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Tumor Discovery

REVIEW ARTICLE

Receptors of advanced glycation end products in oral squamous cell carcinoma: A systematic review

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Abstract

Oxidative stress markers have been shown to be elevated in oral squamous cell carcinomas; plays a crucial role in the build-up of advanced glycation end-receptors of advanced glycation end (AGE-RAGE) products; and has been shown to exacerbate cellular dysfunction, vascular change, apoptosis, and activate inflammatory pathways. The purpose of this study is to assess comprehensively the involvement of RAGE in oral squamous cell malignancies. The findings imply that these receptors and their associated ligands play a significant role in the growth and spread of the tumor, hence impacting the prognosis and life expectancy of the affected individual. This comprehensive review uncovers promising evidence for the clinical use of these molecules, such as RAGEs, in prognostic considerations or as molecular targets for therapy. The available literature shows a role for RAGE in invasion, migration, and angiogenesis in oral cancers. These preliminary findings are encouraging for the therapeutic use of these molecules for prognostic considerations or molecularly targeted therapy.

Keywords: Receptors of advanced glycation end products; Advanced glycation end products; Oral squamous cell carcinoma; Oral cancers

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1. Introduction

Oral squamous cell carcinoma (OSCC) is the sixth most common type of cancer in the world. OSCC accounts for at least 40% of all cancers; it is especially prevalent in India and Sri Lanka. OSCC is a complex cancer in which genetic mutations, environmental factors, and other risks contribute considerably to its malignancy[1]. Local growth and lymph node metastasis are intrinsically linked to the malignant potential of OSCC[2]. It has been established that oxidative stress is enhanced in oral cancers and plays a significant role in the build-up of several toxic substances. Oxidative stress is characterized by an imbalance between the production of free radicals and antioxidants. In addition, it is illustrated by a phenomenon implicated in the pathophysiology of numerous inflammatory disorders and cancers.

Glycation is a non-enzymatic, spontaneous interaction between free reducing sugars and free amino groups of proteins, DNA, and lipids that result in the creation of Amadori products. Multiple irreversible dehydration and rearrangement result in the formation

of advanced glycation end products (AGEs). It has been demonstrated that the presence of AGEs increases cellular dysfunction, vascular alteration, apoptosis, and activation of inflammatory pathways. Receptors of advanced glycation end products (RAGEs) are a receptor for several ligands, including amphoterin, advanced glycation products, b-amyloids, and S100 proteins[3,4].

The gene for RAGE is located on chromosome 6p21.3 at the class II/III junction of the major histocompatibility complex and has a 1.7 kb 5' flanking region, 11 exons, 10 introns, and a 3' untranslated region[5,6]. RAGE products are raised in a variety of clinical conditions, including several cancers. At each stage of the lesion, RAGE is expressed in the tissue in a distinct manner. The RAGE, commonly referred to as a "pattern recognition receptor," is a member of the immunoglobulin superfamily of cell surface molecules with a diverse array of ligand specificities[7].

By interacting with its varied ligand families, RAGE orchestrates several intracellular signaling pathways to govern numerous cellular functions, including inflammation, apoptosis, proliferation, and autophagy. In animal models, it has also been demonstrated that inhibiting RAGE signaling inhibits cancer growth and metastasis through regulating tumor proliferation, invasion, and matrix metalloproteinase expression[8]. The purpose of this literature review is to establish the relationship between RAGEs and OSCC by clarifying the importance of RAGE as a diagnostic and predictive biomarker for oral malignancies as well as a potential treatment strategy.

2. Materials and methods

We conducted a comprehensive search in PubMed, Google, and Cochrane for publications published up to December 2017 that explored the connection between RAGE and oral cancer. Several crucial terminologies were used separately and in conjunction: RAGE, receptor for advanced glycation end products, or AGE, oral cancer, carcinoma, oral neoplasm, and squamous cell carcinoma.

Exclusion criteria included non-English publications, conference abstracts, and studies that did not involve human subjects or samples, reviews, and articles relating to other head and neck tumors, and studies assessing the effect of drug therapy. Articles on oral cancer, cross-sectional research, and RAGE values are included as inclusion criteria. Following a review of article titles and abstracts, seven full-text studies were retrieved for inclusion in the study.

Due to the heterogeneity of the analyzed studies, a meta-analysis was not possible. The collected papers were subjected to a systematic review, and the results were tabulated and analyzed in Table 1.

3. Results

About 28% of the articles utilizing immunohistochemistry (IHC) demonstrated that RAGE products are more prevalent in the invasive front of tumor tissues, and 43% of the articles demonstrated that high expression of these receptors increased the motility of tumor cells. Due to their compatibility with several ligands, these receptors are crucial for tumor cell angiogenesis, invasiveness, and metastasis, making RAGEs an essential biomarker for determining the prognosis of oral carcinomas.

4. Discussion

RAGE is a cell surface receptor belonging to the immunoglobulin superfamily. They display molecule types produced by the non-enzymatic glycation of proteins through Millard's reaction. RAGE is expressed at low levels in normal tissue and vasculature during development. It appears uncontrolled wherever its ligands congregate[9] and is elevated in numerous clinical and non-pathological situations. The pro-inflammatory RAGE ligand high motility group box 1 (HMGB-1) is frequently released by necrotic cells. HMGB-1 and RAGE have also been reported to interact in chronic inflammation and the immune system. The average RAGE concentration in cancer samples was 57 ± 1.9 pg/mL. In a study, Sasahira *et al.* hypothesized that the concentration of RAGE declines with the progression of cancer; this is due to the consumption of such molecules during the process of cancer initiation, and the emergence of numerous other components in the later stages of cancer[10]. Consequently, the concentration of these receptors may be depleted during the later stages of cancer[11].

In seven studies encompassing 820 cases and 626 controls, the overall RAGE levels were shown to be higher in well-differentiated OSCC and lower as differentiation decreased in this systematic review.

Due to its potential to alter the HMGB-1, it is evident that RAGE has a strong relationship with cell motility; this has been demonstrated in 43% of the publications, hence boosting the invasiveness of the tumor. Using the Boyden Chamber experiment, Choi *et al.* demonstrated that RAGE, in conjunction with HMGB-1, considerably increases the motility of the cells, while Ujjal *et al.* demonstrated that antisense RAGE inhibits this motility. In their study, Shun *et al.* demonstrated that RAGE antibodies inhibit cell motility, underscoring the importance of these receptors in the enhanced cell motility observed in cases of OSCC. The antibody against RAGE may inhibit the motility and migration of cells, thereby facilitating targeted therapy.

Table 1. Details of the studies selected for the review

Study	Number of samples	Cell line	Case	Control	Marker	Method	Observation	*P*-value	Inference	Limitations
Choi *et al.*[10]	10		10	-	RAGE HMGB-1	Reverse transcriptase PCR	RAGE mRNA expression (534 bp) was detected		The mobility of cells was found to be increased when both RAGE and HMGB-1 is present.	Various tissue sources were utilized, and the number of cases was reduced.
						Boyden Chamber Assay	At 2000 ng/ml concentration of HMGB-1 the cell migration was increased.			
Bhawal *et al.*[21]	30	10	10-Primary 10-Metastatic	_	RAGE	Reverse transcriptase PCR	RAGE mRNA was identified at various levels in all oral carcinoma cell lines and very weakly in normal mucosa		Metastatic cases expressed RAGE mRNA at a high level compared to primary tumours	Not mentioned.
						Antisense Phosphorothioate (S)-Oligodeoxynucleotide Assay	RAGE antisense (S) oligodeoxynucleotide-treated LMF4 cells migrating was significantly lower (37 8 8.88 cells per well.	$P = 0.0017$		
						Western Blot	After treatment with antisense S-oligodeoxynucleotide, RAGE protein expression was significantly reduced in metastatic cells.			
Shun-Yao Ko[15]					AGE RAGE	Trypan Blue and WST-1	AGEs or BSA were applied to SAS cells. AGEs lowered the number of cells considerably.	$P = 0.01$	AGEs enhance cell migration and also reduce cell Viability. RAGE antibodies suppress cell migration.	Not mentioned.
						Western Blot	Treatment with AGEs significantly increased ERK phosphorylation.	$P = 0.009$		
Su *et al.*[19]	1210		618	592	RAGE pleomorphism	Real time PCR	When combined effect of Heterozygous genotype (TC) for rs1800625 with the homozygotes (CC) for the variant allele of rs1800625, its association with the risk of oral cancer is increased.	-	SNP rs1800652 was found to be associated with risk and progression of oral cancers	Note on the environmental risks not given.

(Cont'd...)

Table 1. ***(Continued)***

Study	Number of samples	Cell line	Case	Control	Marker	Method	Observation	*P*-value	Inference	Limitations
Sasahira *et al.*[16]	74	_	74	_	RAGE	IHC	The disease-free survival rate of RAGE-H patients was considerably lower than that of individuals with a low grade.	$P < 0.00001$	RAGE-H suggests low disease-free survival rate.	Not mentioned
Landesberg *et al.*[22]	50	_	38	14	RAGE	IHC	10 of 10 (100%) well-differentiated OSCCs were RAGE-positive, while 0 of 8 (0%) were poorly differentiated.	$P < 0.05$	The RAGE expression decreases in OSCC as they become less differentiated	Tumor thickness cannot be determined on biopsy derived material
						Western Blot	Reduced band intensity at the molecular weight 55 kDa, seen more in OSCC than normal control.			
Sasahira *et al.*[23]	40		20	20	RAGE VEGF	Elisa	HSC-3 and HSC-4 cells treated with RAGE antisense S-ODN secreted considerably less VEGF	$P = 0.0123$ and 0.0344, respectively	RAGE plays a function in the expression of VEGF in tumors, which is linked to tumor angiogenesis	No correlations between RAGE and histological differentiation

RAGE: Receptors of advanced glycation end products, VEGF: Vascular endothelial growth factor, AGE: Advanced glycation end products, IHC: Immunohistochemistry, PCR: Polymerase chain reaction

IHC is used to study the distribution of these receptors in tumor tissue sections, which revealed that 28% of the articles studied the expression of RAGE in tumor tissues and the surrounding normal mucosa using IHC and concluded that RAGE positivity is more prevalent at the invasive front and is expressed more in well-differentiated than poorly differentiated OSCCs. This demonstrates that the presence and activity of these receptors and their ligands influence the invasiveness of tumor tissues.

Vascular endothelial growth factor (VEGF) is the primary facilitator of tumor angiogenesis, encouraging the creation of new blood vessels from adjacent capillaries, and granting tumors access to the oxygen and nutrients they require to flourish[12]. VEGF also plays a crucial role in tumor development by protecting tumor neovasculature against apoptosis through the activation of anti-apoptotic proteins Bcl-2 and survivin[13]. The elevated amounts of VEGF in tumors also result in architecturally distinct blood vessels compared to normal blood vessels. In contrast to the architecture of normal vasculature, tumor vasculature is irregularly formed, dilated, convoluted, and characterized by a large number of blind ends. Due to the chaotic design of tumor vasculature, tumor blood flow is often poor, with areas of stasis caused by dead-end arteries and disorganized blood flow caused by aberrant vascular connections[13]. This, in turn, predisposes regions to hypoxia, which further stimulates VEGF release and generates disorganized vasculature. *In situ* study of tumor tissues undergoing neovascularization indicates the close proximity of clusters of capillaries and VEGF-producing cells to necrosis[14].

In one of their articles, Sasahira *et al.* evaluated the relationship between RAGE and VEGF, thereby anticipating its role in angiogenesis[15,16]. Long recognized as the most potent angiogenic factor, VEGF-A is frequently related with increased MDV and unfavorable clinicopathological characteristics and results[17]. The expression of VEGF and VEGF-C was substantially correlated with MVD and LVD, suggesting that RAGE also plays a role in angiogenesis. There was no association between VEGF and MVD numbers, either individually or in terms of grade[18].

Higher levels of AGE receptors were detected near the invasive front of tumors, suggesting that these molecules play a role in the invasiveness and spread of cancers. These results imply that these receptors and their associated ligands play a significant role in the growth and spread of the tumor, hence affecting the prognosis and life expectancy of the affected individual.

Su *et al.* examined the genetic predisposition for oral squamous cell carcinoma; this investigation revealed that the presence of at least one polymorphic allele of rs1800625 increases the risk of OSCC[19]. Allelic discriminations of the RAGE rs1800625, rs1800624, rs2070600, and rs184003 allelic polymorphisms were investigated, and it was observed that the RAGE gene polymorphism rs1800625 not only raised the risk of oral cancer but was also related with late-stage and large-size tumors. The study also sheds light on environmental factors that may alter RAGE expression and oral cancer susceptibility. Even in the absence of tobacco chewing or smoking, polymorphism of the rs184003 allele was found to predispose an individual to a higher risk of oral squamous cell cancer. RAGE-ligand antagonists may be able to effectively target the "Achilles' heel" of cancers, namely, poor prognosis, silent metastasis, drug resistance, and cancer recurrence, given that inhibition of RAGE, HMGB-1, or S100 proteins alone has demonstrated a significant reduction in tumor size, invasion, and angiogenesis in a number of cancers[20].

In conclusion, there is promise for the creation of targeted therapeutics using RAGE products. Its potential significance in angiogenesis and tumor progression (cell invasion and motility) makes it an attractive adjuvant therapy target. *In vitro* inhibition of RAGE signaling with RAGE antibodies decreased cell differentiation and migration, thereby establishing RAGE as a unique and specific target for the treatment and management of OSCCs.

5. Conclusion

Despite insufficient understanding of the mechanism of interaction between various ligands and families, the available evidence supports the function of RAGE in invasion, migration, and angiogenesis in oral cancers. There has been no investigation on the diagnostic use of these markers for oral malignancies. Multiple clinicopathological factors are associated with these oral cancer indicators. This evidence is promising for the therapeutic application of these compounds in prognostic considerations and molecular target recognition treatment. To design a more targeted or possibly individualized treatment for patients, further study must be undertaken to acquire a better knowledge of the molecular events.

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Conflict of interest

The authors declare no conflicts of interest.

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