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Review

HLA-G expression in epithelia: proliferation, differentiation and immune regulation

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ABSTRACT

Mucosal epithelia are at the interface with external environment actively interacting with the symbiotic microbiota, pathogens, antigens and chemicals. Epithelia play a crucial role in the regulation of mucosal immune cell responses, through different immune modulatory molecules. Human leukocyte antigen-G (HLA-G) is a non-classical HLA class I molecule and its role in immune tolerance has been well documented. Physiologic expression of HLA-G has been recently detected in different epithelial cells types as well as its ectopic expression has been observed in acute or chronic inflammatory diseases and carcinomas. In addition, HLA-G has been implicated in the proliferation and redifferentiation of human bronchial epithelial cells (HBEC) *in vitro*, in accordance with previous observation of other progenitor cells. An improved understanding of the role of HLA-G in the interaction between mucosal epithelia and the immune system and epithelial stem cells differentiation is important in the development of therapeutics aimed to manage diseases affecting epithelia.

KEYWORDS: epithelia, HLA-G, differentiation, immunomodulation, proliferation.

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ABBREVIATIONS

HLA: Human Leukocyte Antigen; CTL: Cytotoxic T-Lymphocyte; NK: Natural Killer cells; ILT: Immunoglobulin-Like Transcript; KIR: Killer-cell Immunoglobulin-like Receptor; MSC: Mesenchymal Stromal Cells; DC: Dendritic Cells; sHLA-G: soluble HLA-G; UTR: UnTranslated Region; URR: Upstream Regulatory Region; EVT: extravillous trophoblast; HBEC: Human Bronchial Epithelial Cells.

1. Introduction

Human leukocyte antigen-G (HLA-G) is a non-classical HLA class I molecule and its role in immune tolerance has been well documented [1-5]. HLA-G has been initially identified in fetomaternal interface which has been correlated with fetomaternal tolerance [6]. Modulation of HLA-G expression has been observed in numerous pathological situations such as tumours, viral infections, and inflammatory and autoimmune diseases [7, 8]. HLA-G immunomodulatory properties have a crucial role in graft acceptance. HLA-G inhibits immune effectors and protects transplanted organ from rejection [9]. Several studies have shown a clinical correlation between the expressions of soluble and/or membrane-bound HLA-G and reduction of rejection risk in heart, lung, liver and kidney transplant patients [1-5].

HLA-G expression is restricted to specific tissue and cell types such as cytotrophoblast or different

immune cell populations, as monocytes [10-14]. Epithelia such as intestinal epithelium, bronchial epithelium and epidermis have been shown to express this molecule in physiological and/or pathological conditions.

Moreover HLA-G has been proven to be expressed in other progenitor cells. HLA-G is known to mediate erythroid progenitor proliferation/ differentiation [15, 16] as well as MSC differentiation in osteoblast [17, 18]. Recently, our team has suggested that the HLA-G molecule is potentially implicated in human bronchial epithelial cells (HBEC) proliferation and redifferentiation *in vitro* [19]. Modulation of HLA-G expression in different tissues has been observed in numerous pathological situations such as tumours, viral infections, inflammatory and autoimmune diseases [7, 8].

These elements raise the questions about the role of HLA-G expression in these tissues, its implication in the interaction between the different epithelia and the immune system and its influence on the differentiation and proliferation of epithelial stem cells.

2. Epithelium: structure, function and regenerative properties

During gastrulation epithelia develop from different germinal layers. In particular, epidermis generates from ectoderm along with the epithelium covering nasal and anal cavities. Endothelium of blood vessels originates from mesoderm, whereas gut and bronchial epithelium derive from endoderm.

Despite the different embryological origins, epithelia have in common the role as dynamic functional barriers between the external environment and the internal milieu of the body. Epithelial cadherin-based adherent junctions are crucial in adapting and responding to mechanical forces, while tight junctions (TJ) prevent the passage of molecules and ions through the space between the plasma membrane and the adjacent cells [20]. Indeed, the impairment of epithelial function as a barrier has been observed in different diseases involving epithelia. For instance, atopic dermatitis (AD) is associated with a defective expression of claudin-1, one of the protein that form TJ in keratinocytes [21, 22]. AD is also associated with mutations in the epidermal barrier protein filaggrin (encoded by the Flg gene) [23]. Both impaired expression of claudin-1 and mutations in Flg gene lead to a defect in epithelial barrier function, which increases epithelial permeability and penetration of exogenous substances. Lack of TJ junction functionality has also been observed in two diseases affecting bronchial and intestinal epithelia, namely asthma and ulcerative colitis (UC), respectively [24-26].

However, epithelia not only form a passive barrier, but upon external stimuli, such as trauma, bacterial and viral infections, chemical substances, or ultraviolet irradiation, they can actively respond to these menaces. For instance, human bronchial epithelial cells (HBEC) are key sensors of viruses, allergens or pollutants. Different pattern recognition receptors (PPR) such as nucleotide-binding oligomerization domain-containing protein 2 (NOD2) or the family of toll-like receptors (TLR) are present on the surface of HBEC. These receptors can initiate immune response through the release of mediators such as granulocyte colony stimulating factor (GM-CSF), thymic stromal lymphopoietin (TSLP), IL-25 or IL-33, thus communicating directly with immune cells [27]. Intestinal epithelia cells (IEC) also posses PPR that enable them to interact with the microbial environment and to cooperate in the regulation of mucosal immune cell responses, including the production of secretory IgA (sIgA) [28, 29]. In addition to the crucial role of PRR in triggering innate defense, their signaling is finely regulated to prevent chronic inflammatory reactions and destructive resident microbiota. Indeed, the fine activation of IEC's PPR is implicated in the expression of immunomodulating molecules such as TSLP or transforming growth factor beta (TGF-β). These two cytokines are implicated in the activation of mucosal CD103+ DC which is able to prime non-inflammatory responses and induce regulatory Foxp3+ T cells. Lung microbiome has a reduced biomass as compared to gastrointestinal tract. The studies assessing the lung microbiome interaction with bronchial epithelium are relatively recent. Nevertheless, many of them support the interaction of

microbiome with immune cells, and microbiome dysbiosis may contribute to chronic lung disease exacerbations. [30-32]

The regenerative properties of different epithelia are crucial for the maintenance of epithelia integrity and barrier function. In adult potential stem cells, niches have been proposed in different epithelia such as intestinal epithelium, bronchial epithelium and epidermis. Stem cell progenitors have been well described for this last tissue. Indeed, the innermost (basal) epidermal layer consists of undifferentiated progenitors that constantly proliferate before moving upward and differentiate in keratinocytes ensuring a continuous skin renewal [33]. For long time, it was thought that the main source of endothelial stem cells (ESC) for vascular endothelium was located in the bone marrow. However more recently, *in vitro* studies, suggest that vascular ESCs are also present *in situ* [34, 35].

In the small intestine the epithelial stem cells are located at the bottom of intestinal crypts in-between villi. Here crypt base columnar (CBC) cells seem to be imputed as the actual intestinal stem cells [36].

The presence of bronchial epithelial stem cells has been extensively reviewed [36, 37]. Particularly, different potential basal cells (BC) have been proposed as HBEC progenitors [36, 38]. These cells are so-named for their proximity to the underlying basal lamina.

HLA-G expression has been detected in epithelial cells types in physiological conditions as well as ectopic expression induced by acute or chronic inflammatory states and malignancies.

3. HLA-G

3.1. Genetic structure

HLA-G gene is located in the short arm of 6th chromosome in the HLA region (6p21.2-21.3). It is surrounded by HLA class 1a genes HLA-A (115 Kb downstream), HLA-B (1526 Kb downstream) and HLA-C (1441 kb downstream), and HLA class 1b loci HLA-E (662 Kb downstream) and HLA-F (103 Kb upstream) [39].

Compared to classical HLA class I genes, HLA-G is characterized by a low coding polymorphism. Fifty HLA-G coding alleles have been identified coding for 15 full-length proteins (G*01:01, G*01:03, G*01:04, G*01:06, G*01:07, G*01:08, G*01:09, G*01:10, G*01:11, G*01:12, G*01:14, G*01:15, G*01:16, G*01:17, G*01:18) and two modified proteins (G*01:05N, G*01:13N) [7, 40]. All HLA-G alleles belong to the same G*1 serotype, supporting the reduced variability of HLA-G coding region, in opposition with HLA Ia molecules displaying many serotypes.

In comparison with the coding region, HLA-G 5' upstream regulatory region (5'URR) and 3' untranslated region (3'UTR) are highly polymorphic. Castelli and coworkers [41] described 35 single nucleotide variations (SNVs) in the 5'URR (corresponding to the promoter region from the position -1500 to -1) and 17 in the 3'UTR from 1000 Genomes Project data. Among those SNVs only 26 for 5'URR and 9 for 3'UTR display a minor allele frequency (MAF) above 1%.

Linkage disequilibrium of SNPs has been described within the 5'URR region and in the 3'UTR region (Table 1). Castelli *et al.* defined eight UTR HLA-G haplotypes using 3'UTR SNPs in a Brazilian population [42] that were associated with SNPs in 5'URR and coding alleles [43]. This low variability of haplotype in a highly admixed population as Brazilians suggests balanced selective effect acting on UTR haplotypes.

3.2. Transcrptional and post-transcrptional regulation: the implication of regulatory regions' polymorphism

The HLA class I genes might have been generated by duplications, leading to high nucleotide sequence similarities [44]. Consequently, HLA class I promoters share several cis-acting regulatory elements. HLA-G promoter appears to be the most divergent as most of these common regulatory elements are not functional [45, 46].

Two main regulatory modules are present in HLA class Ia genes: enhancer A (EnhA) in combination with an interferon-stimulated response element (ISRE) and the SXY module [47] (Figure 1a). The EnhA element displays two adjacent binding sites (κB1 and κB2) that interact with the transcription factors of nuclear factor-kappa B (NF-κB) family requiring the binding of different

Table 1. Distribution of HLA-G regulatory and coding region haplotypes worldwide. In this table the combined frequencies of HLA-G promoter (PROMO), 3'UTR (UTR) and coding allele haplotypes in different populations are presented [41, 71-73].

Promoter haplotype	Coding allele or coding haplotype	3'UTR haplotype	[41] Nigeria Yoruba; n=89	[41] Kenia Luhya; n=94	[72] Mali; n=229	[73] Cyprus; n=185	[41] Finland; n=92	[71] France; n=123	[41] Great Britain; n=87	[41] Italy; n=98	[41] Spain; n=14	[41] China; Beijin; n=96	[41] China; South; n=100	[41] Japan; n=89	[73] Brazil; n=315
PROMO-010101a	G*01:01:01:01	UTR-01	0.069	0.1489	0.134	0.2054	0.337	0.336	0.2989	0.2755	0.2857	0.2813	0.39	0.236	0.2365
PROMO-010102a	G*01:01:02:01	UTR-02	0.1379	0.1436	0.165	0.1405	0.1196	0.152	0.1954	0.1735	0.25	0.0938	0.035	0.1742	0.146
PROMO-010102a	G*01:05N	UTR-02	0.1207	0.0638	0.109	0.0216	0.0109	0.021	0.0000	0.0408	0.0000	0.0417	0.015	0.0056	0.0222
PROMO-010102a	G*01:06	UTR-02	0.0000	0.0053	0.025	0.0676	0.0272	0.033	0.0632	0.0714	0.1071	0.026	0.01	0.0056	0.046
PROMO-0104a	G*01:04:01	UTR-03	0.0402	0.0106	0.239	0.1216	0.0543	0.123	0.0517	0.102	0.0714	0.2656	0.24	0.3764	0.0714
PROMO-0104a	G*01:04:04	UTR-03	0.2299	0.0745		0.0135	0.0054		0.0115	0.0306	0.0000	0.0000	0.0000	0.0000	0.0635
PROMO-010101b	G*01:01:01:05	UTR-04	0.0632	0.0319	0.05	0.0568	0.2609	0.156	0.1092	0.1429	0.1071	0.0469	0.015	0.0056	0.046
PROMO-010101c	G*01:01:01:05	UTR-04				0.0324									0.046
PROMO-0103a	G*01:03:01:02	UTR-05	0.069	0.0798	0.143	0.0027	0.0163	0.028	0.023	0.0306	0.0000	0.026	0.0000	0.0169	0.0397
PROMO-0103d	G*01:03:01:02	UTR-05				0.0432									0.0159
PROMO-0103e	G*01:03:01:02	UTR-05				0.0135									0.0206
PROMO-010101f	G*01:01:01:04	UTR-06	0.0747	0.1011	0.121	0.0324	0.0109	0.074	0.0632	0.0153	0.0714	0.0000	0.0000	0.0000	0.0032
PROMO-010102a	G*01:01:03:03	UTR-07	0.0000	0.0000	_	0.0784	0.0435	0.074	0.092	0.0408	0.0357	0.1719	0.205	0.0337	0.0571
PROMO-010101f	G*01:01:01:04	UTR-18	0.0747	0.1011	_	0.0162	0.0109	_	0.0632	0.0153	0.0714	0.0000	0.0000	0.0000	0.0317
Others			0.1207	0.2394	0.0132	0.1542	0.1031	0.003	0.0287	0.0613	0.0000	0.0468	0.09	0.146	0.1542
Total			0.8793	0.7606	0.986	0.8458	0.8969	0.997	0.9713	0.9387	0.9998	0.9532	0.91	0.854	0.8458

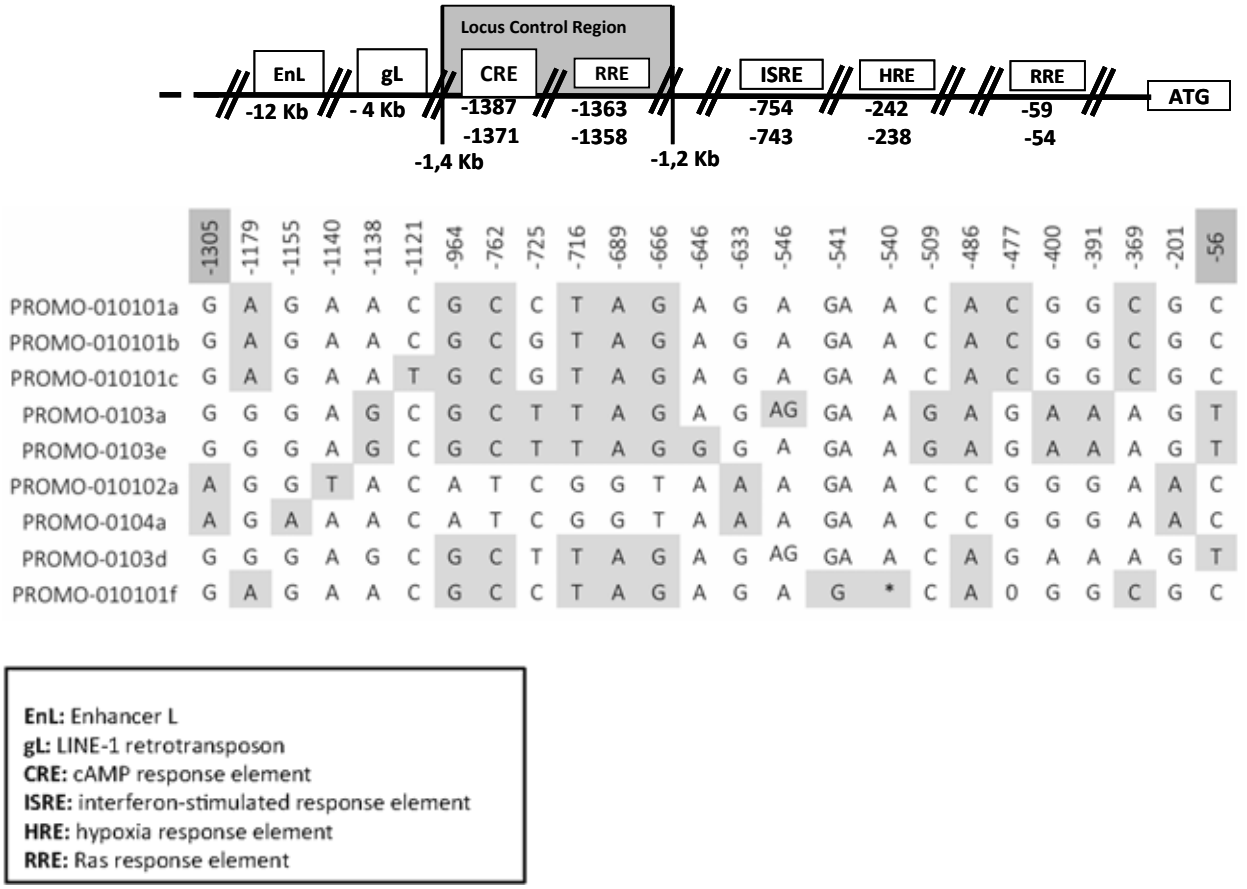


Figure 1a. HLA-G promoter regulatory modules and polymorphisms. Known functional HLA-G regulatory elements. HLA-G promoter polymorphisms, which are located between the Locus control region and the second Ras response element, are presented (dark grey boxes). This figure is adapted from the previous work of Castelli *et al*. [46].

sub-units such as p50, p65, p52, c-Rel, and RelB, [47]. In HLA-G, the EnhA element displays a mutation that allows only p50/p50 homodimers to bind, and do not induce gene expression [48]. ISRE constitutes the binding site for the interferon regulatory factor family interferon regulatory factor-1 (IRF-1, activator), IRF-2, and IRF-8 (inhibitors) [47]. HLA-G ISRE is the most divergent compared to the HLA class I ISRE consensus sequence [45] and no IRF-1 and IRF- 2 binding site was observed. This suggests that HLA-G ISRE is not sensitive to IFN-induced transactivation. However, the constitutively expressed factor Sp1 (Specificity Protein 1) seem to bind to both HLA-G EnhA (κB2 binding site) and ISRE of HLA class I loci including HLA-G [48]. The SXY module includes the binding sites S, X1, X2 and Y boxes [45, 48]; their binding factors interact with the co-activator class II trans-activator (CIITA) [49]. In HLA-G, only S and X1 are functional [45], and CIITA, which is dependent on a functional SXY module, does not transactivate HLA-G [45]. Thus, HLA-G promoter displays nonfunctional regulatory modules common to HLA class I gene and some exclusive regulatory elements.

Only HLA-G displays the heat shock element (HSE) binding site for the heat shock factor 1 (HSF1) [50]. The functionality of this element has been supported by *in vitro* studies showing that HLA-G transcription is induced by physical stress (heat shock) or chemical stress (arsenate treatment) in human melanoma and glioblastoma cell lines *via* the activation of HSF1 [50]. Although

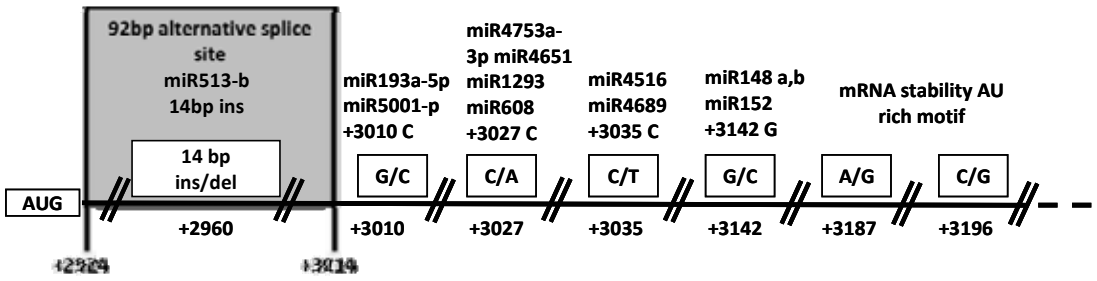
functional studies showed that progesterone enhance HLA-G expression, no progesterone response element (PRE) was found in its promoter region. A PRE displaying 60% of homology to that of the wild-type mouse mammary tumor virus (MMTV) was mapped between positions -52 and -38 on HLA-G promoter. Implication of progesterone in HLA-G expression is supported by the requirement of this endogenous steroid for embryo implantation [51-53].

Ferreira and colleagues identified a cis-regulatory element with an enhancer activity 12 Kb upstream from HLA-G, called *Enhancer L*. This enhancer induces HLA-G expression, allowing a loop to form into the promoter and the interaction with GATA2/3, and CEBPβ transcription factors. These latter are known to be involved in the gene expression of numerous genes in trophoblastic cells [54].

Functional repressor factor binding sites specific to HLA-G have been also reported as ras response element (RRE) binding RREB1 (Ras responsive element binding 1) and distant-acting cis-repressor as gL LINE element [55, 56].

The promoter region of HLA-G is highly polymorphic and these variations account for inter-individual HLA-G expression modulation. Some polymorphisms are within the regulatory elements described above, for example -1305 G>A in the LCR, -716 G>T in HSE and -56 C>T in RRE, and may affect the binding of their transcriptional factors [46]. Other 5'URR polymorphisms are supposed to affect DNA methylation, for example -964 G>A [57] as adenine disrupts a CpG methylation site, or 725 C>G>T as G variant creates a CpG dinucleotide [58]. This was supported by an *in vitro* study based on a luciferase assay showing an impact on HLA-G transcription [59].

The 3'UTR sequence in the mature HLA-G mRNA is composed of 397 nucleotides and displays several polymorphisms associated with post-transcriptional regulation linked to mRNA stability (determined by its nucleotide structure) and/or action of microRNAs (miRNA) (Figure 1b).



3'UTR haplotype	+2960 (14 bp)	+3010	+3027	+3035	+3142	+3187	+3196
UTR-1	Del	G	C	C	C	G	C
UTR-2	Ins	C	C	C	G	A	G
UTR-3	Del	C	C	C	G	A	C
UTR-4	Del	G	C	C	C	A	C
UTR-5	Ins	C	C	T	G	A	C
UTR-6	Del	G	C	C	C	A	C
UTR-7	Ins	C	A	T	G	A	C
UTR-18	Del	G	C	C	C	A	C

Figure 1b. HLA-G 3'UTR polymorphism linked to mRNA stability. 3'UTR polymorphisms defining 3'UTR haplotypes influence miRNA binding, affecting HLA-G half-life.

The insertion/deletion of 14 bp in the 8th exon (14 bp ins/del or ex 8 ins/del) is one of the first polymorphisms described in HLA-G 3'UTR [60]. The 14 bp ins seems to directly affect the HLA-G mRNA stability and is associated with a reduced HLA-G translation in trophoblast [61-63]. However, an *in vitro* study has shown that in 14 bp ins K562 cell line HLA-G membrane bound expression was increased, whereas 14 bp del displayed a higher soluble/membrane bound expression ratio [64]. The 14 bp ins is associated with the 92 bp spliced region in 3'UTR, and this transcript appears to be more stable [65].

The polymorphism at +3142G has been associated with mRNA stability as it creates binding site for miR-152, miR-148a and miR-148b supported by an *in vitro* assay [66, 67], leading to a decrease of HLA-G expression.

The polymorphisms +3187 A/G and +3196 C/G both surround an AU-rich motif reported to influence mRNA stability [68, 69]. The presence of an adenine at the position +3187 increases the total number of A in the AU-rich motif favoring HLA-G mRNA degradation [68]. No functional studies have been conducted on 3196 C/G.

Other polymorphic sites such as +3003, +3010, +3027, and +3035 were not studied for their influence on mRNA stability or HLA-G expression. However an *in silico* study showed their potential interaction with several miRNAs [67].

The heterogeneous nuclear ribonucleoprotein R (HNRNPR, RNA-binding protein family) binds to the 3'UTR region of HLA-G and is involved in processing the pre-mRNA into mature mRNAs. However no impact on HLA-G expression was demonstrated and HNRNPR binding site was not identified [70].

Expression of HLA-G may be driven by the combination of several polymorphisms, and hence our group focused on the influence of haplotypes on the expression of this molecule. Our team and others have showed the high conservation of the haplotypes described by Castelli *et al*. in a Brazilian population [41, 43, 71-73]. Those UTR haplotypes were in strong association with HLA-G alleles: some associations of UTR HLA-G alleles were exclusive, such as UTR3~HLA-G*01:04, whereas UTR2 showed multiple allele associations, with G*01:05N, G*01:06 and G*01:01 and G*01:01 being associated with UTR1, -4, -6, -7 and -8. Finally, these UTRs, rather than isolated SNPs, seem more relevant to predict sHLA-G expression.

3.3. Protein structure and isoforms

HLA-G coding region structure was first described by Geraghty and co-workers in 1987 [74], showing strong similitudes with other class I molecules. Six exons code for the HLA-G protein: exon 1 codes for the signal peptide, exon 2, exon 3 and exon 4 code for the α1, α2 and α3 domains, respectively, exon 5 codes for the transmembrane domain and exon 6 for the cytoplasmic tail (IMGT/HLA database) [40].

One of the distinguishing features of HLA-G is the presence of different isoforms generated by alternative splicing, dimerization ability and the possible association with the β2-microglobulin. Four protein isoforms are membrane bound and three are soluble. HLA-G1 is the full-length membrane-bound isoforms. The three membrane-bound isoforms HLA-G2, -G3 and G4 lacks one or more domains: HLA-G2 lacks α2 domain; HLA-G3 lacks both α2 and α3 domains and HLA-G4 lacks α3 domain. HLA-G5 and -G6 soluble forms possess the same α domains as HLA-G1 and -G2 but no transmembrane domain. HLA-G7 is only composed of α1 (see for review [7]) (Figures 2a and 2b).

All HLA-G isoforms display α1 domain that, with α2 domain, forms the peptide-binding groove (see for review [7]). Only 10 amino acid variations are present in the peptide groove among HLA-G alleles, 4 of them in α1 and 6 in α2. Thus, HLA-G binding peptides' repertoire is very restricted. *In vitro* and *in vivo* studies identified 15 distinct HLA-G self-peptides [75], derived from cytokine-related protein and cytokine receptors, histone H2A, and nuclear and ribosomal proteins. These peptides influence HLA-G stability, its conformation and its turnover on cell surface expression [76]. Hence, they affect HLA-G immune-tolerant potential by both directly influencing structural

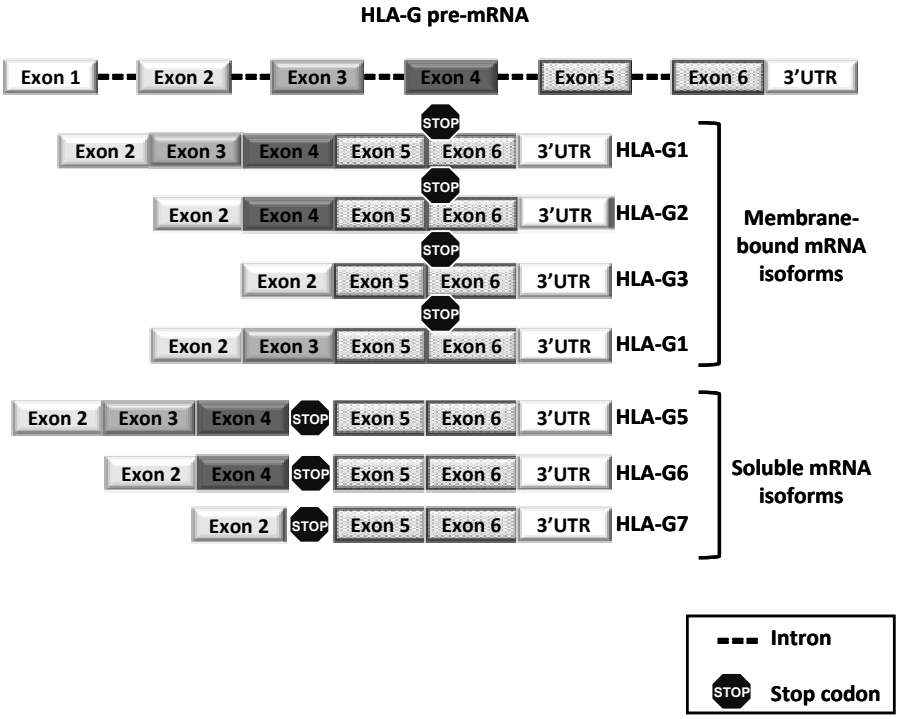


Figure 2a. Alternative splicing of HLA-G transcripts.

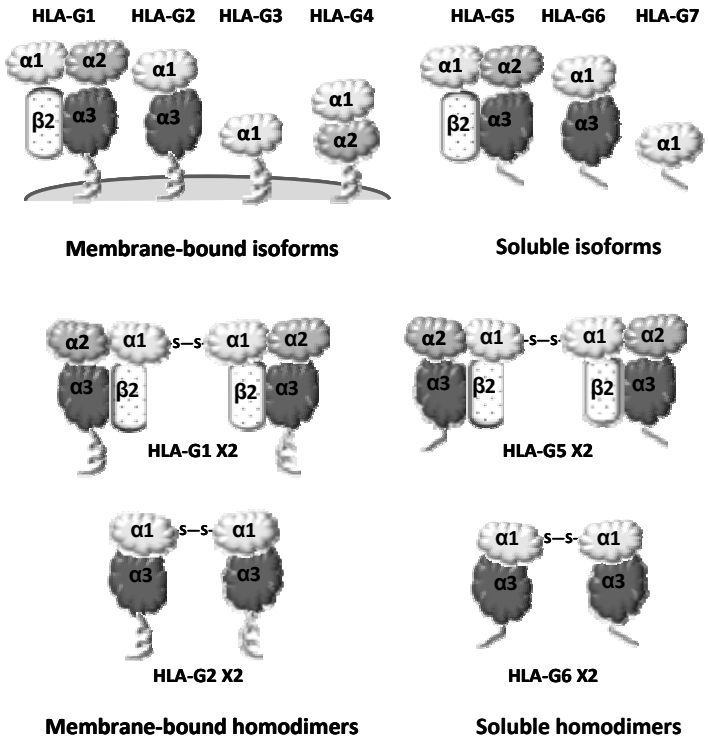


Figure 2b. HLA-G proteins structure and isoforms. Protein structure of membrane-bound and soluble isoforms and different functional HLA-G homodimer combinations are presented.

recognition by HLA-G receptors [77] and indirectly through the regulation of the levels of HLA-G on the cell surface [76].

The α1 and α2 domains are also involved in HLA-G dimerization, unique to HLA-G, as two cysteines (Cys) at position +42 in α1 and +147 in α2 allow the formation of disulfide bonds between HLA-G monomers generating HLA-G dimers. However, Cys 42 appears to have greater importance [78]. Dimerization can occur between membrane-bound or soluble HLA-G (sHLA-G) proteins. HLA-G1 or G5 homodimer has been detected *in vivo* and *in vitro* (see for review [79]) (Figure 2b).

The α3 domain, as for HLA class Ia molecules, is responsible for the non-covalent binding with the β_2-microglobulin.

As mentioned above, HLA-G isoforms can be found in soluble or membrane-bound forms due to alternative splicing. Moreover, HLA-G transmembrane domain can be subject to proteolytic cleavage once the protein reaches the cell surface. Metalloproteinase-2 (MMP-2) can shed all HLA-G membrane-bound isoform into soluble form [80].

HLA-G is subject to post-translational modifications. The signal peptide of HLA-G (also named leader sequence) is cleaved by the signal peptide peptidase (SPPase) during translocation into the endoplasmic reticulum (ER) [81]. HLA-G can be glycosylated on asparagine 86 in the α1 domain (see for review [79]). Noteworthy, HLA-G2, -G3, and -G4 isoforms, unlike HLA-G1 and HLA class Ia molecules, are sensitive to endoglycosidase H suggesting an escape from ER retention and different protein processing [82]. HLA-G protein is processed by nitration on tyrosine residues (see for review [79]) that seems to increase HLA-G shedding.

3.4. Functions and physiological expression

HLA-G immune-inhibitory role acting directly on immune cells is extensively documented. Particularly, HLA-G inhibits natural killer (NK) cytotoxicity and interferon gamma (IFNγ) secretion [83]. This molecule is able also to negatively influence antigen presentation of dendritic cells (DC), B and T lymphocyte activation and proliferation (see for review [79]). HLA-G also indirectly exerts its immune-inhibitory function as HLA-G expressing cells are able to induce regulatory T cell proliferation [14].

HLA-G molecule was first detected at feto-maternal interface [84] and described for its involvement in reproduction. HLA-G is expressed in follicular fluid, and in seminal plasma suggesting an implication in fertility [85-88]. After embryo implantation, HLA-G is expressed by the extra villous trophoblasts (EVTs) [84], outer layer of the the syncytiotrophoblast, that invade the uterine wall [89]. HLA-G molecule expressed by EVTs is thought to be involved in fetus protection from maternal immune cells [90, 91]. HLA-G expression seems also to contribute to EVTs migration and invasion in maternal decidua [92] favoring tissue remodeling and the development of an appropriate maternal-fetal niche [93, 94].

Physiological expression of HLA-G is also observed in nail matrix [95], cornea [96], pancreatic islets [97], erythroid and endothelial precursors [15], thymus [98, 99], mesenchymal stem cells [100, 101] and different immune cell populations, such as monocytes [10], T-cells [11, 12], and antigen-presenting cells [13, 14]. A particular subset of tolerogenic DCs, DC-10, expresses high levels of interleukin 10 (IL-10) and HLA-G [13].

Concerning the functionality of the different HLA-G isoforms, G1 and G5 immune inhibitory functions have been the most described (see for review [79]). These two isoforms have been shown to reduce NK cells' cytotoxicity separately and together with an additive effect [102]. The other HLA-G isoforms, even though they do not posses all the α domains, also regulate immune response. Riteau and co-workers showed that α1 domain from HLA-G2, -G3 and -G6, was sufficient to inhibit NK cells' cytotoxicity [82]. Conflicting results have been published by Zhao *et al*. showing no NK inhibition by HLA-G3 [103]. No functional activity has been reported for HLA-G7.

Besides HLA-G immune-inhibitory function, this molecule is implicated in cell proliferation and differentiation. HLA-G mediates the proliferation/differentiation of erythroid progenitors

and erythroid cell lines [15, 16]. Moreover, mesenchymal stromal cells (MSCs) differentiating in osteoblast strongly express HLA-G5 isoform [17]. HLA-G expression in human amnion epithelial cells (hAECs) increases their proliferation properties and their differentiation into different epithelial cells types *in vitro* [104].

Along with free soluble HLA-G molecules present in different human fluids such as plasma, serum or lung mucus, this molecule can be secreted in extracellular vesicles (EVs) (see for review [79]). HLA-G^+ EVs have been found to be secreted by cytotrophoblasts cells [105], MSCs [106] and tumor cells [107, 108]. EVs can transfer the bioactive molecule content through different mechanisms such as membrane fusion, phagocytosis, clathrin- and caveolin-mediated endocytosis, or micropinocytosis (see for review [79]). These mechanisms might represent a mode of how HLA-G can be transferred from cells. Indeed, the transfer of HLA-G+ EVs between APCs and activated T cells and between tumor cells and T/NK cells has been demonstrated (see for review [9, 79, 109, 110]).

3.5. Receptors

HLA-G interacts with three main receptors: immunoglobulin-like transcript (ILT)-2 (LILRB1, LIR1 and CD85j), (ILT)-4 (LILRB2, LIR2 and CD85d) and killer-cell immunoglobulin-like receptor (KIR)2DL4 (CD158d). HLA-G seems to bind to non-specific receptors such as CD8 and CD160.

Both ILT-2 and ILT-4 receptors are composed of four immunoglobulin superfamily (IgSF) domains, a transmembrane domain and four and three intracellular tyrosine-based inhibitory motifs (ITIMs), in their cytoplasmic tails [77]. ILT-2 receptors are expressed on wide distribution immune cells. ILT-4 is expressed only by monocytes/dendritic cells. These receptors clearly allow the modulation of the adaptive and/or the innate immune responses. HLA-G1 homodimers appear to bind to ILT-2/ILT-4 with a superior avidity than monomers, as dimerization exposes the binding sites [77]. Moreover, studies conducted on HLA-G2 and G6 recombinant proteins showed that only ILT-4 receptor is able to interact with these isoforms. Association with the β_2-microglobulin seems to affect HLA-G binding with ILT-2 but not with ILT-4 receptor [77].

KIR2DL4 receptor differs from the other KIR family member by its structure, signalization, ligand specificity and cellular localization. KIR2DL4 expression is restricted to the $CD56^+$ subsets of NK cells [111, 112]. KIR2DL4 exhibits a unique combination of one single intracellular ITIM and a positively charged arginine within its transmembrane domain. This suggests a dual function for KIR2DL4 as either an activating or an inhibitory receptor, depending on the cellular context. Furthermore, whereas most KIR receptors are expressed on cell surface, KIR2DL4, depending on the allele, has predominant endosomal localization or a surface expression [112-114]. HLA-G interacts with KIR2DL4 through its α1 domain and is the only known KIR2DL4 ligand [111]. Noteworthy, the functional implication of HLA-G and KIR2DL4 interaction is still debated [115].

Interaction between HLA-G and CD160 has been also reported. This is an activator receptor normally expressed by $CD56^{dim}$ peripheral blood NK subset and endothelial cells. *CD160* gene is conserved in different mammalian species such as human, mouse and rabbit [116]. *In vitro*, the binding between this receptor, expressed by activated endothelial cells, and sHLA-G1, inhibits fibroblast growth factor-2 (FGF2)-induced capillary-like tubule formation. Moreover, this CD160/sHLA-G1 interaction can also cause endothelial cell apoptosis. In the same study, Fons *et al*. showed that HLA-G exerts this anti-angiogenic effect *in vivo* in rabbits [117].

4. Expression and functional role of HLA-G in epithelia

4.1. HLA-G expression and functions in epithelia in physiological conditions

HLA-G seems to be expressed in different epithelial cell types in physiological conditions. As previously mentioned, extravillous trophoblast (EVT) cells express HLA-G. These epithelial cells derive from the trophoectoderm of the developing blastocyst; they have a columnar structure and

anchor the placenta to the uterus and invade the decidua (interstitial invasion) and the maternal spiral arteries (endovascular invasion). HLA-G expression by EVT cells helps creating a "tolerant" environment and acts on placental tissue remodeling by promoting the cytotoxic activity of decidual NK cells [93]. EVT cells express the membrane-bound or shredded form of HLA-G1 and the soluble form of HLA-G5 [91, 118-120]. HLA-G2 and HLA-G6 expression has been also observed in EVT cells, particularly in the phenotypes invading the maternal decidua [91, 120].

Basal HLA-G expression has been observed in normal HBEC cell culture or in histological analyses [121-123]. Particularly, White and co-workers have observed that normal HBEC cultured *in vitro* express HLA-G5 isoform. Moreover, these authors observed that HLA-G5 expression was influenced neither by T2-related inflammatory cytokines, IL-4, IL-5 and IL-13, nor after treatment with IL-10 anti-inflammatory molecule. Recently, our team has been able to demonstrate that normal HBEC redifferentiated *in vitro* using ALI culture method express all HLA-G mRNA (HLA-G1 to HLA-G6) [19]. We observed that HLA-G1/HLA-G4/HLA-G5 had the most prominent expression followed by HLA-G2/HLA-G6 and HLA-G3.

HLA-G expression has not been detected in other epithelial cells types in physiological conditions (Figure 3).

4.2. HLA-G expression and function in epithelia in pathological conditions

The role of HLA-G in the acceptance of transplants has been demonstrated *in vivo* in murine models of skin allograft. These studies show that injection of beads coated by the HLA-G in the footpads (away from the graft site) has a

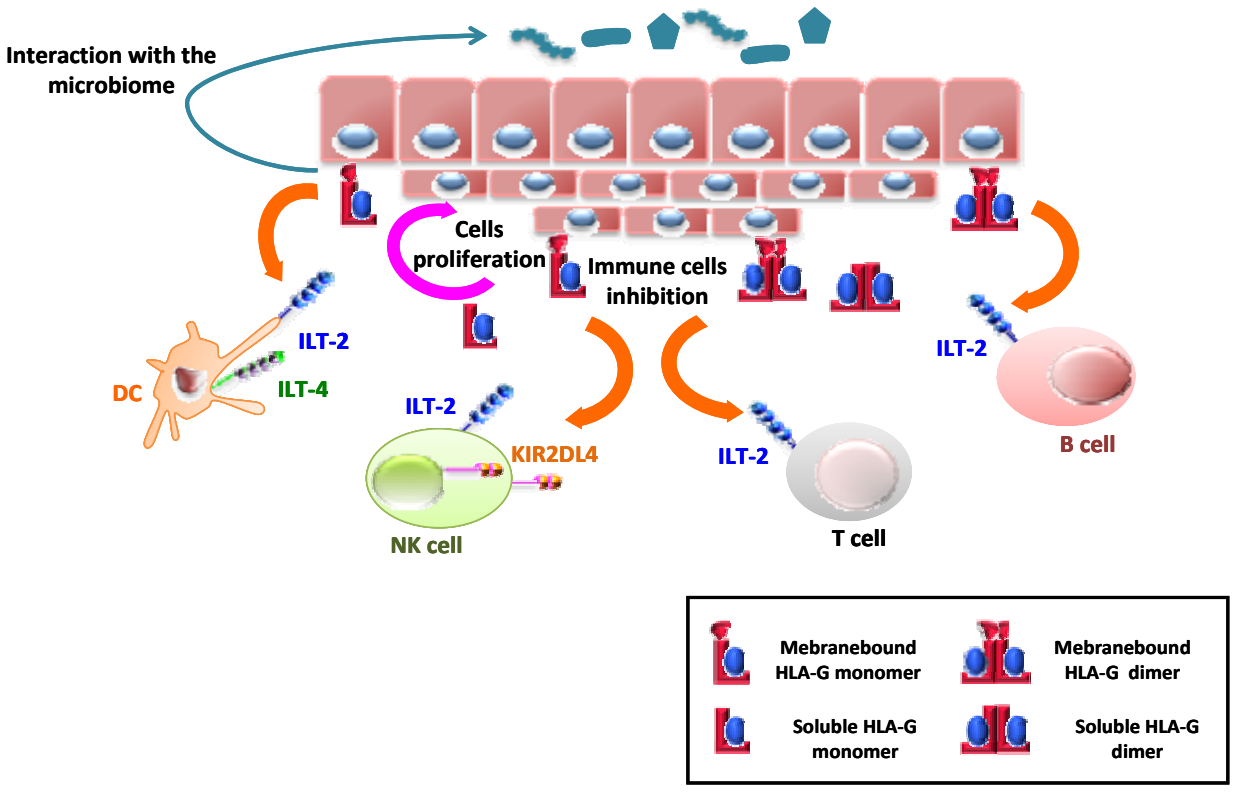


Figure 3. HLA-G in epithelia. This figure suggests the possible role of HLA-G expression by epithelia in modulating local immune response and the interaction with the microbiota as well as the differentiation of epithelial progenitor cells.

potent tolerogenic power and induces survival of the transplant. The tolerogenic role of the molecule HLA-G expressed naturally in patients was confirmed by purification of the HLA-G from the serum of transplanted patients having high levels of HLA-G [124]. Indeed, in *in vitro* tests, HLA-G molecules extracted from the serum were capable of inhibiting the alloproliferation of $CD4^+$ T lymphocytes. In addition, mononuclear cells from peripheral blood of transplanted patients with elevated levels of soluble HLA-G did not respond to allogeneic stimulation and possess a suppressive function. Besides demonstrating tolerance properties of HLA-G *in vitro* and *in vivo*, several studies indicate that when expressed by transplant patients, this molecule inhibits immune effectors thereby protecting the graft from rejection [9]. Particularly HLA-G soluble expression in transplanted patients as well as its expression by the graft itself has been correlated to a reduction in the risk of acute and/or chronic rejection (AR and CR) for cardiac, renal, hepatic and lung transplantations [79]. Indeed, myocardial, liver biliary [125], renal tubular [126] and HBEC epithelial cells express HLA-G [3], in cardiac, liver, renal and lung allografts, respectively. Recently, in lung transplant recipients, Brugière *et al.* showed that HLA-G expression in the bronchial epithelium was higher in stable recipients than in patients with AR [121]. More recently, the same group has shown a protective effect of HLA-G expression in the bronchial epithelium on chronic lung allograft dysfunction occurrence.

HLA-G alleles and 3'UTR polymorphism have been associated with clinical outcome in both renal and cardiac transplantation [127]. Moreover, two HLA-G UTR haplotypes, HLA-G*01:04 UTR3 and HLA-G*01:06 UTR2 have been respectively associated with an impaired survival, increased chronic lung allograft dysfunction occurrence and the production of *de novo* donor-specific antibodies in lung transplant recipients [128].

Expression of HLA-G was found in numerous cancers involving epithelia. The presence of HLA-G seems to be correlated with clinical parameters such as more advanced disease stage, tumor metastasis and/or with a worse prognosis in tumor patients. This suggests that HLA-G could promote tumor immune escape, invasiveness and metastasis results as a poor prognosis factor (see for review [129, 130]).

In particular, patients with HLA-G positive non-small-cell lung carcinoma (NSCLC) displayed a significantly shorter survival time than HLA-G negative patients (see for review [129, 131]). Moreover, the differential expression of HLA-G isoforms seems to be useful in the discrimination of different NSCLC subtypes as HLA-G5/G6 expression showed to be prevalent in adenocarcinoma compared squamous cell carcinoma [132]. The co-expression of both HLA-G and ILT-4 in NSCLC cells was significantly associated with regional lymph node involvement, advanced stages, and the reduction of overall survival in patients [133].

HLA-G overexpression has been observed in epithelial cancers involving the gastro-intestinal tract. *In specie,* HLA-G positivity of esophageal squamous cell carcinoma biopsies was associated with cancer progression and poor prognosis in patients [134-136]. In colorectal cancer HLA-G expression has been associated with poor host immune response, a higher depth of tumor invasion, lymph nodal metastasis and shorter survival time [137].

HLA-G overexpression has been associated with *Pseudomonas aeruginosa* infection in cystic fibrosis patient [138]. Moreover this bacterium appears to be able to enhance HLA-G expression *in vitro via* N-(3-oxododecanoyl)-l-homoserine lactone (3O-C12-HSL) [139]. This suggests a mechanism to create a protected niche for the bacterial reservoir in the lung of cystic fibrosis patient.

HLA-G is involved in some inflammatory or autoimmune disorders involving epithelia. HLA-G overexpression has been demonstrated in skin autoimmune diseases such as psoriasis. This local HLA-G up-regulation could be interpreted as tentative control of epithelial cells to prevent keratinocyte destruction by modulating the activity of cytotoxic lymphocytes and by promoting the development of Treg cells (see for review

[140]). In the bowel, HLA-G is differentially expressed in IECs of Crohn syndrome and ulcerative colitis (UC) patients [141]. Indeed, intestinal biopsies from these latter were the only ones showing HLA-G positive staining, whereas Crohn syndrome's IECs showed no HLA-G expression. It has been proposed that this difference might be linked to the IL-10 expression in UC. Thus it seems that, also in this case, HLA-G overexpression might reflect a failed attempt to stop the inflammatory response.

Bronchial epithelium is abnormal in asthma, with structural changes and thickening of the sub-epithelial layer [142], and its function is characterized by an exaggerated release of various cytokines as well as impaired inflammation resolution [143]. HLA-G differential expression has been observed in serum, plasma and BALF from asthmatics [144, 145]. In these studies, sHLA-G levels in asthmatics were higher than control. Moreover, HLA-G has been defined as an asthma-susceptibility gene by fine-mapping and positional candidate study [146]. Particularly, polymorphisms in the HLA-G regulatory regions were associated with asthma susceptibility [66, 147, 148]. Recently our team showed that HLA-G isoform transcripts were reduced in asthmatics HBEC compared to healthy controls. Hence, an impaired expression in asthmatics is in line with the hypothesis of an active participation of HBEC in asthma inflammatory context. The involvement of HBEC expressing HLA-G in both asthma and lung transplantation supports the hypothesis that this molecule might be involved in other lung inflammatory contexts. Moreover, the influence of a specific HLA-G genetic background should not be excluded, as we showed that in asthmatics HLA-G*01:04 and HLA-G*01:06 alleles were overrepresented.

4.3. Proliferation and differentiation of progenitors

The expression of soluble or membrane HLA-G has been associated with the inhibition and the modulation of cells' proliferation and differentiation. For instance, Deschaseaux *et al*. (2013) have demonstrated that HLA-G5 expression by MSCs differentiating in osteoblast strongly inhibits osteoclastogenesis. Indeed, HLA-G5 acting on the osteoclast through ILT-2 and ILT-4 interferes with receptor activator of nuclear factor kappa-B ligand (RANK) secretion, a crucial cytokine for the differentiation of these cells [17]. HLA-G proliferation inhibition has been also observed in endothelial progenitor cells. Indeed, an *in vitro* and *in vivo* study has shown that HLA-G5 through the action of CD160 receptor induces apoptosis of confluent and proliferating endothelial cells thereby inhibiting angiogenesis (se also section 2.5) [117]. HLA-G also seems to increase proliferation and differentiation properties in progenitor cells, as observed for hAEC differentiation into different epithelial cell types *in vitro* by a study [104]. Considering totipotency and the immune privileged status of hAEC, recent studies suggest the use of these cells in the regenerative strategies to treat different liver and lung diseases.

Recently, our team has been able to observe that during normal HBEC redifferentiation *in vitro*, using the ALI culture method (from Day 0 - undifferentiated epithelium- to Day 21 - fully redifferentiated epithelium-), undifferentiated epithelial cells had the highest HLA-G1/HLA-G4/HLA-G5 and HLA-G2/HLA-G6 expression levels [19]. Basal cells have been proposed as progenitors of HBEC [36, 38]. These cells might be good candidates for the source of HLA-G expression in bronchial epithelium because HLA-G has been proven to be expressed in other progenitor cells [15-18] and HLA-G mRNA is over expressed in fetal lung [149]. Hence HLA-G could be a possible biomarker of HBEC progenitor's activity. However, the epithelia cell subtype responsible for the expression of HLA-G in bronchial epithelium as in other epithelia such as intestinal epithelium, and epidermis has not been identified yet.

4.4. Modulation of HLA-G expression and function in epithelia

A new frontier in treating diseases affecting epithelia might pass through managing HLA-G expression. Different therapeutic approaches can be proposed. For instance HLA-G expression could be enhanced to limit immune response. Indeed immunosuppressive drugs, such as

betalacept, everolimus, tacrolimus or cyclosporine, were able to induce the expression of HLA-G and/or of ILT-2/-4 receptors as is the case with rapamycin [150-153]. Corticosteroids, such as hydrocortisone, dexamethasone and progesterone have also been shown to induce HLA-G expression *in vitro* [53, 154]. Although some aspects on the pharmacodynamic relationship between these molecules and HLA-G have not been highlighted yet, cortisteroids can be good candidates in the pathologic context where the overexpression of HLA-G might constitute an advantage in transplantation outcome in autoimmune/inflammatory diseases.

The use of therapeutic HLA-G recombinant proteins to exploit the immune tolerogenic potential of this molecule has also been proposed. In particular, Favier *et al*. demonstrated that recombinant HLA-G heavy chain fused to β2-microglobulin (B2M) proteins, specifically B2M-HLA-G5 dimer (α1-α2-α3), was able to delay allogeneic skin graft rejection in a murine *in vivo* transplantation model [155]. The immue-tolerogenic properties of B2M-HLA-G5 dimer have been recently confirmed in allogenic intestinal transplantation rat model [156].

Another study from the same team showed that HLA-G2/G6 (α1-α3) bead-coated injection was sufficient to significantly prolong graft survival in a skin graft murine model. Moreover, four-week treatments induced complete tolerance [157]. Even thought HLA-G recombinant proteins are not entered into clinical trials, these molecules are good candidates for tolerance induction in human transplantation.

HLA-G-expressing cells such as MSC are also suggested to manage immune tolerance. HLA-G expression is crucial to maintain MSCs' immune suppression. When this molecule is blocked, MSCs are unable to induce CD4+CD25+FoxP3+ expansion and to inhibit T cell alloproliferative and NK cytotoxic responses [101]. Immunosuppressive properties of MSCs are well known as these cells are able to express other immune tolerant factors such as TGF-β, prostaglandin E2 (PGE2), IL-10, hepatocyte growth factor (HGF), and indoleamine 2,3-dioxygenase (IDO) [158]. Interestingly, preclinical models of different pulmonary inflammatory diseases have shown promise for the use of MSCs [159]. In particular, MSCs have to exert an immunosuppressive activity in different *in vitro* and *in vivo* models of asthma, limiting both alveolar macrophage polarization as well as tissue remodeling [160-162].

In carcinomas, we have an opposite scenario as HLA-G expression provides tumor cells with an immune escape mechanism (see for review [129, 130]). Thus, HLA-G might constitute an attractive target for cancer immune therapy. Interestingly Zhang *et al*. (see for review [163]) have designed nanobubbles containing methotrexate coated with anti-HLA-G antibody [MEM-G/9] that successfully targeted and eliminated HLA-G-positive tumor cells both *in vitro* and *in vivo* (see for review [129, 163]). Promising approaches using HLA-G expression modulation have been tested in renal cell carcinoma. Accordingly, HLA-G expression downregulation through interfering RNA has been shown to increase NK cytolysis against renal cancer cells [164]. In another study, an HLA-G-derived recombinant peptide (HLA-G146-154), that bound to HLA-A24, has been employed to induce peptide-specific CTLs' cytotoxic activity against renal cell carcinoma cells expressing this specific HLA-A allele [165].

5. Concluding remarks

Epithelia are at the interface of the external environment actively interacting with microorganisms, which are composed by the symbiotic microbiota and/or by pathogens, antigens and chemicals. That's why epithelia are crucial in the regulation of mucosal immune cell responses, through different immune modulatory molecules. Physiologic expression of HLA-G has been recently detected in different epithelial cell types as well as its ectopic expression seems to be influenced by acute or chronic inflammatory states and malignancies. In addition, HLA-G has been recently implicated in the proliferation and redifferentiation of HBEC *in vitro* [19], in accordance with previous observation of other progenitor cells [15-18]. Together these findings suggest that HLA-G might be an attractive

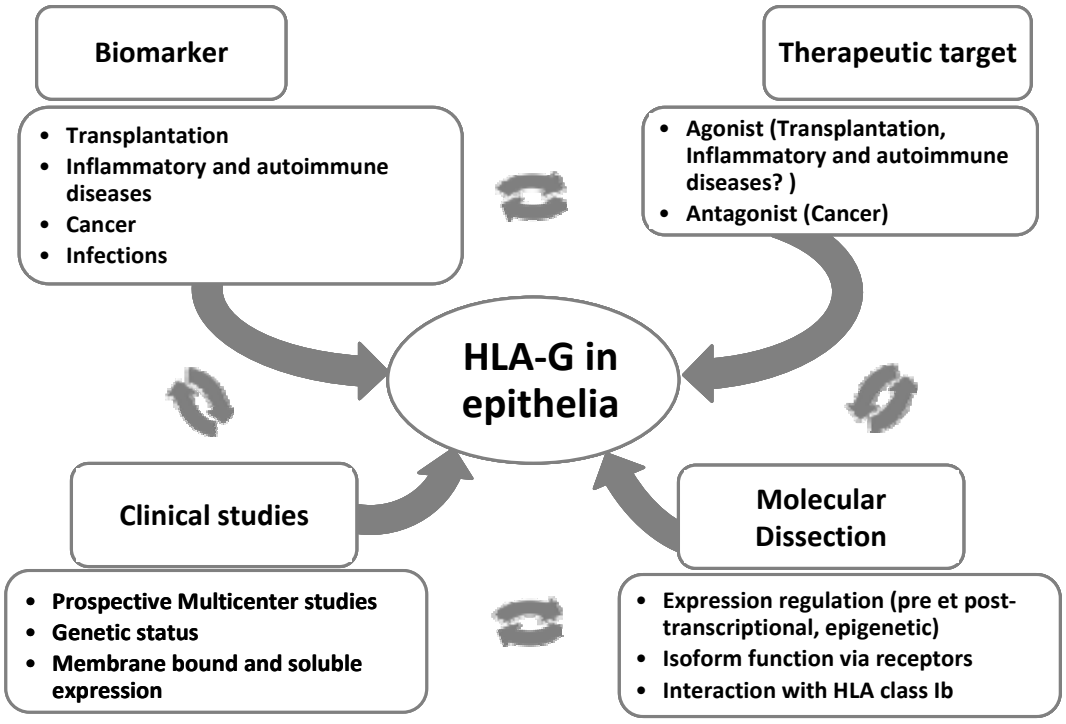


Figure 4. Further perspectives on HLA-G expression function in epithelia.

biomarker and a therapeutic target, *via* the modulation of its tolerogenic effect, in different clinical and immunological situations involving epithelia, such as solid organ transplantation, inflammatory and autoimmune diseases, carcinomas and infections (Figure 4). Further clinical and experimental studies are necessary to highlight the implication of HLA-G in the interaction between different epithelia and the immune system and its influences on the differentiation and proliferation of epithelial stem cells.

CONFLICT OF INTEREST STATEMENT

The authors have no competing conflict of interest.

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