Review Article

Narrative review of the relationship between the maternal-fetal interface immune tolerance and the onset of preeclampsia

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Background and Objective: The establishment of maternal-fetal interface immune tolerance is essential for successful pregnancy. Studies have shown that spontaneous abortion, recurrent abortion, and fetal growth restriction are related to maternal-fetal interface immune dysfunction. Preeclampsia is an idiopathic condition related to pregnancy which manifests as hypertension, proteinuria, and other target organ damage after 20 weeks of gestation. Although the etiology of preeclampsia is still unknown, its pathogenesis is thought to be related to genetics, environment, and metabolism. In recent years, more and more studies have been conducted on the mechanism of immune tolerance at the maternal-fetal interface and the relationship between immune dysregulation and the pathogenesis of preeclampsia. This paper summarizes the latest studies on this topic in order to find new insights into the pathogenesis of preeclampsia and make a reflection on clinical diagnosis and treatment in different phenotype of preeclampsia.

Methods: The research and latest progress published from 2000 to December 2021 on the relationship between maternal-fetal interface immune tolerance and preeclampsia were broadly retrieved and researched using PubMed and Web of Science databases.

Key Content and Findings: The mechanism of natural killer cells (NK cells) and macrophages at the maternal-fetal interface in immune tolerance, as well as their cytotoxicity and cytokine secretion dysfunction, may be related to the pathogenesis of preeclampsia. The expression of nonclassical type I human leukocyte antigen (HLA) on extravillous trophoblast (EVT) cell were down-regulated in decidua of preeclampsia, which may induce increase EVT death caused by activating of cytotoxic NK cell. In addition, genetic polymorphism of nonclassical type I HLA on the EVT cell membrane may be related to the pathogenesis of preeclampsia, although this is likely to be a combination of 3 nonclassical type I HLA genotypes and requires sequencing to verify.

Conclusions: We demonstrated how the maternal-fetal interface immune dysfunction contribute to the pathogenesis of preeclampsia, further study and clinical trial based on this theory of pathogenesis may reveal new immune treatment method of preeclampsia.

Keywords: Immunity; maternal-fetal interface; natural killer cells (NK cells); human leukocyte antigen (HLA); preeclampsia

Submitted Apr 13, 2022. Accepted for publication Jun 14, 2022.
doi: 10.21037/atm-22-2287
View this article at: https://dx.doi.org/10.21037/atm-22-2287

Introduction

The human embryo is a semiallograft to the mother. The interaction between various immune cells, decidual stromal cells, and fetal trophoblasts in the maternal decidua starts from embryo implantation and continues throughout the pregnancy. The interface of this interaction is known as the maternal-fetal interface. The maternal-fetal interface is the first place of the maternal immune system to have contact with fetal alloantigens and is also an important place for the formation of the placenta. The success of a pregnancy largely depends on the immune tolerance of the maternal immune system to the embryo. An imbalance between immunity and tolerance at the maternal-fetal interface has been confirmed to be associated with spontaneous abortion in early pregnancy, preeclampsia in the middle and late stages, and fetal growth restriction. The clinical manifestations of this immune-based preeclampsia may be different from the classical type of preeclampsia. A review of the latest research on the pathogenesis of immune factors in preeclampsia and its conclusions is helpful for the prevention and treatment of immune type preeclampsia. This article aims to explain the mechanism of immune tolerance at the maternal-fetal interface and its role in the pathogenesis of preeclampsia in order to provide new insights for exploring the pathogenesis of preeclampsia and its prevention strategy from the perspective of immunity. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2287/rc).

Methods

We searched PubMed and Web of Science for original research and review articles from 2000 to December 2021. Articles in English and Chinese languages were included. The search strategy summarized in *Table 1*. The following terms were employed in different combinations: "maternal-fetal interface", "immunity", "preeclampsia", "NK cells", "human leukocyte antigen", and "reproductive immunology". Articles citing related studies and citations in relevant articles were also checked as potential sources of information.

Discussion

Maternal-fetal immune tolerance mechanism

The main mechanisms of maternal-fetal immune tolerance are as follows: decidua-specific immune cell populations are dominated by immune regulation and immunosuppression; embryonic trophoblasts do not express classical type I human leukocyte antigen (HLA); and anti-inflammatory and immunosuppressive hormones, cytokines, and immunoregulatory molecules are released by early trophoblasts and late placenta formation.

Decidual immune cells and immune tolerance

Before embryo implantation, semen-derived paternal antigens come into contact with maternal immune cells, and immune cells in the maternal uterus and the whole body begin to adapt to the physiological changes of pregnancy, including embryo implantation and placenta formation. Under the influence of progesterone, the endometrium transforms into the decidua during embryo implantation. Decidual natural killer cells (dNK cells) and innate immune cells such as dendritic and macrophages with special phenotypes accumulate in the decidua, preparing for antigen presentation and immune modulation. Previous studies have shown that dNK cells account for 70–80% of the total number of decidual lymphocytes in early pregnancy (1,2). Unlike cluster of differentiation (CD)$56^{dim}CD16^{+}$ NK cells in peripheral blood that mainly secrete cell-killing and cytotoxic factors, dNK cells are $CD56^{bright}CD16^{-}$ phenotype and can secrete interferon γ (IFN-γ), transforming growth factor β (TGF-β), interleukin-10 (IL-10), and other immunosuppressive functions. The main cytokines play a role in regulating the immune response and inhibiting the inflammatory response. Immunohistochemical study has shown that killer immunoglobulin-like receptors (KIRs)-positive dNK cells are distributed around the spiral arteries and EVTs in early pregnancy, and they secrete vascular endothelial growth factor A (VEGFA) and other proangiogenic factors play a role in promoting the remodeling of uterine spiral arteries (2). A recent single-cell sequencing study at the maternal-fetal interface has shown that there are 3 dNK subsets with distinct immunophenotypes and cellular functions in the decidua of normal early pregnancy, including the dNK1 subset of $CD39^{+}$, leukocyte immunoglobulin-like receptor B1 $(LILRB1)^{+}$, and KIR^{+}, play an important role in immune tolerance (3). Decidua NK1 secretes cytokines mainly characterized by TGF-B1 and macrophage colony-stimulating factor 1 (CSF1), regulates trophoblast invasion, and recruits macrophages to participate in vascular remodeling. LILRB1 and KIR receptors can specifically recognize HLA-G, inhibiting the killing activity of NK cells on trophoblast cells. It can also express CD39, which

Table 1 The search strategy summary

Items	Specification
Date of search (specified to date, month and year)	15/11/2021–31/1/2022
Databases and other sources searched	PubMed and Web of Science
Search terms used	"maternal-fetal interface"; "immunity"; "preeclampsia"; "NK cell"; "HLA"; "reproductive immunology"
Timeframe	From 2000 to December 2021
Inclusion and exclusion criteria	Inclusion criteria: 1. Focus on the research about relationship between maternal-fetal interface immune tolerance and preeclampsia 2. English-language papers 3. Peer-reviewed, published literature, including narrative review papers Exclusion criteria: 1. Main topic not related to the maternal-fetal interface immune tolerance and preeclampsia 2. Non-English-language articles 3. Editorials, letters to the editor, and abstracts
Selection process	Two authors searched the database independently. A third reviewer mediated any disagreements between the two researchers

HLA, human leukocyte antigen; NK, natural killer.

is involved in the conversion of adenosine triphosphate (ATP) to adenosine and inhibits immune activation. The chemokine secreted by dNK3 subsets, chemokine motif ligand 5 (CCL5), can recruit and activate decidual macrophages (dMs), and other studies have shown that CCL5 promotes breast cancer tumor proliferation and angiogenesis (4,5). At the same time, CCL5 inhibits trophoblast apoptosis by binding to atypical chemokine receptor 2 (2ACKR2) on EVTs (6). Three dNK subsets, decidual monocytes/macrophages, dendritic cells, and vascular endothelial cells, interact with EVTs through cell surface receptors/ligands, secrete cytokines and chemokines, and inhibit the release of inflammatory factors from lymphocytes, inhibiting killer cytotoxicity, regulating EVT invasion of uterine spiral arteries (3), and working together to maintain healthy pregnancy.

Decidual macrophages (dMs) are the second largest decidual lymphocyte population. In addition to interacting with EVTs, CSF1/2 secreted by the dNK1/2 subset also stimulates the proliferation and differentiation of dMs and increases phagocytosis and chemotactic activity. There are also 2 types of $CD68^+$ macrophages in the decidua during normal early pregnancy. Previous study has suggested that type 1 macrophages (M1) is a proinflammatory macrophage that secretes IFN-γ, while M2 is an anti-inflammatory cell that secretes IL-4 (7). Recent single-cell nucleotide sequencing also found that type 1 decidual macrophages (dM1) mainly express tumor necrosis factor (TNF), IL-10, CXC motif chemokine ligand 1/2/3 (CXCL1/2/3), other inflammatory regulatory cytokines, and more angiogenesis factors such as epiregulin (EREG) and VEGF than dNK, indicating that dM1 have an important role in vascular remodeling. At the same time, due to the secretion of a variety of chemokines, dM1 interacts with other lymphocytes in the decidua and regulates the local and systemic inflammatory response at the maternal-fetal interface (3).

Regulatory T (Treg) cells and dendritic cells, although a small proportion of decidual lymphocytes, play an important role in the regulation of inflammatory responses in local lymphocytes and the systemic immune system. Immature dendritic cells expressing fewer costimulatory molecules such as class II major histocompatibility complex (MHC-II) can stimulate $CD4^+$ naïve T cells to differentiate into $CD25^+FOXP3^+$ Treg cells, while Treg cells promote macrophages towards anti-inflammatory by secreting

TGF-β and IL-10, etc. Type M2 differentiates and maintains low levels of costimulatory molecule expression in dendritic cells, thereby forming a normal virtuous cycle of immune tolerance at the maternal-fetal interface (8). Treg cells also attenuate IL-2 stimulation of $CD8^+$, T helper type 1 (Th1), and Th17 cells by expressing high-affinity IL-2 receptor A for IL-2, thereby reducing $CD8^+$ cytotoxicity and type I proinflammatory cytokines at the maternal-fetal interface and the systemic immune system, thus maintaining immune tolerance at the maternal-fetal interface and inhibiting systemic inflammatory responses (9,10).

HLA and immune tolerance

Human placental trophoblasts include villous cytotrophoblast (VCT), syncytiotrophoblast (SCT), and EVT. SCTs, which can come into direct contact with maternal blood and immune cells, scarcely express classical HLA types I and II, avoiding the recognition and attack of fetal antigens by maternal immune cells which are thought to be beneficial for pregnancy. EVTs express a variety of HLAs, such as HLA-C, and interact with $CD8^+$ T cells and KIR receptors on the surface of NK cells through the endogenous antigen presentation pathway, blocking its cytotoxic T-lymphocyte (CTL) pathway to kill and induce apoptosis of trophoblast cells, which is important in tumors. EVTs also play an important role in immune evasion mechanisms. At the same time, they also express type II HLA such as HLA-DR/DQ. Through the exogenous antigen presentation pathway, EVTs induce the differentiation of $CD4^+$ T cells, promoting or inhibiting the inflammatory response and playing an immunoregulatory role. In addition, EVT cells mainly express nonclassical type I HLA, namely HLA-G, HLA-E, and HLA-F. These antigens are highly conserved, with little variation, and are less likely to cause severe antigenic rejection (11). The nonclassical type I HLA expressed by EVTs binds to maternal immune cells, decidual stromal cells, and vascular endothelial cells in the form of membrane proteins or soluble proteins, playing an important role in immune tolerance at the maternal-fetal interface and placenta formation.

HLA-G, as a marker molecule of EVT, is widely expressed on EVT cell surface and cytoplasm throughout pregnancy. HLA-G receptors are widespread on lymphocytes at the maternal-fetal interface and can inhibit NK cell killing activity by binding to KIR2DL4 and LILRB1 receptors of NK cells. HLA-G binds to immunoglobulin-like transcript 4 (ILT4) and ILT2 on monocytes, macrophages, and dendritic cells, preventing dendritic cell maturation or activation, causing it to express less MHC-II, thereby maintaining immune tolerance at the maternal-fetal interface. It also inhibits cytotoxicity, induces apoptosis of $CD8^+$ cells, and inhibits proliferation of $CD4^+$ cells by binding to T-cell receptor (TCR) and ILT2 on the surface of $CD8^+$ and $CD4^+$ T cells (12). In addition to membrane-bound HLA-G, soluble HLA-G can bind to HLA-E to form a stable complex, which then acts as a ligand to bind to CD94/NKG2 receptors to inhibit NK cell killing activity (13,14).

HLA-E is mainly expressed in the first trimester EVT, and our previous study and other reports also detected HLA-E protein expression in the placenta in the third trimester (11,15,16). HLA-E helps tumor cells to evade immune response by inhibiting $CD8^+$ antitumor cell activity (17), and a high expression of HLA-G and HLA-E in tumor cells suggests a poor prognosis for cancer patients (18,19). Human senescent cells can also inhibit $CD8^+$ cytotoxicity through p38 mitogen-activated protein kinase (p38MAK) signaling-mediated upregulation of HLA-E expression (20). Various viruses, including 2019's novel coronavirus (2019-nCoV), can evade NK cell killing by inducing upregulation of HLA-E expression in infected cells (21). Some studies have used $CD8^+$ T cells that do not bind to HLA-E to treat human immunodeficiency virus (HIV) and severe 2019-nCoV infection (22,23). In conclusion, HLA-E plays an important role in inhibiting the cytotoxicity of NK cells and $CD8^+$.

EVTs have invasion and migratory behaviors similar to those of tumor cells. By expressing HLA-E, they bind to CD94/NKG2A receptors on decidual NK cells and $CD8^+$ cells, inhibiting the direct cytotoxic killing of NK cells and $CD8^+$ cells on EVT and inducing apoptosis. Previous study has suggested that HLA-G plays a more important role in maintaining immune tolerance at the maternal-fetal interface due to its higher and more prevalent expression in EVTs than HLA-E (11). The latest single-cell sequencing results for the maternal-fetal interface in normal early pregnancy show that the vast majority of dNK1 and dNK2 subsets of decidual NK cells generally express NKG2A/C receptors, while only dNK1 subsets express HLA-G binding receptors KIR and LILRB1 (3). Another important study showed that the proportion of dNK expressing CD94/NKG2C was increased in the decidua of nonprime women, and that this NK cell population significantly increased VEGFA expression in $NKG2C^+$ NK cells after coculture with HLA-E-positive trophoblasts, while HLA-G-positive

trophoblastic cells did not have this effect, and HLA-E had a greater effect on trophoblastic tumor diameter (24). These studies suggest that HLA-E may play a more basic and important role in immune tolerance of the maternal-fetal interface and normal formation of the placenta.

Compared with HLA-G and HLA-E, which have been studied more, there are fewer studies on the expression and effect of HLA-F on EVT (11,16). Earlier immunohistochemical study showed that, similar to HLA-G, HLA-F is also expressed in the cytoplasm and cell surface of EVT cells in the placenta throughout pregnancy, and the expression level increases with increasing gestational age (16). More and more studies have shown that HLA-F plays an important role in immune tolerance at the maternal-fetal interface (11,25,26). Similar to HLA-E/G, which can bind to β2-microglobulin and leader peptide to form a transmembrane complex, HLA-F/leader peptide/β2-microglobulin complex can bind to the inhibitory receptor ILT2 on the surface of NK cells and T cells. HLA-F also forms a dimeric transmembrane protein that binds to inhibitory receptors KIR3DL1/KIR3DL2 and activating receptors KIR3DS1/KIR2DS4 (25). In addition, HLA-F may also be involved in the cross-presentation of extracellular antigens (26).

Study has used plasmids carrying the *HLA-G*0105N* gene (which does not express HLA-G1 protein) to transfect Jar trophoblast cells that do not express nonclassical HLA type I to induce HLA-E protein expression (27), which indicates the most robust structure HLA-G1 protein is not a key presence necessary to maintain normal pregnancy. HLA-E and HLA-G may have coregulatory factors at the level of gene expression and complement each other at the level of protein function. There are few studies on the expression relationship between HLA-F and HLA-G or HLA-E. Researchers have found that the single nucleotide polymorphism (SNP) rs2523393 is a quantitative trait locus for the expression of HLA-F and HLA-G, that is, HLA-F and HLA-G have common gene expression regulation, and rs2523393 A antigen carriers have a higher levels of HLA-F nucleic acid expression in the secretion phase endometrium and that are associated with greater fertilization (28).

In addition to expressing nonclassical HLA I, EVTs inhibit the cytotoxicity of NK cells and effector T cells, and promote the secretion of VEGFA and IFN-γ from NK cells. They can also secrete thymic stromal lymphopoietin (TSLP) to make dendritic cells express fewer MHC-II costimulation molecules, thereby promoting Treg cell differentiation and maintaining immune tolerance at the maternal-fetal interface (29).

Immune dysregulation at the maternal-fetal interface and preeclampsia

Preeclampsia is a comprehensive disease idiopathic to pregnancy and is characterized by increased blood pressure after 20 weeks of gestation and multisystem damage. With an incidence rate of 2–10% worldwide, it is an important cause of maternal mortality (30). Previous studies have suggested that the pathogenesis of preeclampsia includes genetic factors, immune factors, metabolic factors, and environmental factors. To explore the pathogenesis of preeclampsia from the perspective of pathophysiology, most researchers believe that the hindered invasion of trophoblasts into the uterine spiral artery leads to the shallow implantation of the placenta, causing local oxidative stress and vascular endothelial dysfunction, resulting in systemic symptoms. With in-depth study of the pathogenesis of preeclampsia, some researchers have proposed a more refined 6-stage model based on the previous 2-stage pathogenesis theory (31). Recent histopathological study of the placenta in preeclampsia have also identified 2 phenotypes of preeclampsia, the classic type characterized by poor vascular perfusion and the immunotype characterized by immune rejection of allografts (32). Bioinformatics analysis of differentially expressed genes in the placenta also showed that the pathogenesis of preeclampsia is divided into 2 types: (I) pre-existing maternal metabolic diseases or (II) immune dysregulation at the maternal-fetal interface, which is associated with preeclampsia, preterm birth, and fetal growth restriction (33).

Immune cells and preeclampsia

Immune factors operate through all stages of the onset of preeclampsia, especially during placenta formation and organ damage caused by systemic inflammatory responses. Studies of the proportion of lymphocytes at the maternal-fetal interface and circulatory system in patients with preeclampsia have shown that a variety of lymphocytes are disproportionately represented in patients with preeclampsia. At the maternal-fetal interface, the results of studies on the proportion of dNK cells in preeclampsia in the third trimester are inconsistent; some studies have found that the proportion of dNK cells is decreased (34,35),

while others have found that the proportion is increased (36). This may be related to the different placental sites and gestational weeks used in each experiment and also the inability of the selected molecular markers to fully represent the corresponding cells. In addition, the third trimester of pregnancy cannot reflect the composition ratio and function of NK cells during placenta formation. Therefore, further research is needed on the composition ratio and functional changes of dNK cells in patients with preeclampsia. The proportion of adaptive NK cells of $NKG2C^+$ and $LILRB1^+$ in the decidua of nonprime women is higher (24). Whether the proportion of NK cells in the decidua of pregnant women with preeclampsia and patients with different types of preeclampsia changes and its role in pathogenesis deserves further research.

A study of peripheral blood found that the proportion of $CD16^+CD45^+CD56^+$ NK cells in the peripheral blood of patients with preeclampsia increased (37). Fukui *et al.* found that the proportion of NK cells expressing NKp46 receptors in the peripheral blood of patients with preeclampsia decreased. Increased NK cytotoxicity is associated with increased production of inflammatory factors (38). Treg cells play an important role in the normal maintenance of immune tolerance at the maternal-fetal interface. Several studies have shown that the proportion of Treg cells in the maternal-fetal interface and peripheral blood of patients with preeclampsia is reduced and the immunosuppressive function is impaired (39-41). Macrophages are the second largest subgroup of decidual lymphocytes and are closely related to the differentiation of Treg cells. Immunohistochemical studies have found that $CD68^+$ mononuclear macrophages and myeloperoxidase $(MPO)^+$ granulocytes in the placental space of preeclampsia are increased (32,35). The proportion of M1, previously thought to be proinflammatory macrophages, is increased in the decidua of patients with preeclampsia. M1 is characterized by the production of more inflammatory chemokines, such as TNF and IL-6, whereas M2 is characterized by the production of TGF-β, which promotes vascular remodeling (3,7). Buckley *et al.* found that M1 could inhibit the movement and migration of trophoblast cells *in vitro* (7). Changes in the number and function of macrophages during preeclampsia are involved in the abnormal formation of the placenta, but the specific mechanism still needs further study.

HLA and preeclampsia

EVTs express HLA-C and nonclassical type I HLAs (HLA-G, HLA-E, and HLA-F) binding to a variety of receptors expressed by various immune cells in the maternal decidua, which cause inhibition of effector T cell activation of NK cells and secretion of vascular growth factors promote vascular remodeling, inhibition of macrophage maturation, and promotion of Treg cell differentiation. The decreased expression levels of HLA-G, HLA-E, and HLA-F in trophoblast cells or the affinity differences caused by gene polymorphisms are likely to be involved in the pathogenesis of preeclampsia. Several immunohistochemical studies have shown that the expression level of HLA-E and HLA-G proteins in the placenta of patients with preeclampsia are reduced (42-44). However, the experimental methods of these studies were relatively simple and cannot explain the role of expression level changes in the pathogenesis of preeclampsia. The latest results of next-generation sequencing of nucleic acid expression in placental tissues of preeclampsia found that HLA-G nucleic acid expression was reduced in EVT cells of placentas in patients with preeclampsia (45), which is consistent with previous studies, although this study did not suggest other nonclassical type I human leukocytes differences in antigenic nucleic acid expression.

In addition, many previous studies have shown that gene polymorphisms of nonclassical HLA type I may be associated with the pathogenesis of preeclampsia. Study has shown that the genotype of maternal NK cell KIR receptor activating B type and fetal HLA-C2 significantly increased the risk of placental spiral atherosclerosis, which is highly correlated with the onset of preeclampsia (46). However, a recent systematic review found that KIR genotype was not associated with the onset of preeclampsia (47). EVT cells generally express HLA-G, and the relationship between *HLA-G* gene polymorphisms and the pathogenesis of preeclampsia is also the most studied. HLA-G polymorphisms that may be related to the pathogenesis of preeclampsia have been reported, including 14 bp insertion/deletion (rs66554220), *G*01:05N*, *G*01:04:xx*, and *G*01:06*, but results were inconsistent due to the different races and number of cases studied (12). A recent study of 228 cases of preeclampsia using next-generation sequencing technology showed that genetic polymorphism of HLA-G alone had no significant relationship with the incidence of preeclampsia, while a SNP of HLA-E (rs1264457, namely *HLA-E*01:03*) was also not significantly associated with the onset of preeclampsia (48). This conclusion was limited by number and races of subjects and not full length sequencing of whole nonclassical HLA type I gene. The polymorphism

of HLA-F is less than that of HLA-G. The latest research shows that the polymorphism of the *HLA-F* gene promoter is related to the expression of HLA-F messenger RNA (mRNA). Individuals carrying the F* terminal C haplotype have higher HLA-F nucleic acid expression levels (49). Another study found that an SNP rs2523393 at the HLA-F expression quantitative trait locus was associated with endometrial HLA-F mRNA expression levels in secretory antigen carriers, HLA-F nucleic acid expression levels were higher and more fertile in a single menstrual cycle, and rs2523393 was also an SNP on the HLA-G expression quantitative trait locus (28).

Recent studies have shown that progesterone can regulate the expression of HLA-G, HLA-E, and HLA-F in EVT cells (28,50). Other coregulatory elements include IFN-γ, class II transactivator (CIITA), and IL-2/6 (51-53). Transfection of the *HLA-G*01:05N* gene into a JAR cell line that does not express HLA-G induces HLA-E membrane protein expression (27). The above results all indicate that the nucleic acid and protein expressions of the 3 nonclassical type I HLAs in ETVs are regulated by some common factors, such as progesterone and IFN-γ, and the receptors that each bind to decidual lymphocytes are also regulated by common factors. There is overlap, so the 3 are functionally different and complementary (54). This may be part of the reason why previous studies on the relationship between a single nonclassical HLA type I polymorphism and preeclampsia have not been consistent and positive. It is possible that the onset of preeclampsia is associated with some combination of 3 nonclassical HLA type I gene polymorphisms (55), such as *HLA-G*01:05N*, which cannot express HLA-G functional proteins and has lower affinity for NK cells. The combination of *HLA-E*01:01* and SNP rs2523393 G antigen with lower HLA-F nucleic acid expression level requires comprehensive sequencing and verification of nonclassical HLA type I genes with large samples and multiple populations.

Summary and outlook

At present, the predictive molecules and models of preeclampsia are under continuous investigation, but there is still a lack of treatment specifically for preeclampsia. At present, there is a lack of comprehensive studies on the proportion and function changes of cells related to the maternal-fetal interface in preeclampsia, as well as the verification of derivation and mechanism studies, and the relationship between related gene polymorphisms and the pathogenesis of preeclampsia is not comprehensive enough. The development of sequencing technologies, including single-cell sequencing technology and protein profiling technology, will bring new opportunities for the study of this ancient obstetric problem. The application of these techniques to the subpopulation and functional changes of decidual lymphocytes and trophoblasts, as well as the in-depth study of maternal and fetal genetic polymorphisms, may reveal the underlying pathogenesis of the disease and the pathogenesis of different clinical phenotypes.

Acknowledgments

Funding: The present study was supported by the key research and development project of Sichuan Science and Technology Department (No. 21zdyf0549).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2287/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2287/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Dosiou C, Giudice LC. Natural killer cells in pregnancy and recurrent pregnancy loss: endocrine and immunologic perspectives. Endocr Rev 2005;26:44-62.

2. Fraser R, Whitley GS, Thilaganathan B, et al. Decidual natural killer cells regulate vessel stability: implications for impaired spiral artery remodelling. J Reprod Immunol 2015;110:54-60.
3. Vento-Tormo R, Efremova M, Botting RA, et al. Single-cell reconstruction of the early maternal-fetal interface in humans. Nature 2018;563:347-53.
4. Jin Z, Chenghao Y, Cheng P. Anticancer Effect of Tanshinones on Female Breast Cancer and Gynecological Cancer. Front Pharmacol 2022;12:824531.
5. Kuo CH, Liu CJ, Lu CY, et al. 17β-estradiol inhibits mesenchymal stem cells-induced human AGS gastric cancer cell mobility via suppression of CCL5- Src/Cas/Paxillin signaling pathway. Int J Med Sci 2014;11:7-16.
6. Zhang XN, Yang KD, Chen C, et al. Pericytes augment glioblastoma cell resistance to temozolomide through CCL5-CCR5 paracrine signaling. Cell Res 2021;31:1072-87.
7. Buckley RJ, Whitley GS, Dumitriu IE, et al. Macrophage polarisation affects their regulation of trophoblast behaviour. Placenta 2016;47:73-80.
8. Robertson SA, Care AS, Moldenhauer LM. Regulatory T cells in embryo implantation and the immune response to pregnancy. J Clin Invest 2018;128:4224-35.
9. Muñoz-Rojas AR, Mathis D. Tissue regulatory T cells: regulatory chameleons. Nat Rev Immunol 2021;21:597-611.
10. Zhang Y, Liu Z, Tian M, et al. The altered PD-1/PD-L1 pathway delivers the 'one-two punch' effects to promote the Treg/Th17 imbalance in pre-eclampsia. Cell Mol Immunol 2018;15:710-23.
11. Hackmon R, Pinnaduwage L, Zhang J, et al. Definitive class I human leukocyte antigen expression in gestational placentation: HLA-F, HLA-E, HLA-C, and HLA-G in extravillous trophoblast invasion on placentation, pregnancy, and parturition. Am J Reprod Immunol 2017. doi: 10.1111/aji.12643.
12. Djurisic S, Hviid TV. HLA Class Ib Molecules and Immune Cells in Pregnancy and Preeclampsia. Front Immunol 2014;5:652.
13. Rölle A, Meyer M, Calderazzo S, et al. Distinct HLA-E Peptide Complexes Modify Antibody-Driven Effector Functions of Adaptive NK Cells. Cell Rep 2018;24:1967-1976.e4.
14. Rölle A, Jäger D, Momburg F. HLA-E Peptide Repertoire and Dimorphism-Centerpieces in the Adaptive NK Cell Puzzle? Front Immunol 2018;9:2410.
15. Sullivan LC, Nguyen THO, Harpur CM, et al. Natural killer cell receptors regulate responses of HLA-E-restricted T cells. Sci Immunol 2021;6:eabe9057.
16. Shobu T, Sageshima N, Tokui H, et al. The surface expression of HLA-F on decidual trophoblasts increases from mid to term gestation. J Reprod Immunol 2006;72:18-32.
17. Abd Hamid M, Wang RZ, Yao X, et al. Enriched HLA-E and CD94/NKG2A Interaction Limits Antitumor CD8+ Tumor-Infiltrating T Lymphocyte Responses. Cancer Immunol Res 2019;7:1293-306.
18. Guo ZY, Lv YG, Wang L, et al. Predictive value of HLA-G and HLA-E in the prognosis of colorectal cancer patients. Cell Immunol 2015;293:10-6.
19. Ben Yahia H, Boujelbene N, Babay W, et al. Expression analysis of immune-regulatory molecules HLA-G, HLA-E and IDO in endometrial cancer. Hum Immunol 2020;81:305-13.
20. Pereira BI, Devine OP, Vukmanovic-Stejic M, et al. Senescent cells evade immune clearance via HLA-E-mediated NK and CD8+ T cell inhibition. Nat Commun 2019;10:2387.
21. Bortolotti D, Gentili V, Rizzo S, et al. SARS-CoV-2 Spike 1 Protein Controls Natural Killer Cell Activation via the HLA-E/NKG2A Pathway. Cells 2020;9:1975.
22. La Manna MP, Orlando V, Prezzemolo T, et al. HLA-E-restricted CD8+ T Lymphocytes Efficiently Control Mycobacterium tuberculosis and HIV-1 Coinfection. Am J Respir Cell Mol Biol 2020;62:430-9.
23. Caccamo N, Sullivan LC, Brooks AG, et al. Harnessing HLA-E-restricted CD8 T lymphocytes for adoptive cell therapy of patients with severe COVID-19. Br J Haematol 2020;190:e185-7.
24. Gamliel M, Goldman-Wohl D, Isaacson B, et al. Trained Memory of Human Uterine NK Cells Enhances Their Function in Subsequent Pregnancies. Immunity 2018;48:951-962.e5.
25. Burian A, Wang KL, Finton KA, et al. HLA-F and MHC-I Open Conformers Bind Natural Killer Cell Ig-Like Receptor KIR3DS1. PLoS One 2016;11:e0163297.
26. Hò GT, Heinen FJ, Huyton T, et al. HLA-F*01:01 presents peptides with N-terminal flexibility and a preferred length of 16 residues. Immunogenetics 2019;71:353-60.
27. Sala FG, Del Moral PM, Pizzato N, et al. The HLA-G*0105N null allele induces cell surface expression of HLA-E molecule and promotes CD94/NKG2A-mediated recognition in JAR choriocarcinoma cell line. Immunogenetics 2004;56:617-24.
28. Mika KM, Li X, DeMayo FJ, et al. An Ancient

Fecundability-Associated Polymorphism Creates a GATA2 Binding Site in a Distal Enhancer of HLA-F. Am J Hum Genet 2018;103:509-21.
29. Du MR, Guo PF, Piao HL, et al. Embryonic trophoblasts induce decidual regulatory T cell differentiation and maternal-fetal tolerance through thymic stromal lymphopoietin instructing dendritic cells. J Immunol 2014;192:1502-11.
30. Backes CH, Markham K, Moorehead P, et al. Maternal preeclampsia and neonatal outcomes. J Pregnancy 2011;2011:214365.
31. Redman C. The six stages of pre-eclampsia. Pregnancy Hypertens 2014;4:246.
32. Leavey K, Grynspan D, Cox BJ. Both "canonical" and "immunological" preeclampsia subtypes demonstrate changes in placental immune cell composition. Placenta 2019;83:53-6.
33. Than NG, Romero R, Tarca AL, et al. Integrated Systems Biology Approach Identifies Novel Maternal and Placental Pathways of Preeclampsia. Front Immunol 2018;9:1661.
34. Williams PJ, Bulmer JN, Searle RF, et al. Altered decidual leucocyte populations in the placental bed in pre-eclampsia and foetal growth restriction: a comparison with late normal pregnancy. Reproduction 2009;138:177-84.
35. Milosevic-Stevanovic J, Krstic M, Radovic-Janosevic D, et al. Number of decidual natural killer cells & macrophages in pre-eclampsia. Indian J Med Res 2016;144:823-30.
36. Bachmayer N, Rafik Hamad R, Liszka L, et al. Aberrant uterine natural killer (NK)-cell expression and altered placental and serum levels of the NK-cell promoting cytokine interleukin-12 in pre-eclampsia. Am J Reprod Immunol 2006;56:292-301.
37. Laganà AS, Giordano D, Loddo S, et al. Decreased Endothelial Progenitor Cells (EPCs) and increased Natural Killer (NK) cells in peripheral blood as possible early markers of preeclampsia: a case-control analysis. Arch Gynecol Obstet 2017;295:867-72.
38. Fukui A, Yokota M, Funamizu A, et al. Changes of NK cells in preeclampsia. Am J Reprod Immunol 2012;67:278-86.
39. Quinn KH, Lacoursiere DY, Cui L, et al. The unique pathophysiology of early-onset severe preeclampsia: role of decidual T regulatory cells. J Reprod Immunol 2011;91:76-82.
40. Sasaki Y, Darmochwal-Kolarz D, Suzuki D, et al. Proportion of peripheral blood and decidual CD4(+) CD25(bright) regulatory T cells in pre-eclampsia. Clin Exp Immunol 2007;149:139-45.
41. Steinborn A, Schmitt E, Kisielewicz A, et al. Pregnancy-associated diseases are characterized by the composition of the systemic regulatory T cell (Treg) pool with distinct subsets of Tregs. Clin Exp Immunol 2012;167:84-98.
42. Zhuang B, Shang J, Yao Y. HLA-G: An Important Mediator of Maternal-Fetal Immune-Tolerance. Front Immunol 2021;12:744324.
43. Persson G, Stæhr CS, Klok FS, et al. Evidence for a shift in placental HLA-G allelic dominance and the HLA-G isoform profile during a healthy pregnancy and preeclampsia. Biol Reprod 2021;105:846-58.
44. Johnsen GM, Fjeldstad HES, Drabbels JJM, et al. A possible role for HLA-G in development of uteroplacental acute atherosis in preeclampsia. J Reprod Immunol 2021;144:103284.
45. Zhang T, Bian Q, Chen Y, et al. Dissecting human trophoblast cell transcriptional heterogeneity in preeclampsia using single-cell RNA sequencing. Mol Genet Genomic Med 2021;9:e1730.
46. Johnsen GM, Størvold GL, Drabbels JJM, et al. The combination of maternal KIR-B and fetal HLA-C2 is associated with decidua basalis acute atherosis in pregnancies with preeclampsia. J Reprod Immunol 2018;129:23-9.
47. Larsen TG, Hackmon R, Geraghty DE, et al. Fetal human leukocyte antigen-C and maternal killer-cell immunoglobulin-like receptors in cases of severe preeclampsia. Placenta 2019;75:27-33.
48. Nilsson LL, Djurisic S, Andersen AM, et al. Distribution of HLA-G extended haplotypes and one HLA-E polymorphism in a large-scale study of mother-child dyads with and without severe preeclampsia and eclampsia. HLA 2016;88:172-86.
49. Buttura RV, Ramalho J, Lima THA, et al. HLA-F displays highly divergent and frequent haplotype lineages associated with different mRNA expression levels. Hum Immunol 2019;80:112-9.
50. Huang Z, Hyodo H, Fujii T, et al. Effect of progesterone on HLA-E gene expression in JEG-3 choriocarcinoma cell line. Am J Reprod Immunol 2009;61:221-6.
51. Gobin SJ, van den Elsen PJ. Transcriptional regulation of the MHC class Ib genes HLA-E, HLA-F, and HLA-G. Hum Immunol 2000;61:1102-7.
52. Yarmarkovich M, Marshall QF, Warrington JM, et al. Cross-HLA targeting of intracellular oncoproteins with peptide-centric CARs. Nature 2021;599:477-84.

53. Arnaiz-Villena A, Juarez I, Suarez-Trujillo F, et al. HLA-G: Function, polymorphisms and pathology. Int J Immunogenet 2021;48:172-92.
54. Jordier F, Gras D, De Grandis M, et al. HLA-H: Transcriptional Activity and HLA-E Mobilization. Front Immunol 2019;10:2986.
55. Persson G, Picard C, Marin G, et al. Maternal HLA Ib Polymorphisms in Pregnancy Allo-Immunization. Front Immunol 2021;12:657217.

(English Language Editor: A. Muijlwijk)

Cite this article as: Luo F, Yue J, Li L, Mei J, Liu X, Huang Y. Narrative review of the relationship between the maternal-fetal interface immune tolerance and the onset of preeclampsia. Ann Transl Med 2022;10(12):713. doi: 10.21037/atm-22-2287