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REVIEW

HLA class Ib in pregnancy and pregnancy-related disorders

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Abstract The *HLA class Ib* genes, *HLA-E*, *HLA-F*, and *HLA-G*, were discovered long after the classical *HLA class Ia* genes. The elucidation of their functions had a modest beginning. However, their basic functions and involvement in pathophysiology and a range of diseases are now emerging. Although results from a range of studies support the functional roles for the HLA class Ib molecules in adult life, especially HLA-G and HLA-F have most intensively been, and were also primarily, studied in relation to reproduction and pregnancy. The expression of HLA class Ib proteins at the feto-maternal interface in the placenta seems to be important for the maternal acceptance of the semi-allogenic fetus. In contrast to the functions of HLA class Ia, HLA-G possesses immune-modulatory and tolerogenic functions. Here, we review an accumulating amount of data describing the functions of HLA class Ib molecules in relation to fertility, reproduction, and pregnancy, and a possible role for these molecules in certain pregnancy complications, such as implantation failure, recurrent spontaneous abortions, and pre-eclampsia. The results from different kinds of studies point toward a role for HLA class Ib, especially HLA-G, throughout the reproductive cycle from conception to the birth weight of the child.

Keywords *HLA class Ib* genes · Pregnancy · Pregnancy complications · Pre-eclampsia · Assisted reproduction

Introduction

Genes and proteins of the HLA/MHC system vary considerably between individuals. This polymorphism ensures that at least some individuals in a population will be able to mount an adequate specific cellular immune response and evade specific pathogens. A consequence of this genetic diversity of the HLA molecules is that transplants between unrelated individuals will be recognized as foreign and rejected. Historically, the fetus is considered as a semi-allograft as it expresses genes from both the mother and the father. In pregnancy, the immune system of the mother must play dual roles; on one hand, the maternal immune system must be active and alert to protect both the mother and fetus from pathogens, while on the other hand being suppressed or regulated in a way so that the presence of the semi-allogenic fetus is tolerated, despite expressing paternal allo-antigens. Placental animals, including humans, have solved this dilemma by creating a localized and specific immunological environment within the interface between mother and fetus.

The primary contact between the mother and the fetus is the placenta. In this interface, the placental villus consisting of syncytiotrophoblast cells of fetal origin are bathed in maternal blood, and extravillous cytotrophoblast cells invade and form columns into the maternal decidua and replace endothelial cells of the spiral arteries. The development of the placenta

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is critically dependent on the ability of the invading trophoblast cells to interact with cells of the maternal immune system to induce tolerance and avoid elimination (Fig. 1). Correct placentation secures optimal conditions for growth and development of the fetus and prevention of pregnancy complications such as pre-eclampsia. A variety of immune cells and immune effector molecules are found in the feto-maternal interface and have been described as important players for maintaining immune tolerance toward the semi-allogeneic fetus (Munoz-Suano et al. 2011). The fetal trophoblast cells do not express the polymorphic classical HLA class Ia and II molecules, with the exception of a low level of HLA-C, and are thus protected from maternal T cell-mediated alloreactivity. In theory, trophoblast cells would still be vulnerable to attack by NK cells that are specialized in attacking cells without HLA molecules on the surface. A number of studies have shown that the invasive trophoblast cells express a unique combination of the nonclassical HLA class Ib proteins HLA-G, HLA-E, and HLA-F and HLA-C (Ishitani et al. 2006; Ishitani et al. 2003; Kovats et al. 1990; Redman et al. 1984).

In comparison to the classical HLA class Ia molecules, HLA-E, HLA-F, and HLA-G genes and proteins are unique as they show very limited polymorphism, and their expression is limited to particular cells and tissues (Carosella et al. 2015; Geraghty et al. 1987; Hviid 2006) (Fig. 2). The main function of the classical HLA class I and II molecules is to present antigens to immune cells. Although HLA-G is able to bind a limited, but still diverse, set of peptides, the primary role of HLA-G lies most probably in

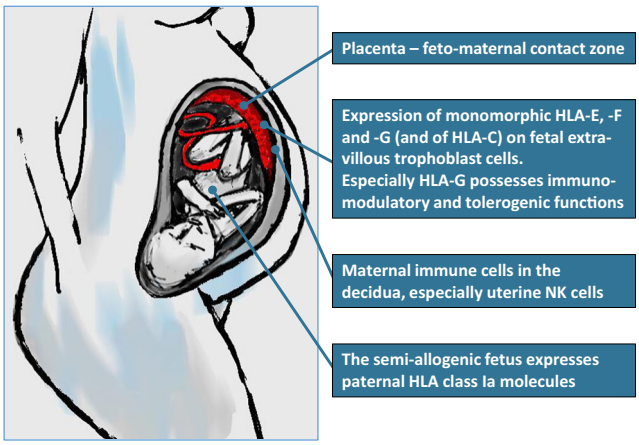

Fig. 1 Schematic drawing indicating the expression of HLA class I molecules at the feto-maternal interface during pregnancy. The fetus inherits a maternal and a paternal *HLA* haplotype and is thereby semi-allogenic for the maternal immune system. However, the fetal extravillous trophoblast cells that invade the decidua do not express the highly polymorphic HLA class Ia molecules, except for a low expression of HLA-C. Instead, the trophoblast cells express the nearly monomorphic HLA-E, HLA-F, and HLA-G molecules. These molecules interact with receptors on the uterine NK cells and probably other maternal immune cells. Especially HLA-G has been shown to possess immune-modulatory and tolerogenic functions

modulating immune functions through direct interaction with several receptors on diverse subsets of immune cells (Carosella et al. 2015; Hviid 2006; Shiroishi et al. 2006). The tolerogenic properties of HLA class Ib molecules, and especially the immunosuppressive role of the HLA-G protein, were initially discovered in relation to feto-maternal tolerance and proved important in relation to a successful pregnancy (Carosella et al. 2015; Gonzalez et al. 2012; Hviid et al. 2004a; Kovats et al. 1990) (Table 1).

HLA-G binds to the inhibitory immunoglobulin-like transcript 2 receptor (ILT2) expressed by all monocytes, B cells, some lineages of T cells, and NK cells; to inhibitory ILT4, which is only present on dendritic cells and monocytes; and to the activating receptor KIR2DL4 expressed on NK cells (Carosella et al. 2015; Colonna et al. 1998; Rajagopalan and Long 1999; Shiroishi et al. 2006) (Fig. 3). HLA-G does not seem to activate the immune system; instead, HLA-G has been shown to exert inhibitory functions against NK cell- and T cell-mediated cytotoxicity (Contini et al. 2003; Le Gal et al. 1999; Rouas-Freiss et al. 1997), to induce immunosuppressive development of antigen-presenting cells (APCs) (Horuzsko et al. 2001), and to induce immunosuppressive $CD4^+$ T cells (LeMaoult et al. 2004). However, the exact mechanisms by which HLA-G elicits its immune-modulating functions still need to be clarified in more detail.

Besides playing a role in the generation of immune tolerance by being expressed on trophoblast cells in the placenta (Kovats et al. 1990), HLA-G expression has been documented in the thymus (Crisa et al. 1997), in the cornea (Le Discorde et al. 2003), in bronchial epithelial cells, in the pancreas, in different types of mesenchymal stem cells, in inflamed muscle tissues (Wiendl et al. 2000), in organ transplants (Lila et al. 2000), in a few subtypes of immune cells, and in erythroid and endothelial precursors (Menier et al. 2004). Soluble isoforms of HLA-G are detected in body fluids, such as blood plasma or serum from pregnant and nonpregnant women and men, cerebrospinal fluid, malignant ascites, pleural effusions, amnion, and semen (Carosella et al. 2015; Hviid 2006; Larsen et al. 2011; Rebmann et al. 1999). Moreover, HLA-G expression has also been linked to pathologies such as cancer, viral infections, recurrent spontaneous abortions, pre-eclampsia, autoimmune diseases, organ transplantation outcome, and inflammatory disease (Carosella et al. 2015; Castelli et al. 2014a; Hviid 2006; Larsen and Hviid 2009; Morandi et al. 2016). Furthermore, HLA-G has been shown to play a role in relation to the success of assisted reproduction techniques (ART) (Hviid et al. 2004a; Niu et al. 2017; Pfeiffer et al. 2000).

HLA-E has dual functional roles and is involved in both the innate and the adaptive parts of the immune system. Self-peptides bound to HLA-E are recognized by the inhibitory CD94-NKG2A receptor on NK cells, and this

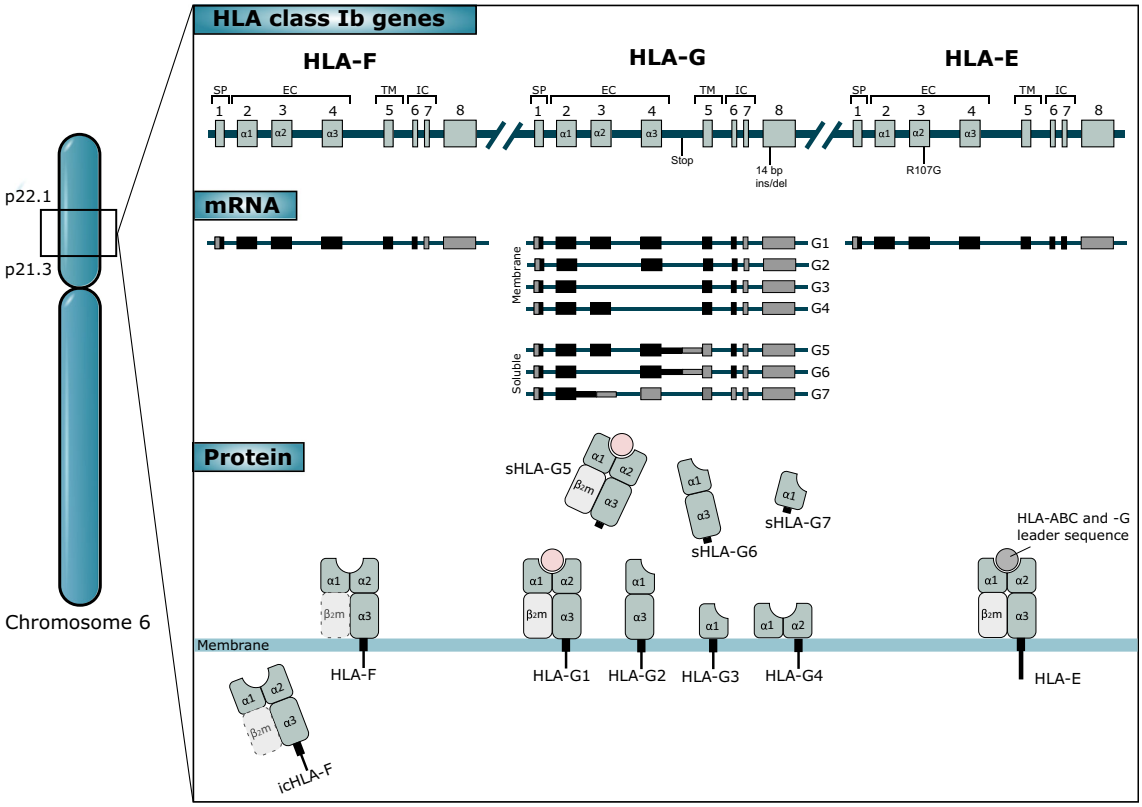

Fig. 2 Gene expression of HLA class Ib molecules. The *HLA class Ib* genes *HLA-E*, *HLA-F*, and *HLA-G* are located within the *HLA class I* locus on the short arm of chromosome 6 (6p21.3-22.1). The genetic structure is similar to the classical *HLA class Ia* genes, consisting of eight exons, with exon 1 encoding the signal peptide (SP); exons 2–4 encoding the extracellular (EC) domains α1, α2, and α3, respectively; exon 5 encoding the transmembrane (TM) domain; exons 6–7 encoding the intracellular (IC) cytoplasmic tail; and exon 8 remains untranslated. For *HLA-G* and *HLA-F*, exon 7 also remains untranscribed. Alternative splicing results in seven different HLA-G mRNA isoforms, with HLA-G1–4 expressed as membrane-bound proteins and HLA-G5–7 expressed as soluble proteins (sHLA-G). HLA-F is expressed either at the cell membrane or intracellularly (icHLA-F). Both HLA-E and the full-length isoforms of HLA-G1 and HLA-G5 bind and present peptide antigens. HLA-G binds a limited but diverse set of peptides, whereas HLA-E binds the leader peptide from HLA class Ia (HLA-ABC) and HLA-G

recognition is a checkpoint for the immune surveillance function performed by NK cells. On the other hand, HLA-E is also recognized by the T cell receptor on $CD8^+$ T cells. In this way, HLA-E will have a function in the adaptive immune response to pathogens (Sullivan et al. 2008).

Table 1 Functions of the HLA class Ib molecules

Gene/protein	Function	References
HLA-E	Inhibition of NK cells through CD94/NKG2A receptors	Braud et al. (1998), Lee et al. (1998)
	Antigen presentation	Guma et al. (2005), Li et al. (2001)
HLA-F	Binding to NK cell Ig-like receptors KIR3DL2 and KIR2DS4 Antigen cross-presentation with MHC I open conformers	Goodridge et al. (2013)
	Open conformers are high-affinity ligands of the activating NK cell receptor KIR3DS1	Garcia-Beltran et al. (2016)
HLA-G	Inhibition of allocytotoxic T lymphocyte response	Kapasi et al. (2000), Maejima et al. (1997)
	Inhibition of NK- and T-cell-mediated cell lysis (decidual/peripheral NK cells and $CD8^+$ cytotoxic T cells)	For example, Navarro et al. (1999), Ponte et al. (1999), Rajagopalan and Long (1999), Rouas-Freiss et al. (1997)
	Shift from a proinflammatory Th1 response to a Th2 response ($CD4^+$ T cells)	For example, Kapasi et al. (2000), Maejima et al. (1997), McIntire et al. (2004), van der Meer et al. (2004)
	Upregulation of inhibitory receptors (NK cells and $CD4^+$ T cells)	LeMaoult et al. (2005)
	Induction of long-term unresponsiveness of $CD4^+$ T cells	LeMaoult et al. (2004)

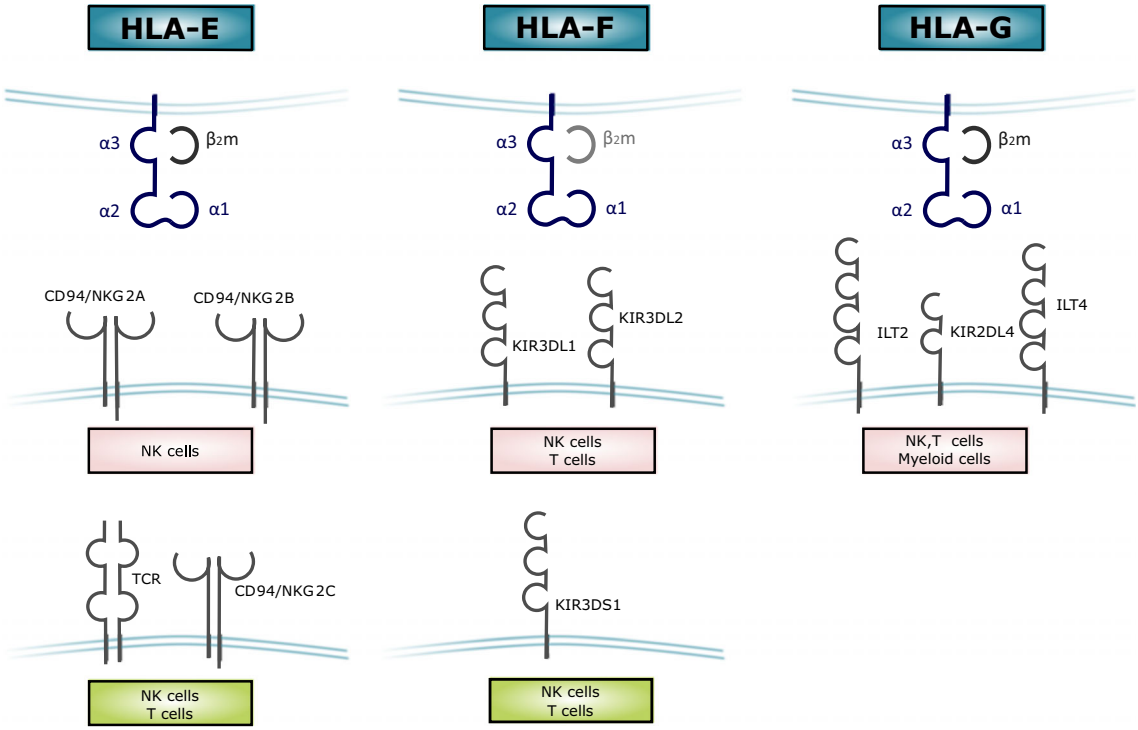

Fig. 3 Schematic representation of receptors for the nonclassical HLA class Ib molecules HLA-E, HLA-F, and HLA-G. The HLA class Ib molecules are recognized by both activating receptors (shown in *green boxes*) and inhibitory receptors (*red boxes*). These receptors are primarily expressed on NK cells and T cells, and HLA class Ib interactions with the receptors may also be important in the uterine environment at the time of implantation and during pregnancy. In general, the affinity of the activating receptors for the HLA class I ligand is lower than the affinity of the inhibitory isoforms for the same ligand. However, an exception of this is the newly described high affinity of KIR3DS1 for open conformers of HLA-F

Compared to HLA-G, little is known about the role and function of HLA-F in pregnancy, and in general, the possible functions of HLA-F have not been much in focus for many years. However, recent basic studies have shown that HLA-F interacts with several receptors on NK cells (Garcia-Beltran et al. 2016; Goodridge et al. 2013).

Although multiple factors are involved in the success of a pregnancy, this review will be limited to highlight and discuss the genetics, polymorphisms, and expression of the nonclassical molecules HLA-E, HLA-F, and HLA-G with relevance for their functional role in implantation and pregnancy and related pathologies such as implantation failure, recurrent spontaneous abortion, and pre-eclampsia.

Structure and polymorphisms of the *HLA class Ib* genes

HLA-E, *HLA-F*, and *HLA-G* belong to the *MHC/HLA* complex that spans an approximately 3.6-Mb region on the short arm of chromosome 6. Within the *HLA class I* cluster, *HLA-E* is located between *HLA-C* and *HLA-A*, and *HLA-G* is located adjacent to *HLA-A* followed by *HLA-F* (Fig. 2). Of the three *HLA Ib* genes, *HLA-G* is the one that is most well-characterized, and was described for the first time in 1987 (Geraghty et al. 1987). The organization of the gene is similar to the classical *HLA-A*, *HLA-B*, and *HLA-C* genes, and it encodes a membrane-bound molecule with similar extracellular domains as class Ia, including association with the β_2-microglobulin (β_2m), although the main function is not antigen presentation (Carosella et al. 2015; Geraghty et al. 1987; Hviid 2006) (Fig. 2).

The *HLA-G* intron/exon structure has been a matter of debate, and there is inconsistency between the National Center for Biotechnology (NCBI), the Ensemble database, and the International Immunogenetics Database (IMGT/HLA). Moreover, there is no consensus regarding where the transcription starts. While *HLA-G* transcripts from NCBI and Ensemble show two transcriptional start sites upstream of the initial translation site, the IMGT/HLA database considers the start codon as the one defining the initial point of translation and thus the beginning of the coding sequence (CDS) as the transcription site (Castelli et al. 2014a). In this review, we use the nomenclature established by the WHO Nomenclature Committee for Factors of the HLA System and sequences obtained from the IMGT/HLA database publicly available at the European Bioinformatics Institute web site (http://www.ebi.ac.uk/ipd/imgt/hla/). Thereby, the third start codon, i.e., first translated codon, is considered as the transcription start, and the adenine nucleotide in this ATG codon is annotated as +1. Nucleotides in the sequence upstream of this coding

region will be denoted with negative values and nucleotides downstream will be given positive values (Marsh et al. 2010; Robinson et al. 2015).

According to the WHO Committee, the *HLA-G* gene consists of eight exons and seven introns, where exon 1 encodes the signal peptide; exons 2–4 encode the α1, α2, and α3 domains, respectively; exon 5 encodes the transmembrane domain; and exon 6 forms the intracellular domain, while exons 7 and 8 remain untranslated due to a premature stop codon in exon 6, resulting in a unique short cytoplasmic tail of HLA-G compared to the classical HLA class Ia molecules (Geraghty et al. 1987) (Fig. 2). The cytoplasmic tail seems to be able to initiate cellular signaling events, although it is only six amino acids long, as it has been shown to induce proliferation in T cells upon cross-linking (Comiskey et al. 2007). Another unique feature of HLA-G is that the molecule can be expressed as seven protein isoforms as the result of alternative splicing of the primary transcript. The isoforms differ by their number of globular domains, presence of intronic sequence, and ability to bind β_2m. Four of the isoforms are membrane-bound (HLA-G1 to HLA-G4), and three isoforms are soluble (HLA-G5 to HLA-G7). In addition, the membrane-bound HLA-G1 can be shed from the cell surface through proteolytic cleavage (Dong et al. 2003; Park et al. 2004). Further complexity is added as HLA-G can exist both as a homodimer and heterodimer and with or without binding to β_2m (Juch et al. 2005; Morales et al. 2007). Moreover, HLA-G has been found to be secreted as part of extracellular vesicles (Nardi Fda et al. 2016).

In contrast to the classical *HLA* class I genes, *HLA-G* shows only limited variation in the coding region. According to the IMGT/HLA database, there are only approximately 50 coding alleles of *HLA-G*. Most of the variation is either synonymous mutations or located in introns, resulting in only 18 different protein variants and two truncated molecules (null variants). As the IMGT/HLA database only contains alleles that have been both cloned, sequenced, and characterized, the number of variation might be higher. In a study made by Castelli et al., in which they re-evaluated data for *HLA-G* from the 1000 Genomes Project, they identified 81 single-nucleotide variations within the coding region from which 93 haplotypes could be identified, of which only 11 were considered true haplotypes found in frequencies above 1% (Castelli et al. 2014a). These 11 haplotypes encoded four different full-length proteins and one null variation, of which more than 60% encoded the same protein variant. Analysis of the 3′-untranslated region (3′UTR) and 5′-upstream regulatory region (5′URR) also revealed limited variation, with only nine true haplotypes of both untranslated regions. For both the 3′ UTR and the 5′URR, these nine haplotypes accounted for more than 95% of the haplotypes found globally, meaning that the most common haplotypes are shared across populations and that haplotype variation between populations can be ascribed population-restricted low-frequency haplotypes (Castelli et al. 2014a). In other words, the variation and number of globally frequent haplotypes are sparse. Our own recent results from a study that sequenced the whole *HLA-G* gene in representatives of a North European population support this (Nilsson et al. 2016). Even less variation is seen at the protein level, where most coding haplotypes encode the same protein variant (Hviid 2006; Lynge Nilsson et al. 2014). It can be speculated whether the immunomodulatory function of HLA-G requires tight regulation and thus subjects the gene under tight evolutionary forces that limit variation. However, as significant associations in genetic variation and expression levels of HLA-G with a range of different pathologies have been reported, variation in the functional HLA-G response in individuals might be ascribed differences in expression, regulation, and in the generation of splice variants.

Two nonsynonymous alleles have been described for the *HLA-E* gene (Geraghty et al. 1992). A variation of nucleotides at the position +756 of the *HLA-E* gene causes an amino acid substitution at position 107 of the protein. The allele *E*0101:xx:xx* encodes the HLA-E^G protein, while the allele *E*01:03:xx:xx* encodes the HLA-E^R protein. The polymorphism results in a substitution of arginine by glycine in the α2 domain of HLA-E heavy chain (Grimsley and Ober 1997).

HLA-F exhibits low polymorphism with only 20 alleles at the DNA level that gives rise to four HLA-F proteins and one null-allele (Moscoso et al. 2007).

Regulation of the expression of HLA class Ib molecules

The expression pattern and role of the HLA-G isoforms in different types of tissues and organs and in different pathologies are not known in detail. Moreover, is it still unclear how HLA-G expression is regulated (Castelli et al. 2014b). Polymorphisms in the promoter region and 5′URR might be important for regulation of transcription, while polymorphisms in the 3′UTR have been proposed to have an effect on messenger RNA (mRNA) stability and micro-RNA-mediated regulation (Castelli et al. 2014b; Djurisic et al. 2015; Hviid et al. 2003). Regulatory elements, such as responsive elements for IFN-γ and NF-κB, that are highly conserved elements found in the promoter regions of the classical HLA class Ia genes, are considered nonfunctional for *HLA-G* (Gobin and van den Elsen 2000). This might be linked to its tight tissue-specific expression. The IMGT/HLA database only presents sequences 300 nucleotides upstream of the translational start site. However, another interferon-stimulated response element (ISRE), a target site for the interferon regulatory factor family, is found at positions −754 to −743, and IFN-β has been shown to enhance HLA-G expression. Other alternative regulatory elements affecting HLA-G

expression have been identified, including a heat shock element (HSE), progesterone response element (PRE), cAMP response elements/TPA response elements (CRE/TRE), Ras response elements (RRE), hypoxia response elements (HRE), the negative regulatory long interspersed elements (LINEs), and the locus control region (LCR) that might regulate when and where HLA-G is expressed (Castelli et al. 2014b). Moreover, other molecules have been shown to induce HLA-G expression, although the underlying genetic mechanism is not known. These factors include the anti-inflammatory cytokine IL-10, leukemia inhibitory factor (LIF), a cytokine expressed at the feto-maternal interphase in cytotrophoblast cells, the granulocyte-macrophage colony-stimulating factor (GM-CSF) in combination with IFN-γ, glucocorticoid hormones, and anticancer drugs (Bamberger et al. 2000; Castelli et al. 2014b; Moreau et al. 1999, 2001). Furthermore, HLA-G expression is regulated through methylation of the promoter and certain combinations of polymorphisms, probably affecting miRNA regulation (Djurisic et al. 2015; Verloes et al. 2017). The 3′UTR of HLA-G mRNA contains one AUUUA motif and one AUUAUUU repeat. Several groups have identified proteins that interact with AU-rich elements, and many of these proteins have been implicated in the regulation of mRNA stability (Hviid et al. 2003). Polymorphism close to and involving the AU-rich motif in the 3′UTR (exon 8) has been found to affect HLA-G mRNA stability and alternative splicing. A 14-bp insertion/deletion (ins/del) polymorphism in exon 8 affects alternative splicing and HLA-G mRNA stability, also generating HLA-G mRNA transcripts lacking 92 bp of exon 8 (Djurisic et al. 2015; Hviid et al. 2003; Rousseau et al. 2003). The polymorphisms that affect *HLA-G* gene expression and mRNA stability are also associated with differences in HLA-G protein expression on the cell surface and in sHLA-G levels in the blood and biological fluids. Especially the 14-bp *HLA-G* ins/ins genotype is associated with low levels of HLA-G on the trophoblast cell surface and in the blood and in semen (Chen et al. 2008; Dahl et al. 2014; Djurisic et al. 2015; Hviid et al. 2004b).

There is evidence of posttranscriptional regulation of HLA-E. It has been shown that HLA-E^R expression on the cell surface is higher than HLA-E^G expression. A difference attributed to a higher thermal stability of the protein is promoted by the amino acid substitution. Furthermore, studies have shown functional differences between the respective proteins of each HLA-E allelic variant (Strong et al. 2003). Analysis of the repertoire of HLA-E^R-acquired peptides in the absence of HLA class I molecules and comparisons of the features of previously identified HLA-E^G peptides from the same proteomic content demonstrated that differences in peptide stabilization could be translated to the density and half-life time of peptide-HLA-E molecules on the cell surface reinforcing that the *HLA-E* allelic variants result in relevant functional differences due to the amino acid substitution (Celik et al. 2016). Additionally, the HLA-E surface expression seems to be not only dependent on the *HLA-E* polymorphisms but also on the sequence of the peptides, since an evident difference in HLA-E upregulation was found with specific peptides from a panel of HLA-E binding peptides derived from CMV, Hsp60, and HLA class I (Lauterbach et al. 2015). At the transcriptional level, HLA-E is induced by IFN-γ and the class II transactivator CIITA (Gobin and van den Elsen 2000).

In the case of HLA-F, an exclusion of exon 7 in the mature HLA-F mRNA transcript results in a shortened cytoplasmic tail. Transactivation of HLA-F has been shown to occur through the binding of NF-κB to enhancer A in the promoter region of the gene, and IFN-γ was shown to induce HLA-F expression through the interferon-sensitive response element (ISRE) (Gobin and van den Elsen 2000).

HLA class Ib genes and proteins in healthy pregnancy

Although HLA-G has been given a role in an increasing number of different pathologies, including cancer, virus infection, autoimmunity, and in organ transplantations, the role of HLA-G has been most extensively studied in relation to pregnancy (Hviid 2006; Lynge Nilsson et al. 2014). During pregnancy, HLA-G is consistently expressed by extravillous trophoblast (EVT) cells in the placenta (Hackmon et al. 2017; Ishitani et al. 2003; Kovats et al. 1990). Expression of HLA-G is used as a marker for EVTs, and a range of different studies indicate that HLA-G might have a central position in immune regulation at conception, implantation, and during pregnancy (Lynge Nilsson et al. 2014; Niu et al. 2017). In very general terms, the expression of HLA-G has been associated with successful pregnancy, whereas low levels of HLA-G have been associated with pregnancy complications in a range of studies (Kofod et al. 2017; Niu et al. 2017; Pfeiffer et al. 2000; Rizzo et al. 2009a).

The functional role of HLA-G seems to be broad and includes as-described interactions with NK cells, cytotoxic T cells, regulatory T cells, and dendritic cells. HLA-G might also be involved in the regulation of angiogenesis and cell migration during formation and maturation of the placenta; however, more specific studies are clearly needed to verify and explore this further (Le Bouteiller et al. 2007).

Recently, we have shown that the birth weight and weight of the placenta is significantly associated with the 14-bp ins/del *HLA-G* genotype of the fetus in heterozygous 14-bp ins/del mothers (Emmery et al. 2017). Both the birth weight (adjusted for gestational age) and placenta weight decreased when the fetus was carrying the 14-bp ins alleles, and was especially pronounced when the fetus was homozygous for the 14-bp *HLA-G* ins/ins genotype. Hierarchical multiple

regression analysis showed that parity, pre-eclampsia, and 14-bp *HLA-G* ins/ins genotype of the newborn had statistically significant influence on the birth weight, whereas only gestational age and the 14-bp del/ins and ins/ins genotypes affected the weight of the placenta. Interestingly, the three 14-bp ins/del *HLA-G* genotypes have been associated with differences in expression levels of HLA-G, which imply a role for HLA-G in the regulation of fetal and placental development. We have reported that the fetal 14-bp del/del genotype is associated with higher surface expression on first trimester trophoblast cells than the 14-bp ins/ins genotype (Djurisic et al. 2015). The birth weight of a child is important, as too low a birth weight might be critical for the survival of the child, whereas too large babies might have consequences for the mother's health and even survival in relation to the delivery of the child. Therefore, it can be speculated, although the differences in absolute weights are small, whether fetuses with intermediate birth weight, more often being heterozygous for the 14-bp ins/del *HLA-G* genotype, might show slightly better options compared with lower weight 14-bp ins/ins or the higher weight 14-bp del/del fetuses. Speaking about this hypothesis, there is a strong balancing selection that seems to affect the variation of the *HLA-G* gene, thus securing maintenance of genetic variation at the *HLA/MHC* region and at chromosome 6 within a population (Hviid et al. 2003; Tan et al. 2005). There are other arguments, including studies showing that fertility success is dependent on genetic variance between the mother and the father and the rather controversial studies in which it has been shown that women seem to select men with different *HLA* genotypes/haplotypes than the ones they carry themselves (Havlicek and Roberts 2009; Wedekind et al. 1995). The *HLA-G* gene could thus play a role in securing genetic variation within a population. However, this theory is still based on speculations and needs further evidence (Hviid 2006).

HLA-G expression seems to be important for the early placentation as it is expressed by the blastocyst and early embryo (Fuzzi et al. 2002; Jurisicova et al. 1996; Niu et al. 2017). However, it has also been proposed that HLA-G might play an even earlier role prior to conception as HLA-G can be found in the genital tract, in the endometrium, in follicular fluid, in the male reproductive system, and in the seminal fluid (Kofod et al. 2017; Larsen et al. 2011; Rizzo et al. 2009b; Shaikly et al. 2008; Thibodeau et al. 2011). Soluble HLA-G can also be detected in the blood of healthy men and nonpregnant women (Chen et al. 2008; Hviid et al. 2004b). The concentrations of sHLA-G in the blood increase two- to fivefold in pregnant women, possibly produced in the placenta, while sHLA-G in men and nonpregnant women seems to derive from at least monocytes (Klitkou et al. 2015; Rebmann et al. 2003).

HLA-E was first detected as being expressed at the transcriptional level in different lymphoid and malignant cells (Koller et al. 1988). Later, the expression of HLA-E was detected in a variety of cell types in addition to extraembryonic tissue (Wei and Orr 1990).

Initially, HLA-F was considered to be primarily intracellularly expressed, perhaps due to lack of a suitable antibody, and expressed in, e.g., lymphoid cells and tissue in a β2-microglobulin-associated form (Geraghty et al. 1990; Wainwright et al. 2000). However, Ishitani et al. demonstrated that HLA-F is in fact expressed on the surface of the extravillous trophoblasts that have invaded the maternal decidua (Ishitani et al. 2003). In continuation of this, Shobu et al. showed that HLA-F surface expression increased during gestation in extravillous trophoblasts and was weakly expressed in the cytoplasm of syncytiotrophoblasts and cytotrophoblasts throughout pregnancy (Shobu et al. 2006). However, a recently published study by Hackmon et al. demonstrated that HLA-F was expressed on the extravillous trophoblasts in the first and second trimester, but not in the third trimester, and that HLA-F was expressed on migratory and invasive extravillous trophoblasts ex vivo and in vitro (Hackmon et al. 2017).

HLA-F has been shown to interact with ILT2 and ILT4 just like HLA-G, which indicates that the protein could have a function in communicating with the maternal immune system (Allan et al. 2002). It has recently been shown that the NK cell receptors KIR3DL2, an inhibitory receptor, and KIR2DS4, an activating receptor, and HLA-F expressed without peptide presentation, physically and functionally interact (Goodridge et al. 2013). Another study has also shown that open conformers of HLA-F are high-affinity ligands of the NK cell receptor KIR3DS1 that is an activating receptor (Garcia-Beltran et al. 2016). This is of special interest in relation to pregnancy because of the NK cell abundancy in the uterus. Common for HLA-C, HLA-E, HLA-F, and HLA-G is that they all interact with receptors on NK cells. Among other receptor-ligand interactions, HLA-C binds to inhibitory KIRDL1/2, HLA-E binds to activating CD94/NKG2C, HLA-F binds to inhibitory KIR3DL1/2 and activating KIR3DS1, and HLA-G binds to activating KIR2DL4 and inhibitory ILT2 and ILT4 (Fig. 3). Cell-cell interactions between leukocytes and trophoblast cells mediated by the HLA class Ib molecules and their receptors are of great interest in order to understand the immune regulation at the feto-maternal interface (Figs. 1 and 3).

HLA class Ib in relation to fertility and assisted reproduction

A number of recent studies emphasize the possible important functions of the HLA class Ib molecules, especially HLA-G, in implantation and early pregnancy. In a small but interesting study, Pfeiffer et al. reported that women with high levels of sHLA-G in their blood, also before pregnancy, had a higher chance of success in IVF treatments (Pfeiffer et al. 2000). We

were the first to link the 14-bp *HLA-G* insertion allele in the 3′ UTR to reduced success in IVF treatments (Hviid et al. 2004a), which has been confirmed in other studies (Lashley et al. 2014; Sipak-Szmigiel et al. 2009) (Table 2). In a new study, we have to the best of our knowledge for the first time shown the importance of HLA-G expression in the preimplantation endometrium in a study of IVF patients and fertile control women (Kofod et al. 2017). In endometrial biopsy samples collected in the implantation window of the menstrual cycle, we analyzed the expression levels of HLA-G and examined the number of cells positive for NK cell markers per area in relation to infertile women versus fertile women and in relation to the outcome of the following IVF treatment. All the women who achieved pregnancy in the following cycle by IVF treatment had a high expression level of sHLA-G in their endometrium. Very interestingly, we also observed a correlation of high sHLA-G levels in the endometrium and a higher number of $CD56^+$ NK cells per mm^2 in the endometrium. The study included in total 61 women, so these initial results need to be reproduced in a larger study. Further investigations of the interactions between uterine NK cells and HLA-G and HLA-F are mandatory to understand the mechanisms behind these associations.

Furthermore, a new meta-analysis including 15 studies and a total of 6170 cases concluded that the presence of sHLA-G in the embryo culture medium favored a higher implantation rate and pregnancy rate in the following IVF treatment (Niu et al. 2017). Soluble HLA-G can be measured in some embryo culture media before the embryo is transferred to the woman. The factors that determine high or low levels of sHLA-G in the embryo culture media have not been determined but genetic factors are probably involved.

Table 2 Studies of polymorphisms in the *HLA* class Ib genes with proposed relevance for pre-eclampsia (PE), implantation failure or infertility (IF), and recurrent spontaneous abortion (RSA). The list may not be complete; however, the main studies and results are shown

Gene	Polymorphism	Pregnancy complication	References
HLA-E	A107G (rs1264457)	Association between the heterozygous genotype *HLA-E*0101/01:03* and RSA in an Iranian study	Fotoohi et al. (2016)
		Association between *HLA-E*0101* allele and RSA in an Indian study	Tripathi et al. (2006)
		No association with RSA in a Danish, a German, and a Japanese study	Kanai et al. (2001), Pfeiffer et al. (2001), Steffensen et al. (1998)
		No association with PE in a Danish study	Nilsson et al. (2016)
HLA-F	rs2523393 (AA/AG/GG). Not a SNP in *HLA-F* but implicated in HLA-F expression	The AA genotype is associated with shortest time to pregnancy	Burrows et al. (2016)
HLA-G	−725G/C in 5′URR (rs915670)	Association with risk of RSA or sporadic fetal loss	Ober et al. (2003), Roussev and Coulam (2007)
		No association with RSA	Jassem et al. (2012), Sipak-Szmigiel et al. (2007)
	Polymorphisms in coding regions	Very inconsistent results for RSA (some studies find associations with *G*010103*, *G*01:04*, *G*01:05N*, or *G*01:06*)	Abbas et al. (2004), Aldrich et al. (2001), Aruna et al. (2010), Hviid et al. (2002), Penzes et al. (1999), Pfeiffer et al. (2001), Yamashita et al. (1999), Yan et al. (2006)
		Very inconsistent results for PE (some studies find associations with *G*01:05 N* or *G*01:06*)	Aldrich et al. (2000), Hylenius et al. (2004), Loisel et al. (2013), Moreau et al. (2008), Nilsson et al. (2016), Tan et al. (2008)
	14 bp ins/del in 3′UTR (exon 8, rs66554220)	Positive association of 14 bp ins *HLA-G* allele with reduced pregnancy success in IVF treatments	Hviid et al. (2004a), Lashley et al. (2014), Sipak-Szmigiel et al. (2009)
		Positive association of carrying 14 bp ins *HLA-G* allele in PE	Hylenius et al. (2004), Larsen et al. (2010), O'Brien et al. (2001), Zhang et al. (2012)
		No association with PE (including meta-analysis)	Humphrey et al. (1995), Iversen et al. (2008), Nilsson et al. (2016), Pabalan et al. (2015)
		Three meta-analyses support an association of the 14-bp *HLA-G* ins allele with risk of RSA (especially for women with ≥3 spontaneous abortions)	Fan et al. (2014), Meuleman et al. (2015), Wang et al. (2013)
	Whole *HLA-G* gene with focus on 55 polymorphisms	No association with severe PE/eclampsia	Nilsson et al. (2016)

Gelmini et al. evaluated the role of HLA-E in the establishment of a viable pregnancy by analyzing *HLA-E* polymorphisms in couples who underwent ART and fertile couples, and found a higher frequency of the *HLA-E*01:03* allele in ART (Gelmini et al. 2016).

A study by Burrows et al. sought to investigate genetic variants important for gene expression regulation in the endometrium of women and the relation to fertility success defined as time to pregnancy. An expression quantitative trait loci (eQTL) mapping study was performed and found two SNPs important for the expression of HLA-F and TAP2 that were associated with fecundability associated with different expression levels of HLA-F. A rs2523393 SNP was associated with different levels of HLA-F mRNA. Interestingly, the AA genotype of this SNP was associated with the highest gene expression of HLA-F in mid-secretory phase endometrium and was associated with the shortest time to pregnancy in women with recurrent pregnancy loss (Burrows et al. 2016).

HLA class Ib genes in recurrent spontaneous abortions

As outlined above, the 14-bp ins/del *HLA-G* polymorphism in exon 8 (the 3′UTR) is associated with differences in expression levels of HLA-G and alternative splice patterns (Djurisic et al. 2015; Hviid et al. 2003). We were the first to report an association between the 14-bp ins allele, especially the 14-bp ins/14-bp ins *HLA-G* genotype that is correlated with low membrane-bound and soluble HLA-G expression, and risk of recurrent spontaneous abortions (Hviid et al. 2002). This has been confirmed in a range of other studies, however, not by all published studies. Three meta-analyses published recently supported an association of the 14-bp ins *HLA-G* allele with risk of RSA, especially for women with ≥3 spontaneous abortions (Fan et al. 2014; Meuleman et al. 2015; Wang et al. 2013).

Regarding a possible role for HLA-E in recurrent spontaneous abortions, several studies have been published. Fotoohi et al. have reported an association between the heterozygous genotype *HLA-E*0101/01:03* polymorphism and unexplained recurrent spontaneous abortion in Iranian women (Fotoohi et al. 2016). Tripathi et al. assessed the effect of *HLA-E* alleles on the success of pregnancy by analyzing normal fertile women and recurrent spontaneous abortion and found a high frequency of the *HLA-E*0101* allele in women with RSA and also a high frequency of the homozygous *HLA-E*0101* genotype (Tripathi et al. 2006). Kanai et al. investigated the gene frequencies and shared alleles of the *HLA-E* gene in Japanese couples with or without recurrent spontaneous abortion. There were no specific distribution patterns for these alleles in recurrent spontaneous abortion suggesting that *HLA-E* polymorphism does not play a central role in recurrent spontaneous abortion (Kanai et al. 2001). Pfeiffer et al. also studied *HLA-G* and *HLA-E* polymorphisms in recurrent spontaneous abortion couples and fertile controls. *HLA-E* genotyping did not show any significant differences between recurrent spontaneous abortion couples and fertile controls (Pfeiffer et al. 2001). Finally, Steffensen et al. compared the frequencies of five *HLA-E* alleles in women with recurrent spontaneous abortions and random Danish controls. However, there were no significant differences in the prevalence of *HLA-E* alleles between recurrent spontaneous abortions in patients and controls, and the authors concluded that *HLA-E* polymorphism per se does not play any role in the pathogenesis of this disorder of pregnancy (Steffensen et al. 1998). The studies illustrates that there are no consensus regarding a possible role of HLA-E in cases of recurrent spontaneous abortions.

Pre-eclampsia and HLA class Ib

Pre-eclampsia is a multisystemic pregnancy disorder characterized by hypertension and often proteinuria in the mother as well as an insufficient blood supply to the fetus. The condition affects 2–10% of all pregnancies and is a major cause of maternal and fetal mortality and morbidity. Although the ethology and pathogenesis behind pre-eclampsia is controversial, it is generally accepted that pre-eclampsia involves improper placentation. Pre-eclampsia can be seen as a two-step process in which preclinical abnormal development of the placenta causes clinical symptoms in pregnant woman in the second and third trimester of pregnancy and can only be remedied by releasing the child and placenta (Fisher 2015; Redman and Sargent 2005; Roberts 1998). As placental tissue is derived primarily from the fetus, a maternal-fetal genetic predisposition, possibly specific genetic combinations between mother and fetus, and environmental factors are thought to be involved in the pathogenesis, but the underlying ethology is still unclear (Dekker and Sukcharoen 2004; Laresgoiti-Servitje et al. 2010; Odegard et al. 2000). Pre-eclampsia is seen more often in nulliparous women and multiparous women changing partner, and the risk of pre-eclampsia is increased if the woman has had a history of pre-eclampsia or any woman in her family has a history of pre-eclampsia. This points toward the immune system being involved in the pathogenesis of pre-eclampsia. One widely accepted hypothesis focus on a maladapted maternal immune response to the semi-allogeneic fetus due to either an increase in an inflammatory response (Redman et al. 1999; Sargent et al. 2006), or a specific alloresponse raised against the paternal antigens (Dekker and Robillard 2005; Saito et al. 2007). For this reason, much focus has been given to genes with immunological functions. In this regard, the nonclassical *HLA class Ib* genes have been considered as key candidates for several reasons: (i) the trophoblast cells in the placenta do not express the classical HLA-A and

HLA-B molecules, but do express high levels of especially HLA-G: (ii) HLA class Ib molecules have immune-modulatory functions important for establishment and maintenance of immunological tolerance toward the fetus; (iii) HLA-G seems to be involved in the regulation of the formation of the spiral arteries that secures blood supply to the feto-maternal contact zone and thus proper placentation.

In the context of a role for *HLA class Ib* genes in the pathogenesis of pre-eclampsia, results remain controversial. Several studies have reported significant lower levels of sHLA-G in maternal blood in cases of pre-eclampsia compared with uncomplicated pregnancy and also a significant reduced expression of HLA-G in pre-eclamptic placentas in comparison with placentas from uncomplicated pregnancies (Goldman-Wohl et al. 2000; Hara et al. 1996; Tang et al. 2015; Yie et al. 2004).

As previously described, polymorphisms in the 3′UTR have been linked to changes in HLA-G mRNA stability and/or expression. Some studies have shown an association between the 14-bp ins polymorphism in exon 8 within the 3′ UTR and pre-eclampsia (Hylenius et al. 2004; O'Brien et al. 2001). This would fit well with the observed association of reduced levels of HLA-G mRNA and soluble HLA-G protein with the 14-bp ins allele (Hviid et al. 2003, 2004b). However, other studies have failed to find any significant relationship between this allele or the homozygous 14-bp ins/ins *HLA-G* genotype and pre-eclampsia, including our own study including more than 200 cases with severe pre-eclampsia or eclampsia (Humphrey et al. 1995; Iversen et al. 2008; Nilsson et al. 2016). In addition, a recent meta-analysis including 11 studies with a combined sample size of 3770 (1625 cases/2145 controls) concludes that there is no association between the *HLA-G* 14-bp ins/del polymorphism and the development of pre-eclampsia in any family triad member (offspring, mother, or father). A subgroup analysis did, however, show an association of the offspring *HLA-G* 14-bp ins/ins or ins/del genotypes to pre-eclampsia in European Caucasian offspring, and offspring of primipara pregnancies, although these data were less robust, when analyzing heterogeneity and sensitivity of the test (Pabalan et al. 2015).

In addition to the 14-bp ins/del polymorphism, other polymorphisms in the 3′UTR of the *HLA-G* gene may have functional significance for mRNA stability and the further processing of the HLA-G transcript (Djurisic et al. 2015; Yie et al. 2008). However, the results from studies investigating these polymorphisms in the 3′UTR in cases of pre-eclampsia and controls have been very inconsistent (Larsen et al. 2010; Quach et al. 2014; Yie et al. 2008). Our recent case-control study including more than 200 mother-child pairs from severe cases of pre-eclampsia, and also eclampsia cases, and matched control mother-child pairs did not find any significant differences in *HLA-G* haplotype distributions between pre-eclampsia/eclampsia cases and controls (Nilsson et al. 2016). Therefore, there is no clear explanation for the mechanism behind the low level of sHLA-G in maternal blood and low HLA-G mRNA and protein expression in the placenta in pre-eclamptic cases compared with controls that most published studies observe (Goldman-Wohl et al. 2000; Hara et al. 1996; Rizzo et al. 2009a; Tang et al. 2015; Yie et al. 2004). A recent study has found that hypermethylation of the *HLA-G* gene promoter region in placental biopsies is associated with cases of pre-eclampsia (Tang et al. 2015).

Although the described inconsistency between studies related to the role of *HLA-G* gene polymorphisms in pre-eclampsia, the HLA-G molecule seems to be important for proper placentation. Further studies of genomic variations linked through strong linkage disequilibrium that might affect HLA-G expression and function should be further analyzed to shed light on this. In addition, as the leader peptide of HLA-G is presented by HLA-E, reduced or aberrant expression of HLA-G might play a role in the expression and function of HLA-E. However, one published study of HLA-E and HLA-G expression in the placenta did not observe any significant differences in expression intensity between cases of pre-eclampsia and controls (Shobu et al. 2006). Furthermore, our recent study of the *HLA-E* polymorphism defining the two alleles *HLA-E*01:01:xx:xx* and *HLA-E*01:03:xx:xx* (rs1264457) in a large-scale study of mother-child dyads with and without severe pre-eclampsia and eclampsia did not find any significant differences between cases and controls (Nilsson et al. 2016). The study by Shobu et al. also investigated the expression of HLA-F in the placenta from pre-eclampsia cases and controls but did not observe any differences (Shobu et al. 2006).

Whether altered expression of HLA class Ib molecules in pre-eclampsia plays a fundamental role in trophoblast invasion, proper placentation, and onset of disease, or if it is a consequence of reduced blood flow and placental hypoxia still remains to be established. In conclusion, although some studies point toward a role for HLA class Ib molecules in pre-eclampsia, more studies investigating the possible correlations between HLA-G protein concentrations in the placental trophoblast cells, *HLA-G* genotype, and production of anti-HLA-G antibodies on the final outcome of pregnancy should be performed. Existing controversies might be due to differences in experimental setup, the size, and the origin of the studied cohort. Moreover, the diagnosis "pre-eclampsia" describes a syndrome of multiple clinical features rather than a disease and thus may cover several conditions with similar symptoms but possible separate causes.

Conclusions and perspectives

Results from an increasing number of studies support a role for HLA-G in especially periconceptional events, embryo implantation, and early pregnancy, although some controversies still exist. Meta-analyses have shown that HLA-G expression by the

blastocyst seems to be important for implantation and pregnancy success, and *HLA-G* genetics seem to influence the risk of recurrent spontaneous abortions and success in IVF treatments. The mechanisms behind these associations need to be elucidated in future studies. The functions of HLA-F have remained obscure for a long period of time. However, recent data have revealed that open conformers of HLA-F interact with both activating and inhibitory receptors on NK cells. As NK cells are very abundant in the uterus, in the endometrium, and at the feto-maternal contact zone during pregnancy, these interactions may also show to be of importance in human reproduction and might be involved in pathology behind infertility and preeclampsia. New studies should look into these possibilities. Especially, future studies should also focus on the HLA class Ib molecules' role in periconceptional mechanisms and in mechanisms important during the peri-implantation period. The HLA/MHC class Ib genes and proteins might be important in reproductive and immune tolerance mechanisms throughout the whole reproductive cycle.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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