

Association Between human leukocyte antigen G (HLA-G) expression and Oral Cancer: A narrative literature review

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Abstract

Background: Oral cancer is a critical current health problem due to its late diagnosis, rapid progressing, poor treatment outcomes, as well as tumor's ability to evade the immune system. One of the significant mechanism to prevent immune attack can be done by expression of non-classical human leukocyte antigen G (HLA-G), which is a type of major histocompatibility MHC class I molecule with powerful immunosuppressive functions. Results of many studies show that rise of HLA-G expression or serum level in oral squamous cell carcinoma (OSCC) patients was related to advanced stages of the disease, metastasis to lymph nodes, reduction in the survival rate, and tumor aggressiveness. In addition, HLA-G expression is highly linked to the presence of regulatory T-cells, which supports the importance of the given factor in the development of an immunosuppressive tumor microclimate. Though the HLA-G therapies are still in their early stage, there are already a number of promising approaches, such as monoclonal antibodies, small-molecule inhibitors, RNA interference, nanoparticle-based drug delivery systems, and Chimeric Antigen Receptor CAR-T cell therapy. This review aim to evaluate the role of human leukocyte antigen (HLA-G)in oral squamous cell carcinoma (OSCC) and it contribution to tumor evasion and disease progression .

Keywords: HLA-G, Oral cancer, OSCC, immunotherapy.

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Introduction

Oral cancer, mostly oral squamous cell carcinoma (OSCC), has become a national health concern and accounts for more than ten cancer types in the top 10, with a large contribution to morbidity and mortality at a rate of approximately 377,000 new cancer cases and 177,000 deaths each year [1]. Even though the treatment is yet to evolve, survival rate, 5 years after therapy is low with the prognosis that is still poor [2]. The reason is that initial symptoms are not often evident and thus lead to a late diagnosis and the invasion of tumors in the surrounding area and metastasis in different locations is strictly connected with patient death in OSCC [3]. In addition, a high tumor growth, metastasis to lymph nodes and unfavorable clinical outcomes are also linked to immunosuppressive tumor microenvironment which favor the development of the disease [4,5].

Despite the immune system being one of the main elements in immune surveillance, genetically modified, or containing mutants cells can develop mechanisms that allow them to suppress or overcome antitumor immunity. Among them is the expression of the human leukocyte antigen G (HLA-G) by tumor cells [6].

HLA-G was first identified to play a crucial role in ensuring maternal immune tolerance towards the semi-allogeneic fetus in pregnancy [7]. Paul,

and colleagues in 1998 were first to report aberrant expression of HLA-G in tumor lesions - although not in adjacent normal tissues which inhibiting natural killer (NK) cell function and escape of tumors from immunosurveillance [8]. Research has already established that high expression of HLA-G in solid tumors is a useful predictor of disease progression to higher stages, tumor metastasis, poor survival, and low disease-free survival. Nevertheless, HLA-G expression may differ among individuals with the same type of cancer, such as OSCC, due to inter- and intra-tumor differences [6].

HLA-G heterogeneity in cancers has been associated with disease stage and outcomes. It also correlates with metastatic status and response to different therapies. HLA-G is a critical marker of immunotolerance in cancer cell immune evasion. It is strongly associated with disease progression and [9]. This prognosis in cancer patients review will comment on the expression of HLA-G, functional role and clinical key in oral cancer and specifically focusing on the OSCC and its potential as a therapeutic target in the management of oral cancer

1. Overview of human leukocyte antigen HLA-G: Genetic and structural features

The human leukocyte antigen G (HLA-G) is a non-classical major histocompatibility complex (MHC) class

Ib heterodimer that is found in the MHC region of chromosome 6p21.3, the most polymorphic portion of the vertebrate genome [10]. Though the structure of HLA-G is similar to classical class I HLA genes (HLA-A, -B, -C), it does not primarily have an antigen presentation purpose. In contrast to the classical class I genes, HLA-G gene has limited tissue expression, limited protein variability and multiple membrane-bound and soluble isoforms. Its unusual molecular structure is such that it does not present peptides to T cells due to its unique peptide-binding groove. HLA-G has polymorphic sites that are scattered throughout across the coding region which includes the exons and introns, unlike in classical HLA class I exons where the number of polymorphisms is very high [10].

As of now seven isoforms structures of HLA-G have been discovered; four of them are membrane-bound (HLA-G1 to HLA-G4) while three soluble visible forms (HLA-G5 to HLA-G7). These isoforms have a truncated cytoplasmic tail with a premature stop codon in exon 6 which is new to classical HLA class I molecules. Particularly, soluble HLA-G5 and HLA-G6 are formed by the presence of a stop codon in intron 4 and intron 2 results in HLA-G7 production [11].

2. HLA-G Expression under physiological conditions:

HLA-G expression limited mainly to the maternal-fetal interface as well as to immune-privileged organs, wherein it was believed to help form and maintain immune tolerance [12]. Its expression on

trophoblasts is essential to guard the fetus against the maternal immune system against the semi-allogeneic tissue. In particular, HLA-G is expressed in a form of membrane-bound and soluble form by cytotrophoblast cells (CTBs) [13]. HLA-G controls the cytotoxicity of uterine natural killer (uNK) cells by suppressing the cytotoxicity with the help of an inhibitory receptor, such as KIR2DL4 [14], LILRB1 and LILRB2 [15]. These molecules safeguard the trophoblast cells against NK cell-mediated lysis and when uNK cytotoxicity is performed on HLA-G-targeting small interfering RNA in JEG-3 choriocarcinoma-derived cell lines, trophoblast cells were found to be more susceptible.

HLA-G also plays a role in immunotherapeutic organ transplant as it serves to prevent graft rejection [17]. Since it helps to prevent the existence of maternal immune attack against the fetus, the same effect should also be achieved in allogeneic organ transplantation [18]. The earliest HLA-G expression study in heart transplantation was in 2000 [17] and thereafter, it has been shown to be present in transplanted solid organs such as heart, kidney, liver, lung, liver-kidney, and kidney-pancreas transplant [19]. Nonetheless, less definitive associations between HLA-G expression and graft acceptance have also been reported, and the HLA-G expression might also be dependent

on the length of time since transplantation [20].

3. HLA-G in cancer immunology

HLA-G is known to be expressed in an array of pathological disorders, such as tumors [21], and has been found to be associated with autoimmune diseases and predisposing to many infections, as well as it will participate to a pathological and dysregulated microenvironment [22]. The HLA-G antigen was detected in many different malignant tumors, and it was frequently correlated to high tumor levels and worse survival, indicating that HLA-G provides a potentially harmful effect in antitumor immunity [9].

HLA-G expression can have several impacts on cancer development, including the induction of apoptosis in immune cells, suppression of cytolytic functions, facilitation of the production of regulatory cells by receptor-mediated binding and phagocytosis, and disruption of chemotaxis on several immune effector cells [23]. LT2 is expressed by all monocytes, dendritic cells (DCs), B cells, certain T cells, and natural killer (NK) cells, while ILT4 is expressed by monocytes, DCs, and neutrophils. NK cells, cytotoxic CD8⁺ T cells, a subset of CD4⁺ T cells, and endothelial cells all express KIR2DL4 and CD160. Although CD8 expression was mostly found on cytotoxic T cells, it can also on NK cells so it will be called cytotoxic natural killer cell [24]. Moreover, HLA-G can stimulate tumor metastasis through its ability to help increase the activity of

factors linked with metastasis like matrix metalloproteins (MMPs) [25].

HLA-G impacts immune cell function, which depends on the type of cell and the receptor profile that is expressed. HLA-G has the capability of directly suppressing of all NK cells, cytotoxic T lymphocytes (CTLs), B cells, neutrophil, and DCs by strongly binding to receptors [24]. It also intermediates indirect immunosuppressive mechanisms, such as the generation of tolerogenic lymphocytes, such as HLA-G-expressing regulatory T cells (Tregs), CD4 low and CD8 low suppressor T cells, type 1 regulatory T (Tr1) cells, myeloid-derived suppressor cells (MDSCs), and DC-10 [26]. Other immunoinhibitory activities are the deactivation of chemotaxis [27].

Endogenous HLA-G expression by tumor cells has been demonstrated by in vitro experiments to block lysis by lymphokine activated killer cells, alloreactive NK cells or by antigen specific CD8⁺ T cells. Experimentally this protective effect can be defeated. There is also recent evidence that HLA-G-expressing DC-10 and CD4⁺ T cells are combined high in patients with acute myeloid leukemia (AML) in which there are HLA-G-positive blasts [28].

4.Oral cancer background:

Oral squamous cell carcinoma (OSCC) represents almost 90% of oral malignancies and tumor recurrences with highest rates of relapse and poor prognosis. The most important risk factors are tobacco and alcohol use, betel

quid chewing, human papillomavirus (HPV) virus, especially types 16 and 18, as well as some additional impact based on genetic vulnerability and environmental carcinogens [29].

Despite the fact that the oral cavity is readily available to clinical examination but the lack of correct diagnosis by clinicians or unawareness of the patient until the disease expands has led to the late diagnosis of OSCC in most cases especially in male [30]. Delayed diagnosis remains a major challenge in oral squamous cell carcinoma. More than 50% of patients are diagnosed at advanced stages, with the five-year survival rate dropping below 50%, highlighting the critical importance of early detection[31].

Adaptation of both innate and adaptive immunity plays a important role in the defense of tumor , it has been discovered that genetically modified or mutated cells can acquire several forms of immune modulatory allow them to evade antitumor immunity. Among these are the expression of human leukocyte antigen G (HLA-G) which tumor cells use to avoid being identified by the immune system [6].

5. HLA-G expression in oral cancer:

Many researches have explored the nature of HLA-G expression and the connection of this type of expression to the occurrence and progression of oral squamous cell carcinoma (OSCC). Goncalves and his team in 2014 studied expression of HLA-G in 60 metastatic and non-metastatic OSCC patients. They discovered that the expression of HLA-

G by tumor cells was considerably elevated in metastatic OSCC than non-metastatic ($P = 0.01$). Moreover, patients who expressed HLA-G lower were found to have a longer survival time (22 months) as compared to the patients that expressed the HLA-G higher (16 months) [6]. These results indicate that a high level of HLA-G in metastatic OSCC could be correlated with tumor immune escape and worse clinical .results

Elsewhere, Imani et al. (2018) evaluated HLA-G in 33 oral squamous cell carcinoma (OSCC) samples and 30 normal mucosa of the oral cavity. They noted that the intensity of staining, proportion of positive cells, and total immunoreactivity scores (IRS) of OSCC was significantly greater than the levels of the same in normal oral mucosa (all $P = 0.001$). Staining intensity of tumor cells was also of great interest by immunohistochemistry for HLA, significant correlation with tumor clinical stage was observed, and there was a higher percentage of staining instances of lymphatic metastasis ($P = 0.026$). There was a significant negative correlation with patient survival ($P = 0.004$ and $P = 0.018$), and a significant positive correlation was found with clinical stage ($P = 0.001$ in either case) [32]. These findings indicate that HLA-G has a role to play in the development of OSCC and metastasis via lymph .nodes

Gonzaga et al. (2019) analyzed the HLA-G levels in 25 oral tongue and 25 lower lip SCCs and related this level to clinical parameters. According to them,

the expression level of HLA-G was more in oral tongue SCCs than in lower lip SCCs. But the HLA-G expression was not significantly correlated with the tumor size, lymph node status, distant metastasis or clinical stage in both of the tumor sites ($P > 0.05$). Interestingly, HLA-G expression in the tumor cells was positively linked with regulatory T (Treg) cells in lower lip SCCs ($P = 0.008$) [33]. This implies that interaction between Treg-HLA-G in OSCC can be implemented in immune evasion in the mouth tongue and lower lip.

6. Targeting of HLA-G for oral cancer immunotherapy:

HLA-G has the potential to become an attractive cancer treatment immune checkpoint. Nevertheless, monoclonal antibodies (mAbs) available that target HLA-G to enable monotherapy are not high. The majority of the available antibodies can identify a single or two HLA-G isoforms [34]. Although all HLA-G isoforms can be detected with antibodies like 4H84 and MEM-G/1, they are also cross-reactive with classical HLA class I molecules [35]. These antibodies were not known if they can prevent HLA-G interaction with ILT2, ILT4 and KIR2DL4, while MEM-G/9 and G233, other antibodies can only bind with HLA-G1 as well as the same site as ILT2 is not targeted [36]. Thus, further research needs to develop antibodies that recognize all HLA-G isoforms without cross-reactivity, as well as have the potential to block HLA-G binding to ILT2, ILT4 and KIR2DL4

Due to these shortcomings, other avenues are also being considered to

prevent HLA-G interactions. Immune checkpoint inhibitors based on antibodies have a series of limitations, such as high cost, instability, immunogenicity, and diminished tumor penetration [37]. As a result, this has led to a change in focus towards small molecules and peptides that have better tissue penetration, stability and are orally available, with a lower immunogenicity [36,37]. Problematic in the design of small molecules are large receptor-ligand when the interactions involve one of the binding pockets must be defined by hydrophobic interactions and are also predominantly of a hydrophobic nature [37].

Another method of down regulating the expression of HLA-G is through RNA interference (RNAi) which may suppress its pro-tumor properties. Nonetheless, it remains a challenge of effective delivery of small regulatory RNAs to produce an effective gene silencing effect [38]. Small-molecule inhibitors and RNAi both are currently being studied and need further investigation to become clinical therapies.

Other approaches that address HLA-G are: 1) inhibition of dimerization, by blocking the cysteine residue on position 42 to block immunosuppressive interactions with ILT2/ILT4; and 2) design of peptides that fit in the HLA-G peptide-binding groove, which could be conjugated with cytotoxic agents to selectively kill tumor cells. Nevertheless, this method can only be compromised by high-affinity peptides that might negatively affect HLA-G internalization

[39]; 3) the blocking of HLA-G receptors by antagonistic antibodies targeting ILT2, ILT4 or KIR2DL4, which can adequately prevent the effects of HLA-G-mediated immune suppression because of the high specificity of such

Nanoparticle-based delivery systems have been found to be promising in increasing the HLA-G-targeted therapies. Zhang et al. [40] created mAb HLA-G and methotrexate (MTX)-encapsulated nanobubbles (mAbHLA-G/MTX/PLGA NBs, where PLGA was poly(lactic-co-glycolic acid)) that specifically targeted HLA-G-positive tumor tissues in cell cultures and in vivo. The nanobubbles were effective in delivering MTX, destroying the left over cancer cells and inhibiting the recurrence of tumors

Other interventions involve blocking the expression of HLA-G to re-instate the immune response. RNA-mediated interference enhances NK-cell cytotoxicity and permits the production of peptide-specific cytotoxic T lymphocytes (CTLs) against HLA-G-derived peptides, like HLA-G146-154, especially in conjunction with suppression of HLA-G-ILT2 interactions. Additionally, anti-HLA-G chimeric antigen receptor (CAR)-T cells have also proven effective against oral cancers with EGFR-mutations and expression, so the possibility of HLA-G-based CAR-T therapy as a new drug in oral cancer treatment could also arise where EGFR-dysfunction is linked to the disease [41].

Conclusions

This review highlights the pivotal role of HLA-G protein in immune evasion and the progression of oral squamous cell carcinoma. Elevated HLA-G expression has been associated with advanced tumor stages, lymph node metastasis, poor prognosis, and reduced patient survival.

HLA-G also contributes to creating an immunosuppressive microenvironment within the tumor by inhibiting various immune cells. Consequently, HLA-G is a promising biomarker for predicting disease prognosis and a potential therapeutic target for oral squamous cell carcinoma. Further studies are needed to confirm the efficacy role of HLA-G in development of OSCC and their impact on improving patient outcomes.

Recommendations

Further studies are needed to incorporate HLA-G measurement into the regular diagnostic and prognostic assessment and find a method to reverse its immunosuppressive actions. Technologies like RNAb therapies, small-molecule inhibitors, and chimeric antigen receptor T-cell (CAR-T) applications have potential, and their clinical validation may greatly benefit OSCC patients.

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