection and Immunity, Cardiff University School of Medicine, Heath Park, Cardiff CF14 4XN, UK

Corresponding authors: McCluskey, James (jamesm1@unimelb.edu.au), Rossjohn, Jamie (Jamie.rossjohn@monash.edu)
[*] Joint first authors.

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Introduction

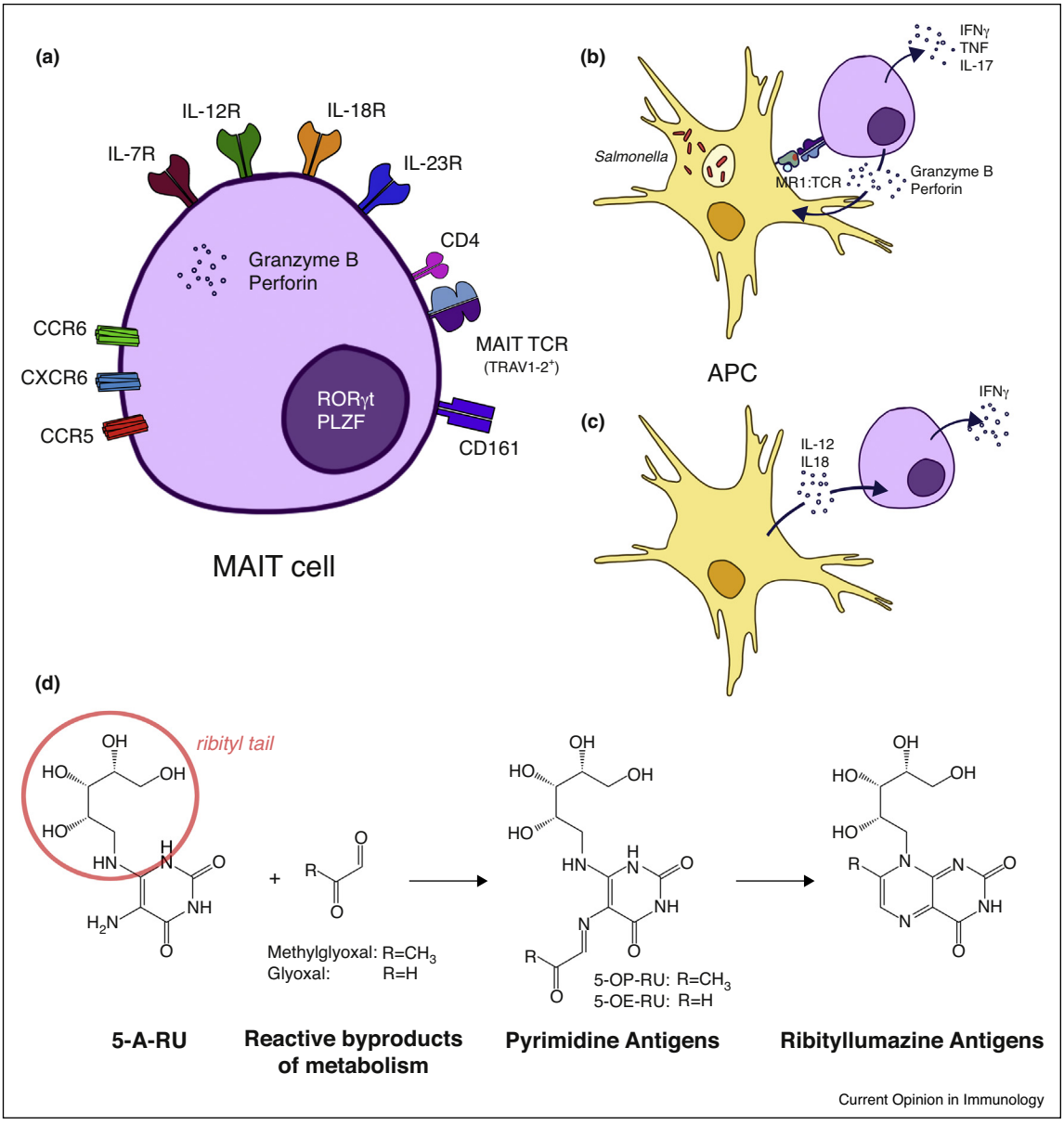
T cells are central players in adaptive immunity that upon activation have the capacity to coordinate formidable and widespread immunological responses. Directing this activity is a highly specific intercellular system centred around the interaction between a surface-expressed heterodimeric antigen receptor on the T cell (the αβT cell receptor; TCR), which surveys the surface of antigen presenting cells for major histocompatibility complex (MHC) molecules presenting peptide epitopes [1]. The highly polymorphic nature of these MHC molecules is a central feature in immunological genetic diversity. Increasingly recognised however, are populations of 'unconventional' T cells, which are dependent on monomorphic MHC-I-like molecules presenting non-peptide antigens. Namely, CD1 and MR1 present lipid-based and vitamin B-based antigens for T cell surveillance. Along with the specific responses of the T cells that recognise CD1 and MR1, these antigen-presenting molecules are generating great interest within the field, from a fundamental and applied aspect [2,3]. This review will focus on recent advances in the function of mucosal-associated invariant T cells (MAIT cells) that recognise vitamin B-related molecules presented by MR1.

MAIT cells

Initially named after being observed as present in the intestinal lamina propria, MAIT cells are a highly abundant T cell subset in humans [4]. They comprise up to 10% of T cells in peripheral blood of adults and up to 45% of T cells in the liver [5,6]. Initially identified whilst investigating $CD4^{-}CD8^{-}$ T cell populations, it is now accepted that they are predominantly $CD8\alpha\alpha^{+}$ in human, mouse and macaque, although the contribution of the CD8 co-receptor on MAIT cell functionality remains unclear [7–9,10•,11]. MAIT cells are typically defined by a number of phenotypic markers, including their semi-invariant TCR, which is restricted to the MHC-I related molecule 1, MR1 [4,5,12]. They are further often distinguished by their expression of high levels of the NK cell receptor CD161 in the peripheral blood of adult humans; receptors for IL-7, IL-12, IL-18 and IL-23; the peptidase CD26; and multiple chemokine receptors including CCR6, CXCR6 and CCR5 (Figure 1a) [5,13–15]. The human MAIT TCR α-chain is typically formed by TRAV1-2 combined with either TRAJ33/12/20, which is paired with a more diverse array of β-chains, although there is bias towards TRBV6/20 [10•,16,17]. The recent development of MR1-antigen tetramers [10•,18••] has circumvented the need of the use of surrogate phenotypic markers for MAIT cell identification, and is likely to become a very useful tool to characterise MAIT cells

[**] Joint senior authors.

Figure 1



MAIT cells react to bacterial infection. **(a)** Common MAIT cell markers used for identification. **(b)** MAIT cells recognise *Salmonella*-infected cells by recognising MR1 that is presenting 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU) or 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU), using their invariant TCR. Once activated, they signal with IFNγ, TNF and IL-17, and can kill target cells by producing Granzyme B and Perforin. **(c)** MAIT cells have been shown to be activated independent of MR1 by IL-12 and IL-18, producing IFNγ. **(d)** Condensation reaction between bacterially produced riboflavin biosynthesis intermediate 5-amino-6-D-ribityaminouracil (5-A-RU) with the reactive byproducts of metabolism glyoxal and methylglyoxal, produces the potent antigens 5-OE-RU and 5-OP-RU, respectively. These rapidly circularise to form ribityllumazines, which are far less potent than the pyrimidine antigens. The ribityl tail motif is circled in red.

ex vivo in a number of settings. Upon MR1-dependent activation, MAIT cells rapidly produce inflammatory cytokines in a Th1/Th17-like response [5]. They are granzyme B and perforin licenced, giving them the capacity to kill bacterially infected targets. Additionally, they are able to be activated independently of MR1 through cytokine signalling (Figure 1a–c) [5,19–21].

MAIT cells develop in the thymus through a pathway dependent on MR1 expression, moving through three distinct developmental stages [22•]. Stage one MAIT cells are small, functionally immature and do not yet express CD161. These cells develop in the thymus through stage two, growing larger, maturing in expression profile and undergoing selection, until finally developing

into stage three, or functionally competent MAIT cells. Yet, their full effector potential is not reached during thymic development—it is only after thymic egress that they develop fully, in a process dependent on the presence of commensal microflora [4,22•]. Notably, mice deficient in type I NKT cells have increased MAIT cell frequencies [22•] and it will be interesting to establish the interrelationship between these two distinct, innate-like T-cell populations.

Biosynthetic vitamin B products as determinants of bacterial infection

MR1 is ubiquitously expressed in all cells (but at very low levels on the cell surface as judged by anti-MR1 staining) and, contrary to its name, it does not present peptide antigens nor traffics similarly to MHC-I molecules. The nature of the MR1 antigen remained unknown long after the first description of MAIT cells [4,9]. The seminal observation that MAIT cells exhibited reactivity to bacterial pathogens that synthesised riboflavin was crucial in determining that MR1 presents precursors of riboflavin to MAIT cells [18••,23••]. Through methodical mutation of the *rib*-operon in *Lactobacillus lactis*, Corbett *et al.* [18••] identified 5-amino-6-D-ribityaminouracil (5-A-RU) as a key intermediate for MAIT cell activity. Furthermore, 5-A-RU contains a free amine that is susceptible to condensation reactions with metabolic by-products. Consequently, it was shown that a non-enzymatic reaction between 5-A-RU and either glyoxal and methylglyoxal, resulted in the production of the highly potent pyrimidine antigens 5-(2-oxoethylideneamino)-6-D-ribitylaminouracil (5-OE-RU) and 5-(2-oxopropylideneamino)-6-D-ribitylaminouracil (5-OP-RU), respectively (Figure 1d). Remarkably, these antigens could be captured and stabilised by MR1, before they underwent rapid and spontaneous dehydrative cyclisation to form their more stable ribityllumazine products, which are far less potent at stimulating MAIT cells [23••].

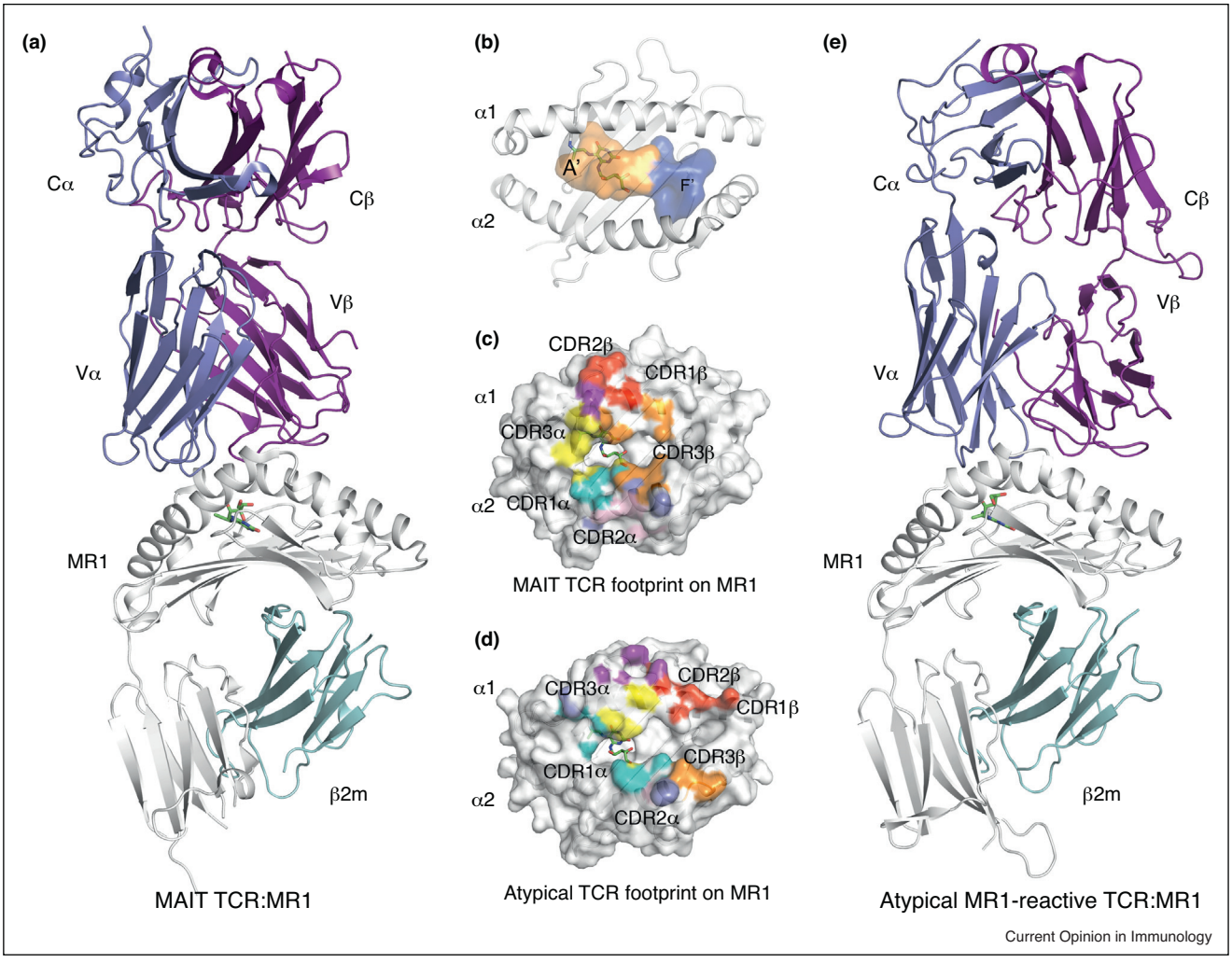
Central to understanding the MAIT-MR1 axis were the associated structural studies that provided insight into the molecular detail of ligand capture and subsequent recognition by the MAIT TCR (Figure 2a–e). MR1 forms a heterodimer with β2m, forming a characteristic MHC-I assembly, where the α1α2 domains form two α-helices sitting atop a 7-strand antiparallel β-sheet (Figure 2a and b) [23••]. Further, the MR1 groove consists of two distinct compartments—the A'pockets and F'pockets (Figure 2b) [23••]. The A'pocket is lined with aromatic and polar residues, within which the pyrimidine, lumazine and pterin-based antigens are bound. The ribityl tail of the riboflavin-based antigens is positioned towards the site of MAIT TCR ligation (Figures 2 a–c and 3 a–d), and represents an important moiety for the stimulatory property of these antigens. Strikingly, there is a Lys residue (K43) at the base of the A'-pocket that forms a Schiff-base (covalent bond) with the carbonyl group of the antigen—further bolstering the capacity of MR1 to sequester these unique and unstable markers of bacterial infection (Figure 3a). This covalent linkage has proven to be a common feature of MR1, with a number of identified MR1 ligands forming this bond. In contrast, the F'-pocket is much shallower, lined with primarily polar residues and, as of yet, there have been no described physiological ligands [23••,24,25]. Thus, the importance of this region in the context of MAIT cell biology remains unclear.

Consistent with the CD1 family, the MR1 trafficking is distinct from conventional MHC molecules. The majority of pre-synthesised MR1 remains trapped within the endoplasmic reticulum in the absence of ligand [26••,27]. Once ligand is available, MR1 associates with β2m and is trafficked through the golgi en-route to the cell surface for presentation [9,26••,27]. After presentation, MR1 is rapidly internalised and the majority degraded via endocytosis. Nonetheless, a small percentage (~5%) is recycled from the endosome back to the cell surface, providing an opportunity for ligand exchange to occur [26••]. The mechanism for ligand processing is largely unknown and it has been argued that the processing of ligand from phagocytosed bacteria may differ from synthetic ligands tested *in vitro* [28]. Nevertheless, it has been determined that antigen processing is TAP and proteasome independent [9,27]. The covalent bond formed between K43 and numerous vitamin B metabolite ligands appears instrumental in the ability of MR1 to be released from the endoplasmic reticulum [26••]. Mutation of this single residue to maintain or abolish a positive charge significantly affects MR1 trafficking, either resulting in constitutive expression or inhibition of MR1 transport [26••]. Therefore, this residue is considered to be a vital molecular switch moderating MR1 surface expression, and a rapid 'off-on-off' mechanism is considered to define MR1 egress to the cell surface.

Structural determinants of vitamin B-related recognition.

The small, unstable antigens presented by MR1 not only require a unique means of capture, but their recognition by the MAIT TCR also necessitates a sensitive and finely tuned mechanism. Indeed, an antigenic pyrimidine is recognised by a single direct contact point between the ribityl moiety of the ligand and a tyrosine residue at position 95 (Y95α) in the CDR3α loop of the MAIT TCR (Figure 3b and d) [18••,29]. Accordingly, the semi-invariant TCR usage facilitates a consistent docking mode, locating the Y95α 'lynch pin' of recognition in position (Figure 2a and c). The MAIT TCR β-chain complements the overall interaction with MR1 and is important for maintaining specificity. Consequently, variation in the β-chain sequences can directly alter the affinity of MAIT-TCR for MR1-antigen [25,30]. Indeed, certain MAIT TCRs that exhibit extensive β-chain

Figure 2



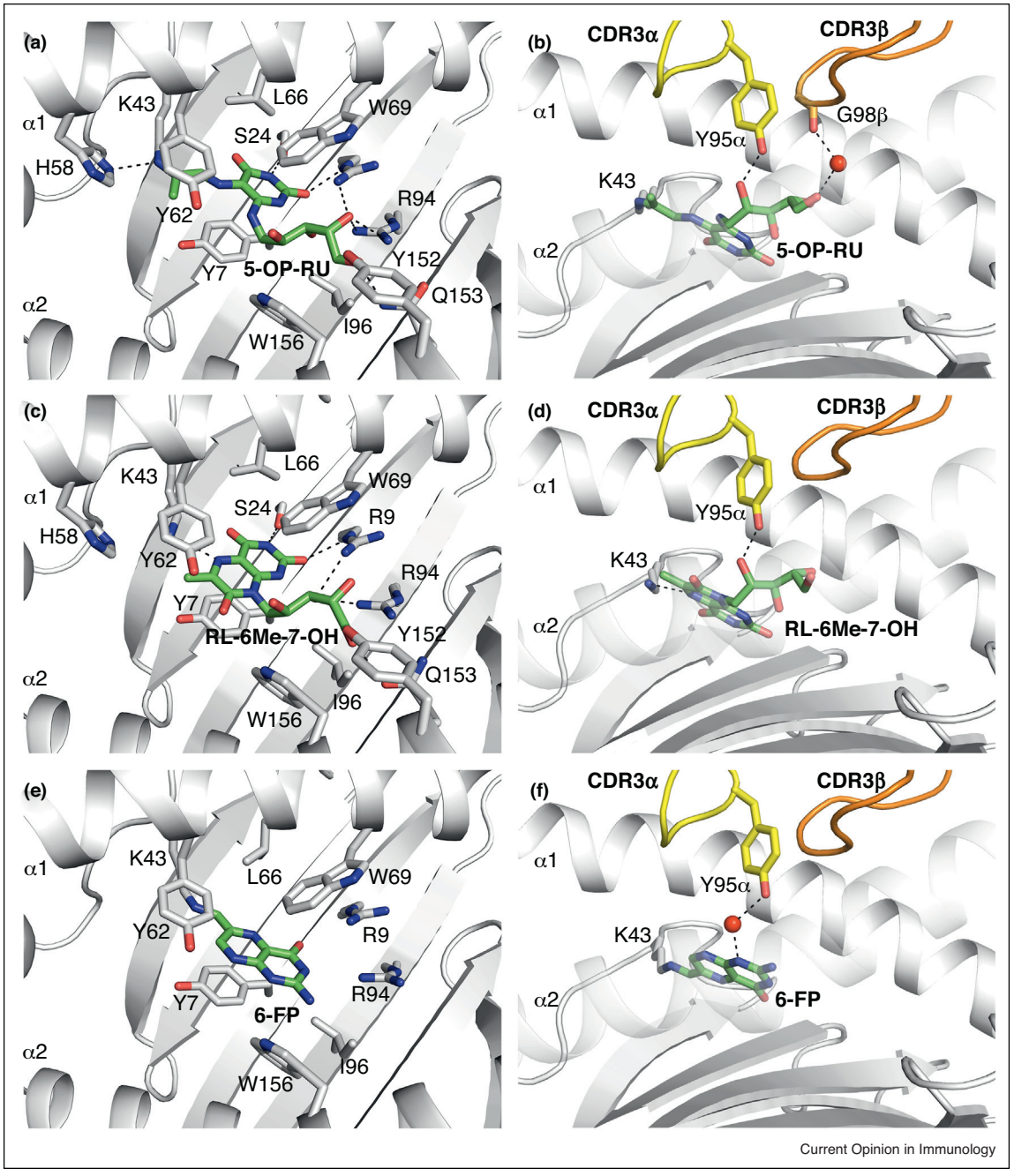
Structural insight into MR1:MAIT TCR ligation. **(a)** Ternary structure of a conventional MAIT TCR (A-F7; α-chain: slate; β-chain: purple) recognising the heterodimer of MR1-β2m (white and cyan, respectively). **(b)** MR1 α1α2 domain forming the A'-binding and F'-binding pockets with antigen (green sticks; 5-OP-RU) bound within the A' pocket. **(c)** and **(d)** Surface of MR1 in the same orientation as (b), highlighting the contact point of (c) a conventional A-F7 TCR and (d) an atypical MR1-reactive TCR (MAV36). The contacts of CDR1α (teal), CDR2α (pink), CDR3α (yellow), CDR1β (cyan), CDR2β (red) and CDR3β (orange) are coloured. **(e)** Ternary structure of atypical MAV36 TCR recognising MR1.

contacts can display heightened autoreactivity towards MR1 [29].

In stark contrast to the semi-invariant MAIT TCR, rare but distinct populations of T cells exist that recognise MR1 without utilising the conventional TRAV1-2^{+} MAIT TCR. Specifically, MR1-restricted T cells that do not utilise the TRAV1-2 α-chain have been described [30,31]. Early structural information pertaining to unconventional MR1-reactive T cells, demonstrates the use of alternative docking topologies upon MR1 consistent with the loss of contacts from the invariant α-chain (Figure 2d and e) [30]. Furthermore, some of these T cells can recognise infection from bacterial strains lacking riboflavin biosynthesis, eluding to presently undetermined small molecules, potentially used by MR1-restricted T cells as additional indicators of bacterial infection [31].

The first small molecule identified as an MR1 ligand was not the pyrimidine-based antigens, but the non-stimulatory compound 6-formylpterin (6-FP)—a photodegradation product of folic acid [23••]. When bound within MR1, this compound remained distal from the MAIT TCR, thus explaining the lack of MAIT cell activation (Figure 3e and f). Nevertheless, the 6-FP scaffold has proven to be an important standard in understanding

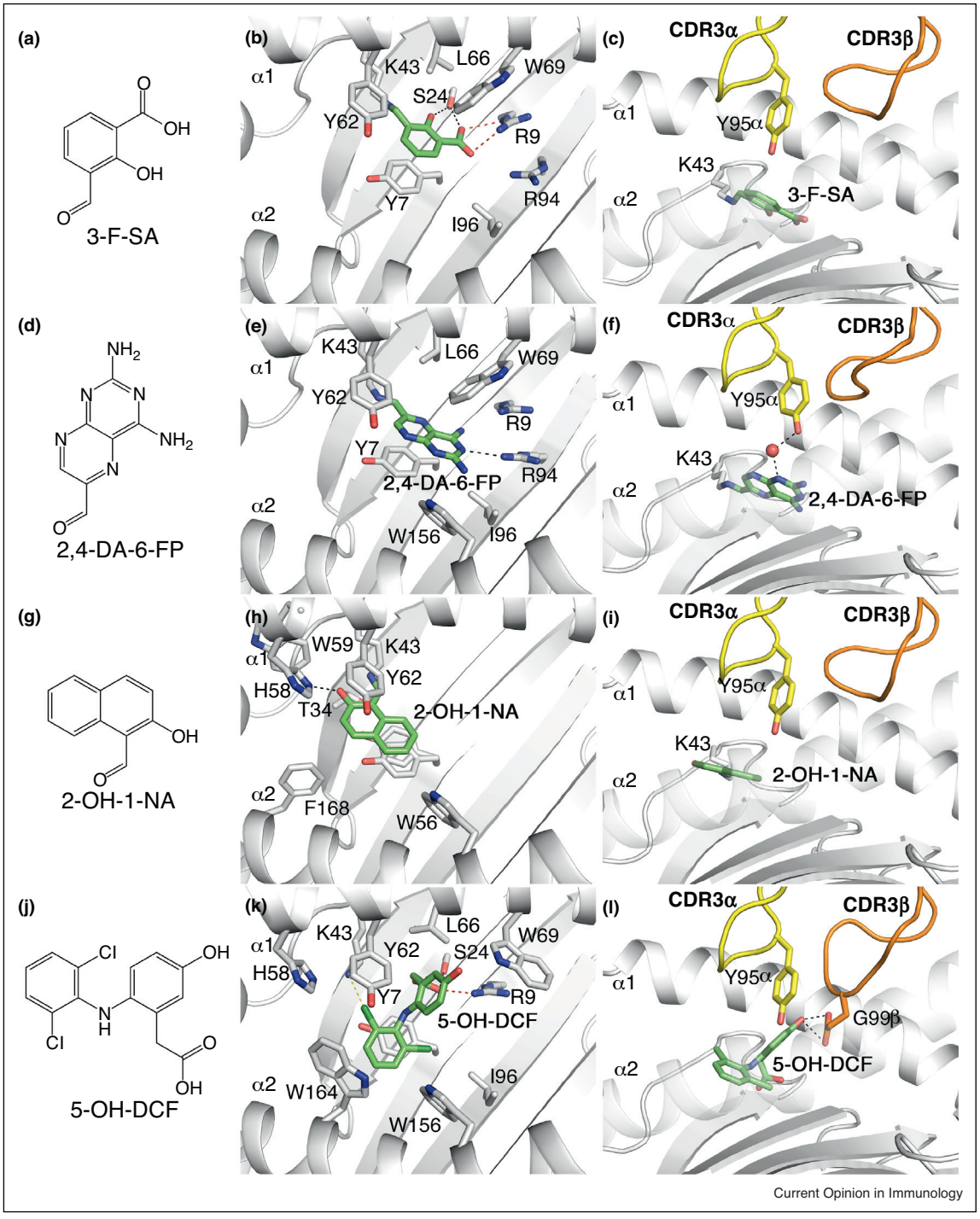
Figure 3



Capture and presentation of vitamin B derived small molecules by MR1. The potent agonist 5-OP-RU **(a)** & **(b)**, weak agonist RL-6Me-7-OH **(c)** and **(d)** and the non-antigenic 6-FP **(e)** and **(f)** are shown bound within the MR1 binding groove (a, c and e; orientation consistent with Figure 2b) and their interaction with the A-F7 MAIT TCR (b, d and f; orientation consistent with Figure 2a). Colours consistent with Figure 2. H-bonds represented as black dashed lines.

MR1 function [23••,26••,28,30]. It, and other subsequently described pterin-based small molecules, trigger high levels of MR1 surface expression and can competitively inhibit MAIT cell activation by 5-OP-RU [25,32,33••]. Whether there is therapeutic potential for vitamin B-based analogues, used as either competitive inhibitors or synthetic activators, is currently unclear. However, recent work has made substantial gains in developing such compounds and methodologies [33••,34].

Figure 4



Diversity of MR1 ligands extends beyond vitamin B derivatives. The non-antigenic small molecules 3-formyl-salycylic acid (3-F-SA; **a–c**), 2,4-diamino-6-formylpterdine (2,4-DA-6-FP; **d–f**) and 2-hydroxy-1-naphthaldehyde (2-OH-1-NA; **g–i**) are shown bound within the MR1 binding groove (b, e, h & **k**). These non-antigenic compounds do not interact directly with the A-F7 MAIT TCR (c, f, i and l). In comparison, the antigenic 5-hydroxy-diclofenac (5-OH-DCF; **j–l**) sits within MR1 (k) and directly contacts the variable MAIT TCR β-chain (l). The orientation b, e, h and k is consistent with Figure 2b, while the orientation of c, f, i and l is consistent with Figure 2a. Colours consistent with Figures 2 and 3. Salt-bridges are represented as red dashed lines and halogen bonds are represented as yellow dashed lines.

MR1 captures drugs and drug-like molecules

The topological differences between the riboflavin-derived and folate-derived antigens are noteworthy and with such apparent plasticity of the MR1 binding groove, it was speculated that MR1 could bind a range of ligands that possessed such scaffolds. Indeed, Keller *et al.* [33••] recently used *in silico* docking techniques to identify a large panel of potential MR1 bound small molecules, which were then validated functionally. With a particular focus on drugs and drug-like molecules, these new MR1-restricted ligands included; synthetic derivatives of salicylic acid (Figure 4a–c), a degradation product of the chemotherapeutic methotrexate (Figure 4d–f), the active moiety of the SIRT inhibitor sirtinol (Figure 4g–i) and metabolites of the non-steroidal anti-inflammatory drug diclofenac (DCF; Figure 4j–l). While the salicyclates and sirtinol-derived ligands were non-stimulatory, the DCF metabolites activated the MAIT TCR in a manner that was dependent of TCR β-chain usage. The ensuing structural studies demonstrated how DCF activation showed subset specificity by modifying the conformation of MR1, thus altering its interaction with the β-chain of the MAIT TCR (Figure 4k and l). These findings suggest that drugs can potentially modulate MAIT cell function *in vivo*, drawing some parallels with HLA-linked drug hypersensitivities [35]. Importantly, this study revealed, for the first time, that the MAIT-MR1 axis is impacted by small molecules with chemical scaffolds distinct from that of the vitamin B-based ligands. Thus, the repertoire of MR1-restricted ligands is likely to be broad.

MAIT cell activation and disease

While MAIT cell activation to microbial infection is dependent on MR1 recognition, MAIT cell activity *in vivo* requires more than this MAIT TCR–MR1-antigen interaction. Specifically, administration of synthetic 5-OP-RU alone causes CD69 upregulation on MAIT cells, but does not result in MAIT cell proliferation in the lungs [36]. 5-OP-RU plus additional TLR-agonists, however, causes higher levels of activation as well as proliferation of the MAIT cell pool [36]. The full range of signals capable of co-stimulating MAIT cell activation is yet to be elucidated. Although many bacterial and yeast pathogens share the riboflavin pathway and are thus likely capable of producing riboflavin-derived antigens, a role for MAIT cells in immune protection has so far been demonstrated for relatively few pathogens [37•,38•,39–41]. In addition, a number of studies show correlation of higher MAIT number with disease or without a protective role, suggesting that MAIT cells may contribute to pathology in infection and other diseases [9,39,42–44]. Noteworthy, is the wide array of diseases that are being described in addition to microbial infection. Indeed, MAIT cells have been implicated in viral infections [20,45], cancer [46–51], chronic inflammation (COPD [52,53], colitis [54], Crohn's disease [54–56]) and auto-immune (rheumatoid arthritis [57], psoriasis [13], lupus [58] and diabetes [59,60]) related diseases. The functional implications of these observations, however, are yet to be determined.

In addition to MR1-mediated activation, MAIT cells can be activated in an MR1-independent manner, mediated by IL-18 and IL-12 mechanisms (Figure 1c) [19]. Although many correlations of reduced MAIT cell numbers and viral infections have been reported, recently Loh *et al.* and van Wilgenburg *et al.* demonstrated MR1-independent MAIT cell activation by viruses [20,45]. The activity of such a large subset of T cells has clinically relevant outcomes. For example, Loh *et al.* [20] described the link between this action and clinical outcomes for influenza virus infection, demonstrating how MAIT cell activity, independent of MR1, can contribute to viral resistance.

The complexity of MR1-dependent and independent signals to MAIT cells in infection, and in diseases such as inflammatory bowel disease, as well as differences in defining MAIT cells, may explain the many apparent inconsistencies in published literature regarding the role of MAIT cells in disease. Nevertheless, with mounting evidence demonstrating their immunological significance, understanding MAIT cell biology could have profound implications for a number of important human diseases.

Conclusions

Since the initial identification of MR1-restricted ligands, significant progress has been made in understanding fundamental aspects of the MAIT TCR–MR1 axis. With greater understanding of MAIT cell function, improved description of the cell phenotype and identification afforded with the use of MR1-tetramers [10•,18••], the role of MAIT cells in diseases will no doubt be elucidated allowing their potential as a therapeutic target to be explored.

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