MINIREVIEW

Host Immune Response to Intracellular Bacteria: A Role for MHC-Linked Class-Ib Antigen-Presenting Molecules (44536)

MARK J. SOLOSKI,*,†,[1] MICHAEL E. SZPERKA,* ADRIAN DAVIES,* AND STACEY L. WOODEN*,†

Division of Rheumatology, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland 21205; and †Department of Molecular Microbiology and Immunology, Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland 21205

Abstract. **MHC-linked class-Ib molecules are a subfamily of class-I molecules that display limited genetic polymorphism. At one time these molecules were considered to have an enigmatic function. However, recent studies have shown that MHC-linked class-Ib molecules can function as antigen presentation structures that bind bacteria-derived epitopes for recognition by $CD8^+$ effector T cells. This role for class-Ib molecules has been demonstrated across broad classes of intracellular bacteria including *Listeria moncytogenes, Salmonella typhimurium, and Mycobacterium tuberculosis.* Additionally, evidence is emerging that MHC-linked class-Ib molecules also serve an integral role as recognition elements for NK cells as well as several TCR α/β and TCR γ/δ T-cell subsets. Thus, MHC-linked class-Ib molecules contribute to the host immune response by serving as antigen presentation molecules and recognition ligands in both the innate and adaptive immune response to infection. In this review, we will attempt to summarize the work that supports a role for MHC-linked class-Ib molecules in the host response to infection with intracellular bacteria.**

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Class-I Molecules, a Family Divided

Class-I molecules are divided into several classes based on structural and functional properties. The class-Ia molecules, also termed the classical class-I molecules, are highly polymorphic, and they stimulate strong alloreactivity, have ubiquitous tissue expression, and present diverse peptide epitopes to $CD8^+$ T cells. In contrast, class-Ib molecules, also termed the nonclassical class-I molecules, are structurally related to class-Ia molecules, but they display considerably less polymorphism, stimulate weak alloresponses, have tissue expression patterns ranging from cell-type-specific to ubiquitous, and appear to bind and present a much more limited range of ligands than the class-Ia molecules. The third group of class-I-related molecules, the CD1 family, also exhibits low polymorphism, has a limited tissue distribution, and functions to present nonpeptide epitopes to T cells (1). Structural information on class-Ia, class-Ib, and CD1 molecules indicates that they encode polypeptides ranging in molecular weight from 39–48 kDa and noncovalently associate with β_2-microglobulin (β_2 m). The sequence homologies between class-Ib proteins and class-Ia proteins predict that the extracellular α1-α2 structural domains of class-Ib molecules form a binding groove. This prediction is confirmed by the high-resolution structural analysis of the class-Ib molecules H2-M3 and HLA-E (2, 3).

The genes encoding the class-Ia and class-Ib molecules are linked together as part of the Major Histocompatibility

[1] To whom requests for reprints should be addressed at the Division of Rheumatology, Department of Medicine, Ross Research Building, Rm. 1042, Johns Hopkins School of Medicine, 720 Rutland Ave, Baltimore, MD 21205. E-mail: mski@welchlink.welch.jhu.edu

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Complex (MHC) found on human chromosome 6 and mouse chromosome 17. In the mouse, the class-Ia molecules are encoded within the H-2 region of the MHC. Class Ib genes map to three defined regions, the Q, T, and M regions, adjacent to the H-2 complex. The CD1 family of molecules is encoded by genes unlinked to the MHC on chromosomes 1 and 3 in the human and the mouse, respectively.

The Q-region encodes multiple, structurally diverse class-Ib molecules including the GPI-anchored Qa-2 molecule and the secreted Q10 and Qb-1 molecules (4). Qa-2 and Q10 are peptide binding molecules based on the elution of peptides from purified Qa-2 or Q10, but a clear antigen presentation role for these molecules has not been demonstrated (5–7). However, Qa-2 expression appears to be a resistance gene in murine cysticercosis (8). Thus, Qa-2 may play a role in the host response to parasitic infection. For the other Q-region genes (*Q1, Q2, Q3, Q5, Q6,* and *Q8*), partial sequence information is available, much of which indicates that these genes should be functional (9).

Depending on the strain of mouse, the T region can contain up to 18 class-I genes. Within this cluster are the genes that encode the Qa-1 molecule (gene *T23*), the serologically defined thymic leukemia antigens, TL, (genes *T3* and *T18*) and the gene products of the T10 and T22 loci, which are recognized by γ/δ T-cell hybridomas (10–14). Qa-1 can serve as a weak transplantation antigen, and peptide-dependent Qa-1–reactive alloreactive CTLs have been identified (15). Qa-1 has been shown to bind peptides derived from the leader sequence of a large number of class-I molecules as well as peptide epitopes from heat shock proteins (16–18). Studies using transgenic mice have shown that T3 and T18 can serve as transplantation antigens, suggesting that they have the capacity to bind and present peptide to $CD8^+$ T cells (19, 20). Surprisingly, the assembly and expression of the T18 protein is independent of the TAP transporter, yet peptides with modified NH_2 termini have been recovered from T18 molecles (20, 21). This would suggest that TL molecules bind chemically modified peptides, a property reminiscent of the class-Ib molecule H2-M3 (see below).

A third cluster of MHC-linked class-Ib genes has been identified adjacent to the T region and is termed the M (formerly Hmt) region (22–25). Within this cluster is the locus (M3) that encodes the Maternally transmitted antigen (Mta) alloantigen. Information on whether the other genes in this locus encode functional molecules is not yet available although several genes have been unambiguously determined to be pseudogenes.

In humans, *HLA-E, HLA-F,* and *HLA-G* are three identified MHC-linked human class-Ib genes (26). Recent studies have indicated that *HLA-E,* like murine *Qa-1,* binds hydrophobic leader sequences derived from other class-I molecules, and peptides that bind HLA-E and Qa-1 have identical anchor residues (27, 28). Identical residues at positions 67 (ala), 143 (ser), and 147 (ser) in both *HLA-E* and *Qa-1* suggested that *HLA-E* and *Qa-1* are functional homologs and likely bind overlapping sets of peptides. Indeed, peptides that have been demonstrated to bind to *HLA-E* have been shown to specifically bind to *Qa-1* (29, 30). *HLA-G* expression is confined to fetal trophoblast cells and can be expressed as both a membrane-bound or secreted form (31). Interestingly, both forms of *HLA-G* can bind peptide nonamers, yet a role in antigen presentation has not been demonstrated. However, *HLA-G* is recognized by the natural killer receptor KIR2DL4 and a role maintaining the maternal-fetal interface during pregnancy has been postulated (32). As with *HLA-E,* a new murine class-Ib gene has recently been identified whose expression pattern in the placenta and blastocyst parallels that of *HLA-G* (33). Using an expression-based system, two homologous class-1–related genes, *MICA* and *MICB* have been identified whose expression is confined to the intestinal epithelium (34).

A unique feature of class-Ib loci is their lack of extensive polymorphism. Protein and nucleic acid studies have failed to detect significant Qa-2 structural polymorphism among $Qa\text{-}2^+$ inbred or wild mouse substrains. Similarly, the Mta-encoding *M3* gene and *Q10* are largely invariant whereas serological or CTL analysis has detected low allelic polymorphism for Qa-1 (five alleles) and TL (five alleles) (9, 35). The $Qa\text{-}1^{a\text{-}d}$ alleles have been sequenced and found to have modest differences in their peptide binding sites (36, 37). Interestingly, the $Qa\text{-}1^a$, $Qa\text{-}1^b$, and $Qa\text{-}1^d$ alleles can bind identical peptides suggesting that these alleles, although serologically distinguishable, are functionally equivalent (16). Two alleles of the human HLA-E molecule have been identified after an extensive analysis of genetically disparate groups (38). These two variants differ by only a single amino acid that is not likely to alter peptide binding. Furthermore, genetic analysis of *HLA-E* among primates has shown that it is the most highly conserved class-I locus (39). It is not completely appreciated why class-Ib genes have failed to evolve extensive polymorphisms, but it is increasingly evident that this set of antigen presentation molecules binds and presents a specialized set of epitopes. Therefore, it has been suggested that class-Ib molecules are under strong selection pressure to maintain a molecular structure that retains their functions (4).

It has been well established that the polymorphic class-Ia molecules function to bind and present a diverse array of eight to ten amino acid peptides derived largely from proteins that undergo degradation in the cytoplasm. Estimates are that a given class-Ia molecule can bind and present over 10,000 distinct peptides (40). The predominant route of protein degradation involves the proteosome complex, and liberated peptides are transported into the lumen of the endoplasmic reticulum (ER) by the ATP-dependent peptide transporters TAP-1 and TAP-2 (41–43). In the ER, the translocated peptides are loaded into the empty peptide binding sites of newly synthesized class-I molecules. The peptide-loading process involves the concerted action of several ER-resident chaperones and results in a stable tri-

molecular complex of peptide, class-I heavy chain, and β_2m that is transported to the cell surface. This is a constitutive process in normal cells, and the peptides found bound to class-I are representative of the total set of proteins synthesized by a given cell. In this manner, the array of self-peptides found associated with class-I molecules likely serves a central role in establishing and maintaining self-tolerance.

The ability of class-Ia molecules to bind peptides from degraded intracellular proteins is a key element in how the immune system responds to viral infections. Following viral entry into cells, there is active synthesis of new viral proteins, which once degraded can donate peptides that are bound to and presented on class-Ia molecules expressed on the cell surface. In this manner, antigen-presenting cells that present viral peptides can stimulate an effector CD8 cytotoxic T-cell (CTL) response capable of detecting and killing virus-infected cells, thus eliminating reservoirs of viral infection. The importance of class-Ia molecules in antiviral immunity is underscored by the finding that all virus-specific $CD8^+$ CTL responses are MHC-restricted and that all viral epitopes identified to date are peptides presented by polymorphic class-Ia molecules. In contrast, class-Ib and CD1 molecules do not appear to stimulate $CD8^+$ CTLs in antiviral immunity. Despite extensive investigation, only one viral epitope has been identified as being presented by a class-Ib molecule (44). Indeed, mice lacking expression of the polymorphic class-Ia molecules do not generate detectable CTL responses following infection with virus (45, 46). Thus, even in the complete absence of class-Ia molecules, class-Ib and CD1 molecules fail to present viral epitopes. At issue is the function of class-Ib and CD1 molecules in the immune response. Past discussions on this topic have included nonimmune functions as well as strong arguments for nonfunction (47–49). However, in a few short years, the study of the host response to infection with intracellular bacteria has revealed a role for MHC-linked class-Ib and MHC-unlinked CD1 molecules as specialized antigen-presenting structures capable of presenting a limited range of novel epitopes to effector T cells. This review will focus on reviewing the information that supports a role for MHC-linked class-Ib molecules in the host response to infection with intracellular bacteria. Several excellent reviews have been written recently detailing the function of CD1 molecules, and the reader is directed to them (1, 50).

Class-Ib Molecules and the Presentation of Bacterial Epitopes

The M-Region Class-Ib Molecule H2-M3. Mta was initially defined as a T-cell alloantigen whose expression was dependent on class-I and maternal inheritance. This unique feature was explained when it was determined that a peptide derived from the NH_2 terminus of mitochondrial NADH dehydrogenase (ND1) was presented by the class-Ib molecule H2-M3 for recognition by Mta-specific CTLs (51). Interestingly, binding of the ND1 peptide to M3 is dependent on the presence of the N-formyl group that forms a tight association with the B pocket in the hydrophobic peptide-binding groove (2, 51, 52). Subsequently it has been shown that N-formyl methionine peptides derived from most mitochondrial proteins can be presented by H2-M3 (53). Since all prokaryotes initiate protein synthesis with N-formyl methionine, it was correctly reasoned that M3 is a specialized peptide-binding structure tailored to bind and present N-formyl peptides derived from microbial antigens (22, 54).

Listeria monocytogenes is a Gram-positive intracellular pathogen that infects a wide variety of cell types including macrophages, hepatocytes, and endothelial cells. Listeria infection can cause a virulent infection in mice, and $CD8^+$ T cells have been shown to play an important role in clearing infection (55–58). Interestingly, during the course of studies characterizing the CTL response to Listeria, it was observed that the CTL recognition pattern often was independent of the polymorphic class-I loci (59, 60). This observation suggested that a significant fraction of the evoked CTLs recognized Listeria epitopes presented by a conserved class-I molecule. This was subsequently confirmed with the determination that the MHC-linked class-Ib molecules H2-M3 and Qa-1 are involved in the presentation of Listeria epitopes to CTLs (61–63).

To date, three H2-M3–restricted Listeria epitopes have been identified (Table 1). Using a mass spectroscopy–based approach, the penta-peptide f-MIVIL was identified (64). The Listeria gene product from which this peptide is derived has not been determined. Expression-cloning strategies identified two more epitopes, f-MIGWIIA derived from the LemA protein, and f-MIVTLF derived from the leader sequence of a putative transcriptional attentuator (65, 66). The finding that H2-M3 can present multiple Listeria-derived epitopes to $CD8^+$ T cells suggests that H2-M3–restricted effector T cells may play a key role in the clearance of infection. This view is supported by Nataraj *et al.*'s (67) demonstration that the transfer of a Listeria-specific H2-M3–restricted clone prior to infection with Listeria reduces the bacterial load two logs relative to untreated controls. Recently, the kinetics of the clonal expansion of f-MIGWIIA–specific H2-M3–restricted or LLO 91–99–specific H-$2K^d$–restricted $CD8^+$ T cells following natural infection with Listeria was examined using peptide-loaded class-Ia and class-Ib tetramers (68). Surprisingly, the H2-M3–restricted T-cell response preceded the H-$2K^d$–restricted response (peak at 5–7 vs 7–9 days) and the H2-M3–restricted T cells were 3–4-fold more abundant. In contrast to the initial infection, there is little expansion of the H2-M3–restricted T cells in the recall response following reinfection with Listeria whereas the H-$2K^d$–restricted $CD8^+$ T cells are the dominant recall effector population. Although the generality of these observations needs to be examined using other H2-M3–restricted epitopes, this would imply that distinct class-I families influence different stages of the $CD8^+$ T-cell response to infection, with H2-

M3–restricted T cells playing a key role in controlling the early stages of Listeria infection.

Given that all prokaryotes initiate protein synthesis with N-formyl methionine, it is reasonable to predict that H2-M3–restricted CTL responses will be a common component of the CTL response to intracellular bacteria. However, studies characterizing Salmonella-specific class-Ib–restricted CTLs failed to demonstrate H2-M3–restricted killing (69). Furthermore, a number of intracellular bacteria, including *Mycobacteria tuberculosis*, have been shown to evoke bacterial-specific CTLs, and no evidence for H2-M3 restriction has emerged. Although it is possible that the information available is limited and further study is needed, it also needs to be considered that H2-M3–restricted recognition is unique to Listeria antigens. At this time it is unclear why this may be so. The presentation of mitochondria and Listeria epitopes by H2-M3 is largely TAP-dependent with the f-MIVTLF epitope being the sole TAP-independent epitope reported (65, 70). H2-M3 cell surface expression is TAP- and β_2m-dependent, and peptide availability limits cell-surface expression (71, 72). All these features are typical of most class-I molecules and thus are not unique properties of H2-M3. In prokaryotes, newly synthesized proteins have the formyl-group rapidly removed by a specific deformylase, and many proteins are further processed to remove the NH_2-terminal methionine *via* the metallopeptidase PepM (73, 74). One possibility is that the deformylation step is inefficient or selective in Listeria resulting in a sizable pool of molecules retaining the N-formyl methionine that can then be processed and presented.

H2-T23 (Qa-1) Presentation of Bacterial Epitopes. In studies using Qa-1^b–specific alloreactive CTLs, the class-Ib molecule Qa-1 has been shown to bind and present hydrophobic nonamer peptides (AMA/VPRTLLL) derived from the leader sequence of H-2D region class-I molecules (16). These leader peptides are the dominant self-peptides bound to the Qa-1 molecule (75, 76). The functional significance of this observation was appreciated when Qa-1 was shown to be a ligand for the CD94/NKG2A inhibitory receptor (77, 78). Thus, the ability to bind leader sequence-derived peptides from other class-I molecules defined a novel NK surveillance system in which recognition of a single conserved class-Ib molecule allows NK cells to monitor globally a broad range of class-I expression levels on normal, transformed or infected cells. Based on this property, it was argued that Qa-1 evolved as an NK recognition structure (79). However, additional evidence in bacterial systems suggests that Qa-1 can also serve an important role in antigen presentation.

The presentation of Listeria epitopes by Qa-1 was the first observation that Qa-1 plays a role in bacterial immunity. Using a cfu-reduction assay to identify $CD8^+$ Listeria-specific CTLs, a population of non-H2-M3, class-Ib–restricted $CD8^+$ T cells was identified (80). Further study revealed Qa-1^b as a key restricting element for these cells (61). At this time the specific Listeria epitope(s) presented by Qa-1 has not been identified so the relative contribution of this effector population has not been examined. Infection of mice lacking class-Ia expression, (H-2 $K^{b-/-}/D^{b-/-}$) evokes both H2-M3 and Qa-1^b–restricted CTLs, and these CTLs are capable of transferring immunity to a naive host (45). Furthermore, H-2 $K^{b-/-}/D^{b-/-}$ mice are capable of clearing a Listeria infection with kinetics similar to wild-type mice. Although the relative contribution of the Qa-1 versus H2-M3–restricted populations in Listeria clearance is not known, it suggests that the class-Ib molecules Qa-1 and H2-M3 contribute to the protective host response to infection with Listeria.

Recently, Qa-1 has been shown to be an important antigen presentation structure in a mouse model of Salmonella infection (69). Salmonella sp. are intracellular pathogens capable of infecting phagocytic and nonphagocytic cells (81, 82). Several studies have implicated $CD8^+$ T cells in immunity to Salmonella infection. In a natural oral challenge model, both immune $CD4^+$ and $CD8^+$ T cells were essential for the effective transfer of protective immunity to virulent *S. typhimurium* (83, 84). Depletion of $CD8^+$ or $CD4^+$ T cells alone impaired the ability to transfer immunity. Similarly, removal of $CD4^+$ and $CD8^+$ T cells completely abrogated transfer of protective immunity to systemic infection with virulent *S. abortovis*, whereas depletion of $CD8^+$ or $CD4^+$ T cells impaired the protective effect (85). Lastly, class-I–deficient ($\beta_2m^{-/-}$, $CD8^+$ T-cell–deficient) mice were shown to be susceptible to infection with both avirulent and virulent *S. typhimurium* strains (69). Collectively, these studies implicate a role for CTLs in the host response to infection with Salmonella. Characterization of the murine CTL response evoked following infection detected a strong CTL response following challenge with virulent Salmonella and that a large fraction of the CTL response recognized bacterial epitopes presented on Qa-1b (69). A mass spectroscopy-based approach was used to identify the Qa-1b–restricted epitope as a nonamer peptide derived from the Salmonella GroEL molecule (Table II)

Table I. Bacterial Peptides Presented by MHC-Linked Class Ib Molecules

Gene	Peptide	Bacteria	Gene product	Reference
H2-M3	f-MIVIL	*L. monocytogenes*	Unknown	(64)
	f-MIGWII	*L. monocytogenes*	LemA	(65)
	f-MIVTLF	*L. monocytogenes*	Novel transcriptional Attenuator	(66)
Qa-1 (T23)	GMQFDRGYL	*S. typhimurium*	GroEL	(18)

Table II. Selected Sources of Homologues of Salmonella GroEL hsp60 (192–200) from the SwissProtein Database

Sequence	Source	Organism
GMQFDRGYL	GroEL aa192–200	*Salmonella typhimurium* *Salmonella typhi* *Escherichia coli* *Yersinia enterocolitica* *Helicobacter pylori* *Klebsiella pneumoniae* *Brucella abortus* *Borrelia burgdorferi* *Pseudomonas aeruginosa* *Neisseria meningitidis* *Bordetella pertussis* *Haemophilus influenzae* *Coxiella burnetti*
GMRFDKGYI	GroEL, aa190–198	*Mycobacteria tubuclerosis*
GMKFDRGYI	GroEL, aa216–224	human, murine

(18). Although measurements of the frequency of GroEL-specific, Qa-1–restricted $CD8^+$ T cells indicate that it is an immunodominant epitope, the degree to which such T cells contribute to protective immunity is unknown.

A search of the protein database revealed that the peptide sequence is common to GroEL molecules from a variety of Gram-negative organisms (Table II). Previous studies indicated that Qa-1 could bind peptides derived from the Mycobacteria GroEL molecule (17, 86). A peptide homologous to the Salmonella GroEL is found in the GroEL from *Mycobacteria tuberculosis* (Table II). Furthermore, it is possible that the Qa-1–restricted CTLs found after Listeria infection may recognize a peptide derived from the Listeria GroEL. Collectively these observations suggest that Qa-1–restricted CTLs, specific for bacterial GroEL peptides, may be a common feature of the host response to a wide variety of intracellular bacteria.

The finding of Qa-1–restricted CTLs as a significant component of the host response to intracellular bacteria may be directly relevant to the human setting. Human HLA-E and murine Qa-1 both bind analogous peptides derived from class-I molecule leader sequences using similar anchor residues, and HLA-E is recognized by the CD94/NKG2A complex (29, 30, 87–89). Consequently, it has been proposed that the human class-Ib molecule HLA-E is a functional homolog of murine Qa-1 (27). Given the overlap in peptide binding and the presence of the conserved anchors in the bacterial GroEL peptides, it is reasonable to speculate that peptides found to bind and be presented by murine Qa-1 are likely to be presented by HLA-E. Thus HLA-E–restricted CTLs may be a component of the human CTLs' response to Salmonella (90–92).

CTL recognition of this conserved Salmonella GroEL peptide may prove to be a double-edged sword since the murine hsp60 counterpart contains a highly homologous peptide mimic (Table II). Indeed, the Qa-1–restricted CTLs evoked following infection cross-react with this self-peptide and can recognize stressed macrophages (18). Thus such GroEL-reactive CTLs may contribute to host immunity, these cells are self-reactive and may contribute to the subsequent development of autoimmune disease. It is well known that Salmonella, as well as other Gram-negative pathogens such as *Yersinia enterocolitica*, *Klebsiella pneumoniae*, and *Borrelia burgdorferi*, are known intracellular pathogens that are etiologically linked to the development of inflammatory arthritis. Therefore Qa-1–restricted, GroEL peptide–specific CTLs, as well as their proposed human counterparts, may play a role in bacterial-induced autoimmunity.

It is interesting to speculate that Qa-1 and possibly HLA-E may serve as a novel immunosurveillance system. Transformation and infection with many viruses downregulate class-Ia cell surface expression (93). Thus human HLA-E and murine Qa-1, by virtue of their ability to bind leader sequence–derived peptides from other class-I molecules define a novel NK receptor surveillance system to monitor class-I expression levels. In addition, the GroEL molecule is a major species detected immediately (within minutes) following bacterial entry into the cell (94). The ability to bind peptides selectively that are derived from either the leader sequences of class-I molecules or the GroEL molecules of intracellular bacteria allows Qa-1 (and possibly HLA-E) to alert the immune system to the early consequences of cellular infection/change, thereby mediating a rapid mobilization of the host response.

MHC-Linked Class-Ib Molecules in Mycobacteria Infection. *Mycobacteria tuberculosis* is an important intracellular pathogen, and the generation of $CD8^+$ CTLs is a key element of the host response (95, 96). Mice deficient in class-I expression ($\beta_2m^{-/-}$) show increased susceptibility to *M. tuberculosis* infection (97). Although this result indicates the involvement of class-I molecules, it does not distinguish between roles for class-Ia or class-Ib molecules. To date, a role for class-Ib molecules has not been established in the murine model for Mycobacteria infection, but involvement of nonclass-Ia molecules has been demonstrated in humans. It has been observed that CD1a, CD1b, and CD1c can bind and present unique Mycobacteria-derived glycolipid antigens to diverse sets of T cells (98–100). In addition, using Mycobacteria-infected autologous dendritic cells, several *M. tuberculosis*-specific $CD8^+$ T-cell lines and clones were generated from PPD^+ healthy individuals (101). These $CD8^+$ T cells specifically recognized Mycobacteria-infected targets in a unique class-I dependent, but CD1- and HLA-A–, -B–, and -C–independent fashion. Although the precise antigen presentation structure(s) used by these cells has not been identified, this work suggests that in addition to CD1, MHC-linked class-Ib molecules play a role in the host-response to Mycobacteria infection.

Novel TCRα/β-Bearing Lymphocyte Subsets that are Controlled by MHC-Linked Class-Ib Molecules

Evidence for the involvement of MHC-linked class-Ib molecules in the control of novel T-cell subsets is emerging. For example, studies using mice deficient in total class-I ($\beta_2m^{-/-}$) or class-Ia expression (H-2 K^{b-r}/D^{b-r}) revealed the presence of a novel β_2m-dependent/class-Ia–independent CD8α/α, TCR α/β subset in the gut epithelium (102–104). Studies using mice deficient in class-Ia and CD1 indicated that this population was likely dependent on MHC-linked class-Ib molecules (104). Also, a TCR α/β subset bearing an invariant T-cell receptor α-chain (Vα7/19-Jα33) has been identified (105). This population appears to be conserved in several mammalian species, and its presence is dependent on β_2m expression but independent of class-Ia or CD1 molecules, again suggesting the involvement of MHC-linked class-Ib molecules. Although there is no information that these novel T-cell subpopulations are mobilized during infection, it needs to be considered that such subsets, some of which are strategically located to interface with pathogens, may play a direct role in recognizing conserved antigens or may serve an indirect (regulatory) role in controlling the host-response to infection.

MHC-Linked Class-Ib Molecules in γ/δ T-Cell Recognition

T cells bearing γ/δ antigen receptors have been shown to localize to epithelial compartments and thus provide a "first-line" of defense during infection (106). Indeed, following bacterial infection there is an expansion of γ/δ T-cell subsets, and γ/δ T-cell deficiency alters early Listeria replication (107–109). This increase in γ/δ T cells is thought to be triggered, not by recognition of a bacterial antigen, but by the recognition of a self-ligand induced during the inflammatory process (110, 111). It was argued that class-Ib molecules and γ/δ T cells co-evolved as a receptor/ligand pair (112). Although it is now clear that class-Ib molecules have evolved to serve a range of functions, there is a body of work that has demonstrated that several T-region class-Ib molecules can be recognized by γ/δ T cells. For example, the Qa-1 molecule has been shown to present poly GT (glutamine-tyrosine) to poly GT-specific γ/δ T-cell hybridomas (113, 114). In addition, the products of the *T10* and *T22* genes are recognized by γ/δ T cells found in the spleen and gut epithelium (10–14, 115). These γ/δ T cells recognize empty T10/22, and attempts to identify peptides bound to T10 and T22 have failed (10–12). Interestingly the T10 and T22 molecules exhibit regulated expression suggesting that the recognition of these molecules may be confined to specific physiological settings (115).

The HLA-linked human class-Ib molecules MICA and MICB are expressed in the intestinal epithelium in a stress-induced fashion and do not bind peptides (116). MICA and MICB are recognized by intestinal epithelial γ/δ T cells expressing the Vδ1 receptor in either a TCR or NKG2D-dependent fashion (116–118). Although it is not clear if the MICA/B and T10/22 recognition systems are cross-species counterparts, it is possible that they represent recognition systems that play a role in the early stages of the host-response to infection.

Immunological Significance of Class-Ib Presentation

Based on the work outlined above it is clear that many class-Ib molecules encode functional molecules that have evolved key roles as antigen presentation molecules and/or recognition structures in the adaptive and/or innate response to intracellular bacteria. Given these central roles, one needs to consider class-Ib molecules as target molecules in the design of immune interventions to either augment or silence immune responses.

The observation that bacterial epitopes can be presented by MHC-linked class-Ib antigen-presenting structures suggests the possibility that class-Ib molecules could be targets for novel vaccine strategies. Most vaccines use epitopes presented by polymorphic MHC molecules that are not uniformly present in the population. Vaccines designed to target antigens that are presented by antigen-presentation structures with limited polymorphism (e.g., class-Ib molecules) are not likely to have this complication. Thus, vaccines that include epitopes presented by class-Ib molecules as universal presenting structures may be of general use in genetically diverse populations (119). Although this principle has yet to be demonstrated, the identification of specific bacterial peptide epitopes presented by class-Ib molecules to effector T cells puts the concept on testable ground.

It has been proposed that the use of anergic peptides, anti-MHC antibodies, or soluble complexes of MHC and peptide may allow one to target and control specifically and selectively immune responses of interest (120). Given that class-Ib molecules (Qa-1) can be targets for self-reactive T cells, studies into the use of these strategies to modify class-Ib–mediated immune reactivity may be of value. Also, class-Ib molecules are recognized by several NK and T-cell subsets, some of which are components of the natural or innate immune system. It has been argued that these cell types represent components of an early hardwired host response to infection and that this early response interfaces with the delayed adaptive response ultimately responsible for the clearance of infection (121). Targeting these cell types using their class-Ib ligands may prove valuable in modulating their function in a quantitative (augment/inhibit) or qualitative (nature of effectors evoked) manner thus indirectly effecting specific adaptive immune responses.

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