Human Leukocyte Antigens in Pregnancy and Preeclampsia

Omonigho Aisagbonhi* and Gerald P. Morris*

Department of Pathology, University of California San Diego, San Diego, CA, United States

Preeclampsia is a pregnancy-induced hypertensive disorder, the pathophysiology of which includes underlying maternal cardiovascular disease, deficient spiral artery remodeling during placenta development, and inflammatory immune responses at the maternal-fetal interface. Human leukocyte antigens (HLA) are major histocompatibility complex molecules essential for the recognition of foreign antigens that is central to immune defense against pathogens and critical determinants for the immune system discriminating between self and non-self tissues, such as in transplantation. Pregnancy represents a naturally existing “transplantation”, where the maternal immune system must be immunologically tolerant to the developing fetus which is 50% allogeneic. It is then unsurprising that HLA also influence normal pregnancy and pregnancy complications including preeclampsia. Here we review the role of classical and non-classical HLA molecules in influencing normal physiologic function during pregnancy and describe the association of HLA with pathophysiology in preeclampsia.

Keywords: pregnancy, preeclampsia, HLA, HLA-G, HLA-C

INTRODUCTION

Pregnancy can be viewed as a naturally-occurring allograft, with a semi-allogeneic fetus requiring access to maternal circulation for provision of nutrients and oxygenation during development. In contrast to the robust immune responses typically elicited by allogeneic stimulation, the maternal immune system does not mount an inflammatory response to the fetus under normal physiology. This immunologic tolerance is facilitated by the development and function of the placenta. The placenta is a fetal organ that develops to become the interface between which maternal and fetal cells interact (Figure 1). Placental trophoblast cells are the primary fetal cells directly exposed to the maternal immune system (Moffett and Loke, 2006). Villous trophoblasts, comprised of an inner layer of cytotrophoblasts and an outer layer of syncytiotrophoblasts, are directly in contact with maternal blood and maternal systemic immune system at the intervillous space. Extravillous trophoblasts (EVTs) migrate from the cytotrophoblast shell through decidual stroma and remodel maternal decidual spiral arteries into low resistance, high conductance dilated vessels without smooth muscle, which enables optimal flow of blood for oxygen exchange to support placental and fetal growth (Burton, et al., 2009). Interaction between fetal trophoblast cells and maternal immune cells at the placental interface are essential for regulating these remodeling processes and maintaining maternal immunologic tolerance to the fetus.

PREECLAMPSIA

Preeclampsia is a pregnancy-induced hypertensive disorder defined as new-onset hypertension and proteinuria or new-onset hypertension and end-organ (heart, lung, brain, kidney, liver) dysfunction,
occurring between 20 weeks of gestation and 6 weeks post-partum (Bouter and Duvekot, 2020). Preeclampsia is relatively common, affecting as many as 4–10% of all pregnancies worldwide. In the most severe cases, preeclampsia can be fatal, with maternal end-organ failure. Despite the significant risks of morbidity and mortality from preeclampsia, no singularly effective cure exists, with treatment relying on early detection and administration of antihypertensive medications to bridge the mother and fetus to delivery. The efficacy of this approach is limited, with preeclampsia persisting as one of the five leading causes of maternal mortality worldwide (Say, et al., 2014). The incidence and clinical outcomes in preeclampsia vary by geographic region and maternal ethnicity, suggesting both environmental and genetic components contribute to the pathophysiology.

Emerging evidence suggests that rather than having a single cause, preeclampsia is a multifactorial syndrome that can result from multiple distinct pathophysiologic processes. Using unsupervised clustering of aggregate microarray datasets (first in 173 patient samples, including 77 with preeclampsia and later in a larger dataset of 330 samples), 3 molecular clusters/subclasses of preeclampsia have been proposed (Table 1) (Leavey, et al., 2015; Leavey, et al., 2016). Preeclampsia samples in cluster 1 showed normal placental histopathology and the birthweights of delivered infants were appropriate for gestational age. At the molecular level, there was no significant difference in gene expression by cells in the placenta between preeclampsia cases from cluster 1 and controls without preeclampsia. Thus, it was reasoned that underlying maternal factors, unrelated to the placenta, are the likely etiology of preeclampsia in cluster 1 patients. Clusters 2 and 3 had more clinically significant presentations, with higher maternal blood pressures, higher proteinuria and uric acid levels. Placentas in cluster 2 demonstrated classic preeclampsia-associated findings (small for gestational age, distal villous hypoplasia, with syncytial knots and infarcts) and were significantly more likely to be associated with infants that were small for gestational age (SGA) and/or had a clinical diagnosis of intrauterine growth restriction. Genes involved with hormone secretion, response to nutrient, redox activity and response to hypoxia/angiogenesis were over-represented in cluster 2. Preeclampsia placentas in cluster 3 showed increased rates of massive perivillous fibrin deposition, a placental lesion associated with maternal anti-fetal rejection (Romero, et al., 2013; Gundogan, et al., 2010), and increased expression of genes associated with allograft rejection, immune and inflammatory responses.

Based on these findings, three etiologic categories for PE have been proposed—1) maternal preeclampsia caused by maternal...
factors unrelated to the placenta; 2) canonical preeclampsia caused by deficient spiral artery remodeling and 3) immunologic preeclampsia caused by maternal-fetal incompatibility. Considering preeclampsia as a syndrome with at least 3 different etiologic categories begins to explain why the disease has different clinical (mild vs severe; early vs late-onset) and pathologic manifestations (small placenta with evidence of maternal vascular malperfusion vs increased perivillous fibrin deposition with or without an associated chronic villitis, vs normal sized placenta without significant pathology) (Roberts, et al., 2021). Within this context of multi-modal pathophysiology it becomes possible to consider the influence of genetics on preeclampsia.

**HUMAN LEUKOCYTE ANTIGEN**

The human leukocyte antigen (HLA) system is a cluster of >100 genes regulating immune function located on the short arm of chromosome 6p21.3 (Shiina, et al., 2009). Most notably, the HLA locus contains genes encoding the HLA genes, human orthologs of Major Histocompatibility Complex (MHC) genes. HLA/MHC proteins’ primary function is to present antigens to T lymphocytes, enabling recognition of foreign antigens by the cellular arm of the adaptive immune system (Neeftjes, et al., 2011). The defining genes of the HLA locus include the classical HLA class Ia genes HLA-A, HLA-B, and HLA-C, encoding the HLA-A, HLA-B, and HLA-C proteins which present peptide antigens to CD8+ cytotoxic T cells, and the HLA class II genes HLA-DRA1, HLA-DRB1, HLA-DRB3/4/5, HLA-DQA1, HLA-DQB1, HLA-DPA1, and HLA-DPB1 which encode the proteins forming the HLA-DR, HLA-DQ, and HLA-DP molecules that present peptide antigens to CD4+ helper T cells, including immunosuppressive regulatory T cells (Tregs). The genes encoding the classical HLA molecules are the most genetically diverse genes in the human genome, with over 25,000 defined allelic variants (Robinson, et al., 2020), with even more alleles being identified regularly. The extensive nucleotide sequence variability translates to protein polymorphisms that influence the ability of HLA molecules to bind and present antigens as well as interact with leukocyte antigen receptors. This diversity underpins the robust immune responses of T lymphocytes to allogeneic tissues, with HLA protein sequence diversity both directly affecting the interaction of T cell antigen receptors with the HLA molecule and indirectly stimulating T cell responses via differential presentation of endogenous tissue antigens (Felix and Allen, 2007).

In addition to presentation of peptide antigens to T lymphocytes, HLA-C (and some HLA-A, and HLA-B molecules, though these are not expressed by EVTs) is involved in the regulation of NK cell activity. Class I HLA molecules interact with NK cells in a (mostly) peptide-independent manner through a combination of activating and inhibitory signals initiated by the binding of Killer Immunoglobulin Receptor (KIR) molecules (Parham, 2005). These interactions involve multiple different KIR molecules, each with differential ability to interact with HLA-C and other ligands, and each containing different intracellular signaling motifs. There are 17 identified KIR genes, each of which have 30–230 known genetic allotypes, located in the Leukocyte Receptor Complex (LRC) region on chromosome 19q13.4 (Barrow and Trowsdale, 2008; Robinson, et al., 2013). KIR genes can be broadly divided into activating “DS” receptors, containing short intracellular domains with activating signaling motifs, and inhibitory “DL” receptors, containing longer intracellular domains with inhibitory signaling motifs. An individual’s KIR gene repertoire varies both by allelic variation as well as gene content, with the presence or absence of specific KIR genes being the primary determinant of the ability of NK cells to interact with HLA-C. NK cell recognition of HLA-C is determined by which amino acid is expressed at position 80 of the HLA-C molecule. In terms of KIR interaction, HLA-C molecules are divided into 2 groups, with the HLA-C1 group having asparagine (Asn) at position 80 while the HLA-C2 group contains lysine (Lys) at position 80. HLA-C1 group molecules have higher expression of genes associated with hypoxia/angiogenesis, hormone secretion, nutrient and redox activity compared to HLA-C2 group molecules. Massive perivillous fibrin deposition is found in the placenta of patients with severe preeclampsia, characterized by over-representation of genes associated with hypoxia/angiogenesis, hormone secretion, nutrient and redox activity.

**TABLE 1** Summary of clinical, pathologic and molecular findings in the 3 proposed etiologic clusters of PE—maternal, canonical and immunologic (Leavey, et al., 2016).

| Findings                  | Maternal Preeclampsia (Cluster 1)                                      | Canonical Preeclampsia (Cluster 2)                                             | Immunologic Preeclampsia (Cluster 3)                                       |
|---------------------------|------------------------------------------------------------------------|---------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| Clinical                  | Infant birthweight appropriate for gestational age                      | Infant birthweight small for gestational age                                    | Infant birthweight small for gestational age                              |
| Gross and histopathologic| Placenta weight appropriate for gestational age                         | Placenta weight small for gestational age                                       | Placenta weight small for gestational age                                 |
| Molecular                 | No significant difference from normotensive controls                    | Maternal vascular malperfusion (distal villous hypoplasia, syncytial knots, funarcti) | Increased expression of genes associated with allograft rejection, immune and inflammatory responses |
| Proposed etiology         | Maternal cardiovascular disease (unrelated to placenta)                 | Deficient spiral artery remodeling during placenta development                 | Maternal-fetal incompatibility manifested in the placenta                |
present a relatively limited set of peptide and non-protein antigens to leukocytes, including T lymphocytes, non-classical T cells, and Natural Killer (NK) cells (Carosella, et al., 2015; Grant, et al., 2020; Persson, et al., 2020). Additionally, some interactions between non-classical HLA molecules and leukocyte receptors are antigen-independent, with recognition of the HLA molecule by receptors being deterministic for inducing immune cell response. The interactions between non-classical HLA molecules and their associated receptors can provide either stimulatory or inhibitory signals to immune cells, depending on the specific HLA-receptor combination. In contrast to classical HLA genes, the genes encoding non-classical HLA molecules have limited genetic diversity (Robinson, et al., 2020). The effects of these limited polymorphisms on interaction with leukocyte receptors is incompletely defined, though there is evidence that this genetic variation, particularly when located in untranslated regulatory regions, can result in differences in non-classical HLA expression (Gobin and van den Elsen, 2000; Strong, et al., 2003; Hvid, et al., 2003). This genetic diversity can result in selective activation of immune cells in response to allogeneic cells, either by interaction with allogeneic HLA molecules that provide a stimulatory signal or via the absence of interactions required to provide inhibitory signals.

### HUMAN LEUKOCYTE ANTIGEN IN NORMAL PREGNANCY

Interactions of HLA molecules with T cells and NK cells are essential determinants of immune function and discrimination between self- and non-self. As such, HLA molecules have a critical role in the interactions between fetal trophoblasts and maternal immune cells. The maternal immune system has to maintain a balance between immunologic tolerance for the semi-allogeneic fetus and the ability to respond to pathogens to prevent infection. HLA-C and the non-classical HLA class Ib molecules are important for normal pregnancy, where they play roles in modulating maternal immune responses to the semi-allogeneic fetus, spiral artery remodeling and pathogen recognition. HLA expression differs between villous trophoblasts and EVT (Figure 1). While neither villous trophoblasts nor EVT normally express HLA-A, HLA-B, or HLA class II molecules, EVT express HLA-C, HLA-E, HLA-F and HLA-G while villous trophoblasts only express soluble forms of HLA-G (Ishitani, et al., 2003; Apps, et al., 2009). It is unclear whether trophoblast expression of HLA molecules changes during gestation. Increased expression of HLA-E and HLA-F by EVT from the first to second to third trimester has been observed (Shou, et al., 2006); however, a contrasting study found HLA-E expression limited to the first trimester and expression of HLA-C, HLA-F and HLA-G decreased as gestation progressed (Hackman, et al., 2017). This restricted and potentially dynamic expression of HLA molecules influences their ability to regulate immune cell function at the maternal-fetal interface.

### Placental Human Leukocyte Antigen and Protective Immune Responses

The most obvious physiologic function of HLA molecules at the maternal-fetal interface is to present antigens from infectious pathogens, enabling the maternal immune system to mediate protective cellular immune responses. Fetal EVT, like all other mature cells, co-dominantly express both chromosomal copies of HLA genes. Thus, the semi-allogeneic fetal EVT express maternal-derived HLA-C, enabling self-MHC-restricted maternal T cells to respond to presented foreign antigens. HLA-C expressed by fetal EVT are also able to present pathogen-derived peptide antigens to maternal NK cells via interactions with KIR2DS1, KIR2DS2, and KIR2DS4 activating receptors, stimulating NK cell-mediated responses to infection (Crespo, et al., 2016; Naiyer, et al., 2017; Sim, et al., 2019). HLA-E is also capable of presenting a limited set of pathogen-derived antigens, including peptides derived from cytomegalovirus (CMV) and Human immunodeficiency virus (HIV), which can cause significant morbidity and mortality in neonates (Grant, et al., 2020). HLA-E is capable of stimulating NK cells via the activating KIR2DS1 and NKG2C receptors (Braud, et al., 1998; Lee, et al., 1998). HLA-F is similarly capable of stimulating NK cells via KIR3DS1 (Garcia-Beltran, et al., 2016; Burian, et al., 2016). Thus, despite the restricted set of HLA molecules expressed by trophoblasts, the maternal immune system is capable of detecting infection and mediating innate and adaptive cellular immune responses. Co-dominant expression of HLA-C alleles also results in expression of likely genetically dissimilar paternal HLA-C by EVT, which presents the challenge of potential alloreactive responses by maternal immune system.

### Placental Human Leukocyte Antigen and Inhibition of Inflammatory Immune Responses

The absence of immunologic rejection of the semi-allogeneic fetus is not due to a lack of ability of the maternal immune system to recognize the foreignness of fetus. Indeed, multiple studies have demonstrated the existence of fetal antigen-reactive T cells, both at the placental interface and in circulation (Tilburgs, et al., 2010; Lissauer, et al., 2012; van der Zwan, et al., 2018). Inhibition of inflammatory immune responses and promotion of immunologic tolerance at the maternal-fetal interface instead relies upon multiple physiologic mechanisms. Expression of the inhibitory co-stimulatory PD-L1 (Nagamatsu, et al., 2009) by EVT, production of the immunosuppressive metabolite indoleamine-2-3-dioxygenase (IDO) (Munn, et al., 1998), and expression of immunosuppressive cytokines such as IL-10 and TGF-β (Guzeloglu-Kayisli, et al., 2009) all act to directly inhibit the activity of inflammatory and cytotoxic lymphocytes in the placental microenvironment. The non-classical HLA class Ib molecules HLA-G, and HLA-E have also been reported to directly inhibit cytotoxic and pro-inflammatory T cells and NK cells at the placenta. HLA-G interacts with decidual NK
cells, T cells, B cells, and myeloid cells via KIR2DL4 receptor on
NK cells, ILT2 receptor on T cells, B cells, and some NK cells, and
ILT4 receptor on myeloid cells (Colonna, et al., 1998; Rajagopalan
and Long, 1999; Shiroishi, et al., 2006). HLA-G is capable of
inhibiting antigen-specific and alloreactive cytotoxic T cell
responses in vitro (Le Gal, et al., 1999; Kapasi, et al., 2000).
Expression of HLA-G is also sufficient to prevent NK cell-
mediated cytolysis (Chumbley, et al., 1994; Pazmany, et al.,
1996). HLA-G can also mediate immunosuppressive function
in the absence of direct cell–cell contact. HLA-G is unique among
HLA molecules, with the existence of alternatively spliced mRNA
forms which produce seven different HLA-G protein isoforms
(Ishitani and Geraghty, 1992; Fujii, et al., 1994). The isoforms
include conventional membrane-bound G1-G4 isoforms and G5-
G7 secreted soluble (sHLA-G) proteins. sHLA-G molecules have
inhibitory effects on T cells and NK cells similar to those of
membrane-bound HLA-G. sHLA-G is produced by trophoblasts
(Solier, et al., 2002), suggesting a role for HLA-G in regulating
maternal immune responses. Indeed, both membrane-bound or
soluble HLA-G inhibits CD4$^+$ and CD8$^+$ T cell responses and NK
cell-mediated cytolysis of allogeneic cytrophoblasts in vitro,
indicating the functional relevance of this inhibition at the
maternal/fetal interface (Rous-Freiss, et al., 1997; Kostlin,
et al., 2017). HLA-E has been shown to be similarly protective
against NK cell-mediated lysis via interactions with activating
NKG2C receptor on NK cells, inhibitory CD94/NKG2A
receptors on NK cells, and CD8 on T cells (Braud, et al., 1998;
Lee, et al., 1998).

Trophoblast-expressed HLA-G also influences the
generation and persistence of CD4$^+$FoxP3$^+$ Tregs. Tregs are
important mediators of immunologic tolerance, capable of
regulating the responses of immune cells and preventing
pathologic inflammatory responses (Sakaguchi, et al., 2020).
The regulatory function of maternal Tregs is essential at the
maternal/fetal interface to prevent maternal alloimmune
response and immunologic rejection of the fetus (Tsuda,
et al., 2021). Maternal Tregs are specific for fetal antigens and
activated via their antigen receptor by peptide antigens
presented by HLA class II molecules. While trophoblasts do not
express HLA class II molecules, maternal Tregs are exposed to
fetal antigens presented by HLA II molecules on antigen-
presenting cells such as dendritic cells and macrophages in
the placental microenvironment. The relative importance of
Tregs in suppressing maternal alloreactive immune responses at
the maternal-fetal interface can be demonstrated by the
observation that Tregs are increased in pregnancies where
maternal and fetal HLA-C genotypes are mismatched
(Tilburgs, et al., 2009). This suggests that the Treg response
must be increased as a necessary response to increased
allogeneic stimulation by the fetus. Several studies have
indicated that placental tissue, specifically EVTs expressing
HLA-G, promote differentiation of CD4$^+$ T cells into Tregs
(LeMaoul, et al., 2004; Tilburgs, et al., 2015; Svensson-
Arvelund, et al., 2015). This Treg induction is associated with
inhibition of alloreactive T cell responses, demonstrating the
potential mechanism by which fetal HLA-G contributes to
immunologic tolerance via Treg induction.

Human Leukocyte Antigen and Placental Development
A more unique role for HLA molecules in pregnancy occurs
during the process of physiologic conversion, whereby maternal
spiral arteries are remodeled into low-resistance, high-
conductance vessels, which is necessary for the growth and
function of the placenta. During this process, EVTs interact
with local maternal decidual NK cells, and stimulate them to
aid in tissue remodeling during fetal development. NK cell
activity is critical during physiologic conversion, and is
regulated by interaction with HLA-C, HLA-G, and HLA-E.
Interactions between HLA-C and activating KIRs stimulate
NK cells to secrete chemokines and cytokines such as GM-
CSF, IL-8, and interferon-inducible protein 10, that promote
trophoblast migration and ultimately contribute to spiral artery
remodeling during normal placentation (Hanna, et al., 2006;
Xiong, et al., 2013). HLA-G also promotes NK cell activity
contributing to trophoblast invasion and spiral artery
remodeling. sHLA-G5 stimulates trophoblast invasion in vitro
by binding KIR2DL4 and IL1RBL1 (a.k.a. ILT2), activating the
ERK signaling pathway and increasing production of tissue
remodeling-associated proteases uPA and MMPs as well as
proangiogenic cytokines and chemokines (Rajagopalan, et al.,
2006; Guo, et al., 2013; Fu, et al., 2017; Gamliel, et al., 2018).
During spiral artery remodeling, HLA-G may also interact with
endothelial cells directly, as HLA-G1 induced endothelial cell
apoptosis via binding endothelial CD160 receptor (Fons, et al.,
2006). Roles for HLA-E and HLA-F in regulation of NK cell
activity during physiologic conversion have not been
demonstrated, though both HLA-E and HLA-F are expressed
by invading EVTs and interact with receptors on NK cells.

HUMAN LEUKOCYTE ANTIGEN IN
PLACENTAL PATHOLOGY

Human Leukocyte Antigen in Maternal Preeclampsia
The 3 pathophysiologic clusters of preeclampsia proposed based
on placental gene expression include preeclampsia resulting from
maternal factors, deficient placental development, and
immunologic incompatibility (Leavey, et al., 2015; Leavey,
et al., 2016). Of these categories, maternal preeclampsia,
considered as a consequence of underlying maternal factors
such as cardiovascular disease and obesity, is the least likely to
be directly influenced by placental HLA genetics. However, it
should be noted that some underlying maternal autoimmune
diseases that increase risk for preeclampsia have susceptibilities
that have been linked to HLA. An example is systemic lupus
erythematosus (SLE), which has been associated with a 1.91
relative risk for preeclampsia in a meta-analysis (Bundhun
et al., 2017). Increased SLE susceptibility has been linked to
HLA-DRB1*15 alleles across multiple ethnic populations
(Selvaraja et al., 2022). Ankylosing spondylitis, a disease whose
susceptibility is strongly linked to HLA-B*27 (Ebrahimiaidib,et al.,
2021) has similarly been associated with poor pregnancy
outcomes (Jakobsson et al., 2016). Other autoimmune diseases
such as type 1 diabetes mellitus and rheumatoid arthritis also have increased risks conferred by HLA class II haplotypes (Ebrahimiadib et al., 2021; Enzmann et al., 2021). Nevertheless, as HLA-B and class II HLA molecules are not normally expressed by placental trophoblasts, the mechanism by which maternal autoimmune diseases lead to poor pregnancy outcomes like preeclampsia and preterm birth needs to be further elucidated.

**Human Leukocyte Antigen in Immunologic Preeclampsia/Maternal-Fetal Incompatibility or Tolerance Failure**

The concept of the fetus as a semi-allogeneic graft is based upon the fact that the fetus is 50% of maternal genetic origin and 50% paternal genetic origin. HLA genes are typically inherited en bloc as a unit containing all of the genes from a single chromosome 6p21 region, inheriting 1 maternal set or haplotype and 1 paternal haplotype. Given the extensive genetic diversity of HLA genes, a fetus is expected to be genetically dissimilar from the mother for HLA genes, most commonly haploidentical or mismatched for 1 allele of each of the classical HLA genes. The influence of maternal-fetal HLA mismatches in immunologic preeclampsia is unclear. Retrospective analysis of oocyte donation pregnancies found pregnancy losses and preeclampsia were associated with increased numbers of HLA gene mismatches between maternal-fetal pairs (Lashley, et al., 2015; van Bentem, et al., 2020). However, studies on HLA mismatches and preeclampsia in spontaneously conceived pregnancies have yielded varied and sometimes contradictory findings with no clear evidence for an association between HLA dissimilarity between the mother and fetus and the incidence of preeclampsia (Hoff, et al., 1992; Biggar, et al., 2010; Triche, et al., 2014; Van’t Hoff, et al., 2021).

A lack of clear association between HLA mismatches and preeclampsia may reflect limitations in the analyses performed. Separation of the effects of individual HLA genes on preeclampsia has similarly mixed results, with demonstration of selective influence by either HLA class I (Lashley, et al., 2015; van’t Hoff, et al., 2021) or HLA class II (Triche, et al., 2014; van Bentem, et al., 2020; van’t Hoff, et al., 2021) genes. Of the class I genes, only HLA-C has been demonstrated to have statistically confident influence independent from other HLA mismatches (van’t Hoff, et al., 2021). This likely reflects the fact that fetal trophoblast cells do not express HLA-A or HLA-B, but do express HLA-C, making it the only classical HLA class I molecule available to interact with maternal immune cells. Dissection of the effect of HLA-C mismatches indicates that fetal expression of paternal alleles in the C2 group are associated with increased risk for preeclampsia and placental immune lesions (Hiby, et al., 2004; Hiby, et al., 2010; Schonkeren, et al., 2012; Larsen, et al., 2019; van’t Hoff, et al., 2021). Presumably, this association is driven by differential interaction of C2 group molecules with either activating or inhibitory KIR molecules. However, this association is complicated by population-specific variability in maternal KIR genetics, which determine the repertoire of NK cell receptors available to interact with HLA-C molecules. Maternal inhibitory KIR AA genotype has been shown to be associated with increased risk of preeclampsia in Europeans from the United Kingdom, East-Africans and Han Chinese and maternal activating KIR B genotypes (KIR2DS1 in Europeans and Ethiopians, KIR2DS5 in East Africans and KIR2DS2/3/5 in Han Chinese) have been shown to be protective against preeclampsia (Hiby, et al., 2004; Hiby, et al., 2010; Long, et al., 2015; Nakimuli, et al., 2015; Kelemu, et al., 2020). However, a Danish study of fetal HLA-C and maternal KIR genotypes in severe preeclampsia found no significant association between maternal KIR AA and fetal HLA-C2 alleles and severe preeclampsia risk (Larsen, et al., 2019). Studies evaluating the expression patterns of HLA-C and activating versus inhibitory KIRs in the placentas of patients with mild vs severe preeclampsia in contrast to those without preeclampsia across different ethnic groups may be informative.

Potential effects for maternal/fetal HLA class II mismatches, specifically HLA-DRB1 and HLA-DQB1, with preeclampsia are less straightforward, as neither villous nor extravillous trophoblasts normally express HLA class II molecules. However, aberrant expression of HLA-DR by syncytiotrophoblasts has been observed in placentas of women with preeclampsia (Small, et al., 2017; Tersigni, et al., 2018). This likely reflects an expected physiologic response to placental inflammation, as MHC class II gene expression is regulated by the Class II Transcription Activator (CIITA) transcription factor, which is upregulated by the inflammatory cytokine interferon γ (Steimle, et al., 1994). The pathophysiologic consequences of this dysregulation are undefined, though it may represent a mechanism for aberrant stimulation of CD4+ helper T cells or dysregulation of Treg function.

The non-classical HLA class I molecules HLA-F and HLA-G have also been identified as potentially dysregulated in preeclampsia. While both HLA-F and HLA-G have relatively limited genetic diversity compared to classical HLA genes, both have identified expression variants, either via prematurely terminating null variants or regulatory elements in non-coding regions (Robinson, et al., 2013). While reduced expression variants of HLA-F have not been associated with preeclampsia, the rs1362126, rs2523405, and rs2523393 variants have been associated with reduced fertility (Langkilde, et al., 2020). The importance of HLA-F in inhibiting NK cell-mediated cytotoxic responses was postulated as a potential mechanism for this association. The influence of HLA-G on preeclampsia is better described. Multiple studies have observed decreased HLA-G expression, both by fetal cells in the placenta as well as soluble forms in circulation, in patients with preeclampsia is associated with impaired maternal-fetal immune tolerance (Yie, et al., 2004; Steinborn, et al., 2007; Vianna, et al., 2016). Decreased HLA-G expression in preeclampsia has been associated with reduced frequencies of regulatory T cells and increased expression of pro-inflammatory cytokines (Vianna, et al., 2016; Wedenoja, et al., 2020). The mechanism by which HLA-G is decreased in preeclampsia is undefined. A number of studies have suggested that a fetal 14bp insertion/deletion polymorphism may account for decreased HLA-G expression and increased preeclampsia risk (O’Brien, et al., 2001; Hylenius, et al., 2004; Hvid, et al., 2004; Rokhafrooz, et al., 2018), though other studies have not found the same association (Pabalan, et al., 2015; Nilsson, et al., 2016). Down-regulation of HLA-G expression via...
hypermethylation of the promoter has been proposed as an alternative mechanism for downregulation of HLA-G in preeclampsia (Tang, et al., 2015). Epigenetic dysregulation of HLA-G is of significant interest as it represents a mutable and potentially actionable target for intervention.

Human Leukocyte Antigen in Deficient Spiral Artery Remodeling
Defective spiral artery remodeling during physiologic conversion is well-recognized as an important etiology of preeclampsia (Brosens, et al., 1972; Lim, et al., 1997; Fisher, 2015). As described above, spiral artery remodeling is dependent on interactions between HLA-C, HLA-G, and HLA-E molecules on EVTs and receptors on decidual NK cells and vascular endothelial cells. The association of fetal HLA-C2 genotypes with preeclampsia has been proposed to result from a lack of appropriate NK cell activation during spiral artery remodeling (Hiby, et al., 2004; Hiby, et al., 2010; Nakimuli, et al., 2015; Long, et al., 2015). Reduced expression of HLA-G by EVTs has been similarly associated with preeclampsia (Colbern, et al., 1994; Hara, et al., 1996; Goldman-Wohl, et al., 2000). However, it is difficult to disentangle the observed effects of HLA-C and HLA-G in spiral artery remodeling from their roles in inhibiting inappropriate inflammatory responses in the majority of studies to date. An interesting possibility is that the differential roles (anti-inflammatory versus spiral artery remodeling) may be related differential interactions with maternal immune, stromal and endothelial cells and their various receptors.

Anti-Human Leukocyte Antigen Antibodies and Preeclampsia
Circulating antibodies directed against paternal-derived HLA antigens can be detected in normal pregnancies (first described by Van Rood et al., 1958 and Payne and Rolfs, 1958). However, whether these antibodies contribute to pregnancy complications like preeclampsia is controversial. A meta-analysis found no consistent effect of anti-HLA class I or class II antibodies on pregnancy outcome (Lashley et al., 2013).

SUMMARY
This review has summarized current understanding of the roles HLA molecules play in pregnancy and preeclampsia (Figures 1, 2; Table 2). Given the central role of HLA molecules in immune function, their near-ubiquitous expression, and the considerable amount of genetic
Some studies suggest that women with preeclampsia are more likely to have inhibitory KIR genotypes whereby interactions between HLA-C and KIR on NK cells fail to stimulate release of pro-migratory chemokines/cytokines and thus result in defective spiral artery remodeling.

Dysregulation/dysfunction in preeclampsia needs to be further investigated.

Decreased placental and circulating HLA-G levels are observed in preeclampsia and are associated with deficient spiral artery remodeling, decreased numbers of Tregs and increased expression of pro-inflammatory cytokines.

Similarly, there may be maternal HLA genetic factors (such as HLA class II genotypes) influencing the maternal immune response that have yet to be appreciated.

The recent proposal classifying preeclampsia as resulting from 3 distinct pathophysiologic pathways (Leavey, et al., 2015; Leavey, et al., 2016) also raises the possibility that any influence of HLA genotypes on preeclampsia may be obfuscated by not having separated analyses into more well-defined categories. Indeed, an absence of an effect of genes regulating immune function such as HLA would not be surprising in non-immune mediated pathology, and thus may be underestimated by not distinguishing immune-mediated and non-immune-mediated mechanisms for preeclampsia. We propose that this distinction in future studies may more clearly reveal genetic associations and functional roles for the HLA genes and help define genetic risk factors in preeclampsia.

**AUTHOR CONTRIBUTIONS**

OA and GM were involved in the conception, research, and writing of this manuscript.

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