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Capturing the antigen landscape: HLA-E, CD1 and MR1

Graham Ogg[1], Vincenzo Cerundolo[2] and Andrew J McMichael[3]

T cell receptor (TCR) recognition of antigens presented by relatively non-polymorphic MHC-like molecules is emerging as a significant contributor to health and disease. These evolutionarily ancient pathways have been inappropriately labelled 'non-conventional' because their roles were discovered after viral-specific peptide presentation by polymorphic MHC class I molecules. We suggest that these pathways are complementary to mainstream peptide presentation. HLA-E, CD1 and MR1 can present diverse self and foreign antigens to TCRs and therefore contribute to tissue homeostasis, pathogen defence, inflammation and immune responses to cancer. Despite presenting different classes of antigens, they share many features and are under common selective pressures. Through understanding their roles in disease, therapeutic manipulation for disease prevention and treatment should become possible.

Addresses
[1] MRC Human Immunology Unit, and Oxford NIHR Biomedical Research Centre, University of Oxford, UK
[2] MRC Human Immunology Unit, University of Oxford, UK
[3] Nuffield Department of Medicine Research Building, University of Oxford, UK

Corresponding author: McMichael, Andrew J (andrew.mcmichael@ndm.ox.ac.uk)

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Introduction

Over the past 20 years, it has become clear that T lymphocytes recognize not only peptides in the context of MHC polymorphic class I and class II molecules, but also diverse antigens bound to non-polymorphic MHC-like molecules, CD1, MR1 and HLA-E in humans. Structural, kinetic, and functional studies have significantly contributed to the understanding of the identity of the antigens presented by these MHC-like molecules and of the mechanisms that mediate their processing and presentation. The ability of T cells to recognize a broad range of self and non-self lipids, peptides and metabolites in the context of CD1, HLA-E and MR1 molecules, respectively (Figure 1) (Table 1), underscores the importance of such T cells in sterile and non-sterile inflammatory conditions.

HLA-E

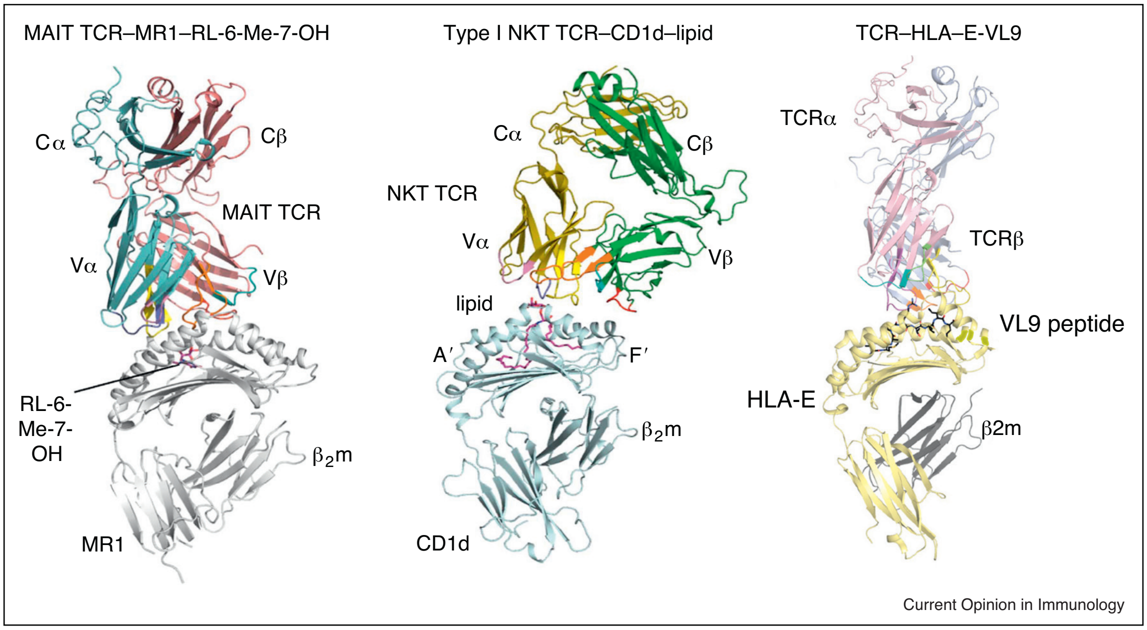
HLA-E, H2-Qa1 in mice and Mamu-E in rhesus monkeys are homologous MHC class Ib molecules (MHC-E) with limited polymorphism. HLA-E has two alleles, differing only at position 107, outside the peptide-binding groove [1]. MHC-E molecules are widely expressed but at low levels and present a nonamer peptide derived from MHC class Ia molecules, typically VMAPRTLVL ("VL9"), to the natural killer cell receptors NKG2A/C-CD94. When in the bound complex, the arginine at peptide position 5 fits between NKG2 and CD94 [2]. The Inhibitory NKG2A binds with higher affinity than activating NKG2C and the balance between them regulates innate immunity.

The VL9 signal peptide dominates the spectrum of bound peptides. In the endoplasmic reticulum (ER) it is cleaved from the MHC protein and further digested by signal peptide peptidase in the ER membrane to put a 14-mer fragment into the cytosol. That peptide is proteasome digested to an 11-mer which is transported by TAP to the peptide loading complex (PLC). There it binds MHC-E [3••,4••] and the two amino-terminal amino acids are cleaved by ERAP amino peptidases to give VL9. VL9 binds to HLA-E in the PLC displacing the scoop loop of tapasin. If TAP or ERAP are disrupted, alternative peptides bind to MHC-E [5].

VL9 regulates NK cells, and a subset of NKG2A$^+$ T cells, controlling innate immunity. In humans, a balance between NKG2A-dependent and KIR-dependent control of innate immunity is regulated by the expression levels of HLA-E (for NKG2A) or particular HLA, A, B and C allomorphs (for KIR) [6••]. Given the limited genetic polymorphism in VL9 which affects HLA-E binding and also HLA-ABC binding to KIR receptors, HLA type strongly influences antiviral innate immunity [6••]. Recently, NKG2A has emerged as a regulatory checkpoint for CD8 T cells [7•].

MHC-E also presents peptides to T cell receptors (TCRs). The human cytomegalovirus (HCMV) UL40 protein includes a nonamer peptide that matches human VL9. There is limited polymorphism at positions 6–8 in VL9 in both humans and HCMV strains; if mismatched, CMV can prime HLA-E restricted UL40-specific CD8 T cells [8,9]. Gene deletion of mouse ERAAP resulted in

Figure 1



T Cell Receptor Recognition of MR1, CD1 and HLA-E. Left panel; T cell receptor recognition of the riboflavin derivative 7-hydroxy-6-methyl- 8-D-ribityllumazine (RL-6-Me-7-OH) by the conserved MAIT T cell receptor (TRAV1–2–TRAJ33– TRBV6-1). Middle panel; type I NKT TCR (TRAV10–TRAJ18-TRBV25-1)-CD1d-a-galactosylceramide (a-GalCer) complex. Right panel; HLA-E containing the RMAPRTLVL (VL9) peptide with the T cell receptor TRAV-35*02-TRAJ53*01-TRVB9*01-TRBJ 1-4*01. The left hand two panels are from Patel *et al.* [45] and the right hand panel is from Sullivan [9] *et al.*, with permission.

binding of another peptide, derived from the self-protein Fam49b, instead of VL9 to H2-Qa1. Similarly, H2-Qa1 restricted T cells respond to a Salmonella GroEL peptide GMQFDRGYL, which is very similar to hsp60 peptide GMKFDRGYI. CD8 T cells specific for the latter regulate auto-reactive follicular T and B cells [10].

Recently MHC-E restricted T cells have been found to be more abundant than previously recognized. Multiple *mycobacterial* peptide epitopes prime HLA-E restricted CD8 T cells in most humans [11,12•]. Knock-out of H-2 Qa1 resulted in higher bacterial loads and more severe disease after *Mtb* infection [13]. Furthermore, monkeys vaccinated with RhCMV strain 68-1, recombinant for SIV genes, made strong Mamu-E and Mamu-class II restricted CD8 T cell responses. Half of vaccinated animals cleared experimental SIV infection within a few weeks of challenge. This unique protection was dependent on the atypical SIV-specific CD8 T cell responses [14••]. Vaccine induction of Mamu-E restricted T cell responses is dependent on the deletion of four RhCMV genes, and requires certain others in the vaccine [14••]. The HCMV US11 homologue, that targets nascent class Ia MHC molecules for proteasomal degradation, removes classical MHC-Ia restricted T cell responses. Two of the deleted genes encode for components of the pentameric viral protein that binds to cell receptors, changing viral tropism. This suggests that a particular type of infected cells, possibly macrophages by analogy with *mycobacterial* induction of HLA-E restricted T cells, primes this unusual T cell response. Cross priming by dendritic cells, which disconnects CMV gene effects, must be blocked or suppressed.

Both Mtb- and SIV-specific, RhCMV-68-1 primed, MHC-E restricted T cells respond to multiple peptide epitopes. HLA-E, Mamu-E and Mafa-E in humans, rhesus and cynomolgus monkeys respectively bind the same peptides [15•]. These epitopes have no simple amino acid motif in the immunodominant epitopes [14••,16], which contravenes classical antigen processing rules, where particular amino acids optimise binding to pockets in the different MHC class Ia molecules. This optimization of binding affinity ensures that epitopes compete out the scoop loop of tapasin and bind to the class I MHC molecules in the PLC. The related protein TAPBPR serves a similar quality control function downstream in the ER or Golgi [3••,4••]. In *mycobacterial* and RhCMV68-1 infection, the classical antigen processing pathway is bypassed. Infecting *mycobacteria* reside in macrophage phagolysosomes and peptide antigen is processed there (Figure 2). Phagolysosomes richly express HLA-E, which recycles from the cell surface facilitating peptide exchange; peptide presentation is not dependent on new HLA-E synthesis [17]. In RhCMV68-1 infected cells, the classical antigen presentation pathway is

Table 1

Antigen presentation comparisons between classical MHC-I, MHC-E, MR1, CD1 and MHC-II

	MHC-I	MHC-E	MR1	CD1	MHC-II
Ligand	Peptide 8–11 aa	Peptide: VL9 self Multiple foreign	Riboflavin intermediates	Lipids	Peptides ~15 aa
Ligand loading	ER: Peptide loading complex: TAP and Tapasin dependent	VL9: ER: Peptide loading complex TAP, tapasin and ERAP dependent Microbial peptides: endosomal	ER, Endosomal.	Endosomal, lysosomal and ER. Supported by lipids, lipid transfer proteins, for example saposins, MTP, CD1e, and others	Endosomal
Chaperones	Calnexin, calreticulin, ERp57, tapasin in ER	Calnexin, calreticulin, ERp57, tapasin in ER	?	calnexin, calreticulin, ERp57 at ER.	Ii (CD74) HLA-DM
Receptors	TCR αβ-polyclonal; KIR2 and KIR3 – (selective)	NKG2A/C- CD94 TCR αβ polyclonal	TCR αβ monoclonal	TCR αβ limited and diverse, TCR γδ, Non-TCR	TCR αβ polyclonal

blocked by US2, US3 and US11 which degrade most Class Ia MHC molecules. Also US6 inactivates the TAP transporter. Consequently, HLA-E is released from the peptide loading complex by an alternative VL9 peptide coming from CMV protein EL40 (Rh67 in RhCMV) within the ER. Thus HLA-E bypasses the tapasin and TAPBPR quality controls and exits the ER/Golgi. What happens next is uncertain, but MHC-E may traffic like class II MHC to access peripheral endosomal or lysosomal compartments where locally generated peptides are exchanged.

Given the sequence diversity of *Mtb* and SIV epitope peptides, it is unsurprising that they bind MHC-E with low affinity, facilitated by the relative stability of peptide-free HLA-E [14••,16]. Empty HLA-E is incompletely folded but is peptide receptive [16]. High affinity peptides give a classical refold, but most of the low affinity SIV and Mtb epitopes fold HLA-E incompletely *in vitro*. T cell receptors may see either form or may push the equilibrium towards the classical fold. Low affinity peptides are excluded from the classical pathway by the tapasin and TAPBPR, but in endosomal compartments, such constraints are lacking, so they can bind and stimulate very broad polyclonal T cell responses. For anti-SIV immunity, this breadth could be advantageous, by making mutational immune escape impossible.

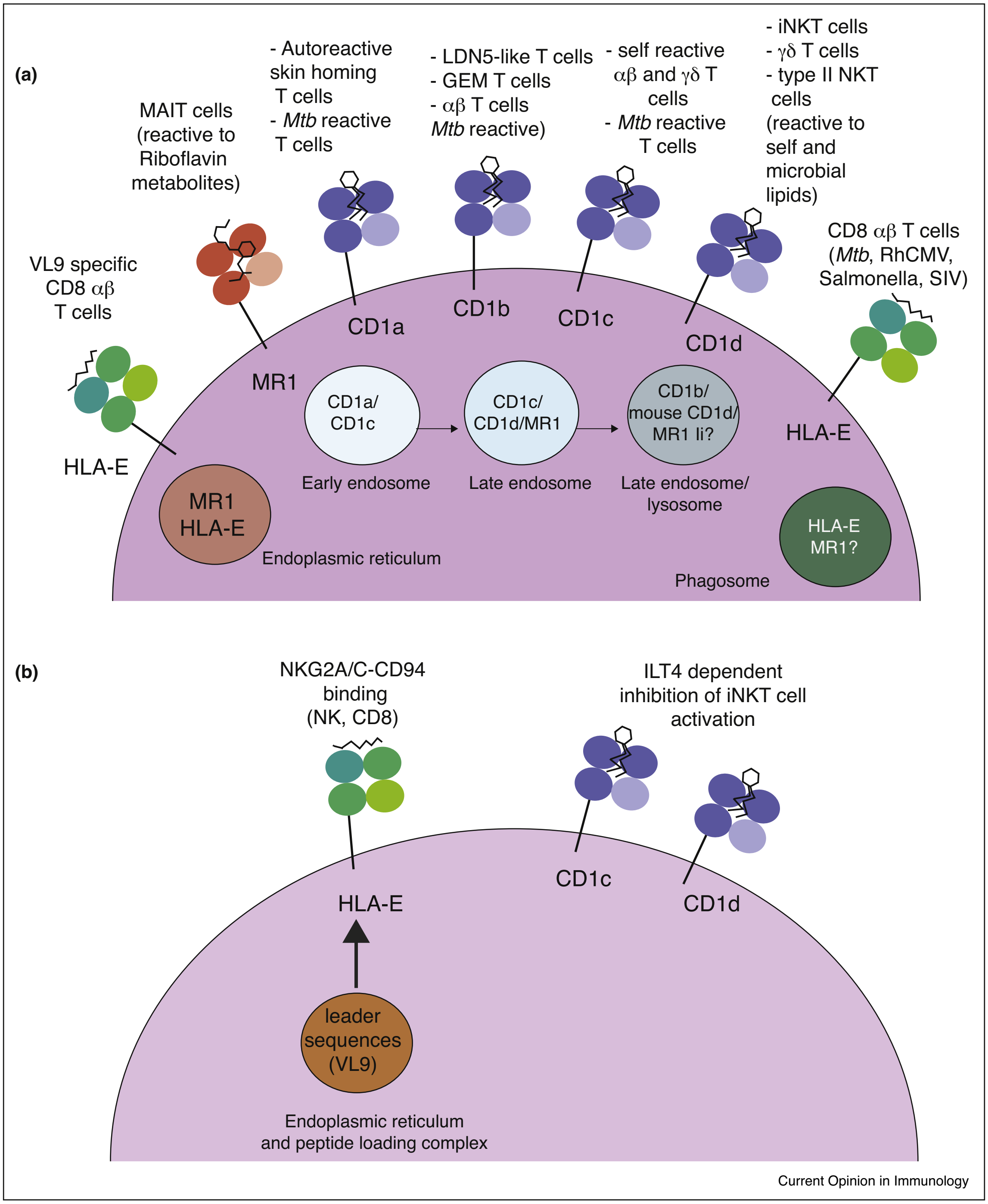
Other intracellular bacterial pathogens could access intracellular compartments where MHC-E is relatively well expressed, eliciting MHC-E restricted T cell responses. Thus, MHC-E would serve a dual function, regulating innate NK cell responses as well as presenting low affinity bacterial peptides processed in peripheral intracellular compartments.

CD1

The CD1 system is specialised for lipid antigen presentation through CD1a, CD1b, CD1c and CD1d proteins. CD1a, CD1b and CD1c are expressed by thymocytes, dendritic subsets and other mononuclear phagocytes, and other cells, including some peripheral lymphoid cells [18]. CD1d is more broadly expressed including constitutive expression by thymocytes, B cells, monocytes, macrophages, dendritic cells and epithelia. CD1 members are relatively non-polymorphic, leading to the concept of donor-unrestricted T cells and the potential for broad therapeutic intervention [19]. These molecules non-covalently associate with ß2-microglobulin, forming two anti-parallel α-helices, overlying a membrane-distal β-pleated sheet. Compared to MHC-class I, CD1 molecules have a relatively narrow entry portal leading to deep hydrophobic pockets. The entry portal is formed partly by the A'-roof resulting from tethers between the α1- helices and α2-helices. The A'-roof provides an asymmetric platform, but is rather tenuous and can be disrupted by dominant-negative "non-permissive" antigens such as sphingomyelin in the setting of CD1a, which can abrogate TCR interactions [20••]. Within the groove, lipid hydrocarbon chains are able to locate flexibly and there may be more than one lipid with incorporation of spacer molecules, enhancing functionality of CD1 binding. Indeed two detergent molecules could fill the surplus capacity of the CD1b-binding groove when in complex with phosphatidylinositol or the ganglioside GM2, suggesting that endogenous short chain fatty acids may fulfil a similar role [21]. Subsequent structural and mass spectrometry studies showed fatty acid chains acting as spacer lipids in other CD1-binding grooves [22].

The structure of an empty CD1d molecule shows inherent flexibility in the binding groove [23], resulting from a

Figure 2



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Antigen Presentation by CD1, MR1 and HLA-E. (a). The antigen processing pathways involved in generating CD1, MR1 and HLA-E bound ligands that stimulate T cell immune responses. CD1 variants acquire their lipid ligands in endosomal compartments. Cytoplasmic tails of the different CD1 isoforms direct them to the different intracellular compartments, where they encounter lipids of appropriate length and complexity for each antigen presenting groove. MR1 is loaded with riboflavin derivatives in the ER, HLA-E acquires the VL9 peptide in the ER and low affinity *Mtb* and CMV peptides in endosomes, when the ER/PLC pathway is bypassed (*Mtb*) or blocked (RhCMV). (b). Activation of innate receptors by HLA-E and CD1 molecules. HLA-E molecules bound to the VL9 peptide, derived from HLA-ABC signal peptide or from UL40 signal peptide bind NKG2A/C-CD94 on the surface of NK cells and NKG2A on CD8 cells, delivering inhibitory signals (costimulatory for NKG2C). CD1d and CD1c can bind to ILT4 (LILRB2) expressed on myeloid cells and inhibit iNKT cell activation [26].

shift in the α1- helices and α2-helices, potentially facilitating lipid loading. In addition, lipid length modulates TCR affinity and the threshold of NKT cell activation [24]. Incomplete occupation of CD1d results in conformational differences at the TCR recognition surface, providing a mechanism where lipid-specific lymphocytes are capable of indirectly recognizing both the group head and the length of lipid antigens, ensuring greater specificity.

The overall cleft volume of CD1 molecules is large, ranging from 1280–1780 A^3 for CD1a, CD1c and CD1d, up to 2200 A^3 for CD1b. The structure of human CD1b revealed a maze-like groove, comprising a C′-channel and T′-tunnel in addition to the A′- channels and F′-channels [21]. The interconnected A′-channels, T′-channels, and F′-channels can extend the binding capacity of CD1b enabling presentation of long-chain mycolate lipids [25], whereas the C′-channel gives further leeway in alkyl chain length by providing an exit via the C′-portal situated under the α2-helix.

The diverse volumes, shapes, entries, interconnectivities, and exits of the hydrophobic channels of the group I family members allow these molecules to present a broad selection of antigens. The range of eluted lipids is diverse with most being amphipathic molecules with the hydrophilic head-group positioned at the external surface providing opportunity for TCR engagement. Lipid antigens can be self or foreign, and many of the known foreign lipids are derived from bacteria (e.g. Gras *et al.*, 2016 [26]). This may reflect experimental focus, or may be indicative of a specialised role in bacterial defence. The ability to recognise self-lipids implicates roles in regulation [27], homeostasis and tissue repair, but also may be means to detect missing-self, pathogen-associated or tumour-associated lipids [28••,29–33]. Such a strategy would offer a relatively conserved system of defence from which it is harder to escape than it is through point mutation of MHC class I-binding peptides. Like for HLA-E, non-TCR ligand binding has been shown for several CD1 molecules, for example [34,33], but the full nature and relative contributions of the TCR and non-TCR interactions has yet to emerge.

The T cell subsets which respond to CD1 presented lipids are under intense study and may express CD8, CD4 or neither [29]. The cells can produce diverse cytokines relevant to disease, and can be cytolytic. TCR usage appears to be dominated by alpha-beta TCR, but gamma-delta TCR can also bind to CD1 (see below). Preferred TCRα gene segment usage across the population has been well-described, particularly studied for CD1d; in humans the TCR α-chain of so-called invariant NKT (iNKT) is non-clonal but is typically encoded by *TRAV10* with *TRAJ18*; and TCR β preferred gene usage has been described (e.g. *TRBV25*). In contrast, type II NKT cells express a diverse TCR repertoire, yet show many shared characteristics with iNKT cells, including potential autoreactivity, PLZF-dependence, and rapid effector function [35]. Interestingly, there are also reports of distinct, and sometimes antagonist functions of iNKT and diverse NKT which will be better understood as ligand specificity further emerges [36]. TCR repertoires of cells recognising CD1a, CD1b, and CD1c are just being defined, and show examples of highly diverse, and restricted subsets [29,37]. For example, T cells with encoded *TRAV1-2/TRAJ9* (sometimes in association with *TRBV6-2*), lack of N-region additions, and specificity for *mycobacterial* antigens presented by CD1b were named germline-encoded mycolyl reactive (GEM) T cells [38]. Subsequently an "LDN5-like" TCR comprising *TRAV17-TRAJ9*-encoded TCR α-chain paired with a *TRABV4-1*-encoded β-chain showed specificity for the same glycolipid but at lower affinity [37]. Gamma-delta TCR recognition of CD1 is less well studied, but there are many examples, including an original study of CD1c by Porcelli *et al.* (1989). Human γδ T cells have been described that can respond to CD1d, CD1a or CD1c presenting self- and foreign lipid antigens, with structural support for γδ TCR co-recognition of CD1d/lipid [39,40,41••,42]. An interesting recent report, suggests that the human Vδ1 TCR might bind CD1 via the CDR1-CDR3 region but may also bind BTNL3–BTNL8 on the same target cell via the germ-line encoded HV4 region [43]. Collectively, these studies show that the CD1 system provides an opportunity to capture and present lipid-based antigens to TCR and non-TCR molecules expressed by T cells. The antigens may be self-lipids or foreign-lipids implicating roles in defence and inflammation, but also in regulation and homeostasis; and it is therefore likely that the system will provide opportunities for prevention and treatment of disease.

MR1

MR1 is a ubiquitously expressed non-polymorphic MHC class I-like molecule, which presents a unique family of bacterial-derived metabolites to Mucosal-associated invariant T (MAIT) cells. Lantz and colleagues proposed MR1 as a candidate [44] and later formally demonstrated MR1 for MAIT selection [45]. Importantly, MAIT cells are frequent in humans, making up to 10% of T cells in peripheral blood and up to 50% in the liver, making them one of the most abundant αβ T-cell population with a single specificity in the human immune system.

In 2012 a landmark publication demonstrated that MR1 molecules present intermediates of the vitamin B2 biosynthetic pathway to MAIT cells [46]. While folic acid derivatives were shown to bind and stabilise MR1 molecules through a Schiff base complex, riboflavin intermediates were shown to be stimulatory, as the ribityl moiety present only in the riboflavin derivatives can be specifically recognised by the TCR from MAIT cells [47••]. Because these vitamins are not produced by mammals, they are molecular signatures of microbial infection, and microbes, lacking the ability to synthesize riboflavins through functional Rib enzymes (such as *Streptococcus pyogenes* or *Enterococcus faecalis*), are unable to activated MR1-dependent MAIT cells [48]. Importantly, all the currently identified ligands bind into the A′ pocket of the MR1-binding groove; there remains the possibility that other classes of ligands might extend into the more exposed F′ pocket.

Combined in silico docking approaches with functional assays and structural studies have recently broadened the range of ligands presented by MR1 molecules beyond riboflavin and folate-based metabolites, by trapping chemicals including drug and drug metabolites, such as the anti-inflammatory drug diclofenac and some of its metabolites, which were shown to be MAIT cell agonists [49]. These findings suggest a possible link between such drugs or their metabolites and the function of MAIT cells and suggesting a possible link between common intolerances to a drug and modulation of the activity of MAIT cells.

It has become clearer that MAIT cells can be identified in all sites where conventional T cells are present. However, their presence at mucosal sites implies an important role for these cells in barrier tissue immunity, supported by mouse models where the deletion of MR1, and hence MAIT cells, rendered mice more susceptible to bacterial infections. These included *BCG*, *Francisella tularensis*, *Klebsiella pneumoniae* and more recently *Legionella* [50]. Importantly, similarly to earlier findings in iNKT cells and γδ cells, MAIT cells have constitutively high surface expression of the IL-18 and IL-12 receptors. They can also be activated in a TCR/MR1-independent manner, through the stimulatory activity of IL-18 in synergy with IL-12 or IL-15 or type I IFNs to induce expression of IFN-γ and Granzyme B. Consistent with these findings, evidence is emerging that MAIT cells are involved in immune responses to viruses. MAIT cells contribute to protection against lethal influenza infection in mouse models [51] and are activated during human viral infections. Mice and humans contain functionally distinct populations of MAIT cells. The major population of MAIT cells in mice expresses RORγt and secretes IL-17 upon activation, while a smaller subset expresses T-bet and produces IFN-γ upon activation [52]. In contrast, while very few MAIT cells from human blood produce IL-17, MAIT cells from other human tissues can secrete IL-17. Thus, MAIT cells isolated from the female genital tract express more IL-17 in response to microbial stimuli compared to MAIT cells from peripheral blood [53•] and several studies have reported a role for IL-17 producing MAIT cells in autoimmune diseases [54].

Although lack of MAIT cells in mouse models makes them susceptible to several bacterial or viral infections, it remains unclear as to whether this effect is due to their ability to lyse infected cells and to secrete proinflammatory cytokines such as IFN-γ and TNF, or whether MAIT cells, similarly to iNKT cells, can also fast track priming of adaptive immune responses. Recent findings have provided important insights supporting the latter possibility by demonstrating that human MAIT cells rapidly upregulate CD40 L upon activation by the cognate antigens presented by MR1 molecules and instruct DC maturation in a CD40L-dependent and MR1-dependent manner, resulting in secretion of bioactive IL-12 [55]. These findings pave the way towards the possibility that MAIT cells could be harnessed *in vivo* to enhance immune responses against pathogens and cancer.

Human MAIT cells predominantly express Vα7.2 joined to Jα33, Jα20 or Jα12, and these pair with Vβ2 or Vβ13. However, smaller subsets of MR1-restricted Vα7.20-T cells have also been identified in humans [56••]. The high abundance of MAIT cells in humans likely reflects ongoing exposure to microbial stimuli, which drive oligoclonal expansion of MAIT cells that have a reduced TCR repertoire [57]. Consistent with this possibility, recent findings clarified the timing and dynamics of the MAIT cell response and TCR usage to bacterial infections by demonstrating that host exposure to antigen may drive clonal expansion of MAIT cells with increased functional avidity. By utilizing samples from a controlled human infection model of the invasive bacterial pathogen S. Paratyphi A in healthy volunteers, it was shown that MAIT cells undergo an adaptive clonal response during infection [58]. These findings demonstrate that MAIT cells are at the interface between innate and adaptive immunity and that lifetime exposure to different microbial infections could impact and shape their TCR repertoire.

Collectively, HLA-E, CD1 and MR1 illustrate how the immune system will capture a broad array of antigen types for presentation to T cells, and we anticipate that more will emerge. By focussing initially on viral-specific MHC-class I responses, the field has perhaps incorrectly assigned these molecules to “non-classical” or “non-conventional” pathways, but recent advances prompt a re-evaluation, with likely broad relevance to disease pathogenesis and new approaches to treatment. A common thread in recent studies of these MHC-like molecules is their role in bacterial infections: mycobacterial peptides with MHC-E, bacterial lipids with CD1 and multiple bacteria generating riboflavin derivatives that bind to MR1. Given that the range of bacterial exposure is even greater than with viral and parasitic antigens, these antigen presentation pathways are likely to be as important as the ‘classical’ MHC-Ia route. Viral and self-epitopes are not excluded and all could also have roles in cancer immunity. More attention paid to these pathways in the future could open up new therapeutic approaches.

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