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REVIEW

Soluble HLA-G, its diagnostic and prognostic value and potential target molecule for future therapy in cancer

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ABSTRACT
Human leukocyte antigen G (HLA-G) is a non-classical MHC class I molecule that regulates many immune functions. The physiologic HLA-G expression is restricted to foetal tissues such as: amniotic cells, erythroid precursors, and cytotrophoblasts, and, in adults, to immune-privileged organs. The ectopic expression in tumours could point out to a strategy used by malignant cells to escape the immune surveillance. There are two forms of HLA-G, membrane-bound and soluble. The structure of the soluble and membrane bound isoforms differs at the C-terminus. The extracellular domain and the intracytoplasmic tail are replaced in the secreted isoforms by a short hydrophilic tail. These differences could serve as a marker to distinguish shed or proteolytically cleaved HLA-G isoforms from secreted HLA-G isoforms. HLA-G induces tolerance by inhibiting different cells and this function is mediated by binding of both soluble and membrane-bound HLA-G to the inhibitory receptors. There exists a consistent evidence in literature that HLA-G represents an important factor in determining prognosis in various types of cancer. In this review, we will focus on soluble form of HLA-G (sHLA-G) in cancers and its association with the prognosis of cancer patients, because this immune check-point molecule appears as a promising relevant target for cancer immunotherapy *(Fig. 2, Ref. 115)*. Text in PDF *www.elis.sk*
KEY WORDS: cancer, diagnosis, HLA-G, soluble HLA-G, tumour.

Introduction

Human leukocyte antigen G (HLA-G) is a non-classical MHC class I molecule and immune function regulator. It was first observed/studied in the placenta, where it participates in the maternal tolerance toward the foetus (McMaster et al, 1995). The expression of HLA-G was also later discovered/observed in embryonic tissues, adult immune privileged organs, and cells of the hematopoietic lineage (Carosella et al, 2008). Ectopic HLA-G expression can be stimulated in varying types of cancer, such as melanoma (Bezuhly et al, 2008, Degenhardt et al, 2010, Ghandri et al, 2011, Paul et al, 1999, Paul et al, 1998, Wagner et al, 2000), head and neck (Dardano et al, 2012, Ghandri et al, 2011, Nunes et al, 2013), brain (Fan et al, 2016, Kren et al, 2010, Kren et al, 2011, Wastowski et al, 2013, Wiendl et al, 2002, Wischhusen et al, 2007), lung (Montilla et al, 2016, Urosevic et al, 2001, Wisniewski et al, 2015, Yan et al, 2015, Yie et al, 2007, Yie et al, 2007, Zhang et al, 2016), urogenital (Bijen et al, 2010, Gimenes et al, 2014, Hanak et al, 2009, Ibrahim et al, 2001, Langat et al, 2006, Li et al, 2012, Lin et al, 2013, Rodriguez et al, 2012, Rutten et al, 2014, Tronik-LeRoux et al, 2017, Zhang et al, 2016, Zheng et al, 2011), gastrointestinal (Cao et al, 2011, Guo et al, 2015, Lin et al, 2011, Reimers et al, 2014, Swets et al, 2016, Zhu et al, 2010, Zeestraten et al, 2014), and breast cancers (daSilva et al, 2013, de Kruijf et al, 2010, Ferguson et al, 2012, He et al, 2010, Jeong et al, 2014, Kleinberg et al, 2006, Palmisano et al, 2002, Rolfsen et al, 2014, Singer et al, 2003), leukemias (Almeida et al, 2018, Nuckel et al, 2005, Xu et al, 2018), and lymphomas (Bielska et al, 2015, Diepstra et al, 2008, Urosevic et al, 2002). The expression of HLA-G in tumour lesions was first observed in melanoma (Wagner et al, 2000) and has been correlated with poor clinical outcomes (Amiot et al, 2011, de Kruijf et al, 2010, Guo et al, 2015, Nuckel et al, 2005, Yan et al, 2008). The ectopic expression in tumours could detail a strategy used by malignant cells to escape the immune detection (Curigliano et al, 2013).

This review will focus on the soluble form of HLA-G (sHLA-G) in cancers and its association with the prognosis of cancer patients, because this immune check-point molecule appears to be a promising target for cancer immunotherapy (Carosella et al, 2015).

Origin, structure, and functions of HLA-G

Like other HLA genes, HLA-G is located on chromosome 6p21.3. Within the non-classical HLA group, this gene remains the most polymorphic among the otherwise nearly non-polymorphic genes. To date, 69 alleles, 19 proteins, and 3 null alleles have been identified (IMGT/HLA release 3.39.0, January 2020, Carosella et al, 2015, Castelli et al, 2014, Robinson et al, 2015). HLA-G con-

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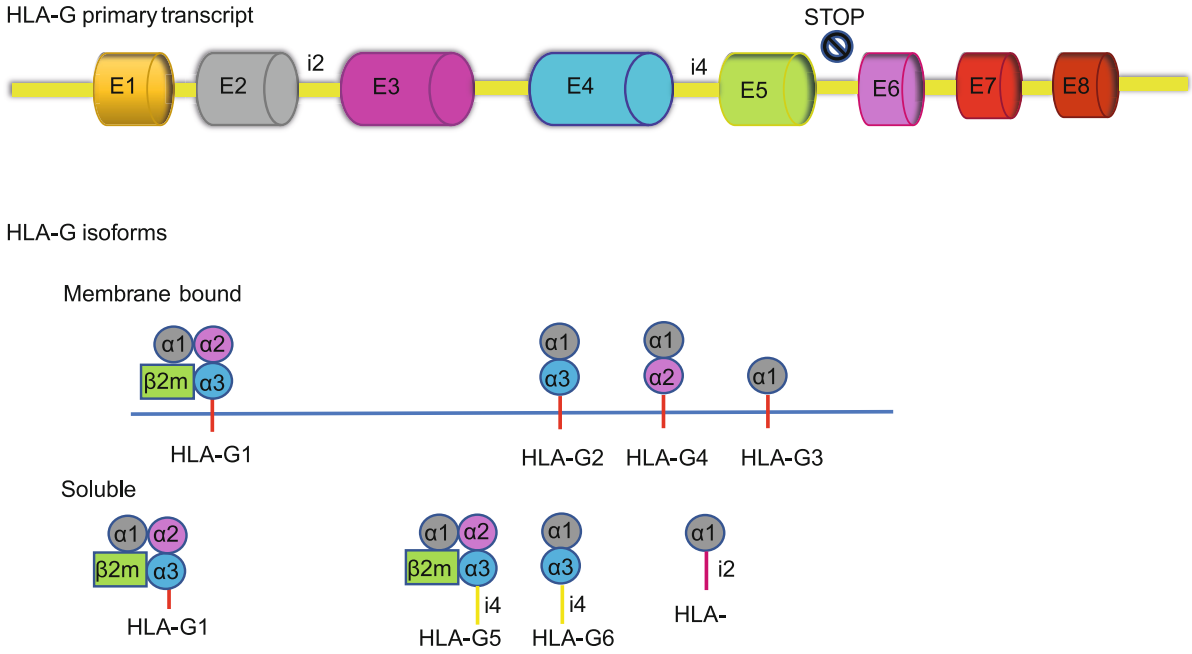

Fig. 1. Seven identified HLA-G isoforms generated by alternative splicing of HLA-G mRNA. Four membrane-bound (HLA-G1, -G2, -G3, -G4) and three soluble (HLA-G5, -G6, -G7) molecules. The extracellular structures of HLA-G1 and HLA-G5 contain α1, α2, and α3 domains; HLA-G2 and HLA-G6 contain α1 and α3 domains; HLA-G3 contains α1 domains; HLA-G4 contains α1 and α2 domains; HLA-G7 contains an α1 domain linked to two amino acids encoded by intron 2.

sists of 8 exons; in all databases, exon 8 remains untranslated due to the presence of a stop code in exon 7. The non-translated region of exon 8 is termed "3´untranslated region (3'UTR)" (Donadi et al, 2011). Eighteen SNPs, a 14 bp insertion/deletion, and 44 haplotypes have been identified in the 3'UTR region (Carosella et al, 2015), which are known to influence the translation of HLA-G proteins through either a reduced transcription, mRNA stability, or aberrant alternative splicing.

The physiologic expression of HLA-G is limited to foetal tissues such as: amniotic cells, erythroid precursors, and cytotrophoblasts, and, in adults, to immune-privileged organs, including the cornea, thymus, pancreatic islets, endothelial cell precursors, and erythroblasts (Carosella et al, 2008). Dendritic cells and macrophages can also express HLA-G. HLA-G can be generated by alternative splicing of primary transcript membrane-bound (HLA-G1 to -G4) and soluble (HLA-G5 to -G7) isoforms (Fig. 1) (Ishitani et al, 1992, Kirszenbaum et al, 1994). Four isoforms – HLA-G1, -G2, -G3, and -G4 have transmembrane and cytoplasmic domains and are, therefore, membrane bound. HLA-G5 is the soluble counterpart of HLA-G1, whereas HLA-G6 is the soluble counterpart of HLA-G2 (Carosella et al, 2008). They are comprised of a heavy chain consisting of three globular domains (α1, α2, and α3) which are non-covalently bound to a nanopeptide and β2-microglobulin (β2m) (Carosella et al, 2008).

HLA-G induces tolerance by inhibiting different cells (Fig. 2). This main function is mediated by binding of both soluble and membrane-bound HLA-G to inhibitory receptors. These inhibitory receptors include immunoglobulin-like transcript (ILT) receptor 2 (CD85j; LILRB1) appearing on lymphoid and myelomonocytic cells, ILT-4 (CD85d; LILRB2) expressed by dendritic cells (DC), macrophages, and monocytes (Fons et al, 2006, Gao et al, 2000, Lopez-Botet et al, 1999), and the killer cell immunoglobulin-like receptor (KIR) 2DL4/p49 (CD158d) expressed by natural killer (NK) cells (Yan et al, 2005). HLA-G directly influences different stages of the immune response, including differentiation, proliferation, cytolysis, or cytokine secretion. In the peripheral blood of cancer patients, HLA-G antigens can also be expressed by tumour-infiltrating immune cells (Pangault et al, 2002, Urosevic et al, 2002, Wagner et al, 2000). HLA-G may impair the immune response of patients against tumour. The function of $CD4^+$ T cells can be inhibited by the $HLA\text{-}G^+$ APC (antigen presenting cell) complex, which then induces their differentiation into regulatory T cells (Treg) (LeMaoult et al, 2004). HLA-G can also exert an immune-suppressive activity; specifically it can induce the expression of the non-classical HLA class I molecule HLA-E, which binds peptides derived from HLA-G. This molecule sometimes interacts with the inhibitory receptor CD94/NKG2A to block NK and T-cell reactivity (Gooden et al, 2012). Through the use of inhibitory receptors, HLA-G1 isoform also impedes the cytolytic function of uterine and peripheral NK cells (Rouas-Freiss et al, 1997, Rouas-Freiss et al, 1997). In additional studies, HLA-G was shown to inhibit the function of cytotoxic T lymphocytes (CTL), through a direct interaction with ILT2 or ILT4 inhibitory receptors (Fons et al, 2006, Gao et al, 2000, Lopez-Botet et al, 1999). Recently,

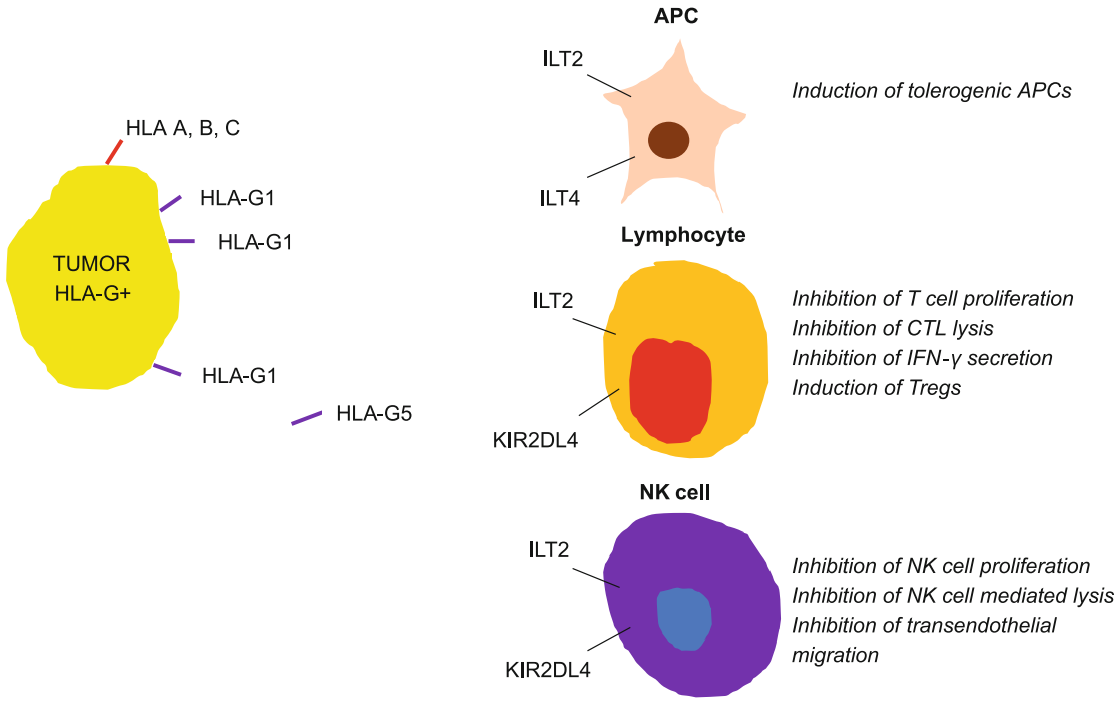

Fig. 2. Mechanisms of both membrane-bound and soluble HLA-G-mediated immune suppression in tumour immune evasion.

new evidence has demonstrated the binding of HLA-G to ILT-2 receptor to suppress B cell responses (Naji et al, 2014). Soluble HLA-G can induce apoptosis of NK cells and cytotoxic T cells, whereas soluble and membrane-bound HLA-G can influence both the expression and release of IFN-γ by NK cells (Rajagopalan et al, 2006, van der Meer et al, 2004, van der Meer et al, 2007). It also contains anti-angiogenic functionality by binding to CD160 on endothelial cells (Fons et al, 2006).

Soluble form of HLA-G – origin, structure, and function

The structure of the soluble and membrane bound isoforms differs at the C-terminus. A short hydrophilic tail replaces the extracellular domain and the intracytoplasmic tail in the secreted isoforms (Fujii et al, 1994, Ishitani et al, 1992, Kirszenbaum et al, 1994). These differences could serve as a marker to distinguish shed or proteolytically cleaved HLA-G isoforms from secreted HLA-G isoforms.

Soluble HLA-G1 was observed to inhibit the cytotoxic activity of HLA class I antigen restricted CTL (Contini et al, 2003, Le Gal et al, 1999, Rouas-Freiss et al, 1999), and sHLA-G5 was observed to inhibit $CD4^+$ and $CD8^+$ T cell alloproliferation by blocking a cell cycle progression. However, sHLA-G5 does not induce apoptosis of alloreactive T cells (Bahri et al, 2006).

Under physiological conditions, monocytes/macrophages combined with myeloid and plasmacytoid dendritic cells produce a major part of sHLA-G (Rebmann et al, 2003).

The level of sHLA-G in serum is approximately one order of magnitude below the amount required to induce apoptosis of some cells *in vitro*, e.g. of $CD8^+$ T cells and $CD8^+$ NK cells (Contini et al, 2003). Therefore, probably under physiological conditions, sHLA-G molecules do not play a major role in triggering $CD8^+$ cell apoptosis. Thus, the potential role of HLA-G in the regulation of the immune response would be restricted to pathological conditions associated with a marked increase of sHLA-G level in blood or in a concrete specific anatomic site.

Soluble HLA-G has also been detected in the plasma/serum of healthy individuals; however, the levels are significantly lower than the levels of other classical HLA class I antigens (Contini et al, 2003), and are influenced by several variables. The gender of the donor has been showed to influence these levels: sHLA-G levels are higher in women than in men (Rudstein-Svetlicky et al, 2007). Furthermore, as previously observed for classical HLA class I antigens (Puppo et al, 1995, Puppo et al, 1997), another important variable is the polymorphism of HLA-G. Healthy individuals carrying the HLA-G*01013 allele or the "null" allele HLA-G*0105N have significantly lower sHLA-G levels than subjects carrying the more frequent HLA-G*01011 and HLA-G*01012 alleles. In addition, subjects with the latter alleles have significantly lower sHLA-G levels than individuals with the HLA-G*01041 allele. Polymorphisms in the 3′UTR and the 5′URR of the HLA-G gene may further influence the levels of sHLA-G in plasma/serum (Hviid et al, 2004). Many studies have evaluated the 14-bp ins/del polymorphism in the 3'UTR, and the 14bp insertion was associated with decreased levels of soluble HLA-G (Chen et al,, 2008, Martelli-Palomino et al, 2013, Rousseau et al,, 2003,). Other polymorphisms in the 3'UTR may influence the binding

of specific microRNAs (SNP at position +3003C/T, +3010C/G, +3142G/C, and +3196C/G) or the mRNA stability by AU-rich elements (SNP at position +3187A/G) leading to an impaired expression of HLA-G (Castelli et al,, 2010, Hviid et al,, 2003). Martelli-Palomino et al (2013) found an association of UTR -5, and -7 haplotypes containing 14 bp insertion, +3142G and +3187A alleles with a low expression of sHLA-G in a healthy population (Martelli-Palomino et al, 2013). Among the SNPs in the promotor at 5'URR, the -716TT and -201GG genotypes have been associated with high soluble HLA-G levels (Carlini et al, 2013).

Under physiological conditions, sHLA-G levels are increased in serum and amniotic fluid of pregnant women. Hunt et al (Hunt et al, 2000) showed that serum levels of sHLA-G are significantly higher in pregnant women than in non-pregnant women. Furthermore, sHLA-G1 levels are higher in amniotic fluid than in cord serum and maternal serum, and the levels decrease significantly as time to parturition decreases (Hackmon et al, 2004).

Since trophoblast cell invasion and placentogenesis show biological features like those of carcinogenesis, malignant tumour invasion and growth could be mediated by similar cellular pathways (Kurlak et al, 2017). Several studies have shown that the expression of "embryonic" HLA groups (HLA-G, HLA-E, HLA-F) by tumour cells led to a similar inhibition of the innate and adaptive immune system and thus facilitated the tumour immune escape (therapy) (Diepstra et al, 2008, Ibrahim et al, 2001, Kurlak et al, 2017, Paul et al, 1998, Wischhusen et al, 2007).

Soluble HLA-G in cancer

There exists a consistent evidence in literature that HLA-G represents an important factor in determining prognosis in various types of cancer.

Breast cancer

Provatopoulou et al (2012) found significantly higher plasma levels of soluble HLA-G in 120 breast cancer (BC) patients, when comparing them to 40 healthy controls. Also, a significantly increased sHLA-G expression was detected in patients with a mixed type of coexisting ductal and lobular breast lesions, as compared to the patients with pure ductal carcinoma or pure lobular neoplasia (Provatopoulou et al, 2012). König et al investigated the use of soluble HLA-G forms as a prognostic marker for predicting the clinical outcome of breast cancer patients being treated with neoadjuvant chemotherapy (NACT). They found that the total and free sHLA-G levels (ExoQuick derived extracellular vesicles fractions) were significantly higher in NACT treated BC patients (n = 154), when compared to the healthy controls (n = 16). The high levels of sHLA-Gfree were exclusively associated to oestrogen receptor expression before NACT. Importantly, high sHLA-G EV (extracellular vesicles) levels before NACT were associated with a disease progression and the detection of stem cell-like circulating tumour cells, however, high sHLA-Gfree levels indicated an improved clinical outcome. They demonstrated for the first time that different sHLA-G subcomponents had different prognostic impacts on the clinical outcome of NACT treated BC patients (König et al, 2016). Zidi et al (2016) correlated the concentration of sHLA-G in women with breast cancer (BC) to their history of pregnancy and breastfeeding, reporting significant differences in sHLA-G levels between BC patients with/without breastfeeding experience. In her study, only those patients, who had no history of pregnancy or breastfeeding presented significant increases in sHLA-G and, moreover, she demonstrated that these patients had advanced SBR (Scraff-Bloom-Richardson grade) III grade of tumour (Zidi et al, 2016). Another study from Jeong et al (2014) demonstrated higher levels of sHLA-G in the breast cancer group (n = 80) as compared to the healthy control group (n = 80) (Jeong et al, 2014). Interestingly, the Adolf et al, study in 2019 found the opposing results: lower levels of sHLA-G were present in breast cancer patients (n = 75) than in the healthy controls (n = 84) in Tanzania. Levels of sHLA-G were also significantly lower in mastectomized patients compared to the non-mastectomized patients. However, this study enrolled patients that had previously been treated with chemotherapy or radiotherapy, hormone therapy or a combination, and 81.3 % of these patients had a mastectomy within the past 12 months (Adolf et al, 2019)

Lung cancer

Ben Amor et al (2016) investigated the influence of HLA-G allelic variants and serum soluble HLA-G (sHLA-G) levels on the risk of non-small-cell lung cancer (NSCLC). Their study found significantly higher serum sHLA-G levels in the patients with NSCLC, particularly in those with advanced disease stages, as compared to the healthy controls (Ben-Amor et al, 2016). Montilla et al (2016) measured the relationship between the level of sHLA-G in bronchoalveolar lavage (BAL) fluid in patients with tumour histological type and overall patient status according to the Karnofsky scale. No correlation was found between soluble HLA-G levels and age, gender, or smoking status. However, a highly significant difference was observed in the levels of sHLA-G in BAL fluid of patients with different histological types of lung cancer, especially in metastatic tumours. The Karnofsky index showed a significant and inverse correlation with the level of sHLA-G in BAL fluid (Montilla et al, 2016).

Gastrointestinal tumours

Recently, Lázaro-Sánchez et al (2019) compared sHLA-G expression in 20 colorectal (CRC) patients with a control sample of 10 healthy subjects. The results showed significantly higher levels of salivary sHLA-G in patients with CRC than in the healthy controls, and higher salivary levels of sHLA-G were observed also in advanced stage CRC patients than in the patients in earlier stages. A significant correlation was found between the concentration of sHLA-G in the serum and saliva of the analysed samples (Lázaro-Sánchez et al, 2019). In 2018, Farjadian et al, published the results from their research work, in which they evaluated the expression of HLA-G in tumour tissues and the plasma levels of sHLA-G in 82 patients with gastrointestinal cancer. The presence of *H. pylori* genome was investigated in tumour tissues

from 25 patients with gastric cancer by PCR (polymerase chain reaction) method. There was a significant correlation between an increased sHLA-G level and stage I tumours. Soluble HLA-G levels were above the cut-off value in all the *H. pylori*-positive patients. They concluded that the level of soluble HLA-G could be a useful indicator for the early diagnosis of gastric and colorectal adenocarcinoma (Farjadian et al, 2018). Li et al (2017) showed that plasma sHLA-G levels in 178 colorectal cancer (CRC) patients were significantly increased compared to the normal controls. CRC patients with sHLA-G above median levels had a significantly shorter survival time than those with lower sHLA-G levels. Soluble HLA-G levels provided a significant predictive value for CRC patients specifically from the following groups: females, the elderly, advanced tumour burden, regional lymph node status, both metastasis status and clinical stage (Li et al, 2017). Similarly, Kirana et al (2017) investigated the prognostic value of preoperative plasma sHLA-G in 133 CRC patients. They observed, within the high 33rd percentile of sHLA-G levels, a higher frequency of mucinous carcinoma (MC) patients and higher sHLA-G levels in the patients with vascular invasion. Moreover, MC patients had significantly higher sHLA-G levels compared to those with adenocarcinoma. Only in stage III patients, high sHLA-G levels were associated with a significantly longer liver metastasis free survival (LMFS) time, and sHLA-G levels displayed a positive correlation with LMFS. They conjectured that sHLA-G levels were associated with distinct progression patterns in consecutive disease stages (Kirana et al, 2017). One year earlier (Pan et al, 2016) measured plasma level of sHLA-G in 81 gastric cancer (GC) patients, 53 benign gastric disease patients and 77 normal controls. They showed that plasma levels of sHLA-G were dramatically increased in GC compared with normal controls and benign gastric disease patients. The AUC (area under curve) for sHLA-G was 0.730 greater than serum AFP, CEA, CA125, CA19-9 and CA72-4.

Urogenital cancer

In 2018, Ben Yahia et al focused on the expression of sHLA-G in endometrial cancer (EC). They examined the total sHLA-G expression, as well as the sHLA-G1 and HLA-G5 isoforms expression in plasma samples from 40 patients and 45 healthy controls. Immunoprecipitation and Coomassie blue staining were performed to explore the presence of plasmatic sHLA-G monomers and dimers. sHLA-G plasma level was significantly increased in the patients with EC compared to the healthy controls. Additionally, HLA-G5 molecules were more represented than sHLA-G1 molecules in EC. Interestingly, sHLA-G has been shown to be elevated in early stages (Stages I and II) of EC, as well as in high grade EC (Grade 3) that is associated with a rapid spread (Ben Yahia et al, 2018). Heidari et al (2017) studied the role of sHLA-G in patients with malignant prostate tumour (n = 26), patients with benign prostate tumour (n = 26), and a group of healthy men (n = 26) and showed that the mean level of sHLA-G was higher in instances of cancer and found a significant difference in sHLA-G serum level between the three groups (Heidari et al, 2017). In contrary, Szipak-Szmigiel et al (2017) showed that serum and peritoneal fluid concentrations of sHLA-G in ovarian cancer patients had no diagnostic values for differentiating between ovarian malignancies (n = 38), benign serous cysts (n = 54), and endometriomas (n = 43) (Szipak-Szmigiel et al, 2017).

Head and neck cancer

In 2020, Agnihotri et al published the study that compared sHLA-G in 122 patients with head and neck squamous cell carcinoma and 99 healthy controls. Significantly elevated levels of sHLA-G were observed in the cancer patients compared to the controls (levels decreased in patients in response to therapy (Agnihotri et al, 2020)).

Childhood malignancies
Neuroblastoma

Morandi et al (2016) was the first to analyse the concentration of sHLA-G in bone marrow (BM) plasma samples from neuroblastoma patients (n = 31) at the time of their diagnosis and healthy donors (n =13). However, the study found the levels to be similar. In contrast, BM plasma levels of sHLA-G were higher in patients with metastatic disease than in patients with localized neuroblastoma (Morandi et al, 2016).

Leukaemia

Almeida et al (2018) measured Th1, Th2, Th17 cytokines and soluble HLA-G levels in the bone marrow of 32 Brazilian children on three separate occasions: at the time of diagnosis, after induction of chemotherapy, and after completion of chemotherapy. Increased levels of sHLA-G at time of diagnosis were found to be associated with an increased leukocyte count, which is a well-known factor for poor prognosis (Almeida et al, 2018). Gros et al (2006) pointed out that an increased secretion of sHLA-G seems to be more pronounced in acute leukaemia subtypes affecting monocytic and lymphoid lineages such as FABM4 and FABM5, as well as both B and T acute lymphoblastic leukaemia. Correlations between sHLA-G plasma level and clinical biologic features suggest a link between the elevated sHLA-G level and the absence of anterior myelodysplasia and high-level leucocytosis. (Gros et al, 2006)

Unspecific malignant diseases

Sun et al (2017) detected soluble HLA-G concentrations in ascites of 94 patients (64 with malignant and 30 with benign ascites). Ascitic levels of sHLA-G were significantly higher in malignant ascites group than in the group of benign ascites. The detection of ascitic soluble human leukocyte antigen-G was deemed a good predictor for distinguishing between the malignant and benign ascites, particularly in cases that are cytology-negative and biopsy-positive (Sun et al, 2017).

Conclusion

Many studies have highlighted the function of the HLA-G gene (and corresponding molecule) as a diagnostic and prognostic factor for cancer patients' clinical outcome. HLA-G has been promoted as a promising immunotherapy target. International recommended standardization protocols, larger cohorts, and prospective studies are required to confirm and validate HLA-G as a target before routine clinical application. Furthermore, in addition to the seven well-known HLA-G isoforms, novel unrecognized HLA-G isoforms do exist. However, as shown in this review, soluble HLA-G is elevated in most cancer patients, when compared to the healthy subjects. Serum/plasma/fluid specimens can be obtained easily and quickly and could aid in the differential diagnosis.

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