

REVIEW

Human leucocyte antigen-G: expression and function in airway allergic disease

S. R. White

Department of Medicine, The University of Chicago, Chicago, IL, USA

Clinical and Experimental Allergy

Summary

Human leucocyte antigen-G (HLA-G) is a non-classical HLA class I molecule demonstrated originally in placental trophoblast cells. Recognition of the importance of HLA-G to the maternal immune accommodation of the semi-allogeneic fetus has led to investigations of its role in the suppression of immune responses and induction of tolerance. More recently, HLA-G has been shown to have increased expression in several immunological diseases including asthma and allergic rhinitis. The focus of this review is the potential role of HLA-G in immunological airway diseases.

Correspondence:

S. R. White, University of Chicago,
Section of Pulmonary and Critical
Care Medicine, 5841 S. Maryland Ave.,
MC 6076s, Chicago, IL 60637, USA.
E-mail: swhite@medicine.bsd.uchicago.edu

Introduction

Human leucocyte antigen-G (HLA-G) is a major histocompatibility complex class I antigen encoded by a gene on chromosome 6p21 with the other class I HLA genes, *HLA-A*, *-B*, *-C*, *-E* and *-F* [1]. Since its original description in the 1980s in choriocarcinoma cells and primary trophoblast cells in the placenta [2–4], considerable evidence supports a role for HLA-G in the suppression of immune responses, long-term immune escape or tolerance and modulation of inflammation. The purpose of this review was to present the current knowledge of HLA-G in inflammation, specifically in airways diseases such as asthma and allergic rhinitis.

Human leucocyte antigen-G structure, polymorphism and regulation

Human leucocyte antigen-G is a 'non-classical' HLA because of its limited polymorphism in the coding

region and a relatively restricted tissue distribution. While few polymorphic sites are observed in the coding region, both the promoter and the 3' untranslated region (UTR) of *HLA-G* are highly polymorphic [5, 6]. There are currently 46 alleles recognized between exon 1 and intron 6 [7]; many of these variation sites are either intronic or synonymous substitutions such that only 15 different proteins are recognized, and only five isoforms are observed with any frequency [8]. Four membrane-bound isoforms (G1–G4) and three soluble isoforms (G5–G7) exist due to alternative splicing, differential multimerization and differential association with β 2-microglobulin [17, 18] (Figure 1). Truncated isoforms are generated by excision of one or two exons encoding globular domains (G1–G4), whereas translation of either intron 4 or intron 2 yields soluble isoforms (G5–G7) that lack the transmembrane domain [8]. In addition, a soluble G1 isoform (shed G1 or shG1) is generated by proteolytic cleavage of the membrane-bound G1. Alternate splicing of the primary transcript is important not only because of the generation of both membrane-bound and soluble protein isoforms but also because it can be regulated, so that certain cells and

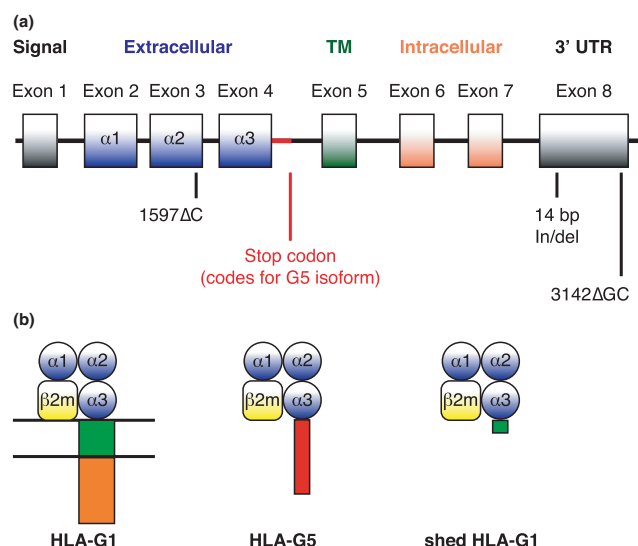


Fig. 1. Primary structure of *HLA-G* (a) and the major isoforms (b) found outside the placenta encoded by the gene. Alternate splicing permits a stop codon in intron 4 to be coded, leaving off the trans-membrane and intracellular domains in the soluble G5 vs. membrane-bound G1. The membrane-bound G1 can also be cleaved by metallo-proteinases near the transmembrane region and shed. Other alternative splicing generates isoforms with fewer alpha chains (not shown); these do not complex with $\beta 2$ -microglobulin and are not found outside the placenta. Both G1 and G5 can create homodimers with or without their association with $\beta 2$ -microglobulin. A 14 bp insertion/deletion polymorphism, and a SNP at +3142, in exon 8 both potentially regulate expression.

tissues express only a single isoform [8, 19]. Both G1 and G5 have an extracellular structure that is similar to other classic class I HLA antigens: a heavy chain of three globular domains that are linked non-covalently to $\beta 2$ -microglobulin. The other isoforms have a structure similar to class II HLAs due to truncation and do not bind $\beta 2$ -microglobulin. Both G1 and G5 can homodimerize, either in association with $\beta 2$ -microglobulin or as free heavy chains, and these dimers bind the LILRB1/2 (ILT-2/4) receptors for HLA-G (described below) with greater affinity compared with monomeric HLA-G [20, 21]. This suggests greater diversity in HLA-G, which is as yet not well understood.

Two isoforms, G1 and G5 (sHLA-G), have been found outside the placenta. While originally described as 'highly' restricted in its tissue expression, constitutive expression of G1 and/or G5 protein has been recognized in a number of tissues including thymic medulla, pancreatic islet cells, cornea, erythroid cell precursors (reviewed in [24]) and peripheral CD14⁺ mononuclear cells [25]. Induced expression is recognized in fetal immune tolerance [26–29], protection of cancer cells from immune surveillance [30–33], solid-organ transplantation [34–37] and inflammatory diseases such as psoriasis [38], ulcerative colitis [39, 40] and multiple sclerosis [41].

Significant variation has been identified in the 5' URR, and to date, 29 different SNPs have been identified in the *HLA-G* promoter region [6, 22, 42–44]. A number of these SNPs are located within or near regulatory elements in the promoter and thus may have a role in expression. Several sites in the 5' URR are in linkage disequilibrium with polymorphic sites in the 3' UTR [1, 13] and may influence alternative splicing [1]. At least three variations in the 3' UTR, a 14 bp insertion/deletion [9–14], a SNP substituting guanine at +3142 [13, 15, 16] and a SNP substituting adenine at +3187 [15] can lead to differences in expression [8, 16]. These regulatory regions suggest that *HLA-G* lineages may be related to differential expression profiles [45].

Distinct variations in expression of different alleles are also seen based on race and ethnicity [22]. The pattern of variation and unusual haplotype structure of the *HLA-G* promoter suggests long-standing balancing selection maintaining two highly divergent haplotype clades, defined by two promoter SNPs (–964 and –1306) that are in perfect linkage disequilibrium [22]. A single bp deletion of a C at nt 1597 in exon 3 results in a null allele that does not produce HLA-G protein; this null allele is common in Africans and African Americans, but rare in Europeans and European Americans [23]. The 14 bp insertion/deletion (in/del) polymorphism in exon 8 involves mRNA stability and expression [11–14], and the SNP at +3142 in exon 8 is located within a microRNA (miRNA) binding site that regulates expression [13, 16]. A recent study in Brazilians, one of the most heterogeneous populations in the world [46], demonstrates a promoter haplotype frequency distribution [45] that resembles that described in both African American and European American populations [22], and certain haplotypes found in European Americans [43] are not seen in the Brazilian population. Whether these differences are reflected in the function of HLA-G in asthma and allergic diseases in diverse populations remains unclear.

Mechanisms of action

Human leucocyte antigen-G complexes modulate the activation and effector function of key immune cells such as dendritic cells, macrophages, T lymphocytes and NK cells by binding to Immunoreceptor Tyrosine-based Inhibitory Motif (ITIM)-containing transmembrane receptors. HLA-G binds three different receptors: the inhibitory receptor Ig-like transcript (ILT)2/LILRB1/CD85j, expressed by human NK cells, monocytes, T cells, B cells and dendritic cells [47], the myeloid-cell specific ILT4/LILRB2/CD85d receptor [48] and the KIR2DL4/CD158d (KIR2DL4) receptor, which is found mainly in CD56⁺ subsets of NK cells [49, 50], particularly in the uterus [51]. Both receptors have four Ig-like

domains in the extracellular region, and in the N-terminal, two Ig-like domains are responsible for MHC class I molecule recognition [20]. While both ILT2 and ILT4 are inhibitory and bind HLA-G as well as other class I HLA antigens at high affinity [47, 48], KIR2DL4 can be either inhibitory or activating [52, 53] and binds only HLA-G [54]. ILT2 and ILT4 differ not only in distribution but also in the isoforms of HLA-G recognized: ILT2 binds HLA-G associated with β 2-microglobulin, whereas ILT4 recognizes HLA-G free heavy chains [20, 55], and HLA-G dimers have higher affinity than monomers for the ILTs [55, 56]. The receptor number, distribution and ligand specificity clearly point to the potential for HLA-G to exert multiple, discrete influences on the immune system.

Human leucocyte antigen-G generally serves to inhibit immune functions and does so by several mechanisms. Both membrane-bound G1, shed G1 and soluble G5 inhibit both uterine and peripheral NK cell activation [57, 58], CD8+ T cell mediated cytotoxicity [59], and CD4+ T cell alloproliferative responses [60]. Both G1 and G5 also can induce apoptosis of CD8+ T cells [61] and block the maturation and function of dendritic cells [62, 63]. HLA-G may also down-regulate alloproliferative responses and induce immune tolerance by promoting the expansion of CD4+ CD25+ FoxP3+ regulatory T (Treg) cells [47, 64]. Perhaps more important for long-term tolerance, HLA-G-bearing antigen-presenting cells not only inhibit CD4+ cell proliferation but also induce the differentiation of CD4+ cells into suppressor cells [65, 66]. This may explain its potential association with allograft success in solid-organ transplantation.

Beyond CD4+ CD25+ FoxP3+ Treg cells, inducible Treg cells can be identified in humans. These cells do not express FoxP3, but are characterized by secretion of either IL-10 (Tr1 cells) or TGF- β (Th3 cells). Tr1 cells are inducible, adaptive suppressor cells characterized by a cytokine production profile that includes IL-10 and TGF- β , but not IL-4 [67]. Both membrane and shed G1, and soluble G5, can induce a subclass of Tr1 cells that are phenotypically distinct from classic Tr1 cells: these are not anergic, do not secrete high amounts of IL-10 and do not suppress T-cell mediated responses via IL-10 [68, 69]. How these Tr1-like cells participate in inflammation and allo-immunity remains unclear.

A newer subset of Treg cells that are CD4+ but FoxP3- also express HLA-G [70]. In a lymphocyte suppression assay free of antigen-presenting cells, these regulatory cells elicit suppression of responder T cells that is independent of cell-cell contact, is reversible and is critically dependent on the secretion of IL-10. The role of these HLA-G+ Treg cells in inflammation and allo-immunity is yet to be explained.

More recently, novel mechanisms of action for HLA-G have been proposed. For example, sHLA-G can

impair expression and function of different chemokine receptors: in CD4+ lymphocytes, the presence of sHLA-G can down-regulate expression of CCR2, CXCR3 and CXCR5, whereas in CD8+ lymphocytes, sHLA-G can down-regulate expression of CXCR3 [71]. This down-regulation requires the engagement of sHLA-G with the ILT2 receptor; and in chemotaxis assays, sHLA-G presence inhibited CD4+ and CD8+ lymphocyte chemotaxis towards selected ligands. The down-regulation preferentially targets Th1 lymphocytes that express CXCR3 [72]; Th2 lymphocytes express CCR3, CCR4 and CCR8 [72] and were unaffected by the presence of sHLA-G. This is consistent with the hypothesis that HLA-G contributes to the maintenance of a Th2-polarized immune response that may in turn be important in asthma and allergic diseases [73].

Another novel mechanism of action for HLA-G is *trogocytosis*, representing 'fast, cell-to-cell contact dependent uptake of membranes and associated molecules' [74]. This phenomenon has been demonstrated in a variety of immune cells (reviewed in [75]) and represents a process by which HLA-G-containing membrane patches can be transferred from antigen-presenting cells or tumour cells to T- or NK- cells [76–78], particularly if the receiving cell has been activated [75]. This can create a temporary regulatory cell that can in turn inhibit other T- and NK- cell functions. Whether this occurs in the context of T-lymphocyte regulation of allergic inflammation in asthma or allergic rhinitis has not been demonstrated.

Human leucocyte antigen-G in asthma

Persistent airway inflammation, structural remodelling and bronchial hyperresponsiveness (BHR) in lower airways are hallmarks of chronic asthma [79, 80]. Asthma pathogenesis includes a loss of control in the influx of T lymphocytes and eosinophils into the airway [81, 82]. Allergen-driven activation of T helper 2 (Th2)-subclass CD4+ lymphocytes, consistently found in asthmatic airways [81–86], release cytokines such as IL-4, IL-5 and IL-13 that perpetuate inflammation via recruitment of other lymphocyte classes, eosinophils and mononuclear cells [81, 87, 88].

Current theories of asthma suggest that its development and chronicity may be due, in part, to an 'over-zealous' Th2-driven response with release of cytokines and chemokines in the airway mucosa [89, 90]. The dysregulated balance between Th1 and Th2 responses may actually begin *in utero* [91–93] and continue to develop in childhood as a loss of tolerance to inhaled allergens [90, 94]. In addition to Th2-associated cytokines, it is now appreciated that asthma is immunologically complex and may involve other types of T-cell responses, such as Th17, Th9 and the absence or

dysfunction of Treg cells [95]. These Th2 responses clearly involve a two-way communication between T lymphocytes and epithelial and dendritic cells in the airway mucosa, and fibroblasts and smooth muscle in the submucosa [88].

Genetic factors also clearly have a role in asthma pathogenesis. Heritability estimates suggest that between 35% and 80% of inter-individual variation in asthma susceptibility is due to genetic variation [96, 97], and over 100 genes have been implicated in asthma or atopy susceptibility [98]. One such gene may be *HLA-G*. Nicolae et al. [1] in 2005 demonstrated by fine-mapping and positional candidate studies that genetic polymorphisms in *HLA-G* confer susceptibility to airway hyperresponsiveness and asthma; thus, *HLA-G* is an asthma susceptibility gene. This same study also demonstrated that susceptibility varied depending on whether the mother had asthma or BHR. A G/G genotype at SNP -964G/A in the promoter region was associated with asthma in the offspring of mothers with either asthma or BHR, whereas the A/A genotype was associated with asthma in the offspring of asthma- and BHR-free mothers. In a follow-up study that examined subjects of European, African and Han Chinese ancestry, the -964G/A SNP tagged two major promoter haplotype clades with evidence of longstanding balancing selection [22].

A more recent study from the same group investigated another potential regulator of *HLA-G* expression, the +3142G/C SNP in the 3'UTR [16]. This SNP resides within a target site for three miRNAs; allele-specific targeting of these miRNA could potentially account in part for the association of *HLA-G* to asthma risk. For each of the miRNA examined, miR-148a, miR-148b and miR-152, the G/G genotype was associated with miRNA binding and reduction in *HLA-G* expression in the JEG3 choriocarcinoma cell line. Luciferase assays performed by transfecting plasmids with either the G or C allele at +3142 in the 3'UTR with each miRNA in turn into an airway epithelial cell line demonstrated that the presence of the G allele substantially decreased luciferase activity. This study also demonstrated that the +3142G/G genotype was protective against asthma among offspring of asthmatic mothers participating in the Childhood Origins of Asthma (COAST), a birth cohort study [99], whereas the same C allele was associated with risk in the offspring of mothers without asthma. While each of the miRNA genes are located in chromosome regions (miR148a: 7p15.2, miR148b: 12q13.13, miR152: 17a21.32) that have not been linked to asthma or to IgE to date [100, 101], variation in miRNA expression might contribute to asthma risk by interacting with *HLA-G*.

While *HLA-G* clearly is an asthma susceptibility gene, one question to be answered is how this and other identified asthma susceptibility genes influence human lung development. The 'developmental origins' hypoth-

esis [102] proposes that select *in utero* events at critical times in organogenesis and maturation may contribute to disease in later life. One group has recently examined the role of expression patterns in asthma susceptibility genes in the developing human lung in the pseudoglandular (7–16 weeks gestational age) and canalicular (17–26 weeks) stages of development [103]. Of the 96 asthma candidate genes examined, none were significantly over-expressed in the two stages of development, though several, including *HLA-G*, were differentially expressed with significant mean changes during the studied periods. Similar differential expression was noted for the mouse *H2-M3* gene analogue. This study suggests a functional role for *HLA-G* during human lung development, although further studies are required to demonstrate localization and interactions.

Nicolae et al. demonstrated the presence of one isoform of *HLA-G*, soluble G5, but not G1, G2 or G6, in the airway epithelium of two subjects, one without lung disease and one with asthma [1]. Localization was confirmed in a larger study from our group that examined both normal subjects and subjects with mild asthma. In this study, endobronchial biopsies were collected at a time of clinical stability in a cohort of subjects with carefully phenotyped, mild asthma. sHLA-G could be demonstrated in the epithelium using standard immunohistochemistry in both groups (Figure 2) with a trend towards more demonstrable *HLA-G* in the biopsies of the asthmatic subjects [104]. This study also examined the presence of sHLA-G in bronchoalveolar lavage (BAL) fluid obtained from non-asthmatic control subjects and subjects with mild, persistent asthma: sHLA-G was more abundant in the BAL fluid collected from the asthmatic subjects [104]. In this study, there was a trend towards greater expression in African American subjects with asthma compared with European Americans, but number of patients was too small to demonstrate significance.

In addition to the local presence in airways, sHLA-G may also be found in asthmatic subjects outside the lung. One study suggests that serum (circulating) sHLA-G is increased in atopic asthmatic children vs. both non-atopic, asthmatic and non-atopic, non-asthmatic children [105]. A more recent study from Wenzhou, China examined plasma sHLA-G and IL-10 levels in 72 children with atopic asthma vs. 76 non-atopic, normal controls. Circulating plasma sHLA-G was higher (median 179.3 U/ml, range 86.5–375.9 for asthmatics vs. 35.2 U/ml, range 10.9–169.0 for controls), and plasma IL-10 was lower (median 5.0 pg/ml, range 3.6–30.8 for asthmatics vs. 12.8 pg/ml, range 2.7–32.6 for controls), in the atopic, asthmatic children. The presence of the 14-bp insertion in the 3'-UTR had no impact on plasma sHLA-G levels in the atopic, asthmatic children [106]. Thus, circulating *HLA-G* may be important as a biomarker and could potentially modulate immune function

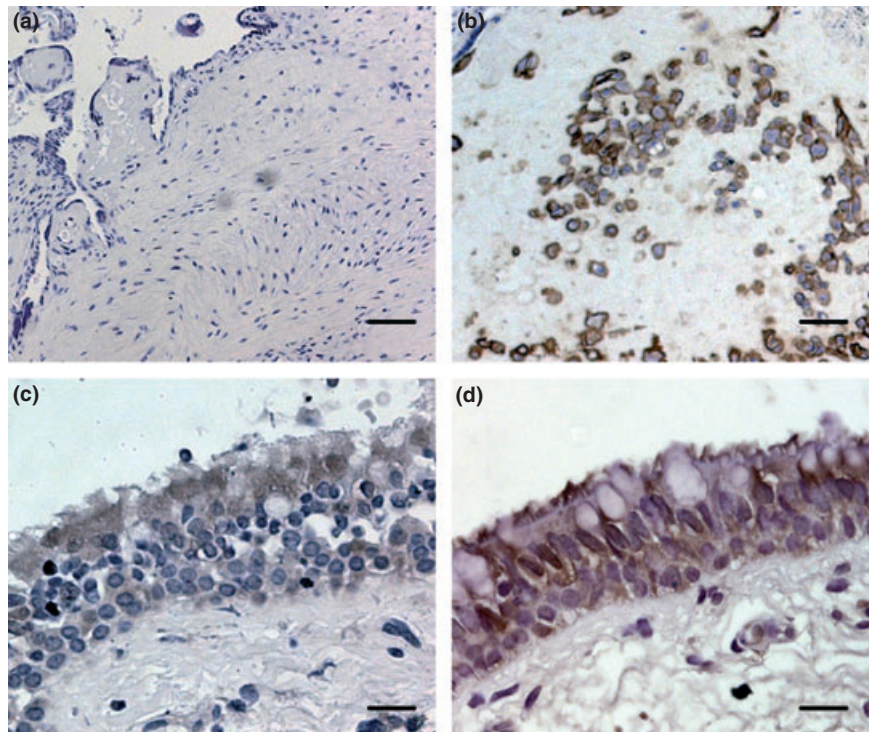


Fig. 2. Presence of HLA-G5, as demonstrated by immunohistochemical labelling, in the airway epithelium of endobronchial biopsies collected from a control (c) and an asthmatic (d) patient. The antibody 2A12, specific for binding to the soluble G5, was used; an isotype control (a) and a positive control of choriotrophoblast staining in placenta (b) are shown. Bar, 100 μ m for (a) and 25 μ m for (b–d). Images from subjects presented in reference 91.

more broadly, while the local abundance in airways may have a more direct relationship with immune modulation in the mucosa.

There is also *in vitro* evidence that the presence of HLA-G may differ in asthma: one study showed a greater release of HLA-G from peripheral blood monocytes *in vitro* from subjects with occupational asthma than that seen in monocytes from normal subjects [107]. However, another study showed impaired *in vitro* release of HLA-G, stimulated by the cytokine IL-10, from peripheral blood monocytes collected from allergic asthmatics compared with normal subjects [108]. The apparent conflict between these two studies has not yet been resolved: it may represent differences in experimental methods or in study populations, or it may suggest different biological roles in different disease contexts. A loss of HLA-G could be postulated to reduce immunosuppression and perpetuate inflammation in asthma, whereas increased HLA-G in asthma could be either compensatory, an attempt to reassert immunosuppression in the presence of a deficiency, or pathogenetic via methods not yet explored. Clearly, further studies are required to resolve this conflict.

Current understanding of the influence of sHLA-G on T-cell function and differentiation stems primarily from the finding that HLA-G is up-regulated during pregnancy: HLA-G may function to suppress the immune

response or divert it towards a more non-threatening Th2-type response [reviewed in [109]]. How sHLA-G might affect T-cell responses during the hyper-immunity of asthma is yet to be elucidated. Furthermore, while it is often asserted that sHLA-G plays a role in the alteration of the immune Th1/Th2 balance in pregnancy [110–114], a careful review of the literature does not find convincing evidence that demonstrates skewing towards a Th2 phenotype caused by HLA-G. In some studies, the 'index' Th2 cytokine marker evaluated was IL-10 [115], which is no longer accepted as a marker of Th2 responses. There are studies that demonstrate the induction of IL-10 producing Tr1 class regulatory cells when cultured with HLA-G [68], but these were not carried out in the cytokine environments found in asthmatic lungs and systemic allergic responses. Therefore, whether HLA-G modulates asthma and other allergic diseases by diverting the immune response towards a Th2 phenotype, or perhaps by altering the presence and function of one or more classes of T regulatory cells or by altering tolerance in a way not regulated by suppressor T cells, requires further investigation.

Taken together, these studies suggest that HLA-G is an asthma susceptibility gene and is present in airway epithelium. Importantly, local airway abundance of HLA-G in asthmatics is greater than in normal subjects [104], and circulating HLA-G is greater in atopic

asthmatics than in normal subjects [105]. What remains unclear is whether the presence of HLA-G is reactive; that is, an attempt to restore a proper balance in inflammatory cells and cascades that have been activated in chronic asthma, or is a part of the on-going pathogenesis of chronic asthma by its repression of selected classes of Treg and other immunologically active cells, or via a shift towards the Th2 phenotype. How this may be useful in the context of either diagnosis or treatment of chronic asthma remains unclear. While a difference linked to disease state now seems plausible, further work is needed to establish whether either circulating or local airway presence of HLA-G is a reliable marker of disease activity. Understanding whether HLA-G presence is contributory or reactive in chronic asthma will suggest whether antagonist or agonist agents, respectively, would be candidates in asthma therapy.

Human leucocyte antigen-G in allergic rhinitis

Allergic rhinitis is, like asthma, a disease of mucosal and submucosal inflammation orchestrated in part by Th2 cells [116]. Th2-associated cytokines such as IL-4, IL-5 and IL-13 promote IgE synthesis [117, 118] and accumulation of eosinophils in the nasal mucosa [118–120]. Peripheral blood mononuclear cells produce more IL-4 than IFN- γ , demonstrating a Th2 polarization [121], which may be controlled in part by Treg cells (reviewed in [122]). As HLA-G might have a role in asthma, a similar role could be postulated in allergic rhinitis.

One recent study demonstrated the increased abundance of circulating (plasma) soluble G5 in patients with allergic rhinitis and demonstrated pollen allergy compared with subjects with no atopy or history of rhinitis [123]. Subjects were studied outside of pollen season. Interestingly, levels of soluble class I antigens HLA-A, B and C were also increased in subjects with pollen-induced rhinitis, and there was moderate correlation between these levels and levels of circulating G5. The findings of this study were recently extended by the same group in subjects with perennial allergic rhinitis; again, increased circulating sHLA-G compared with control subjects could be demonstrated, and there was a strong correlation between circulating sHLA-G and both symptom severity, as assessed by the visual analogue scale and by the use of levocetirizine rescue medication [73]. In a 2009 study, the same group examined the use

of sublingual immunotherapy (SLIT) in a cohort of subjects with allergic rhinitis [124]. Forty patients with pollen allergy were treated with pre-seasonal SLIT for 3 months; both sHLA-G and soluble HLA-A, B and C were measured before and after therapy. For both sHLA-G and soluble HLA-A, B and C, circulating levels were decreased after SLIT therapy, and these decreases correlated with improvements in symptom severity, although circulating levels of IL-4 and interferon-gamma were not affected.

These studies suggest that HLA-G may be a modulating factor in allergic rhinitis, although as in asthma, the mechanisms by which it does so remain to be explored. That circulating sHLA-G may be modulated by treatment of the underlying disease suggests that this molecule may be a marker for effective therapy.

Conclusions

Human leucocyte antigen-G is an important tolerogenic factor at the maternal–fetal interface [24, 125]. It is clear that HLA-G has a complex regulatory role in transplantation, cancer cell immune surveillance and the pathogenesis of several important inflammatory diseases. *HLA-G* is linked to asthma, and there is both an increased abundance of sHLA-G in asthmatic airways and increased circulating sHLA-G in patients with asthma. Likewise, there is increased abundance of sHLA-G in patients with allergic rhinitis. Whether its influence is via changes in the expression or function of regulatory T cells or in the Th2 balance in airways remains unclear, yet answering this question would be fundamental to understanding its potential role in chronic asthma. A clear demonstration of the role of HLA-G in asthma and allergic rhinitis will not only permit a better understanding of inflammation in these diseases but also lead to a more general understanding of HLA-G in inflammation, and perhaps to its use as a diagnostic, prognostic and therapeutic tool.

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