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# Biology of the immunomodulatory molecule HLA-G in human liver diseases

Laurence Amiot<sup>1,2,3,4,\*</sup>, Nicolas Vu<sup>1,2,3</sup>, Michel Samson<sup>1,2,3</sup>

<sup>1</sup>Institut National de la Santé et de la Recherche Médicale (Inserm), U.1085, Institut de Recherche Santé Environnement & Travail (IRSET), F-35043 Rennes, France; <sup>2</sup>Université de Rennes 1, F-35043 Rennes, France; <sup>3</sup>Fédération de Recherche BioSit de Rennes UMS 3480, F-35043 Rennes, France; <sup>4</sup>Department of Biology, University Hospital Pontchaillou, CHU Pontchaillou, Rennes, France

## Summary

The non-classical human leukocyte antigen-G (HLA-G), plays an important role in inducing tolerance, through its immunosuppressive effects on all types of immune cells. Immune tolerance is a key issue in the liver, both in liver homeostasis and in the response to liver injury or cancer. It would therefore appear likely that HLA-G plays an important role in liver diseases. Indeed, this molecule was recently shown to be produced by mast cells in the livers of patients infected with hepatitis C virus (HCV). Furthermore, the number of HLA-G-positive mast cells was significantly associated with fibrosis progression. The generation of immune tolerance is a role common to both HLA-G, as a molecule, and the liver, as an organ. This review provides a summary of the evidence implicating HLA-G in liver diseases. In the normal liver, HLA-G transcripts can be detected, but there is no HLA-G protein. However, HLA-G protein is detectable in the liver tissues and/or plasma of patients suffering from hepatocellular carcinoma, hepatitis B or C, or visceral leishmaniasis and in liver transplant recipients. The cells responsible for producing HLA-G differ between diseases. HLA-G expression is probably induced by microenvironmental factors, such as cytokines. The expression of HLA-G receptors, such as ILT2, ILT4, and KIRD2L4, on liver cells has yet to be investigated, but these receptors have been detected on all types of immune cells, and such cells are present in liver. The tolerogenic properties

of HLA-G explain its deleterious effects in cancers and its beneficial effects in transplantation. Given the key role of HLA-G in immune tolerance, new therapeutic agents targeting HLA-G could be tested for the treatment of these diseases in the future.

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## Introduction

Human leukocyte antigen-G (HLA-G) is the best characterized non-classical major histocompatibility complex (MHC) class Ib molecule [1]. It is best known for its tolerogenic function at the maternal-fetal interface, where it protects the fetus from destruction by its mother's immune system [2]. There have been many studies of the role of HLA-G in tumors and infectious diseases, autoimmunity and transplantation. We suggest that HLA-G may play an important role in liver diseases because: (i) it is tolerogenic; (ii) in the basal state, its expression is restricted to tissues involved in immune tolerance, such as the cornea and thymus [3,4]; and (iii) the liver is an organ known to induce immunological tolerance to T lymphocytes [5].

Mice have no HLA-G. Therefore, there is no murine model of HLA-G deficiency, such as knockout (KO) mice, and Qa-2 is the putative functional homolog of HLA-G [6]. The only HLA-G transgenic mice developed to date express H-2kb/HLA-G [7]. However, this model differs from humans in that HLA-G is expressed in all cells. The lack of an appropriate murine model clearly hinders investigations of the function of HLA-G in pathophysiology, including its role in liver diseases.

This review aims to summarize the role of HLA-G in cancers and infections of the liver in humans, and in liver transplant recipients, together with a brief overview of the characteristics of transplantation, after a brief review of HLA-G and recent findings concerning its physiological expression in the liver.

Keywords: HLA-G; Viral hepatitis; Liver failure; Transplantation; Hepatocellular carcinoma.

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\* Corresponding author. Address: IRSET U.1085 Inserm, University of Rennes 1, 2 Avenue du Pr. Leon Bernard CS 34317, 35043 Rennes Cedex, France. Tel.: +33 299 289 141; fax: +33 223 234 794.

E-mail address: [laurence.amiot@univ-rennes1.fr](mailto:laurence.amiot@univ-rennes1.fr) (L. Amiot).



**Key Points**

- HLA-G, a non-classical MHC (major histocompatibility complex) class Ib molecule, is known to have tolerogenic properties and a restricted pattern of expression in healthy tissues
- HLA-G proteins are detected in the tissues and plasma of patients with hepatocellular carcinoma or viral hepatitis, and after liver transplantation
- Microenvironmental factors may influence the production of HLA-G by various cells, including tumor cells, cells of the monocyte lineage, mast cells, and biliary epithelial cells, with the cellular source of this molecule depending on the context
- HLA-G receptors (ILT2, ILT4, KIR2DL4) are present on all immune cells but have yet to be studied in liver cells. However, HLA-G is known to be detrimental in cancers, but beneficial in transplantation. Its role in hepatitis remains to be determined
- HLA-G may induce local temporary immune suppression, counteracting autoimmune or infection-linked inflammatory responses and downregulating immune responses, such as the anti-tumor response

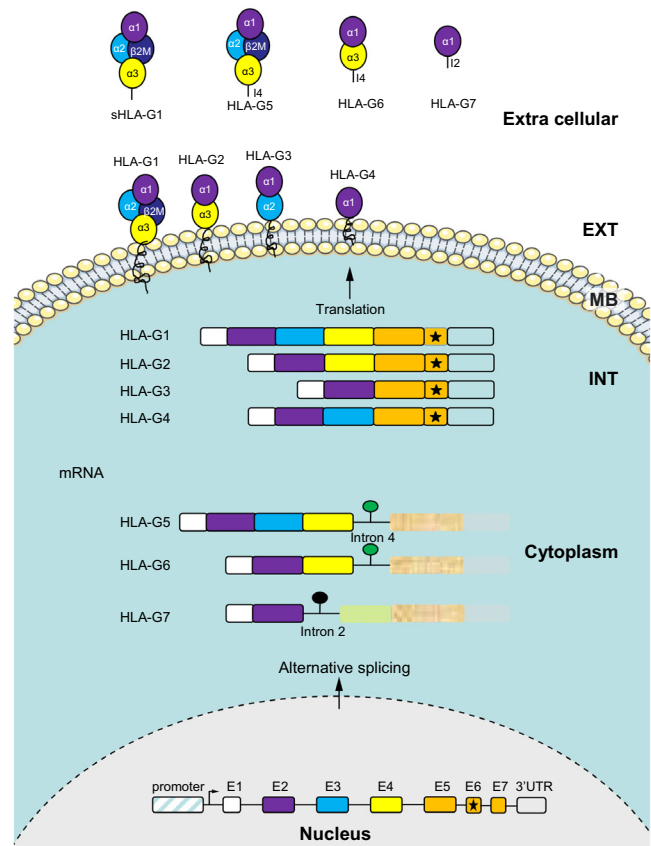
**Basic properties of HLA-G**

The *HLA-G* gene is located on the short arm of chromosome 6, in the HLA region (6p21.2-21.3), between the *HLA-A* and *HLA-F* genes [8]. Its structure is similar to that of other *HLA* class I genes, consisting of seven introns and eight introns, encoding the heavy chain of the molecule (Fig. 1). Exon 1 encodes the signal peptide, whereas exons 2, 3, and 4 encode the extracellular domains,  $\alpha 1$ ,  $\alpha 2$ , and  $\alpha 3$ , of the heavy chain, respectively. Exons 5 and 6 encode the transmembrane and cytoplasmic domains. Exon 7 is never present in the mature mRNA, due to the presence of a stop codon in exon 6, and exon 8 is also not translated [9]. The *HLA-G* gene promoter has an enhancer A (enh A), S and X1 sequence slightly different from that of other class I genes, and a few alternative regulatory elements to regulate *HLA-G* gene transcription [10]. The 3'-UTR of the *HLA-G* gene also contains several regulatory elements, including AU-rich motifs and a poly-A signal, influencing mRNA stability, turnover, mobility and splicing patterns [9].

*HLA-G* displays only limited polymorphism, with 50 alleles (IMGT HLA database, December 2013) and 16 proteins, far fewer than for some of the more highly polymorphic HLA class I molecules.

The alternative splicing of primary transcripts is a key feature of *HLA-G*, because it is strictly controlled and may be subject to cell type-dependent regulation. Indeed, the primary transcript of *HLA-G* is spliced into seven alternative mRNAs encoding membrane-bound (HLA-G1, -G2, -G3, -G4) and soluble (HLA-G5, -G6, -G7) protein isoforms [11]. In addition, HLA-G1 is released into the medium by proteolytic cleavage, as shed HLA-G1 [12].

The *HLA-G1* mRNA encodes the full-length HLA-G molecule; the *HLA-G2* mRNA lacks exon 3, the *HLA-G3* mRNA lacks exons 3 and 4, and the *HLA-G4* mRNA lacks exon 4. *HLA-G1* to -G4



**Fig. 1. The *HLA-G* gene, transcripts and proteins.** The *HLA-G* gene consists of 8 exons and 7 introns. Exon 1(E1) encodes the signal peptide, exon 7(E7) is not transcribed and exons 2, 3 (E2, E3) and 4 (E4) encode the  $\alpha$ -1 domain, the  $\alpha$ -2 domain, and the  $\alpha$ -3 domain, respectively; exon 5 (E5) encodes the transmembrane domain and exons 6 (E6) and 7 (E7) encode the cytoplasmic domain, with the final exon, exon 8 corresponding to the 3' UTR region. The star (\*) in E6 as the symbols in intron 2 and 4 are corresponding to stop codon. The primary transcript produced by transcription of the *HLA-G* gene undergoes alternative splicing, which generates four isoforms with transmembrane and cytoplasmic domains – HLA-G1, -G2, -G3, -G4 – and three different soluble isoforms – sHLA-G1 or HLA-G5, HLA-G6, and HLA-G7.

encode membrane-bound molecules, due to the presence of the transmembrane domain and cytoplasmic tail encoded by exons 5 and 6. The *HLA-G5* mRNA is similar to *HLA-G1* but retains intron 4, whereas the *HLA-G6* mRNA lacks exon 3 but retains intron 4, and the *HLA-G7* mRNA lacks exon 3 but retains intron 2. *HLA-G5* and -G6 encode soluble forms, due to the presence of intron 4, which contains a premature stop codon, preventing translation of the transmembrane domain and the cytoplasmic tail [12]. *HLA-G7* encodes a soluble form, due to the presence of intron 2, which contains a premature stop codon [13].

*HLA-G* is a transmembrane protein with a molecular weight of 39 kDa. It is a heterodimer of a heavy chain associated with a light chain ( $\beta 2$ -microglobulin). The heavy chain consists of three globular domains (the  $\alpha 1$ ,  $\alpha 2$ , and  $\alpha 3$  domains), a transmembrane region and a short cytoplasmic domain. Seven protein isoforms are generated by alternative splicing of the primary transcript. HLA-G molecules can also form dimers through the establishment of disulfide bonds between the two single cysteine residues at positions 42 (Cys42-Cys42 bonds) and 147

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(Cys42-Cys147 bonds) of the HLA-G heavy chain [14]. The resulting HLA-G dimers bind receptors with a higher affinity and slower dissociation rates than monomers [15]. Another characteristic of the HLA-G protein distinguishing it from other class I proteins is its short cytoplasmic tail, which contains no endocytosis motifs [16].

Unlike ubiquitously expressed HLA class I antigens, HLA-G displays a restricted pattern of expression in healthy individuals in basal conditions. The HLA-G protein is found only in trophoblast cells, the placenta, cornea, thymus, proximal nail matrix, erythroblasts and mesenchymal stem cells [2-4,17-21]. By contrast, soluble HLA-G (sHLA-G) is detectable in the serum/plasma of both men and women. It is produced principally by monocytes [21] and, to a lesser degree, T lymphocytes, in particular conditions [22,23].

Furthermore, HLA-G expression is induced in many diseases, including cancers, multiple sclerosis, inflammatory diseases and viral infections and in transplantation [24].

HLA-G expression is controlled principally at the transcriptional level, by a unique gene promoter, and at the posttranscriptional level by mechanisms involving alternative splicing, mRNA stability, translation and protein transport to the cell surface. Many factors potentially affecting the transcriptional and posttranscriptional mechanisms of HLA-G regulation have been described previously [25].

### Factors involved in HLA-G liver expression

HLA-G expression generally depends strongly on factors present in the microenvironment, such as cytokines. Indeed, various cytokines, including interferons, interleukin (IL)-10, GM-CSF, IL-2, and TGF- $\beta$  increase HLA-G expression in several *in vitro* models [25-27]. Other local factors, such as hypoxia [28] and Indoleamine 2,3-dioxygenase [29], influence HLA-G expression. These microenvironmental factors probably also play a role in the liver. Support for this hypothesis is provided by the controversies on HLA class I antigen expression on hepatocytes in basal conditions and the induction of HLA class I molecule expression in most hepatic diseases and its correlation with the intensity of intralobular inflammation [30,31].

The expression profiles of microenvironmental factors differ between diseases, but they may go some way towards explaining HLA-G expression patterns in liver cancers, hepatitis and transplantation. Moreover, epigenetic mechanisms, such as DNA methylation and histone deacetylation, have been implicated in cancers and in some anti-tumor treatments, and are known to regulate HLA-G expression. In viral infections, the viral proteins interfere with the intracellular trafficking of HLA-G [32], providing an additional mechanism for the modulation of HLA-G expression.

### Tolerogenic properties

The tolerogenic properties of HLA-G are mediated by the direct binding of both soluble and membrane-bound HLA-G to inhibitory receptors.

The binding to HLA-G of the immunoglobulin-like transcript (ILT) receptor 2 (CD85j; LILRB1) on natural killer (NK) cells and T lymphocytes leads to an inhibition of T lymphocyte or NK cell function due to changes in proliferation, cytotoxicity or the

induction of regulatory T or NK cells [33]. The expression of ILT2 on NK cells accounts for the restoration of NK cell cytotoxicity to hepatocellular carcinoma (HCC) cells transfected with HLA-G1 after the addition of a blocking ILT2 HLA-G receptor [34]. This receptor is also present on B lymphocytes and may account for the higher tolerance of liver allografts expressing HLA-G, due to the inhibition of B-cell antibody secretion [35].

The interaction of the CD8 receptor present on NK cells and T8 lymphocytes with sHLA-G triggers apoptosis [36]. This property is shared by other soluble HLA class I antigens but elevated sHLA-G levels are observed in neoplastic diseases. This results in an inhibition of the immune response, particularly for the anti-tumor response to liver cancers.

The role of the killer cell immunoglobulin-like receptor (KIR) 2DL4/p49 (CD158d) or KIR2DL4 expressed on NK cells and on some CD8 T lymphocytes is complex, because this receptor may have activating or inhibitory function [37]. The immunoglobulin-like transcript 4 receptor, ILT-4 (CD85d; LILRB2) is known to be expressed by dendritic cells (DCs), macrophages and monocytes [38], all of which are present in the liver. The ILT-4/HLA-G interaction may inhibit the antigen-presenting function of these cells, weakening adaptive immunity and allowing liver tumors to escape host immunity. This interaction may also inhibit DC maturation, resulting in anergic DCs that induce the differentiation of regulatory T cells, thereby helping to prolong allograft survival [39]. However, primary human neutrophils also express the ILT4 inhibitory receptor and the interaction of this receptor with HLA-G inhibits the phagocytic function of neutrophils [40]. This modulation of neutrophil activity may be beneficial in patients with sepsis, preventing the neutrophil dysfunctions observed during inflammatory disorders.

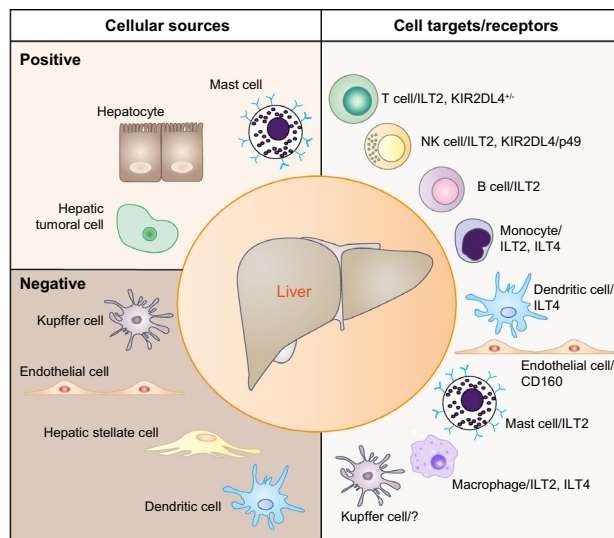
CD160 is a HLA-G receptor expressed on endothelial cells, which are abundant in the liver. The soluble HLA-G1 (sHLA-G1) isoform has been reported to inhibit fibroblast growth factor-2 (FGF2)-induced capillary-like tubule formation and, thus, to inhibit FGF2-induced angiogenesis *in vivo* [41].

No data are currently available concerning the expression of HLA-G receptors in liver. However, all of the immune cells expressing these receptors, as described above, are found in the liver, originating in most cases from the margination and extravasation of cells circulating in the blood during pathological conditions (Fig. 2). It also seems likely that the endothelial cells of the liver express CD160. However, the expression of these receptors on Kupffer cells, hepatocytes and hepatic stellate cells has yet to be studied.

HLA-G is not expressed in the liver in physiological conditions, however sHLA-G can be found, provided by peripheral blood or from transendothelial migration of circulating cells in the liver. HLA-G is able to induce tolerogenic DCs or regulatory T (Treg) cells which are implicated in the maintenance of liver homeostasis. Thus, it participates indirectly in inducing tolerogenic properties on immune cells to avoid activation of immune cells and inflammation.

### HLA-G in the normal liver

HLA-G gene transcription has been observed in both fetal and adult livers, but transcript levels are higher in fetal tissues. The HLA-G transcript detected corresponded to the full-length form [42]. The mesenchymal stem cells (MSC) present in fetal liver



**Fig. 2. Cellular source and putative targets of HLA-G in the liver.** HLA-G has been reported to be expressed by hepatocytes and mast cells, but there remains some debate concerning its possible expression by hepatocytes. In certain conditions, HLA-G may also be detected in T lymphocytes and in cells of the monocytic lineage, such as monocytes or dendritic cells. The putative target cells of HLA-G are peripheral cells expressing HLA-G receptors (T and B lymphocytes, NK cells, monocytes), T lymphocytes and cells of the monocytic lineage present in inflammatory areas, endothelial cells and mast cells.

contains intracellular deposits of HLA-G [43]. Hepatocyte-like cells (HLCs) generated from human amniotic epithelial cells (hAECs) from the placenta continue to secrete HLA-G [44], but in smaller amounts, and this secretion is maintained in HLCs differentiating from hAECs engrafted into the mouse liver [45]. No HLA-G protein is detected in hepatocytes and bile duct cells from the normal liver ([www.proteinatlas.org](http://www.proteinatlas.org)).

**HLA-G and liver cancer**

Both HLA-G mRNA and protein are detectable in human HCC cell lines [46].

HLA-G expression was found in 50.2% (110/219) of the primary HCCs assessed in one study; staining was heterogeneous in these HCCs, but undetectable in the adjacent normal liver tissues [34]. HLA-G expression has also been detected in biliary cancers [47]. The HepG2 hepatocarcinoma cell line was found to contain HLA-G mRNA, but not protein ([www.proteinatlas.org](http://www.proteinatlas.org)). The transfection of HepG2 cells with HLA-G1 decreases NK cytotoxicity, whereas a blockade of HLA-G or its receptor ILT2 reverses this effect [34]. HLA-G expression is strongly associated with advanced disease stage and patient age. In another series, cytoplasmic HLA-G overexpression (99/173 cases), as revealed by immunohistochemistry, was associated with a high risk of poor survival and recurrence in patients in the early stages of HCC. A positive correlation has also been found between HLA-G levels and the Treg/CD8 T lymphocyte ratio [48]. These findings are consistent with those of Wang [49], who detected HLA-G by Western blot of liver tissues, at 66.7% (24/36) of the HCC sites studied, but not in benign cirrhotic lesions. Survival after surgery was shorter for patients with HLA-G-positive tumors than for patients with HLA-G-negative tumors.

Blood sHLA-G concentration was shown to be significantly higher in HCC patients (n = 36) than in patients with liver cirrhosis (n = 25) and healthy subjects (n = 25) [49]. Lin *et al.* also reported a significantly higher plasma sHLA-G concentration in HCC patients (n = 19) than in healthy subjects (n = 86), with no correlation between sHLA-G concentration and the staining of the tumor for HLA-G [34]. The 14 bp insertion/deletion (in/del) polymorphism of the 3' UTR of HLA-G is known to regulate HLA-G expression. This led to studies of this polymorphism in HCC patients. HLA-G expression was found to be stronger in HCC tissues with a 14 bp del/del genotype than in those with a heterozygous or 14-bp ins/ins genotype [50].

To conclude, HLA-G expression in liver tumor or high level of sHLA-G in HCC patients allows escape of tumoral cells from immune response in inhibiting the properties of immune cells i.e. T8 lymphocytes, NK cells, B cells, DCs. HLA-G expression is a factor of bad prognosis similarly to other cancers.

**HLA-G and viral hepatitis**

HLA-G expression has been reported in the hepatocytes and biliary epithelial cells of the livers of patients with chronic hepatitis B [51]. Similar findings have been obtained for chronic hepatitis C [52]. In a previous work, we found a strong HLA-G staining of numerous cells in fibrosis septa and not in hepatocyte nodules of paraffin-embedded HCV liver. The HLA-G-positive cell number is significantly correlated with fibrosis area on tissue sections of HCV-induced liver fibrosis. HLA-G-positive cells were identified as being mast cells and not cells of monocytic lineage and T lymphocytes as previously reported in other models. Mast cells promote fibrosis in other organs such as heart, lung and kidney. As in other sites, hepatic mast cells may promote the activation of liver fibrosis via the proliferation of hepatic stellate cells [53]. Cytokines involved in liver fibrosis such as TGF-β, IL-4, IL-33 are chemoattracting or activating for mast cell [54]. We hypothesise that HLA-G can serve as a fibrosis marker in reflecting the number of mast cells [55] and in addition HLA-G makes fibrosis worse in favoring Th-2 cytokines profile.

Plasma sHLA-G levels were higher in patients with hepatitis B than in healthy subjects, regardless of disease stage, and HLA-G levels were found to differ between stages. Indeed significant differences were observed between; (i) acute hepatitis B (n = 90) and chronic hepatitis B (n = 131); (ii) acute hepatitis B and resolved hepatitis B (n = 152); and (iii) chronic hepatitis B and resolved hepatitis B [56]. Similarly, chronic hepatitis C patients (n = 67), were found to have a much higher plasma sHLA-G concentration than healthy subjects (n = 129) [57].

**HLA-G and hepatotropic parasite infections**

Visceral leishmaniasis (*Leishmania infantum*) (VL) causes morphological and functional disturbances in the liver, resulting in focal fibrosis rather than cirrhosis. We showed that sHLA-G levels were higher in 35% of HIV-negative patients with VL and in 57% of patients coinfecting with HIV and *Leishmania infantum* than in healthy individuals [58]. This upregulation of sHLA-G was reported to be correlated with cyst activity [59]. HLA-G expression could constitute an immune-evasion strategy in the host-parasite interplay.

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### HLA-G and liver failure

HLA-G expression during liver failure has not yet been investigated, to the best of our knowledge. Data are available only for septic shock. There is a critical reduction of tissue perfusion during severe sepsis and septic shock that may trigger the acute failure of multiple organs, including the liver. A sustained, marked increase in plasma sHLA-G levels was found to be predictor of survival [60]. A tissue expression of HLA-G or an increase of plasma levels would reflect an appropriate and efficient response to the inflammatory process in limiting this process.

### HLA-G and autoimmune hepatic diseases

The role of HLA-G has been investigated in several inflammatory diseases, including multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and psoriasis, and it has been suggested that HLA-G is both a biomarker useful for the monitoring of disease activity and an anti-inflammatory molecule [24]. However, no data have yet been published for autoimmune hepatic diseases, such as autoimmune hepatitis, sclerosing cholangitis and primary biliary cirrhosis. Similarly to other inflammatory diseases, HLA-G molecules may play a protective role in autoimmune hepatic diseases by its anti-inflammatory activity.

### HLA-G and liver transplantation

In combined liver-kidney transplantation, immunohistochemistry revealed HLA-G expression in 14 of the 40 liver biopsy specimens and five of the nine kidney transplant biopsy specimens examined. HLA-G is expressed *de novo* by known target cells of acute rejection: liver epithelial cells, but not in hepatocytes and renal tubular epithelial cells. HLA-G expression in the liver allograft is associated with a lower frequency of hepatic and renal graft rejection [61]. An inverse correlation was also found between serum HLA-G concentration and liver function in liver transplant patients ( $n = 37$ ). Indeed, a decrease in serum HLA-G concentration was found to be predictive of liver dysfunction or rejection one month later.

Serum sHLA-G concentration was high in liver-kidney transplant patients but not in kidney transplant patients [61]. Thus, sHLA-G levels and cell surface HLA-G expression on regulatory T cells increase during cyclosporine treatment and can be used in the follow-up of liver transplant patients [39]. Similarly, increases in serum HLA-G levels in pediatric and young adult liver transplant patients can be used to detect tolerance of the liver graft and to predict favorable outcomes in liver transplant recipients [62]. Serum sHLA-G concentration appears to be higher in adult liver transplant recipients treated with tacrolimus as an immunosuppressive agent, but this difference is not statistically significant [63]. Higher levels of expression have also been reported on the circulating monocytoïd DCs (mDCs) of patients with operational liver transplant tolerance than in patients on maintenance immunosuppression or healthy controls, although these differences were, again, not statistically significant [64]. The immunosuppressive treatments used in liver transplantation can modulate HLA-G expression, and this may partly account for their impact on prognosis. Indeed, some therapeutic agents such

as dexamethasone and hydrocortisone, upregulate HLA-G expression [65]. Cyclosporine and tacrolimus are the principal immunosuppressive agents used in liver transplantation, and mycophenolate is used to treat renal failure. Cyclosporine A and mycophenolate have no effect on HLA-G expression [66], whereas tacrolimus increases sHLA-G levels [63].

To conclude this section, expression of HLA-G in liver tissue or increase of circulating sHLA-G is associated with a better graft acceptance, that hypothesis is reinforced by the upregulation of HLA-G by some therapeutic agents used to prevent rejection.

### HLA-G and graft vs. host response

Liver is one of the sites at which graft vs. host (GVH) disease following hematopoietic stem cell transplantation is observed. Examination of the liver during acute GVH reveals foci of eosinophilic necrosis, bile duct destruction, Kupffer cell hypertrophy and peribiliary lymphocytic infiltrates. Fibrosis and atrophy are observed in chronic cases of GVH disease.

It seems likely that sHLA-G is involved in acute GVH disease (aGVHD) prevention, because increases in sHLA-G5 concentration on post-transplant days 15 and 30 were found to be inversely correlated with aGVHD severity [67]. This role of sHLA-G5 may be accounted for by the positive correlation between sHLA-G level and natural Treg cell frequency in the blood of transplant patients [68].

### General discussion

The cellular source of HLA-G differs between diseases. HLA-G is produced by some tumor cells, but it may also be generated by cells of the monocytic lineage, including monocytes, and DCs or T lymphocytes may express HLA-G in particular conditions. Furthermore, we have demonstrated the involvement of another cell type in HCV-induced liver fibrosis. Indeed, in this condition, it is the mast cells that produce HLA-G [55]. In the context of transplantation, HLA-G may be secreted by the biliary epithelial cells of the liver graft [61]. Alternatively, HLA-G5 may be secreted by allo-specific CD4<sup>+</sup> T lymphocytes, as shown in mixed lymphocyte cultures *in vitro* [22]. Kupffer cells or DCs may also serve as a source of HLA-G during transplantation, because both monocytes and DCs can express or secrete sHLA-G [21,69].

Numerous studies in the field of transplantation have demonstrated an association between high levels of HLA-G expression in biopsy specimens or high blood sHLA-G levels and higher rates of graft acceptance. Indeed, this association with a better post-transplantation outcome was first demonstrated for heart transplantation [70,71], and then for the transplantation of liver [39,61,72], kidney [73,74] and lung [75] grafts and for the transplantation of hematopoietic stem cells [68]. This beneficial effect may reflect a peripheral increase in the size of the CD3<sup>+</sup>CD4<sup>low</sup> and CD3<sup>+</sup>CD8<sup>low</sup> T-cell subpopulations associated with high levels of peripheral IL-10 production [76]. These two subsets constitute novel blood suppressor T-cell populations and are induced by HLA-G, potentially accounting for transplant tolerance. Patients with high sHLA-G levels after transplantation overproduce these suppressor T cells. HLA-G induces several types of regulatory/suppressive cells of various subtypes. The orientation towards tolerance can be accounted for by the effects of HLA-G

on the different subtypes of immune cells, including B cells in particular, resulting in the inhibition of antibody secretion by B cells in a mouse xenograft model [35]. Graft acceptance has been shown to be better in patients undergoing liver transplantation or combined liver-kidney transplantation than in those undergoing kidney transplantation alone [61]. These data are consistent with the immunological status of the liver [5]. The better graft tolerance observed in patients overexpressing HLA-G may be attributed to liver factors. These liver factors may be cytokines, such as the IL-10 produced by the liver during liver transplantation [77,78], HLA-G secreted by the biliary epithelial cells of the grafted liver [72] or allo-specific CD4<sup>+</sup> T lymphocytes, as shown in mixed lymphocyte culture *in vitro* [22]. Two other possible sources of HLA-G during transplantation are the Kupffer cells and hepatic DCs, which belong to the monocytic lineage able to produce or secrete HLA-G. Alternatively, HLA-G expression, which may be restricted to a few cells, could be propagated to neighboring cells by trogocytosis [79].

The tolerogenic properties of HLA-G account for its deleterious effects in cancers and beneficial effects in transplantation.

The abnormal expression of HLA-G in HCC cell lines plays an important role in protecting these cells against NK cell attack. The significant correlation between HLA-G expression and NK cell lysis implies that abnormal HLA-G expression may contribute to the mechanism of escape from host immune surveillance in HCC. Indeed, the effects of HLA-G on immune cells greatly affect both innate and adaptive immune responses, allowing the HCC to escape host immunity, resulting in tumor progression. Moreover, a comparison of HLA-G with the carcinoembryonic antigen AFP as markers of cancer has shown that HLA-G is specific to malignant liver cancers, like AFP in breast and ovarian cancers [80]. A positive correlation between HLA-G and Treg/CD8 T-cell ratio, with a negative impact of HLA-G on outcome, can be accounted for by the immunosuppressive properties of HLA-G and Treg cells. Other studies have demonstrated an association between HLA-G and Treg, due to the induction, by HLA-G, of different populations of Treg cells. Thus HLA-G appears to be an independent indicator of poor outcome in HCC, particularly during the early stages of the disease [48].

Plasma HLA-G concentration may be useful for the monitoring of immunosuppressive therapy after transplantation. The function of HLA-G in viral infections remains to be determined and may be detrimental, as in cancers, or beneficial, as in septic shock.

The receptors of HLA-G have not yet been investigated in the liver, and such studies are required if we are to understand the function of HLA-G.

## Conclusions

HLA-G could generally be considered a potent tolerogenic molecule. Its immunosuppressive properties play a role in liver diseases and transplantation, with negative effects on cancers and beneficial effects in liver transplantation. HLA-G may constitute a novel therapeutic target in the future. Indeed, new therapeutic agents for modulating HLA-G expression are being developed and tested, including synthetic HLA-G proteins potentially useful in transplantation [81] and antibodies blocking HLA-G activity in cancer [82]. Further exploration of the role of HLA-G receptors in liver diseases and a better knowledge of its function in liver are also required before considering their potential use in liver diseases.

## Conflict of interest

The authors who have taken part in this review declared that they do not have anything to disclose regarding funding or conflict of interest.

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