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Chapter 3

HLA-E, HLA-F and HLA-G — The Non-Classical Side of the MHC Cluster

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Additional information is available at the end of the chapter

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1. Introduction

Traditionally, the MHC is divided into the classes containing groups of genes with related functions; the MHC class I and II genes encode for human leukocyte antigens (HLA), proteins that are displayed on the cell surface. In humans, MHC class I molecules comprise the classical (class I-a) HLA-A, -B, and -C, and the non-classical (class I-b) HLA-E, -F, -G and – H (HFE) molecules (Pietra et al., 2009). Both categories are similar in their mechanisms of peptide binding and presentation and in the induced T-cell responses (Rodgers and Cook, 2005). The most remarkable feature of MHC class I-b molecules is their highly conserved nature (van Hall et al., 2010). In contrast with class Ia molecules they have been under a distinct selective pressure, exhibiting very low levels of allelic polymorphism (Strong et al., 2003). Classical MHC class I gene transcription is mediated by several cis-acting regulatory elements, in the proximal promoter region (Gobin and van den Elsen, 2000). Those elements determine the constitutive and cytokine induced expression levels of the molecule (Gobin and van den Elsen, 2000).

The literature on the different roles played by class I-b molecules is in rapid expansion and focus in pathogen recognition, virus-induced immunopathology, tumor immunosurveillance and regulation of autoimmunity (Hofstetter et al., 2011). The HLA-G, HLA-E and HLA-F genes encode for molecules that have been shown to be involved in regulation of autoimmune disease (Donadi et al., 2011; Kim et al., 2008). HLA-G biological features include: restricted tissue expression, the presence of membrane bound and soluble isoforms, generated by alternative splicing, limited protein variability, unique molecular structure, with a reduced citoplasmic

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tail and modulation of the immune response. The presence of HLA-G molecules in both membranes bound and soluble forms was associated with tolerogenic functions (Baricordi et al., 2008). HLA-E is the best characterized MHC Class Ib molecule. With a low level of polymorphism its role is thought to be confined to the regulation of NK cell function (Pietra et al., 2009). The HLA-F gene was first identified in 1990 by Geraghty et al. (Geraghty et al., 1990; Ishitani et al., 2006). So far it is the nonclassical class I molecule least characterized and neither its native structure nor function is known (Boyle et al., 2006; Goodridge et al., 2010; Lee et al., 2010). Several studies confirmed HLA-F protein expression in a number of diverse tissues and cell lines, including bladder, skin and liver cell lines, but no surface expression was detected in the majority of them (Lee et al., 2010). Just like other class Ib molecules, HLA-F restrictive tissue expression suggests specialized functions and tight transcriptional control of the gene (Gobin and van den Elsen, 2000). Furthermore, unique potential regulator motifs were identified consistent with tissue-specific expression (Geraghty et al., 1990).

In this chapter we aim to provide a wide view about:

1. The characteristic of non-classical HLA-E, F and G molecules based on the data available in scientific literature;
2. The polymorphism of HLA-E, HLA-F, and HLA-G in the world populations;
3. The association of non-classical HLA-E, F and G alleles and disease.

2. Morfo-functional description of HLA-E molecule

In humans, the major histocompatibility complex (MHC) class I molecules include the classical (class Ia) human leukocyte antigens (HLA)-A, -B, and -C, and the non-classical (class Ib) HLA-E, -F, -G and -H (HFE) molecules. HLA-E is the best-characterized MHC class Ib molecule, defined by a limited polymorphism and a restricted pattern of cellular expression (Iwaszko and Bogunia-Kubik, 2011; Pietra et al., 2009).

The HLA-E gene is situated in the MHC cluster on cromossome 6, about 650 kb from HLA-C, and consists of seven exons. The first one encodes the leader peptide. The next three exons encode a1, a2 and a3 domains, respectively. Exon 5 encodes the transmembrane region and the last two, the intracellular tail (Iwaszko and Bogunia-Kubik, 2011). HLA-E promoter regulatory sequence is divergent from other MHC class Ib molecules, determining differential transcription factor binding and transcriptional regulation. HLA-E is induced by CIITA through the SXY module. This is in line with the conserved sequences for the S, X, and Y boxes in the SXY module and shows that the divergent Y box (AATGG) does not influence the complex formation and transactivation by CIITA. However, this gene is not regulated by its upstream module. In fact, is strongly responsive to IFN-γ through a further upstream STAT1 binding site (Gobin and van den Elsen, 2000).

The HLA-E protein is the least polymorphic, one of the most studied and, unlike other MHC class Ib molecules, is transcribed in practically all human tissues (Braud et al., 1997). Ten alleles

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in the human population encoding for three different peptides have been reported. Only two of these alleles, HLA-E*0101 and HLA-E*0103, are widely distributed (approximately 50% each). The proteins encoded by these alleles differ from each other in one amino acid (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. The difference between these proteins manifests itself in surface expression levels, affinities to leader peptides and thermal stabilities of their complexes (Iwaszko and Bogunia-Kubik, 2011).

Like classical class I molecules, the complex stability on the cell surface requires a peptide, but unlike classical MHC-I proteins binding sites, which are typically limited at two or three positions, HLA-E has five anchor residues. This imposes strict restrictions on the sequence of peptides capable of binding to HLA-E (Sullivan et al., 2008). Five conserved hydrophobic pockets in the groove of HLA-E anchor the peptides in residues P2, P3, P6, P7, and P9; a wide hydrogen-bonding network between the heavy chain and the peptide main chain, as well as conserved charged interactions, further stabilize the peptides; these peptides derive from leader sequences of classical MHC proteins and provides a link to the primary function of HLA-E in the innate immune response as ligands for the family of CD94/NKG2 receptors expressed by natural killer (NK) and T cells (Braud et al., 1998).

The leader peptides originate in signal sequences of transmembrane proteins. HLA-E preferentially present peptides derived from leader sequences of other classical class I molecules (Aldrich et al., 1994; Braud et al., 1997). The signal sequence is cut during translocation of the protein by a signal peptidase; it remains in the membrane, where it is cleaved and its hydrophilic N-part is released into the cytosol (Lemberg et al., 2001). The hydrophilic oligopeptide is processed further by the proteasome, resulting in a leader peptide (Bland et al., 2003). Transporters associated with antigen processing (TAP), in cooperation with tapasin, transfer leader peptides to the endoplasmic reticulum (ER), where they can be associated to HLA-E molecules permitting their surface expression (Braud et al., 1997; Braud et al., 1998; Lee et al., 1998). HLA-E–peptide complex is then transported via Golgi apparatus to the cell surface where it interacts with CD94/NKG2A receptor expressed on NK cell or CTL (Iwaszko and Bogunia-Kubik, 2011). The availability of leader sequences is compromised by downregulation of classical class I protein production, thus interfering with the expression of HLA-E on the cell surface. Without the inhibitory signal that these molecules provide for the CD94/NKG2A receptor, cytolytic cells such as NK cells can detect and eliminate compromised host cells (Adams and Luoma, 2013).

Unlike other highly conserved systems, there is no cross-reactivity between human and mouse CD94/NKG2 receptors. This is likely due to a cluster of species-specific residues present near the peptide-binding region (Zeng et al., 2012) that constitutes part of the CD94/NKG2- binding site as revealed in the HLA-E/CD94/NKG2A complex crystal structures (Kaiser et al., 2008; Petrie et al., 2008). The correspondence of the CD94/NKG2A receptor on HLA-E covers the peptide-binding groove, with the CD94 and NKG2A subunits binding almost exclusively to the α1- and α2- helices, respectively (Adams and Luoma, 2013). This places the receptor over the P5, P6, and P8 positions of the peptide and explains the extreme

sensitivity of CD94/NKG2 binding to subtle changes in peptide conformation at these positions (Adams and Luoma, 2013).

HLA-E was first described as a non-polymorphic ligand of the CD94/NKG2 receptors expressed mainly by natural killer (NK) cells and its role was thus limited to the regulation of NK cell function (Pietra et al., 2009). At present it is known that HLA-E molecule is a ligand for CD94/NKG2 receptors on NK cells and TCR receptors on NK-CTL (NK-cytotoxic T lymphocyte) cells, so it plays a double role in both innate and adaptive immunity (Iwaszko and Bogunia-Kubik, 2011). 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., 1998; Lopez-Botet and Bellon, 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).

The interaction of HLA-E with the CD94/NKG2 receptors can result in either inhibition or activation of NK cells, depending on the peptide presented and on the association of the NKG2 receptor CD94. So, the association CD94/NKG2A functions as an inhibitory receptor, whereas CD94/NKG2C functions as an activating receptor. However, recent evidences showed that HLA-E represents a novel restriction element for $\alpha\beta$ T-cell receptor (TCR)-mediated recognition. Although HLA-E displays a selective preference for nonameric peptides derived from the leader sequences of various HLA class I alleles, several reports showed that, in specific situations, it can also present other peptides derived from both stress-related and pathogen-associated proteins. Since HLA-E displays binding specificity for innate CD94/NKG2 receptors but also has the features of an antigen-presenting molecule, including the ability to be recognized by $\alpha\beta$ T cells, it seems that this MHC class Ib molecule is implicated in both natural and acquired immune responses (Pietra et al., 2009).

In stress conditions, such as malignant cell transformation or intracellular infection with chronic pathogens, HLA-E has an alternative role. In such conditions the bound signal peptides are replaced by a novel much more diverse collection of peptides, which can be identified by $\alpha\beta$ TCRs. It was recently described two such novel peptide repertoires, presented by HLA-E molecules to specific $CD8^+$ T cells, related to the detection of intracellular infection with mycobacteria, or to antigen processing defects in tumors (Joosten et al., 2010; Oliveira et al., 2010). These two situations of intracellular stress show that HLA-E probably serves a much wider function in adaptive immunity than thus far anticipated (van Hall et al., 2010). The peptides characterized from these responses can differ markedly in sequence from the established leader peptide sequence or can be highly similar. The human CMV UL40 is identical in sequence to some HLA leader sequences. This way, the expression of HLA-E on the cell surface is maintained and avoided the CD94/NKG2 detection of downregulated classical class I. This peptide can cause a strong CD8+ Tcell response in individuals lacking the identical endogenous leader sequence because these T cells have escaped negative selection. They can go on to make up a significant proportion of the CD8+ T cell memory pool in some immune individuals (Adams and Luoma, 2013; Hoare et al., 2006). The crystal structure of a $\alpha\beta$ TCR interacts with HLA-E/UL40 peptide complex (Hoare et al., 2006; Adams and Luoma, 2013).

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3. Morfo-functional description of HLA F molecule

The human MHC-F class Ib was the third non-classical HLA loci identified by Geraghty et al. in 1987 (Geraghty et al., 1987; Geraghty et al., 1990). HLA-F gene is located at the terminal end of the chromosome 6 and contains eight exons: exon 1 encodes the leader peptide; exons 2, 3, and 4 encode the alpha1, alpha2, and alpha3 domains; exons 5 and 6 encode the transmembrane region; and exons 7 and 8 encode the cytoplasmic tail. The intron/exon organization of the HLA-F is very similar to the HLA I class, except for the in-frame translation termination codon located at codon 2 in exon 6 (Geraghty et al., 1987). Thus the entire seventh and eight exons are not translated. The HLA-F gene is expressed as transmembrane heavy chain (HC) associated noncovalently on the cell surface with an invariant light chain β2-microglobulin (β2m). The glycoprotein is approximately 42 kDa, two KDa shorter than typical HLA class I, due to the exclusion of exons 7 and 8 from the mature mRNA. The leader peptide consists of 21 amino acids present at the N-terminus of the HLA-F protein. The extracellular domain consists of the heavy chain folded into three globular domains plus the light chain β2m. The α1, α2, and α3 regions together with β2m form a peptide binding groove. Most polymorphisms are located in this region influencing the peptide binding and the T-cell recognition (Howcroft and Singer, 2003). The transmembran spanning domain consists of a hydrophobic region of 26 amino acid of heavy chain. The carboxy-terminal cytoplasmic segment consists of only six amino acids: the COOH-terminal, plus five amino acids encoded by exon 5 and the aspartic acid residue encoded by exon 6.

The expression pattern of HLA-F molecule is generally tissue-restricted and cell specific. It can be detected in a number of diverse tissue and cell lines, including tonsil, bladder, liver, skin, and spleen. Predominantly it is express in an intracellular, unstable, and immature form in monocytes and most lymphocyte subsets, including NK cells, B cells, and T cells, except T reg cells (Lee et al., 2010).

The expression of HLA-F molecules is regulated at transcriptional level. The most of the regulatory elements reside in the 5′ proximal promoter regions. Those regulating elements are determinant for the tissue-specific expression and for the response to hormones and cytokines (Girdlestone, 1996; Le Bouteiller, 1994; Singer and Maguire, 1990). Additional sequence elements, like distal flanking regions and core promoter sequences, are also important in determining an appropriate expression. The main regions within the core promoter are the CCAAT box, G/C-rich region, TATA box, and the Initiator (INR) (Howcroft and Singer, 2003). The CCAAT box is a distinct pattern of nucleotides with GGCCAATCT consensus sequence that occur upstream to the initial transcription site. It represents a binding site for various transcription factors and it facilities the proper positioning of RNA polymerase. The G/C-rich region is located between CCAAT box and TATA box. It is still unknown its contribution to HLA class I genes. The TATA box is the binding site of the general transcription factors TFIID and is involved in the process of transcription by RNA polymerase. The INR element overlaps the transcript start site and facilitates the binding of transcription Factor II D (TBP). The principal modules that drive the HLA-F expression in the proximal promoter region are the upstream module consisting of the Enhancer A and ISRE element and the downstream module

consisting of the SXY regions. The Enhancer A and ISRE element modulate the transactivation by two kB sites that bind nuclear (NF)-kB family factors and one binding site for IFNs. The SXY module consists of S, X, and Y box sequences. The X_1 and X_2 boxes are binding sites for RFX transcription factor and CREB/ATF family factors. The Y box is recognized by NF-Y factors. The SXY module is necessary to the activation of the HLA-F promoter by the CIITA master control factor induced by γINF.

HLA-F is currently the most enigmatic of the HLA molecules, as its function (mainly intracellular) is not clear. Human HLA Ia class molecules posses ten highly conserved amino acids responsible for the Ag recognition (Wainwright et al., 2000). The class Ib HLA-E and HLA-G present eight and nine amino acids of ten characteristic of HLA Ia, respectively. Instead HLA-F highly conserves only 5 residues of ten, suggesting a different biological function than a general peptide presentation to the T cells (Ishitani et al., 2006).

Although HLA-F is intracellular expressed in normal lymphocytes, under specific circumstances such protein can reach the cell surface (Lee et al., 2010). High level of HLA-F surface expression was observed in activated B, T, and NK cells (Lee et al., 2010). It appears that HLA-F is express in conjunction with the activated immune response, very early after the lymphocytes activation. An unusual property of HLA-F expressed on activated B and T cells is the high-mannose hybrid-type glycosilation. The glycosilation is a post-translational modification common to all the proteins transported from ER, through the Golgi, to cell surface. Similarly, CD1d protein is expressed in cell surface as 45 kDa endo-H-sensisitive glycoprotein (Kim et al., 1999). The endosomal localization of CD1d is mediated by its cytoplasmatic tail. The key residues for the signaling mechanism present on the CD1d tail are shared with HLA-F cytoplasmatic tail (Lawton et al., 2005). The HLA-F cytoplasmic tail shows a C-terminal valine essential for the ER export and the R x R motif responsible for the Golgi localization (Boyle et al., 2006; Iodice et al., 2001; Nufer et al., 2002). In different studies HLA-F was found associated with TAP but its surface expression was not reduced in TAP-mutant lines, but there was a low reduction in Tapasin-deficent lines (Lee and Geraghty, 2003). Moreover, a classical 10 amino acid-peptide has never been eluted from the peptide binding groove of HLA-F protein. These results could suggest that such glycoprotein is capable to escape the ER lumen and reaching the cell surface independently from TAP, Tapasina, and peptide binding, but using an alternative ER signal encoded in its cytoplasmic tail.

Some studies on molecular modeling of HLA-F reported a particular peptide binding groove conformation defined "open-ended" (Goodridge et al., 2010). It is well known that HLA I proteins binds 8-10 aa peptides and the end of the pocket is closed (Peaper and Cresswell, 2008). Theoretically, the peptide opened ended binding groove is able to include large peptides of up to 25 amino acids in length. It was demonstrated that HLA-F could be found in multiple conformational forms, at least three: complexed with the light chain β2m, in open conformation, and complexed with a HLA I heavy chain (HC). In a recent studies Goodridge et al. demonstrated that HLA-F expression was not only coincident with HLA I HC expression but also that HLA-F expression was downregulated after modification of HLA I HC structure (Goodridge et al., 2010). They also demonstrated that HLA I HC interacted only with HLA-F in open conformation (OC) and not in peptide bound complex (Goodridge et al., 2010).

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Normally, MHC I molecules in open conformation are instable while HLA-F showed enough stability to enter into Golgi traffic and to reach and remain on the cell surface. It is possible that after immune response activation, HLA-F OC binds free forms of HLA I and as heterodimer reaches the cell surface (Goodridge et al., 2010). This data suggests that in absence of peptide bound complex HLA-F OC acts as chaperone to stabilize HLA I HC and to transport the free HLA I to, on, and from the cell surface (Goodridge et al., 2013). It was observed that after addition of free Ag, expressed HLA-F molecules were internalized through the endosomal pathway into lysosomes, where proteins are degradated to produce new peptides for Ag presentation in TAP independent way. Besides, the internalization and localization of Ag were coincident with the internalization and localization of HLA I HC and HLA-F (Goodridge et al., 2013). In addition, the downmodulation of HLA-F was coincident with the downmodulation of HLA I and in interference with Ag binding and presentation (Goodridge et al., 2013). On the base of these recent reports, HLA-F appears to cooperate with free HLA I molecules in a novel pathway for Ag cross-presentation on activated lymphocytes and monocytes (Goodridge et al., 2013).

It is known that HLA-F glycoproteins interacts with killer-cell immunoglobulin-like receptor (KIR) inhibiting their cytotoxic response. KIR receptors show a very high ability to differentiate between different allotypes (Parham et al., 2012). Considering the high expression of HLA-F on activated cells, its ability to form heterodymers with free forms of HLA I, and the alternative pathway of Ag cross presentation, Goodridge et al. supposed that the interaction between HLA-F-HLA I HC complex with KIRs may represent a new class of ligands (Goodridge et al., 2013). Clearly, this new relation receptor-ligand suggests a deeper function of KIR-HLA-F in the activated immune response (Goodridge et al., 2013). It has been found that the LILRB2 receptor binds peptide-free HLA I molecules in both folder and open conformation forms (Jones et al., 2011). Moreover in inflammatory conditions, KIR3DL2 and KIR3DL1 receptors expression highly increases early after NK cells activation (Chrul et al., 2006). The coincident upregulation of KIR receptors with the upregulation of the HLA-F-HLA I HC complex suggests an immunoregulatory role of HLA-F in inflammatory response.

4. Morfo-functional description of HLA-G molecule

The alternate splicing of HLA-G primary transcript generates seven different mRNAs. Thus, the same number of isoforms is encoded, and are divided into four membrane-bound (HLA-G1, G2, G3 and G4) and three soluble proteins (HLA-G5, G6 and G7) (Carosella et al., 2003). The alternative splicing that occurs in the primary transcripts is noteworthy not only because it is directly related to the production of soluble and truncated proteins, but specially because it can be regulated and, consequently, the expression of a specific HLA-G isoform will depend on the cell type and location (Le Rond et al., 2004; LeMaoult et al., 2005; Morales et al., 2003). Despite this alternate splicing of the mRNAs, the gene structure of HLA-G is homologous to other HLA class I genes, the so called classic HLA genes.

The extracellular structure of HLA-G1 and HLA-G5 is identical to the well described structure of classic HLA class I molecules. They are composed by three globular domains heavy-chain

non-covalentely bound to beta2-microglobulin and a nonapeptide (Carosella et al., 2008). The other isoforms are simpler structures with only one or two globular domains, not binding to beta2-microglobulin neither presenting peptides (figure 1) (Carosella et al., 2008; Clements et al., 2005). The presence of an alpha-3 domain represents a binding site for HLA-G receptors, being consensual that this domain has an important role in the molecule function (Clements et al., 2005). HLA-G1 and HLA-G5 are the most described isoforms in healthy tissue, as well as shed HLA-G1, a soluble HLA-G1 isoform. This soluble shed HLA-G1 derives from the proteolytic shedding of the membrane HLA-G1. This process is dependent on metalloproteinase activity, at post-translational level, and is regulated by different levels of nitric oxide concentration and the activation of Tumor Necrosis Factor – alpha/NFkB pathway (Diaz-Lagares et al., 2009; Park et al., 2004; Zidi et al., 2006).

The HLA-G capability to form dimmers is one of its main features, since they bind to HLA-G receptors, showing higher affinity and slower dissociation rates, when compared to the monomers (Boyson et al., 2002; Shiroishi et al., 2006). Accordingly, it is thought that dimmers are responsible for the majority of HLA-G functions (Gonen-Gross et al., 2003). The dimerization of HLA-G, by intramolecular disulfide bonds, is a result of the presence of two unique cysteine residues, located in the position 42 of the alpha-1 domain and in the position 147 of the alpha-2 domain (Boyson et al., 2002).

The HLA-G molecules do not seem to have significant functions at immune response level, unlike classic HLA class I molecules (Carosella et al., 2008). However, they have the same capability to bind inhibitory receptors, just like the HLA class I molecules (Colonna et al., 1997; Colonna et al., 1998; Rajagopalan and Long, 1999). Three HLA-G receptors have been described, namely: immunoglobulin-like transcript 2 (ILT2) (CD8 5j/LILRB1), ILT4 (CD85d/LILRB2) and the killer cell immunoglobulin-like receptor (KIR) 2DL4 (CD1 58d) (Colonna et al., 1997; Colonna et al., 1998; Rajagopalan and Long, 1999).

ILT2 is expressed by B cells, some T cells (both CD4+ and CD8+), some NK cells and all monocytes/dendritric cells (Colonna et al., 1997). On the contrary, ILT4 is myeloid-specified and is only expressed by monocytes/dendritric cells (Colonna et al., 1998). The higher affinity of HLA-G for LILR1 and, consequently, ILT2, may result from the presence of phenylalanine and tyrosine in the positions 195 and 197 of the alpha-3 domain, respectively. This altered structured, when compared with other HLA class I molecules, increase hydrophobicity, which seems to be the basis of this affinity increased level (Clements et al., 2005). Both ILT receptors are able to recognize different HLA-G structures. ILT2 binds only to beta-2m-associated HLA-G1/G5 isoforms, while ILT4 is also able to recognize the beta-2m-free counter parts from this isoforms (Gonen-Gross et al., 2005; Shiroishi et al., 2006). The presence of antibodies reactive with ILT receptors revealed that the interaction of HLA-G tetramers with blood monocytes was largely due to binding to ILT4, so, higher expression of ILT2 was necessary for efficient HLA-G tetramer binding (Allan et al., 1999). This suggests that the interaction of ILT2 has lower affinity, compared to that of ILT4.

The other ligand, KIR2DL4, is expressed by some CD8+ T and NK cells (Goodridge et al., 2003). These subsets of NK cells (CD56) are a minority of peripheral NK cells, but a majority of uterine NK cells (Goodridge et al., 2003; Kikuchi-Maki et al., 2003). While ILT2 and ILT4 are

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clearly described as inhibitory receptors, the same cannot be said about KIR2DL4, in such an absolute way. Despite the capacity of KIR2DL4 of sending inhibitory signals, it can send also activatory signals. This receptor has a single immunoreceptor tyrosine-based inhibitory motif in its cytoplamsatic tail and a positively charged arginine in the transmembrane region (Selvakumar et al., 1996; Yusa et al., 2002). Finally, this receptor also differentiates from ILTs because these ones bind classic HLA molecules, whereas HLA-G molecules are the only ligands of KIR2DL4 (Colonna et al., 1997; Colonna et al., 1998).

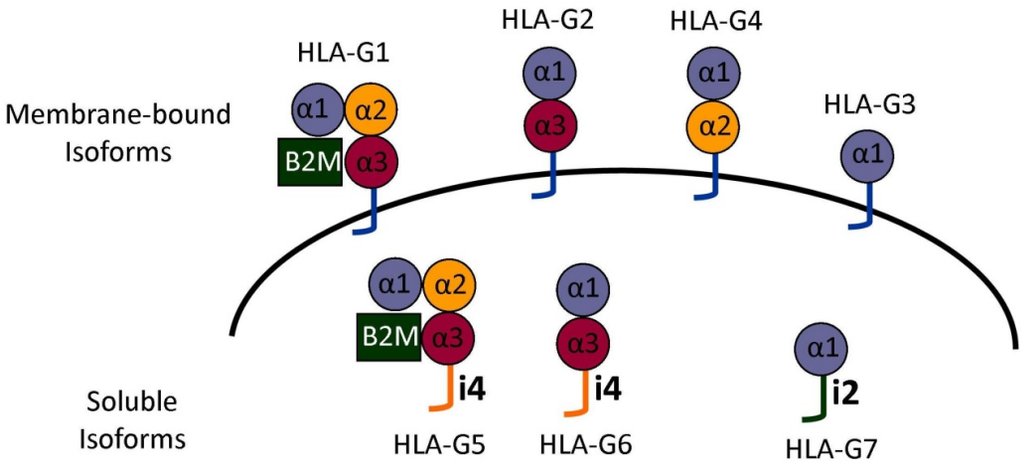

Figure 1. HLA-G isoforms. The alternate splicing of HLA-G primary transcript generates seven different mRNAs. The same number of isoforms is encoded, divided into four membrane-bound and three soluble proteins. Truncated isoforms are generated by excision of one or 2 exons encoding globular domains, whereas translation of intron 4 or intron 2 yields soluble isoforms that lack the transmembrane domain.

5. The HLA-E, HLA-F, and HLA-G polymorphism in world populations

The Human Major Histocompability Complex (MHC) consists of 224 genes encoding proteins controlling cell-to-cell interactions. These genes include the classical class Ia and the non classical class Ib loci. The Ia class is involved in immunological recognition and the Ib class is associated with modulation of the immune system (Hviid, 2006; Townsend and Bodmer, 1989). Each of the nonclassical molecules can be distinguished by well identified biological features: low expression levels, restricted tissue expression, reduced cytoplasmatic tail, unique molecular structure, limited protein variability, and modulation of the immune response cells (Carosella et al., 2008; Diehl et al., 1996; Ishitani et al., 2003; Kovats et al., 1990; Lee et al., 1998). Although the Ia class genes are the most polymorphic known in human, the Ib class genes show a low level of polymorphism. Such variation can be explained by different evolutionary forces acting on HLA family genes. It is believed that the nonclassical gene have been maintained under a distinct selective pressure while the classical gene have been characterized by overdominant selection (Little and Parham, 1999). The polymorphisms of the Ib class do not involve the peptide binding groove (unlike the classical HLA Ia) but it is distributed among the α1, α2, and α3 domains (van der Ven et al., 1998). The limited poly-

morphism of nonclassical HLA has long been believed to reflect the functional diversity required of these molecules (Little and Parham, 1999). The low variability is probably due to a very limited repertoire of peptides presented to T cells (Castro et al., 2000). In fact, HLA-E proteins exhibit on the cell surface a restricted subset of peptides derived from other HLA sequences (Braud et al., 1998; Llano et al., 1998). Moreover, a non variable molecule structure allows an opportune modulation of the immune response in vital situations. HLA-G proteins act as mediator of maternal-fetal tolerance, in order to anergizing the maternal allo-response to antigens. Lack of polymorphism ensures that the paternally derived HLA-G molecules are similar to those of the mother (Le Bouteiller, 1997; Ober, 1998). On the other side, a variation concentrated at the peptide binding groove let the Ia class bind diverse and overlapping sets of peptides. This way, their high polymorphism permits the exhibition as many different peptides as possible to the $\alpha\beta$ T-cell receptors (TCR).

Compared to classical HLA class I that exhibit hundreds of alleles, the HLA Ib present only few variants. With the increasing number of HLA alleles identified, much effort has been devoted to standardize HLA nomenclature. Currently an allele name may be composed by HLA prefix, following by the name of the gene and four, six, or eight digits. Longer names with more digits are only assigned when necessary. A separator (*) is necessary to clearly separate the name of the gene from the number identifying the allele and a colon (:) is necessary to delimit each single fields. The first two digits refer to the allele family, which often corresponds to the serological specificity. The third and the fourth assign the order in which the sequence were determined (Marsh et al., 2010). Alleles whose names differ in the first four digits must have at least one non-synonymous nucleotide substitution that changes the amino acid sequence of the encoded protein. Exemplifying, the HLA G*01:03 allele differs from HLA G* 01:01 allele by a non-synonymous substitution (A-T) at codon 31 in exon 2, exchanging a threonine for serine. Alleles showing synonymous substitution within the coding sequence are distinguished by the use of the fifth and sixth digits (Marsh et al., 2010). For instance the HLA E*01:03:01 allele differs from HLA E* 01:03:02 allele by a silent substitution (C-T) at codon 77 in exon 2. Finally, nucleotide modification observed in introns and in 3′ or 5′ untranslated regions are distinguished by the use of the seventh and the eight digits (Marsh et al., 2010). In addition, an optional suffix may be added to the end of the allele name to indicate its expression status. For example, the HLA G*01:05N (null) allele shows a cytosine deletion at the codon 130 in exon 3 that changes the reading frame and creates a premature stop at codon 171.

5.1. HLA-E polymorphism

HLA-E loci are the most conserved of all the HLA system (Grimsley and Ober, 1997). Currently, 11 HLA-E alleles have been identified in worldwide human populations, encoding three distinct functional proteins (HLA E*01:01, E*01:02, E*01:03) (http://www.ebi.ac.uk/ipd/imgt/hla., Ocober 2013; Robinson et al., 2013). The HLA E*01:03 allele differs from HLA E* 01:01 allele by a non-synonymous substitution (A-G) at codon 107 in exon 3, exchanging arginine/glycine. In spite of its limited polymorphism, the major two alleles showed different biological properties and expression patterns (Tripathi et al., 2006). HLA E*01:04 allele is characterized by two non-synonymous substitutions: the first is the (A-G) mutation at codon 107 in exon 3 and the second is a (A-G) mutation at codon 157 in exon 3, exchanging arginine /glycine (Strong

et al., 2003). Previously, another HLA-E allele has been identified (HLA E*01:02), but this sequence has been deleted from IMGT/HLA database because it was identical to HLA E*01:01:01:01 allele (Lauterbach et al., 2012). Until now the existence of the HLA E*01:04 allele has been subject of many controversy. In 1990, the HLA E*01:04 was originally identified in 1 Japanese out of 22 individuals (Ohya et al., 1990). In 2000, the allele was found in an English population with a low allele frequency (Hodgkinson et al., 2000). Thereafter, the E*01:04 allele has not been identified in any other population so far studied. Some authors speculated that such allele could represent a consequence of a sequencing artifact (Antoun et al., 2009; Grimsley et al., 2002; Park et al., 2007; Romero et al., 2007).

HLA-E polymorphism has been already well studied in several populations and clinical cohorts. Table 1 lists the HLA-E distribution in different ethnic populations. Although several alleles were found among the ethnic groups, the two major alleles (HLA E*01:01 and HLA E*01:03) have been always reported with high frequencies, suggesting a balancing selection operating in order to maintain the two sequences unaltered (Grimsley and Ober, 1997). In 1992 four ape species sequences were examined and the mutation A107G was found in all genomes. This implies that HLA E*01:03 is the original allele and the mutation occurred during the human evolution, probably before the *H. sapiens* expansion, as the two alleles are present in worldwide populations (Grimsley and Ober, 1997).

The geography and the ethnicity were associated to HLA-E variation. In occidental populations the HLA E*01:01 allele was the predominant, while in oriental populations the allele frequency of *01:03 was equal or higher than HLA E*01:01 frequency. The only exceptions were two population of South America (Wayu Indian and Afro-Colombian) where *01:03 was found more frequently than *01:01 (Arnaiz-Villena et al., 2007). It is possible that in these cases the high frequency of the *01:03 allele derives from Caucasian admixture where such allele is the second most common (Arnaiz-Villena et al., 2007). In North America, the Caucasian populations presented the two alleles at nearly equal proportions while the Afro-Americans presented a pattern more similar to that one from African populations, with *01:01 more frequent than *01:03 (Ferguson et al., 2011; Geraghty et al., 1992; Grimsley and Ober, 1997). Furthmore, higher variability was found inside the HLA E*01:03 group. A silent substitution (C-T) at codon 77 in exon 2 distinguished HLA E*01:03:01 from HLA E*01:03:02. In Africa and in Asia the two variants showed nearly equal frequencies. In Europe and in South America populations the *01:03:02 allele was more common than *01:03:01 allele. An exception was an Afro-Caribbean study where the two alleles showed the same frequencies, like in African populations (Antoun et al., 2009). The similarity in the allelic pattern of Afro-Americans and Afro-Caribbean with African population probably reflects their ethnic history, composition and evolution.

5.2. HLA-F polymorphism

There is very little information about HLA-F allelic polymorphism among worldwide populations. Only two studies on HLA-F investigating multiple human populations exist so far (Pan et al., 2013; Pyo et al., 2006). Currently, 22 distinct HLA-F alleles encoding for four distinct proteins (HLA F*01:01, HLA F*01:02, HLA F*01:03, HLA F*01:04) are currently described in human populations (http://www.ebi.ac.uk/ipd/imgt/hla., Ocober 2013; Robinson et al., 2013). The HLA F*01:02 allele differs from HLA F* 01:01 allele by a (C-T) mutation at

codon 13 in exon 1, exchanging alanine /valine. The HLA F*01:03 allele is characterized by a (C-A) mutation at codon 71 in exon 2, exchanging a proline for a glutamine. HLA F*01:04 contains a (T-C) substitution at codon 272 in exon 4, exchanging a serine for a proline. Table 2 lists the HLA-F distribution in different ethnic populations studied so far. The HLA-F polymorphism differed among the ethnic groups. The HLA F*01:01 was the most common with a frequency always up to 90% (Pan et al., 2013). HLA F*01:03 was the second most common but with a low frequency (4-6%) and with even lower frequency in two populations of South China (1-2%) (Pan et al., 2013). The HLA F*01:04 and *01:02 were rare (Pan et al., 2013; Pyo et al., 2006). It is reasonable to consider HLA F*01:01 the ancestral allele considering the strong predominance of HLA F*01:01 and the rarity of other HLA-F alleles (Pan et al., 2013).

5.3. HLA-G polymorphism

HLA-G polymorphism has been extensively analyzed (Hviid, 2006; Morales et al., 1993; Ober et al., 1996). According to the international ImmunoGeneTics Database, 50 HLA-G alleles are currently described, generating 16 distinct functional proteins (HLA G*01:01, *01:02, *01:03, *01:04, *01:06, *01:07, *01:08, *01:09, *01:10, *01:11, *01:12, *01:14, *01:15, *01:16, *01:17 *01:18) and two null alleles (*01:05N, *01:13N) (http://www.ebi.ac.uk/ipd/imgt/hla., Ocober 2013; Robinson et al., 2013). Table 3 lists the HLA-G distribution in different ethnic populations. Beside the original allele HLA G*01:01, only four variations related to amino acid exchange in the coding regions were frequent in worldwide populations (HLA G*01:03, *01:04, *01:05N, and *01:06) (Castelli et al., 2007). The HLA G*01:04 allele differs from HLA G* 01:01 allele by a non-synonymous substitution (C-A) at codon 110 in exon 3, exchanging leucine/isoleucine. The HLA G*01:06 allele is characterized by a C-T mutation at codon 258 in exon 4, exchanging a threonine for a methionine. HLA-G alleles frequencies vary among different ethnic groups, but an accurate comparison among populations is difficult, as there are not many reports using a high resolution data and each study was performed at different time (Park et al., 2012).

The distribution of the HLA-G was not significantly different among populations with respect to HLA G*01:01 group. HLA G*01:01:01 was the predominant allele with a frequency of 60% in Europe, 50% North America, 40% in South America and Africa, and 30% in Asia. It was originally described in 1987 and probably it is the wild-type sequence as it is present in other primate genomes (Geraghty et al., 1987). The frequency of HLA G*01:01:02 was high, constituting approximately 50% in Europe populations, 30% in North America, 20% in South America and Africa, and 15 % in Asia. This allele is characterized by a nonsynonymous C-T mutation at codon 142 in exon 3. HLA G* 01:01:08 was a rare allele in most populations with exception of Brazil (8 and 15%), Zimbabwe (6%), and Poland (5%) (Simoes et al., 2009; Sipak-Szmigiel et al., 2008). This allele is characterized by a nonsynonimous G-A mutation at codon 57 in exon 2.

The HLA G*01:02 allele was found only in South America while it was completely absent in other populations (Arnaiz-Villena et al., 2013). This allele is characterized by a nonsynonimous mutation at codon 54 in exon 2, exchanging a glycine for an arginine.

The HLA G* 01:04:01 allele was found with high frequencies in Canadian, Asian, and Africa populations while it was low in Brazil and Caucasian population. The population of Nunavik

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in Canada presented the highest level of frequency with 50%, followed by Singapore (45%), Japan (38%), Korea (34%), and Iran (29%) (Ishitani et al., 1999; Metcalfe et al., 2013; Park et al., 2012; Tan et al., 2008). This allele is characterized by a synonymous G-A mutation at codon 57 in exon 2 and a nonsynonymous C-A mutation at codon 110 in exon 3 exchanging a leucine for an isoleucine.

The null allele HLA G*01:05N was detected with high frequency in Spanish (6%) and in Africa-Americans (7%) and with even higher frequency in Iraqi (8%), Indians (14%), and Iranians (18%) (Abbas et al., 2004; Ishitani et al., 1999; Jassem et al., 2012; Rahimi et al., 2010; Suarez et al., 1997). The frequency of the null allele among Caucasian from Europe and South America was low. In Brazil the prevalence of the allele varied from 1% to 3%, while in Europe from 1% to 6%. In Singapore, China, and in some populations of USA the null allele was rare (Abbas et al., 2004; Aldrich et al., 2001; Lin et al., 2006; Yan et al., 2006). In Peru, Guatemala, Japan, and Portugal the allele was completely absent (Alvarez et al., 1999; Arnaiz-Villena et al., 2013; Ishitani et al., 1999). Those reports suggest that the null mutation arose recently in the human population, probably in Africa. Considering the role of HLA-G in the placenta and the selective pressures operating at this stage of development, a new allele could be easily fixed in a population (Ishitani et al., 1999). Then, from Africa it could be introduced into the Spanish population by Arab invaders and into African America population with the slave deportation (Ishitani et al., 1999).

The distribution of the HLA G* 01:06 allele revealed some differences among the populations. This allele contains a nonconservative amino acid substitution (C-T) at codon 258 in exon 4, exchanging threonine/methionine. It occurred with frequencies minor then 8% in Europe, Canada, and Brazil. It showed low frequencies in Asia, and it is completely absent in Africa.

Nine alleles exhibited a point substitution detected only in a single study: the HLA G*01:07, *01:12, *01:13N, *01:14, *01:16, and *01:18 alleles were detected only in one population in Canada (Lajoie et al., 2008; Roger et al., 2012); the HLA G*01:10, *01:11, *01:17 alleles were detected only in Kenia (Luo et al., 2013); and HLA G*01:15 was detected only in Kenya and Canada (Alvarez et al., 1999; Lajoie et al., 2008; Roger et al., 2012).

Country	Reference	HLA E alleles									
		01:01	01:01:01	01:02	01:03	01:03:01	01:03:02	01:03:03	01:03:04	01:03:05	01:04
Spain	(Gomez-Casado et al., 1997)	•		•		o	•				
Spain	(Guzman-Fulgencio et al., 2013)	•			•						
England	(Hodgkinson et al., 2000)	•		•	•						•
Germany	(Furst et al., 2012)	•			•						
Italy	(Paladini et al., 2009)		•			•	•				
South France	(Di Cristofaro et al., 2011)	•				•	•	•	•		
The Neitherland	(Paquay et al., 2009)	•			•						
France	(Tamouza et al., 2006)				*						

Country	Reference	HLA E alleles									
		01:01	01:01:01	01:02	01:03	01:03:01	01:03:02	01:03:03	01:03:04	01:03:05	01:04
Austria	(Danzer et al., 2009)				*						
Caucasian	(Grimsley et al., 2002)	•				•	•				
Caucasian	(Pyo et al., 2006)		•			•	•		•		
Euro-Caucasian	(Antoun et al., 2009)		•			•	•	•	•		
Hispanic	(Grimsley and Ober, 1997)	•			•						
Caucasian	(Grimsley and Ober, 1997)	•			•						
Caucasian	(Arnaiz-Villena et al., 2007)	•				•	•				
Canada	(Ferguson et al., 2011)	•			•						
USA	(Geraghty et al., 1992)	•			•						
Hutterites	(Grimsley and Ober, 1997)	•			•						
Afro-American	(Grimsley and Ober, 1997)	•			•						
Afro-American	(Pyo et al., 2006)		•			•	•		•		
Afro-American	(Grimsley et al., 2002)	•				•	•				
Mazatecan	(Arnaiz-Villena et al., 2007)	•				•	•				
Mexico	(Arnaiz-Villena et al., 2007)	•				•	•				
Wayu	(Arnaiz-Villena et al., 2007)	•				•	•				
Colombia	(Arnaiz-Villena et al., 2007)	•				•	•				
Afro-Colombia	(Arnaiz-Villena et al., 2007)	•				•	•				
Afro-Carabbean	(Antoun et al., 2009)		•			•	•	•	•		
Mapuche	(Arnaiz-Villena et al., 2007)	•				•	•				
Brazil	(Veiga-Castelli et al., 2012)		•			•	•				
Brazil	(Veiga-Castelli et al., 2012)									o	
South Brazil	(Carvalho dos Santos et al., 2013)	•				•	•	•	•		
Negroids	(Arnaiz-Villena et al., 2007)	•				•	•				
Tunisia	(Hassen et al., 2011)	•			•						
Egypt	(Mosaad et al., 2011)	•			•						
Mapuche	(Arnaiz-Villena et al., 2007)	•				•	•				
Teke Congolese	(Di Cristofaro et al., 2011)	•				•	•	•	•		
Tswa Pygmies	(Di Cristofaro et al., 2011)	•				•	•	•	•		
Zimbawe	(Lajoie et al., 2006)	•			•						
Africa (Shona)	(Matte et al., 2000)	•				•	•				
Japan	(Grimsley et al., 2002)	•				•	•	•			
Japan	(Pyo et al., 2006)		•			•	•		•		
Shangai Han	(Zhao et al., 2001)	•				•	•				
Thailand	(Kimkong et al., 2003)	•				•	•				
Thai -China	(Kimkong et al., 2003)	•				•	•				

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Country	Reference	HLA E alleles									
		01:01	01:01:01	01:02	01:03	01:03:01	01:03:02	01:03:03	01:03:04	01:03:05	01:04
Thailand	(Hirankarn et al., 2004)	•			•						
Korea	(Park et al., 2007)	•				•	•				
India	(Arnaiz-Villena et al., 2007)	•				•	•				
India	(Tripathi et al., 2006)	•				•	•				
China (Hunan han)	(Liu et al., 2012)	•			•						
China (Mongolia Han)	(Liu et al., 2012)	•			•						
China (Mongolia Mongol)	(Liu et al., 2012)	•			•						
China (Guangdong Han)	(Liu et al., 2012)	•			•						
China	(Zhen et al., 2013)	•				•	•				
China	(Grimsley and Ober, 1997)	•			•						
Indo-Asian	(Antoun et al., 2009)	•				•	•	•	•		
Orientals	(Arnaiz-Villena et al., 2007)	•				•	•				
Australia	(Hosseini et al., 2013)	•			•						

*: HLA E 01:03 specific study

o New allele identification

Table 1. HLA E distribution in different ethnic populations.

Country	Reference	HLA F Alleles																						
		01:01	01:01:01:01	01:01:01:02	01:01:01:03	01:01:01:04	01:01:01:05	01:01:01:06	01:01:01:07	01:01:02	01:01:02:01	01:01:02:02	01:01:02:03	01:01:02:04	01:01:02:05	01:01:03:01	01:01:03:02	01:01:03:03	01:01:03:04	01:02	01:03	01:03:01:01	01:03:01:02	01:04
Japan	(Uchigiri et al., 1997)	•																						
Japan	(Pyo et al., 2006)		•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•		•	•	•
Japan	(He et al., 2004)									o														
Hunana-Han	(Pan et al., 2013)	•																			•			•
Mongolia-Han	(Pan et al., 2013)	•																			•			•
Mongolia-Mongol	(Pan et al., 2013)	•																			•			•
Guangdong-Han	(Pan et al., 2013)	•																			•			•
Caucasian	(Pyo et al., 2006)		•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•		•	•	•
Afro-American	(Pyo et al., 2006)		•	•	•	•	•	•	•		•	•	•	•	•	•	•	•	•	•		•	•	•

o New allele identification.

Table 2. HLA F distribution in different ethnic populations.

Country	Reference	HLA G alleles 01:01	01:01:01	01:01:02	01:01:03	01:01:04	01:01:05	01:01:06	01:01:07	01:01:08	01:01:09	01:01:10	01:01:11	01:01:12	01:01:14	01:01:15	01:01:17	01:01:20	01:02	01:03	01:03:01	01:04	01:04:01	01:04:02	01:04:03	01:04:04	01:04:05	01:05N	01:06	01:07	01:09	01:10	01:11	01:12	01:13N	01:14	01:15	01:16	01:17	01:18
Quebec (Inuit)	(Metcalfe et al., 2013)		•	•	•					•										•			•							•										
Quebec	(Metcalfe et al., 2013)		•	•	•																		•						•											
Quebec	(Ferguson et al., 2011)		•	•	•		•		•	•										•			•		•			•												
Canada	(Lajoie et al., 2008)																																	o	o	o	o	o		
Canada	(Roger et al., 2012)																																							o
Canada	(Ferguson et al., 2012)		•	•	•					•										•			•			•		•	•											
Caucasian	(Warner et al., 2002)		•	•	•															•			•					•	•											
USA - Canada	(Aldrich et al., 2001)		•	•	•		•	•	•	•										•			•	•	•			•												
Africa - America	(Ishitani et al., 1999)		•	•	•																	•						•												
Guatemala	(Arnaiz-Villena et al., 2013)	•	•	•	•														•		•		•						•		•									
Peru	(Arnaiz-Villena et al., 2013)	•	•	•	•														•		•		•						•		•									
Euro-Brazilian	(Nardi Fda et al., 2012)		•	•	•			•	•	•				•	•			•			•		•		•	•		•	•											
Brazil	(Castelli et al., 2011)	•	•	•	•		•				•									•		•	•			•	•	•	•		•									
Brazil	(Simoes et al., 2009)	•																		•		•						•												
Brazil	(Castelli et al., 2008)	•	•	•	•	•	•	•		•			•							•		•	•			•		•	•		•									
Brazil	(Pirri et al., 2009)	•			•	•				•										•			•					•												
Brazil	(Castelli et al., 2007)		•	•	•	•		•		•										•			•			•		•	•											
France	(Di Cristofaro et al., 2011)	•																		•		•						•	•											
Poland	(Sipak-Szmigiel et al., 2009)		•	•	•			•		•	•												•					•	•											
Poland	(Sipak-Szmigiel et al., 2008)		•	•	•	•	•	•		•		•								•			•					•												
Italy	(Rizzo et al., 2008)			•	•															•								•												
Italy	(Moreau et al., 2008)	•																		•		•						•	•											
Denmark	(Hviid et al., 2002)		•	•	•		•			•										•			•		•			•	•											
Germany	(Pfeiffer et al., 2001)		•	•	•																		•	•				•												
Portugal	(Alvarez et al., 1999)		•	•	•															•		•																		
Finland	(Karhukorpi et al., 1996)		•	•	•																																			
Spain	(Suarez et al., 1997)		•	•	•																	•						o												
Caucasian	(van der Ven et al., 1998)	•	•	•	•																•	•	•					•												
Kenia	(Luo et al., 2013)		•	•	•					•	•					•	•				•		•				•	•				•	•						•	
Teke Congo	(Di Cristofaro et al., 2011)	•																		•		•						•									•			
Tswa Pygmie	(Di Cristofaro et al., 2011)	•																		•		•						•												
Zimbabwe	(Matte et al., 2004)		•	•						•										•			•					•												
Tunisia	(Ghandri et al., 2011)	•																				•						•												
Ghana	(Ishitani et al., 1999)		•	•																		•						•												
East Africa	(Matte et al., 2002)		•	•						•										•			•					•												
Iraq	(Jassem et al., 2012)	•	•	•	•															•		•						•	•											
Korea	(Park et al., 2012)		•	•	•					•										•			•					•	•											
Iran	(Rahimi et al., 2010)		•	•	•		•		•	•													•		•			•												
Singapore	(Tan et al., 2008)	•	•	•	•					•										•			•					•	•											
India	(Abbas et al., 2004)		•	•	•	•	•			•									•	•		•						•	•											
Japan	(Ishitani et al., 1999)		•	•	•																	•																		
China Han	(Yan et al., 2006)		•	•	•					•										•			•	•	•			•												
China Han	(Lin et al., 2006)		•	•	•					•										•			•	•	•			•												

o New allele identification.

Table 3. Table 3. HLA G distribution in different ethnic populations.

6. HLA-G and disease association

Since its cloning and sequencing, in 1987 (Geraghty et al., 1987), and the discovery of HLA-G expression in early gestation human cytotrophoblasts (Kovats et al., 1990) that this locus has been investigated for its tolerogenic function. The maternal-fetal interface is known to protect the fetus from destruction by the immune system of its mother (Loustau et al., 2013). Besides

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this function, HLA-G and its pathological relevance have long been investigated, in several areas of research, and it has already been associated with numerous conditions (Carosella et al., 2008; Donadi et al., 2011).

As previously mentioned, HLA-G gene exhibits several distinctive biological features that differ from other HLA Class I molecules: 1) limited protein variability due to low number of polymorphic sites within the coding region, 2) presence of several membrane-bound and soluble isoforms (G1-G5), generated by alternative splicing, 3) unique molecular structure with a reduced cytoplasmic tail due to a STOP codon in exon 6, 4) modulation of the immune response, being a potent tolerogenic molecule with known inhibitory functions, 5) and restricted tissue expression to trophoblast cells (Kovats et al., 1990), adult thymic medulla (Mallet et al., 1999) and stem cells (Selmani et al., 2008). However, HLA-G neo expression can be induced in several pathological conditions such as cancers, transplantation, multiple sclerosis, inflammatory diseases and viral infections.

The association of the HLA-G molecule and diseases/conditions is obviously related to its function (Table 4) and many studies provide evidence of this association. The objective of this section is not to review all of those studies but to highlight the most recent and significant.

Action	Cells	Activity	References
inhibits	NK cell and cytotoxic T lymphocyte	cytolytic activity	(Riteau et al., 2001; Rouas-Freiss et al., 1997)
inhibits	CD4+ T cell	alloproliferative responses	(LeMaoult et al., 2004)
inhibits	T cell and NK cell	ongoing proliferation	(Bahri et al., 2006; Caumartin et al., 2007; LeMaoult et al., 2004)
inhibits	dendritic cell	maturation	(Gros et al., 2008; Liang et al., 2008)
induces	suppressive T cells	generation	(Agaugue et al., 2011; Gros et al., 2008)

Table 4. The association of the HLA-G molecule with diseases/conditions and its function.

6.1. HLA-G and pregnancy related problems

Human leukocyte antigen (HLA)-G has long been considered an important participant on the fetal-maternal tolerance and is thought to play a crucial role in ensuring a successful pregnancy. A vast number of studies have suggested that the expression of HLA-G, influenced by the genetic variation in the gene, is associated with pregnancy related problems. However, there is no actual consensus about the real clinical value of specific genetic variations. Furthermore, some authors stress out that most of the studies on this topic assessed the role of HLA-G taking into account only the maternal genotype and ignored the contribution of the fetus. The authors suggest that studies on placental diseases should address HLA-G expression and genetic variations also to the fetus/placenta (Cecati et al., 2011).

In the latest published studies there is a special interest in the 14bp insertion(ins)/deletion(del), which may have an effect on the HLA-G protein stability and soluble HLA-G quantity. A meta-analysis study was recently performed to evaluate the association of this polymorphism with unexplained recurrent spontaneous abortions (URSA). 14 studies with 1464 cases and 1247 controls were included. Significant associations between 14 bp ins/del polymorphism and risk of URSA were observed in both dominant and codominant models, suggesting that this polymorphism is indeed associated with increased risk of URSA (Wang et al., 2013). Another study investigated the homozygous carriage of the 14 base pair (bp) insertion and recurrent miscarriage (RM). The authors investigated the G14bp insertion(ins)/deletion(del) polymorphism in 339 women with unexplained RM and 125 control women. The authors observed that homozygosity for G14bp ins predisposes to RM. The combination of G14 ins homozygosity and carriage of an HLA class II (HYrHLA) allele restricting immunity against male-specific minor HY antigens predisposes to secondary RM in women with a firstborn boy and negatively affects birth weight in these boys (Christiansen et al., 2012).

A recent case-control study, investigated the association between the genetic variability of the HLA-G gene and serum levels of soluble HLA-G in cases of embryo implantation failure (IF). 40 couples with implantation failure and 83 fertile couples were investigated. HLA-G alleles were typed (SBT) and the quantification of soluble HLA-G (sHLA-G) was performed by ELISA. There was a significant difference between the HLA-G allelic distributions between IF couples and the control couples. The HLA-G*01:03:01 allele was increased in the IF couples. There were no significant differences in the serum levels of sHLA-G in the IF and control groups. The authors suggest that the distribution of HLA-G products may play a significant role in the modulation of maternal-fetal immune response (Nardi Fda et al., 2012).

Another study shows evidence of HLA-G regulation at the post-transcriptional level. The authors investigated the role of a specific micro RNA (miR-133a) in regulating HLA-G expression and the pathogenesis of recurrent spontaneous abortion (RSA). Twelve patients with RSA at 7 gestational weeks were screened by array-based comparative genome hybridization. The villi of RSA with normal karyotype were further screened by miRNA microarrays. Multi-software prediction and real-time PCR confirmed that miR-133a was most likely to bind to HLA-G 3' untranscribed region (UTR). Relevance analysis showed that, compared with IA villi, miR-133a was greatly overexpressed in RSA villi with normal karyotype ($P<0.01$), but not in abnormal RSA villi. A luciferase reporter assay suggested that miR-133a interacted with HLA-G 3' UTR. Overexpression of miR-133a in JEG-3 cells decreased HLA-G expression at the protein level, with no effect on mRNA. These findings provide strong evidence that miR-133a regulates HLA-G expression by reducing translation and is involved in the pathogenesis of RSA (Wang et al., 2012).

There is still much to be learnt about the HLA-G and pregnancy related topics. The interest of HLA-G in Assisted Reproduction Technology (ART) has been growing since the existence of markers to determine a successful pre-implantation embryo would definitely minimize the negative outcomes of In vitro fertilization (IVF) techniques. A multicenter retrospective study was recently undertaken to determine whether the presence of soluble human leukocyte antigen G (sHLA-G) affects implantation and pregnancy outcomes *in vitro*. Embryos obtained

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from 2,040 patients from six different IVF clinics were investigated. Soluble HLA-G determination on day-2 embryos after intracytoplasmic sperm injection, with embryos transferred on day 3 using the sHLA-G data. All embryos were individually cultured, and a chemiluminescence enzyme-linked immunosorbent assay was used to detect the presence of sHLA-G in the culture medium surrounding the embryos. Embryos were selected based on a positive sHLA-G result and a graduated embryo scoring (GES) score >70, or on embryo morphology if the test was negative. In all centers, a positive sHLA-G result was associated with an increase in the odds of an ongoing pregnancy. The incidence of an ongoing pregnancy was 2.52 times greater in embryos transferred on day 3 with a positive sHLA-G test result than the incidence of an ongoing pregnancy in embryos with a negative sHLA-G test result. As a conclusion, data from this multicenter study confirm that sHLA-G expression is a valuable noninvasive embryo marker to assist in improving pregnancy outcomes (Kotze et al., 2013).

The results of this study are promising but further confirmation is needed.

6.2. HLA-G and cancer

Cancer cells exhibit tumor-associated antigens which are coded by mutated or normal deregulated genes that, once presented by classical MHC class I molecules, may be recognized by host immune system, being frequently eliminated. Neoplastic cells are capable of growing and evolving, by tumour immunoediting, to aggressive malignant lesions (Carosella and Horuzsko, 2007; Donadi et al., 2011; Dunn et al., 2004). Tumor immunoediting consists of three major steps based on the elimination, equilibrium and escape (Dunn et al., 2004):

1. Most immunogenic tumor cells are eliminated by cytotoxic T and NK cells;
2. Tumour cells with reduced immunogenicity are selected;
3. Variants that no longer respond to the host immune system are maintained.

The ectopic expression of HLA-G in cancer occurs in several types of primary tumors, metastases and malignant effusions and can be found in tumour cells and tumour infiltrating cells. This expression has been shown important for the first step of the immunoediting process as it inhibits the cytotoxic function of T and NK cells (Carosella and Horuzsko, 2007).

A recent review paper written by Curigliano and colleagues highlights the underlying molecular mechanisms of impaired HLA-G expression, the immune tolerant function of HLA-G in tumors, and the potential diagnostic use of membrane-bound and soluble HLA-G as a biomarker to identify tumors and to monitor disease stage. The authors stress out the importance of HLA-G as an attractive therapeutic strategy against cancer (Curigliano et al., 2013).

A recent study made the evaluation of plasma soluble HLA-G (sHLA-G) concentrations and the 14-bp insertion/deletion polymorphism of the HLA-G gene in patients with papillary thyroid carcinoma (PTC) or Hashimoto's thyroiditis (HT) to assess the possible association of these parameters with PTC aggressiveness. Besides the confirmation of the frequent association between PTC and chronic autoimmune thyroiditis, this study suggests that elevated circulating sHLA-G levels, can be an important signal of alterations of immune homeostasis that can possibly be considered a potential novel marker of PTC histopathological aggressive-

ness at diagnosis. However, additional studies are needed to confirm the actual role and clinical relevance of the HLA-G complex in PTC development and progression (Dardano et al., 2012).

An interesting study investigated whether or not HLA-G expression is associated with breast cancer molecular subtypes. HLA-G expression was immunohistochemically investigated in 104 patients with invasive ductal breast carcinoma, in which 56 were luminal A, 17 were luminal B, 19 were HER-2, and 12 were basal-like/normal breast-like subtype classified according to immunohistochemical staining results of ER, HER-2, CK5/6, and EGFR. Host immune response status was assessed by estimating the density of tumor infiltrating lymphocytes (TIL). The authors reported that there were more cases with high expressions of HLA-G in non-luminal than in luminal subtypes (P=0.035). In contrast, more cases with high density of TIL was found in luminal than in non-luminal subtypes (P=0.023). Compared to all the biomarkers studied, only HLA-G expression was found to be inversely associated with the density of TIL (P=0.004). Furthermore, patients with HLA-G(high)/TIL(low) status had a higher risk of recurrence than those with HLA-G(low)/TIL(high) status, regardless of the molecular subtypes. The authors suggest that a combination of the status of HLA-G and TIL could improve the prognostic prediction for patients with various molecular subtypes of breast cancer (Dong et al., 2012). HLA-G expression has also been recently investigated in acute lymphoblastic leukemia (ALL) patients. HLA-G showed a negative correlation with NK cells confirming its importance in tumor escape through down-regulation of NK cells. The authors suggest that HLA-G expression could be used as a prognostic tumor marker to monitor disease state and improvement in ALL (Alkhouly et al., 2013).

There has been considerable interest on the association of HLA-G and cervical neoplasia as well as HPV infection. HLA-G expression was recently examined by immunohistochemistry in 22 normal cervical tissues, 14 cervical intraepithelial neoplasia (CIN) patients and 129 patients with squamous cell cervical cancer. It was found that HLA-G expression was absent in normal cervical tissues, and that HLA-G expression was increased from patients with CIN III (35.7%, 4/14) to patients with cervical cancer (62.8%, 81/129). Among the cervical cancer patients, HLA-G expression in FIGO stage I, II, and stage III+IV was 53.6% (45/84), 76.3% (29/38), and 100.0% (7/7), respectively. This study gives a clear indication that HLA-G expression is associated with the disease progression in patients with cervical cancer (Li et al., 2012).

6.3. HLA-G and viral infections

Viruses have developed numerous strategies to sabotage host immune surveillance and responses. The immune-inhibitory functions of HLA-G, elect this molecule as a potential immune escape strategy that would protect virus infected cells against immune effectors, thus facilitating viral progression (Gonzalez et al., 2012). Given the HLA-G role in immune tolerance, its function in viral infections has been increasingly investigated.

A recent study investigated the association between HLA-G polymorphisms and human papillomavirus (HPV) infection and squamous intraepithelial lesions (SIL). The results suggest that HLA-G polymorphisms may play a role in the natural history of HPV infection, likely at the stage of host immune recognition. The authors conclude that HLA-G polymorphisms

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interacted differently with the three alpha papillomavirus groups (Metcalfe et al., 2013). Another study investigated the possible influence of two HLA-G polymorphisms located on the 3'UTR, 14 bp In/Del and +3142C/G, on the susceptibility to cervical cancer. The authors conclude that the 3'UTR of HLA-G is associated with an increased risk of developing cervical cancer, especially in smokers (Silva et al., 2013).

The association of HLA-G polymorphisms and HCV infection has previously been reported (Cordero et al., 2009; Martinetti et al., 2006) however, the reason why HLA-G is up regulated and expressed in the presence of different viruses is still not clear. It is thought that cytokines such as IFNs or IIL-10 are involved in this expression. The specific role of HLA-G molecules was recently investigated in chronic hepatitis C. For the first time, the HLA-G^+ cells were identified as being mast cells. HLA-G secretion was significantly induced in human mast cells stimulated by IL-10 or interferons of class I. The transcriptome of the secretome of this cell line stimulated by IFN-α revealed that i) the HLA-G gene is upregulated late, ii) T lymphocytes and NK cells are recruited. Based on this study the authors suggest an autocrine loop in the genesis of HCV liver fibrosis, based on mast cells expressing HLA-G (Amiot et al., 2013).

The first evidence of an association between HLA-G polymorphisms and malaria infection was recently provided (Garcia et al., 2013). However, further investigations will have to be undertaken before establishing this possible involvement of the HLA-G molecule in the control of *P. falciparum* infection.

HLA-G polymorphism and expression are also associated with the risk of human immunodeficiency virus (HIV) infection (Lajoie et al., 2006; Matte et al., 2004). A recent study showed that non-classical HLA-G-expressing CD4 Treg are highly susceptible to HIV-1 infection and significantly reduced in persons with progressive HIV-1 disease courses. In addition, the authors found that the proportion of HLA-G^+ CD4 and CD8 T cells was inversely correlated to markers of HIV-1 associated immune activation. Mechanistically, this corresponded to an increased ability of HLA-G^+ Treg to reduce bystander immune activation, while only minimally inhibiting the functional properties of HIV-1-specific T cells. This study suggests an important role of HLA-G^+ Treg; the loss of these cells, during advanced HIV-1 infection, may contribute to immune dysregulation and HIV-1 disease progression (Li et al., 2013). The role of HLA-G in mother-to-child HIV transmission (MCHT) was also recently investigated in Kenya. HLA-G was sequenced and genotyped in 266 mothers and 251 children. Among 14 HLA-G alleles identified, only 4 alleles have a phenotype frequency above 10%. Correlation analysis showed that HLA-G(∗)01:03^+ mothers were less likely to perinatally transmit HIV-1 to their children (p=0.038, Odds ratio:0.472, 95%CI:0.229-0.973). Mother-child HLA-G concordance was not associated with the increased perinatal HIV transmission. There was no significant difference in the general health between the transmitting mothers and the mothers who did not transmit HIV to their children (Luo et al., 2013).

The association between HLA-G and cytomegalovirus infection has been long investigated. In 2000, Onno and colleagues investigated the hypothesis that HLA-G molecules could be induced during HCMV reactivation in activated macrophages to favor virus dissemination. The authors suggested that the modulation of HLA-G protein expression during HCMV replication occurs at a post-transcriptional level and that this could be an additional mecha-

nism that helps HCMV to subvert host defenses (Onno et al., 2000). A study found evidences that support a potential role of HLA-G 14 bp insertion/deletion polymorphism as a susceptible factor for the active hCMV infection (Zheng et al., 2009). The same polymorphism (14bp in/del) was recently investigated in the risk of acute rejection (AR) and CMV infection. Multivariate analysis demonstrated that HLA-G homozygous +14 bp and -14 bp genotypes were an independent risk factor for allograft rejection and CMV infection, respectively (Jin et al., 2012).

6.4. HLA-G and autoimmune diseases

HLA-G has been associated to several autoimmune and inflammatory diseases. The implication of HLA-G in the development of autoimmune diseases is probably related to its suppressive effect of the immune response in these diseases.

HLA-G role in ankylosing spondylitis (AS) is poorly understood since it has not been thoroughly studied. It has been shown that lower serum levels of sHLA-G contribute to susceptibility to AS, and predispose to poor spinal mobility. The expression of HLA-G on PMBCs is up-regulated in AS, which is correlated with acute phase reactants, decreasing after TNF-alpha blocker therapy (Chen et al., 2010). A recent study investigated the role of HLA-G in sacroiliitis of Ankylosing spondylitis (AS) and concluded that there is a significant association between HLA-G expression and the AS sacroiliitis stages suggesting that HLA-G is possibly involved in the pathology of the disease. The authors suggest that detection of HLA-G expression may be a useful laboratory test to reveal disease progress in AS patients (Zhang et al., 2013). HLA-G has also been recently investigated in rheumatoid arthritis patients. The authors report that sHLA-G, mHLA-G and ILT2 expression were inversely correlated with DAS28 disease scores. The frequency of 14 bp deletion allele was increased in patients with disease remission. Thus, HLA-G is suggested to be a candidate biomarker to evaluate early prognosis and disease activity in rheumatoid arthritis patients (Rizzo et al., 2013). However, discrepant results about the association of HLA-G and rheumatoid arthritis have also been presented (Kim et al., 2012). HLA-G has been investigated in another inflammatory autoimmune disease, systemic lupus erythematosus (SLE), with unknown etiology. The influence of two HLA-G polymorphisms, 14bp indel polymorphism and the +3142 C>G, was investigated in European patients with SLE. The authors report a significant increase of the +3142G allele frequency among patients as compared with controls (0.58 vs 0.47, $P = 0.011$). Also, patients presented a higher frequency of the GG genotype (OR = 1.90, 95% CI: 1.08-3.42). Double heterozygotes for the two polymorphisms presented a milder mean systemic lupus erythematosus disease activity index (SLEDAI) than heterozygotes for only one of the variants or non-heterozygous individuals (1.56 vs 3.15 and 3.26, respectively, corrected $P = 0.044$). These results suggest the involvement of the HLA-G molecule on SLE susceptibility and outcome (Consiglio et al., 2011). The interest of HLA-G in multiple sclerosis (MS) has been growing in the last decade. Original findings suggested a potential immunoregulatory role for IL-10 in the control of MS disease activity by shifting the sHLA-I/sHLA-G balance towards sHLA-G response (Fainardi et al., 2003). Furthermore, HLA-G and its receptor ILT2 has been identified on CNS cells and in areas of microglia activation. These findings further implicated HLA-G as a contributor to the fundamental mechanisms regulating immune reactivity in the CNS. The authors postulated that this

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pathway may act as an inhibitory feedback aimed to downregulate the deleterious effects of T-cell infiltration in neuroinflammation (Wiendl et al., 2005). Several HLA-G polymorphisms have been thoroughly investigated; some were shown to be associated with MS in different populations (Rizzo et al., 2012; Wisniewski et al., 2010). A recent genome wide association study opened new perspectives on MS pathogenesis and further implicated HLA loci, in particular HLA-G, in the genetic susceptibility (Song et al., 2013).

7. HLA-E and HLA-F disease association

HLA class Ib family members include HLA-E, -F, -G, and HFE (HLA-H). They are poorly polymorphic, have a lower surface expression when compared with the classic MHC class Ia molecules, and have a narrow tissue distribution. They are best known for their capability of regulating innate immune responses (Rodgers and Cook, 2005). However, there is also evidence that, like the MHC class Ia molecules, certain class Ib can participate in the regulation of acquired immune responses to bacteria and viruses (Lenfant et al., 2003; Rodgers and Cook, 2005).

7.1. HLA-E and HLA-F in cancer and infection

Downregulation of MHC class Ia molecule expression is a mechanism used by tumor cells to escape antitumor T-cell-mediated immune responses. However, it was not known why tumors escape from NK cells activity, and it was postulated that the aberrant expression of nonclassical HLA class Ia molecules could provide the required inhibitory signal to NK cells. The possible role of HLA-E molecules in providing tumor cells with an NK escape mechanism was analyzed, through the investigation of this class Ib molecule in a variety of tumor cell lines (Marin et al., 2003). The result of this investigation showed that further to HLE-E expression in leukemia-derived cell lines, this allele was detected in tumor cells of different origin.

HLA-E is involved in the regulation of NK cell function (Pietra et al., 2009), and is the only known ligand for the lecitin receptor CD94 combined with different NKG2 subunits (Kaiser et al., 2005; Lee et al., 1998), expressed on NK and CD8+ $\alpha\beta$ T cells. This interaction may augment (CD94/NGK2C), or inhibit (CD94/NGK2A) NK cell mediated cytotoxicity and cytokine production. HLA-E, unlike other MHC class Ib molecules is transcribed in virtually all human tissues and cell lines, although at lower levels than MHC class Ia (Braud et al., 1997; Wei and Orr, 1990) and bind nonamer peptides derived from other HLA class I signal sequences with a high restricted repertoire (Lee et al., 1998). As stated in previous sections of this chapter, the coding variation of HLA-E is mainly limited to two alleles, with similar frequencies in most populations. These alleles probably are the result of balancing selection and although there are few specific coding variants, they may have functional consequences affecting quantitatively or qualitatively protein expression. The non-synonymous alleles of HLA-E are referred as HLA-E^r (E*0101) and HLA-E^g (E*0103) since they are distinguished by having either an arginine or a glycine at position 107 of the protein. Clear differences exist between the two alleles in relative peptide affinity, which correlated with and may be ex-

plained by differences between their thermal stabilities. (Strong et al., 2003). The functional diferences between the two HLA-E alleles also correlates with the expression levels which has been shown to affect inhibitory activity (Lee et al., 1998). According to several reports the increased inhibitory activity may be involved in increasing inhibitory signals to NK cells, allowing tumor escape. A recent manuscript, investigating HLA-E gene polymorphisms expression in colorectal cancer tissue of two hundred thirty patients, using immunohistochemistry, found that patients with overexpression exhibited the lowest long-term survival rate. Interestingly the authors found out that the type of HLA-E polymorphism did not had an impact on HLA-E expression or prognosis in patients with stage III colorectal cancer (Zhen et al., 2013). A previuos report on colorectal cancer had demonstrated, in situ, that HLA-E/beta2m overexpression on tumor cells was a factor for unfavorable prognosis and that the overexpression was associated with celular infiltration with intraepithelial tumor infiltrating lymphocytes (IEL – TIL) (Wischhusen et al., 2005). Cetuximab, an anti-epidermal growth factor receptor monoclonal antibody which renders cancer cells more sensitive to antibody–dependent cellular toxicity (ADCC), has increased activity if cells are treated previously with an anti-NKG2A monoclonal antibody, that restored the ability of immune cells to kill their target. This result demonstrates that HLA-E at the cell surface can reliably suppress the ADCC effect (Levy et al., 2009).

Using an immunohistochemistry approach, a correlation was also found in early breast cancer between increased expression of HLA-E, loss of classical HLA class I and a worse relapse-free period (de Kruijf et al., 2010). Using the same technique, increased in vivo expression of HLA-E in lower grade gliomas and a massive overexpression in grade IV glioblastomas compared with normal CNS tissue and, siRNA-mediated silencing of HLA-E or blocking of CD94/NKG2A, enabled NKG2D-mediated lysis of 51Cr-labeled tumor cells by NK cells, provided the first evidence that expression and interaction of HLA-E on cancer cells with CD94/NKG2A expressed on lymphocytes compromises innate anti-tumor immune responses (Wischhusen et al., 2005). The overexpression of HLA-E was again detected in WHO grade IV glioblastoma, and a correlation with the identification of immune cell infiltration (NK and Tcells) was established (Mittelbronn et al., 2007). The expression of HLA-G and HLA-E by neoplastic cells in 39 cases of glioblastoma was recently evaluated, and a positive correlation between the expression of HLA-E and length of survival was found (Kren et al., 2011). It was also demonstrated that HLA-E expression at the cell surface of melanoma and ovarian carcinoma cell lines decreased their susceptibility to CTL lysis. (Derre et al., 2006; Malmberg et al., 2002). Both studies also shows that IFN-gamma modulation of target cells, although facilitates the T-cell receptor-mediated recognition by CD8+ T cells, by increasing the expression of HLA class I molecules, decreases target cell sensitivity to lysis by NK cells, a phenomenon that is dependent on enhanced inhibitory signaling via CD94/NKG2A receptors expressed on the effector cells. Recently another study showed that overall survival of ovarian cancer patients is strongly influenced by HLA-E, and that CTL infiltration in ovarian cancer is associated with better survival only when HLA-E expression is low, and that intratumoral CTLs are inhibited by CD94/NKG2A receptors in the tumor microenvironment (Gooden et al., 2011).

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Recent evidence revealed that several proteins other than MHC class I molecules encode peptides that can bind to HLA-E. These peptides may be derived from pathogens, stress-related or from normal proteins, and they markedly differ in sequence from the canonical MHC class I-derived leader sequence peptides. The best characterized peptides are derived from the gpUL40 leader sequence of two cytomegalovirus (CMV) strains, and are assembled with HLA-E via a TAP independent mechanism. Other peptides are derived from the human heat shock protein 60 (hsp60) (Michaelsson et al., 2002), the multidrug resistance-associated protein 7 (MRP7) (Wooden et al., 2005), the human immunodeficiency virus (HIV) gag protein (HIV p24) (Nattermann et al., 2005), the Salmonella entérica serovar Typhi GroEL protein (GroEL) (Salerno-Goncalves et al., 2004), and gliadin (gliadin α2 chain) (Terrazzano et al., 2007).

Other viral proteins previously shown to bind MHC class I molecules, may also bind HLA-E, like peptides from the Epstein Barr virus (EBV) BZLF-1 protein, the influenza matrix protein (InflM) (Ulbrecht et al., 1998), and the Hepatitis C vírus (HCV) core protein (HCV Core) (Nattermann et al., 2005). EBV vírus has been associated with nasopharyngeal carcinoma (NPC), a geographically restricted tumor of epitelial cell lining nasopharynx, with several MHC class I associations reported in the literature (Ren and Chan, 1996). The NPC susceptibility is associated with HLA-E*0103 allele, suggesting that this allele may be one of several causes contributing to NPC development. (Hirankarn et al., 2004). A genome-wide association study on NPC found significant association within the HLA region at chromosome 6p21.3, with HLA-A, gamma aminobutyric acid 1 (GABBR1), and HLA-F (Tse et al., 2009). HIV down-regulates the expression of MHC class I proteins H, but not HLA-C, HLA-E and HLA-G molecules on the surface of infected cells via the action of Nef protein. Women who are homozygous for the HLA-E*0103 allele have a 4.0-fold decreased risk of human immunodeficiency vírus 1 (HIV-1) infection in Zimbabwean women. This protection increased to 12.5-fold in women carrying the combination of the protective HLA-E*0103 genotype and HLA-G*0105N heterozygote genotype. The authors of these findings speculate that the differential regulation of HLA molecular expression may modulate mucosal imune response to HIV facilitating or preventing the establishment of disease in the female genital tract (Lajoie et al., 2006).

Further to its important role in innate immunity functioning as a ligand for the CD94/NKG2 receptors, expressed by NK cells and a subset of CTLs (Braud et al., 2003), HLA-E can present peptide antigens for $\alpha\beta$ TCR-mediated recognition (Li et al., 2001) (Li J et al 2001). HLA-E dependent presentation of bacteria-derived antigens to human CD8+ T cells has been reported particularly in bacteria, like Mycobacterium tuberculosis (Mtb)(Heinzel et al., 2002) and Salmonella enterica serovar Typhi GroEL (Salerno-Goncalves et al., 2004). It was also demonstrated that an HLA-E-restricted CD8+ T cells subset represents a significant component of the adaptive immune response to CMV in genetically predisposed individuals (Mazzarino et al., 2005). Furthermore, recent findings demonstrated that HCV gives rise to a peptide that is recognized by CD8+ T cells via their TCR. The same authors also demonstrated that chronic hepatitis C is associated with increased intrahepatic HLA-E expression (Schulte et al., 2009). More recently, however, HLA-E allelic variant HLA-E*0101, was associated with increased

odds of HCV clearance and may help to predict sustained virological response among HIV/HC-coinfected patients under therapy with pegylated-interpheron-alpha and ribavirin (Guzman-Fulgencio et al., 2013). These patients have a high level of antiviral HLA-E CD8+ Tcells with a high degree of antiviral HLA-E restricted IFN-gama secretion which is associated with low HCV viral load. HLA-E*0101 has lower affinity to their natural ligands when compared to HLA-E*0103, and possibly is more available to bind the HCV peptides facilitating HLA-E-restricted CD8+ T-cell responses (Schulte et al., 2009).

HLA-F shows limited polymorphism, and the function of its mainly intracellular protein is not clear. The key residues of the peptide-binding region are highly conserved in all primate studies, suggesting an importante role in cellular physiology (Moscoso et al., 2007). HLA-F is the nonclassical class I molecule least characterized. (Boyle et al., 2006; Lee et al., 2010). Several studies confirmed HLA-F protein expression in diverse tissues and cell lines including B cell, monocytes, bladder, skin, liver, tonsils, spleen and thymus, but no surface expression was detected in the majority of them. Unique potential regulator motifs were identified in HLA-F consistent with tissue specific expression and suggesting specialized functions and tight transcriptional control of the gene (Geraghty et al., 1990; Gobin and van den Elsen, 2000)). No data have been reported regarding peptide or other ligand-binding properties of HLA-F, although the predicted dimensions of the grove are similar to class I molecules which bind peptides (Braud et al., 1998). There are few reports in the literature about the association of HLA-F with disease. Lin A et al (Lin et al., 2011) investigated HLA-F expression in non small-cell lung cancer (NSCLC), and found out that the expression identified in a significant number of câncer cells was not associated with the clinical parameters such as grade of tumor differentiation and disease stage, but NSCL patients with high expression had a poor prognosis. Esophageal câncer was investigated by the same group, and the authors found that patients with upregulated HLA-F expression (lesion vs normal tissue), had significantly worse survival, than those with HLA-F unchanged and downregulated (Zhang et al., 2013).

7.2. HLA-E and autoimmune disease

Behçet disease (BD) is a chronic inflammatory disorder characterized by recurrent genital and oral aphtous ulcers, uveitis, skin lesions and arthritis. Association with variants of candidate genes were reported - HLA-B51, MICA-A6 and MICA-009 (Mizuki et al., 1999). However, the genetic mechanisms underlying this disease are still unrecognized and other genetic variants are under investigation. A study performed in 312 patients with BD and 486 controls, in Korea, reported an association of HLA-E*0101 and HLA-G*010101 and reduced risk of BD. In contrast, the variants HLA-E*010302, HLA-G* 010102, G*0105N and 3741_3754ins14bp were all associated with increased BD risk. The authors conclude that HLA-E and –G appear to function independently and synergistically, increasing BD risk through an imbalance of lymphocyte functions (Park et al., 2007). A report associates HLA-E gene polymorphism with Ankylosing Spondylitis (AS) in Sardinia. The authors genotyped 120 patients with AS, 175 HLA-B27 positive controls and 200 random controls, for six single nucleotide polymorphisms (SNPs) spanning the HLA region between the HLA-E and HLA-C loci. The strongest association was

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found with the HLA-E functional polymorphism rs1264457, raising the possibility that natural killer cells tmay have a possible role in the pathogenesis of AS (Paladini et al., 2009).

Although the genetic susceptibility of Type I Diabetes Mellitus reside in the major histocompatibility complex (MHC) (Todd, 1995), particularly with the class II DQA1 and DQB1 loci, other alleles have been investigated inside the HLA region. An association between HLA-E locus and age at onset and susceptibility to type 1 diabetes mellitus was reported (Hodgkinson et al., 2000). The authors speculate that abnormal expression or presentation of leader sequences by HLA-E may lead to an autoagressive act by NK cells on self tissue, although the role of these cells in the autoimmune destruction of islet B-cells is poorly understood.

In a recent study on Multiple Sclerosis (MS). Serum and cerebrospinal fluid (CSF) samples from MS patients were compared with other inflammatory disorders and non-inflammatory neurological disorders. The data obtained suggest that soluble HLA-E may have a protective role in MS patients, contributing to the inhibition of the intrathecal inflammatory response (Morandi et al., 2013). Another study in Juvenile Idiopathic Arthritis detected higher concentrations of soluble HLA-E (sHLA-E) in the synovial fluid (SF) in extended oligoarticular/polyarticular than in limited articular disease; the higher concentrations correlated with the number of affected joints. The authors speculate that higher SF HLA-E concentrations may protect against cytolysis (Prigione et al., 2011).

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