Molecular Medicine

Human Leukocyte Antigen-G (HLA-G) Expression in Cancers: Roles in Immune Evasion, Metastasis and Target for Therapy

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Aberrant induction of human leukocyte antigen-G (HLA-G) expression has been observed in various malignancies and is strongly associated with tumor immune escape, metastasis and poor prognosis. To date, great achievements have been made in understanding the underlying mechanisms of HLA-G involved in tumor progression. HLA-G could lead to tumor evasion by inhibition of immune cell cytolysis, differentiation and proliferation and inhibition of cytokine production, induction of immune cell apoptosis, generation of regulatory cells and expansion of myeloid-derived suppressive cells and by impairment of chemotaxis. Moreover, HLA-G could arm tumor cells with a higher invasive and metastatic potential with the upregulation of tumor-promoting factor expression such as matrix metalloproteinases (MMPs), indicating that ectopic HLA-G expression could render multiple effects during the progression of malignancies. In this review, we summarized the mechanisms of HLA-G involved in promoting tumor cell immune escaping, metastasis and disease progression. Special attention will be paid to its significance as an attractive therapeutic target in cancers.
Online address: http://www.molmed.org
doi: 10.2119/molmed.2015.00083

INTRODUCTION

The pace of tumor growth is dictated by the continuous interaction between cancer cells and the host immune system. With the selection pressure exerted by immune system, various strategies have been developed and applied by tumor cells to avoid recognition and destruction by different immune effectors (1,2). One of the common strategies used by tumor cells to escape innate and adaptive immune response is associated with an induced aberrant expression of the nonclassical class I molecule human leukocyte antigen-G (HLA-G) (3).

HLA-G is the best characterized nonclassical HLA-class Ib molecules, which includes HLA-E, -F and -H (4). Due to its primary mRNA alternative splicing, seven HLA-G isoforms can be generated, where four of them are membrane-bound (HLA-G1 to -G4) and three soluble (HLA-G5 to -G7) (5). Moreover, another soluble isoform termed "shed HLA-G1" can be generated by proteolytic cleavage of the membrane-bound HLA-G1 by metalloproteinases (6).

HLA-G expression was first observed in cytotrophoblasts (7). In physiological conditions, HLA-G expression was also found in erythroid precursors, cornea, thymic medulla and pancreatic islets (8,9–11). However, HLA-G can be neo-expressed in pathological conditions including cancers, transplantation, and inflammatory and autoimmune diseases and viral infections (3,5,12,13).

In malignancies, ectopic induction of HLA-G expression has been observed in various types of tumors where it was more frequently observed in tumor lesions with advanced stage and its clinical relevance has been addressed (5,14). HLA-G can directly inhibit immune cell function through receptor binding and/or through trogocytosis and impairment of chemotaxis (15,16); moreover, HLA-G can render tumor cells with a higher invasive, metastatic potential and an unfavorable prognosis in tumor patients, indicating that HLA-G expression has multiple effects including promoting tumor cells to escape immune surveillance and enhancing their metastasis during the progression of malignancies (17–19). Therefore, the role of HLA-G in malignancies has gained considerable clinical interest for the possibility of exploiting it as a molecular biomarker and a therapeutic target.

MECHANISMS OF HLA-G INVOLVED IN TUMOR IMMUNOLOGY

HLA-G expression could render multiple effects during the progression of malignancies, such as inhibiting immune cell cytolysis, inducing immune cell apoptosis and the generation of regulatory cells through receptor binding and/or trogocytosis, and impairing chemotaxis of different immune effector

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Submitted April 9, 2015; Accepted for publication August 20, 2015; Published Online (www.molmed.org) August 24, 2015.

cells (14,16). Several types of HLA-G receptors including immunoglobulin-like transcript 2 (ILT2)/cluster of differentiation 85j (CD85j), ILT4/CD85d, killer cell immunoglobulin-like receptor 2DL4 (KIR2DL4)/CD158d, CD8 and CD160 have been reported. ILT2 is expressed on B cells, some T cells and NK cells and all monocytes and dendritic cells. ILT4 is expressed only by monocytes, dendritic cells and neutrophils. KIR2DL4 is expressed on natural killer (NK) cells, and CD160 expressed by cytotoxic $CD8^+$ T cells and NK cells, a small proportion of $CD4^+$ T cells, as well as endothelial cells. The CD8 is predominantly expressed on the surface of cytotoxic T cells, but can also be found on NK cells (5,20). Moreover, HLA-G could enhance the expression of tumor metastasis-related factors such as matrix metalloproteinases (MMPs), providing profound effects on tumor progression (18,21,22).

HLA-G-mediated inhibition of the functions of both innate and adaptive immune cells depends on cell types and the profiles of HLA-G receptors they expressed. By binding receptors expressed on various cells, HLA-G could directly inhibit the functions of NK cells, cytotoxic T-lymphocyte (CTLs), B cells, neutrophils and dendritic cells (DCs) (5). HLA-G also has long-lasting indirect immunoregulatory activities by inducing tolerogenic cells including HLA-G-expressing T regulatory (Treg) cells, $CD4^{low}$ and $CD8^{low}$ suppressor T cells, T regulatory type 1 (Tr1) cells, myeloid-derived suppressor cells (MDSC) and DC-10 (23–25). Moreover, other immunoinhibitory consequences, including impairment of chemotaxis induced by HLA-G, were also emphasized (26,27) (Figure 1).

The direct immunosuppression induced by HLA-G included inhibition of CTL and NK cell lysis, allogeneic $CD4^+$ T-cell proliferation and the induction of the activated $CD8^+$ T cells and $CD8^+$ NK cell apoptosis (28–31). HLA-G also affects DC maturation, migration, trafficking, antigen presentation and their cross-talk with T and NK cells, and inhibits Vγ9Vδ2 T-cell proliferation and IFN-γ production and

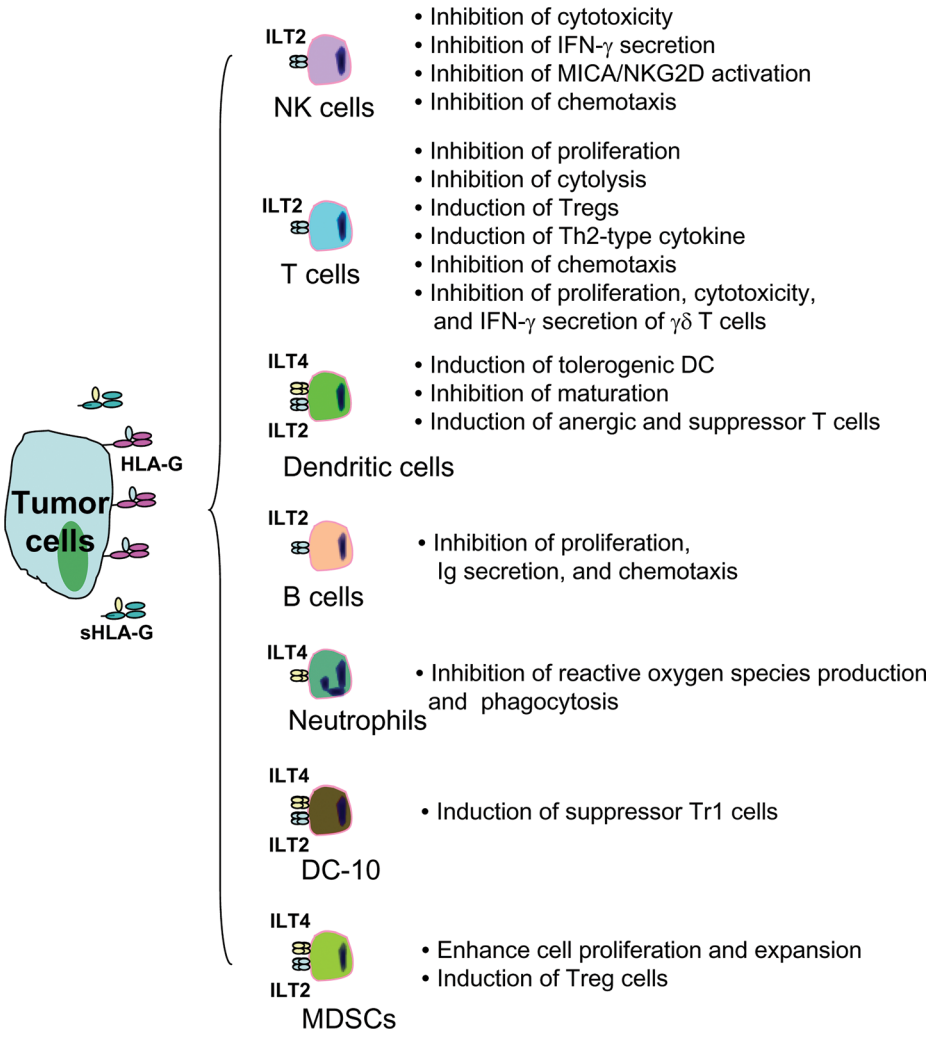

Figure 1. Tolerogenic functions of HLA-G through binding to receptors expressed on different types of immune cells. MICA, major histocompatibility complex class I–related chain A molecule; NKG2D, natural-killer group 2 member D.

cytotoxicity by interacting with the ILT2 inhibitory receptor (32–35). We recently reported that NK cell cytolysis inhibited by HLA-G1 in an expression proportion-dependent manner, and HLA-G1 and HLA-G5 isoforms have an additive inhibitory effect on NK cytolysis (36,37). Indeed, *in vitro* studies with cell lines of ovarian carcinoma, hepatocellular carcinoma, glioma, melanoma and renal cell carcinoma demonstrated that, upon expression of endogenous HLA-G antigens, tumor cells were protected from lysis by allore-active NK cells and lymphokine-activated killer cells and/or antigen-specific $CD8^+$ T cells, and that this protective effect could be reversed by masking HLA-G antigens using HLA-G or its receptor-specific antibody (18,38–40). It has been demonstrated that soluble HLA-G (sHLA-G) could inhibit B-cell proliferation, differentiation and immunoglobulin (Ig) secretion in both T-cell–dependent and –independent models of B-cell activation through the receptor ILT2 (41). To be noted, HLA-G5 was shown to inhibit phagocytosis and reactive oxygen species production of neutrophils through ILT4 (42).

Indirect inhibitory immune effects of HLA-G could induce the generation

of tolerant cells including Treg, DC and MDSC, or by the process of trogocytosis where activated NK cells, T cells and monocytes could also temporarily inhibit immune responses by acquiring HLA-G-containing membranes from cells in their vicinity (43,44). HLA-G-induced Treg cells were observed after allogeneic stimulation by HLA-G1-expressing antigen-presenting cells (APC), which could induce $CD4^+$ T cell anergy and differentiate into suppressive cells (45). Tolerogenic DCs could be generated through HLA-G1 tetramers or HLA-G5 dimers via ILT4-mediated IL-6 signaling pathway and STAT3 activation. Functionally, HLA-G-induced tolerogenic DCs could induce the generation of $CD4^+CD25^+CTLA\text{-}4^+$ (with CTLA being "cytotoxic T-lymphocyte-associated protein") and $CD8^+CD28^+$ regulatory T cells (20,46).

A novel subset of tolerogenic DCs (DC-10), which secrete high levels of IL-10, and express high levels of HLA-G and its receptors ILT2, ILT4 and ILT3, has a potent specific function to induce IL-10-producing adaptive Tr1 through the ILT4/HLA-G signaling pathway. Data showed that the high expression levels of ILT4, HLA-G and IL-10 are necessary for the tolerogenic activity of DC-10 and their ability to prime T cells to become Tr1 cells (47). Recent data showed that HLA-G-expressing DC-10 and $CD4^+$ T cells are highly represented in acute myeloid leukemia (AML) patients with HLA-G positive blasts (48).

MDSC are present in cancer patients and tumor-bearing mice and are, in part, responsible for the inhibition of the cell-mediated immune response against the tumor (49). It has been shown that infiltration of MDSCs in solid tumors is associated with poor prognosis as circulating MDSCs have a negative impact on survival and inversely correlate with the presence of functional antigen-specific T cells in patients with advanced melanoma (50,51). In ILT2-transgenic mice, HLA-G has been found to induce the emergence of $CD11b^+$ $Gr1^+$ MDSCs with an enhanced suppressive activity and is directly involved in the prolongation of allogeneic skin graft survival (52). In an immunocompetent HLA-$G1^+$ M8 (a human melanoma cell line) tumor-bearing mouse model, interaction between HLA-G and the murine receptor PIR-B could expand the population of $CD11b^+Gr1^+PIR\text{-}B^+$ MDSC, which could decrease NK cytotoxic activity (19). In another study, in a mouse model with murine mammary 4T1 cell line, HLA-G5 was observed to favor the $CD11b^+$ $Ly6G^+$ mice G-MDSC expansion *in vivo* (17).

Trogocytosis is a process of transferring cell-surface membrane proteins and membrane patches from one cell to another during contact. Relevance of trogocytosis is evidenced in tumor immunology such as HLA-G (53). HLA-G expressed by tumor cells can be acquired by activated cytotoxic NK cells and generates the HLA-G-positive NK cells, which behave as suppressor cells capable of protecting tumor cells from NK-mediated cytolysis (54). Similarly, resting or activated $CD4^+$, $CD8^+$ T and monocytes cells could acquire immunosuppressive HLA-G1 from tumor cells or APCs, which could immediately reverse their function from effectors to regulatory cells. Consequently, HLA-G-mediated immune evasion can be extended to HLA-G-negative tumor cells and further amplify HLA-G tolerogenic effect by trogocytosis (55). In multiple myeloma (MM) patients, HLA-G on malignant plasma cells was associated with a poor prognosis and HLA-G could be acquired by T cells from malignant plasma cells via trogocytosis (56).

Moreover, sHLA-G could impair expression and function of different chemokine receptors in T cells, NK cells and B cells through the receptor ILT2 (16). sHLA-G was observed to downregulate the expression of C-C motif chemokine receptor 2 (CCR2), C-X-C motif chemokine receptor 3 (CXCR3) and CXCR5 in $CD4^+$ and follicular helper T cells, CXCR3 in $CD8^+$ T cells, CXCR3 in Th1 clones, CXCR3 in T-cell receptor (TCR) Vδ2γ9 T cells, which was mediated by the interaction with ILT2. In addition, sHLA-G could inhibit chemotaxis of $CD4^+$ T cells toward CCL2, CCL8, C-X-C motif chemokine ligand 10 (CXCL10) and CXCL11, $CD8^+$ T cells toward CXCL10 and CXCL11, Th1 clones toward CXCL10, TCR Vδ2γ9 T cells toward CXCL10 and CXCL11 and follicular helper T cells toward CXCL13 (27). For NK cells, sHLA-G binding to ILT2 could also impair chemotaxis, cytokine and chemokine secretion in $CD56^{bright}$ and $CD56^{dim}$ NK cells in a dose-dependent manner. Morandi *et al*. (26) found that sHLA-G downmodulates expression of CXCR3, CX3CR1 and CCR2 and migration toward their specific ligands such as peripheral blood NK cells toward CXCL10, CXCL11 and CX3CL1 and CD56bright NK cells toward CCL2 and CXCL10. Also, HLA-G could downregulate CXCR4 and CXCR5 expression on germinal center B cells (41).

RELEVANCE OF HLA-G EXPRESSION IN CANCERS

The expression of HLA-G in cancer was first demonstrated in the context of melanoma (57). Since then, HLA-G expression in more than 2,000 malignant samples among thirty types of tumors including both solid and hematological malignancies has been studied, where HLA-G expression was observed in different sources such as on the cell surface, secreted or in tumor-derived exosomes (14,58). Among these studies, there is a high frequency of tumor cell-surface HLA-G expression with an absence in healthy tissue, and increased sHLA-G levels has been detected in various body fluids in a variety of cancers (14). Expression of HLA-G was found to be correlated with clinical parameters such as more advanced disease stage, tumor metastasis and/or with a worse prognosis in tumor patients, indicating that HLA-G could facilitate tumor immune escape, invasiveness and metastasis; thereby HLA-G expression was found to be associated with advanced clinical stage and disease progression and HLA-G expression was also documented as an unfavorable prognostic factor for many kinds of solid malignancies, including breast cancer (59–64), colorectal cancer (65,66), cervical cancer (67,68), endometrial

carcinoma (69,70), esophageal squamous cell carcinoma (71–74), gastric cancer (75–77), glioblastoma (78), hepatocellular carcinoma (79–81), lung cancer (82–84), nasopharyngeal carcinoma (85), oral cavity squamous cell carcinoma (86), ovarian cancer (87–89), pancreatic adenocarcinoma (90), thyroid carcinoma (91,92). These data were summarized in Table 1. Moreover, HLA-G expression was found to distinguish metastatic from nonmetastatic endometrial carcinoma (69). In our recent study, we found lesion HLA-G5/-G6 isoform expression could discriminate adenocarcinoma from squamous cell carcinoma in lung cancer patients, where tumor cell sHLA-G expression was predominately observed in adenocarcinoma lesions (84). These data indicated that lesion HLA-G or specific HLA-G isoform expression may serve as a clinical marker for tumor metastasis or types of histopathological discrimination.

Although HLA-G expression in solid tumors as mentioned above was associated with an unfavorable outcome or prognosis, no clear correlation was established between HLA-G expression and unfavorable clinical outcome in hematological malignancies, thus the clinical significance of HLA-G expression in liquid tumors remains controversial (93–99), as presented in Table 2.

The discrepancy in the clinical significance of HLA-G between solid and liquid tumors may be due to the nature of the tumor cells which, in malignant hematological diseases, are immune cells capable of expressing the HLA-G inhibitory receptor. In this context, studies by Naji *et al*. (41,100) revealed that, through interaction with ILT2, HLA-G could inhibit the proliferation, differentiation and antibody secretion of activated B cells originating from peripheral blood and secondary lymphoid organs, such as tonsils, and HLA-G could also inhibit the proliferation of ILT2-bearing neoplastic B cell lines such as human B cell lymphomas (Raji, Daudi and Ramos), multiple myelomas (OPM-2, LP1 and RPMI 8226), and B cell leukemia (BV173). These data imply that HLA-G could be correlated with a good prognosis by inhibiting the proliferation of ILT2-expressing tumor cells. Other factors may also account for these controversial results, including differences in expression and interaction of ILT2 and HLA-G by tumor cells, and effects of different chemotherapy status on HLA-G expression between the studies.

To be noted, regulation of HLA-G expression is controlled at the epigenetic, transcriptional and post-transcriptional level. The polymorphic variations in the 5′ upstream regulatory region (5′ URR) and 3′ untranslated regions (3′ UTR) in the *HLA-G* gene were reported to affect the *HLA-G* mRNA translation and HLA-G expression by microRNA binding and/or by modifying mRNA stability (101). In this context, a possible association of *HLA-G* gene polymorphism with susceptibility and/or clinical outcome of malignancies was documented. A 14-base pair insertion/deletion (ins/del) polymorphism (rs66554220) in the 3′ UTR was revealed; both chronic lymphocytic leukemia (CLL) and diffuse large B-cell lymphoma (DLBCL) patients with the del/del genotype had shorter survival than patients with the ins/del or ins/ins genotype (102,103). Additionally, DLBCL patients who carry the *HLA-G*-725CC genotype in the 5′ URR had a significantly higher probability of overall survival than individuals with other genotype combinations of *HLA-G*-725C/G/T (103). Furthermore, in the coding segment of the *HLA-G* gene, the codon 130C deletion occurrence was observed to be significantly associated with a decreased free disease and overall survival in nasopharyngeal carcinoma patients (104). However, more studies on the complete *HLA-G* gene and its linkage disequilibrium with other genes and on HLA-G expression at both the tumor site and plasma in a specific microenvironment are required to consolidate these findings.

ADVANCES OF TUMOR-BEARING ANIMAL MODELS FOR HLA-G STUDY

Recently, the development of animal models consolidated the concept that HLA-G$^+$ tumor cells can develop and tolerize the host antitumor immune response *in vivo*. Although there is no murine homologue of HLA-G, *in vivo* studies were made possible by the fact that human HLA-G can bind and mediate a signal via the murine receptor-paired immunoglobulin-like receptor (PIR)-B, the homologue of human ILTs (105). Previous data showed that human or murine tumor cells expressing HLA-G can grow in immunocompetent host mice and that blocking HLA-G function by a specific antibody inhibits the development of the tumor, where HLA-G could impair both innate and adaptive immunity resulting in an expansion of CD11b$^+$ Gr1$^+$ myeloid-derived suppressor cells, loss of peripheral T cells and a cytokine balance in favor of a Th2 profile versus Th1/Th17 (17,19).

Other than the tolerant functions of HLA-G in tumor immune escaping, HLA-G was also found in association with the status of tumor invasion and metastasis in patients and preclinical models with the mechanism of upregulating the expression of MMPs (18,106) (Figure 2). MMPs are one of the central mediators of the biology of tumor invasion and metastasis with their ability to degrade basement membrane and extracellular matrix components (107). Indeed, the relationship between HLA-G and MMP expression was addressed in previous studies. Hiden *et al*. (108) addressed that MMP-15 expression could be induced by TNF-α only in the HLA-G positive first trimester human trophoblast cell line ACH-3P, and only the HLA-G positive extravillous trophoblasts (EVT) have the invasive potential. Much higher MMP-14 expression was also found in HLA-G positive first-trimester invasive trophoblasts (109). Both tumor cells and EVT share similar characteristics in many regards, such as the capability

Table 1. Clinical relevance of HLA-G protein expression in tumor cells.[a]

Cancer types	Sample size	Methods[b] (Ab)	HLA-G expression	Main conclusions	Ref.
Breast cancer	39	IHC (4H84)	41%	HLA-G positive is associated with shorter disease-free survival.	(59)
	58	IHC (4H84)	70.7%	HLA-G expression was more frequently observed in advanced disease stage.	(60)
	235	IHC (HGY)	66%	HLA-G is positively correlated to tumor size, nodal status, and advanced disease stage. HLA-G is an independent prognosis factor.	(61)
	501	IHC (4H84)	60%	HLA-G expression is unrelated to relapse free period or overall survival in the whole cohort; however, among classical HLA class I negative patients, HLA-G expression is a prognostic factor.	(62)
	52	IHC (5A6G7)	59.6%	HLA-G is associated with immune response evasion and breast cancer aggressiveness.	(63)
	45	IHC (MEM-G/2)	62.2%	HLA-G expression is associated metastasis in lymph nodes and with shorter survival time.	(64)
Colorectal cancer	201	IHC (HGY)	64.6%	HLA-G is an independent prognosis factor.	(65)
	102	IHC (MEM-G/2)	70.6%	HLA-G expression has a significantly poorer overall survival than those without HLA-G expression.	(66)
Cervical cancer	58	IHC (5A6G7)	75.86%	HLA-G expression might be an early marker for assessing the progression of cervical lesion progression.	(67)
	143	IHC (4H84)	60%	HLA-G expression was associated with disease progression.	(68)
Endometrial carcinoma	44	IHC (4H84)	55%	HLA-G expression was associated with disease stages. HLA-G was found to be a valuable discriminator for metastatic disease.	(69)
	525	IHC (4H84)	39.8%	HLA-G expression is unrelated to worse disease specific survival.	(70)
Esophageal squamous cell carcinoma	121	IHC (HGY)	90.9%	HLA-G is an independent prognosis factor.	(71)
	79	IHC (4H84)	65.8%	HLA-G is an independent prognosis factor.	(72)
	60	IHC (MEM-G/1)	70%	HLA-G expression was correlated with cancer cell differentiation, lymph node metastasis.	(73)
	60	IHC (HGY)	75%	HLA-G expression was closely related to depth of invasion and clinical stage.	(74)
Gastric cancer	160	IHC (HGY)	71%	HLA-G is an independent prognosis factor.	(75)
	52	IHC (5A6G7)	31.%	HLA-G is an independent prognosis factor.	(76)
	179	IHC (4H84)	49.7%	HLA-G is an independent prognosis factor.	(77)
Glioblastoma	108	IHC (MEM-G/2)	60.2%	HLA-G-negative patients were alive longer than HLA-G positive patients.	(78)
Hepatocellular carcinoma	173	IHC (MEM-G/1)	low (43%); high (57%)	High expression HLA-G is independently associated with short survival and increased recurrence; HLA-G level is positively related to Tregs/$CD8^+$ ratio and their combination served as a better prognosticator.	(79)
	36	WB (MEM-G/1)	66.7%	HLA-G is an independent prognosis factor.	(80)
	219	IHC (4H84)	50.2%	HLA-G expression is strongly correlated to advanced disease stage.	(81)
Lung cancer	106	IHC (HGY)	75%	HLA-G is an independent prognosis factor.	(82)
	101	IHC (4H84)	41.6%	HLA-G expression is strongly correlated to advanced disease stage.	(83)
	131	IHC (5A6G7)	34%	HLA-G was predominately expressed in lung adenocarcinoma, which could be a useful biomarker to discriminate adenocarcinoma from squamous cell carcinoma in NSCLC patients.	(84)

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Table 1. ***Continued.***

Nasopharyngeal carcinoma	552	IHC (4H84)	79.2%	HLA-G is an independent unfavorable prognosis factor. High HLA-G expression was positively correlated with tumor classification and recurrence or metastasis.	(85)
Oral cavity squamous cell carcinoma (OCSCC)	60	IHC (MEM-G/2)	metastatic (72%); nonmetastatic (28%)	HLA-G expression was significantly higher in metastatic compared with nonmetastatic OCSCC. Patients with lower HLA-G expression exhibited a longer survival than those with higher HLA-G expression.	(86)
Ovarian cancer	40	IHC (4H84)	low (55%); moderate (20%); strong (25%)	Patients with HLA-G expression >17% shows poor survival.	(87)
	169	IHC (4H84)	47.9%	HLA-G expression is correlated with residual disease after surgery.	(88)
	34	IHC (MEM-G/2)	35%	HLA-G is selectively expressed in advanced-stage with high-grade histology.	(89)
Pancreatic adenocarcinoma	122	IHC (Rabbit polyclonal Ab)	low (36.1%); high (63.9%)	HLA-G is an independent prognosis factor. High level of HLA-G significantly correlated with more advanced stage extrapancreatic infiltration, lymph node involvement and poor differentiation.	(90)
Thyroid carcinoma	138	IHC (5A6G7)	90.6%	Gradual increase of HLA-G expression from hyperplasia areas to carcinoma areas and poor prognosis	(91)
	70	IHC (MEM-G/2)	44.3%	HLA-G expression was significantly associated with an increased occurrence of lymph node metastasis and capsular invasion.	(92)

Ab, antibody; IHC, immunohistochemistry; WB, Western blot.
[a]Corresponding normal tissue is absent of HLA-G expression.
[b]4H84, MEM-G/1, MEM-G/2, HGY, Rabbit polyclonal Ab, detecting denatured HLA-G heavy chain of all HLA-G(HLA-G1 to HLA-G7) isoforms; 5A6G7, detecting denatured heavy chain of HLA-G5/HLA-G6 isoforms.

Table 2. Clinical relevance of HLA-G protein expression in hematological malignancies.

Cancer types	Sample size	Methods[a] (Ab)	Range of HLA-G expression	Main conclusions	Ref.
ALL	25	RT-PCR	ALL (1.35 ± 0.54); control (0.082 ± 0.04)	HLA-G expression showed a significant positive correlation with lactate dehydrogenase, peripheral blood and bone marrow blast cells, and with IL-10 and INF-γ production.	(93)
AML	77	FCM (MEM-G/9)	AML, 0~93.96%; controls, 0%~0.5%	HLA-G is irrelevant to prognosis.	(94)
B-CLL	30	FCM (MEM-G/9)	34%~62%	HLA-G expression correlates with prognostic markers of a B-CLL outcome, mainly Binet clinical staging and CD38 expression.	(95)
	47	FCM (MEM-G/9)	1.0%~4%.	HLA-G is an independent prognosis factor with the cutoff of 23%.	(96)
	20	FCM (MEM-G/9)	1.0%~34%	HLA-G is an independent prognosis factor with the cutoff of 12%.	(97)
	169	FCM (MEM-G/9)	B-CLL, 0~14.5%; controls, 0.2%~0.4%	HLA-G is irrelevant to prognosis.	(98)
	20	FCM (MEM-G/9)	0.3%~60.3%	HLA-G is irrelevant to prognosis.	(99)

Ab, antibody; ALL, acute lymphoblastic leukemia; RT-PCR, reverse-transcription PCR; AML, acute myeloid leukemia; B-cell chronic lymphocytic leukemia (B-CLL); FCM, flow cytometry.
[a]MEM-G/9, detecting native form of human HLA-G1 on cell surface as well as with soluble HLA-G5 isoform in its beta2-microglobulin associated form.

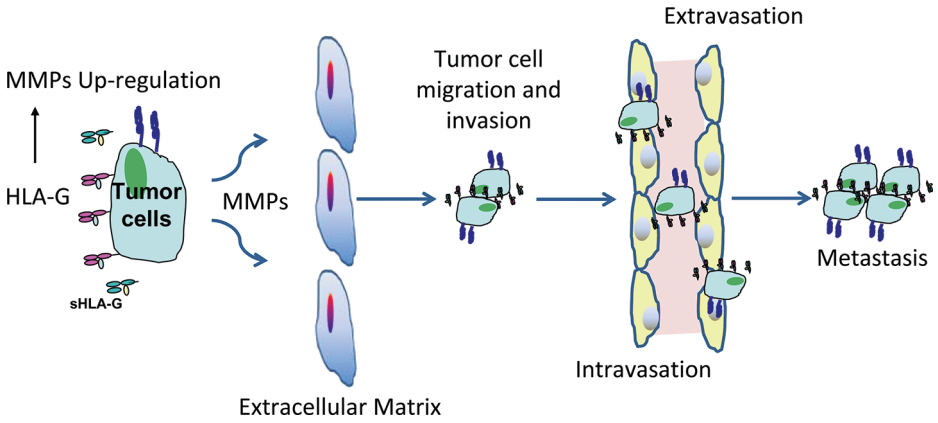

Figure 2. HLA-G promoting tumor cell invasion and metastasis by upregulation of MMPs expression.

of proliferation, invasion, vasculogenic mimicry, angiogenesis and systemic immune modulation (110). Therefore, similar tactics may be involved in invasion and metastasis of tumor cells.

Using a Balb/c nu/nu model, we reported that with exogenous HLA-G expression the ovarian cancer cell HO-8910 has a higher invasion and metastasis potential and the host is much less likely to survive, suggesting for the first time that HLA-G expression is associated with tumor metastasis and with poor survival in an animal model *in vivo* (18). Characterization of the mechanisms by which HLA-G is involved in tumor cell invasion and metastasis shows that upregulated MMP-15 expression was in accordance with HLA-G expression and a strong correlation was also observed between HLA-G and MMP-15 expression in a cohort of ovarian cancer lesions. Furthermore, knockdown of the HLA-G-induced MMP-15 expression significantly decreased cell migration and tumor metastasis (18). In accordance with our findings, HLA-G5 was documented to stimulate primary trophoblasts and trophoblastic cell line (JAR and JEG-3) invasion and to increase MMP-2 transcripts and their activity by binding to KIR2DL4 and ILT2 (22). In another study, suppression of HLA-G expression in JEG-3 cells was observed to decrease the MMP-2 and MMP-9 mRNA and protein expression dramatically (21).

IMPLICATIONS FOR HLA-G-BASED STRATEGIES IN CANCER IMMUNOTHERAPY

Since HLA-G is frequently and specifically expressed on tumor cells, and its expression is associated with unfavorable prognosis in various malignancies, HLA-G is an attractive target for cancer therapies (15,111).

Taking the journey of HLA-G-expressing malignant cells and targeting HLA-G-expressing cancer cells with a delivery system based on nanoparticles carrying anticancer drugs to the tumor site would be also important in maximizing the efficacy of anticancer therapies. In this context, Zhang *et al*. (112) successfully developed mAb HLA-G and methotrexate (MTX)-loaded nanobubbles (mAb_{HLA-G}/MTX/PLGA NBs [with PLGA being "poly(lactic-co-glycolic acid)"]) as an HLA-G-targeted drug carrier. Data showed that the nanobubbles could efficiently target HLA-G-positive tumor tissues both *in vitro* and *in vivo*, and that the released MTX from mAb_{HLA-G}/MTX/PLGA NBs could remove the residual cancer cells and inhibit the reoccurrence of tumors. Moreover, given the immune inhibitory properties of the HLA-G molecule, it would be important to suppress its expression in tumor cells. Previous studies showed that suppression or downregulation of HLA-G by interfering RNA was found to increase NK cell cytolysis against targets, that antibodies blocking HLA-G or its receptors ILT2 and/or ILT4 could restore the functions of T cells and NK cells, and that the HLA-G-derived peptide HLA-G146-154 could effectively induce peptide-specific CTLs cytotoxic activity against HLA-G-expressing HLA-A24$^+$ renal cell carcinoma cells (15,113,114).

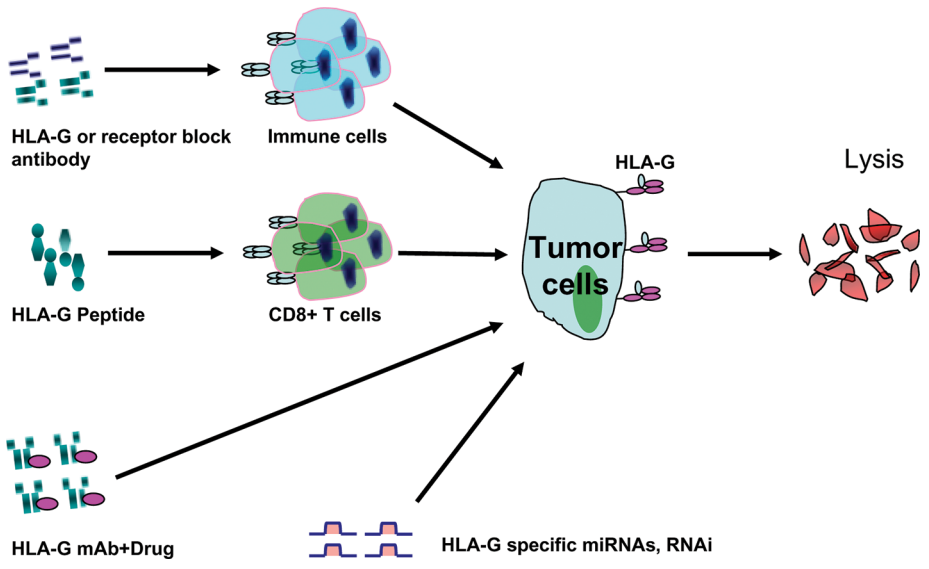

Figure 3. Schematic representation of HLA-G-based cancer immunotherapy strategies.

CONCLUSION

On the basis of the above observations, an HLA-G-based immunotherapy can be achieved by employing HLA-G or HLA-G receptor antibodies to block HLA-G expression or interaction between its receptors, by RNA interfering to down-regulate the HLA-G expression levels, or by using HLA-G-derived immunogenic peptide and anti-idiotype antibodies to stimulate immune cell function. Thus, HLA-G-targeted strategies in malignancies could be attractive in the future for the development of nanomedicine and noninvasive medicine for simultaneously targeted imaging, drug delivery and therapy in cancers (Figure 3). Nevertheless, in hematological tumors, HLA-G could inhibit the proliferation of B-cell malignancies, and, therefore, exogenously produced HLA-G or HLA-G-derived polypeptides can be considered as therapeutic agents for leukemia therapy.

ACKNOWLEDGMENTS

This work was supported by grants from the National Natural Science Foundation of China (31170879, 31370920, 81372247), the Natural Science Foundation of Zhejiang Province (LR13H160001) and the Zhejiang Provincial program for the cultivation of high-level innovative health talents.

DISCLOSURE

The authors declare that they have no competing interests as defined by *Molecular Medicine*, or other interests that might be perceived to influence the results and discussion reported in this paper.

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Cite this article as: Lin A, Yan W-H. (2015) Human leukocyte antigen-G (HLA-G) expression in cancers: roles in immune evasion, metastasis and target for therapy. *Mol. Med*. 21:782–91.