The multiple roles of major histocompatibility complex class-I-like molecules in mucosal immune function

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The human major histocompatibility complex (MHC) on chromosome 6 encodes three classical class-I genes: human leukocyte antigens (HLA) A, B, and C. These polymorphic genes encode a 43- to 45-kDa cell surface glycoprotein that, in association with the 12-kDa β_2-microglobulin molecule, functions in the presentation of nine amino acid peptides to the T-cell receptor of CD8-bearing T lymphocytes and killer inhibitory receptors on natural killer cells. In addition to these ubiquitously expressed, polymorphic proteins, the human genome also encodes several nonclassical MHC class-I-like, or class Ib, genes that, in general, encode nonpolymorphic molecules involved in various specific immunological functions. Many of these genes, including CD1, the neonatal Fc receptor for IgG, HLA-G, HLA-E, the MHC class-I chain-related gene A, and *Hfe*, are prominently displayed on epithelial cells, suggesting an important role in epithelial cell biology. □ *Epithelium; intestine; major histocompatibility complex*

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It is increasingly recognized that epithelial cells, especially intestinal epithelial cells (IEC), play an important role in innate and adaptive immune functions in addition to their important barrier, absorption, and transport functions (1). A structural form that is particularly useful to the epithelial cells in fulfilling these immunological functions is that provided by the major histocompatibility complex (MHC) class-I-related molecules. By understanding the composition of these molecules, insight can be provided into possible functions of these molecules in epithelial cells.

Classical MHC class I molecules

The basic structure of the MHC class-I-related molecules reflects that encoded by the classical MHC class-I or class Ia genes (2, 3). These genes are encoded within the MHC class-I locus on human chromosome 6 and consist of the human leukocyte antigens (HLA) A, B, and C. The open reading frame of these genes consists of structural domains encoded by discrete exons that translate into an approximately 43- to 45-kDa glycoprotein containing three membrane distal domains (α1, α2, and α3), a transmembrane domain, and a cytoplasmic tail. The most membrane-proximal ectodomain, the α3 domain, provides the major contact sites for the noncovalently associated, 12-kDa, β2-microglobulin (β_2m) molecule, which is encoded outside the MHC class-I locus (4). β_2m coassociation with the MHC class-I heavy chain is prerequisite for functional expression of the protein complex on the cell surface. The most membrane distal α1 and α2 domains contribute to the formation of a series of β-pleated sheets bound on the sides by two α-helices forming a groove consisting of a series of pockets capable of binding nine amino acid peptides for presentation to the T-cell receptor (TCR) of CD8-bearing T cells (3, 5). In making contact with the α-helices and peptide of the α1 and α2 domains, stabilized by interactions between CD8 on the T cell and clusters of amino acids within the α3 domain of the MHC class Ia molecule (6), the T cell is activated to fulfill its effector function, whether it be proliferation, cytolysis, and/or cytokine secretion. Since the peptides contained within the groove of the MHC class Ia molecules are predominantly derived from the degradation of intracellular molecules by proteasomes, $CD8^+$ T cells are generally concerned with monitoring the intracellular health of MHC class-Ia-bearing cells such as epithelial cells. Delivery of peptides to the MHC class Ia molecule/β_2m complex is assisted by ER-associated proteins, the transporter associated with antigen presentation (TAP) 1 and 2 (5, 6). The vast majority of intraepithelial lymphocytes residing above the basal lamina adjacent to the basolateral surface of the epithelial cells of the intestine are $CD8^+$, indicating the potential importance of this pathway in dealing with deleterious intracellular events that might occur during viral infection, cellular stress, and neoplastic transformation; common events for epithelial cells (7). The MHC class Ia genes display significant allelic polymorphism, due to variations in the amino acid composition of the α1 and α2 domains, each capable of binding a slightly different

large array of nonameric peptides (2). In addition, each individual is endowed with six different alleles, predicting that the peptide-binding capacity of an individual is enormous and well suited to dealing with unforeseen antigenic assaults. This pathway of antigen presentation is so efficient that microorganisms, especially viruses, have spent a great deal of evolutionary energy devising strategies to subvert this pathway, such as through the expression of molecules that interfere with cell surface display of MHC class-Ia molecules (8, 9) and the generation of decoy molecules encoded by the genome of the pathogen which structurally resemble the MHC class-I molecule (10). The common gastrointestinal pathogens, adenovirus (9) and cytomegalovirus (10), can accommodate each of these mechanisms of immune evasion.

The classical MHC class-I molecules serve as ligands not only for the TCR of CD8-bearing lymphocytes capable of eliciting cytolysis but also for killer inhibitory receptors (KIR) on the cell surface of natural killer (NK) cells (11). When ligated by MHC class Ia, KIRs transmit inhibitory signals to the NK cell bearing the KIR. As a consequence, MHC class-Ia-bearing cells are not lysed. However, in the absence of MHC class I, as commonly occurs during neoplasia, including tumors of the epithelium (12), NK-mediated lysis can be induced by ligation of killer-activating receptors (KAR) on the NK cell (11). KIRs show allelic specificity for MHC class Ia molecules, and their binding can be affected by the nonameric peptides that specific MHC class Ia alleles present. Although NK cells are not a prominent component of the epithelial compartment, the increasing recognition that subsets of T cells are capable of expressing KIRs indicates the potential importance of this mechanism of cytolysis induction for T cells and the utility of these regulatory mechanisms at epithelial surfaces (13).

Nonclassical MHC class I molecules

Human evolution has been so enamored with the general utility of this MHC structure in performing discrete tasks of immunologic recognition that a plethora of human genes has developed from the ancestral MHC class-I gene. These MHC class-I-related genes, other than the classical class-I genes, are called nonclassical MHC class-I molecules or MHC class Ib molecules (14). The MHC class Ib molecules are either encoded by genes linked to the classical HLA-A, -B and -C genes on chromosome 6 (HLA-E, -F, -G, -H, and MHC class-I chain-related gene A (MICA)) or by genes outside the MHC class-I locus. These latter genes include the CD1 family and a gene of unknown function, MR1 (15), on chromosome 1, the human homologue of the rodent neonatal Fc receptor for IgG (FcRn) on chromosome 19 and the Zinc- α2-glycoprotein (ZAG), a soluble serum protein of unknown function, probably involved in lipid metabolism (16) encoded on chromosome 7. In mouse species an even larger number of MHC-linked genes is encoded within three genetic loci (Q, T, and M) on chromosome 17 (14).

These genes are considered MHC class-I-like on the basis of similarities of exon-intron structure with MHC class-Ia molecules (α1-α3 ectodomains, transmembrane domain, and cytoplasmic tail encoded by discrete exons) and dependence on β_2m for cell surface display and function, with some exceptions. CD1d (see below) MICA (17, 18) and ZAG (16) can be expressed without β_2m, suggesting an element of independence from β_2m in function. However, the MHC class-Ib molecule molecules differ in their general lack of polymorphism in the amino acid composition of their respective α1 and α2 domains, such that they are considered to be nonpolymorphic (2, 14). This lack of polymorphism, with some exceptions (as described below), suggests that the α1 and α2 domains of the MHC class-Ib molecules bind very distinct structures. This further suggests that they have evolved to specialize in binding distinct ligands. In conjunction with other structural information encoded in their primary amino acid sequences, their specific ligand recognition also correlates with specific types of functions as a consequence of ligand binding. Finally, the MHC class-I molecules, in contrast to MHC class-Ia molecules, which are ubiquitously expressed, show a restriction in their expression to specific cell types and, corollarily, tissues (14). This is especially relevant to human epithelial cells, which appear to be a particularly prominent cell type that shows expression of several MHC class-Ib molecules, including CD1, FcRn, HLA-G, HLA-E, MICA, and HLA-H, *Hfe*.

CD1

The human CD1 gene family consists of five genes, CD1A-E (19). A gene product for CD1E has not yet been defined. (By convention, CD1 genes are represented by capital letters, and CD1 proteins by lower-case letters.) Nucleotide and deduced amino acid homologies predict that these gene products segregate into two groups: CD1a-c and CD1d. CD1A–C homologues are not present in mouse and rats, which contain CD1D homologues highly related to human CD1D. Whereas CD1a-c is expressed by thymocytes and certain professional antigen-presenting cells such as B lymphocytes, Langerhans cells of the skin, and activated monocytes, CD1d is expressed by thymocytes, B cells, monocytes, dendritic cells, hepatocytes, and, importantly, epithelial cells in a wide variety of organs. CD1b and c appear to function in the presentation of exogenous and, possibly, endogenous lipid antigens to T cells (20). In general, these CD1-restricted, lipid-responsive T cells are either $CD8^+$ or lack CD4 and CD8 (double negative). The response of double-negative cells suggests either no need for coreceptor function in TCR binding or the use of another novel, not yet described, coreceptor molecule. The antigen-presenting pathway by which CD1b and c acquire lipid-related antigens is TAP-independent and overlaps with that utilized by MHC class-II

molecules (21). The MHC class-II homologies include similarities in the nucleotide sequence within the α3 domain and the presence of a YXXZ motif (tyrosine-amino acid-amino acid-hydrophobic amino acid) in the cytoplasmic tail that controls protein movement to an endocytic compartment where MHC class-II processing occurs. CD1d shares the YXXZ motif with CD1b and c and shows a narrow but deep hydrophobic pocket (22), consistent with its ability to bind and present exogenous and/or endogenous lipid antigens to T cells that are generated by a processing pathway that likely bisects MHC class II (23). In contrast to MHC class-Ia molecules, however, CD1d is clearly stable in the absence of β_2m in transfected model systems, raising the possibility for other immunoregulatory functions of CD1d (24, 25). This may be especially relevant to CD1d function in epithelial cells. In IECs, CD1d transcription occurs within the lower zones of the crypt epithelium with protein expression predominantly on IECs within the upper crypts and villi (26). Moreover, a form of CD1d on IELs is expressed independently of β_2m and carbohydrate side-chain modification (24) and may be recognized by $CD8^+$ T cells. However, the major form of CD1d on IELs is a 48-KDa, β_2m-associated glycoprotein (28). Fully glycosylated, β_2m-associated CD1d appears to be a ligand for an invariant TCR-αchain expressed on double-negative human T cells bearing NKR-P1A, a C-type lectin expressed on NK-T cells (29). On CD1d ligation, these $CD4^+$ and double-negative NK-T cells secrete high quantities of γ-interferon and interleukin-4, suggesting an important immunoregulatory function. Whether epithelial cell-associated CD1d performs a similar immunoregulatory function for local CD1d-restricted T cells remains to be established (30). However, it is clear that CD1d on IECs can regulate IL-10 production by the cells (31) (Fig. 1) and activation of NK-T cells with a model glycolipid antigen (α-galactosylceramide) can ameliorate colitis (32). Taken together, these studies suggest that CD1d and CD1d-restricted T cells have a role in down-regulating mucosal inflammation.

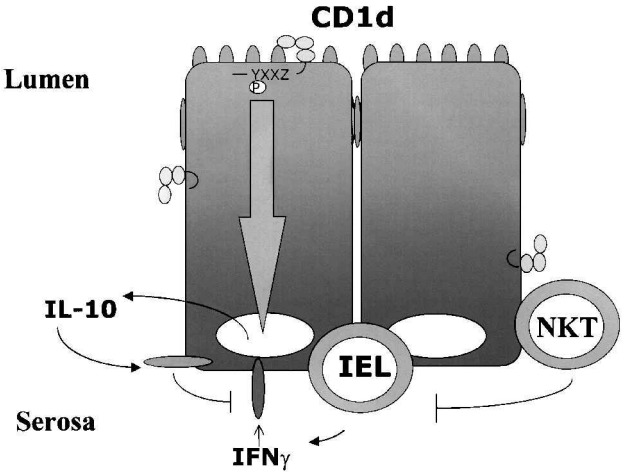

Fig. 1. Model of CD1d on intestinal epithelial cells (IELs). Activation of CD1d on IELs induces production of barrier-promoting and downregulatory cytokines such as interleukin (IL)-10 (from Refs. 31 and 32). IFN = interferon; NKT = natural killer T cells.

Neonatal Fc-receptor for IgG (FcRn)

FcRn was originally defined as the rat receptor expressed by neonatal IECs responsible for vectorial transport of maternal IgG into neonatal animals (33). Recent studies with β_2m knockout mice support the role of FcRn in similar functions in mice, confirm the prerequisite role of β_2m association for FcRn function, and support the role of FcRn in regulating IgG catabolism through protection of IgG in an endocytic cycling pathway involving endothelial cells, which also express FcRn. To accomplish these functions, FcRn has maintained the basic MHC class-I structure with some embellishments. Due primarily to a proline residue at position 162 in the α2 domain, the potential antigen binding groove of FcRn is disabled such that binding to its ligand, the Fc portion of IgG, occurs on the outer face of the α-helices. FcRn-IgG interactions are pH-dependent (binding at acidic pH, dissociation at neutral pH) due to charged residues at the contact sites of FcRn and the hinge region of IgG. As a result, binding and transport occur at acidic pH, the pH of the neonatal lumen and endosomes, and release occurs at neutral pH, the pH of tissue and plasma. In humans, such structural properties are useful to the syncytiotrophoblast of the placenta, which is responsible for passive acquisition of maternal IgG by the fetus, from where FcRn has recently been identified. What is not clear, however, is the functional role of FcRn expression on epithelia during adult rodent life (34) and, especially, the high level FcRn expression in adult human intestinal epithelium and lung (35). We have found that FcRn functions in the bidirectional transport of IgG across the intestinal epithelial cell barrier (36). This differentiates FcRn from the poly-immunoglobulin receptor and suggests a role in mucosal immune surveillance (Fig. 2).

HLA-G and HLA-E

The trophoblastic epithelium of human placenta, which is in direct contact with maternal tissues, lacks classical MHC class-I and class-II (HLA-DR, -DP, and -DQ) proteins, making it susceptible to lysis by maternal NK cells, which are present in large numbers in human decidua. This problem may be remedied by the expression of HLA-G on syncytiotrophoblasts. Although considered a nonclassical MHC class-I molecule that is linked to the MHC locus on chromosome 6, HLA-G shows a limited amount of allelic polymorphism in the α1 and α2 domains, shows prerequisite dependency on β_2m and contains α1 and α2 domains that fold into a groove competent to bind nonameric peptides (37, 38). Recent evidence also suggests that HLA-G may be a relatively public receptor for KIRs

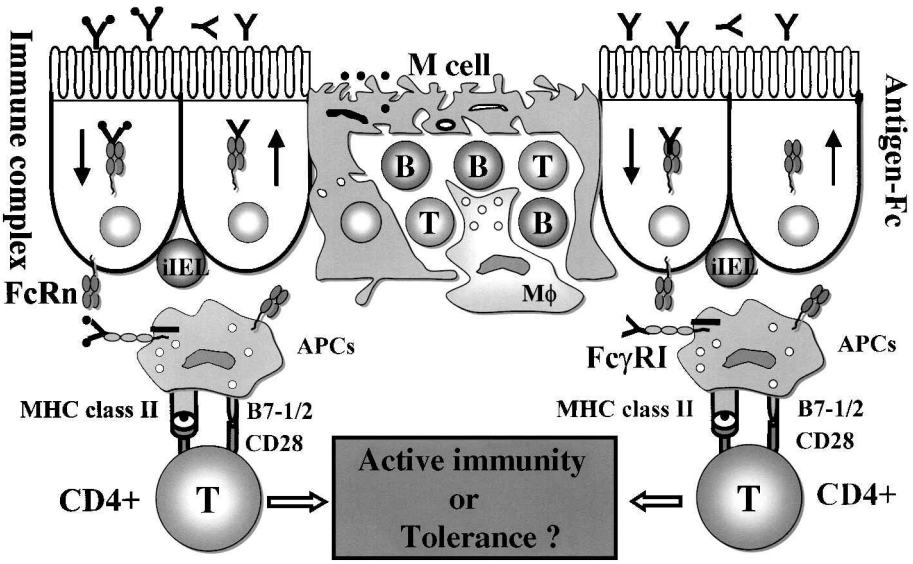

Fig. 2. Model of rodent neonatal Fc receptor (FcRn) function in adult life. The bidirectional transport of IgG may lead to uptake of antigen–antibody complexes from the lumen. MHC = major histocompatibility complex; APC = antigen-presenting cells; IEL = intestinal intraepithelial lymphocyte; RI = Fcγ receptor 1.

specific for HLA-G. More importantly, however, the leader peptide of HLA-G is presented by HLA-E, which also shows prominent epithelial expression (39). The ternary complex of HLA-E, β_2m and HLA-class I leader peptide is a ligand for a class of KIRs. Given the possibility that HLA-G is more widely expressed than originally believed, including possibly on other epithelial surfaces, the possibility should be considered that these mechanisms of NK inhibition may be more generally applicable.

MHC chain-related gene A (MICA)

MICA is a recently described, MHC-linked, class Ib molecule that appears to show relatively restricted expression to intestinal epithelium and, like CD1d, is somewhat indifferent to β_2m for cell surface expression (16, 17). The promoter region of MICA shows functional heat-shock response elements (17). This has suggested a possible functional role as a cell surface flag that provides a danger signal as a consequence of some ubiquitous stress signal. This would predict that local T cells expressing ligands for MICA may possibly be responsible for eliciting a cellular response to epithelial cell injury. Indeed, heat-shocked IECs express MICA that is recognized by Vδ1$^+$ IELs that bind MICA via expression of a killer-activating receptor, CD94/NKG2, thus eliciting cytolysis of the stressed or altered IEC (40, 41).

HLA-H (*Hfe*)

Finally, the newest member of the MHC class Ib group relevant to epithelial biology is the recently described HLA-H gene product, which has recently been renamed *Hfe* (42). The *Hfe* gene product is widely expressed through the gastrointestinal epithelium, with most prominent expression in the crypts of the small intestine (43). Mutations of this protein have been linked to the iron overload disorder, hemochromatosis. Almost all hemochromatosis subjects manifest a cysteine 282 $\rightarrow$ tyrosine (C282Y) mutation, which disrupts association of *Hfe* with β_2m and, consequently, cell surface expression of this molecule (44). Of note, the *Hfe* gene also contains iron response elements. The specific relationship of this allelic variant to iron transport is unknown but may lie through intermolecular associations with recently described iron transporters. These iron transporters are multiple membrane spanners (45). Interestingly, similar molecules, such as CD82, have been shown to coassociate with MHC class Ia molecules (46). This raises the possibility that these newly described iron transporters may coassociate with *Hfe*/β_2m to somehow regulate intracellular iron levels. The specific ligand of *Hfe* remains to be determined, and its crystal structure is at present unknown (47).

Conclusion

In summary, the MHC class-I protein structure contains a significant amount of information useful to accomplish various cellular tasks commonly performed by epithelial cells specifically in areas of cellular transport (*Hfe*, FcRn) and regulation of lymphocyte responses to altered epithelial cells (HLA-G, HLA-E, MICA) and possibly bacterial antigens (CD1). What is unique about MHC class-I-like

structure that makes it useful to epithelial cells? It can only be conjectured that its value lies in the ability of these molecules to link specific ligand binding to various hard-wired cellular pathways involved in protein trafficking, which ultimately result in regulating lymphocyte responses. Regardless, there is an enormous amount of work still to be done in elucidating the functional mechanisms of these, and other yet to be discovered, MHC class-Ib molecules in epithelial cell biology.

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