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Review

HLA-G with Benefits and Damages: A Review

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ABSTRACT

Human leucocyte antigen-G (HLA-G) is a non-classical HLA that researchers primarily focused on association with the complications of pregnancy. Recent studies about the immunomodulatory characteristics of HLA-G showed that this molecule is not only important in pregnancy but also have effects on transplantation, autoimmune diseases, cancer and infectious diseases. The restricted polymorphic nature and the disease association has also showed in various studies. In this review it was aimed to evaluate the benefits and damages of the HLA-G by considering both the expression levels and polymorphisms

Keywords: Cancer, HLA-G, immune tolerance, pregnancy, transplantation

INTRODUCTION

Human leukocyte antigen-G gene, a member of the nonclassical HLA Class I genes, is located on the short arm of the 6th chromosome 6p21.3 (1-3). Being a member of classical Class I genes, it is characterized by a low polymorphism (4, 5). The gene comprises eight exons and seven introns, which are co-dominantly expressed (2). Exon 1 encodes signal peptide, while exon 2, 3, and 4 encode extracellular domain, alfa 1, alfa 2, and alfa 3, respectively. Exon 5 and 6 encode cytoplasmic and transmembrane domains. Exon 7 does not exist in mature mRNA due to the stop codon in exon 6. Consequently, Exon 8 is not translated into mRNA (3). HLA-G gene expression is regulated by miRNA's, nucleotide variations, and epigenetic mechanisms (6). Environmental factors such as growth factors, anti-inflammatory agents, hypoxia, progesteron, interleukin 10, and interferons can also effect HLA-G expression. Moreover, immunosuppressing agents can induce also HLA-G expression (6).

HLA-G has 51 alleles and 16 different varriants (5). Therefore, HLA-G has a highly limited number of peptides (7). HLA-G alleles encode 16 transmembrane proteins and two abbreviated proteins (8).

HLA-G gene, which is located between HLA-A and F genes, expresses four membrane bounded (G1, G2, G3, G4) and three soluble (G5, G6, G7) isoforms which are formed by splicing of mRNA, with G1 and G5 isoforms being the most accomplished (9). In addition, HLA-G has a soluble isoform which is formed by proteolytic cleavage (10). HLA-G1 and G5 comprise a heavy chain, three alpha globular domain which binds noncovalently to beta-2 microglobuline, and a peptide. G2 and G6 do not have α-2 globular domains. Also, G3 and G7 do not have α-2 and α-3, while G4 do not have α-3 globular domains. G5, G6 and G7 isoforms have a stop codon in exon 4. Therefore, they do not have transmembrane and cytoplasmic domains (6).

The 3′ untranslated region (3′UTR) of HLA-G gene contains a variety of regulator elements that influence the splicing of mRNA, and stability in terms of poly-A signal and AU rich patterns, while 5′ upstream regulator region strictly regulates transcription (3, 11). The 3′ UTR of HLA-G comprises seven haplotypes (UTR-1 to UTR-7) that can be detected in most populations. Among the haplotypes, UTR-1 is the most expressed (4). Three polymorphic regions in 3′UTR can affect HLA-G expression by different mechanisms such as influence of mRNA stability, sHLA-G protein expression, and binding of microRNAs (miRNAs) (12). One of these polymorphic regions is the 14 bp polymorphism (rs371194629), which is associated with mRNA stability and alternative splicing. The HLA-G isoform is pertinent to decreased sHLA-G levels. The second polymorphic region is the C/G SNP at +3142 (rs1063320) position, which affects the binding affinity of miRNA. Ultimately, the decrease in the mRNA degradation and HLA-G production can be detected. The third polymorphic region is the G/A SNP at position +3187 (rs9380142), which is implicated in the decrease in mRNA stability (4, 12).

HLA-G interacts with killer immunoglobulin-like receptor-2DL4, immunoglobulin-like transcript receptor-4; and with ILT2 ex-

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pressed on B lymphocytes, T lymphocytes, natural killer (NK) cells, and antigen presenting cells (13, 14). ILT4 recognizes and responds to HLA-G free heavy chains, while ILT2 recognizes and responds to b2-microglobulin (14).

HLA-G is capable of inhibiting immune response through several mechanisms by interacting with these specific receptors (15). HLA-G is able to impede T cells alloproliferation, and cytotoxicity of CD8 (+) T-cell and NK cells (9). Furthermore, HLA-G can bind to dendritic cells, thereby inhibiting maturation, migration, trafficking antigen presentation and its association with T and NK cells (16). It also regulates the production of cytokines by T helper-1 and T helper-2 cells (10). Soluble HLA-G molecules exhibit similar effects as their membrane-bound relative (16). During pregnancy, HLA-G molecules expressed by the trophoblast cells interact with killer immunoglobulin-like receptor on maternal NK cells. By this way, immune tolerance is enhanced, which makes maternal immune system incapable of destroying the fetal tissues (17).

HLA-G antigen, an immunomodulatory molecule, was initially identified in cytotrophoblast cells in placenta (18). In addition, the expression of HLA-G antigen was observed in cornea, thymus, mesenchymal stem cells, islets of pancrease; and pathological conditions including cancer, viral infections, inflammatory and autoimmune diseases, and during transplantation (5).

In this review, we discussed the effect of HLA-G expression and polymorphism on serum levels in pregnancy, cancer, autoimmune disorders and transplantation.

CLINICAL AND RESEARCH CONSEQUENCES

Association between HLA-G and pregnancy

In several studies, it was demonstrated that HLA-G is implicated in complications of pregnancy such as recurrent miscarriage, pre-eclempsia, and spontaneous abortus. A decreased expression of HLA-G isoforms was observed in pre-eclempsia and recurrent spontaneous abortus. It was also indicated that uterine sHLA-G levels were decreased in idiopathic infertility (9). Bhalla et al. (20) defined recurrent miscarriage (RM) as ≥3 pregnancy losses within the first 20 weeks conception. The expression patterns of HLA-G in women with RM compared to healthy pregnant women were insignificantly different. Yie et al. (21) reported lower sHLA-G levels in maternal blood of pre-eclempsia than in healthy pregnancies at the end of last trimester. This was corroborated by the studies in which sHLA-G levels were measured at second and first tirmester (22, 23). Moreover, it was reported that spontaneous abortions had lower levels of sHLA-G when compared to successful pregnancies (24). In a study performed among obese pregnant women, sHLA-G level in serum increased in the second trimester and before delivery, while in healthy controls it was decreased between the second trimester and delivery (25).

García-Láez et al. (26) found that HLA-G was not responsible for spontaneous abotions in first trimester. However, several studies have reported lower levels of sHLA-G in pregnancies with pre-eclempsia in the second and third trimester (12). The HLA-G 14 bp insertion polymorphism and serum HLA-G levels are also investigated in pregnant women with pre-eclempsia (27). Berminham et al. (27) observed no influence of HLA-G 14 bp genotype on pre-eclempsia, while positive and negative associations with pre-eclempsia were reported. However, HLA-G 14 bp IN/DEL polymorphism in 30 UTR did not show any influence (28).

During pregnancy it was suggested that HLA-G molecule serve to prevent the rejection of trophoblast cells by the maternal NK cells (29). Therefore, HLA-G expression in pregnancy is regarded as one of the most important mechanisms of maternal tolerance to fetal cells.

Relationship between Cancer and HLA-G

As an immune response regulator molecule, although HLA-G expression is beneficial in pregnancies, the expression in the tumor cells is known to be detrimental to host cells in cancer patients. Paul et al. (30) reported, for the first time, that HLA-G is expressed in solid tumors, and that this expression can protect the cancer cells from NK cytolysis. Since then, expression levels of HLA-G has been observed by immunohistochemistry, western bloting and qPCR in various solid tumors such as breast, renal, hepatocellular, neuro, ovarian, lung, gastric, colorectal, cervical and retina carcinomas, among other malignant situations such as B cell chronic lymphocytic leukemia and acute myeloid leukemia. However, there are controversial findings on the prognostic relevance and expression levels of HLA-G in cancer (31).

HLA-G expression can be detected in exosomes that were derived from tumors in hematological and cell surface malignancies, in addition to the cell surface-secreted form. Recent studies have demonstrated that HLA-G upregulates the expression of the tumor promoting factor. It was also showed that HLA-G expression was strongly correlated with tumor metastasis, worse tumor prognosis, and transition to disease stage in tumor patients (19).

Guo et al. (32) investigated HLA-G and E levels in colorectal cancer patients by immunohistochemistry, and observed an increased expression with respect to control. However, HLA-G expression significantly varies between different types of tumor. This may be due to the distinct antibodies used for the immunohistochemistry (33).

Relationship between Transplantation and HLA-G

The immunomodulatory characteristics of HLA-G spurred the investigators into determining the association between HLA-G

Main Points:

- Expression of HLA-G downregulates the immune reaction against fetus, self antigens and allograft. Therefore it is an important antigen in pregnancy, autoimmune diseases and transplantation.
- HLA-G has effective and inhibitory roles in cancer and viral infections.
- HLA-G polymorphism can be associated with several clinical situations as cancer, transplantation, etc.

levels, polymorphisms and risk of rejection. Therefore, HLA-G expression levels were investigated after kidney, liver, heart, and liver-kidney transplantation (34). The results showed that HLA-G expression in transplant patients was associated with a better graft acceptance (35). Also, increased levels of HLA-G were associated with reduced acute and chronic rejection in patients with heart and combined liver-kidney transplantations (36). Polakova et al. (37) detected a decreased HLA-G expression levels in serum and biopsy samples of patients who had rejection attack after kidney transplantation. They also observed that while expression levels were lower in the first week of transplantation, it increased over time.

Relationship between Autoimmune diseases and HLA-G

The inhibition of autoreactive cells by HLA-G expression can be beneficial to patients with autoimmune disorders. In some studies, this beneficial effect was indicated (38). Beneventi et al. (39) detected higher sHLA-G concentrations in pregnant women

Table 1. Observations of HLA-G expression and polymorphisms according to the clinical situations

Observation	Type of Clinical Situation/disease	Author
Uterine sHLA-G were decreased in infertility	İnfertility	Zidi et al. (9)
No significant expression pettern of HLA-G between recurrent misscarriage and healthy pregnancy	Recurrent misscarriage	Bhalla et al. (20)
Lower sHLA-G levels were detected in maternal blood of preeclempsia than healthy pregnancy	Preeclempsia	Yie et al., Steinborn et al., Yie et al., (21, 22, 23)
Lower HLA-G expression was detected in spontaneous abortus	Spontaneous abortus	Rizzo et al. (24)
Higher sHLA-G concentrations detected in serum in second trimester and before delivery	Obese pregnant women	Beneventi et al. (25)
HLA-G was not responsible for spontaneous abortus	Spontaneous abortus	Garcia-Laez et al. (26)
HLA-G 14 genotype has no effect on preeclempsia	Preeclempsia	Bermingham et al. (27)
HLA-G expression protect the cancer cells from immune response	Cancer	Paul et al. (30)
HLA-G expression increase in colorectal cancer patients	Colorectal cancer	Guo et al. (32)
HLA-G expression varies between tumor types	Cancer	Seliger et al. (33)
HLA-G expresion in trasplant patients were associated with better graft acceptance	Transplantation	Lila et al. (35)
Increased levels of HLA-G were reduced the risk of rejection in heart and comibend liver-kidney transplantation.	Liver-kidney transplantation Heart transplantation	Carosella et al. (36)
Decreased levels of HLA-G were increased the risk of rejection after kidney transplantation.	Kidney transplantation	Polankova et al. (37)
Increased sHLA-G concentrations were detected in rheumatoid disorder	Rheumatoid arthritis	Beneventi et al. (39)
14bp HLA-G allele frequency was increased in patients with Behcet's disease	Behcet's disease	Sakly et al. (42)
HLA-G 3741-3754ins14 variant is associated with increased risk for Behcet's disease.	Behcet's disease	Park et al. (40)
HLA-G010101 reduce the risk of Behcet's disease	Behcet's disease	Park et al. (41)
HLA-G 14 bp ins might increased the lupus erythematosus risk	Lupus erythematosus	Zhang et al. (43)
sHLA-G levels inversely correlated with ankylosing spondylitis	Ankylosing spondylitis	Zhang et al. (44)
HLA-G +3142 C/G polymorphism could have a role in susceptibility to coronary arter disease	Coronary arter disease	Gonen- Gross and Mandelboim. (29)
No associateion was observed betseen sHLA-G levels and schizophrenia	Schizophrenia	Rajasekaran et al. (45)
HLA-G can be associated with multiple sclerosis	Multiple sclerosis	Fredj et al. (46)
Increased levels of sHLA-G can cause to develop celiac disease	Celiac	Torres et al. (47)
Patients that have 14bp in/del polymorphism can have susceptibility to celiac disease	Celiac	Catamo et al. (49)

with autoimmune romatoid disorders than in healthy pregnant women. The association between HLA-G polymorphism and Behcet's Disease (BD) has been investigated in different studies (40, 41). According to Park et al. (40), HLA-G 3741_3754ins14 variant was associated with an increased risk of BD. On the other hand, it was shown that HLA-G*010101 can reduced the risk of BD (41). Sakly et al. (42) observed that –14 bp HLA-G allele frequency was increased in patients with BD.

Zhang et al. (43) investigated Systemic lupus erythematosus (SLE) patients and observed differences between SLE and healthy controls in terms of allelic and genotypic frequencies of the HLA-G 14bp ins/del polymorphism. They found that HLA-G 14 bp allele insertion can increase the risk of SLE. In another study, a significant association between Ancylosan Spondilit (AS) sacroiliitis stages and HLA-G expressions was reported (44). Zhang et al. (44) demonstrated that while plasma sHLA-G level was inversely correlated with AS, HLA-G expression on the cell surface may increase or decrease base on the stages of AS.

Association of HLA-G with other diseases

The associations between HLA-G levels and/or polymorphisms and several diseases have been investigated. Zidi et al. (29) reported, for the first time, that HLA-G +3142C/G polymorphism could be a genetic marker of coronary artery disease. Rajasekaran et al. (45) found no association between sHLA-G levels and schizophrenia. It was also reported that HLA-G allele plays a role in the development of multiple sclerosis (46). Torres et al. (47) found an association between celiac disease (CD) and soluble HLA-G (sHLA-G) expression. They found that increased levels of sHLA-G can cause succeptibility to CD. Also, the authors hypothesized that the increased expression of sHLA-G could play a vital role in the mechanism of gluten tolerance in CD patients. Fabris et al. (48) also demonstrated the association between CD and HLA-G polymorphism. Catamo et al. (49) reported a 14 bp del/ins polymorphism in CD.

Viral infections were shown to increase HLA-G expression in cells, and this may also be a mechanism to escape from the host immune system. CD8+ T cells and monocytes upregulated the expression of HLA-G in HIV-infected patients (50) (Table 1).

CONCLUSION

HLA-G expression is beneficial in transplantation, autoimmune diseases and especially in pregnancy, in which it down-regulates the immune reaction against allograft, self components or fetus. In cancer and viral infections, it has deleterious effects in the host cell. In this regard, future HLA-G based therapies can be developed for the pregnancy complications, transplantation and autoimmune diseases, while expression of HLA-G should be blocked in patients with cancer or viral infections. There are growing conflicting research findings between various research groups investigating the association between HLA-G and other diseases. To elucidate this association, it is important to perform multi centered studies including large study populations.

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