REVIEW ARTICLE

Tumor Markers and Squamous Cell Carcinoma of Oral Cavity

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ABSTRACT

Tumor markers are substances that are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign conditions that can aid in the diagnosis of cancer. These markers may be employed to predict primary or secondary tumor risk. Sometimes, noncancerous conditions can also cause elevation of some tumor markers to be higher than normal. Besides, not every cancer patient may have raised level of a tumor marker. For these reasons, knowledge about cancer biomarkers is essential. This review highlights potential molecular markers relevant to oral neoplasia in terms of their perspective role of in prevention and detection.

Keywords: Biomarker, Oral cancer, Squamous cell carcinoma, Tumor, Tumor markers.

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INTRODUCTION

Oral cavity cancer is among the most prevalent cancers worldwide and incidence rates are higher in men than women. There are an estimated 529,000 new cases of cancers of the oral cavity and pharynx each year, and more than 300,000 deaths. Oral cancers include the main subsites of lip, oral cavity, nasopharynx, and pharynx and have a, particularly high burden in South Central Asia due to risk factor exposures.[1,2] A tumor marker can be defined as a molecule that indicates the likely presence of cancer or can also be defined as one that provides information about the likely future behavior of an existing cancer (e.g., ability to metastasize or to respond to therapy).[1] The majority of existing tumor markers are mostly useful in making a clinical decision after initial suspicion of cancer or its behavior which has been already raised by more conventional means.[2]

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IDEAL CHARACTERISTICS OF TUMOR MARKERS

During the course of time, only a few tumor markers have stood the test of time and entered in the diagnostic or management algorithms for clinicians. Most important ideal characteristics and use of potential markers are as follows.[3]

- It should be highly specific to a given tumor type
- It should provide a lead time over clinical diagnosis and
- It should be highly sensitive to avoid false-positive results.

Uses

- Estimating the risk of developing cancer
- Screening
- Differential diagnosis
- Determine the prognosis of disease
- Predict response to therapy
- Monitor for disease recurrence
- Monitor for response or progression in metastatic disease.

TUMOR MARKERS IN RELATION TO SQUAMOUS CELL CARCINOMA (SCC)

Albumin

Ecological and observational studies suggest that low serum albumin is associated with higher mortality from cancer. Research conducted over the last decade or so has demonstrated that serum albumin levels (either considered alone or in combination with other parameters) can provide useful prognostic information in a variety of cancers. Pre-treatment serum albumin levels provide useful prognostic significance in cancer.[1]

Autoantibodies as Tumor Biomarkers

Tumor proteins may induce the formation of autoantibodies which can be detected in patient serum. The approach for these studies is to separate protein lysates from human SCC cell lines followed by Western blotting

using patient sera. Antigens are then identified using mass spectrometry (e.g., heat shock protein 70 as an early marker for SCC of the esophagus and sideroflexin three for oral SCC [OSCC]). It has been suggested that these autoantibodies might be used to establish effective new immune therapies, besides using them for early diagnosis of these tumors.[4]

Catalase

Antioxidant enzymes such as superoxide dismutase and catalase can directly counterbalance the oxidant attack and may protect cells against DNA damage. Superoxide dismutase inhibits hydroxyl radicals (OH−) production; therefore, it acts as an inhibitor at the initiation and promotion stages during carcinogenesis. Studies have shown that erythrocyte superoxide dismutase activity was decreased in oral cancer patients than in healthy individuals and patients with oral lichen planus (OLP). The low activity of erythrocyte superoxide dismutase can be due to the depletion of antioxidant defense system, occurring as a consequence of overwhelming free radicals.[2]

CD44

The CD44 family of receptors includes multiple variant isoforms, several of which have been linked to malignant properties including migration, invasion, and metastasis. Analysis of the expression of standard CD44s and the CD44 variant isoforms v3, v6, and v10 was carried out in the head and neck SCC (HNSCC) cell line, HSC-3. The role of CD44 isoforms in migration, proliferation, and cisplatin resistance was determined. HSC-3 cells express at least four CD44 isoforms, and these CD44 isoforms mediate migration, proliferation, and cisplatin sensitivity. Compared with primary tumors, a greater proportion of metastatic lymph nodes demonstrated strong expression of CD44 v3, CD44 v6, and CD44 v10, while expression of standard CD44 was not significantly different in metastatic lymph nodes and primary tumors. Expression of CD44 variant isoforms was associated with advanced T stage (v3 and v6), regional (v3) and distant (v10) metastasis, perineural invasion (v6), and radiation failure (v10). CD44 v6 and CD44 v10 were also significantly associated with shorter disease-free survival.[5]

CD59

CD59 inhibits the complement membrane attack complex by binding C5b678 and preventing C9 from binding and polymerizing. It is presented on "self" cells to prevent complement from damaging them. Tumor cells can escape complement-dependent cytotoxicity by expressing complement restriction factors (CRFs), CD46, CD55, and CD59. CD46, CD55, and CD59 were highly expressed in HNSCC cells including T1/T2N0M0 stages. The CRF expression was much lower or absent in nonneoplastic squamous epithelia or in the submucosa of both normal and tumor tissues.[6]

Endothelins (ET)

ETs are 21-amino acid vasoconstricting peptides produced primarily in the endothelium and have a key role in vascular homeostasis. Salivary ET-1 could be a good biomarker for OSCC development in OLP patients regardless of the degree of OLP disease activity. However, it appeared not to be a good biomarker for detecting recurrence of OSCC in patients in remission.[7]

Glutathione (GSH)

GSH concentrations in human epidermoid carcinoma tissues were measured by high-performance liquid chromatography. The GSH content of epidermoid carcinoma intratumor tissue specimens was significantly higher than that in adjacent non-tumor tissue parts. Tissue GSH levels were not correlated with the age of the patients or tumor size.[8]

Interleukin (IL)-1-α

In a study, the authors analyzed and compared the level of tumor necrosis factor-alpha (TNF-α), IL-1α, IL-6, and IL-8 in whole unstimulated saliva among the OLP patients with dysplasia and individuals of the control group and OSCC. In moderate and severe dysplasia, the level of each cytokine was significantly higher than in control. In moderate dysplasia, TNF-α and IL-1α levels were significantly increased without being different from that in OSCC, but IL-6 and IL-8 were detected at a concentration significantly lower than in OSCC. In severe dysplasia, the level of TNF-α was also not significantly different from that in OSCC and the levels of IL-1α, IL-6, and IL-8 were still significantly lower than those in OSCC.[9]

IL-6

Chronic inflammation constitutes one of the key risk factors for OSCC. Studies indicate that IL-6-induced inflammation promotes tumorigenesis in the oral cavity by altering global long interspersed nuclear elements (LINE)-1 hypomethylation. In addition, concurrent hypermethylation of multiple tumor suppressor genes by IL-6 suggests that epigenetic gene silencing may be an important consequence of chronic inflammation in the oral cavity.[8]

IL-8

IL-8 is an angiogenic chemokine with a high expression level in the tumor tissues. This plays important roles in developing many human malignancies including OSCC. Liu *et al.* at Chung Shan Medical University, Taiwan, examined the association of IL-8 gene polymorphisms with the susceptibility and clinicopathological characteristics of OSCC. Their results suggested that combination of IL-8 gene polymorphisms and environmental carcinogens might be highly related to the risk of oral cancer.[10]

SCC Antigen

SCC antigen, a 48 kD protein, is purified from uterine cervix. The antigen concentration is elevated in SCCs of head and neck, lung, esophagus, and anal canal. The highest concentration of SCC antigen is found in patients with metastases.[11]

Tumor Suppressor Gene P53

P53, a 53 kD nuclear phosphoprotein, functions as a tumor suppressor by inhibiting cell proliferation. P53 plays a dominant role in cellular apoptosis. P53 gene mutations are reported in approximately 50% of all types of cancers. P53 gene mutations are reported to occur commonly in primary breast, colon, ovarian, lung, and esophageal carcinomas.[12]

Telomerase

Genetic damage affects many chromosomes and genes and it is the accumulation of these changes that appear to lead to carcinoma. Telomere maintenance by telomerase or, in its absence, alternative lengthening of telomeres protects this acquired altered genetic information ensuring immortality without losing eukaryotic linear DNA; when this does not occur, DNA is lost and end-replication problems arise. Telomerase is reactivated in 80–90% of cancers and can be used as a target for anticancer therapy and to develop better diagnostic and prognostic markers.[13]

TNF-α

The possible correlation of TNF-α and -β genes with the risk of oral cancer was investigated in a study. The functional polymorphisms TNF-α and TNF-β, which affect gene expression, were investigated by restriction fragment length polymorphism analysis. The frequencies of high expression A2 TNF-α allele and high expression B1 TNF-β allele were significantly increased in cancer patients compared to control.[14]

CONCLUSIONS

It has been concluded that a large number of molecular markers are associated with occurrence, progression, and prognosis of SCC. Tumor markers of increased proliferation in oral carcinoma have been identified and explored for more than a decade now. Although a large body of literature exists on the association of these markers with tumor grading and different degrees of dysplasia in premalignant lesions, it is surprising to note that there are only a few markers that have an impact on prognosis. Nevertheless, markers of cellular proliferation are difficult to interpret as an independent scale for judgment of tumor prognosis.

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