Prognostic Value of HLA-G in Malignant Liver and Pancreas Lesions

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ABSTRACT

Background: Human leukocyte antigen (HLA)-G is a nonclassical HLA class I molecule with modulatory effects on NK and T cells. Because HLA-G expression is frequently detected in different solid tumors, it may be involved in tumor immune evasion. **Objective:** This study was designed to elucidate the prognostic value of HLA-G in hepatocellular carcinoma (HCC) and pancreatic adenocarcinoma (PADC). The influence of hepatitis B virus (HBV) infection on HLA-G expression was also evaluated in patients with HCC. **Methods:** HLA-G expression was investigated in tumor tissues from patients with HCC (n=74) or PADC (n=42) with immunohistochemical techniques. The presence of HBV genome was also examined in HCC tumor tissues by PCR. **Results:** HLA-G expression was detected in 66% of PADC and in 31% of HCC samples. In contrast to HCC, HLA-G overexpression was associated with advanced stages and grades in PADC. HBV genome was detected in 31% of HCC samples but we found no correlation between HLA-G expression and the presence of HBV genome in these tumors. **Conclusion:** Our findings showed that HLA-G overexpression in tumor tissue correlated with poor prognosis in PADC. HLA-G expression is apparently affected by the patient's genetic background and other epigenetic factors rather than by HBV infection.

Shahraki PK, et al. Iran J Immunol. 2018; 15(1):28-37.

Keywords: Human Leukocyte Antigen-G, Hepatocellular Carcinoma, Hepatitis B Virus, Pancreatic Adenocarcinoma

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INTRODUCTION

Cancer cells use various mechanisms to escape immune surveillance. Upregulation of human leukocyte antigen (HLA)-G by tumors is one of these evasion mechanisms. HLA-G is a nonclassical MHC-I molecule encoded by a gene located on chromosome 6p21 (1). This molecule interacts with multiple receptors such as immunoglobulin-like transcript (ILT)2, ILT4 and killer-cell immunoglobulin-like receptor (KIR)2DL4 expressed on different immune cells such as NK cells, T cells, dendritic cells and monocytes/macrophages (1). Tumoral expression of HLA-G was first shown in melanoma in 1998 (2). Since then, HLA-G expression has been detected frequently in different solid tumors. Numerous recent studies have investigated the clinical relevance of HLA-G expression in different cancers, such as esophageal squamous cell carcinoma, gastric cancer and colorectal cancer (3-5). In general, high HLA-G expression has been found to correlate with lower survival rates (3-5). Moreover, this molecule was suggested as a potential biomarker for cancer prognosis and diagnosis (5,6) and chemotherapy susceptibility (7). Because of its inhibitory effects on NK and T cell responses (8), HLA-G-targeted immunotherapy in combination with other therapeutic approaches might enhance the efficacy of cancer treatment (9). Gastrointestinal malignancies as the most common cancer, often have a high mortality rate in both sexes. These cancers may involve different parts of the digestive tract like esophagus, stomach, small intestine, large intestine, rectum and anus as well as accessory organs of digestion such as tongue, salivary glands, pancreas, liver and gallbladder (10). Although liver and pancreas cancers have a relatively low incidence and are generally not ranked among the ten most prevalent cancers, they are among the ten types of cancer with the highest mortality rates (11). Despite the fact that the mortality rates of most fatal cancers are being controlled and are in decline, studies have shown that the incidence of these cancers is growing (10). Hepatocellular carcinoma (HCC) and pancreatic ductal adenocarcinoma (PADC) are the most common types of liver and pancreas malignancies (11,12). One of the viral strategies for immune evasion is changes in classical and nonclassical HLA-I expression in infected cells. Upregulation of HLA-G was detected in infected cells by human immunodeficiency virus, cytomegalovirus, herpes simplex virus and rabies virus (14). On the other hand, chronic infection by HBV is the most important risk factors for HCC (15). Therefor HLA-G expression might give us a clue to better understanding of hepatitis B virus (HBV) behavior in susceptibility to HCC.

In this study we evaluated the prognostic significance of HLA-G expression in malignant liver and pancreas lesions. We also investigated the relationship between the concomitant presence of HBVgenome and HLA-G overexpression in liver cancer.

MATERIALS AND METHODS

Patients. In this retrospective study, formalin-fixed paraffin-embedded (FFPE) tumor samples were collected from 74 patients with HCC and 42 patients with PADC diagnosed between 2012 and 2016 at Namazi Hospital affiliated with Shiraz University of Medical Sciences, Iran. None of them had received any preoperative chemotherapy or radiotherapy. All of these patients had provided written informed consent before their operation to permit the use of their samples in future research works. The protocol of

this study was approved by the ethics committee of our university (Decision Number: 955152, Decision Date: 25.09.2015). Demographic information for each patient and their pathology reports were collected from their medical files. All tumors were graded according to current pathology standards. Tumor stages were determined according to the American Joint Committee on Cancer (AJCC) staging system (13).

HLA-G Detection in Tumor Tissues. Tissue sections were deparaffinized in xylene and endogenous peroxidase was inactivated with 3% H_2O_2 in methanol for 20 min. For antigen retrieval, sections were placed in Tris-EDTA buffer, pH 9 and heated in a pressure cooker for 6 min. Nonspecific binding was blocked with 1% goat serum for 25 min. Anti-HLA-G mAb, 4H84, (Exbio, Prague, Czech Republic) 1:250 in PBS was added to each section and incubated for 2 h at room temperature. Immunostained sites were visualized with horseradish peroxidase (HRP)-conjugated secondary antibody (Dako, Glostrup, Denmark) and its corresponding substrate. Finally, the tissue sections were counterstained with hematoxylin and mounted. HLA-G-stained sections were scored in a blind manner by two local pathologists based on a previously reported scoring system in HCC (14). HLA-G expression was scored as negative (<1%), 1-25%, 26-50%, 51-75% and >75%, irrespective of staining intensity. First-trimester normal trophoblast sections were used as a positive control for HLA-G expression and adjacent normal tissue to neighboring tumor tissue was considered as negative control. The former samples were donated voluntarily for research purposes to the pathology laboratory of Zeynabieh Hospital, affiliated with our university, Shiraz, Iran, by women who underwent elective abortions.

Evaluation of HBV Genome in Liver Tumor Tissues. Four liver sections were deparaffinized twice with 1 ml xylene. Tissues were then rehydrated through graded ethanol (100% and 80%) and air dried. Total DNA was extracted with a QIAamp DNA mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol. The presence of HBV DNA in these samples was then evaluated with a commercial HBV PCR detection kit (Cinagen, Tehran, Iran) according to the manufacturer's instructions. To detect the presence of amplicons, 10 µl of PCR product was loaded on 1.5% agarose gels.

Statistical Analysis. The association between HLA-G expression in tumor tissues and each of the clinicopathological parameters was examined by chi-square test. Fisher's exact test was used when more than 20% of cells in a contingency table had an expected value less than five. Statistical analyses were done using SPSS 19 and $P \leq 0.05$ was considered statistically significant.

RESULTS

HLA-G Expression in Tumor Tissues.

The patients' characteristics are shown in Table 1. Since that inhibition effect of HLA-G can only be induced after the interaction of membrane form of HLA-G molecules with their ligands on immune cells and the intensity of staining varied in not only in our different samples but also even in different parts of the same section; therefore, we reported our data as the percentage of positive cells with membrane HLA-G expression (Figure 1). HLA-G expression was detected in 66% of PADC and in 31% of HCC samples. The association of HLA-G expression with clinicopathological parameters for PADC and HCC is summarized in Tables 2 and 3.

Table 1. Characteristics of patients with pancreatic adenocarcinoma (PADC) and hepatocellular carcinoma (HCC).

Variables		PADC (n=74) No. (%)	HCC (n=42) No. (%)
Age	Mean	56.86 ± 11.54	45.24 ± 11.47
	Median	57.50	52.00
	Range	33-82	3-72
Gender	Male	20 (47.6%)	56 (75.7%)
	Female	22 (52.4%)	18 (24.3%)
Grade	Well	33 (78.6%)	56 (75.7%)
	Moderate	7 (16.7%)	14 (18.9%)
	Poor	2 (4.8%)	4 (5.4%)
Stage	I	15 (35.7%)	45 (60.8%)
	II	25 (59.5%)	20 (27.0%)
	III	2 (4.8%)	7 (9.5%)
	IV	0 (0.0%)	2 (2.7%)

Table 2. Association of HLA-G expression in pancreatic adenocarcinoma (PADC) and hepatocellular carcinoma (HCC) with cancer stage.

Tumor			HLA-G expression in tumor cells					P-value
			Negative	1-25%	25-50%	50-75%	>75%	
PADC	Stage I	Count	7	5	2	0	1	0.038*
		% within stage stratum	46.7%	33.3%	13.3%	0.0%	6.7%	
	Stage II	Count	7	5	3	2	8	
		% within stage stratum	28.0%	20.0%	12.0%	8.0%	32.0%	
	Stage III	Count	0	0	0	2	0	
		% within stage stratum	0.0%	0.0%	0.0%	100.0%	0.0%	
HCC	Stage I	Count	31	8	2	1	3	0.616
		% within stage stratum	68.9%	17.8%	4.4%	2.2%	6.7%	
	Stage II	Count	14	4	0	1	1	
		% within stage stratum	70.0%	20.0%	0.0%	5.0%	5.0%	
	Stage III	Count	5	1	0	1	0	
		% within stage stratum	71.4%	14.3%	0.0%	14.3%	0.0%	
	Stage IV	Count	1	0	0	1	0	
		% within stage stratum	50.0%	0.0%	0.0%	50.0%	0.0%	

Table 3. Association of HLA-G expression in pancreatic adenocarcinoma (PADC) and hepatocellular carcinoma (HCC) with cancer grade.

Tumor			HLA-G expression in tumor cells					P-value
			Negative	1-25%	25-50%	50-75%	>75%	
PADC	Well	Count	12	10	1	4	6	0.007*
		% within grade stratum	36.4%	30.3%	3.0%	12.1%	18.2%	
	Moderate	Count	2	0	2	0	3	
		% within grade stratum	28.6%	0.0%	28.6%	0.0%	42.9%	
	Poor	Count	0	0	2	0	0	
		% within grade stratum	0.0%	0.0%	100.0%	0.0%	0.0%	
HCC	Well	Count	36	11	2	3	4	0.653
		% within grade stratum	64.3%	19.6%	3.6%	5.4%	7.1%	
	Moderate	Count	12	2	0	0	0	
		% within grade stratum	85.7%	14.3%	0.0%	0.0%	0.0%	
	Poor	Count	3	0	0	1	0	
		% within grade stratum	75.0%	0.0%	0.0%	25.0%	0.0%	

Table 4. Association between tumor stage and HLA-G expression with different cut-off scores in patient with pancreatic adenocarcinoma.

Stage	HLA-G		P-value
	Negative	**Positive**	
I	7 (46.7%)	8 (53.3%)	0.378
II	7 (28.0%)	18 (72.0%)	
III	0 (0.0%)	2 (100.0%)	
	<25%	**≥25%**	
I	12 (80.0%)	3 (20.0%)	0.020*
II	12 (48.0%)	13 (52.0%)	
III	0 (0.0%)	2 (100.0%)	
	<50%	**≥50%**	
I	14 (93.3%)	1 (6.7%)	0.005*
II	15 (60.0%)	10 (40.0%)	
III	0 (0.0%)	2 (100.0%)	
	<75%	**≥75%**	
I	14 (93.3%)	1 (6.7%)	0.189
II	17 (68.0%)	8 (32.0%)	
III	2 (100.0%)	0 (0.0%)	

As shown, in contrast to HCC, HLA-G overexpression showed correlation with advanced stages and grades in PADC. The association between tumor stage or tumor grade and HLA-G expression with different cut-off scores was shown in Tables 4 and 5.

Table 5. Association between tumor grade and HLA-G expression with different cut-off scores in patient with pancreatic adenocarcinoma.

Grade	HLA-G		P-value
	Negative	**Positive**	
Well	12 (36.4%)	21 (63.6%)	
Poor	2 (28.6)	5 (71.4%)	0.846
Moderate	0 (0.0%)	2 (100.0%)	
	<25%	**≥25%**	
Well	22 (66.7%)	11 (33.3%)	
Poor	2 (28.6%)	5 (71.4%)	0.042*
Moderate	0 (0.0%)	2 (100.0%)	
	<50%	**≥50%**	
Well	23 (69.7%)	10 (30.3%)	
Poor	4 (57.1%)	3 (42.9%)	0.688
Moderate	2 (100.0%)	0 (0.0%)	
	<75%	**≥75%**	
Well	27 (81.8%)	6 (18.2%)	
Poor	4 (57.1%)	3 (42.9%)	0.342
Moderate	2 (100.0%)	0 (0.0%)	

Evaluation of HBV Genome in HCC Tissues.

The presence of HBV genome in liver tissues (n=74) was evaluated by PCR. The results showed that 23 HCC samples (31%) were HBV positive and 14 (32.1%) HBV-positive HCC tumor lesions were also positive for HLA-G. There was no correlation between HLA-G expression and the presence of HBV genome in HCC tissues (Table 6). Moreover, no correlation was observed between HBV and cancer stage or grade.

Table 6. Association between HLA-G expression and HBV infection in liver tumor tissues.

		Percentage HLA-G positivity in liver tumor tissues					
		Negative	**1-25%**	**25-50%**	**50-75%**	**>75%**	**P-value**
HBV	**Negative**	32 69.6%	8 17.4%	1 2.2%	3 6.5%	2 4.3%	
	Positive	19 67.9%	5 17.9%	1 3.6%	1 3.6%	2 7.1%	0.98

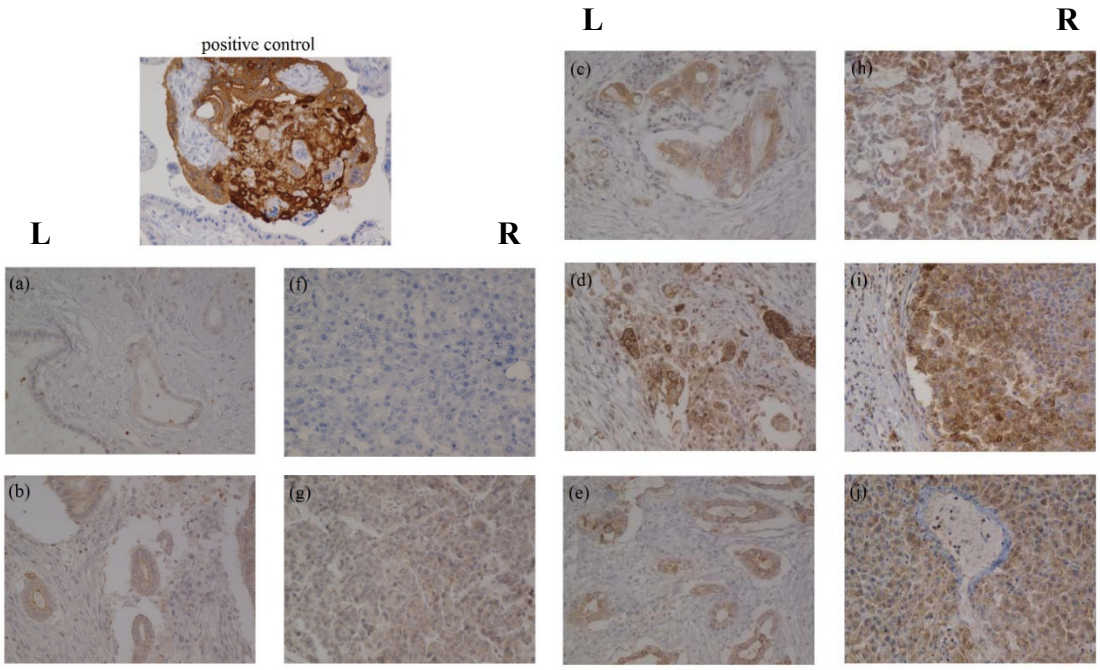

Figure 1. Immunohistochemical staining of HLA-G in pancreatic adenocarcinoma lesions (left) and hepatocellular carcinoma lesions (right). a and f: HLA-G negative tumor lesions, b and g: 1%-25% HLA-G positive tumor lesions, c and h: 25%-50% HLA-G positive tumor lesions, d and i: 50%-75% HLA-G positive tumor lesions, e and j: >75% HLA-G positive tumor lesions (magnification 400x).

DISCUSSION

Cancer cells typically develop mechanisms such as alterations in classical and nonclassical HLA-I expression that allow them to evade antitumor immune responses. HLA-G is a nonclassical MHC-I molecule with the ability to inhibit NK cell- and T cell-mediated cytolysis. HLA-G upregulation has been detected in different tumors; however, heterogeneous patterns of HLA-G expression may reflect differences in tumor biology as well as individual or racial differences. Moreover, the sensitivity of methods used thus far to detect HLA-G in malignant lesions is also important (15). In addition to predisposing genetic factors, regulatory factors in cancer such as the tumor microenvironment and viral infections may also have some impacts on HLA-G expression (16). In this study, HLA-G expression was detected in 31% (23 out of 74) of HCC samples and 66% (28 out of 42) of PADC samples. Unlike HCC, HLA-G expression was significantly associated with tumor stage (Tables 2 and 4) and grade (Tables 3 and 5) in patients with PADC. However, the causal relationship between HLA-G and tumor stage is still not clear, genetic instability and epigenetic changes due to cancer progression might contribute to the development of less immunogenic tumors with increased HLA-G and decreased HLA-I molecules (15). Furthermore, chronic inflammation and hypoxia in advanced tumors seem to induce HLA-G expression (17,18). Moreover, HLA-G may play a critical role in the creation of appropriate conditions for tumor progression by inducing tolerogenic antigen presenting cells and regulatory T cells, which produce IL-10 and TGF-β in the tumor microenvironment

(8,19). This positive loop usually occurs in patients with advanced-stage cancer. Low HLA-G expression might be sufficient to suppress immune responses in early stages, whereas HLA-G expression would be increased by tumor progression. Accordingly, our results are consistent with previous observations in pancreatic adenoma (20), gastric cancer (4) and breast cancer (21). High-grade tumors are usually poorly differentiated or undifferentiated, and tend to be fast-growing and more aggressive. We observed an association between HLA-G expression and high tumor grades in PADC, indicating that HLA-G status may be involved in tumor progression and hence associated with a poor prognosis. Zhou *et al.* and Cai *et al.* also previously reported an association between high HLA-G expression, shortened overall survival and increased tumor recurrence in pancreatic and hepatocellular cancers (22,23), which was consistent with reports on other type of cancers (3,5). These findings suggest that HLA-G can be considered a potential biomarker for cancer prognosis. Zeng *et al.* also found a remarkable increase in NK cell cytolysis after downregulation of HLA-G by siRNA (24). Therefore, HLA-G may serve as a possible target molecule for immunotherapy in combination with other therapeutic strategies to enhance the efficacy of cancer treatments. According to a report by Carosella *et al.*, blocking antibodies against HLA-G are currently in preclinical testing for cancer therapy (25).

In this study, we also attempted to determine whether HBV has any effect on HLA-G expression and cancer progression in patients with HCC. Our results showed that HLA-G did not correlate significantly with HBV infection (Table 6). Moreover, no correlation was observed between HBV infection and tumor stage or grade. Park *et al.* detected higher levels of sHLA-G in patients with active HBV and HCC than healthy controls and patients with chronic HBV or liver cirrhosis (26). These authors also reported increased sHLA-G levels in the early stages of HBV-mediated HCC. However, it is still unclear whether sHLA-G is a major mechanism of hepatocarcinogenesis associated with HBV. In this study, we did not have access to plasma samples from all patients to evaluate sHLA-G levels. However, we detected higher sHLA-G levels in 12 available plasma samples of the patients compared to sex- and age-matched normal controls (data not shown because of limited samples). Because HLA-G expression is controlled not only by HLA-G alleles but also by single nucleotide polymorphisms in its promoter or 3′UTR, patients' susceptibility to HBV-mediated HCC may depend indirectly on the host genetic background and its potential to increase HLA-G expression after HBV infection, which may in turn lead to viral persistence and ultimately result in HCC. Functional polymorphisms of HLA-G were first reported in 1993 (27), and it was later observed that a 14-bp insertion in 3′UTR was associated with lower HLA-G expression, reduced susceptibility to HBV infection and the development of HCC (28). A meta-analysis by Zhang *et al.* identified a prominent role for this polymorphism in susceptibility to HCC but not other cancers (29). It therefore appears that carriers of the14-bp deleted allele who have high HLA-G production are more susceptible to HCC, because of an appropriate milieu for HBV persistence. Gene polymorphisms usually differ among ethnicities, so further studies in different populations might provide clues to a better understanding of HBV behavior and susceptibility to HCC. Although genetic factors are important in HLA-G expression, the role of epigenetic changes induced by environmental factors should not be ignored (30).

In conclusion, our results suggest that HLA-G expression in tumor lesions may be an appropriate prognostic marker in some cancers, particularly in more severe types such

as PADC. HLA-G expression is apparently affected more by genetic factors rather than by HBV infection.

ACKNOWLEDGEMENTS

This work was performed in partial fulfillment of the requirements for the MSc degree in Immunology (Parisa Khodabandeh Shahraki), and was financially supported by a grant from Shiraz University of Medical Sciences (No: 95-11325). We thank K. Shashok (Author AID in the Eastern Mediterranean) for improving the use of English in the manuscript.

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