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Review

Immunotolerant functions of HLA-G

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Abstract. HLA-G is a nonclassical major histocompatibility complex class I molecule selectively expressed on cytotrophoblasts at the fetal-maternal interface, where it plays a role in materno-fetal tolerance. In contrast to classical HLA-A, -B and -C class I molecules, HLA-G is characterized by (i) a tissue-restricted distribution, (ii) a limited polymorphism and (iii) a transcription of spliced messenger RNAs encoding for at least four membrane-bound and two soluble HLA-G isoforms. Extensive studies over the past few years have identified HLA-G as a molecule involved in immune tolerance. In this review, attempts were made to summarize the current state of knowledge of the effects of HLA-G on both natural killer and T cell functions and their implications in materno-fetal tolerance and tumor immunosurveillance.

Key words. HLA-G; immunotolerance; killing inhibitory receptors; NK; T cells.

Introduction

Unlike classical HLA class I molecules, the nonclassical major histocompatibility complex (MHC) class I molecule HLA-G is characterized by (i) tissue-restricted distribution. Whereas expression of classical HLA class I molecules is known to be ubiquitous, HLA-G was first described on extraembryonic trophoblast tissues that invade the maternal decidua during implantation of the embryo [1]. Recently, its expression was also reported in endothelial cells from first trimester placental chorionic blood vessel, in thymic epithelial cells and activated peripheral blood monocytes [2, 3]; (ii) limited polymorphism. Sixteen HLA-G alleles have been described to date, four of which may encode membrane-bound HLA-G proteins [4], plus one truncated soluble protein which bears the 'delC^{130} mutation' [5]; and (iii) alternative transcription of spliced messenger RNAs (mRNAs) that encode at least six different HLA-G isoforms, namely the HLA-G1, -G2, -G3 and -G4 membrane-bound and HLA-G5 and -G6 soluble proteins [6–8]. The presence of a stop codon in intron 4 of the HLA-G primary gene transcript deletes the transmembrane domain, constituting an original process which results in the production of HLA-G5 and HLA-G6 soluble proteins [9].

While both HLA-A, -B, and -C class I molecules and class II molecules play an important role in the induction of a specific immune response by presenting peptide antigens to T cells [10, 11], HLA-G has been identified as a key mediator in immune tolerance[12]. This review focuses on studies performed over the past few years that permit the characterization of the immunological function of HLA-G. Because HLA-G was selectively found at the materno-fetal interface on the surface of trophoblast cells, first investigations were motivated by a desire to understand the role of HLA-G

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in materno-fetal immune tolerance. In light of this, we have carried out ex vivo experiments which showed that HLA-G molecules expressed on trophoblast cells protected them from maternal decidua natural killer (NK) lysis. These experiments led us to conjecture that HLA-G molecules contribute, in addition to other mechanisms [14], to the survival of the fetal semiallograft by conferring immunological tolerance of fetal tissues. This was supported by in vitro studies that demonstrated the immunotolerant role of both membrane-bound and soluble HLA-G proteins, which inhibit MHC-unrestricted (NK) and -restricted (T cell) immune responses.

HLA-G and NK cell interactions

HLA-G molecules inhibit NK cytolysis. Studies on the immunological function of HLA-G over the past few years have focused on the effect of HLA-G on NK function. Results demonstrated that HLA-G-positive target cells are protected from NK cytolysis through interaction with killing inhibitory receptors (KIRs) [15–19]. In line of this, we have characterized the protective role of the membrane-bound HLA-G1 and HLA-G2 isoforms against NK cytotoxicity [20]. For this purpose, HLA-G1 and HLA-G2 complementary DNAs (cDNAs) were transfected into the HLA class I-negative human K562 cell line, a known reference target for NK lysis. The HLA-G1 isoform, encoded by full-length mRNA, associates with β2-microglobulin and has a structure similar to that of classical HLA class I molecules. The HLA-G2 isoform, encoded by a transcript lacking exon 3, was found to be present at the cell surface in association with β2-microglobulin [20]. NK cytolysis, observed in peripheral blood mononuclear cells (PBMC) and in polyclonal $CD3^-CD16^+CD56^+$ NK cells obtained from at least 40 donors, was inhibited by both HLA-G1 and HLA-G2. This inhibition could be reversed by blocking HLA-G molecules with a specific monoclonal antibody (mAb).

Since HLA-G was recently identified as possessing, within its leader sequence, a nonapeptide capable of inducing both HLA-E cell-surface expression and interaction with the CD94/NKG2A inhibitory receptor [21, 22], we wondered whether NK lysis inhibition was indeed due to HLA-G or to the coexpression of HLA-E and HLA-G. HLA-E is another nonclassical HLA class I molecule whose expression is dependent on that of HLA class I molecules which within their leader sequences possess a peptide ligand for HLA-E. Since (i) no endogenous HLA-E protein is expressed in K562 cells, and (ii) HLA-G-mediated NK lysis inhibition could be totally reversed by blocking HLA-G1 with the anti-HLA-G1 87G mAb, we postulated that HLA-G inhibits NK lysis by itself (fig. 1).

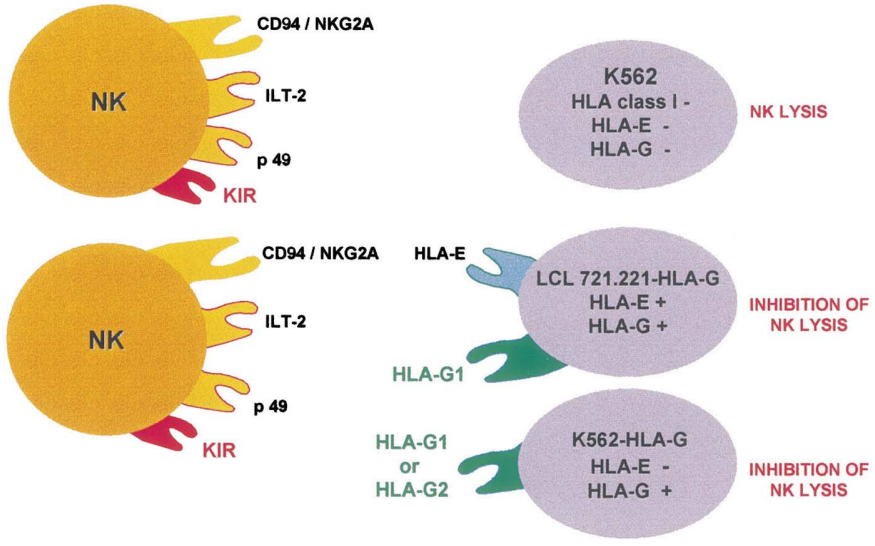

Figure 1. Both HLA-G and HLA-E inhibit NK lysis. NK cells are specialized in killing cells that no longer express MHC class I molecules, such as the HLA class I-negative human K562 cell line. In contrast, the K562 cell line transfected with HLA-G1 or HLA-G2 inhibits NK cytolysis through direct interaction with KIR, such as p49, ILT-2 and an as yet uncharacterized inhibitory receptor specific for HLA-G. The HLA class I-negative LCL721.221 cell line, once transfected with HLA-G, expresses both HLA-G and HLA-E, which both inhibit NK cytolysis. This coexpression of HLA-E is due to the presence, within the leader sequence of HLA-G, of a nonapeptide capable of inducing both HLA-E cell-surface expression and interaction with the CD94/NKG2A inhibitory receptor.

These results were recently supported by our observation that a soluble recombinant HLA-G fusion protein produced in *Escherichia coli* exhibits NK inhibitory properties. Indeed, by carrying out cytotoxicity assays with the K562 cell line as an NK target, we have found that the GST (glutathione S-transferase)-HLA-G soluble fusion protein impaired peripheral blood NK lytic activity, whereas the control GST protein produced under the same conditions did not [12]. This study showed that, in addition to membrane-bound HLA-G molecules, soluble HLA-G isoforms could function as immunotolerant molecules by inhibiting NK function. This is important in the context of materno-fetal tolerance where soluble HLA-G molecules are secreted in large quantities [23]. Such HLA-G molecules, once released into the maternal peripheral blood, could display systemic immunotolerant effects on the maternal immune system.

This NK inhibitory effect of HLA-G molecules is mediated through interaction with KIRs present on NK cells. The p58.1, p58.2 [15] and p70 [16] KIRs, which belong to the immunoglobulin superfamily (Ig-SF), were first proposed as able to bind HLA-G. However, it is now well established that these Ig-SF KIRs interact only with classical HLA class I molecules and not with HLA-G [17, 18]. Later, several reports identified for this role the CD94/NKG2A inhibitory receptor, which belongs to the C-type lectin superfamily [17–19]. It was recently shown that this receptor interacts with HLA-E, which consequently inhibits NK lysis [24, 25]. Finally, specific HLA-G receptors have been identified: immunoglobulin-like transcript (ILT)-2 [26, 27] and p49 [28] Ig-SF KIRs, which expressed on both NK and T cells.

We recently identified a new inhibitory receptor which interacts specifically with HLA-G but not with HLA-A, -B, -C and -E molecules. This was demonstrated by experiments using the nonadult T cell leukemia NK-like YT2C2-PR subclone whose lytic activity is inhibited by K562-HLA-G transfectants [20]. Indeed, this NK subclone neither expressed the p58.1, p58.2 nor p70 Ig-SF KIRs nor the CD94/NKG2A receptor. More relevant, neither of the known HLA-G-specific KIRs, ILT-2 and p49, are detected at the cell surface of this subclone (unpublished results). This yet-unknown specific HLA-G inhibitory receptor remains to be characterized.

HLA-G and T cell interactions. Interactions between HLA-G and T cells have been mainly evaluated in terms of peptide presentation by HLA-G. The current state of knowledge of this point will be presented first. Whether HLA-G also interacts with T cells at the KIR level will be revealed by studies of the inhibitory roles of HLA-G on both the antigen-specific cytotoxic T cell (CTL) and the allogeneic proliferative responses.

HLA-G binds nonamer peptides. Like classical HLA class I molecules, both the membrane-bound HLA-G1 and soluble HLA-G5 isoforms, which exhibit an overall classical HLA class I structure, are able to present peptides [29]. Both proteins bind the same peptide set derived from intracellular proteins. Based on the sequencing of eluted peptides from transfected cells, the peptide-binding motif for HLA-G favours nonamer peptides with leucine at position 9. Further, comparison with peptides eluted from HLA-A2 suggested that peptide diversity is lower than in classical HLA class I molecules [30]. Whether peptides bound to HLA-G are presented to T cells in order to induce an HLA-G-restricted T cell response remains to be elucidated. In light of this, a relatively good conservation of the CD8-binding loops as well as an interaction between CD8 and HLA-G have been reported [31]. If HLA-G presents peptides to T cells, then expression of HLA-G in the thymus would be expected for T cell education. Accordingly, HLA-G has been identified in the human thymus by immunohistochemical analysis showing that HLA-G is expressed at the cell surface of thymic medullary and subcapsular epithelial cells [2].

HLA-G inhibits T cell responses. Interactions between HLA-G and T cells at the KIR level are supported by the expression of p49 and ILT-2 KIR not only on NK cells, but also on T cell subsets [27, 28]. In light of this, we recently demonstrated that HLA-G could impair T cell cytolytic function by analyzing an Antigen (Ag)-specific T cell response mediated by $CD8^+$ T cells specific for a viral peptide presented by HLA-A2. Transfection of HLA-G1 cDNA into an HLA-A2-positive target cell line presenting the viral epitope inhibited lysis by the specific CTL. This HLA-G1-mediated inhibition was (i) peptide-dose dependent, (ii) reversed by masking HLA-G1 with a specific mAb, and (iii) independent of the CD94/NKG2A and p58.1/p58.2 inhibitory receptors [12]. These results show for the first time that HLA-G1 molecules act on the recognition of MHC-restricted Ag-specific T cells. Since we compared CTL lysis in a target cell expressing the usual HLA class I molecules (HLA-A, -B, -C and -E) with the same target cell coexpressing HLA-G, we concluded that HLA-G-mediated inhibition is a much more powerful inhibitory mechanism than that obtained with HLA-A, -B, -C, and -E molecules (fig. 2).

A second in vitro model of T cell response was analyzed in the context of the allogeneic proliferative response. By carrying out classical mixed lymphocyte reactions (MLR) in vitro, we found that the K562-HLA-G1 transfectant used as a third inhibitor cell was able to inhibit the MLR between two peripheral PBMCs from donors exhibiting distinct HLA class I and II alleles [12]. Since HLA-G1 is the only HLA class I molecule expressed on K562-HLA-G1, we concluded that HLA-

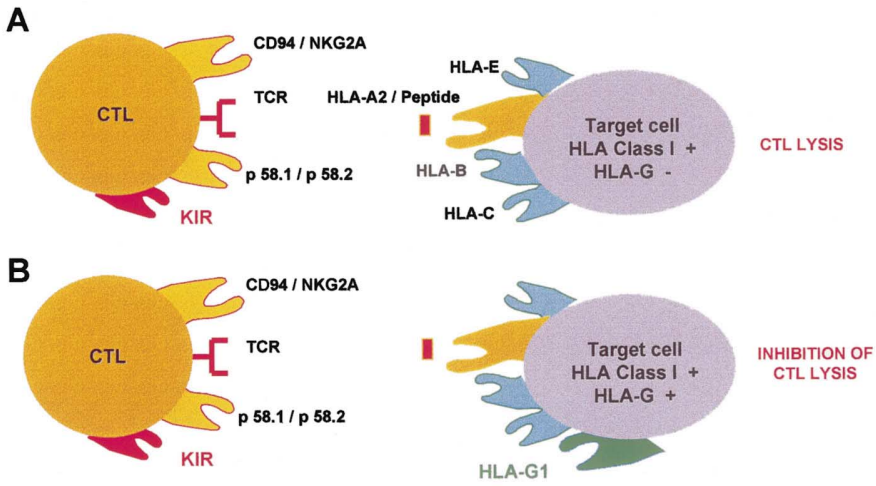

Figure 2. Implications of interactions between HLA-G1 and KIR in MHC-restricted antigen-specific CD8 + CTL response. (*A*) While HLA-A2-restricted peptide-specific CTL efficiently lyses target cells presenting the HLA-A2/peptide complex, (*B*) coexpression of HLA-G1 (with the usual HLA-A, -B, -C and -E class I molecules) inhibits such CTL lysis through interaction with KIR present on CTL.

G1 can by itself inhibit T cell allo responses (fig. 3). Both $CD4^+$ and $CD8^+$ T cells present in the responder population mediate the allogeneic proliferative response. We can thus postulate that HLA-G1 impairs alloproliferation by inhibiting both classes of T cells, probably via its interaction with inhibitory receptors present on them [32].

These studies demonstrated a novel role for HLA-G with regard to the T cell response, showing that HLA-G1, in addition to its NK inhibitory properties, inhibits T cell functions at the proliferative as well as the cytolytic levels.

Role of HLA-G in materno-fetal immune tolerance

HLA-G is expressed on extravillous cytotrophoblast cells invading the maternal uterine decidua during implantation of the embryo. This tissue distribution is consistent with a role of HLA-G in the interface with the maternal immune system by mediating the immunological privilege which semiallotypic fetal tissue requires.

NK cells are found in large numbers in the uterine decidua and are in contact with the extravillous trophoblast. HLA class I molecules present on a target cell inhibit NK lysis by interacting with class I NK inhibitory receptor counterparts [33, 34]. Consequently, NK cells destroy cells which do not express HLA class I molecules. Since cytotrophoblast cells lack the classical HLA-A and HLA-B class I molecules, they constitute an HLA class I-deficient NK target. However, fetal cells are not rejected during pregnancy.

In order to investigate the role of HLA-G in protecting fetal tissues from maternal NK rejection, we carried out ex vivo experiments using freshly obtained fetal and maternal tissues from first-trimester terminations of normal pregnancies. We have shown that trophoblast cells were protected from decidual NK cytolysis in 6 semiallogenic (maternal uterine NK cells and their trophoblast counterparts) as well as in 20 allogenic (maternal uterine NK cells and trophoblast cells from different mothers) combinations [13]. This protection was indeed mediated by HLA-G, since NK lysis could be restored by blocking it with a specific monoclonal antibody. Further, our results strongly suggested that the low level of HLA-C molecules expressed on trophoblasts [35] did not contribute to such HLA-class I-mediated NK inhibition.

The role of HLA-G was further confirmed by carrying out experiments with K562-HLA-G1 transfectants which also inhibit decidual NK cell lytic activity. This inhibition could also be restored when HLA-G1 was blocked with a specific mAb. Trophoblasts as well as K562-HLA-G1 cells were also able to inhibit the lytic activity of peripheral blood NK cells and of the YT2C2-PR subclone [13]. Since no HLA-E molecule is expressed in the K562-HLA-G1 cells, HLA-G1 molecules directly protect the fetus from maternal decidua NK rejection. These results agree well with recent studies showing that decidual NK cells express p49 and

ILT-2 KIRs, which interact with HLA-G1 [36]. A new KIR, ILT-4, was recently identified that directly interacts with HLA-G as well as with HLA class I molecules [37]. This KIR is expressed on all monocytes, macrophages and dendritic cells, suggesting that HLA-G interactions may be important in the inhibition of both innate and acquired maternal immune responses against the fetus. Implications of HLA-G in gestational pathologies strongly support its role in materno-fetal tolerance. A lack of HLA-G expression in extravillous trophoblast has been reported in preeclampsia patients [38]. It has also been demonstrated that trophoblastic cells infected by *Herpes simplex* virus, which has been associated with spontaneous loss of pregnancy, lack HLA-G cell surface expression [39].

Whether HLA-E, which may be expressed on trophoblasts as a result of HLA-G expression, contribute also to protect fetal tissues by inhibiting maternal NK lytic activity, remains to be characterized. In this context, CD94/NKG2A receptor, which interacts with HLA-E, is highly expressed on decidua NK cells [13, 40].

Role of HLA-G in tumor immunosurveillance

In our laboratory, the group of Pascale Paul has recently described for the first time expression of HLA-G in solid tumor cells [41]. Both malignant human melanoma cell lines and ex vivo biopsies were found to exhibit high levels of HLA-G transcription with differential HLA-G isoform transcription and protein expression patterns. Such HLA-G expression inhibited NK cytolysis of HLA-G-positive tumors. These findings showed that, in addition to its immunomodulatory role in materno-fetal tolerance, HLA-G can participate in the escape of tumors from immunosurveillance. Further, the expression of HLA-G in HLA class I-loss tumor variants, which are otherwise susceptible to NK lysis, constitutes a mechanism that might permit their escape from NK immunosurveillance. In addition, cytokines produced by tumors, such as interleukin-10, may exert immunosuppressive effects by inducing expression of HLA-G on tumors as well as of inhibibitory receptors on immune effector cells [12].

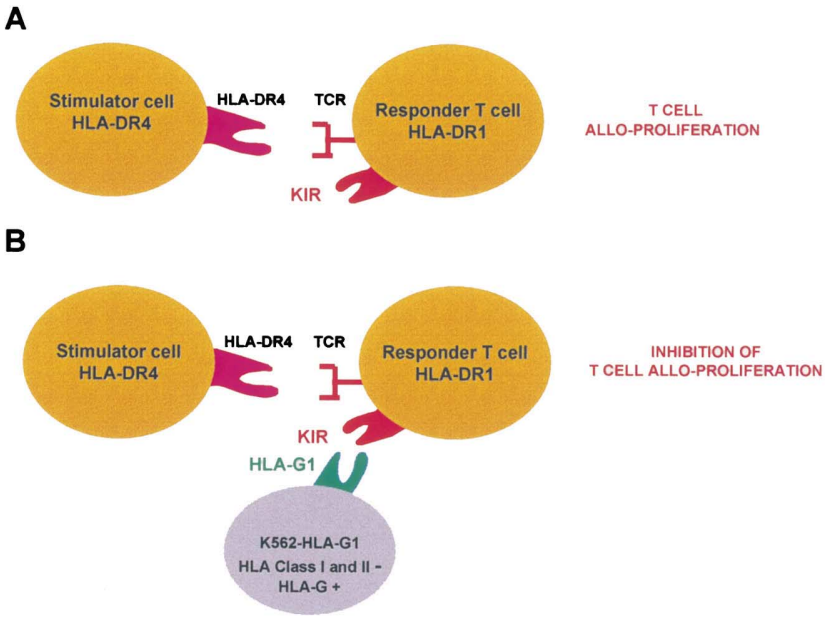

Figure 3. Implications of interactions between HLA-G1 and KIR in T cell alloresponses. (*A*) T cells present in the responder cell population from an HLA-DR1-positive donor proliferate when stimulated by PBMC from an HLA-DR4-positive donor in a mixed lymphocyte reaction (MLR). This T cell alloproliferative response is inhibited when the classical class I- and II-negative K562-HLA-G1 cells are added in the MLR. This inhibition may be mediated through interaction between HLA-G and KIR present on responder T cells.

Conclusion

This review focuses on results concerning the effects of HLA-G on the cellular immune response, where it impairs both NK and T cell functions. If these results can be extrapolated to immunosurveillance in vivo, HLA-G expressed on target cells (such as trophoblast, allograft, xenograft, autoimmune target and tumor) should inhibit (i) the lytic activity of antigen-specific $CD8^+$ CTL, (ii) the proliferative response of T cells and (iii) NK cell-mediated cytolysis. These HLA-G-mediated effects are the result of interaction with KIRs present on the immune effector cells. Further, in addition to membrane-bound HLA-G, soluble HLA-G proteins secreted by HLA-G-positive cells would also contribute to induce immune tolerance. Together, these mechanisms may be of benefit in materno-fetal tolerance, xeno- or allograft tolerance, and in autoimmune diseases, where HLA-G would be protective from NK and CTL rejection. In contrast, such mechanisms would be harmful in HLA-G-positive tumors, since it would allow them to escape from NK and T cell immunosurveillance. It has also been shown that HLA-G-positive cells modulate the ability of PBMC to release cytokines by enhancing the quantities of interleukin-3 and interleukin-1 released, while decreasing the quantity of tumor necrosis factor [42]. These data are in good agreement with the immunotolerant role of HLA-G

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