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

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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.

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

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.[6] However, in mice and...
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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,
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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 with Arithmetic Mean method as implemented by Clustal w (DDBJ), Bootstraps and indicated.

![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. Phylogenetic tree is constructed by Unweighted Pair Group Method with Arithmetic Mean method as implemented by Clustal w (DDBJ), Bootstraps and 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 (Maca 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-H (P. troglodytes, GENE ID: 7415544) MHC-G-like (Gorilla gorilla GENE ID: 101114112), MHC-F-like (G. gorilla GENE ID: 101143360), 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/10): GAA6157, Qa-1b (C57BL/10): NP_034528, Qa-1 (NOD/Lt mice); AAD3968, Qa-1c (B10.RIII): AAD12244.1, Qa-1d (B10.M): AAD31381, HFE (C57BL/6): NP_034554, RT1-M6(BN): NP_00108852, 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_00108853, MHC-G-partial (P. troglodytes): AAQ0812, MHC-F (P. troglodytes): AAQ13481, HFE (P. troglodytes): NP_00109101, MHC-E (M. mulatta): NP_001108438, MHC-F (M. mulatta): ABD3925, HFE (M. mulatta): NP_001247505.](image)
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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 MCH-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.[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 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 |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 TCRal chain of Vα14Jα18 (Vα24Jα15 in humans) and a semi variant TCRβ, which are found to be associated with Vβ8 (Vβ11 in humans), Vβ2 and Vβ7 receptors.[50-52] V'14 TCR recognizes glycolipid antigens, such as α-galactosylceramide and its analogues presented on MHC-I like molecule CD1d.[51,52,54-56] InNKT 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 | Patr-G | Patr-F | Patr-H | MHC-G-like | MHC-E-like | HFE-Gorilla | Gorilla gorilla | HFE-Gorilla | Gorilla gorilla | Mamu-G | Mamu-E | Mamu-F | HFE-H | H-T23 | H-Q9 | H-Q8 | MR2-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-Maca mulatta | 90  | 80    | 80    | 84    | 82     | 91     | 30     | 84     | 68        | 82        | 88        | 100        |            |              |        |        |        |        |        |        |        |                |         |
| Mamu-E-Maca mulatta | 78  | 94    | 75    | 77    | 93     | 34     | 34     | 77     | 49        | 93        | 87        | 31        | 100        |            |        |        |        |        |        |        |        |                |         |
| Mamu-F-Maca mulatta | 82  | 71    | 84    | 77    | 76     | 63     | 72     | 82        | 73        | 77        | 76        | 81        | 75        | 100        |            |        |        |        |        |        |        |        |                |         |
| HFE-Maca 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 | 69    | 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| C57BL/10| NOD/Lt| B10.RIII | B10.M| HFE-C57BL/6 | BN|RT1-I|BN|RT1-Ib|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 trogodytes | MHC-G-Pan trogodytes-partial | MHC-F-Pan trogodytes | HFE-Pan trogodytes | MHC-E-Macaca mulatta | MHC-F-Macaca mulatta | MHC-G-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        | 98    | 100         |    |     |    |     |    |      |     |     |        |       |       |       |                       |                     |                  |                     |                  |                  |                     |                     |                     |
| HFE-C57BL/6   | 31      | 34      | 33      | 34      | 33    | 100         |    |     |    |     |    |      |     |     |        |       |       |       |                       |                     |                  |                     |                  |                  |                     |                     |                     |
| BN|RT1-I|M6      | 51      | 49      | 49      | 49      | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 49    | 26     | 100   |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| BN|RT1-Ib|M5      | 58      | 56      | 51      | 51      | 50    | 51    | 51    | 51    | 51    | 51    | 51    | 51    | 51    | 51    | 51    | 51    | 100   |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| BN|RT1-Ib|M4      | 52      | 52      | 53      | 51      | 52    | 52    | 52    | 52    | 52    | 52    | 52    | 52    | 52    | 52    | 52    | 32     | 100   |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| HFE|BN      | 33      | 34      | 32      | 32      | 32    | 32    | 32    | 32    | 32    | 32    | 32    | 32    | 32    | 32    | 32    | 27     | 100   |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| HLA-E       | 62      | 62      | 61      | 62      | 62    | 63    | 34    | 48    | 58    | 58    | 34    | 75    | 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    | 100   |       |       |       |       |       |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| HLA-H       | 65      | 64      | 59      | 59      | 59    | 59    | 33    | 53    | 57    | 56    | 32    | 74    | 99    | 100   |       |       |       |       |       |                     |                     |                  |                     |                  |                  |                     |                     |                     |
| MHC-G-Gorilla gorilla-partial | 65 | 61 | 67 | 64 | 67 | 67 | 35 | 50 | 61 | 59 | 34 | 77 | 99 | 79 | 79 | 79 | 79 | 100 |
| MHC-F-Gorilla gorilla | 64 | 62 | 60 | 58 | 60 | 60 | 32 | 51 | 57 | 56 | 32 | 72 | 77 | 97 | 79 | 78 | 78 | 100 |
| MHC-E-Pan trogodytes | 64 | 62 | 64 | 61 | 64 | 64 | 33 | 51 | 58 | 57 | 33 | 97 | 76 | 73 | 76 | 78 | 73 | 100 |
| MHC-G-Pan trogodytes-partial | 65 | 61 | 67 | 64 | 67 | 66 | 35 | 49 | 60 | 60 | 34 | 77 | 99 | 78 | 79 | 98 | 77 | 78 | 100 |
| MHC-F-Pan trogodytes | 64 | 62 | 61 | 59 | 61 | 61 | 32 | 48 | 56 | 55 | 32 | 72 | 78 | 98 | 79 | 78 | 97 | 73 | 78 | 100 |
| HFE-Pan trogodytes | 34 | 35 | 33 | 33 | 33 | 33 | 33 | 68 | 27 | 32 | 31 | 69 | 34 | 35 | 34 | 35 | 36 | 34 | 36 | 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 |
| MHC-G-Macaca mulatta | 34 | 34 | 33 | 33 | 33 | 33 | 33 | 68 | 27 | 32 | 30 | 68 | 33 | 35 | 34 | 34 | 36 | 33 | 36 | 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. Moreover, most of the MHC class Ib molecules along with β2 microglobulin (β2m) 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). 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 CD8αα+ Tregs can regulate EAE antigen-specific Vβ8.2+ CD4+ T-cell response.

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. In systemic lupus erythematosus patients, negative correlation of CD69 with CD94/NKG2A inactivated γδ TCR bearing T-cell (γδ+ T-cell) reveals that down-regulation of CD94/NKG2A may be due to over-activation of such γδ+ T-cell.

**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. There are several reports which show CD94/NKG2 expression is markedly up-regulated on CD8+ T-cells during viral and bacterial infections. It has been shown that CD94/NKG2 is capable of hindering the CTL activity against Qa-1 and HLA-E positive cells 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.

Several reports on the role of MHC-Ib for viral diseases are available. 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. However, nonclassical MHC-I, such as HLA-G is found to be resistant to HIV Nef protein mediated cell surface down-regulation.

**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. 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 interleukin-15 by cervical cancer, which may elevate the CD94/NKG2A receptors. 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.

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]. 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. 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.
Several groups have demonstrated the involvement of CD94/NKG2 receptors in modulation and regulation of NK cells. 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.

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. 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. 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. Soluble and membrane-bound HLA-G proteins are found to induce inhibition of T-cell alloproliferation through both ILT-2 and ILT-4. 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.

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. However, some reports contradict the role of HLA-G in fetal survival by the detection of G*0105N allele in homozygous adults. 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.

HLA-E is found to regulate CD94/NKG2A receptor-mediated cytolytic activity of NK cells during pregnancy. 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. 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.

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. 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 pregnancy.

### 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. ACAID: Anterior chamber associated immune deviation; DTH: Delayed type hypersensitivity; ACAID: Anterior chamber associated immune deviation.
gestation, but not of later stages. 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.

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. 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.

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.

**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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