GYNECOLOGY AND OBSTETRICS RESEARCH

Openventio PUBLISHERS

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-121

Opinion

*Corresponding author
Parveen Parasar, DVM, PhD
Boston Center for Endometriosis
Brigham and Women's Hospital
Boston Children's Hospital
Harvard Medical School
300 Longwood Avenue
Boston, MA 02115, USA
E-mail: suprovet@gmail.com

Volume 2 : Issue 4
Article Ref. #: 1000GOROJ2121

Article History
Received: November 14th, 2015
Accepted: November 30th, 2015
Published: December 1st, 2015

Citation
Parasar P. Interactions of immunomodulatory HLA-G with immune cells during pregnancy and endometriosis. *Gynecol Obstet Res Open J.* 2015; 2(4): 93-95. doi: 10.17140/GOROJ-2-121

Copyright
©2015 Parasar P. This is an open access article distributed under the Creative Commons Attribution 4.0 International License (CC BY 4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

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

Parveen Parasar*

Boston Center for Endometriosis, Brigham and Women's Hospital, Boston Children's Hospital, Harvard Medical School, 300 Longwood Avenue, Boston, MA 02115, USA

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)-β1 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 oligomorphic, 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

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-121

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.

REFERENCES

1. Klein J. Biology of the mouse histocompatibility-2 complex: principles of immunogenetics applied to a single system, Berlin and New York: Springer-Verlag, 1975.

2. Hunt JS, Petroff MG, McIntire RH, Ober C. HLA-G and immune tolerance in pregnancy. *FASEB J.* 2005; 19: 681-693.

3. Davies CJ. Why is the fetal allograft not rejected? *J Anim Sci.* 2007; 85(13 Suppl): E32-E35.

4. Ellis SA, Sargent IL, Redman CW, McMichael AJ. Evidence for a novel HLA antigen found on human extravillous trophoblast and a choriocarcinoma cell line. *Immunology.* 1986; 59: 595-601.

5. Redman CW, McMichael AJ, Stirrat GM, Sunderland CA, Ting A. Class 1 major histocompatibility complex antigens on human extra-villous tro-phoblast. *Immunology.* 1984; 52(3): 457-468.

6. Geraghty DE, Koller BH, Orr HT. A human major histocompatibility complex class I gene that encodes a protein with a shortened cytoplasmic segment. *Proc Natl Acad Sci USA.* 1987; 84(24): 9145-9149.

7. Warner CM, Gollnick SO, Flaherty L, Goldbard SB. Analysis of Qa-2 antigen expression by preimplantation mouse embryos: possible relationship to the preimplantation-embryo-development (Ped) gene product. *Biol Reprod.* 1987; 36(3): 611-616. doi: 10.1095/biolreprod36.3.611

8. Boyson JE, Iwanaga KK, Golos TG, Watkins DI. Identification of the rhesus monkey HLA-G ortholog. Mamu-G is a pseudogene. *J Immunol.* 1996; 157: 5428-5437.

9. Langat DK, Morales PJ, Fazleabas AT, Mwenda JM, Hunt JS. Baboon placentas express soluble and membrane-bound Paan-AG proteins encoded by alternatively spliced transcripts of the class Ib major histocompatibility complex gene, Paan-AG. *Immunogenetics.* 2002; 54: 164-173. doi: 10.1007/s00251-002-0454-8

10. Djurisic S, Hviid TV. HLA Class Ib molecules and immune cells in pregnancy and preeclampsia. *Front Immunol.* 2014; 5: 652. doi: 10.3389/fimmu.2014.00652

11. LeMaoult J, Krawice-Radanne I, Dausset J, Carosella ED. HLA-G1-expressing antigen-presenting cells induce immunosuppressive CD4+ T cells. *Proc Natl Acad Sci USA*. 2004; 101(18): 7064-7069. doi: 10.1073/pnas.0401922101

12. Feger U, Tolosa E, Huang YH, et al. HLA-G expression defines a novel regulatory T-cell subset present in human peripheral blood and sites of inflammation. *Blood.* 2007; 110(2): 568-577. doi: 10.1182/blood-2006-11-057125

13. Alegre E, Diaz-Lagares A, Lemaoult J, Lopez-Moratalla N, Carosella ED, Gon-zalez A. Maternal antigen presenting cells are a source of plasmatic HLA-G during pregnancy: longitudinal study during pregnancy. *Hum Immunol.* 2007; 68(8): 661-667.

14. Le Bouteiller P, Legrand-Abravanel F, Solier C. Soluble

ISSN 2377-1542 Open Journal http://dx.doi.org/10.17140/GOROJ-2-121

HLA-G1 at the maternofoetal interface-a review. *Placenta.* 2003; 17: S10-S15. doi: 10.1053/plac.2002.0931

15. Solier C, Aguerre-Girr M, Lenfant F, et al. Secretion of pro-apoptotic soluble HLA-G1 by human villous trophoblast. *Eur J Immunol.* 2002; 32: 3576-3586. doi: 10.1002/1521-4141(200212)32:12<3576::AID-IMMU3576>3.0.CO;2-M

16. Lila N, Rouass-Freiss N, Dausset J, Carpentier A, Carosella ED. Soluble HLA-G protein secreted by allo-specific CD4+ T cells suppresses the alloproliferative response: a CD4+ T cell regulatory mechanism. *Proc Natl Acad Sci USA.* 2001; 98: 12150-12155. doi: 10.1073/pnas.201407398

17. Lindaman A, Dowden A, Zavazava N. Soluble HLA-G molecules induce apoptosis in natural killer cells. *Am J Reprod Immunol.* 2006; 56: 68-76. doi: 10.1111/j.1600-0897.2006.00395.x

18. Park GM, Lee S, Park B, et al. Soluble HLA-G generated by proteolytic shedding inhibits NK-mediated cell lysis. *Biochem Biophys Res Commun.* 2004; 313: 606-611. doi: 10.1016/j.bbrc.2003.11.153

19. Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L. Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4+ CD25highFOXP3+ regulatory T cells. *Stem Cells.* 2008; 26(1): 212-222. doi: 10.1634/stemcells.2007-0554

20. Maeda N, Izumiya C, Taniguchi K, Matsushima S, Fukaya T. Role of NK cells and HLA-G in endometriosis. *Front Biosci (Schol Ed).* 2012; 4: 1568-1581.

21. Barrier BF, Kendall BS, Ryan CE, Sharpe-Timms KL. HLA-G is expressed by the glandular epithelium of peritoneal endometriosis but not in eutopic endometrium. *Hum Reprod.* 2006; 21(4): 864-869. doi: 10.1093/humrep/dei408

22. Oosterlynck DJ, Cornillie FJ, Waer M, Vandeputte M, Koninckx PR. Women with endometriosis show a defect in natural killer activity resulting in a decreased cytotoxicity to autologous endometrium. *Fertil Steril.* 1991; 56(1): 45-51.