PRINT: ISSN 0972-3757 ONLINE: 2456-6360
Int J Hum Genet, 12(1): 33-36 (2012)
DOI: 10.31901/24566330.2012/12.01.05

Role of HLA in Human Pregnancy

Jyothi V. Mallia, Dhanjit Kumar Das and Anurupa Maitra

National Institute for Research in Reproductive Health, Parel, Mumbai 400 012, Mahrashtra, India

KEYWORDS HLA. Fetal Cytotrophoblast Cells. Reproduction. Recurrent Abortion

ABSTRACT Human leukocyte antigen (HLA) genes are the human versions of the MHC genes that are most genetically variable coding loci in mammals, found in most vertebrates. In addition to its role in the regulation of cell-cell interactions in the immune response, it also influences reproductive success. HLA-G gene is of particular interest in reproductive biology because of its specific expression on fetal cytotrophoblast cells and is also reported in protection of the human embryo. In this review we discuss about the role of HLA in reproduction, mainly highlighting the importance of HLA-G and E in recurrent abortion.

INTRODUCTION

Human pregnancy is commonly considered as a semi-allograft as half of the fetal genome derives from the father. However in normal pregnancy several tolerance mechanisms have been demonstrated to counteract the maternal immune response. Among these, the expression of HLA-G by invasive cytotrophoblasts has been shown to play a fundamental role in creating a tolerogenic condition at the feto-maternal interface.

HLA genes are the human versions of the MHC genes that are genetically most variable coding loci in mammals, found in most vertebrates and encoded by a series of genes (~130) located on the short arm of chromosome 6 that are responsible for lymphocyte recognition, "antigen presentation" and immune response regulation. They are classified into three classes viz. Class I, Class II and Class III (Ober 1998). Class I consists of minor classes *HLA* E and G which are reported to be relevant to recurrent spontaneous abortion Pfeiffer et al. (2001). Studies in some outbred, and in closely related, human populations indicate that *HLA* or *HLA*-linked genes and HLA regulatory factors affect gamete development, embryo cleavage, blastocyst and trophoblast formation, implantation, fetal development and survival (Choudhury and Knapp 2001). In this review, we examine the published data that deals with role of HLA in reproduction giving special reference to HLA G and E.

Address for correspondence:
Dr. Anurupa Maitra
National Institute for Research in Reproductive Health (ICMR),
J. M. Street, Parel, Mumbai 400 012,
Mahrashtra, India
Phone: 022-24192009,
E-mail: anurupamaitra@yahoo.co.in; maitraa@nirrh.res.in

HLA play critical roles during different stages of pregnancy. HLA locus is a high gene density locus with a high frequency of gene rearrangements resulting in the formation of null alleles producing variant antigens or no antigen. HLA antigens play a major role in transplantation and are critical in pregnancy from gamete formation to completion of development. Class-I antigens express on the invasive trophoblast and play a role at the maternal-fetal interface **(**Hviid 2006). HLA sharing (DQ alpha) between the embryo recipient (female partner) and the sperm provider (male partner) inevitably leads to implantation dysfunction and reproductive loss. This fetal loss results from homozygosity of recessive lethal or deleterious alleles in gametic disequilibrium with HLA antigens (Shankarkumar et al. 2008). Mainly because when DQ alpha and/or HLA sharing exists between a female and male it will usually require repeated embryo exposures for the host's uterine natural killer cells to become sufficiently activated to cause damage to the embryo's root system (trophoblast). Once natural killer cells become activated, they begin to over-produce substances known as TH-1 cytokines which attack the trophoblast and so damage it that the embryo is promptly rejected (Moghraby et al. 2010). The results of studies in different populations have revealed significant association of different HLA alleles in each population. For example, studies by Pfeiffer et al. (2001) suggest an increased frequency of HLA-G *01013 and HLA-G *0105N carriers in the recurrent spontaneous abortion (RSA) group compared to controls while a study by Aldrich et al. (2001) suggests

Table 1: Studies reported in Indian population to know the relation between HLA and RSA

S. No.	*Reference*	*Study*	*Pts*	*Ctl*	*Asso-ciation*	*Allele associated*
1	Shankarkumar et al. 2008	Case Control	81 RSA couple	97 control couple	Yes	HLA-A*030101,B*5701, CW*120201,DRB1*030101
2	Aruna et al. 2011	Case control	143 RSA couple	150 control	Yes	HLA-DQBI
3	Abbas et al. 2004	Case control	120 RSA women	120 fertile women	Yes	HLAG*010103
4	Suryanarayana et al. 2008	Case control	169 RSA couple	92 control	Yes	HLA G 3'UTR
5	Tripathi et al. 2006	Case control	120 RSA women	120 fertile women	Yes	14/+14 bp HLA-G genotype of female associated
6	Aruna et al. 2010	Case control	143 RSA couple	150 control	No	

increased frequencies of the alleles HLA-G *0104 or *0105N in RSA group. Another study reveals that RSA patients carry HLA-G *0106 allele which exhibits a 14 bp deletion in exon 8. In a case control study using the RFLP, the frequencies of the HLA- DRB1* 01 and HLA- DR* 03 allogenotypes were significantly increased among the patients with at least four previous miscarriages (Kruse et al. 2004). According to them Complement component C4 gene polymorphisms also are found to be associated with RSA. C4A null alleles increased in the primary abortions group wives and husbands compared to the controls and C4B null alleles show an increase in the secondary abortion wives and husbands compared to the controls. Moreover, to the best of our knowledge, only few studies have been conducted in India to reveal the association of HLA alleles with RSA (Table1).

HLA-G and HLA-E

HLA-G transcripts are present in quite significant amounts in first-trimester placental tissue, particularly in the extravillous membranes, while the opposite occurs at term. This kind of expression is consistent with the theory that HLA-G might play a role in fetal protection. This could be consequent to either non-immune (structural) or immune functions at the maternal–fetal interface. Current evidence suggests an immune function wherein HLA-G protects fetal cells from maternal uterine natural killer (NK) cells, which are found in large numbers within cells invading the trophoblasts. T helper (Th) cells of the immune system recognize antigens presented on HLA class II proteins. Thus, HLA-G is believed to be an important factor in pregnancy complications such as RSA and pre-eclampsia (Hara et al. 1996; Goldman et al. 2000; Obrien et al. 2001; Yie et al. 2004). According to Chaouat et al. (2004), HLA-G might be a key protein in the shift of the proinflammatory Th1 response to Th2, which is essential for a successful pregnancy. In addition, methylation of HLA-G and expression of sHLA-G may also be implicated in RSA (Ober et al. 2003). Low concentrations of HLA-G are found in patients with pre-eclampsia which indicates that an adequate level of HLA-G expressed by extravillous trophoblast cells is important during pregnancy (Colbern et al. 1994; Lim et al. 1997). Moreauv et al. (2008) reported the risk of developing RSA is higher among women being homozygous for the HLA-G14 bp insertion polymorphism in comparison to women who are heterozygous because the plasma concentration of sHLA-G is also lower among the +14 bp homozygous women in comparison with women with the two other 14 bp HLA-G genotypes (Hviid et al. 2004a; Hviid et al. 2004b). Some studies suggest that HLA-G alleles, including the 14-bp sequence in the 3,UTR, might be associated with certain complications of pregnancy, such as pre-eclampsia and recurrent spontaneous abortions (RSA). On the other hand, a range of studies does not support this (Hiby et al.1999). However, the previously discussed studies of associations between the HLA-G genotype and HLA-G expression levels and studies of significant associations of low sHLA-G levels and risk of pre-eclampsia or spontaneous abortion (Ishitani et al. 2003; Morales et al. 2003) might also indicate an association between HLA-G genetics and these complications of pregnancy. In a study of SNPs in the 5, URR of the HLA-G gene in a cohort of Hutterite couples, Ober et al. (2003) observed an increased risk of abortion in couples where both members carried the _725G allele described above (Allan et al. 1999). HLA-G has been shown to bind to the immunoglobulin-like transcript (ILT)-2 and

killer inhibitory receptor (KIR)2DL4 which are inhibitory receptors on NK cells and may confer protection to Extra Villous Trophoblasts (EVTs) via these receptors (Lee et al. 1998; Biassoni et al.1999). The reduction of HLA-G molecules could deregulate uterine natural killer (uNK) cells which are supposed to participate in the process of placentation and in uterine spiral artery transformation. Soluble HLA-G may contribute to trigger functional maturation of the uNK cells and vascular remodeling and de-cidualization. The reduced release of sHLA-G into the maternal circulation in preeclampsia and IUGR may alter the maternal-fetal immune relationship and thus be involved in the cause of these disorders. However, in order to fully determine the function of HLA-G, more research is required.

Another important component of the immunological network at fetomaternal interface is HLA- E. HLA-E are believed to help the fetus to avoid maternal immune surveillance, possibly by interacting with the CD94/NKG2A NK-cell inhibitory receptor (Biassoni et al.1999). Compared to HLA-G, HLA- E expression is not only confined to fetomaternal interface but has wider tissue distribution including T cells, B cells, activated T lymphocytes and various other cells (Houlihan et al. 1995). HLA-E antigens are identified as ligands of a subset of immunoglobulin superfamily of NK cell receptors and their interaction with KIR of NK cells may be responsible for inhibition of killer activities of NK cells (Vales-Gomez et al. 1999). HLA-E specifically interacts with CD94/NKG2A that leads to the recruitment of the phosphatase SHP-1 to phosphorylated tyrosine of NKG2A and results in the inhibition of NK cells (Carretero et al 1997). This immunomodulating activity of HLA-E may be helpful in the success of pregnancy, as >90% of CD56+ lymphocytes of decidua are constituted by CD94/NKG2 + NK cells (Gudelj et al.1996).

This immunoregulatory activity suggests a possible role of HLA-E molecules in protection of fetus from maternal immune response in normal pregnancy. In addition, as HLA-E is expressed on fetomaternal interface that normally expresses only HLA-G, it can be expected to perform unique immunomodulating activities in the placenta. Two non synonymous alleles of HLA-E are present in human population (Geraghty et al.1992; Matte et al. 2000) maintained through strong balancing selection (Grimsley and Ober 1997) distinguished by a single sequence dimorphism at position 107, arginine (E*0101; HLA-E –R) or glycine (E*0103; HLA-E-G).The suppressive effect of HLA-G and HLA-E on the secretion of TNF-alpha (Th1 cytokine), IL-10 (Th2 cytokine) and IL-8 (chemokine) by immature dendritic cells could be interpreted as further evidence for the central immunotolerance role of HLA-G and HLA-E during early pregnancy (Steck et al. 2002).

CONCLUSION

To summarize, the HLA genes are the main genetic determinants of the repertoire of possible immune responses of an individual. Apart from this, they have significant role in reproduction.

REFERENCES

Abbas A, Tripathi P, Naik S, Agrawal S 2004. Analysis of human leukocyte antigen (HLA)-G polymorphism in normal women and in women with recurrent spontaneous abortions. *Eur J Immunogenet*, 31: 275–278.

Aldrich CL, Stephenson MD, Karrison T, Odem RR, Branch et al. 2001. HLA-G genotypes and pregnancy outcome in couples with unexplained recurrent miscarriage. *Mol Hum Reprod*, 7: 1167–1172

Allan D, Colonna M, Lanier L, Churakova T, Abrams J et al. 1999.Tetrameric complexes of human histocompatibility leukocyte antigen HLA-G bind to peripheral blood myelomonocytic cells. *Journal of Experimental Medicine*, 189: 1149–1156.

Aruna MPS, Sudheer S, Andal S, Tarakeswari A, Reddy G, Thangaraj K, Singh L, Reddy BM 2010. HLA-G polymorphism patterns show lack of detectable association with recurrent spontaneous abortion. *Tissue Antigens*, 76(3): 216–222.

Aruna MPS, Sudheer S, Andal S, Tarakeswari A, Reddy G, Thangaraj K, Singh L, Reddy BM 2011. Novel alleles of HLA-DQ and -DR loci show association with recurrent miscarriages among South Indian women. *Human Reproduction*, 0(0): 1– 10.

Biassoni R, Bottino C, Millo R, Moretta L, Moretta A 1999. Natural killer cell-mediated recognition of human trophoblast. *Seminars in Cancer Biology*, 9: 13–18.

Carretero M, Cantoni C, Bellon T, Bottino C, Biassoni R et al. 1997. The CD94 and NKG2-A C-type lectins covalently assemble to form a natural killer cell inhibitory receptor for HLA class I molecules. *Eur J Immunol*, 27: 563-567.

Chaouat G, Ledee-Bataille N, Dubanchet S, Zourbas S, Sandra O, Martal J 2004.TH1/TH2 paradigm in pregnancy: Paradigm lost? Cytokines in pregnancy/ early abortion: Reexamining the TH1/TH2 paradigm. *Int Arch Allergy Immunol*, 134: 93–119.

Colbern GT, Chiang MH,Main EK 1994. Expression of the nonclassic histocompatibility antigen HLA-G by

preeclamptic placenta. *Am J Obstet Gynecol*, 170: 1244–1250.

Choudhury S R, Knapp LA 2001. Human reproductive failure II: Immunogenetic and interacting factors. *Human Reproduction Update,* 7(2): 135-160.

Geraghty D E, Stockschleader M, Ishitani A, Hansen JA 1992. Polymorphism at the HLA-E locus predates most HLA-A and -B polymorphism. *Hum Immunol,* 33: 174-184.

Goldman-Wohl DS, Ariel I, Greenfield C, Hochner-Celnikier D, Cross J, Fisher S, Yagel S 2000. Lack of human leukocyte antigen-G expression in extravillous trophoblasts is associated with pre-eclampsia. *Mol Hum Reprod,* 6: 88–95.

Grimsley C, Ober C 1997. Population genetic studies of HLA-E: Evidence for selection. *Hum Immunol,* 52: 33 – 40.

Gudelj L, Deniz G, Rukavina D, Johnson PM, Christmas SE 1996. Expression of functional molecules by human CD-3 decidual granular leucocyte clones. *Immunology,* 87: 609-615.

Hara N, Fujii T, Yamashita T, Kozuma S, Okai T, Taketani Y 1996. Altered expression of human leukocyte antigen G (HLA-G) on extravillous trophoblasts in preeclampsia: Immunohistological demonstration with anti-HLA-G specific antibody "87G" and anti-cytokeratin antibody "CAM5.2". *Am J Reprod Immunol,* 36: 349–358.

Hiby SE, King A, Sharkey A, Loke YW 1999. Molecular studies of trophoblast HLA-G: Polymorphism, isoforms, imprinting and expression in preimplantation embryo. *Tissue Antigens,* 53: 1–13.

Houlihan JM, Biro PA, Harper HM, Jackson HJ, Holmes CH 1995. The human amnion is a site of MHC class Ib expression: Evidence for the expression of HLA-E and HLA-G. *Journal of Immunology,* 154: 5665–5674.

Hviid TV, Hylenius S, Lindhard A,Christiansen OB 2004a. Association between human leukocyte antigen-G genotype and success of in vitro fertilization and pregnancy outcome. *Tissue Antigens*, 64: 66–69.

Hviid TV, Rizzo R, Christiansen OB, Melchiorri L, Lindhard A, Baricordi OR 2004b. HLA-G and IL-10 in serum in relation to HLA-G genotype and polymorphisms. *Immunogenetics,* 56: 135–141.

Hviid TV 2006. HLA-G in human reproduction: Aspects of genetics, function and pregnancy complications. *Human Reproduction Update,* 12(3): 209–232.

Ishitani A, Kishida M, Sageshima N,Yashiki S, Sonoda S et al. 2003. Re-examination of HLA-G polymorphism in African Americans. *Immunogenetics,* 49: 808–811.

Kruse C, Steffensen R, Varming K, Christiansen OB 2004. A study of HLA-DR and -DQ alleles in 588 patients and 562 controls confirms that HLA-DRB1*03 is associated with recurrent miscarriage. *Hum Reprod,* 19: 1215-1221.

Lim KH, Zhou Y, Janatpour M, McMaster M, Bass K, Chun SH, Fisher SJ 1997. Human cytotrophoblast differentiation/invasion is abnormal in preeclampsia. *Am J Pathol,* 151: 1809–1818.

Lee N, Liano M, Carretero M, Ishitani A, Navarro F, Lopez-Botet M, Geraghty DE 1998. HLA-E is a major ligand for the natural killer inhibitory receptor CD94/NKG2A. *Proc Natl Acad Sci USA,* 95: 5199–5204.

Matte C, Lacaille J, Zijenah L, Ward B, Roger M 2000. HLA-G and HLAE polymorphisms in an indigenous African population. *Hum Immunol,* 61: 1150–1156.

Moreauv P, Contu L, Alba F, Lai S,Simoes R et al. 2008.HLA-G gene polymorphism in human placentas: Possible association of G*0106 allele with preeclampsia and miscarriage. *Biol Reprod,* 79: 459-467.

Morales PJ, Pace JL, Platt JS, Phillips TA, Morgan K, Fazleabas AT, Hunt JS 2003. Placental cell expression of HLA-G2 isoforms is limited to the invasive trophoblast phenotype. *J Immunol,* 171: 6215–6224.

O'Brien M, McCarthy T, Jenkins D, Paul P, Dausset J, Carosella ED, Moreau P 2001. Altered HLA-G transcription in pre-eclampsia is associated with allele specific inheritance: Possible role of the HLA-G gene in susceptibility to the disease. *Cell Mol Life Sci,* 58: 1943–1949.

Ober C 1998. HLA and pregnancy: The paradox of the fetal allograft. *Am J Hum Genet,* 62*:* 1–5.

Ober C, Aldrich CL, Chervoneva I, Billstrand C, Rahimov F, Gray HL, Hyslop T 2003. Variation in the HLA-G promoter region influences miscarriage rates. *Am J Hum Genet,* 72: 1425–1435.

Pfeiffer KA, Fimmers R, Engels G, van der Ven H, van der Ven K 2001. The HLA-G genotype is potentially associated with idiopathic recurrent spontaneous abortion. Mol Hum Reprod, 7: 373–378.

Shankarkumar U, Pawar A, Gaonkar P, Parasannavar D, Salvi V, Ghosh K 2008. HLA allele associations in idiopathic recurrent spontaneous abortion patients from India. *J Hum Reprod Sci,* 1: 19-24.

Steck T, Rieger L, Rodel E, Dietl J, Kammerer U 2002. Expression of the molecules HLA-G and HLA-E modulates cytokine production of monocyte generated dendritic cells 2002. *Zentralbl Gynakol,* 124(5): 304-309.

Suryanarayana V, Rao L, Kanakavalli M,Padmalatha V, Raseswari T, Deenadayal M, Singh L 2008. Association between novel HLA-G genotypes and risk of recurrent miscarriages: A case-control study in a South Indian population. *Reprod Sci,* 15: 817-824.

Tripathi P, Naik S, Agrawal S 2006.HLA-E and immunobiology of pregnancy. *Journal Compilation,* 67: 207-213.

Vales-Gomez M, Reyburn HT, Erskine RA,Lopez-Botet M,Strominger JL 1999. Kinetics and peptide dependency of the binding of the inhibitory NK receptor CD94/NKG2-A and the activating receptor CD94/NKG2-C to HLA-E. *EMBO J,* 18: 4250.

Yie SM, Li LH, Li YM, Librach C 2004. HLA-G protein concentrations in maternal serum and placental tissue are decreased in preeclampsia. *Am J Obstet Gynecol,* 191(2): 525-529.