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# The role of MHC class Ib-restricted T cells during infection

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## Abstract

Even though MHC class Ia and many Ib molecules have similarities in structure, MHC class Ib molecules tend to have more specialized functions, which include the presentation of non-peptidic antigens to non-classical T cells. Likewise, non-classical T cells also have unique characteristics, including an innate-like phenotype in naïve animals and rapid effector functions. In this review, we discuss the role of MAIT and NKT cells during infection, but also the contribution of less studied MHC class Ib-restricted T cells such as Qa-1-, Qa-2-, and M3-restricted T cells. We focus on describing the types of antigens presented to non-classical T cells, their response and cytokine profile following infection, as well as the overall impact of these T cells to the immune system.

### Keywords

Non-classical T cells; Infectious diseases; MHC class Ib; NKT & MAIT cells

## A. Introduction

The innate and adaptive branches of the immune system are not mutually exclusive, and there is a growing interest in innate-like T cells, many of which are restricted by non-classical MHC molecules. Cytotoxic $CD8^+$ T cells are restricted by MHC class I molecules and categorized into two groups: classical MHC class Ia and non-classical MHC class Ib. MHC class Ia molecules are highly polymorphic and encoded in the *Mhc* locus by *H-2K*, *H-2D*, and *H-2L* in mice and *HLA-A, HLA-B*, and *HLA-C* in humans. The MHC class Ib family has evolved more diverse, and specialized, functions than their classical counterparts. These molecules are predominantly found in the *H2-Q, H2-T*, and *H2-M* regions in mice and *HLA-E, HLA-F*, and *HLA-G* in humans within the *Mhc* locus. Many are capable of presenting antigens, while others are incapable of antigen binding or participate in responses outside of the immune system. For example, murine M1 and M10 bind to V2R G protein-coupled receptors and play a role in pheromone detection (Loconto et al. 2003), while ZAG in humans and mice binds fatty acids and polyethylene glycol, contributing to lipid metabolism (Delker et al. 2004; Hirai et al. 1998). MHC class Ib molecules are also well known to interact with NK cell receptors (Braud et al. 1998; Lee et al. 1998b; Vance et al. 1999; Vance et al. 1998). Some have proposed to classify MHC class Ib molecules according

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to their age, such as ‘Young,’ ‘Middle-aged,’ and ‘Old’ (Rodgers and Cook 2005). For example, ‘Old’ genes diverged during early vertebrate evolution and many members of this subset fall outside the *Mhc* gene locus in humans and rodents, such as *CD1, MR1*, and *HFE* (Rodgers and Cook 2005). Generally, non-classical MHC molecules present a more diverse array of antigens, *e.g.* CD1 presents glycolipid antigens (Beckman et al. 1994), MR1 presents Vitamin B metabolites (Kjer-Nielsen et al. 2012), and M3 presents formylated peptides (Smith et al. 1994) (**Table 1**). These molecules also tend to have more restricted tissue localization, lower expression at the cell surface, limited polymorphism, and shorter cytoplasmic tails (Stroynowski and Lindahl 1994). In this review, we will discuss MHC class Ib-restricted T cell responses in humans and mice in the context of infection. We will focus on 1) the antigens (or lack thereof) presented by this family of molecules, 2) the cytokine profile of MHC class Ib-restricted T cells, and 3) the overall contribution of non-classical T cells to the immune response (**Table 2**).

## B. Positive selection of non-classically restricted CD8⁺ T cells

Non-classical $CD8^+$ T cells often have an innate-like phenotype, which includes increased expression of CD44 and decreased CD62L expression (Jay et al. 2008; Kurepa et al. 2003). It has been proposed that this results from unusual positive selection. For example, the conditions that T10- and T22-restricted γδ T cells undergo positive selection affect their effector phenotype. Cells that develop in the presence of T22 are able to produce IFN-γ, whereas antigen-naïve T10- and T22-reactive γδ T cells during development produce IL-17 (Jensen et al. 2008). Thymic epithelial cells (TECs) are essential for the positive selection of conventional T cells (Anderson et al. 1994). On the other hand, invariant natural killer T (iNKT) cells are selected by $CD4^+CD8^+$ double positive (DP) cortical thymocytes that present CD1d (Bendelac 1995). Similarly to iNKT cells, MAIT cells are also selected by hematopoietic cells (HCs) (Treiner et al. 2003), which are DP thymocytes expressing MR1 (Seach et al. 2013). MHC class Ib-restricted $CD8^+$ T cells that are specific for *Listeria monocytogenes* antigens are also selected for by HCs, whereas MHC class Ia-restricted T cells are inadequately selected (Urdahl et al. 2002). Interestingly, it was recently shown that M3-restricted T cells could be selected by TECs or HCs, but that the selecting cell type played a role in their phenotype (Chiu et al. 1999b; Cho et al. 2011). Cells selected by HCs acquired enhanced effector functions (Cho et al. 2011). Similarly, using transgenic mice possessing a TCR specific for a Qa-1- presented insulin-derived peptide, it was determined that either TECs or HCs selected Qa-1-restricted $CD8^+$ T cells (Sullivan et al. 2002). However, in contrast to M3’s role during positive selection, there was no observable difference in phenotype between these two differentially selected populations (Sullivan et al. 2002). Altogether, these findings demonstrate that individual MHC class Ib-restricted T cell populations have unique requirements for positive selection.

## C. MHC class Ib-restricted CD8+ T cells and their participation during infection

### The CD1-restricted family of T cells

The *CD1* locus is not linked to the *Mhc* locus. CD1 presents self and foreign lipid antigens to multiple CD1-restricted T cell populations, rather than peptides (**Figure 1**) (Beckman et al. 1994). Five isoforms of human CD1 are expressed, which are organized into three groups: Group 1 CD1 (CD1a, b, c), Group 2 CD1 (CD1d), and Group 3 CD1 (CD1e). T cells are able to directly recognize lipids presented by all CD1 isoforms except CD1e, which is thought to aid CD1b in ligand processing and presentation (de la Salle et al. 2005). Unlike MHC class Ia molecules, the transporter associated with antigen processing (TAP) is not required for CD1 antigen loading (Brutkiewicz et al. 1995; Hanau et al. 1994). CD1d is the only isoform expressed in rodents. There are two types of Group 2 CD1-restricted T cells, type I iNKT cells and type II NKT cells, which were initially classified based on TCR diversity (Cardell et al. 1995). iNKT cells participate during a variety of infectious diseases and can be activated in a TCR-dependent or TCR-independent manner by responding to environmental cytokines, like IL-12 and IL-18, rather than ligand stimulation (Leite-De-Moraes et al. 1999). This is evident following murine cytomegalovirus (MCMV) infection, where iNKT cells become activated in an IL-12-dependent manner, and is partially contingent on type I interferons (Holzapfel et al. 2014; Tyznik et al. 2014; Wesley et al. 2008). On the other hand, type II NKT cell activation mainly occurs in a TCR-dependent manner to self-glycolipids of self-phospholipids, whose antigen repertoire can be either exclusive or promiscuous (Jahng et al. 2004; Tatituri et al. 2013). Type II NKT cells appear to have opposing roles, capable of participating in protective responses or promoting pathology. However, the information about this subset has remained limited because type II NKT cells cannot be labeled as a single population with CD1d tetramers like iNKT cells. In addition, early studies to determine the functions of type II NKT cells using Jα18$^{-/-}$ mice may need to be revisited, due to an impaired TCR repertoire of the original mice (Bedel et al. 2012).

iNKT cells respond to CD1d-presented ligands derived from a number of bacteria and even protozoa, including: *bacteroides fragilis*-derived sphingolipid α-galactosylceramide (An et al. 2014; Wieland Brown et al. 2013); *borrelia burgdorferi*-derived galactosyl diacylglycerol (Kinjo et al. 2006); *helicobacter pylori*-derived cholesteryl α-glucoside (Ito et al. 2013); *Sphingomonas* bacteria-derived α-linked galacturonic acid (Kinjo et al. 2005); *Streptococus pneumoniae*-derived glycolipids containing diacylglycerol (Kinjo et al. 2011); and lipopeptidophosphoglycan derivatives from the protozoan *entamoeba histolytica* (Lotter et al. 2009). Human and murine iNKT cells also respond to *M. tuberculosis (Mtb)* phosphatidylinositol mannoside (PIM) ligands (Fischer et al. 2004). However, iNKT cells are dispensable during mycobacterial infection, as illustrated using CD1d$^{-/-}$ animals (Behar et al. 1999). In contrast, iNKT cells are physiologically relevant for clearance and protection against other pathogenic microorganisms. iNKT cells produce IFN-γ in response to *B. burgdorferi* infection *in vivo* and both CD1d-deficient animals (Kumar et al. 2000) and Jα18$^{-/-}$BALB/c mice were more susceptible to infection, developing chronic joint inflammation and arthritis (Tupin et al. 2008). iNKT cell participation is also implied during

*E. histolytica* infection, which causes increased amebic liver abscesses in the absence of iNKT cells in Jα18$^{-/-}$ mice (Lotter et al. 2006) and CD1d$^{-/-}$ mice, (Lotter et al. 2009). Jα18$^{-/-}$ animals have also been reported to be susceptible to *Streptococcus* infections (Kawakami et al. 2003). Predictably, due to expression of CD1d ligands the CD1d-restricted response was shown to be necessary for protection against *S. pneumoniae* and Group B *Streptococcus* through IFN-γ and IL-17 production in the lung (Kinjo et al. 2011). This CD1d restricted response was validated using Nur77$^{GFP}$ transgenic mice, which upregulate GFP following TCR engagement (Holzapfel et al. 2014). Unexpectedly however, although it was shown that iNKT cells respond to *S. typhimurium* infection in a CD1d restricted manner (Brigl et al. 2003), iNKT cells produced IFN-γ without TCR engagement (Holzapfel et al. 2014).

In contrast to type I and II NKT cells, investigations into Group 1 CD1-restricted T cell responses have mainly focused on mycobacterial infection. CD1a, CD1b, and CD1c molecules present different types of glycolipids, owing to structural differences in their antigen-binding grooves (Gadola et al. 2002; Scharf et al. 2010; Zajonc et al. 2005). Circulating CD1-restricted T cells are observed in patients previously infected with *Mtb* or immunized with *Mycobacterium bovis* bacillus Calmette-Guerin (BCG) (Kawashima et al. 2003; Ulrichs et al. 2003). These *Mycobacterium*-specific T cells are capable of producing IFN-γ *ex vivo* and recognize *M. bovis* BCG-infected cells (Kawashima et al. 2003). Interestingly, there is also a small population of CD1b-restricted germline-encoded, mycolyl lipid-reactive (GEM) T cells present in uninfected patients (Van Rhijn et al. 2013). To counteract the lack of an animal model to study Group 1 CD1 molecules *in vivo*, human group 1 CD1 transgenic (hCD1Tg) mice were generated, which express all Group 1 CD1 isoforms (Felio et al. 2009). *Mtb* infection and immunization of hCD1Tg mice are both capable of inducing a CD1-restricted T cell response, characteristic of classical T cells; this includes a slow primary response to immunization and rapid secondary response (Felio et al. 2009). Importantly, in hCD1Tg mice expressing a mycolic acid-specific TCR transgene, immune protection against *Mtb* was observed (Zhao et al. 2015). A second group investigated the CD1 repertoire in a humanized mouse model using NSG mice engrafted with human fetal thymus and fetal liver, as well as CD34$^{+}$ hematopoietic cells (Lockridge et al. 2011). CD1a, CD1b, CD1c, and CD1d were all expressed in these animals, and Group 1 CD1-restricted T cells were present (Lockridge et al. 2011), though their response following *Mtb* infection still remains to be seen. To date, Group 1 CD1 molecules have been shown to present eight *Mycobacterium*-derived ligands, the majority of which are loaded in CD1b (Siddiqui et al. 2015). However, a role for Group 1-restricted T cell populations during other infections has not been reported.

## MR1-restricted mucosal associated invariant T (MAIT) cells

MAIT cells were first described in 1993 (Porcelli et al. 1993), but it was not until six years later that they were recognized as a distinct population (**Figure 2**) (Tilloy et al. 1999). MAIT cells are unique innate-like T cells found at mucosal sites and in the circulation of humans and mammals. MAIT cells are restricted by MR1 (MHC-related protein 1) (Treiner et al. 2003), which is encoded outside the *Mhc* gene locus. There is 90% sequence homology between MR1 in humans and mice (Riegert et al. 1998). Wild-type mice generally have low

frequencies of MAIT cells (Rahimpour et al. 2015), but they are more abundant in humans and make up approximately 1-4% of circulating T cells (Martin et al. 2009). The antimicrobial role of MAIT cells was first alluded to based on their absence in germ-free (GF) mice (Treiner et al. 2003), however they can successfully expand in GF mice following inoculation with a single bacterial species, i.e. Bacteroides thetaiotaomicron, Bifidobacterium animalis, Enterobacter cloacae, or *Lactobacillus casei* (Le Bourhis et al. 2010). Two groups then found that MAIT cells are able to respond to a number of bacterial and fungal species *in vitro* using infected PMDCs or BMDCs, but not to viruses, e.g. Lactobacillus acidophilus, Mtb, Pseudomonas aeroginosa, Salmonella typhimurium, Staphylococcus aureus, Saccharomyces cerevisiae, and *Candida albicans* (Gold et al. 2010; Le Bourhis et al. 2010). A major breakthrough in this field was the discovery that MR1 presents Vitamin B metabolites, such as Vitamin B2 (riboflavin) and Vitamin B9 (folic acid) derivatives (Kjer-Nielsen et al. 2012). MR1 is able to bind and stabilize the unstable intermediates of the riboflavin biosynthesis pathway for presentation (Corbett et al. 2014). Interestingly, these ligands can be activating or non-activating in nature by presenting riboflavin or folic acid derivatives, respectively (Kjer-Nielsen et al. 2012).

MAIT cells are now thought to be involved in the early control of a number of bacterial pathogens. Following up on the observation that $\beta 2m^{-/-}$ mice are more vulnerable to *Klebsiella pneumonia* than wild-type mice (Cogen and Moore 2009), Georgel *et al.* determined that $MR1^{-/-}$ mice also had increased susceptibility compared to MR1-sufficient animals (Georgel et al. 2011). MAIT cells also robustly expand in the lungs of mice infected with the live vaccine strain (LVS) of *Francisella tularensis* in an MR1- and IL-12p40-dependent manner (Meierovics et al. 2013). Their expansion inversely correlated with bacterial burden, and was accompanied by the production of IFN-γ, TNF-α, and IL-17A (Meierovics et al. 2013). Interestingly, MAIT cells were also observed to contribute during chronic infection of *F. tularensis* LVS, even when classical $CD4^+$ and $CD8^+$ T cells were recruited, but were insufficient for bacterial clearance alone (Meierovics et al. 2013). $MR1^{-/-}$ mice also have increased bacterial burden on Day 10 following *M. bovis* BCG infection, compared to wild-type mice (Chua et al. 2012). This disparity was no longer observed at later time points (Day 30), illustrating the importance of MAIT cells during early immunological control (Chua et al. 2012). Interestingly, this was suggested to be an MR1-independent, but IL-12-dependent response (Chua et al. 2012). In contrast, it appears that human MAIT cells require MR1 for appropriate IFN-γ production in response to *Mtb* infected APCs (Gold et al. 2010; Le Bourhis et al. 2010). Many studies have observed decreased numbers of circulating MAIT cells in tuberculosis (TB) patients (Gold et al. 2010; Le Bourhis et al. 2010). The remaining MAIT cell population in patients with active TB produced significantly more IFN-γ and TNF-α in response to BCG and decreased cytokine production following *E. coli* infection (Jiang et al. 2014). This suggests that MAIT cells are enriched in this environment to respond to *Mtb* (Jiang et al. 2014). In support of this concept, it was shown that the heterogeneity of the MAIT cell TCR repertoire might allow for pathogen specificity (Eckle et al. 2014; Gold et al. 2014). Cell lines expressing MAIT cell TCRs also become activated in an MR1-dependent manner following *S. enterica* serovar Typhimurium infection (Reantragoon et al. 2012). Additionally, human MAIT cells produce IFN-γ, TNF-α, and IL-2 following incubation with either *S. typhimurium* supernatant or the

synthetic riboflavin derivative 6-hydroxymethyl-8-D-ribityllumazine (rRL-6-$CH^2OH$) in the presence of MR1-expressing APCs (Reantragoon et al. 2013). Overall however, the functional role of MAIT cells is more ambiguous in humans than mice.

The MAIT cell field is relatively young, but has recently burgeoned due to the development of MR1 tetramers (Reantragoon et al. 2013). Nevertheless, a number of lingering questions remain. For instance, the role of MAIT cells during bacterial infection has been relatively well documented, however the *in vivo* role of MR1- restricted T cells has not been well defined for yeast. There is also the potential that MR1 could bind and present additional ligands to Vitamin B derivatives. Finally, it appears that MAIT cell activation can occur in a TCR-independent manner, similarly to iNKT cells, irrespective of bacterial/fungal riboflavin metabolism (Chua et al. 2012; Meierovics et al. 2013; Ussher et al. 2014). This opens up potential avenues to study MAIT cell responses during viral infections and autoimmune disorders, such as HIV (Fernandez et al. 2015; Leeansyah et al. 2013), multiple sclerosis (Treiner and Liblau 2015), inflammatory bowel disease (Treiner 2015), and Celiac disease (Dunne et al. 2013).

## HFE-specific $CD8^+$ T cells

HFE, or human hemochromatosis protein, was first discovered due to its association with hereditary hemochromatosis (HH) patients, a genetic disorder that results in iron overload (Feder et al. 1996). The HFE heavy chain forms a noncovalent bond with an associated β2m light chain (Feder et al. 1996; Feder et al. 1997), similarly to many other MHC class Ib molecules. However, in one common HFE mutation seen in HH patients, the C282Y mutation, the ability to bind β2m is disrupted. This prevents HFE expression at the cell surface by perturbing a critical disulfide bridge in the α3 domain (Feder et al. 1997). HFE-deficient and β2m-deficient mice both recapitulate the HH phenotype (Santos et al. 1996; Zhou et al. 1998). Even though HFE is structurally similar to other MHC class I molecules, its peptide-binding groove does not support antigen binding (similarly to TL, see below). This is due to the α1 and α2 domains being in closer proximity, since the α1 helix has a 4Å translocation towards the α2 domain this results in a narrower groove (Lebron et al. 1998). Rather than antigen binding, HFE is predominantly known for associating with the transferrin receptors to regulate iron homeostasis (Goswami and Andrews 2006; Lebron et al. 1998; Parkkila et al. 1997). However, there is evidence that suggests a potential immunological role for HFE as well. For example, the iron overload phenotype is even more pronounced in mice that are deficient for both β2m and RAG1, compared to $\beta2m^{-/-}$ animals (Santos et al. 2000). HFE-deficient animals on a RAG1 background also have increased iron overload, compared to $HFE^{-/-}$ animals (Miranda et al. 2004).

A role for $CD8^+$ T cells was initially proposed because many HH patients have unusually small $CD8^+$ T cell populations in circulation (Macedo et al. 2010; Porto et al. 1994). However, the exact nature of this deficiency is unclear, as it could be an indirect result of iron overload or a direct result of HFE regulating $CD8^+$ T cells (Costa et al. 2015; Reuben et al. 2014). Interestingly, HFE is thought to impede activation via its α1 and α2 helixes by influencing MHC class I antigen processing and presentation (Reuben et al. 2014). Rohrlich *et al.* also showed that HFE influences the TCR repertoire, as evidenced by a decreased

number of Vα6 TCRs in HFE-deficient mice (Rohrlich et al. 2005). Importantly, a subset of $CD8^+$ T cells directly recognize HFE via their TCR and produce IL-6, IL-10, and hepcidin (Boucherma et al. 2012; Rohrlich et al. 2005). Overall, although HFE is not capable of binding and presenting antigens, there is evidence for an immunological role of HFE. Additional studies will be necessary to investigate the functions of HFE-reactive $CD8^+$ T cells, as well as the immune system's role in iron metabolism.

## TL-restricted $CD8^+$ T cells

Thymus leukemia antigen (TL) was first discovered during the development of spontaneous or radiation induced leukemia (Old and Boyse 1963) and subsequently mapped to the *Mhc* locus (Boyse et al. 1964). TL is encoded by the *H2-T3* and *H2-T18* genes in mice and is considered an ancient MHC class Ib gene that diverged over 100 million years ago (Davis et al. 2002). There is no human homologue for TL, but it has been suggested that HLA-G is a functional homologue (Attinger et al. 2005; Huang et al. 2011). TL is expressed on intestinal epithelial cells (IELs) (Hershberg et al. 1990; Wu et al. 1991) and immature thymocytes of certain mouse strains (Chen et al. 1985). Following activation, T cells and APCs also express TL (Cook and Landolfi 1983; Madakamutil et al. 2004). T cells can also "snatch" TL from intestinal epithelial cells to present it on their cell surface (Pardigon et al. 2006). The expression of TL at the cell surface is dependent on β2m (Yokoyama et al. 1982), but not on peptide binding (Weber et al. 2002). Even though TL exhibits approximately 70% identity with MHC class Ia molecules, its peptide-binding groove is closed due to the α1 helix being 7Å closer to the α2 helix (Liu et al. 2003). TL cell surface expression is also TAP-independent, which distinguishes it from classical MHC class Ia molecules (Holcombe et al. 1995; Rodgers et al. 1995). TL binds the CD8αα homodimer with higher affinity than to CD8αβ (Leishman et al. 2001; Tsujimura et al. 2001). This is a result of three exposed amino acids in the α3 helix of TL (Attinger et al. 2005). In contrast, MHC class Ia molecules have comparable affinities to CD8αβ and CD8αα (Kern et al. 1999). Unlike CD8αβ heterodimers (Bosselut et al. 1999), the CD8αα homodimer does not act as a co-receptor, rather it inhibits activation by acting as a co-repressor (Cheroutre and Lambolez 2008). CD8αβ T cells that co-express CD8αα are abundant in the intestinal mucosa. However, TL is not required for the formation of $CD8^+$ T cell memory (Williams and Bevan 2005). It has also been shown that TL is important for controlling IEL function, for example inhibiting IEL proliferation (Olivares-Villagomez et al. 2008). Both αβ (Morita et al. 1994) and γδ TCRs (Tsujimura et al. 1996) can recognize TL. These TL-specific cytotoxic $CD8^+$ T cells recognize the α1 and α2 domains of TL with CD8αα helping to stabilize the TL/TCR interaction (Tsujimura et al. 2003) in a TAP-independent mechanism (Tsujimura et al. 2000). Perhaps not surprisingly, due to its closed binding groove, the role of TL-restricted T cells during infectious disease clearance is limited.

## M3-specific $CD8^+$ T cells

In contrast to MHC class Ia molecules and many MHC class Ib molecules, M3 binds N-formylated peptides (Shawar et al. 1993; Smith et al. 1994). Thus, M3 is able to present peptides of prokaryotic or mitochondrial origin (Wang et al. 1991). There is also evidence that M3 can bind non-formylated peptides (Byers and Fischer Lindahl 1998), however M3 binds N-formylated peptides with much higher affinity than unformylated ones (Smith et al.

1994). The crystal structure of M3 showed that the specificity for N-formylated peptides was a result of alterations in its peptide-binding groove (Wang et al. 1995). There are very few endogenous N-formylated peptides available, which results in low M3 expression at the cell surface (Levitt et al. 2001), and sequesters M3 in the endoplasmic reticulum. TAP is required for M3 stabilization in the ER, while tapasin is necessary for intracellular peptide loading (Chun et al. 2001a). Dependency on TAP further differentiates M3 from other MHC class Ib molecules like CD1 and TL (Brutkiewicz et al. 1995; Hanau et al. 1994; Holcombe et al. 1995; Rodgers et al. 1995). However, both TAP-dependent and -independent presentation have been observed for *L. monocytogenes* peptides (Rolph and Kaufmann 2000). Exogenous antigens are capable of inducing M3 expression at the cell surface, unlike lowered temperatures (Chiu et al. 1999a), which occurs with MHC class Ia molecules (Ljunggren et al. 1990).

M3-restricted $CD8^+$ T cells specific to a number of intracellular pathogens have been characterized, *e.g. Mtb, L. monocytogenes, Chlamydia pneumonia*, and *S. enterica* serovar Typhimurium (Chun et al. 2001b; Gulden et al. 1996; Lenz et al. 1996; Princiotta et al. 1998; Tvinnereim and Wizel 2007; Ugrinovic et al. 2005). The most well studied M3-restricted $CD8^+$ T cells are specific to *L. monocytogenes*. Using MHC class Ia-deficient ($K^bD^{b-/-}$) mice, it has been shown that M3-restricted $CD8^+$ T cells are sufficient to protect against *L. monocytogenes* infection (D'Orazio et al. 2003; Seaman et al. 1999). In this context, M3 presents three *L. monocytogenes*-derived peptides: Attm (f-MIVTLF) (Princiotta et al. 1998), Fr38 (f-MIVIL) (Gulden et al. 1996), and LemA (f-MIGWII) (Lenz et al. 1996). However, M3-restricted $CD8^+$ T cells are not required for protection against *L. monocytogenes* (D'Orazio et al. 2006). Nevertheless, using M3-deficient animals it was determined that the M3-restricted and MHC class Ia-restricted immune responses are not redundant (Xu et al. 2006). The significance of M3-restricted memory $CD8^+$ T cells during *L. monocytogenes* infection is more ambiguous. In contrast to primary infection, after secondary infection M3-restricted $CD8^+$ T cells do not significantly expand (Kerksiek et al. 1999). It has been suggested that rather than contributing to a memory phenotype during a secondary infection, M3-restricted $CD8^+$ T cells are already in a memory state in naïve animals, due to interactions with cross-reactive antigens from commensal bacteria (Lenz and Bevan 1997). Alternatively, it has been proposed that M3-restricted memory $CD8^+$ T cells are constrained in the presence of MHC class Ia-restricted memory cells (Hamilton et al. 2004). M3 also appears to contribute to the immune response against *MTB* infection. Chun *et al*. showed that the *Mtb* genome contained a number of N-formylated peptides capable of binding to M3, and that M3-restricted $CD8^+$ T cells can recognize a number of these peptides in mice (Chun et al. 2001b). Immunization of mice with dendritic cells pulsed with an N-formylated *Mtb* peptide are also able to elicit an H2-M3-mediated response (Doi et al. 2007). However, although MHC class Ib-restricted T cells accumulate in the lung, they provide minimal protection against *Mtb* infection (Urdahl et al. 2003). Further investigations are necessary to determine whether N-formylated peptides from other bacterial species elicit an M3-specific response.

### CD8$^+$ T cells-restricted by Qa-2 and HLA-G

The *H2-Q6, -Q7, -Q8*, and *-Q9* genes in mice encode Qa-2. It is thought that the Qa-2 region resulted from a series of gene pair duplications, for example *H2-Q7* and *H2-Q9* are nearly identical, with over 99% homology (Devlin et al. 1985). Originally, Qa-2 was thought to have a restricted peptide repertoire (Rotzschke et al. 1993), however it is capable of binding a diverse array of endogenous and foreign peptides (Joyce et al. 1994; Tabaczewski et al. 1997). The crystal structure of Q9 revealed that it associates with β2m, and the peptide-binding groove is more hydrophobic and shallower than classical MHC molecules, which could play a role in its promiscuous peptide repertoire (He et al. 2001). Qa-2 is unique among MHC molecules for being anchored to the cell membrane by a glycophosphatidyl inositol (GPI) linker (Stroynowski et al. 1987), which is necessary for T cell activation (Robinson et al. 1989). In addition, there are soluble and membrane-linked forms of Qa-2, both of which require TAP (Tabaczewski and Stroynowski 1994), that arise because of alternative splicing or cleavage post-translation (Tabaczewski et al. 1994). However, the α3 domain of Qa-2 is unable to effectively interact with CD8 to appropriately activate cytotoxic T cells (Teitell et al. 1993).

There is evidence that Qa-2 participates in resistance to the murine parasite *Taenia crassiceps*. This was based on the observation that BALB/cAnN mice (Qa-2$^{null}$) are susceptible to *T. crassiceps*, while BALB/cJ mice (Qa-2$^+$) are resistant (Fragoso et al. 1996). In support of these findings, it was later shown that Qa-2 transgenic mice have increased clearance of the parasite (Fragoso et al. 1998). In addition, Q9-specific CD8$^+$ T cells have been extensively characterized during the response to mouse polyoma virus (MPyV). Q9-restricted T cells from K$^b$D$^{b-/-}$ mice are able to control MPyV infection, impede tumor formation, and recognize a nonameric peptide derived from the virus's VP2 capsid protein (termed VP2.139) (Swanson et al. 2008). This population is present in wild-type mice as well. However, Q9-restricted T cells are somewhat different from classical CD8$^+$ T cells because they form an inflationary population during persistent infection for approximately 12 weeks (Swanson et al. 2008). Further characterization showed that immunization with a VP2.139 peptide in mice carrying different MHC haplotypes could generate an MPyV-specific non-classical CD8$^+$ T cell response (Hofstetter et al. 2013). However, the authors were not able to determine whether this population provided enhanced control during MPyV infection (Hofstetter et al. 2013).

Importantly, human HLA-G is proposed to be the functional homologue of Qa-2 (Comiskey et al. 2003). The expression of HLA-G is primarily limited to placental tissues such as cytotrophoblasts (Kovats et al. 1990), whereas classical MHC molecules are believed to be poorly expressed (Hunt et al. 1987). There are four membrane-bound isoforms of HLA-G, HLA-G1-G4, and three soluble isoforms, HLA-G5-G7, which occur via alternative splicing (Fujii et al. 1994; Ishitani and Geraghty 1992; Kirszenbaum et al. 1994; Paul et al. 2000). Secreted and membrane-bound forms can both present endogenous nonameric peptides (Diehl et al. 1996; Lee et al. 1995), however truncated isoforms do not associate with β2m (Morales et al. 2007). HLA-G has a number of immunomodulatory effects (Amiot et al. 2014; Guleria and Sayegh 2007), presumably mediated via interaction with the inhibitory receptors ILT2, ILT4, and KIR2DL4 (CD158d) (LeMaoult et al. 2005; Rajagopalan and

Long 2012). HLA-G may be critical for immune tolerance during pregnancy to protect the fetus from rejection by maternal effector cells (Rouas-Freiss et al. 1997). In mice, Qa-2 is thought to participate during embryonic cleavage division and survival following preimplantation (McElhinny et al. 2000; Warner et al. 1987). Similarly to Qa-2, HLA-G molecules are capable of invoking a cytotoxic T cell response that is specific to HLA-G. This was first illustrated using HLA-G transgenic mice and skin graft experiments (Horuzsko et al. 1997; Schmidt et al. 1997). In a follow up experiment utilizing HLA-G tetramers for the predominant human cytomegalovirus (HCMV) peptide pp65, some HCMV-specific $CD8^+$ T cells restricted by HLA-G were observed (Lenfant et al. 2003). However, the relevance of these HLA-G-restricted T cells, and their presence in humans, remains to be seen.

## Qa-1 and HLA-E-restricted $CD8^+$ T cells

Before HLA-E was known to present antigenic peptides to HLA-E-restricted T cell populations, it was first shown to be a ligand for the CD94/NKG2 family of NK cell receptors (NKG2A, NKG2B, and NKG2C) (Braud et al. 1998; Lee et al. 1998b). Qa-1 in mice (encoded by *H2-T23)* can similarly bind to CD94/NKG2 receptors (Vance et al. 1999; Vance et al. 1998). Expression of HLA-E at the cell surface is dependent on TAP (Lee et al. 1998a) and loading of nonamer peptides derived from the leader sequences of HLA-A, HLA-B, HLA-C, or HLA-G molecules (Braud et al. 1997; Lee et al. 1998a). Likewise, Qa-1 also binds signal sequence-derived peptides (AMAPRTLLL) from MHC class Ia molecules in a TAP-dependent manner (Aldrich et al. 1994). The primary ligands for Qa-1 and HLA-E are denoted Qdm, or Qa-1 determinant modifier, however other peptides can be loaded under different circumstances. For instance, the self-peptide FL9 (FYAEATPML) was recently identified in ERAAP-deficient mice (Nagarajan et al. 2012). These are not the only similarities between Qa-1 and HLA-E, which are considered functional homologues that arose by convergent evolution (Yeager et al. 1997). Both have low cell surface expression and broad tissue distribution, limited polymorphism, and structural homology (Zeng et al. 2012). This also includes similarities within their peptide-binding groove, such as unique substitutions at positions 143 and 147 (Connolly et al. 1993). HLA-E, for example, is the least polymorphic of the human non-classical MHC molecules. Caucasians only have two alleles, designated HLA-E*0101 and HLA-E*0103, which differ from each other at one amino acid position (Geraghty et al. 1992; Grimsley et al. 2002).

In addition to the role of HLA-E and Qa-1 during innate immunity, these MHC class Ib molecules can also present microbial antigens to $CD8^+$ T cells. HLA-E and Qa-1 bind peptides from bacteria, such as *S. typhimurium, S. enterica* serovar Typhi, *L. monocytogenes*, and *Mtb* (Bouwer et al. 1997; Caccamo et al. 2015; Lo et al. 2000; Salerno-Goncalves et al. 2004; van Meijgaarden et al. 2015). Interestingly, in the absence of Qdm, a peptide derived from heat shock protein 60 (Hsp60) is primarily loaded into Qa-1 (GMKFDRGYI) (Davies et al. 2003). Hsp60 is well conserved in prokaryotes, whose homologue is GroEL in bacteria. In agreement with these observations, it was found that Qa-1 presents a *S. typhimurium*-derived peptide from GroEL (GMQFDRGYL) to $CD8^+$ cytotoxic T cells (Lo et al. 2000). These GroEL-specific $CD8^+$ T cells were also cross-reactive with Hsp60 and lyse stressed macrophages (Lo et al. 2000). Similarly, HLA-E

presentation of GroEL-derived antigens from *S. enterica* caused targeted cell lysis of infected cells, as well as IFN-γ production (Salerno-Goncalves et al. 2004). HLA-E also participates during *Mtb* infection. This was first proposed when it was determined that the predominant $CD8^+$ T cell response in latently infected patients was MHC class Ia and CD1 independent (Heinzel et al. 2002; Lewinsohn et al. 2000). The recognition of *Mtb*--derived peptides presented by HLA-E (Caccamo et al. 2015; van Meijgaarden et al. 2015) differs from the classically restricted $CD8^+$ T cell response. HLA-E-restricted T cells appear to acquire a Th2 phenotype, producing TNF-α, IL-4, IL-5, IL-10, and IL-13, but have poor cytotoxicity in response to stimulation (Caccamo et al. 2015; van Meijgaarden et al. 2015). HLA-E and Qa-1 are also capable of presenting virally derived peptides. For example, HLA-E-reactive T cells to Epstein-Barr virus recognize a peptide from its BZLF-1 protein (SQAPLPCVL) (Garcia et al. 2002; Jorgensen et al. 2012). A peptide derived from a Hepatitis C virus (HCV) core protein (YLLPRRGPRL) was also shown to bind HLA-E, stabilize its cell surface expression, and protect cells from NK cell lysis (Nattermann et al. 2005). Additionally, 40% of an HCV infected cohort was determined to have an HLA-E-reactive T cell response, resulting in IFN-γ production, which was not observed from healthy control samples (Schulte et al. 2009). Interestingly, there was an increased incidence of HLA-E-specific $CD8^+$ T cells to HCV in patients with the HLA-E*0101 allele, compared to the HLA-E*0103 allele (Schulte et al. 2009).

Perhaps the most intriguing HLA-E-restricted response occurs during HCMV infection. HCMV employs a variety of mechanisms to downregulate the expression of conventional HLA molecules at the cell surface and avoid the classical $CD8^+$ T cell response. One immunoevasive mechanism HCMV employs is to inhibit ERAP1 function, the human homolog of murine ERAAP, through miR-US4-1 (Kim et al. 2011). This miRNA obstructs cytotoxic $CD8^+$ T cells from lysing infected cells by inhibiting HCMV antigen derivation (Kim et al. 2011). HCMV also provides its own peptide, derived from the signal sequence of its glycoprotein UL40 (gpUL40) to load in HLA-E molecules, increasing cell surface expression independently of TAP (Tomasec et al. 2000; Ulbrecht et al. 2000). The UL40 leader sequence from the AD169 and Toledo HCMV strains are both able to provide peptides (VMAPRTLIL and VMAPRTLVL, respectively) that bind HLA-E. This is thought to be a mechanism for escaping the NK cell response because *UL40* deletion mutants are unable to evade NK cells through CD94/NKG2A inhibition (Wang et al. 2002). However, HLA-E-restricted $CD8^+$ T cells can also recognize these gpUL40-derived peptides via their TCR (Pietra et al. 2003). HLA-E-restricted HCMV-specific T cells have an effector memory phenotype, can kill HCMV infected target cells, and produce IFN-γ in response to contact with UL40 leader peptides (Mazzarino et al. 2005). Interestingly, the gpUL40 leader sequence of AD169 and Toledo HCMV strains is identical to certain HLA-A and HLA-Cw leader peptide alleles, possibly leading to a non-classical T cell evasion mechanism (Pietra et al. 2010; Pietra et al. 2003). In addition to increased expression of HLA-E, HCMV also disrupts ERAP1 function (Kim et al. 2011). As mentioned previously, Qa-1-restricted cells kill ERAAP-deficient cells in naï ve mice (Nagarajan et al. 2012). Therefore, it would be interesting to determine whether HLA-E-restricted $CD8^+$ T cells play a similar role during HCMV infection. Overall, the role of Qa-1/HLA-E-restricted T cells may only be revealed

when the MHC class I and/or conventional $CD8^+$ T cell response is failing (**Figure 3**, see proposed model below).

### T cell responses restricted by unidentified MHC class Ib molecules and other non-classical T cell responses

Certain non-classical T cell responses are a result of, as of yet, undetermined MHC class Ib molecules. For example, non-classically restricted $CD8^+$ T cells from $K^bD^{b-/-}$ mice are sufficient to control chronic *γ-herpesvirus 68* (Braaten et al. 2006). While the exact restriction of this population is currently unknown, it is dependent on β2m and CD1d is dispensable (Braaten et al. 2006). In addition, MHC class Ib-restricted T cells respond following lymphocytic choriomeningitis virus (LCMV) infection in both $K^bD^{b-/-}$ and $K^bD^bCIITA^{-/-}$ mice, which also lack MHC class II molecules, however they were inadequate to fully clear the virus (Chen et al. 2011). Non-classical T cells are also present in a wide range of species. For instance, in the amphibian *Xenopus laevis*, iVα6 T cells are restricted by the MHC class Ib molecule XNC10 and resemble iNKT cells found mice and humans (Edholm et al. 2013). XNC10-restricted T cells were essential for an appropriate antiviral response, and successful viral clearance, following infection with frog virus 3 (Edholm et al. 2015). Studies such as these illustrate the importance of non-classical MHC class Ib-restricted T cells, and their biological relevance, in a wide range of species.

### Concluding remarks and proposed models

Non-classical T cells are unique in many ways – strategic localization at barrier sites, recognition of a wide array of unique microbial pathogens, and rapid effector responses. These features led to the hypothesis that the primary function of non-classical T cells such as iNKT and MAIT cells is to rapidly respond to infections. We propose that another, non-mutually exclusive, function for these cells may be revealed during chronic infection when classical T cell and NK cell responses are impaired (**Figure 3**). This has been recently documented in the case of Qa-1/HLA-E-restricted T cells, which exploit pathogen immunoevasion adaptations (Hansen et al. 2016). Together with the low polymorphism of MHC class Ib molecules, the unique characteristics of MHC class Ib-restricted T cells render them attractive targets for vaccine development, especially when the immune system is compromised.

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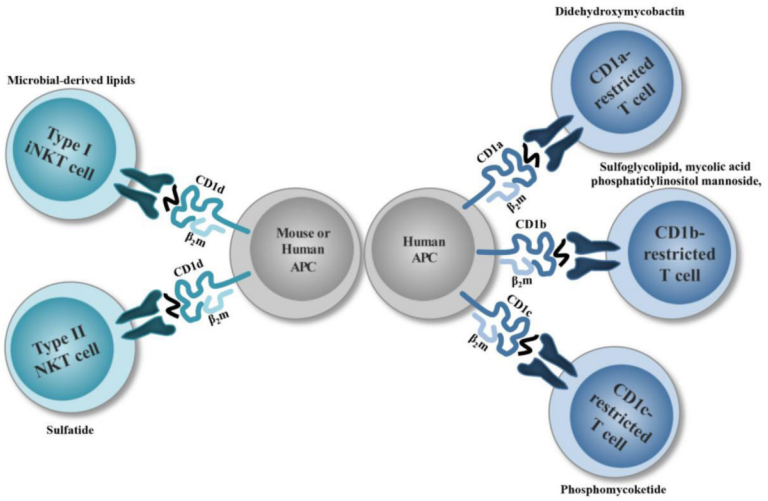


**Figure 1. The family of CD1-restricted αβ T cells**

Group 1 CD1-specific T cells are depicted with examples of *Mtb* glycolipid antigens.

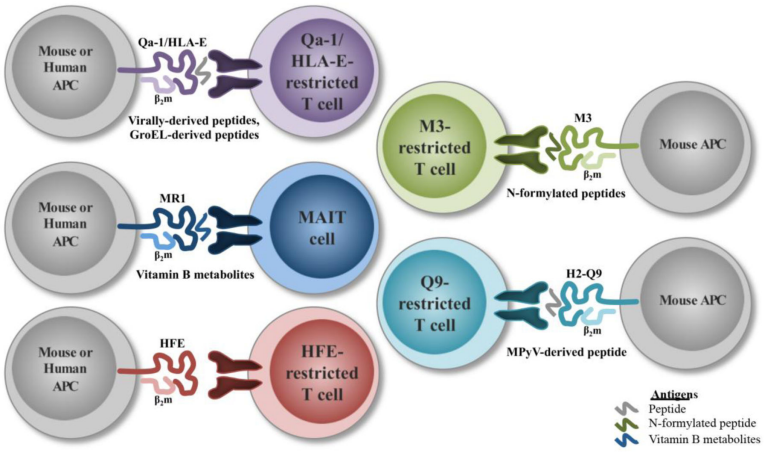


**Figure 2. Examples of non-classical αβ T cell populations during microbial infection.**

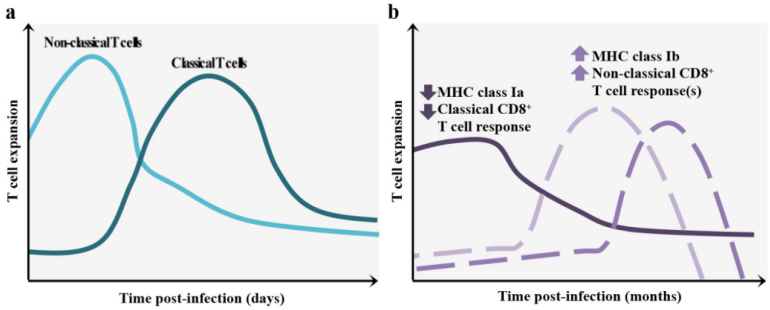


**Figure 3. Proposed roles of non-classical CD8$^+$ αβ T cell populations in humans and mice, compared to conventional CD8$^+$ T cells**

A) MHC class Ib-restricted CD8$^+$ T cells, *e.g.* iNKT cells and MAIT cells, have a faster effector response following infection, compared to MHC class Ia-restricted T cells. B) During chronic infection, microorganisms can employ immunoevasion mechanisms to dampen the classical T cell response and/or NK cell response. MHC class Ib-specific responses could represent a backup system that responds following MHC class Ib upregulation, for example HLA-E.

**Table 1**

MHC class Ib molecules that participate in TCR mediated responses

| Mouse | Human | *Mhc* locus | TCR-interaeting ligand |
|---|---|---|---|
| CD1d | CD1a, CD1b, CD1c, CD1d, CD1e | No | Lipids |
| MR1 | MR1 | No | Vitamin B derivatives |
| HFE | HFE | No | Transferrin receptors |
| H2-M3 | - | Yes | N-formylated peptides |
| Qa-1 | HLA-E | Yes | Peptides |
| TL | - | Yes | None |
| T10/T22 | - | Yes | None |
| Qa-2 | - | Yes | Peptides |
| - | HLA-G | Yes | Peptides |

**Table 2**

The antimicrobial response of MHC class Ib-restricted T cells in mice and humans

| T cell | Positive Selection | Recognized Antigens | PIZF | Cytokine Prolife |
|---|---|---|---|---|
| Group 1 CD 1-restricted T cells | HC | *Mtb* lipids | Yes | IFN-γ, TNF-α, IL-6, IL-13 |
| Type I NKT cells | HC | α-Galcer, microbial lipids | Yes | IFN-γ, TNF-α, IL-4, IL-13, IL-17 etc. |
| Type II NKT cells | HC | Sulfatide, glycolipids and phospholipids | Yes | IFN-γ, TNF-α, IL-17 |
| MAIT cells | HC | Bacterial and fungal riboflavin metabolites | Yes | IFN-γ, TNF-α, IL-2, IL-17 |
| HFE-restricted T cells | ND | N/A | No | IL-6, IL-10, hepcidin |
| M3-restricted T cells | HC or TEC | Bacterial and fungal N-formylatcd peptides | No | IFN-γ , TNF-α |
| Qa-1/HLA-E-restricted T cells | HC or TEC | CMV- and GroEL-derived peptides | ND | IFN-γ, TNF-α, IL-4, IL-5, IL-10, IL-13 |
| TL-restricted T cells | ND | N/A | ND | IFN-γ |
| Q9-restricted T cells | ND | MPyV-derived peptide | ND | IFN-γ, TNF-α |
| HLA-G-restricted T cells | ND | HCMV-derived peptide | ND | ND |

HC: hematopoietic cell; TEC: thymic epithelial cell; ND; no data