Arch. Immunol. Ther. Exp. (2011) 59:353–367
DOI 10.1007/s00005-011-0137-y

REVIEW

Clinical Significance of the HLA-E and CD94/NKG2 Interaction

Milena Iwaszko · Katarzyna Bogunia-Kubik

Received: 4 January 2011 / Accepted: 26 April 2011 / Published online: 29 July 2011

Abstract HLA-E belongs to the non-classical HLA (class Ib family) broadly defined by a limited polymorphism and a restricted pattern of cellular expression. So far, only two functional alleles differing at only one amino acid position (non-synonymous mutation) in the α2 heavy chain domain, where an arginine in position 107 in HLA-E*0101 is replaced by a glycine in HLA-E*0103, have been reported. The interaction between non-classical HLA-E molecule and CD94/NKG2A receptor plays a crucial role in the immunological response involving natural killer (NK) cells and cytotoxic T lymphocytes. All proteins forming CD94/NKG2 receptors are encoded by genes situated in the same cluster on chromosome 12, allowing tight control over the order of their expression. The inhibitory members of the NKG2 receptor family are available on the cell surface before activating the members to prevent autoimmune incidents during immune cells' ontogenesis. In the present review, the potential role of this interaction in viral infection, pregnancy and transplantation of allogeneic hematopoietic stem cells (HSC) is presented and discussed. The review will also include the effect of HLA-E polymorphism on the outcome of HSC transplants in humans.

Keywords HLA-E · CD94/NKG2 receptor · Pregnancy · Viral infections · Transplantation of hematopoietic stem cells

M. Iwaszko · K. Bogunia-Kubik (✉)
L. Hirszfeld Institute of Immunology and Experimental Therapy, Polish Academy of Sciences, R. Weigla 12, 53-114 Wrocław, Poland
e-mail: bogunia@iitd.pan.wroc.pl

Organization and Expression of Genes within the CD94/NKG2 Cluster

Genes encoding primate and murine CD94/NKG2 receptor components are grouped into a cluster. In humans, this cluster is located on chromosome 12. The genes inside the cluster follow the order: *CD94 (KLRD1), NKG2D (KLRK1), NKG2F (KLRC4), NKG2E (KLRC3), NKG2C (KLRC2), NKG2A (KLRC1)* (Fig. 1). Sequences of these genes and their order in the cluster are well conserved in primates (Glienke et al. 1998; Sobanov et al. 1999; Vance et al. 1999). The ability to be inhibited has primary importance for natural killer (NK) cells in order to prevent autoimmune incidents. Therefore the expression of CD94/NKG2 receptors in NK cells has a predefined order: the first available protein is usually CD94, then inhibiting members of the NKG2 family and finally activating members (Lian et al. 2002).

The *CD94* gene is located at the beginning of the sequence of genes in the CD94/NKG2 cluster. It has two promoters and six exons producing six known different alternatively spliced transcripts. Both promoters have interferon (IFN)-γ and ETS binding sites, but they differ in sensitivity to interleukin (IL)-2 and IL-15 (Lieto et al. 2003; Rodríguez et al. 1998). The six known transcripts are: CD94, CD94b, CD94-T4, CD94-T2, CD94B-T2 and CD94-T3. Despite slight differences at the RNA level, both CD94 and CD94b transcripts encode similar proteins. CD94-T4 transcript encodes a variant of CD94 protein, which lacks a stem region, whose preferred ligand is NKG2B. The latter three transcripts CD94-T2, CD94B-T2 and CD94-T3 encode proteins that do not associate with NKG2 ligands and their expression is restricted to intracellular compartments (Lieto et al. 2006).

The protein encoded by the *CD94* gene has a short cytoplasmic domain. The structure of extracellular portion

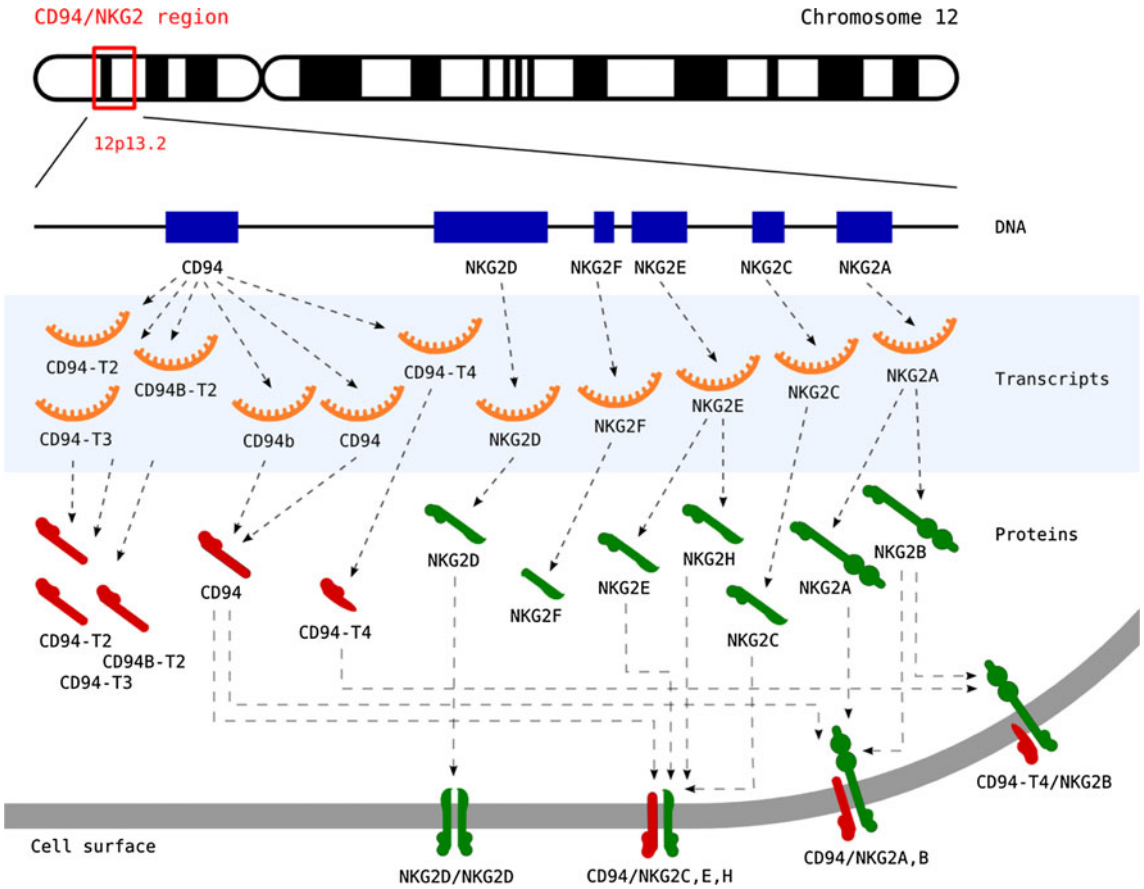

Fig. 1 Schematic representation of the *CD94 / NKG2* gene cluster on chromosome 12 and its products. The *CD94* gene produces six known different alternatively spliced transcripts. Despite slight differences at the RNA level, both CD94 and CD94b transcripts encode similar proteins. CD94-T4 transcript encodes a variant of CD94 protein, which lacks a stem region, whose preferred ligand is NKG2B. The latter three transcripts CD94-T2, CD94B-T2 and CD94-T3 encode proteins that do not associate with NKG2 ligands and their expression is restricted to intracellular compartments (Lieto et al. 2006). From seven described NKG2 family members only NKG2D and NKG2F do not form a heterodimer with CD94 protein. The inhibitory molecules: NKG2A and NKG2B are alternatively spliced variants of the same transcript of the NKG2A gene (Braud et al. 1998a; Lee et al. 1998b). NKG2C, NKG2E, NKG2F and NKG2H are proteins with activating functionality (Lanier et al. 1998). NKG2E and NKG2H are alternatively spliced variants of the same transcript of the NKG2E gene (Braud et al. 1998a; Lee et al. 1998b). NKG2D protein forms a homodimer with a short cytoplasmic tail. NKG2F protein lacks an extracellular domain

has a variation of the classical C-type lectin fold. It is unlikely that this protein uses this domain, because its carbohydrates and Ca^{2+} binding sites appear to be non-functional (Boyington et al. 1999). CD94 molecule can be expressed as a homodimer (Pérez-Villar et al. 1996), but it is mainly expressed as a heterodimer with CD94 disulfide linked to NKG2A, NKG2B, NKG2C, NKG2E or NKG2H protein (Borrego et al. 2006).

The evidence suggests that the *NKG2* gene cluster arose via gene duplication mechanisms from a common ancestral gene. It is probable that an initial duplication event gave rise to *NKG2A* and a second gene that underwent subsequent duplications to result in *NKG2F* and finally *NKG2C* i *NKG2E*. All *NKG2* family member genes are oriented in the same direction. All these genes show high similarity in structure of their exon–intron sequences (Sobanov et al. 1999). Moreover, in all NKG2 family members the distribution of LINE elements is similar (Plougastel and Trowsdale 1997). Amino acid sequences of proteins encoded by *NKG2A*, *NKG2C*, *NKG2E* and *NKG2F* genes are highly similar. The sequences differ mostly in parts coding intracellular regions of the proteins, allowing them to cover different internal signaling abilities. The sequences coding extracellular regions of the proteins are highly conserved to provide unbiased ligation with the CD94 counterpart to each family member. On the other hand, the amino acid sequence of NKG2D shows no more similarity to any other member of the NKG2 family than to CD94 (Glienke et al. 1998; Borrego et al. 2002).

NKG2 proteins consist of an extracellular lectin-like domain, as well as transmembrane and cytoplasmic segments. There are seven described NKG2 family members:

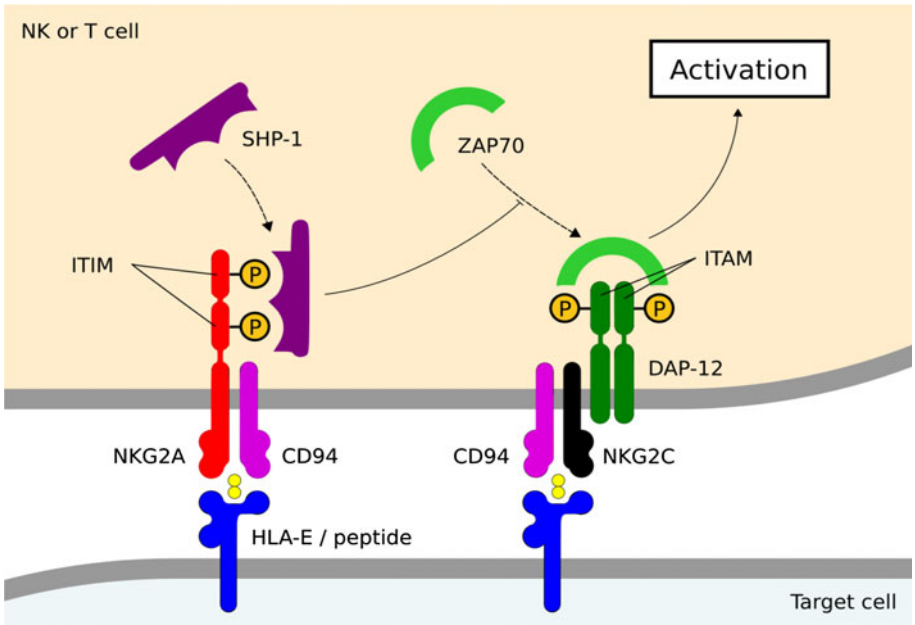

Fig. 2 Activating and inhibitory signal transduction and regulation in NK cells or CTLs. The CD94/NKG2C activating receptor's (shown on the right in *purple* and *black*) interaction with peptide-presenting HLA-E molecule (*blue*) leads to binding of adapter molecule DAP-12 (*dark green*) containing immunoreceptor tyrosine-based activation motifs (ITAM), which in turn interact with ZAP70 protein (*light green*), triggering the signal cascade resulting in NK or T cell activation. The CD94/NKG2A inhibitory receptor (shown on the left in *red* and *purple*) interaction with peptide-presenting HLA-E molecule (*blue*) results in phosphorylation of NKG2A immunoreceptor tyrosine-based inhibition motifs (ITIM) leading to recruitment of SHP-1 protein (*dark purple*), which causes dephosphorylation of ZAP70 protein, preventing its ability to bind ITAM domains, thus restraining the activatory pathway (Mingari et al. 2005; Moretta and Moretta 1997)

NKG2A, NKG2B, NKG2C, NKG2D, NKG2E, NKG2F and NKG2H. Only NKG2D and NKG2F do not form a heterodimer with CD94 protein. NKG2A and NKG2B have inhibiting functionality. They are alternatively spliced variants of the same transcript of the *NKG2A* gene. They contain two immunoreceptor tyrosine-based inhibition motif (ITIM) domains in cytoplasmic regions and their extracellular regions recognize HLA-E (Fig. 2) (Braud et al. 1998a; Lee et al. 1998b). NKG2C, NKG2E, NKG2F and NKG2H are proteins with activating functionality. Although they recognize HLA-E, they contain no ITIM domains. Instead, they have a positively charged residue in the transmembrane region that binds the adapter molecule DAP-12, which contains the immunoreceptor tyrosine-based activation motif (Fig. 2) (Lanier et al. 1998). NKG2E and NKG2H are alternatively spliced variants of the same transcript of the *NKG2E* gene (Braud et al. 1998a; Lee et al. 1998b). NKG2D protein forms a homodimer with a short cytoplasmic tail. Beside NK cells, it is also expressed on T lymphocytes and macrophages. NKG2D binds DAP-10 adapter protein (Wu et al. 1999). NKG2D recognizes stress-inducible MHC class I chain-related molecules MICA and MICB, as well as at least four UL16-binding proteins: ULBP1–4 (Bauer et al. 1999). NKG2F protein lacks an extracellular domain due to a frame shift mutation resulting in a premature stop codon caused by an insertion within its fourth exon.

There is a dozen or so polymorphisms detected within the CD94/NKG2 gene cluster. Though no variation was detected in coding regions of *CD94* gene, it has SNP at position c. −134 A>T (5′UTR). Within the *NKG2* genes following variations were detected. In the *NKG2A* gene c. −4258 C>G (in promoter region); c. −169 G>A (5′UTR), c. −314 A>G (intron 1), c. 28467_62 delAA ACTT (intron 3), c. 338-90 G>A (intron 4), c. 1015 C>T (3′UTR), c. 1077 C>T (3′UTR), c. 1146_1150 delGATTT (3′UTR) and c. 238 T>A (Cys80Ser). The *NKG2C* gene has c. 5 G>A (Ser2Asn) (exon 1), c. 305 C>T (Ser102Phe) (exon 3), c. 287-29 T>A (exon 3) and c. 704_705 GC>AA (exon 6). Finally in *NKG2D* there are rs2255336 (G>A, Ala72Thr) (exon 6), rs1049172 (A>G, Thr208Thr) (exon 10) and rs1049174 (G>C, 3′UTR) (Hikami et al. 2003; Park et al. 2008; Seo et al. 2007).

Several studies reported an association between the polymorphisms within the *CD94/NKG2* cluster and diseases. The *NKG2A* SNPs c. −4258*C and c. 338-90*G, as well as the *CD94* SNP c. −134*T were connected with decreased risk of Behçet's disease (Seo et al. 2007). Moreover, the *NKG2A* c. 338-90*AA, *NKG2C* 102 Ser/Ser, and *NKG2D* 72*Ala/Ala were significantly correlated

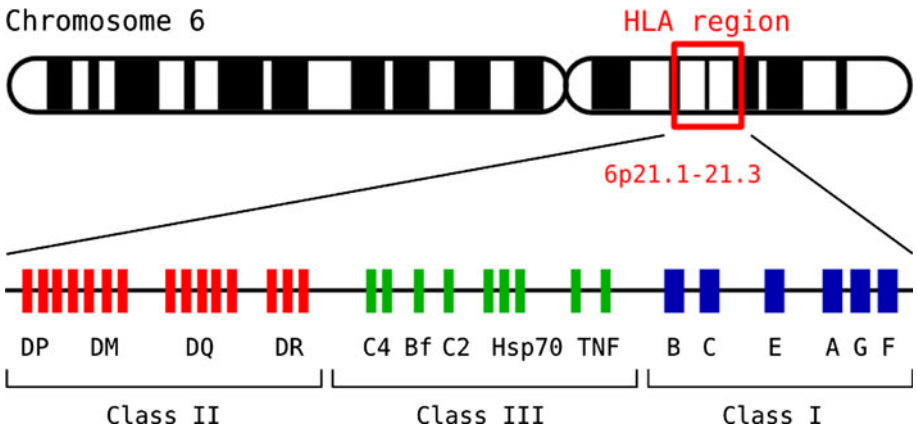

Fig. 3 Schematic representation of the human MHC gene complex on chromosome 6. HLA class I and class II genes are shown in *blue* and *red*, respectively. Non-HLA class III genes are marked in *green*

with rheumatoid arthritis (Park et al. 2008). Systemic lupus erythematosus was linked to the presence of rs2255336 GG Ala/Ala SNP in the *NKG2D* gene (Kabalak et al. 2010). Another study shown that this gene polymorphism rs1049174 has influence on post-transplant mortality rate in HLA fully matched unrelated bone marrow transplantations. This SNP is a single locus featuring a G-C substitution distinguishing between the HNK1 (G) and LNK1 (C) haplotypes. The patients with standard risk disease receiving transplants from donors with the HNK1 haplotype had a significantly better 5-year overall survival and lower transplant-related mortality (TRM) rate than those receiving transplants from donors without the HNK1 haplotype (Espinoza et al. 2009). The same genotype was found to be associated with a decreased risk of colorectal cancer (Furue et al. 2008).

HLA-E as a Representative of Non-Classical HLA Molecules

Major histocompatibility complex (MHC), human leukocyte antigens (HLA) in man, is a highly polymorphic system. The complex of genes encoding the HLA system is found on the sixth chromosome and contains over a hundred genes. Its primary function is antigen binding and presentation. The high variability of MHC molecules is a consequence of selection pressures to counteract the parasites' adaptability.

HLA molecules are divided into two classes: I and II. Class I contains Ia classical molecules (HLA-A, HLA-B and HLA-C) and Ib non-classical molecules (HLA-E, HLA-F, HLA-G, MICA and MICB). Class II is similarly divided into classical (HLA-DP, HLA-DQ, HLA-DR) and non-classical (HLA-DM, HLA-DO) molecules. More polymorphic HLA class Ia genes are expressed in most tissues, while relatively conserved class Ib genes have restricted tissue distribution. Among class Ib genes one of the better studied genes is HLA-E. It has relatively wide tissue distribution, yet its expression level is still lower than the expression levels of most of the HLA class Ia genes. All these genes are concentrated in one region on chromosome 6 (Fig. 3).

The HLA-E gene consists of eight exons. The first one encodes leader peptide. The next three exons encode domains $\alpha 1$, $\alpha 2$ and $\alpha 3$, respectively. The fifth exon encodes the transmembrane region and the last two exons encode the intracellular portion of the protein.

HLA class I molecules are assembled from two protein chains, light and heavy. The light chain, β-microglobulin, is similar in most MHC class I proteins and is encoded by a gene positioned outside of the MHC gene complex, on chromosome 15. The heavy chain protein consists of a long extracellular N-tail, short transmembrane and short intracellular regions. The extracellular tail is built from three domains: $\alpha 1$, $\alpha 2$ and $\alpha 3$. The first two domains are highly polymorphic. They are responsible for variation of MHC class I molecules between individuals. Both $\alpha 1$ and $\alpha 2$ domains consist of one α helix and four β folds. Together they form a peptide-binding groove with eight β folds at its bottom and two α helices as its edges. Inside the groove there are pockets with anchor amino acids, which have the ability to bind leader peptide molecules. Unlike classical MHC-I proteins' binding sites, which are typically constrained only at two or three positions, HLA-E has five anchor residues at positions P2, P3, P6, P7 and P9. This imposes stringent restrictions on the sequence of peptides capable of binding to HLA-E (Sullivan et al. 2008).

The leader peptides come from signal sequences of transmembrane proteins, mostly leader from HLA class I proteins. During translocation of the protein its signal sequence is cut by signal peptidase. The sequence remains in the membrane, where it is cleaved by signal peptide peptidase, and its hydrophilic N-part is released to the cytosol (Lemberg et al. 2001). The hydrophilic oligopeptide is processed further by proteasome, resulting in leader peptide (Bland et al. 2003). Transporters associated with antigen processing (TAP) cooperating with tapasin carry

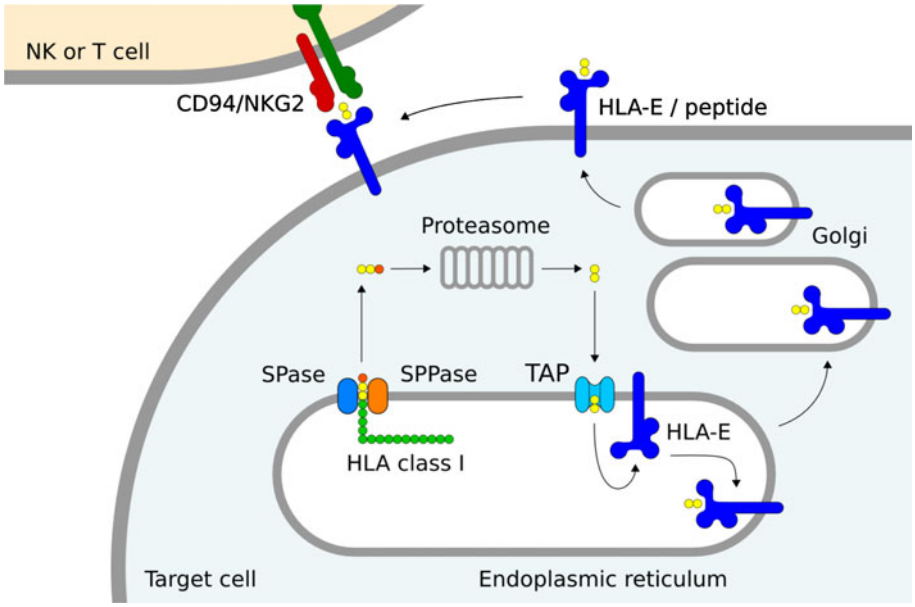

Fig. 4 Formation of HLA-E peptide complexes and antigen presentation to CD94/NKG2 receptor. The leader peptides come from signal sequences of transmembrane proteins, mostly leader from HLA class I proteins. During translocation of the protein its signal sequence is cut by signal peptidase (SPase). The sequence remains in the membrane, where it is cleaved by signal peptide peptidase (SPPase) and its hydrophilic N-part is released to the cytosol (Lemberg et al. 2001). The hydrophilic oligopeptide is processed further by proteasome, resulting in leader peptide (Bland et al. 2003). In the endoplasmic reticulum (ER) HLA-E molecules (shown in *blue*) are formed from $\beta 2$ microglobulin and heavy chain. Transporters associated with antigen processing (TAP) cooperating with tapasin carry leader peptides to the ER, where they can be bound by HLA-E molecules, allowing surface expression of these proteins (Braud et al. 1997, 1998b; Lee et al. 1998a). HLA-E–peptide complex is transported from ER via Golgi apparatus to the cell surface and interacts with CD94/NKG2A receptor (shown in *red* and *green*) expressed on NK cell or CTL

leader peptides to the endoplasmic reticulum (ER), where they can be bound by HLA-E molecules allowing their surface expression (Braud et al. 1997, 1998b; Lee et al. 1998a).

HLA-E molecules are one of the least polymorphic members of the HLA I family. It was proposed that in the human population there are eight alleles coding three known proteins. However, recent studies question the existence of at least two alleles, HLA-E*0102 and HLA-E*0104 (Grimsley et al. 2002). Only HLA-E*0101 and HLA-E*0103 alleles occur in significant frequencies (nearly 50% each). The two alleles differ in only one amino acid at position 107. In HLA-E*0101 it is arginine and glycine in HLA-E*0103. These isoforms vary in peptide binding affinity, with HLA-E*0103 encoded protein having higher affinity. Proteins encoded by both alleles have the same protein expression levels, but HLA-E*0101 encoded proteins have lower cell surface expression in comparison to HLA-E*0103 encoded proteins (Strong et al. 2003). Balancing selection rather than a neutral effect is proposed as a mechanism causing the distribution of these alleles, implying significant functional differences between these two variants.

The cell surface expression of HLA-E requires an availability of peptides able to bind these molecules. By presenting on the cell surface a random peptide available in intracellular compartments, the HLA-E informs immune cells about the current state of the cell's protein synthesis processes, primarily about the state of one of the most important histocompatibility protein synthesis pathways: the pathway of HLA class I molecules' maturation. Viral infection or cancer transformation usually impacts the availability of HLA class I derived leader peptides. It happens either by HLA class I gene expression inhibition or by malfunction of TAP complex responsible for loading of these peptides onto HLA-E (Fig. 4). Simultaneously, some viruses encode peptides that mimic sequences of the standard HLA-E ligands and are able to maintain its surface expression. Once the suitable peptide is available, the efficiency of the expression depends on an affinity between the HLA-E and the peptide. As mentioned, the protein derived from the HLA-E*0103 allele has a higher affinity to a majority of adequate peptides and produces more stable bound; thus this allele has higher cell surface expression level than the HLA-E*0101 (Strong et al. 2003).

It has been shown that the HLA-E*0101 allele is more frequent in Indian patients with recurrent spontaneous abortion, suggesting that deficient expression of this protein at the feto-maternal interface may result in maternal NK cell activation leading to fetal damage (Tripathi et al.

2006). However, an earlier, similar study on Danish patients did not show HLA-E polymorphism's influence (Steffensen et al. 1998). On the other hand, high surface expression of the HLA-E*0103 allele was observed among patients with nasopharyngeal cancer, allowing the conclusion that this elevated expression may provide enhanced inhibitory signals to NK cells, facilitating the tumor's escape from lysis (Hirankarn et al. 2004). The HLA-E*0103 allele is associated with reduced risk of human immunodeficiency virus (HIV) infection (Lajoie et al. 2006). The polymorphism of the HLA-E gene was also shown to influence pathogenesis of such autoimmune syndromes as the chronic inflammatory disease ankylosing spondylitis (Paladini et al. 2009), Behçet's disease (Park et al. 2007) and diabetes mellitus (Hodgkinson et al. 2000). Moreover, studies on Chinese patients suggest that this polymorphism may play a role in the pathogenesis of Kawasaki disease, a type of pediatric systemic vasculitis (Lin et al. 2009).

The HLA-E molecule is also one of the key components in neoplastic cells' ability to escape immune cells surveillance. It has been reported that a number of malignant cell types are characterized by increased HLA-E expression combined with silenced expression of other HLA class I proteins (Marín et al. 2003). It appears that during a tumor progression and viral infection similar components of cell machinery are modulated in order to avoid immune response. The classic HLA class I proteins expression is restrained to hide abnormal internal state of a target cell. Simultaneously the surface expression of HLA-E molecules is amplified; thus the cell has higher chance to interact with immune cells on the inhibitory CD94/NKG2A pathway. The beneficial overexpression of HLA-E was observed in ovarian carcinomas (Malmberg et al. 2002), lymphomas (Marín et al. 2003), gliomas (Wischhusen et al. 2005), colon cancer (Bianchini et al. 2006), melanomas (Derré et al. 2006) and breast cancer (de Kruijf et al. 2010). It may be assumed that the HLA-E polymorphism has influence on tumor development with the HLA-E*0103 allele providing more advantage for malignant cell. The positive association between this allele and the occurrence of nasopharyngeal carcinoma was reported (Hirankarn et al. 2004). However, studies on glioblastoma patients showed that the presence of the allele increases survival length (Kren et al. 2010).

HLA-E homologues in other primate species show similarly low polymorphism, with differences mostly in regions outside the active site. Moreover, murine HLA-E homologues are able to bind human MHC-I derived leader peptides and human HLA-E are able to bind murine derived leader peptides. The evolutionary conservation of HLA-E protein structure and functionality indicates the protein's importance as one of the foundation elements of mammalian immune systems. In fact, it has been shown that this ubiquitously expressed molecule plays a dual role as a modulator of NK cell activity in the innate immune pathway interacting with CD94/NKG2 receptors (Borrego et al. 2002; Braud et al. 1998a; López-Botet and Bellón 1999; Shawar et al. 1994), as well as a molecule presenting antigens to $\alpha\beta$ T cells in a specific immune response (Heinzel et al. 2002; Tomasec et al. 2000; Ulbrecht et al. 1998).

NK Cell Immunological Synapses: Interaction between HLA-E and CD94/NKG2

The interaction between HLA-E molecules and CD94/NKG2 receptors is one of the fundamental immune surveillance mechanisms. There are numerous examples showing the importance of this interaction (Table 1). The mechanism has been primarily observed and then extensively studied on NK immune cells. The NK cells are a heterogeneous lymphoid population defined by a $CD3^{-}$, $CD16^{+}$ and $CD56^{+}$ surface phenotype. They are characterized by their ability to detect neoplastic transformation or viral infection and to lyse a wide spectrum of cell types. NK cells need to gather information about the targeted cell in order to decide on the target's fate. The target cell is analyzed by various macromolecular complexes emerging at the site of contact between NK and target membranes. We refer to these molecular machineries as NK cell immunological synapses (NKIS). There are two general types of NKIS, activating (aNKIS) and inhibiting (iNKIS). The aNKIS receptors activate NK cells. They require intact cytoskeleton, lipid raft polarization and ATP for their formation and aggregation. On the other hand, iNKIS receptors inhibit NK cells and their expression and polarization at the contact site are independent of the cytoskeleton (Borrego et al. 2006; Watzl and Long 2003).

CD94/NKG2A binds HLA-E by a key-lock mechanism and the binding immobilizes both the ligands. The CD94 part is responsible for the interaction, while the NKG2A component of the receptor transmits the signal to intracellular compartments of the immune cell. For example, in the interaction between CD94/NKG2A receptor and HLA-E/peptide complex, primarily an acidic region of CD94 interacts with a basic region on the α1 helix of HLA-E. An acidic region on HLA-E's α2 helix can interact with a basic patch on NKG2A, but this interaction has no significant influence on HLA-E–CD94/NKG2 signaling (Sullivan et al. 2008).

Binding affinity between HLA-E and CD94/NKG2 receptors has been shown to correlate strongly with the strength of the killer cells' response. A number of studies display a broad distribution of CD94/NKG2 receptor

Table 1 Role of interaction between HLA-E and CD94/NKG2 in different conditions

Condition	HLA-E–CD94/NKG2 interaction
HLA class I synthesis	Detection of the HLA-E bound with leader peptide by the CD94/NKG2 receptors is considered a sensitive mechanism evolved to immunosurvey the normal biosynthesis of HLA class I molecules (Borrego et al. 1998; Lee et al. 1998b)
Hsp60	During cellular stress the Hsp60 derived peptide competes with usual HLA-E specific peptides. The resulting complex is inactive and without this protective inhibitory mechanism the stressed cell is vulnerable to immune response (Michaëlsson et al. 2002)
Pregnancy	There are HLA-E, HLA-G and HLA-C molecules expressed in trophoblast cells. The fetal tissues avoid maternal immune response by inhibitory interaction between HLA-E, presenting signal peptide from either HLA-G or HLA-C, and CD94/NKG2A (Ishitani et al. 2003)
Recurrent spontaneous abortions	In consequence of the mechanism described in pregnancy, the HLA-E*0101 allele predisposes to the condition. This allele has lower affinity to signal peptides, so such fetal cells are impaired in respect to inhibitory HLA-E–CD94/NKG2A interaction (Tripathi et al. 2006)
HCMV	The US40 viral peptide binds HLA-E facilitating its surface expression. The virus infected cells avoid immune response by inhibitory interaction between HLA-E presenting viral peptide and CD94/NKG2A (Lin et al. 2007)
HIV	The aa14-22 viral peptide binds HLA-E facilitating its surface expression and ability to interact with immune cells. The HLA-E*0103 allele has a protective effect against viral infection. Probably due to its stability of peptide bound the allele can more precisely present peptides to immune cells allowing higher precision of interaction and recognition of viral antigen (Tripathi and Agrawal 2007)
HCV	The aa35-44 viral peptide binds HLA-E facilitating its surface expression. The virus infected cells avoid immune response by inhibitory interaction between HLA-E presenting viral peptide and CD94/NKG2A (Nattermann et al. 2005a)
HPV	The virus upregulates expression of HLA-E. The infected cells avoid immune response by inhibitory interaction between HLA-E and CD94/NKG2A (Gonçalves et al. 2008)
Nasopharyngeal carcinoma	The HLA-E*0103 allele predisposes to disease progression. The malignant cells having this allele benefit in higher number of surface expressed HLA-E molecules, thus having higher chance to avoid immune response by inhibitory interaction between HLA-E and CD94/NKG2A (Hirankarn et al. 2004)
Behçet's disease	The HLA-E*0103 allele predisposes to disease progression in a manner similar to the described above (Park et al. 2007)
Ovarian carcinoma, lymphoma, glioma, colon cancer, melanoma, breast cancer	The malignant cells are characterized by amplified surface expression of HLA-E, thus they have higher chance to interact with immune cells on the inhibitory CD94/NKG2A pathway (Bianchini et al. 2006; Derré et al. 2006; de Kruijf et al. 2010; Malmberg et al. 2002; Marín et al. 2003; Wischhusen et al. 2005)
Diabetes mellitus, ankylosing spondylitis	The HLA-E*0101 allele predisposes to this autoimmune disease. The allele has lower affinity to signal peptides, so the cells are impaired in respect to inhibitory HLA-E–CD94/NKG2A interaction and are more prone to autoimmune reaction (Hodgkinson et al. 2000; Paladini et al. 2009)

HPV human papillomavirus

variants' sensitivity to interaction with HLA-E/peptide complexes. A difference is observed between CD94/NKG2A inhibiting receptors and CD94/NKG2C activating receptors, where inhibiting signal transmitting receptors are more sensitive to interaction with most known HLA-E/peptide complexes than those transmitting activating signals. In addition, it has recently been shown that CD94/NKG2E activating receptor has higher binding affinity than the previously considered activating receptor and the affinity is comparable to the affinity of CD94/NKG2A receptor. It has been hypothesized that these CD94/NKG2 receptors' properties allow for dynamic control of cytotoxicity and cytokine secretion. Lysis is triggered only when the reactive dominance of inhibitory receptors falls below a critical threshold. This pattern of affinities changes when HLA-E is bound with peptides derived from HLA-G. In such a case, binding affinity between HLA-E/peptide$_{\text{HLA-G}}$ and any of CD94/NKG2A, C or E receptors is exceptionally high in comparison to other peptides. It is high enough to efficiently trigger killer cells' cytotoxicity through CD94/NKG2C receptor signaling (Kaiser et al. 2005; Sullivan et al. 2008).

Moreover, the binding affinity between HLA-E and CD94/NKG2 receptors is influenced by the sequence of

Table 2 Peptides binding with HLA-E and abilities of HLA-E/peptide complexes to interact with immune cells through CD94/NKG2 and/or TCR pathways

Peptide sequence	Peptide source	Interaction with CD94/NKG2	Interaction with TCR	References
VMAPRTLIL	HLA class I	+	−	Braud et al. (1998a, 1999)
VMAPRTLVL				
VMAPRTLFL				
VMAPRTLLL				
VMAPRALLL				
QMRPVSRVL	Hsp60	−		Michaëlsson et al. (2002)
ALALVRMLI	ABC MRP7	+		Wooden et al. (2005)
VMAPRTLIL	HCMV UL40	+	+	Pietra et al. (2003)
VMAPRTLVL				
YLLPRRGPRL	Hepatitis C virus	+	+	Nattermann et al. (2005a), Schulte et al. (2009)
AISPRTLNA	HIV p24	+		Nattermann et al. (2005b)
SQAPLPCVL	EBV BZLF-$1_{39–47}$	−	+	Brooks et al. (1999), García et al. (2002)
ILGFVFTLT	Influenza $InflM_{59–67}$		+	García et al. (2002)
KMLRGVNVL	*Salmonella enterica* chaperonin (15–23)		+	Salerno-Gonçalves et al. (2004)
	Mycobacterium		+	Heinzel et al. (2002)

'+' signifies a confirmed interaction, '−' signifies a confirmed lack of interaction, empty cell signifies no data available

EBV Epstein-Barr virus

peptides presented by HLA-E. The prominent group of peptides that bind to HLA-E are leader sequences of HLA class Ia signal peptides. In addition, HLA-E can also bind various other human, as well as bacterial and viral, peptides (Table 2). It has been shown that it can bind peptides derived from HLA-G, ATP-binding cassette transporter multidrug resistance-associated protein 7 (MRP7) and heat shock protein (Hsp60). The HLA-G derived peptides increase HLA-E's affinity to CD94/NKG2A receptor to a level even greater than HLA class Ia derived peptides. Also MRP7 derived peptide is recognized by CD94/NKG2A, but peptides derived from Hsp60 disable HLA-E's ability to interact with CD94/NKG2 receptors. This ability of Hsp60 derived peptides to compete for HLA-E with peptides derived from HLA class I can lead during cellular stress to monopolization of available HLA-E molecules by Hsp60 derived peptides and reduction of the cell's capacity to inhibit NK cytotoxicity through the CD94/NKG2 pathway, providing one of the mechanisms for the immune system to detect cells affected by stress (Brooks et al. 1999; Michaëlsson et al. 2002; Wooden et al. 2005).

In addition, HLA-E binds a number of xenogenic peptides. The most well known case is the leader peptide of human cytomegalovirus (HCMV) glycoprotein UL40 (gpUL40). The gpUL40 itself upregulates HLA-E expression in infected cells and the whole system can efficiently inhibit NK cells' action through CD94/NKG2 receptor signaling (Tomasec et al. 2000; Llano et al. 2003). It has been shown that HLA-E binds viral peptides from Epstein-Barr (Ulbrecht et al. 1998), influenza (Ulbrecht et al. 1998), hepatitis C (HCV) (Nattermann et al. 2005a) and HIV (Nattermann et al. 2005b) viruses, as well as bacterial peptides from at least one *Salmonella enterica* strain (Salerno-Gonçalves et al. 2004) and *Mycobacterium tuberculosis* (Heinzel et al. 2002). In a part of these cases the cytotoxicity of NK cells is impeded through recognition of HLA-E/peptide by inhibitory CD94/NKG2 receptors. However, the same HLA-E/peptide molecules trigger target cell lysis and IFN-γ production in a fraction of $CD8^+$ cytotoxic T lymphocytes (CTLs) referred to as NK-CTL. They seem to be a significant component of the adaptive immune response to viral or bacterial infections. Their interaction with target cells is not mediated by CD94/NKG2 receptors, but most probably by T cell receptors (TCR) $\alpha\beta$. One of the best known examples is TCR interaction with HCMV UL40 antigen. The sequence of this peptide is identical to many HLA-C alleles, yet there exist alleles (HLA-Cw2, -Cw7, -Cw15 and -Cw18) whose sequences differ from the canonical form. In these cases HLA-E–UL40 derived peptide complex is recognizable by NK-CTL cells as foreign. To counterweight TCR functionality NK-CTL cells also express inhibitory receptors interacting with HLA class I peptides. However, these are not CD94/NKG2A receptors, but KIR2DL molecules (Romagnani et al. 2002; Pietra et al. 2003).

HLA-E CD94/NKG2 Interaction in Viral Infections

HCMV belongs to the *Herpesviridae* family and is also known as human herpesvirus-5. It has a relatively large genome consisting of 230 kbp encoding about 200 open reading frames. The efficiency of HCMV infection differs between various cell types. The virus is able to infect fibroblasts, smooth muscle, epithelial, endothelial and hematopoietic cells. It is believed that some cell types, such as myelomonocytic and some endothelial cells, are resistant to HCMV. Though infected, they show no viral protein expression and as a result such cells become reservoirs of latent virions.

In humans, the majority of adults are infected with the virus. Most of the infections have a mild course, though those occurring during pregnancy can lead to fetal damage. The immune system can immobilize and restrict the viruses, but it is unable to eradicate them and it takes resources to keep them in check. HCMV reactivation appears often in immunocompromised individuals, when the immune system fails to fulfill all of its duties. Such reactivation effects differ between individuals, but they lead in some cases to disorders including retinitis in AIDS patients and interstitial pneumonitis associated with allogeneic bone marrow transplantation. The viral reactivation is also believed to cause enterocolitis, oesophagitis, and hepatitis, and to be a cofactor in the development of arteriosclerosis.

HCMV evolved several mechanisms to evade immune cell recognition and viral host's lysis (Fig. 5). Their primary function is impairment of the antigen presentation system to hide viral peptide production. A number of HCMV proteins are involved in selective down-regulation of endogenous MHC class I proteins acting at various stages of the replication cycle. It is proposed that these proteins were sequentially acquired during HCMV evolution to counteract the pressure of host defense systems. One of the earliest expressed viral proteins, US3, retains class I molecules at the ER. The late stage protein, US6, binds TAP and impairs the transport of peptides to the ER, preventing their interaction with HLA-E molecules. Moreover, there are viral proteins expressed along the replication cycle, such as US2 and US11, which bind in the ER to heavy chains of HLA class I molecules and translocate them to the cytosol to be degraded by proteasome. US6 inhibits expression of all class I HLA proteins, but US2 and US11 preserve expression of HLA-E molecules. The presence of these proteins, which are key ligands for NK cells' inhibitory receptors, is exploited by UL40 viral protein, whose leader sequence is identical to HLA class I sequences presented by HLA-E and has the ability to stabilize this molecule in the membrane allowing it to interact with inhibitory receptors on killer cells. Loading of UL40 on HLA-E is TAP independent, thus resistant to US6 action. Despite MHC class I protein down-regulation, HCMV encodes UL18 glycoprotein homologous to molecules from this class, which binds to ILT2 (LIR-1, CD85j) inhibitory receptors with affinity higher than that of class I molecules, but its exact role remains uncertain. UL16 viral protein prevents cell surface expression of a number of stress-inducible molecules, such as MIC or ULBP variants, which act as ligands for killer cells' activating receptor CD94/NKG2D. Only MICA and ULBP3 have been observed to resist the viral inhibition (Lin et al. 2007).

Although the virus can evade $CD8^+$ lymphocyte and NK cell surveillance by, respectively, interference with class Ia-dependent antigen presentation and maintenance of expression of ligands of NK inhibitory CD94/NKG2 receptors, it is detected by NK-CTL cells. NK-CTL cells constitute a significant component of the immune response to HCMV infection. They can cause destruction of virus infected cells by rapid secretion of perforins and IFN-γ. NK-CTL's $\alpha\beta$ TCR activating receptor interacts with HLA-E's active pocket in a manner similar to CD94/NKG2A receptor. Hence, these two receptors are mutually exclusive, and it appears that $\alpha\beta$ TCR receptor has higher affinity and out-competes inhibitory CD94/NKG2A receptors in a race for available HLA-E molecules, triggering target cell lysis and blocking the inhibitory signal.

There are two variants of HCMV UL40 peptide known, one contains VMAPRTLIL and the other VMAPRTLVL sequence. There is also a variance in NK-CTL cells response to these peptides. Two subpopulations of these cells can be distinguished. One of them is characterized by equally efficient recognition of the mentioned sequences and the other by impeded recognition of VMAPRTLVL sequence. As an implication, individuals having the VMAPRTLIL sequence in their HLA class I alleles fail to provide any NK-CTL response against the virus, since in order to prevent autoreactivity there is a negative selection during these cells training against cells recognizing this own peptides (Pietra et al. 2003). On the other side, individuals that are able to develop an anti-HCMV HLA-E restricted $CD8^+$ T cell response can be divided into two groups according to their HLA-A and HLA-Cw haplotypes. The first group's HLA class I alleles contain neither VMAPRTLIL nor VMAPRTLVL sequences, so either viral peptide variant is recognized as foreign antigen. The second group has the VMAPRTLVL sequence in their HLA class I peptides, so the VMAPRTLIL sequence is identified as foreign (Pietra et al. 2003). These data suggest that the HLA class I host genotype, as well as infecting HCMV strain, may seriously affect the ability of different individuals to utilize HLA-E restricted NK-CTL mediated defense against the viral infection.

The HLA-E molecule has been also shown as one of the key players during HIV infection. Studies on human

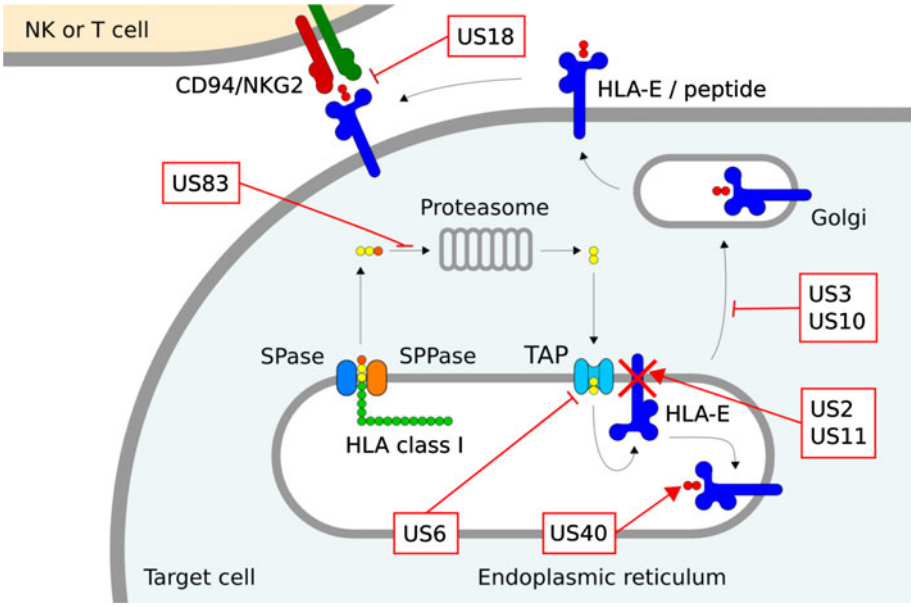

Fig. 5 Interference of HCMV proteins with HLA class I antigen presentation. The US83 inhibits antigen peptides generation by blocking protein entry into the proteasome. The US6 blocks TAP and disrupts transport of antigens into the endoplasmic reticulum. The US40 leader sequence mimics HLA class I sequences and binds HLA-E. The US2 and US11 proteins translocate HLA-E to the proteasome for degradation. The US3 and US10 proteins impair HLA-E surface expression by retaining them in the ER. The US18 protein is HLA class I homolog binding to the inhibitory NK receptors with the affinity higher than HLA-E (Lin et al. 2007)

immune cells in vitro revealed that the virus differentially modulates the expression of genes from HLA family. It selectively down-regulates HLA-A and HLA-B genes expression to prevent these molecules to present its antigens on the surface of the cell. At the same time HIV does not affect the expression of HLA-C (Cohen et al. 1999) and there is evidence that the expression of HLA-G and HLA-E genes is upregulated (Nattermann et al. 2005b). The viral Nef protein recognizes a binding site on cytoplasmic domain of newly synthesized HLA class I proteins preventing their phosphorylation and subsequently acting as an adaptor for trans-Golgi network proteins resulting in redirection of the newly synthesized molecules to endosomal pathway instead of cell surface (Tripathi and Agrawal 2007). This way the HIV-infected cells lack on their surfaces classic HLA molecules able to present viral peptides and activate CTL cells, but express HLA-E proteins allowing inhibition of NK cells through CD94/NKG2A receptor. Since the surface expression of HLA-E is dependent on its binding with specific oligopeptide, several sources of peptides were proposed. These could include the co-upregulated HLA-G proteins (Nattermann et al. 2005b), the HLA-C proteins unaffected by virus (Cohen et al. 1999) or viral encoded peptides as p24 (Tripathi and Agrawal 2007). The p24 peptide's signal sequence aa14-22a is just slightly different from the sequences of other known peptides binding to HLA-E. The aa14-22a has an isoleucine at position 2 essential for HLA-E interaction. It has residues at positions 4, 6 and 7 similar to those at respective positions in other HLA-E specific peptides. The HIV aa14-22a peptide has also an asparagine at position 5 believed to be important in interaction with CD94/NK2A receptor. It has been reported that presentation of aa14-22a by HLA-E can inhibit cytotoxic function of NK cells through CD94/NKG2A pathway (Tripathi and Agrawal 2007). It might be assumed that owing to the described mechanisms the virus has excellent means to avoid detection by the immune system. However, there is evidence from population studies that the HLA-E polymorphism has an influence on progression of HIV. The HLA-E*0103 allele is associated with fourfold decreased risk of HIV-1 infection in Zimbabwean women (Lajoie et al. 2006). The authors propose as an explanation to the ability of HLA-E to bind viral aa14-22a peptide. In light of the fact that HLA-E*0103 molecule has higher affinity and stability during peptide binding, the killer cells' CD94/NKG2 receptors have higher chance to recognize more subtle differences in presented oligomeric molecules, thus to detect viral peptide and to lyse infected cells in result.

HCV from *Flaviviridae* family causes chronic hepatitis. During its progression it utilizes still poorly understood means to impair the host's immune response. It has been shown that HLA-E related signaling modulation might contribute to this effect. The HCV inducted chronic hepatitis is associated with HLA-E expression amplification. One the viral peptides, aa35-44, has the ability to bind HLA-E, be presented on cell surface and be recognized by CD94/NKG2A receptor, thus facilitating inhibition of immune response (Nattermann et al. 2005a). The HLA-E polymorphism appears to have influence on course of infection. It has been reported that homozygous HLA-E*0101/HLA-E*0101 genotype is associated with increased resistance to HCV infection (Schulte et al. 2009). It is contradictory to the situation during HIV infection, where as mentioned above, the HLA-E*0103 allele is associated with a decreased risk of infection. Two

explanations were proposed. It may simply be a fact that HLA-E*0101 allele, as the less stable one, inefficiently triggers NK cells' inhibition through CD94/NKG2A receptor. However, it was shown that HLA-E/peptide complexes can also interact with TCR receptors of T $CD8^+$ lymphocytes (Pietra et al. 2003). Therefore there is a possibility that the HLA-E*0101 allele, due to its lower binding affinity to standard HLA-E specific peptides, binds HCV derived aa35-44 peptide more efficiently. Since the viral peptides outcompete standard ones, the cells having this allele have higher chance than the cells having the HLA-E*0103 allele to present the viral peptide to T lymphocytes.

Human papillomavirus infection is believed to be a main cause of cervical cancer. A reduction of surface expression of HLA class Ia proteins along with the amplification of HLA-E expression during the infection progression was reported. This modulation of HLA proteins' expression may be used initially by the virus and subsequently by malignant cells to avoid immune response. This way the infected cells gradually lose the ability to HLA class Ia restricted presentation of peptides to T cells and exposition of viral presence. At the same time the surface density of HLA-E molecules on the infected cells increases allowing more efficient inhibition of NK cells, presumably through CD94/NKG2A interaction (Gonçalves et al. 2008).

Involvement of HLA-E CD94/NKG2 Interaction in Immunological Response during Pregnancy

During human pregnancy fetal trophoblast cells invade the decidua and connect with maternal uterine arteries. Trophoblast cells have, in comparison to other cells, a unique immunological phenotype to cope with maternal decidual NK cells. Trophoblast cells express mainly HLA class Ib, HLA-C, -E, -F or -G. No other HLA class Ia or II proteins are expressed. HLA-E cannot bind peptides derived from HLA-F; hence trophoblast HLA-E molecules can only bind signal peptides from HLA-G or -C. As described above, HLA-E bound with peptide derived from HLA-G signal sequences have very high affinities to CD94/NKG2 receptors, primarily to inhibitory variants. Therefore, such cells may be protected from NK cytotoxicity (Ishitani et al. 2003).

The decidua has a distinct NK cell phenotype distribution in comparison to the peripheral blood. Its NK cell population is dominated by $CD56^+$ phenotype. Approximately 90% of the population express high levels of CD56 and are negative for CD16 receptors. In contrast, peripheral blood NK cells express high levels of CD16 and relatively low levels of CD56 receptors. $CD56^+$ cells are the main cytokine-producing NK cells. They demonstrate low cytotoxicity and express higher levels of CD94/NKG2 receptors compared to highly cytotoxic $CD16^+CD56^{low}$ cells. $CD56^+$ NK cells accumulate in large numbers at the implantation site and probably recognize trophoblast cells and regulate their invasion. It has been suggested that HLA-E bound with HLA-G derived peptide plays a dual role in this functionality. It acts primarily as a homing receptor for NK cells, binding and efficiently immobilizing them. The second role is their activation. The $CD56^+$ NK cells, when activated without a cytotoxic response, secrete many kinds of cytokines including macrophage inflammation protein-1α, granulocyte-macrophage colony-stimulating factor, tumor necrosis factor α, leukemia inhibitory factor, transforming growth factor-β and IFN-γ. These cytokines play a role in NK cell differentiation and fetus vascularization. Hence, it is important for implantation that trophoblast cells are not only able to inhibit NK cells' cytotoxicity, but also to induce their cytokine secretion. Analyses of receptor expression confirm the presence of inhibiting CD94/NKG2A and activating CD94/NKG2C molecules on decidual NK $CD56^+$ cells (Ashkar et al. 2003; Cooper et al. 2001; Trundley and Moffett 2004).

In the decidual leukocyte population around 10% are T cells. Available data suggest that these cells are more active than the peripheral blood population and their activation pathway involves HLA-E–CD94/NKG2 receptors' interaction. The result of their activity is mainly cytokine secretion without a cytotoxic response. As mentioned above, cytokine distribution regulates leukocytes differentiation and vascularization of the implantation site, facilitating correct placentation. The decidual T cells consist of $\alpha\beta$ T and $\gamma\delta$ T clones, with the proportion of $\gamma\delta$ T significantly increasing during the course of pregnancy. The $\gamma\delta$ T cells have a relatively high level of expression of CD94 molecules. It makes them different from $\alpha\beta$ T cells, but comparable with NK cells (Barakonyi et al. 2002; Trundley and Moffett 2004).

It has been reported that HLA-E polymorphism may have an influence on the course of pregnancy. The study carried out on a group of Indian women show that the homozygous state of HLA-E*0101 allele is more frequent in individuals suffering from recurrent spontaneous abortions than in healthy control group. As mentioned above HLA-E molecule interacts with CD94/NKG2A inhibitory receptor on immune cells protecting fetal cells from lysis. Since the HLA-E*0101 protein has lower affinity to signal peptides and thus lower surface expression these data suggest that deficient expression of this protein at the feto-maternal interface may result in maternal NK cell activation leading to fetal damage (Tripathi et al. 2006).

Potential Role of HLA-E and CD94/NKG2A in Transplantation of Hematopoietic Stem Cells

The potential involvement of HLA-E in the immunological response following allogeneic hematopoietic stem cell transplantation (HSCT) has been suggested by the results of studies using transgenic mice (HLA-E*01033 and β2 microglobulin gene) (Pacasova et al. 1999; Romagnani et al. 2002), in which HLA-E exhibited alloantigenic properties that are indistinguishable from classical HLA class I molecules, and it was observed that HLA-E specific alloreactive T cells could proliferate in response to allogeneic stimulation and could lyse most donor cells. There have been a number of studies in humans showing the effect of the HLA-E polymorphism on the transplant outcome, including the results of our recent study (Bogunia-Kubik et al. 2009, 2010).

In patients undergoing allogeneic HSCT at the Lower Silesian Center for Cellular Transplantation a significantly higher incidence of acute graft-versus-host disease (GvHD) has been observed after HLA-E mismatched transplants being matched at the high resolution level for five classical HLA loci (HLA-A, B, C, DRB1 and DQB1) (Bogunia-Kubik et al. 2009, 2010). Moreover, an association of recipient HLA-E*0103 homozygosity with improved likelihood of patient overall survival has been observed (Bogunia-Kubik et al. 2009, 2010), which concurs with the results of Tamouza et al. (2006) and Danzer et al. (2009). They have observed that the presence of HLA-E*0103 allele in donors, either in homozygous or heterozygous state, is associated with increased survival rate expressed by decreased TRM and decreased risk of acute GvHD (Danzer et al. 2009; Tamouza et al. 2006). Other studies have also confirmed the anti-GvHD effect (Ludajic et al. 2009). In addition, homozygous state for the HLA-E*0101 allele is a risk factor for early severe bacterial infections in bone marrow transplantations (Tamouza et al. 2005).

It has been proposed that impeded recognition of the host's cells by the donor's T cells is responsible for the outcome of HSCT. In HLA matched transplants this impeded recognition is probably caused by the HLA-E*0103 allele's impaired efficiency of presentation of minor histocompatibility antigens (mHags). In HLA mismatched transplants allogeneic HSCT donor T cells react directly with major histocompatibility antigens; however, in HLA matched transplants, when donor and recipient share the same HLA-A, -B and -C alleles, the T cells recognize mHags. Minor histocompatibility antigens are presented primarily by classical HLA molecules and such complexes may activate T cells. It is hypothesized that either HLA-E outcompetes classical HLA proteins in mHags binding and disrupts the classical pathway, or it binds non-standard mHags peptides that could specifically mediate graft-versus-leukemia (GvL) rather than GvHD (Tamouza et al. 2006).

On the other hand, the presence of the HLA-E*0103 allele in the recipient's cells may negatively influence the GvL reaction. It has been shown that to prevent autoreactivity, immature NK cells secrete a high level of cytokines and express CD94/NKG2A inhibitory receptors. This way, young NK cells derived from the donor's hematopoietic cells may hinder their own desired functionality. While their cytokines, mainly IFN-γ, induce HLA-E expression in all cells and due to higher cell surface expression of HLA-E*0103 in comparison to HLA-E*0101 (Strong et al. 2003), the presence of the former allele provides more molecules on the surface of cells, and thus higher capability to inhibit immune cells through CD94/NKG2A receptors (Nguyen et al. 2005).

It has also been reported that the risk of bacterial infections after transplantation can be influenced by HLA-E polymorphism. For the previously mentioned reasons, a homozygous state for an inefficiently expressed HLA-E*0101 allele may impair pathogen-derived peptide binding, and thus diminish the possibility of T cell activation and destruction of infected cells (Tamouza et al. 2007).

These results suggest that the HLA-E polymorphism can be of prognostic value for the outcome of allogeneic HSCT. The presence of HLA-E*0101 seems to act as a risk factor of bacterial infections and GvHD, while HLA-E*0103 is associated with improved likelihood of patient survival. Moreover, patient–donor compatibility with respect to the HLA-E alleles affects the development of post-transplant complications, with reduced risk of GvHD after HLA-A, -B, -C, -DRB1, -DQB1 and HLA-E matched transplants, as compared to HLA-E mismatched transplants being matched at the high-resolution level for five classical HLA loci (HLA-A, -B, -C, -DRB1 and -DQB1). Moreover, our preliminary study suggests that *NKG2A* gene polymorphism may be of prognostic value for the outcome of alloHSCT. Patients carrying the *NKG2A* (−4258 C>G) C allele more frequently suffered from herpes virus reactivations than GG homozygotes. Moreover, patients transplanted with donors carrying the *NKG2A* heterozygous genotype were characterized with the worst overall survival with a significant difference in comparison to patients grafted from CC homozygous donors (Bogunia-Kubik et al. personal communication).

The presented facts indicate that the interaction between HLA-E and CD94/NKG2 receptors plays a crucial role in information transduction between NK cells or CTLs and their target cells. The interaction was shown to be involved in the immunological response to HCMV infection. It has also been observed as one of the signaling pathways regulating the fetal trophoblast's migration into the maternal decidua during pregnancy. Moreover, the mentioned data

suggest that this interaction has primary importance in the immune system's reaction to transplanted graft cells.

The HLA-E polymorphism has been shown to affect the outcome of viral infections, fetal implantation and allogeneic HSCTs. Similarly, the polymorphisms in CD94/NKG2 gene cluster has been shown to influence a course of Behçet's disease, rheumatoid arthritis, systemic lupus erythematosus, colorectal cancer, as well as post-transplant mortality rate. The presented data provide evidence that an information on the polymorphism of these genes could be a powerful predictor during planning of clinical treatment of various viral infections, recurrent spontaneous abortions and transplantation related complications.

Acknowledgments This work was supported by the Polish Ministry of Science and Higher Education grant no. N-N402-193335.

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