

Review

Human leukocyte antigens in cancer metastasis: Prognostic approach and therapeutic susceptibility

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Summary. Human leukocyte antigens (HLA), which are a group of antigen-presenting proteins, are classified into two main groups: classic (including HLA-I, HLA-II, HLA-III) and non-classic. These molecules are expressed on the surface of several immune cells, which contribute to the defense of body against foreign antigens. Changing expressions of these molecules on tumor cells can be related to reduced ability of the immune system in killing tumor cells, as well as metastasis induction of many solid tumors. The purpose of this review article is to assess the possible relationship between changing expressions of HLA molecules with cancer metastasis and relapse. It can be stated that the changes in the expressions of HLA molecules on tumor cells are an important mechanism for tumor cell escape from immune cells. Therefore, these changes can be associated with tumor development, metastasis, or relapse. Given the essential role of HLA molecule expression in cancer metastasis and relapse, identification of prognostic value of these alterations as well as targeting HLA molecules with new therapeutic approaches may lead to the prevention of these complications.

Key words: Metastasis, Cancer, Human Leukocyte Antigens

Introduction

Human Leucocyte Antigen (HLA) molecules, including classic HLA-I (HLA-A, HLA-B, HLA-C), HLA-II (HLA-DP, HLA-DQ, HLA-DR), HLA-III (CYP-21, TNF, C2, C4, Bf), and non-classic HLAs (such as HLA-G, HLA-F, HLA-E), are proteins located on different cells of the body (Palmisano et al., 2005; Sconocchia et al., 2014). HLA molecules can play an important role in the immune system function. For example, HLA-I molecules can stimulate the immune system and kill tumor cells via antigen presentation to cytotoxic T lymphocytes (CTLs) (Thibodeau et al., 2012). On the other hand, HLA-II molecules also play an important role in antigen delivery to T helper (Th) lymphocytes, as well as in stimulating the immune response (Moller et al., 1989). Unlike the classic HLA, non-classic HLA molecules can directly or indirectly suppress the immune system by affecting a variety of immune cells such as natural killer (NK) cells, T lymphocytes, macrophages, and other immune cells (Xu et al., 2015b). A large number of solid tumors can metastasize, which form a wide range of malignancies affecting various organs of the body. Depending on cancer type, tumor cells can metastasize to various organs; for example, tumor cells associated with breast cancer are mainly metastatic to the bone, lungs, liver, and brain. Similarly, metastasis of melanoma and colorectal tumor cells to lungs, liver, brain, and skin have been demonstrated (Nguyen et al., 2009). Studies have suggested the metastasis of cancer cells as the most common cause of mortality in patients with solid tumors (Rahim et al., 2014). Increasing or decreasing

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expressions of classic and non-classic HLA molecules on tumor cells can be an escape mechanism of tumor cells and create appropriate conditions for metastasis of tumor cells to tissues or lymph nodes around the tumor site. Therefore, tumor cells can evade the immune system, which leads to the relapse of cancer (Mohme et al., 2017). Recent developments in the relationship between changing HLA expression in various cancers with susceptibility to metastasis and relapse highlighted the key role of these changes in progression and prognosis of these disorders. For this reason, we will assess the most common changes of HLA expressions and their possible mechanisms in metastasis of solid tumors as well as new therapeutic approaches that may prevent this complication.

Breast cancer

Breast cancer is one of the most common types of cancer commonly associated with metastasis to lymph nodes, especially axillary lymph nodes and tissues surrounding the tumor site (Yip et al., 2014). It seems that the delivery of tumor-specific antigens to TCD8⁺ cells by antigen presenting cells (APCs) in lymph nodes is not able to induce a functional response of CTLs to tumor cells. Therefore, metastatic cells to lymph nodes around the thorax are likely to protect themselves against the immune system and metastasize to other tissues in the body (Tlsty and Hein, 2001). Several studies demonstrated that decreased expression of HLA-A, HLA-B, and HLA-C molecules in breast cancer can be associated with metastasis and a poor prognosis (Gudmundsdottir et al., 2000; Zia et al., 2001). Decreased HLA-DR expression and increased HLA-DQ expression have also been reported in this type of cancer. Since HLA-DR has an important role in the proliferation of Th cells, decreased expression of HLA-DR in breast cancer causes tumor cells escape from the immune response elicited by this T-cell population. In contrast, HLA-DQ mainly inhibits the activity of T lymphocytes, including T cytotoxic or T suppressor cells (or both), so that HLA-DQ overexpression has been reported as a possible mechanism for escape of breast cancer tumor cells from immune function of T-cells (Smith et al., 1987; Silva et al., 2013; Yaprak et al., 2015). On the other hand, Silva et al. have shown an increased expression of HLA-G in breast cancer (Silva et al., 2013). HLA-G is a highly conserved molecule overexpressed in a large number of cancers (Garziera et al., 2017; Rizzo et al., 2017). This type of HLA is classified into two general groups: membrane (HLA-G1, -G2, -G3) and soluble (HLA-G5, -G6, -G7). Soluble HLA-G (SHLA-G) is secreted by tumor cells and has been reported to play a role in the metastasis of tumor cells (Park et al., 2004). Also, SHLA-G is considered as the main immune modulator via downregulation of T-cell chemokine receptors, including CCR2, CXCR3, and CXCR5, as well as inhibiting *in vitro* chemotaxis of T-cells chemotaxis towards CCL2, CCL8, CXCL10, and

CXCL11. This finding suggests that SHLA-G can suppress the immune system by modulation of T-cell recruitment in physiological and pathological conditions (Morandi et al., 2010). Therefore, SHLA-G overexpression in breast cancer is likely to be associated with metastasis by suppression of T lymphocytes' effector functions against tumor cells. HLA-G5 is another subtype of SHLA-G (Carosella et al., 2008b). Tumor cells can deform the vascular wall and increase its permeability through the stimulation of immune system through contact with the vascular wall epithelial cells, which results in increased influx of immune cells into the tumor site. On the other hand, HLA-G5 secreted by tumor cells can inhibit immune cells within the tumor site (Garziera et al., 2017). Therefore, it can be stated that the tumor cells releasing HLA-G5 can protect themselves against the immune system and metastasize to lymph nodes and tissues surrounding the tumor area. Therefore, measurement of HLA-G5 may be used as a marker for the evaluation of metastasis in breast cancer and other malignancies (Table 1) (Garziera et al., 2017). By determining the HLA profile of breast cancer patients, it is possible to predict the likelihood of metastasis to lymph nodes and tissues around the tumor.

Colorectal carcinoma

Colorectal carcinoma (CRC) is one of the most lethal cancers in both males and females (Özdemir et al., 2016), and studies have shown that HLA-II molecules are expressed in 23% of patients with CRC (Sconocchia et al., 2014). Along with costimulatory molecules on tumor cells, HLA-II molecules stimulate TCD4⁺ lymphocytes and the generation of interferon- γ (IFN- γ) by presenting tumor antigens to lymphocytes (Banchereau and Steinman, 1998). The IFN- γ produced during the inflammation process increases the expression of HLA-II molecules on the surface of 50% of CRC cells (Michel et al., 2010). Studies show that the expression rate of HLA-II subtypes on tumor cells in CRC is as follows: HLA-DR>HLA-DP>HLA-DQ (Degener et al., 1988). Since HLA-II molecules show anti-tumor responses (Thibodeau et al., 2012), the expression of HLA-II on tumor cells is often associated with a favorable prognosis. Sconocchia et al. demonstrated that the expression of HLA-II on CRC cells can induce the production of IL-1 α by resting monocytes. Also, in this study, it was shown that HLA class II antigen expression on CRC cells can be associated with increased overall survival (OS) of patients, and HLA-II was identified as a marker of favorable prognosis (Sconocchia et al., 2014). In contrast, metastasis of tumor cells in CRC is associated with decreased expression of HLA-II (poor prognosis), as well as increased expression of HLA-G (especially SHLA-G) and HLA-E on tumor cells. The overexpression of HLA-G and HLA-E, which are immune-tolerant non-classical HLAs, is associated with a poor prognosis, metastatic exacerbation, and reduced survival (Özdemir et al., 2016; Kirana et al., 2017).

HLA and cancer metastasis

Studies indicated that SHLA-G affects FAS/FAS-L-dependent mechanisms and can induce apoptosis in TCD8⁺ and NK cells to suppress the immune system (Contini et al., 2003; LeMaout et al., 2004). In this regard, Kirana et al. in their recent study have shown a negative correlation between SHLA-G levels with liver metastasis free survival (LMFS) in stage II CRC, while high SHLA-G levels in stage III patients is positively associated with longer LMFS. This finding suggested

that SHLA-G levels can be associated with CRC progression and may have a potential prognostic value in this disease (Kirana et al., 2017). Similar to SHLA-G, HLA-E can suppress cytotoxic T lymphocytes and NK cell function by affecting the inhibitory receptors (including CD94/NKG2A) in these cells (Table 1) (Iwaszko and Bogunia-Kubik, 2011). Considering the fact that the expression of HLA-II molecules is increased by IFN- γ , the relationship between this cytokine with the

Table 1. Association between HLA and cancer metastasis.

Cancer	HLA	Expression	Explanations	Subtypes	Reference
*Breast Cancer	SHLA-G	Increase	Can be associated with inhibiting or decreasing the receptor expression of T-cell chemokines	Some studies suggest increasing HLA-DQB1 chr6_32737733 and HLA-A-24 expressions and decreasing HLA-DRB5 chr6_32606112 expression	Silva et al., 2013
	HLA-I	Decrease	Associated with lack of identification by T-cells		Gudmundsdottir et al., 2000; Zia et al., 2001; Razmkhah and Ghaderi, 2013
	HLA-DR	Decrease	Can be associated with Th cells function		Smith et al., 1987; Yang et al., 2011a; Yaprak et al., 2015
	HLA-DQ	Increase	Associated with inhibition of T- cell activity		
Colorectal Carcinoma	HLA-E	Increase	Associated with inhibited activity of T-cells and NK cells	Some studies suggest that the expression of SHLA-G is different at different stages of disease progression; for example, despite the negative relationship between the SHLA-G and LMFS in colon cancer stage II, there is a positive relationship between them in step III	Özdemir et al., 2016; Kirana et al., 2017
	HLA-II	Decrease	Associated with lack of detection by Th cells		
	HLA-G (SHLA-G)	Increase	Can induce apoptosis in TCD8 cells and NK cells		
NSCLC	HLA-G	Increase	Can be associated with increased metastasis to lymph nodes, cancer stage, prognosis	There is no controversy between authors on HLAs expression changes and cancer progression	Yie et al., 2007a
	HLA-I	Decrease	In most of the primary lung tumors and all metastases of the lymph nodes		He et al., 2013; Gettinger et al., 2017
	HLA-DR	Decrease	Can be associated with expression of gp91phox and inhibition of T-cells		Huang et al., 2013
HCC	HLA-F	Increase	Can be associated with inducing immunity tolerance through influence on inhibitor receptors ILT-2 and ILT-4	Some studies suggest increasing HLA-A1, -Cw7, -B8, -DR3 expression in almost all groups of HCC patients	Ricci et al., 1995; Xu et al., 2015b
	HLA-I	Decrease	There is a direct relationship between the reduction of HLA-I expression and the increase in metastases of tumor cells		Cordon-Cardo et al., 1991
	HLA-DR	Increase	Increased CD68(+)HLA-DR(+) M1-like macrophages is associated with cancer metastasis. Increased HLA-DR related to expression of B7-H1 and secretion of TNF- α , IL-6, IL-23 and CCL15		Wang et al., 2014
**Cervical cancer	HLA-G5	Decrease	Can be related to a genetic mutation in (6p2.3) region in only one allele of HLA-G5	Some studies suggest that increasing HLA-DQB1*03, -DRB1*07, -DQB1*0301, -A*0201, -B*4402, -Cw*0501, -DRB1*0401, -DQB1*0301, -B*4402, -DRB1*1101, DQB1*0301 expressions are associated with increasing risk for cervical cancer especially when involving HPV16 infection	Guimarães et al., 2010
	HLA-I	Decrease	Associated with lack of detection by T-cells		Ryu et al., 2001; Madeleine et al., 2008; Hu et al., 2018
	HLA-II	Decrease	Associated with no identification by Th		
Oral osteosarcoma	HLA-E	Increase	Associated with a poor prognosis, shorter survival, and disease progression	There is no controversy between authors on HLAs expression changes and cancer progression	Arantes et al., 2017
	HLA-G	Increase			
ESCC	HLA-I	Decrease	An independent prognostic factor associated with poor prognosis	There is no controversy between authors on HLAs expression changes and cancer progression	Hosch et al., 1997; Mizukami et al., 2008
	HLA-DR	Decrease	Associated with increased expression of PDL-1 and suppression of anti-tumor response		Huang et al., 2015
	HLA-G	Increase	Increasing HLA-G expression is associated with IL-10 expression, cancer cell differentiation, and lymph node metastasis		Zheng et al., 2014

(Continued).

expression of HLA-II molecules could be used for future CRC therapies (Michel et al., 2010). In addition to the prognostic role of HLA-II, HLA-E, and HLA-G in CRC, further studies can be conducted on these molecules concerning response to treatment due to their involvement in the immune system and secretion of cytokines.

Non-small cell lung cancer

Non-small cell lung cancer (NSCLC) is the most prevalent type of lung cancer (Araz et al., 2015). Reports indicate that the level of HLA-I (HLA-A, -B, -C) molecules is reduced in most primary lung tumors and in all lymph node metastases of NSCLCs. Given that HLA-

Table 1. Association between HLA and cancer metastasis (Continued).

Cancer	HLA	Expression	Explanations	Subtypes	Reference
Endometrial cancer	HLA-I	Decrease	Associated with lymphovascular involvement and lymph node metastasis	Endometrial cancer based on expression HLA- Cw7 and -DRw8 and the simultaneous occurrence of triple diabetes complications (mellitus, obesity, and hypertensive), classified into 4 groups***	Albert and Child, 1977; Kanurna and Igarashi, 1987; Bijen et al., 2010
PADC	HLA-G	Increase	Subsets of HLA-II expression pattern is HLA-DR>DP>DQ	There is no controversy between authors on HLAs expression changes and cancer progression	Scupoli et al., 1996; Imai et al., 2017; Shahraki et al., 2018
	HLA-I	Decrease			
	HLA-II	Decrease			
Prostate cancer	HLA-I	Decrease	Increasing HLA-A*0201 expression and reducing HLA-A*24 expression are two prognostic biomarkers in malignant and metastatic prostate cancers, which distinguishes benign from malignant cancer	HLA-A*0201 expression increases in metastatic and invasive prostate cancer	Younger et al., 2008; Doonan and Haque, 2015; Liu et al., 2017; Stokidis et al., 2017
	HLA-II	Decrease			
Ovarian cancer	HLA-I	Decrease	HLA-G by reducing the NK cell cytotoxicity against tumor cells, promotes the progression and metastasis of ovarian cancer	In ovarian cancer, increased HLA-DRA chain expression and decreased HLA-DRB chain expression can be seen. Therefore, it may be possible to express the HLA-DRA chain expression as a prognostic biomarker in ovarian cancer	Rangel et al., 2004; Vitale et al., 2005; Kübler et al., 2008; Lin et al., 2013; Mariya et al., 2014; Wang et al., 2017
	HLA-II	Decrease			
	HLA-G	Increase			
Gastric cancer	HLA-I and SHLA-I	Decrease	Long non-coding RNA HOTAIR increases HLA-G expression through inhibition of miR-152	HLA-DR4 and HLA-B52 expression are associated with lymph node metastasis	Cavelier et al., 1980; Shimura et al., 1994; Ricci et al., 1995; Ogoshi et al., 1996; Thor Straten et al., 1997; Murata et al., 1998; Yie et al., 2007b; Ye et al., 2010; Yang et al., 2011b; Song et al., 2015; Sottile et al., 2016
	HLA-DR	Decrease			
	HLA-G	Increase			
RCC	HLA-I	Decrease	The amount of CD14+HLA-DRlo/neg monocytes in the blood can be associated with prognosis in people with RCC	In RCC, increasing expression of HLA-DRB1*0403 and *1202 alleles are observed	Gastl et al., 1996; Kojima et al., 2000; Bukur and Seliger, 2003; Romero et al., 2006; Gustafson et al., 2015; Seliger et al., 2016
	HLA-II	Decrease			
	HLA-E	Increase			
	HLA-G	Increase			
Melanoma	HLA-I	Decrease	Some studies suggest that there is a direct correlation between the percentage of DC-HIL+ CD14+ HLA-DRno/low cells in the blood and the progression of melanoma	Some studies suggest increasing HLA-C*14 and decreasing HLA-C*02 expression	Aoudjit et al., 2004; Turrentine et al., 2014; Kandilarova et al., 2016; Schrors et al., 2017
	HLA-DR	Increase			
HNSCC	HLA-I	Decrease	Increased homozygous HLA-Cw and HLA-DRB4 expression are associated with decreased PFS	In HNSCC, increasing HLA-B*13,-B*52, -B*57, Homozygous HLA-Cw and HLA-DRB4 expression as well as decreasing HLA-B*44 expression are observed	Grandis et al., 2000; Wichmann et al., 2017
Thyroid cancer	HLA-G	Increase	The occurrence of increased HLA-DR expression along with lymphocyte infiltration is mainly associated with metastasis of regional lymph nodes	Some studies show increased HLA-B*51:01, HLA-C*07:06 and HLA-DR expression. Also, a decrease in serum HLA-G expression is suggested	Feinmesser et al., 1996; Jo et al., 2008; Nunes et al., 2013; de Figueiredo Feitosa et al., 2014; Shuxian et al., 2014; Akin et al., 2017
	MHC-II	Decrease			
	MHC-I	Mainly Increase			

*: With axillary lymph node metastasis; **: Associated with HPV; ***: Group I is positive for Cw7 or DRw8 group; group II is negative for Cw7 and DRw8 and positive for the triple complications; group III is negative for Cw7 and DRw8, negative for triple complications, and positive for DR 5; group IV is a non-A, non-B, and non-C group. HLA: Human leukocyte antigen, HPV: Human papilloma virus, NSCLC: Non-small cell lung cancer, gp91: glycoprotein 91, HCC: Hepatocellular carcinoma, ILT: Immunoglobulin-like transcripts, ESCC: Esophagus squamous cell carcinoma, PD-L1: Programmed death ligand-1, PADC: Pancreatic adenocarcinoma, NK: Natural killer, HOTAIR: hox transcript antisense intergenic, RCC: Renal cell carcinoma, SHLA-I: Soluble HLA-I, HNSCC: Head and neck squamous cell carcinoma, PFS: Progression-free survival.

I molecules are involved in stimulating the immune system against tumor cells, reducing or inhibiting the expression of HLA-I molecules on tumor cells may be a possible mechanism for non-recognition of tumor cells by the host immune system, the evasion of tumor cells from the immune system, as well as growth and metastasis of tumor to tissues and lymph nodes around the tumor region (He et al., 2013; Gettinger et al., 2017). On the other hand, it has been reported that CD14⁺ HLA-DR^{-/low} myeloid-derived suppressor cells in NSCLC can be associated with suppression of T lymphocyte function, a poor response to chemotherapy, as well as extrathoracic metastasis through the expression of glycoprotein (gp91) phox (a component of ROS-generating NADPH oxidase) (Huang et al., 2013). A number of studies on HLA-G gene promoter have indicated that the translation level of HLA-G gene and its expression are affected by single nucleotide polymorphisms (SNPs) such as -725 C>G>T and 716 T>G (Ober et al., 2006; Amiot et al., 2011). Although these SNPs can have an impact on the activity of HLA-G gene promoter by affecting the binding site of the gene involved in the expression of HLA-G molecule, no relationship has been found between the mentioned SNPs with survival rates of NSCLC patients. On the other hand, there is a significant relationship between -725 C>G>T SNP with the metastasis rate of tumor cells from the lung to lymph nodes (Kowal et al., 2015). Investigations have shown that increased expression of HLA-G molecules on tumor cells in NSCLC can be associated with lymph node metastasis, clinical stages of disease, and host immune response (Table 1) (Yie et al., 2007a). Considering the involvement of HLA-G expression in suppression of CTLs and NK cells, it seems this HLA-G function is a possible mechanism for escape of tumor cell from immune system function, as well as inducing metastasis in NSCLC. Therefore, the identification of changes in the expressions of HLA molecules and the mechanisms affecting NSCLC progression can be useful in timely management of this cancer. However, future studies are required to confirm that HLA molecules can be a potential target for prevention of tumor cell metastasis by new therapeutic agents.

Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is the fifth most common type of cancer and the most prevalent liver malignancy with increasing incidence worldwide (Xu et al., 2015b; Mizukoshi et al., 2016). Metastasis is found in only 5-15% of patients with HCC, which is associated with a poor prognosis. The lungs, lymph nodes, bones, brain, and adrenal glands are the most common sites for HCC metastasis, and brain metastasis can be associated with intraparenchymal hemorrhage (Balbinot et al., 2017). Reports have suggested the increased expressions of HLA-F molecules during venous and lymphatic invasion of HCC patients. HLA-F is a non-classic HLA-

I molecule that has been recently recognized as an immune system suppressor (Lin et al., 2011; Xu et al., 2015a). Goodridge et al. indicated that the HLA-F molecule can induce immune tolerance and tumor cell escape from the host immune system by affecting inhibitory receptors such as immunoglobulin-like transcripts-2 (ILT-2) and ILT-4 (Goodridge et al., 2013). Therefore, it can be stated that the increased expression of HLA-F molecules may be associated with a poor survival in HCC patients. On the other hand, it has been shown that a higher density of CD68⁺ HLA-DR⁺ M1-like macrophages in HCC tissues and release of cytokines such as IL-6, tumor necrosis factor alpha (TNF- α), CCL15, and IL-23 (metastatic inducers) by these macrophages can promote migration and metastasis of HCC cells (Table 1) (Wang et al., 2014). Perhaps the identification of changes in the expressions of HLA-F and HLA-DR molecules in HCC patients can be helpful in their introduction as new biomarkers for early diagnosis and treatment of invasive HCC, as well as preventing metastasis of HCC tumor cells.

Invasive cervical cancer

Cervical cancer (CC) is a malignant cancer, which is mainly developed following infection with Human papilloma virus (HPV) (Piersma, 2011; Chen et al., 2017). Despite the increased expression of HLA-G5 in a majority of cancer types, its expression decreases in HPV-associated CC (Carosella et al., 2008a). Normally, tumor cells in different types of cancers lose their surface HLA-I molecules by various mechanisms to cover their surface with HLA-G5 molecules. This change (HLA-G5 overexpression) results in the escape of tumor cells from the immune system as well as promotion of their metastasis to tissues around the tumor region. However, there is a reduction in the expression of HLA-G5 molecules in all HPV-associated metastatic/non-metastatic CC samples (Guimarães et al., 2010). HLA-G5 molecules trigger the release of Th2 cytokines (IL-4, IL-5, and IL-10), causing the survival of HPV, as well as growth and spread of CC tumor (Nakanishi et al., 2001). However, genetic changes associated with an invasive cervical cancer (e.g. mutation in a single HLA-G5 allele of 6p2.3 region) can lead to the reduced expression of this HLA on tumor cells (Vermeulen et al., 2005). On the other hand, loss of a heterozygous transporter associated with the antigen processing (TAP) region is related with impaired transport of HLA-G molecule (Vermeulen et al., 2007). Considering the association between HLA-G5 expression with cancer metastasis, it can be stated that reduced HLA-G5 expression in CC may be associated with a reduction of metastasis and good prognosis. Also, the decreased expression of HLA-I (-A, -B) and HLA-II (-DP, -DQ, -DR) has been observed in CC (Ryu et al., 2001). HLA-I and HLA-II molecules play a role in the presentation of tumor antigens to T lymphocytes and the activation of the immune system. In this regard, Ryu et al. demonstrated that CC tumor cells can escape the

immune system and metastasize to surrounding lymph nodes and tissues by reducing the expressions of HLA-I and HLA-II molecules (Table 1) (Ryu et al., 2001). Therefore, the expression of HLA-I, HLA-II, and HLA-G molecules can be used as a prognostic biomarker of CC progression and metastasis.

Other solid tumors

Osteosarcoma (OS)

Osteosarcoma is the most common primary bone tumor in childhood and adolescence (Sakamoto and Iwamoto, 2008), which is highly invasive and mainly causes metastasis to the lung (Longhi et al., 2006). Higher expression levels of HLA-E and HLA-G molecules have been reported in oral osteosarcoma (OO), especially histologic metastasis forms. There is also a link between high expression levels of the above-mentioned molecules with a poor prognosis, lower survival, disease progression, relapse, and tumor metastasis (Arantes et al., 2017). According to Rouas-Freiss et al., suppression of CTLs and NK function via expression of HLA-G and HLA-E molecules is a possible mechanism for facilitating the metastasis of OO tumor cells (Rouas-Freiss et al., 2005, 2014).

Esophageal squamous cell carcinoma (ESCC)

ESCC is among the deadliest malignant cancers (Ando et al., 2003). In this cancer, the reduced expression of HLA-I molecules can be considered as an independent poor prognostic factor for increased metastasis because HLA-I molecules play a role in stimulating the immune system by presenting tumor antigens to CTLs. It seems that the decreased expression of HLA-I molecules on tumor cells leads to tumor cell escape from the immune system and exacerbates metastasis (Hosch et al., 1997; Mizukami et al., 2008). Since myeloid-derived suppressor CD14+HLA-DR^{-low} cells can induce immunosuppressive effects through increased programmed death ligand 1 (PD-L1) expression on functional T-cells in patients with ESCC, elevated levels of these cells is known as a poor prognostic biomarker in this disease (Huang et al., 2015). Therefore, inducing PD-1/PD-L1 expression on T lymphocytes may increase the susceptibility of tumor cells to chemotherapy and increase the survival of ESCC patients (Huang et al., 2015; Rezaeeyan et al., 2017).

Endometrial cancer

Following the examination of samples from endometrial cancer patients, lymphovascular involvement and lymph node metastasis were observed in patients with reduced or suppressed expressions of HLA-I molecules on tumor cells (Bijen et al., 2010). Also, compared with other patients (having normal HLA-I expression), the patients who had reduced or

suppressed HLA-I expression showed poorer progression-free survival (PFS) and OS. Therefore, HLA-I expression evaluation on tumor cells could be helpful for prediction of prognosis and metastasis to lymph nodes. However, after numerous studies, HLA-I has not been recognized as an independent factor to predict PFS and OS (Yakabe et al., 2015). On the other hand, it has been observed in some cases that the number of T-cells in endometrial cancer patients showing reduced expression of HLA-I on their tumor cells is significantly lower than those with normal HLA-I expression, indicating the involvement of HLA-I in the recruitment of T-cells (Table 1) (de Jong et al., 2012). As a result, the expression patterns of different HLA molecules on tumor cells may be useful to determine the prognosis of cancer and to find new ways in order to prevent metastatic cancer. The pattern of HLA expression in other solid tumors is shown in Table 1.

Discussion

Metastasis is one of the most common causes of death in cancer patients. So far, several causes for metastatic cancer have been investigated, including changing expressions of HLA molecules that play a key role in the host's immune system, activating or inhibiting the immune system according to the HLA type. Given that the expression patterns of HLA molecules vary in cancers, increasing or decreasing expressions of these molecules in tumor cells can reduce the sensitivity of these cells to the immune system function. These changes may lead to the evasion of tumor cells from the host's immune system, discharge of tumor cells to lymphoid tissue around the tumor area, protection of tumor cells from chemotherapy, and ultimate relapse of cancer. Evidence has shown that a number of factors, including the origin and growth stage of tumor cells, release of chemokines, and activation of specific chemokine receptors (such as CCR7, CXCR5 and its ligand of CXCL13) can be involved in cancer metastasis to lymph nodes or other tissues. Interestingly, the differences in the expressions of various molecules on vascular endothelial cells (such as ICAM-I) and lymphatic vessels (such as C-Met/HGF), as well as lymphatic angiogenesis (which is mainly observed in chronic inflammation and cancer) can play a crucial role in the choice of tumor cells metastasis to blood vessels or lymph nodes. For example, C-Met/HGF expression has been introduced as an essential biomarker for increased metastasis to lymph nodes. Since changing expressions of HLA molecules have a tendency to lymph nodes metastasis in various cancers, overexpression of C-Met/HGF molecules as well as lymph nodes metastasis may be related to the impact of HLA expression on the mentioned molecules. In addition, tumor cells can enter the interstitial fluid along with plasma and plasma-soluble proteins through the capillary network due to differences in osmotic pressure. However, tumor cells are not able to return into

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circulation via blood vessels and are thus absorbed by the lymph vessels along with proteins and sent to lymph nodes. Therefore, if not destroyed by immune cells in the lymph nodes, lymphatic tumor cells either persist in lymph, involve lymph nodes, or move on to the lymphatic vessels, eventually re-entering blood vessels and metastasizing to organs other than their origin. Therefore, the inhibition of lymph node metastasis may prevent the release of tumor cells into blood vessels.

However, this is not always the case, since the tumor cells are likely to enter into the blood vessels directly and do not metastasize to the lymphatic vessels. Research has shown that transforming growth factor beta (TGF- β) and epidermal growth factor (EGF) decrease the expression of HLA-I molecules on tumor cells, inducing the epithelial-mesenchymal transition (EMT) process in which the epithelial cells take a fibroblast-like mesenchymal phenotype under the influence of a series

Table 2. Comparison of common HLA typing methods.

Methods	Basis and application	Advantages and disadvantages	Sample	Reference
NGS	<ul style="list-style-type: none"> ➢ Produces a large number of clonal sequences in a single sequencing run 	<ul style="list-style-type: none"> ✓ Can determine all gene sequence ✓ Can survey genetic mutations in tumor tissues ✓ High-throughput ✗ Despite being relatively inexpensive, it is still expensive for some small labs 	<ul style="list-style-type: none"> ➢ DNA /RNA was extracted from PB samples with EDTA anticoagulant 	Dunn, 2011; Hajeer et al., 2013; Gabriel et al., 2014; Lucan et al., 2016
New SSO-based Luminex method	<ul style="list-style-type: none"> ➢ Based on pairing the reverse sequence specific oligonucleotide probes with a microsphere beads in an array platform ➢ Used to improve the level of HLA typing of hematologic patients, voluntary donors, cord blood units 	<ul style="list-style-type: none"> ✓ High sensitivity ✓ High specificity ✓ Reproducibility ✓ Reduces the time required for BM donor selection process 	<ul style="list-style-type: none"> ➢ DNA was extracted from PB samples with EDTA anticoagulant 	Hurley, 1997; Adams et al., 2004; Charron, 2005; Testi et al., 2012
High-resolution DNA melting curve	<ul style="list-style-type: none"> ➢ Used to screen between siblings prior to living-related transplantation ➢ Used for genotyping and heteroduplex detection after polymerase chain reaction 	<ul style="list-style-type: none"> ➢ Quick ➢ Simple ➢ Inexpensive ✗ Does not sequence or determine specific HLA alleles ➢ To identify at highly polymorphic HLA loci 	<ul style="list-style-type: none"> ➢ DNA was extracted from PB samples 	Gundry et al., 2003; Wittwer et al., 2003; Zhou et al., 2004
MAILA technique	<ul style="list-style-type: none"> ➢ Detection of specific antibodies against HLA antigens on lymphocytes ➢ Identification of HLA using detected allo-antiserum against HLA 	<ul style="list-style-type: none"> ✓ In identifying specific antibodies, it is better than cellular methods, indirect immunofluorescence, and flow-cytometric analysis, and radioimmunoprecipitation followed by 1-D SDS-PAGE 	<ul style="list-style-type: none"> ➢ Serum 	Mueller-Eckhardt et al., 1990; Sanchez et al., 1993
SSP-PCR	<ul style="list-style-type: none"> ➢ Based on sequence specific primers ➢ Detection of individual HLA alleles ➢ Routine test for determining the HLA-A, HLA-B, and HLA-DR antigens for transplant recipients and donors 	<ul style="list-style-type: none"> ✓ Simple ✓ Convenient ✓ Less sensitive than LCT ✓ Specific ✗ Inexpensive in-house test kit but the price of commercial test kits is relatively high and not suitable for laboratories with limited funds 	<ul style="list-style-type: none"> ➢ DNA was extracted from PB samples 	Olerup and Zetterquist, 1992; Schaffer and Olerup, 2001; Nathalang et al., 2006; Vojvodic, 2009; Amstutz et al., 2018
micro-platelet ELISA technique	<ul style="list-style-type: none"> ➢ Detects HLA antibodies ➢ Used to predict the transplant outcome 	<ul style="list-style-type: none"> ✓ Needs less antigen per well ✓ Needs few microlitres of antiserum and reagents per well ✓ Simple ✓ Cost effective 	<ul style="list-style-type: none"> ➢ PB with ACD antiuagulant 	Zaer et al., 1997; Shankarkumar et al., 2002
Complement fixation	<ul style="list-style-type: none"> ➢ Used for HLA tissue typing and antibody screening 	<ul style="list-style-type: none"> ✗ Less sensitive and more cumbersome than the LCT ✗ Less sensitive than ELISA ✗ Only able to identify serum with high titer 	<ul style="list-style-type: none"> ➢ Serum 	Christiaans et al., 2000; Shankarkumar et al., 2002
SSOP-PCR	<ul style="list-style-type: none"> ➢ Based on sequence specific oligonucleotide probes ➢ Commonly used in HLA typing ➢ Useful method for solid organ transplantations 	<ul style="list-style-type: none"> ✓ High accuracy ✓ Specific ✓ Reliable ✗ Data analysis required 	<ul style="list-style-type: none"> ➢ DNA was extracted from PB samples 	Ng et al., 1996; Hurley et al., 2000; Vojvodic, 2009; Won, 2017
LCT	<ul style="list-style-type: none"> ➢ Routine serological method for identifying anti HLA antibodies in a tissue Typing laboratory that needs viable lymphocytes with adequately expressed desired HLA 	<ul style="list-style-type: none"> ✗ False-negative results can be generated of reduced desired HLA expression ✗ False-positive results can be generated from expression of HLAs that have cross-reactivity with the desired HLA expression. ✓ To identify the desired HLA, lymphocytes that adequately express desired HLA are needed 	<ul style="list-style-type: none"> ➢ Serum 	Terasaki and McClelland, 1964; Neumuller et al., 1996; Kirveskari et al., 1997; Nathalang et al., 2006

NGS: Next generation sequencing, LCT: Microlymphocytotoxicity test, MAILA: Monoclonal antibody-specific immobilization of lymphocyte antigens, SSOP: Sequence specific oligonucleotide probes, PB: Peripheral blood, EDTA: ethylenediamine tetra acetic acid, ACD: Anticoagulant citrate dextrose solution.

of biochemical changes, a phenotype that is associated with increasing immigration capability, resistance to apoptosis, and invasion, which leads to the increased metastasis of these cells. In addition, several studies have shown that decreased HLA-I and increased HLA-G expressions have a direct role in suppressing the immune system, which is associated with induced metastasis of various cancers, especially breast cancer. These findings suggest that decreased HLA-I expression as well as increased HLA-G expression are poor prognostic markers for various cancers. On the other hand, several studies indicate that increasing HLA-II expression can be a possible mechanism for reduction of cancer cells metastasis. Similar to HLA-G, increased HLA-DQ and HLA-DR (CD68⁺ HLA-DR⁺ M1-like macrophages) expressions are considered as poor prognostic markers for the induction of metastasis in breast cancer, melanoma, and hepatocellular carcinoma, respectively. Although few studies have assessed the changes in HLA-E and HLA-F expressions in solid tumors, some studies have demonstrated the association between increasing HLA-E and HLA-F expressions in metastasis of CC, OO, renal cell carcinoma, and HCC. These findings suggest that the evaluation of changes in HLA expressions can help in timely management of undesirable clinical outcomes in solid tumors. In spite of

several studies that have stressed on the role of HLA expression in cancer metastasis, there is still controversy among researchers regarding the application of the appropriate method capable of detecting the changes in HLA expressions with high sensitivity and accuracy in a short period. In this regard, we compared the different methods of HLA typing in Table 2. There are several methods in relation to HLA typing, which are different in terms of applications, advantages, and disadvantages, each of which has a range of applications depending on their benefits and specific purposes. For example, the enzyme-linked immunosorbent assay (ELISA) and next generation sequencing (NGS) are commonly used methods in HLA typing because of ease, reliability, and ability to determine all gene sequence. However, these methods are still expensive for some small laboratories. Given that different methods of HLA typing are different in terms of economic benefits and specificity, it seems that the choice of method depends on the purpose of HLA evaluation. For example, sequence specific oligonucleotide probes (SSOP) and sequence specific probes (SSP) are two common methods in HLA typing, with the difference that SSOP has higher accuracy, specificity, and reliability than SSP. Although microlymphocytotoxicity test (LCT) is a routine serological test that is more sensitive than the mentioned

Table 3. A number of HLA typing therapeutic applications in cancer.

Treatment	Explanations	Reference
Tumor vaccines	In this method, in order to increase the presentation of TAA to T lymphocytes and stimulate host immune response against tumor cells, a series of cytokines such as IFN- γ are used that can increase the expression of HLA-II on the surface of APCs, as well as cytokines that increase the processing of endogenous antigens in APC	Hendrix et al., 1990; Boehm et al., 1997; English et al., 2009
Dendritic cell-based vaccines	Dendritic cells are one of the strongest APCs that increase the stimulation of the host immune system against tumor cells	Nestle et al., 1998; Tuyaerts et al., 2007
recombinant antigens -based vaccines	Following changes in the expression of HLA molecules on the surface of tumor cells, the lack of identification of these cells by the immune system and tumor cell metastasis, it is possible to use recombinant antigens coupled with monoclonal antibodies against superficial receptors of dendritic cells and stimulate CTL and Th lymphocytes	Lu et al., 2004; Pudney et al., 2010
Swainsonine	Swainsonine is an indolizidine alkaloid, which can increase HLA-I mRNA production and HLA-I Ag expression and result in decrease the metastasis of tumor cells	Mohla et al., 1990
Therapeutic target for melanoma	Due to the direct connection between increasing blood DC-HIL+ CD14+ HLA-DR no/low C cells with melanoma progression, blood DC-HIL+ CD14+ HLA-DR no/low C cells can be used as a prognostic marker and therapeutic target for melanoma	Turrentine et al., 2014
HCRT	Studies have shown that there is a significant increase in HLA-I expression in rectal cancer patients treated with the HCRT method, which increases immune stimulation against tumor cells	Sato et al., 2014
HLA-restricted gp100-in4 peptide vaccination	Gp100 epitope peptide restricted to HLA-A*2402 is a melanoma TAA, that can cause antigen-specific T-cell responses in patients with HLA-A*2402	Baba et al., 2010
HLA-G -based Immunotherapy	Considering that in many studies, the HLA-G has been named as the initiator of the cascade of immune suppression system and a promoter of metastasis of tumor cells, HLA-G can be used as the target of many immunotherapy methods	Komohara et al., 2007
*Covered B-lymphocytes of recombinant HLA-I-based vaccines	Intravenous injection of B-lymphocytes covered with recombinant HLA-I can cause T and B lymphocytes stimulation. On the other hand, the injection of lymphocytes that have been previously treated in vitro with HLA-I-peptide complexes through genetic engineering can stimulate CTLs more intensely than the indicated method	Wong and Pamer, 2003; Forero et al., 2004; Leclerc et al., 2007; Savage et al., 2007

*: B-lymphocytes play a role in stimulating the Th lymphocytes and MHC-I cross presentation. After being covered with MHC-I through genetic manipulation, in addition to the two mentioned functions, they will be able to stimulate lymphocytes. TAA: Tumor-associated antigens, IFN- γ : Interferon- γ , APC: antigen-presenting cells, CTL: cytotoxic T lymphocytes, Th: T helper, HCRT: hyperthermia chemo radiotherapy.

methods, false-negative and false-positive results restrict the use of LCT for HLA typing in laboratories. Despite simple and routine serological methods of HLA typing, transplantation process in solid tumors and hematological malignancies requires molecular techniques such as New SSO-based Luminex and high-resolution DNA melting curve to be able to type HLA with high sensitivity and specificity. Although both of these methods can minimize hybridization of HLA antigens between recipient and donor in transplant process, studies have shown that New SSO-based Luminex is more sensitive, specific, and reproducible than high-resolution DNA melting curve, which is able to select the appropriate donor in shortest time. Therefore, with proper recognition of HLA typing pattern and its targeting with appropriate therapeutic agents, we can prevent unfavorable clinical outcomes resulting from changing HLA expressions. Today, a number of cancer treatment methods have been developed based on the relationship between molecular expression and metastasis of cancer. In this overview, we compared some of the treatments that have been invented to counteract the immunosuppression caused by HLA expression changes (Table 3). As a result, by identifying the factors affecting the metastasis of tumor cells to blood vessels or lymphatic vessels, as well as becoming aware of changes in the expressions of HLA molecules on tumor cells in different types of cancers, we may be able to further concentrate on the prognosis of various types of cancer in order to develop new methods for the prevention and treatment of metastasis in cancer (Table 1).

Conclusion

In this review paper, the relationship between the expression profile of HLA molecules and the metastasis of cancer was assessed. Therefore, depending on HLA type and its impact on metastasis to lymph nodes and blood vessels, the detection of changing expressions of HLA molecules in different types of cancers can be useful in early diagnosis of invasive cancers. Therefore, targeting HLA molecules by new therapeutic agents is likely to improve response to therapy as well as prevention of tumor cell metastasis and relapse in cancers.

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