

Opinion

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Interactions of Immunomodulatory HLA-G with Immune Cells during Pregnancy and Endometriosis

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The Major Histocompatibility Complex (MHC), the genetic region that encodes the proteins responsible for tissue graft rejection,¹ encodes MHC Class I (MHC-I) and MHC Class II (MHC-II) glycoproteins. There are two subclasses of MHC-I proteins. Classical MHC-I (MHC-Ia) proteins are membrane-bound isoforms that are expressed in all nucleated cells of the body and present intracellular pathogen-derived peptides or the animal's own peptides on the cell surface for immune recognition by CD8 T cells. Contrary to MHC-Ia proteins, non-classical MHC-I (MHC-Ib) molecules are less polymorphic, possess specific molecular motifs in their transmembrane domains and contain premature stop codons. MHC-II proteins are expressed only by professional Antigen Presenting Cells (APC), which present extracellular pathogen-derived or self-peptides bound to MHC-II proteins on their cell surface for recognition by CD4 T cells. Immunological recognition of pathogens involves proteolysis of foreign pathogen into peptides which are assembled on MHC-I and -II glycoproteins. Interaction of MHC-I and MHC-II-peptide complexes with CD8 and CD4 T Cell Receptors (TCR), respectively, leads to effector functions including removal of infected cells to clear the infection. The fetal allograft must remain unharmed by the mother's potentially hostile immune system throughout the term. Several mechanisms have been reported which contribute to immune tolerance to the fetus including the production of Transforming Growth Factor beta 1 (TGF)- β 1 and Interleukin-10 (IL-10) by T-regulatory cells (Tregs), secretion of prolactin, progesterone and gonadotropin by both fetal and endometrial cells, secretion of immunosuppressive cytokines, chemokines, and prostaglandins which dampen T lymphocyte proliferation.²

An appropriate regulation of MHC class I genes at the maternal fetal interface is critical for immunological acceptance of allogeneic conceptus.³ Trophoblast cells do not express MHC-II antigens that are expressed mainly on antigen presenting cells (APCs). However, trophoblast cells express immunomodulatory non-classical HLA-I antigens (HLA-Ib) molecules. Contrary to ubiquitous and highly polymorphic classical class I glycoproteins (HLA-Ia), HLA-Ib proteins are oligomeric, undergo alternative splicing to produce membrane and soluble isoforms in specific cell/tissue types. Examples of class Ib proteins are Human Leukocyte Antigens HLA-E, -F and -G,^{4,6} *Qa-2* in mice,⁷ *Mamu-AG* in Rhesus Macaques,⁸ and *Paan-AG* in Olive baboons.⁹

HLA-G has been studied most and is a potent immunomodulatory during pregnancy. This protein is alternatively spliced to produce seven messenger RNA (mRNA) isoforms, four membrane-bound isoforms (HLA-G1, -G2, -G3, and -G4) and three soluble isoforms (HLA-G5, -G6 and -G7).¹⁰ Expression of membrane and soluble HLA-G isoforms is critically important phenomenon which renders maternal immune cells inactive by serving as a ligand for leukocyte receptors during pregnancy. HLA-G is expressed, in the first trimester and at term, by extravillous and placental villous syncytiotrophoblast cells; latter only expressing non-membrane forms.¹⁰ Membrane HLA-G isoforms induce suppression of CD4⁺ T cells and Natural Killer (NK) cells.¹¹ Soluble HLA-G is primarily shed or released by trophoblast cells. A minute quantity is also produced by regulatory T cells and antigen presenting cells (APCs) such as monocytes and dendritic cells.^{12,13} Soluble HLA-G in non-pregnant individuals reflects

the quantity expressed by monocytes. Soluble HLA-G1 isoform induces apoptosis of activated CD8 T cells,^{14,15} down regulates CD4⁺ T cell proliferation and inhibits NK-cell mediated cytotoxicity.¹⁶⁻¹⁹ HLA-G interacts with Immunoglobulin-like transcript 2 (ILT2), Immunoglobulin-like transcript 4 (ILT4), killer cell immunoglobulin-like receptor KIR2DL4, and CD94/NKG2A receptors expressed by maternal NK-cells and inhibits their cell lysis properties. The ILT receptors are expressed by NK cells, monocytes and macrophage cells; ILT2 by B-lymphocytes, and some CD4⁺ and CD8⁺ T-lymphocytes. HLA-G, therefore, is an important immunomodulatory protein during pregnancy circumventing the maternal immune system during pregnancy and protecting the fetus.

Interactions of HLA-G with immune cells on one hand modulates the climate favorably within uterus but on the other is associated with gynecologic diseases such as preeclampsia.¹⁰ Endometriosis is an estrogen dependent disease that is characterized by the presence of endometrial glands and stroma in ectopic locations, mainly the pelvic peritoneum, ovaries and rectovaginal septum. Studies suggest that eutopic endometrium expressed HLA-G only in menstrual phase and not in secretory or proliferative phase. They also identified HLA-G expressing cells in the peritoneal cavity.²⁰ In contrast, another study revealed expression of HLA-G by glandular epithelium of peritoneal endometriotic lesions and not eutopic epithelium of the subjects.²¹ The HLA-G expressing endometrial cells may dampen peritoneal NK cell-cytotoxicity *via* HLA-G-leukocyte receptor interaction thus letting endometrial implants survive and establish onto the peritoneal sites and consequently develop into endometriotic tissue implants. Eutopic endometrium of women with endometriosis is more resistant to NK cell lysis compared to eutopic endometrium from women without the disease. Impaired NK cell function can favor endometrial cells evade immune system and thus develop lesions in the peritoneum.²²

Endometriosis is an enigmatic and multifactorial disease. An intriguing factor in the onset of endometriosis is that refluxed endometrial implants that are cleared off normally by immune cells evade the maternal immune system and establish during progression of the disease. Immunomodulatory interactions of HLA-G and other class Ib molecules with immune cells which protect fetal allograft may play a role in pathophysiology of endometriosis and therefore need to be addressed and considered during development of research platform and therapeutic strategies for this disease.

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