Review Article

Mammalian non-classical major histocompatibility complex I and its receptors: Important contexts of gene, evolution, and immunity

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The evolutionary conserved, less-polymorphic, nonclassical major histocompatibility complex (MHC) class I molecules: Qa-1 and its human homologue human leukocyte antigen-E (HLA-E) along with HLA-F, G and H cross-talk with the T-cell receptors and also interact with natural killer T-cells and other lymphocytes. Moreover, these nonclassical MHC molecules are known to interact with CD94/NKG2 heterodimeric receptors to induce immune responses and immune regulations. This dual role of Qa-1/HLA-E in terms of innate and adaptive immunity makes them more interesting. This review highlights the new updates of the mammalian nonclassical MHC-I molecules in terms of their gene organization, evolutionary perspective and their role in immunity.

Key words: CD94/NKG2, human leukocyte antigen-E, major histocompatibility complex, Qa-1

Introduction

Major histocompatibility complex class I molecules (MHC-I) are cell surface glycoproteins expressed on most of the cells. On antigen presenting cells, they are involved in the presentation of endogenous peptide to $CD8^+$ T-cells through T-cell receptors (TCR) for the antigens that are originated from the cytosolic protein by proteasomal degradation. Nevertheless, MHC-I molecules also present peptides, which are generated from exogenous proteins by a process called cross-presentation.[1] In humans, MHC-I proteins are encoded by (a) highly polymorphic classical MHC class Ia and (b) less-polymorphic nonclassical MHC class Ib genes. Classical MHC-Is are human leukocyte antigen (HLA)-A, -B and -C. On the other hand, human nonclassical MHC-Is are HLA-E, -F, -G, and -H (also called "High Fe" or HFE), which are homologous to Qa-1, Qa-2, HFE and RT1 haplotypes in mouse and rat, respectively.[2-7] In this review, we briefly describe the gene organization, a phylogenetic analysis of nonclassical MHC molecules and updates on their immunological interaction with receptors like TCR and CD94/NKG2 on T, NK and natural killer T (NKT) cells. We also discuss their role in the pathological state of some important diseases that are associated with altered host cell immunity, which has implication in the basic and translational research of mammalian immune responses and their regulation.

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Gene Organization and Evolutionary Perspective of Nonclassical Major Histocompatibility Complex Class I Molecules

Genes of nonclassical MHC-I are located in chromosome 6 (locus p21.1-21.3) in humans.[8] However, in mice and

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rats they are found in chromosome 17 (locus B1) and 20 (locus p12), respectively [Figure 1].[9,10] Classical MHC-I molecules and nonclassical MHC-I are expressed in most of the tissues in modest levels, but these are expressed in high quantities in some neoplastic cells.[11-14] Nonclassical MHC-Is are known to be evolutionary conserved.

It has been suggested from numerous studies that two alleles of HLA-E (HLA-E*0101 and HLA-E*0103) have minimum polymorphism among all HLAs and are found in high frequencies in Caucasians.[15,16] Among these two alleles, HLA-E*0101 (also known as HLA-E^{107R}) is expressed strongly in normal cells and in higher frequency than HLA-E*0103 (HLA-E^{107G}). HLA-E*0101 differs from HLA-E*0103 at amino acid position 107 where arginine is replaced by glycine.[16]

Mouse MHC complex is known as H-2 complex located on chromosome 17.[6,10] In mice several MHC-Ibs are found in the H-2Q, H-2T, and H-2M regions of MHC, whereas Qa-1b is a mouse MHC-Ib molecule encoded by the T23 gene.[17] It was first identified in peripheral T-cells as a serological determinant and later identified as the previously isolated gene 37.[17] Sequence analysis suggests that there are only four known alleles of Qa-1. Qa-1b is expressed in the majority of inbred laboratory

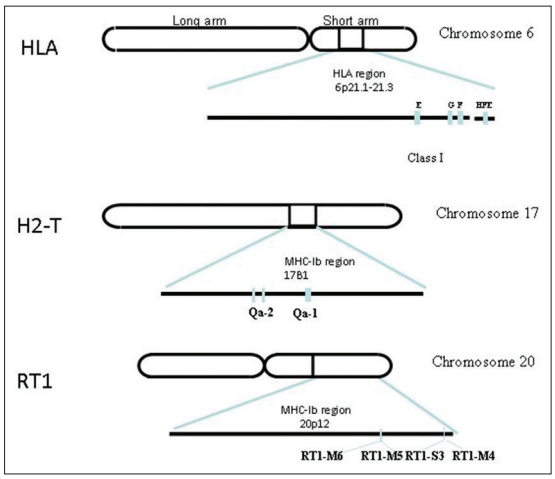

Figure 1: Schematic representation of nonclassical major histocompatibility complex (MHC) class I genes of human, mouse and rat: Nonclassical MHC class I genes found in human, mouse, rat in chromosome 6, 17 and 20 respectively. The nonclassical MHC-I genes of human leukocyte antigen (HLA-E,-F,-G,-H.) are found in locus p21.1, mouse (Qa-1, Qa-2) are found in B1 region, rat (RT1-M4,-M5,-M6,-S3) are found in region 20p12 of chromosome 20

strains, whereas Qa-1a is expressed in most of other strains. On the other hand, Qa-1c and Qa-1d frequencies are very rare.[18]

The ability to induce an allogeneic immune response by Qa-1 defines the function of Qa-1 as an MHC ligand for T-cells, which is not restricted by H-2D or H-2K haplotype.[19] An investigation by Aldrich *et al.*[20] decipher the cell surface expression of the Qa-1 alloantigens with the help of monoclonal anti-Qa-1 cytotoxic T lymphocyte (CTL) cell lines. It has been found that the expression of Qa-1 is high, similar to class I H-2K/D molecules. Moreover, the Qa-1 determinant modifier (Qdm) has been found to be linked with H-2D gene. It is also observed that Qdm may control over expression of certain CTLs-defined Qa-1 antigenic determinants.[20] Another report also suggests that a majority of alloreactive Qa-1-specific CTL clones recognize a specific Qa-1 bound peptide, which is a derivative leader sequence of H-2D.[21] Several studies in the recent past suggest a key role of Qa-1 in innate immunity. Qa-1 is also reported as a ligand for CD94/NKG2 receptors in mouse NK cells, NKT cells and some subset of T-cells.[22-26] Accordingly, it appears that other than interaction with TCR; the nonclassical MHCs are important for signaling through CD94/NKG2 receptors to modulate host cell immunity. The role of CD94/NKG2 receptors in Qa-1 and HLA-E mediated immune responses is discussed in a subsequent section.

In several nonhuman primates, existence of MHC-Ib has been suggested earlier. MHC-G has been described in some nonhuman primates.[27-31] It has been mentioned that in chimpanzee (*Pan troglodytes*) MHC-Ib is known to be organized in similar way as human MHC-Ib.[32] It has also been described in case of many other nonhuman primate species.[27,32-37] MHC-I genes of New World primates appear to be homologous to HLA-G genes than classical HLA-I genes.[27,28] Mamu-G is ortholog of HLA-G in the rhesus monkey (*Macaca mulatta*) and it is appeared to be a pseudogene. Another nonclassical MHC-I locus called Mamu-AG is also found to be expressed in the placenta of rhesus monkeys. Mamu-AG encodes MHC-IA locus-related molecules with all the features of human HLA-G, apart from features like a truncated cytoplasmic domain and limited polymorphism.[31] Phylogenetic study comprising exon 2,

exon 3, and intron 2 sequences of MHC-G of 7 nonhuman primates along with HLA-G have shown that cotton top tamarin (*Saguinus oedipus*) MHC-G sequences are more closer to human and great apes (Pongids).[30]

HLA-E and-F homologues have been described in orangutans and macaques.[36-39] The orthologs of MHC-E have also been identified in nonhuman primates such as gorillas, chimpanzees, bonobos, and vervet (green) monkeys.[38,40] Phylogenetic analysis of MHC-E locus of six New World monkey species and full-length MHC-E cDNAs of four unrelated cotton-top tamarins (*S. oedipus*) along with HLA-E have shown that Saoe*01 (*S. oedipus*) is orthologous to HLA-E.[35] Moreover, multiple sequence alignment of MHC-F cDNA sequences of human, chimpanzee, macaque and cotton-top tamarin have shown that in cotton-top tamarin, accumulation of nonsynonymous differences are more than synonymous differences in the peptide binding region of this gene.[37] Analysis of the nucleotide sequences of MHC-H in gorillas and chimpanzees revealed that they have a high degree of homology among their alleles.[41] Phylogenetic analysis of some MHC-I genes of gorilla and chimpanzee along with human, shows the close clustering of Gogo-H*01 (gorilla) and Patr-H*01 (chimpanzee) with HLA-H alleles, indicating close evolutionary relationship between them.[41]

The gene and protein sequences [Figure 2 and Tables 1 and 2] of nonclassical MHC-I molecules of rat, mouse, nonhuman primates (*Gorilla gorilla, P. troglodytes, M. mulatta*) and human have been analyzed by web based Clustal W 2.1 tool from DNA Data bank of Japan (DDBJ) with Unweighted Pair Group Method

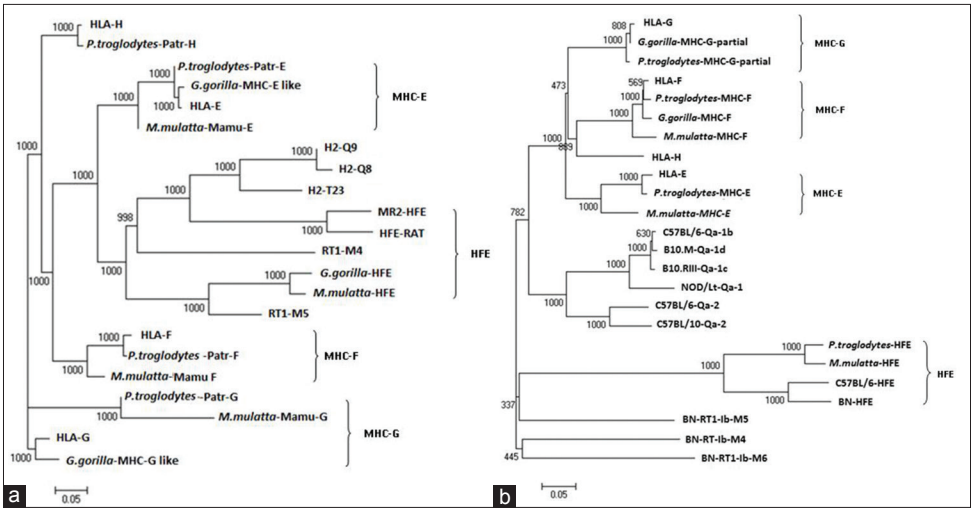

Figure 2: Phylogenetic analysis of some of the sequences of genes and proteins of nonclassical major histocompatibility complex -I(MHC-I) of the human leukocyte antigen-I (HLA-I), nonhuman primates, rat (RT1) and mouse (Qa) with respective mouse and rat strains. Nonclassical MHC-I molecules showed that these are clustered according to types of non-classical MHC-I molecules. Phylogentic tree is constructed by Unweighted Pair Group Method with Arithmetic Mean method as implemented by Clustal w (DDBJ), Bootstra *P* value (1000 replicates) are indicated. (a) Nucleotide sequences of the genes included are: HLA-E (Gene ID: 3133):, HLA-G (GENE ID:3135), HLA-F (GENE ID:3134):, HLA-H (GENE ID:3136), H-Q9 (C57BL/6, GENE ID: 110558), H2-Q8 (C57BL/10, GENE ID: 15019), H2-T23 (C57BL/6,GENE ID: 15040), MR2-HFE (C57BL/6, GENE ID: 15216), RT1-M5 (BN, GENE ID:499400), RT1-M4 (BN, GENE ID: 309584), HFE (BN, GENE ID: 29199), Mamu-E (*Macaca mulatta*, GENE ID: 711532), Mamu-F (*M. mulatta*, GENE ID: 709076), Mamu-G (*M. mulatta*, GENE ID: 697260), HFE (*M. mulatta*, GENE ID: 696129), Patr-F (*Pan troglodytes*, GENE ID: 100169977), Patr-E (*P. troglodytes*, GENE ID: 462540), Patr-G (*P. troglodytes*, GENE ID: 494187), Patr-H(*P. troglodytes*, GENE ID: 741554) MHC-G-like (*Gorilla gorilla* GENE ID: 101143843), MHC-E-like (*G. gorilla* GENE ID: 101153360), HFE (*G. gorilla* GENE ID: 101126285). (b) Protein sequence from Genbank included in the analyses have the following accession numbers: HLA-E: BAB63328, HLA-G: BAB63336.1, HLA-F: ABD38924, HLA-H: P01893, Qa-2 (C57BL/6): AAX98170, Qa-2 (C57BL/10): AAB41657, Qa-1b (C57BL/6): NP_034528, Qa-1 (NOD/Lt mice): AAD53968, Qa-1c (B10.RIII): AAD12244.1, Qa-1d (B10.M): AAD31381, HFE (C57BL/6): NP_034554, RT1-M6(BN): NP_001008852, RT1-M4(BN): NP_001161815, RT1-M5(BN): NP_001161825, HFE(BN): NP_445753, MHC-G-partial (*G. gorilla*): AAL40082, MHC-F (*G. gorilla*): AAQ13398, Patr-E (*P. troglodytes*): NP_001038963, MHC-G-partial (*P. troglodytes*): AAK08128, MHC-F (*P. troglodytes*): AAQ13481, HFE (*P. troglodytes*): NP_001009101, MHC-E (*M. mulatta*): NP_001108438, MHC-F (*M. mulatta*): ABD38925, HFE (*M. mulatta*): NP_001247505

with Arithmetic Mean, 1000 bootstra *P* value (http://clustalw.ddbj.nig.ac.jp/). The gene sequence analysis of MHC-F of *G. gorilla* and protein sequence analysis of HLA-H or HFE and MHC-E are not included due to unavailability of proper sequences. It has been observed that nonclassical MHC-I molecules are clustered according to the different types. The protein sequences of nonhuman primates and human have shown maximum homology in case of MHC-G and MHC-F (MHC-G-98-99%, MHC-F-93–98%) whereas they are less conserved in case of MHC-H or HFE and MHC-E (MHC-E-57–64%, HFE or MHC-H-34–35%). Mouse and rat protein sequences are showing maximum identity only in HFE or MHC-H (87%), but for other types of nonclassical MHC-I molecules, they are showing around 50% identity (MHC-G-41–51%, MHC-E-51–53%). Protein sequences of human and nonhuman primates have revealed around 55% homology with rat and mouse and in case of all nonclassical MHC-I molecules (MHC-G-48–50%, MHC-E-56–57%, MHC-F-56–57%). Similar type of observation have been noticed in phylogenetic analyses in earlier studies of MHC-F and MHC-G of human and nonhuman primates.[30,37] In addition, gene sequences analysis of nonclassical MHC-I revealed that there are around 34–90% similarity in case of MHC-G, 53–98% similarity for MHC-E, whereas among MHC-F and MHC-H or HFE have 48–87% and 54–98% similarity, respectively. Similar observation has been reported for MHC-H gene of human and nonhuman primates.[41]

Moreover, it has been observed that human and nonhuman primates share maximum homology among each other for most of the nonclassical MHC-I genes (MHC-E-86–98%, MHC-F-72–87%, MHC-H or HFE-71–98%) as compared to other species [Figure 2a and Table 1].

Involvement of Qa-1/HLA-E and CD94/NKG2 System in Altered Immunity and Diseases

Cellular and molecular basis of Qa-1/HLA-E and CD94/NKG2 system

HLA-E is found to be a ligand for CD94/NKG2A, B and C receptors on NK cells.[42] Moreover, it has been shown that CD94/NKG2A receptor expresses on $CD8^+$ T-cells to induce immune inhibitory effect.[26] NK cells in mouse and human express heteromeric C-type lectin receptors comprising CD94 and NKG2. The NKG2A isoform is expressed more than other isoforms and has immunoreceptor tyrosine-based inhibitory motifs in its cytoplasmic domain, which form heterodimer with CD94 to inhibit NK cell function.[25,43,44]

CD94/NKG2C, an activating NK cell receptor of the C-type lectin superfamily, has been found to bind to HLA-E. Moreover, it noncovalently associates with DNAX-activation protein 12 (DAP12), a membrane receptor containing an immunoreceptor tyrosine-based activating motif (ITAM).[45] NK cells are found to recognize and destroy infected cells through Qa-1/HLA-E and CD94/NKG2 receptors. This "missing-self" phenomenon of NK cells plays a key role in recognizing and destroying abnormal cells. These attributes may facilitate viruses to acquire an important immune escape mechanism deviating host protective immunity.[46,47]

Receptor profile of Qa-1/HLA-E and CD94/NKG2 system

Evidences in the recent past suggest that HLA-E has a role in restricting the $\alpha\beta$ TCR bearing subsets of T-cells.[48,49] Qa-1 and HLA-E are functional homologues, which are known to have an exclusive role in the regulation of NK cells. Moreover, it has been found that NKT cells co-express TCR and NK1.1 receptors.[50-53]

Mouse invariant NKT (iNKT) cells that express NK cell receptors and TCR α chain of Vα14Jα18 (Vα24Jα15 in humans) and a semi variant TCR-β, which are found to be associated with Vβ8 (Vβ11 in humans), Vβ2 and Vβ7 receptors.[50-52] V_α14 TCR recognizes glycolipid antigens, such as α-galactosylceramide and its analogues presented on MHC-I like molecule CD1d.[51,52,54-58] iNKT cells are also known to be associated with CD94/NKG2 receptor subsets for their immunoregulatory role in mammalian immunity.[59] It has been shown that differential co-stimulatory signals can be mediated through CD80/86 and CD40 in antigen-presenting cells interacting with NKT cells expressing CD28 and CD154 respectively.[60] Moreover, these results suggest that CD28-CD80/CD86 and CD40-CD154 co-stimulatory pathways may differentially contribute to regulate Th1 and Th2 associated responses of NKT cells *in vivo*.

Table 1: Similarity matrix of some nonclassical MHC-I gene sequences

	HLA-G	HLA-E	HLA-F	HLA-H	Patr-E *Pan troglodytes*	Patr-G *Pan troglodytes*	Patr-F *Pan troglodytes*	Patr-H *Pan troglodytes*	MHC-G-like *Gorilla gorilla*	MHC-E-like *Gorilla gorilla*	HFE-*Gorilla gorilla*	Mamu-G *Macaca mulatta*	Mamu-E *Macaca mulatta*	Mamu-F *Macaca mulatta*	HFE-*Macaca mulatta*	H-T23	H-Q9	H-Q8	MR2-HFE	RT-M4	RT-M5	HFE|RAT
HLA-G	100																					
HLA-E	66	100																				
HLA-F	72	75	100																			
HLA-H	85	81	83	100																		
Patr-E-*Pan troglodytes*	72	90	66	77	100																	
Patr-G-*Pan troglodytes*	77	56	57	66	59	100																
Patr-F-*Pan troglodytes*	60	52	87	64	61	70	100															
Patr-H-*Pan troglodytes*	85	75	76	98	75	67	64	100														
MHC-G-like *Gorilla gorilla*	82	54	69	73	64	63	53	76	100													
MHC-E-like *Gorilla gorilla*	72	86	69	79	98	57	58	77	64	100												
HFE-*Gorilla gorilla*	72	69	71	73	72	59	58	73	62	70	100											
Mamu-G *Macaca mulatta*	90	80	80	84	82	91	30	84	68	82	88	100										
Mamu-E *Macaca mulatta*	78	94	75	77	93	34	34	77	49	93	87	31	100									
Mamu-F *Macaca mulatta*	82	71	84	77	76	63	72	82	73	77	76	81	75	100								
HFE-*Macaca mulatta*	69	64	70	71	69	57	57	71	59	70	93	87	89	73	100							
H-T23	71	71	69	69	70	50	50	70	60	71	78	65	68	67	77	100						
H-Q9	54	50	57	65	56	44	39	61	45	52	67	68	81	62	66	75	100					
H-Q8	88	81	78	78	72	73	60	74	78	85	76	66	89	71	76	80	94	100				
MR2-HFE	62	59	64	66	64	52	48	65	50	59	58	83	84	68	58	73	60	83	100			
RT-M4	52	57	53	54	53	46	46	52	50	54	73	68	78	46	67	55	56	87	64	100		
RT-M5	71	68	66	67	70	48	48	70	57	71	81	57	68	69	80	64	72	71	76	66	100	
HFE-RAT	63	62	65	67	65	54	53	64	53	61	58	83	86	70	54	71	63	82	82	67	77	100

Percentage of identity obtained from pairwise sequence alignment between nonclassical MHC-I gene sequences of human, nonhuman primates, rat and mouse using Clustal W (DDBJ) [http://clustalw.ddbj.nig.ac.jp/].
MHC: Major histocompatibility complex; HFE: High Fe; HLA: Human leukocyte antigen

Table 2: Similarity matrix of some nonclassical MHC-I protein sequences

	C57BL/6|Qa-2	C57BL/10|Qa-2	7BL/6|Qa-1b	NOD/Lt|Qa-1	B10.RIII|Qa-1c	B10.M|Qa-1d	HFE C57BL/6	BN|RT1-I|M6	BN|RT1-Ib|M5	BN|RT1-Ib|M4	HFE|BN	HLA-E	HLA-G	HLA-F	HLA-H	MHC-G-*Gorilla gorilla*-partial	MHC-F-*Gorilla gorilla*	MHC-E-*Pan troglodytes*	MHC-G-*Pan troglodytes*-partial	MHC-F-*Pan troglodytes*	HFE-*Pan troglodytes*	MHC-E-*Macaca mulatta*	MHC-F-*Macaca mulatta*	HFE-*Macaca mulatta*
C57BL/6|Qa-2	100																							
C57BL/10|Qa-2	87	100																						
C57BL/6|Qa-1b	72	71	100																					
NOD/Lt|Qa-1	70	70	89	100																				
B10.RIII Qa-1c	73	72	98	89	100																			
B10.M|Qa-1d	72	71	98	89	98	100																		
HFE-C57BL/6	31	34	33	34	33	33	100																	
BN|RT1-I|M6	51	49	49	48	49	49	26	100																
BN|RT1-Ib|M5	58	56	51	51	50	51	31	50	100															
BN|RT1-Ib|M4	52	52	53	51	52	52	29	47	52	100														
HFE|BN	33	34	32	33	32	32	87	27	31	30	100													
HLA-E	62	62	61	61	62	62	33	51	56	56	32	100												
HLA-G	64	63	62	59	62	61	34	48	58	58	34	75	100											
HLA-F	64	62	60	57	60	60	32	51	57	56	30	72	78	100										
HLA-H	65	64	59	59	59	59	33	53	57	56	32	74	79	80	100									
MHC-G-*Gorilla gorilla*-partial	65	61	67	64	67	67	35	50	61	59	34	77	99	79	79	100								
MHC-F-*Gorilla gorilla*	64	62	60	58	60	60	32	51	57	56	32	72	77	97	79	78	100							
MHC-E-*Pan troglodytes*	64	62	64	61	64	64	33	51	58	57	33	97	76	73	76	78	73	100						
MHC-G-*Pan troglodytes*-partial	65	61	67	64	67	66	35	49	60	60	34	77	99	78	79	98	77	78	100					
MHC-F-*Pan troglodytes*	64	62	61	59	61	61	32	48	56	55	32	72	78	98	79	78	97	73	78	100				
HFE-*Pan troglodytes*	34	35	33	33	33	33	68	27	32	31	69	34	35	34	35	36	34	34	36	34	100			
MHC-E-*Macaca mulatta*	64	62	64	63	64	64	33	48	54	57	33	84	78	76	77	81	75	85	80	74	35	100		
MHC-F-*Macaca mulatta*	64	61	60	58	60	60	32	50	56	54	29	70	77	93	77	77	93	71	77	93	34	74	100	
HFE-*Macaca mulatta*	34	34	33	33	33	33	68	27	32	30	68	33	35	34	34	36	33	33	36	33	94	35	33	100

Percentage of identity obtained from pairwise sequence alignment between nonclassical MHC-I protein sequences of human, nonhuman primates, rat and mouse strains using Clustal W (DDBJ). [http://clustalw.ddbj.nig.ac.jp/]. MHC: Major histocompatibility complex; HFE: High Fe; HLA: Human leukocyte antigen

However, the specific role of NKT cells in association to CD94/NKG2 and co-stimulatory responses needs further investigation.

Involvement of Qa-1/HLA-E and CD94/NKG2 system in autoimmune diseases

It has been suggested that induction of immunosuppressive $CD8^+$ T-cells may be restricted by MH-Ib/Qa-1 to regulate $CD4^+$ T-cell response.[61,62] Moreover, most of the MHC class Ib molecules along with β_2 microglobulin (β_{2m}) molecules are known to have interaction with CD8 co-receptors. TCR mediated suppression of $CD4^+$ T-cell response by Qa-1 restricted $CD8^+$ Treg cells has been demonstrated in an autoimmunity mice model of experimental autoimmune encephalomyelitis (EAE).[63] Moreover, it has been shown that the Qa-1-CD94/NKG2A mediated $CD8^+$ Treg cell activity or activation may lead to complete restriction of EAE development. It has been shown that Qa-1 restricted a specific population of $CD8\alpha\alpha^+$ Tregs can regulate EAE antigen-specific $V\beta8.2^+$ $CD4^+$ T-cell response.[64]

High CD94/NKG2A expression by T-cells has been demonstrated in remission patients following tumor necrosis factor (TNF) based TNF inhibitor therapy compared to active rheumatoid arthritis. Low CD94/NKG2A expression has been associated with disease severity following withdrawal of therapy.[65] In systemic lupus erythematosus patients, negative correlation of CD69 with CD94/NKG2A inactivated $\gamma\delta$ TCR bearing T-cell ($\gamma\delta^+$ T-cell) reveals that down-regulation of CD94/NKG2A may be due to over-activation of such $\gamma\delta^+$ T-cell.[66]

Involvement of Qa-1/HLA-E and CD94/NKG2 system in infectious diseases

It has been proposed that CD94/NKG2 heterodimers may co-stimulate effector functions of differentiated Th1 cells.[67] There are several reports which show CD94/NKG2 expression is markedly up-regulated on $CD8^+$ T-cells during viral and bacterial infections.[68,69] It has been shown that CD94/NKG2 is capable of hindering the CTL activity against Qa-1 and HLA-E positive cells[43] and recently it has been proposed that it may be involved in attenuation of activation induced cell death, which may possibly help in $CD8^+$ T-cell survival during *Listeria monocytogenes* infection.[70]

Several reports on the role of MHC-Ib for viral diseases are available.[71-73] MHC-Ib like HLA-G is found to be over-expressed or up-regulated in immune cells, which is found to be immune suppressive in nature during viral infections. In some viruses like human cytomegalovirus infection, HLA-G is found to be down-regulated by viral US10 protein, unlike classical HLAs.[74] However, nonclassical MHC-I, such as HLA-G is found to be resistant to HIV Nef protein mediated cell surface down-regulation.[75]

Involvement of Qa-1/HLA-E and CD94/NKG2 system in cancer, immune privilege and altered immunity

Association of CD94/NKG2 receptors is found in several cancers, where CD94/NKG2A receptors are found to be widely expressed in tumor infiltrating T-cells. They are found to be involved in blocking tumor lytic activity.[76] In cervical cancer, it has been reported that CD94/NKG2A receptors are up-regulated in tumor infiltrating T-cells compared to normal cervix. This is also found to be correlated with secretion of cytokines like transforming growth factor-beta and interlukin-15 by cervical cancer, which may elevate the CD94/NKG2A receptors.[77] Moreover, it has been shown that Interferon gamma treatment may protect ovarian carcinoma cell lines from CTL lysis through human nonclassical MHC-Is and CD94/NKG2A-dependent mechanism.[78]

In a study with ocular anterior chamber associated immune deviation model in mice, CD94/NKG2 deficient DBA/2J strain of mice have been compared to other mouse strains, where the functional significance of Qa-1-CD94/NKG2A system has been demonstrated in peripheral immune suppression as evident by suppression of antigen-specific delayed-type hypersensitivity (DTH) [Table 3 and Figure 3].[79] Moreover, it has been shown that compatibility of Qa-1 haplotype between $CD8^+$ Tregs cells and the immunized recipients is a prerequisite for $CD8^+$ Tregs to suppress the expression of antigen-specific DTH in the recipient mice.[80] The expression of Qa-2, a nonclassical MHC-Ib, has been reported in the corneal endothelium and other substructure lining of the ocular anterior chamber, which suggests that Qa-2 protein may also contribute to the immune-privileged status of the mammalian eye.[81]

Table 3: Examples of mouse strains responsive to CD94/NKG2A-Qa-1 associated suppression of antigen specific DTH

Mice strain	Suppression of DTH by ACAID	Haplotype	Expression of CD94/NKG2A
BALB/C	+	H-2d	+
C57BL/6	+	H-2b	+
DBA/2NCr	+	H-2d	+
DBA/2NHsd	+	H-2d	+
DBA/2J	–	H-2d	–

Except DBA/2J mouse strain, which are naturally deficient in CD94/NKG2A gene expression, most of the mice strains having either H-2d or H-2b haplotypes are responsive to ACAID mediated peripheral immune suppression, as evident by suppression antigen specific DTH.[79] DTH: Delayed type hypersensitivity; ACAID: Anterior chamber associated immune deviation

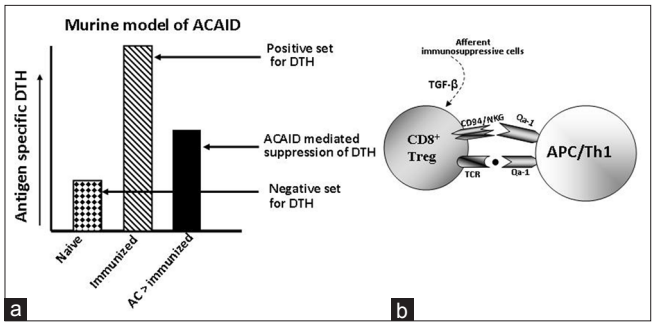

Figure 3: Qa-1-CD94/NKG2A dependent suppression of delayed type hypersensitivity (DTH) response in anterior chamber associated immune deviation (ACAID) model in mice. ACAID associated suppression of antigen specific DTH is observed in CD94/NKG2A expressing mouse strain, but not in CD94/NKG2A deficient DBA/2J mice.[79] (a) Schematic representation of ACAID model, which illustrate ACAID mediated suppression of antigen mediated DTH in mice. (b) Suggested role of CD94/NKG2A-Qa-1 system for $CD8^+$ immunosuppressive Tregs in ACAID[79], where transforming growth factor beta may influence the generation of $CD8^+$ Tregs[104-107]

Several groups have demonstrated the involvement of CD94/NKG2 receptors in modulation and regulation of NK cells.[82] However, a study conducted by Vance *et al.* showed that DBA/2J strain of mice is naturally deficient in CD94/NKG2A receptor expression in adult and neonatal NK cells without disturbing neonatal development. This work suggests that immunological self-tolerance of neonatal NK cells may not be attributed to CD94/NKG2A expression.[83]

Among MHC-Ib molecules, membrane-bound HLA-G and HLA-E have been reported in invasive extravillous trophoblast (EVT) cells and trophoblast cells of decidual tissues, respectively.[84,85] HLA-G interacts with membrane-bound inhibitory receptors, immunoglobulin-like transcript-2 and -4 (ILT-2 and ILT-4) of monocytes, macrophages, and dendritic cells, respectively.[86,87] It has also been demonstrated that HLA-G may up-regulate ILT-2, ILT-4 and killer-cell immunoglobulin-like receptor-2DL4 on the membrane of antigen presenting cells, NK cells and $CD4^+$ T-cells without preceding for antigenic co-stimulation.[88] Soluble and membrane-bound HLA-G proteins are found to induce inhibition of T-cell alloproliferation through both ILT-2 and ILT-4.[89] Leukocyte immunoglobulin-like receptor-1 (LIR-1) has been reported to express on surface of a large subpopulation of NK cells, particularly in deciduas and appears to be HLA-G specific, which has immunoregulatory importance during pregnancy.[90] Numerous studies indicate that G*0105N allele frequency increases in recurrent miscarriages and that may function as a risk factor for such loss of pregnancy.[91,92] However, some reports contradict the role of HLA-G in fetal survival by the detection of G*0105N allele in homozygous adults.[93,94] Another study suggests that soluble HLA-G (sHLA-G) is present in seminal plasma, and HLA-G is expressed in normal testis and epididymal tissue of male reproductive system. It gives an indication of possible immunoregulatory role of HLA-G in the male reproductive system.[95]

HLA-E is found to regulate CD94/NKG2A receptor-mediated cytolytic activity of NK cells during pregnancy.[85] In another report it has been suggested that HLA-E has a high affinity for NKG2A receptor, which has an inhibitory role than activating NKG2C receptor.[96] Kusumi *et al.* showed that NKG2A receptors are expressed in most of the decidual $CD56^{bright}$ NK cells rather than peripheral $CD56^{dim}$ NK cells. NKG2C expression in $CD56^{dim}$ is reciprocal to inhibitory NKG2A. In decidual $CD56^{bright}$ NK cells NKG2A and NKG2C receptors are known to be expressed simultaneously.[97]

In 2003, Ishitani *et al.* has reported the surface expression of HLA-F in placenta and low expression in syncytiotrophoblast (ST) cells, villous trophoblast (VT) cells and invasive EVT cells.[98] It is contradicting to a study by Nagamatsu *et al.* where they have found the intracellular expression of HLA-F only in EVT, ST and VT. This variation is probably because they have investigated the placenta from the first stage of

gestation, but not of later stages.[99] HLA-F is found to interact with ILT-2 and ILT-4, which expressed on the surface of monocytes and $CD19^+$ B cells, but not on $CD56^+$ NK cells or $CD3^+$ T-cells.[100]

In tumors such as malignant larynx lesions, HLA-G expression is elevated in benign and premalignant lesions and is reduced in invasive carcinomas and in associated draining cervical lymph nodes. However, HLA-E expression was found to be elevated with increased lesion grade, suggesting the expression of HLA-G as an indicator of tumor invasiveness in malignant laryngeal lesions.[101] In ovarian cancer, it is found that the expression of HLA-E plays an important role in neutralizing CTL infiltration. Low expression of HLA-E is found to be associated with enhanced survival rate.[102] Recently, in the mouse B16 melanoma tumor model, it has been showed that activation of $CD4^+$ Foxp3 – T-cells enable melanoma metastasis, which is mediated by Qa-1 dependent suppression of NK-cell cytotoxicity.[103]

Summary and Future Perspective

Here, we have reviewed the gene organization of nonclassical MHC, their phylogenetic analysis and important updates on their interaction with receptors such as TCR, CD94/NKG2 in T, NK, and NKT cells. Moreover, the association of Qa-1/HLA-E to CD94/NKG2 receptor systems with the pathological state of some important diseases and its relation to altered host cell immunity has also been discussed. In brief, the nonclassical MHCs and its receptors CD94/NKG2 are found to be involved in maintaining immune privilege, immune surveillance as a mammalian host protective and beneficial response. However, their effect can be detrimental through an immunosuppressive response during viral infection and cancer/tumor progression. There are many more questions which remain to be explored in future regarding the biology of non-classical MHC-I molecules. Accordingly, specificity of these evolutionary conserved, less-polymorphic, nonclassical MHCs and their receptors towards modulating adaptive immunity is still under investigation. Further studies are warranted to open up new avenues in understanding the nonclassical MHC responses in the perspective of genetic, evolutionary and immunological studies.

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