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Role of S100 in oral cancer

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Abstract

Oral cancer refers to all malignancies that arise in the oral cavity, lips and pharynx, with 90% of all oral cancers being oral squamous cell carcinoma. Despite the recent treatment advances, oral cancer is reported as having one of the highest mortality ratios amongst other malignancies. The new emerging technologies in molecular biology have enabled the discovery of new molecular markers (DNA, RNA and protein markers) for oral cancer diagnosis and surveillance. Tumor markers are the substances produced in response to the presence of cancer either by the body itself or by the cancer cells. These markers mostly are the proteins that are produced at a greater rate by the cancer cells. Increased levels of these substances can be detected in urine, blood, or body tissues of the patients with certain types of cancer. One such markers made center stage is S100 proteins which have been also implicated in tumerogenesis. This review pays much attention on the role of S100 proteins in oral cancer.

Keywords: Oral Cancer, Lips, Pharynx

Introduction

Oral cancer constitutes a cancer of the lip and oral cavity and is regarded as the fifth most common type of cancer worldwide. More than 90% of oral cancers are squamous cell carcinomas.[1]

This cancer, when found early, has an 80 to 90% survival rate. Despite this fact and the great treatment advances, the World Health Organization has reported oral cancer as having one of the highest mortality ratios amongst other malignancies with a death rate of five years from diagnosis of 45%. [2]

Moreover, oral cancer patients at comparable stages may run contrasting clinical courses and may respond differently to similar treatments. The clinical staging, therefore, has a limited predictive value for identifying patients with a high risk of disease relapse, and this is

especially true for early-stage oral cancers. Twenty-five to thirty percent of early-stage oral cancer patients develop recurrence and half of these deaths. Since clinical staging is ineffective, further studies examining possible prognostic factors are required, focusing mainly on the assessment of the biological aggressiveness of individual tumors underlying clinical malignancy. The discovery of a prognostic marker permitting the identification of early-stage oral cancer patients with a high risk of early recurrence would be extremely helpful in the implementation of a vigorous treatment modality and an intensive follow-up schedule for this patients.[3]

Use of Markers in Screening for Cancer

1. Markers can be measured in fluids such as blood and urine that can be obtained with minimal inconvenience to the individuals undergoing screening.

2. For many markers, automated assays are available, allowing the processing of large numbers of samples in a relatively short period of time.

3. Tests for markers provide quantitative results with objective endpoints.

4. Assays for markers are relatively cheap compared to radiological, histological, and endoscopy procedures.

Identification of appropriate biomarkers can lead to early detection of oral cancer. It is commonly accepted that a tumor biomarker is a molecular signal or process-based change that reflects the status of an underlying malignant disease and can be detected by one or more assays or tests. However, a tumor biomarker must be characterized by accuracy, reproducibility, and reliability to be clinically useful and guide management. In oral cancer, several biomarkers have emerged, showing promising results in diagnosis, early detection, and prognosis of oral cancer. [4]

Tumor markers types

Mesenchymal Markers

Muscle antigens

- Desmin
- Actin
- Myoglobin
- Myosin

Vascular antigen

- CD 34
- CD 31

Neural antigens

- S 100
- Neuron-specific enolase (NSE)
- Glial fibrillary acidic protein (GFAP)
- Synaptophysin
- Nerve growth factor receptor

S100

S100 protein is so named because of its 100% solubility in ammonium sulphate. It is an acidic protein. It is widely distributed in the central and peripheral nervous systems. Its function is unknown but its relation to calcium and potassium has lead to the hypothesis that it plays a role in ionic regulation in the brain.

It is expressed in glia, Schwann cells, melanocytes, Langerhans cells of the epidermis, histiocytes, chondrocytes, lipocytes, skeletal, and cardiac muscle, myoepithelial cells and some epithelial cells of the breast, salivary, and sweat gland epithelium. It is used in the diagnosis of soft tissue lesions such as benign nerve sheath tumors and melanoma. It is present in virtually all neurilemmomas and neurofibromas. It is helpful in separating malignant peripheral nerve sheath tumors from other similar appearing sarcomas (e.g. fibrosarcoma).[4]

The S100 protein family has been implicated in many cellular events, including cell cycle regulation, growth, differentiation, and motility.[3]

S100 is a family of low molecular weight (10,000 Da) proteins found in vertebrates. It has two calcium-binding sites that have helix-loop helix EF-hand type conformation. The S100 protein family consists of 25 closely related members that have been investigated in humans. Investigations have revealed that S100 proteins are associated with regulation of epithelial-mesenchymal transition, cancer stem cells and tumor heterogeneity in human carcinoma. In addition, the S100 protein family members are implicated in a number of biological processes that may include protein phosphorylation, cell growth and motility, cell cycle regulation, transcription, differentiation, apoptosis and cell survival. [5]

S100 in tumors

Recently, there is a growing interest in the S100 protein members and their possible roles in tumorigenesis because of their differential expression in OSCC. Quantification and recognition of the genes involved in tumorigenesis of OSCCs may facilitate the use of S100 gene proteins as biomarkers for early diagnosis, prognosis and/or targets for therapy. For this purpose, identification of S100 proteins in OSCCs may be a first step in understanding their possible association in the development of oral cancers. Controversy exists in the literature regarding the differential expression of S100 proteins and their functional correlations found in OSCCs. For instance, in a study by Sapkota et al. , S100A8 and A9 were found to be overexpressed in OSCC patients as compared to healthy controls. However, Driemel et al. showed contradictory results and reported under expression of the same proteins in OSCC. To the best of our knowledge from indexed literature, there has been no study that has reviewed the expression of the S100 protein family in OSCCs.[5]

S100 family of proteins including S100A7, A8 and A9 have been reported to play essential roles in inflammation and carcinogenesis. These proteins are involved in disturbances of calcium signaling pathways which is the central mechanism in tumorigenesis and specifically in the process of invasion and metastasis . S100A8 and S100A9 can be synthesized and secreted by granulocytes, monocytes and macrophages, and are identified as cytokine-like and transcriptional factor-like molecules affecting expression of proinflammatory cytokines such as tumor necrosis factor-α, interleukin-1 and matrix metalloproteinases. S100A7, in particular has been shown to play a significant role in assisting the host-inflammatory cell response, where it is implicated as a chemotactic factor for lymphocytes and neutrophils and has been associated with increased inflammatory cell infiltrates across all types of invasive tumors. In addition, it is well documented that S100A7 is up-regulated in inflammatory epidermis, correlating with epithelial malignancies. It is noteworthy from the included studies that investigated the expression of S100A7 in OSCC (an epithelial origin metastatic disease), all studies reported over expression of S100A7 in patients with OSCC as compared to healthy individuals. Therefore, it is suggested that altered expression of S100A7 protein is associated with oral cancer development and the secreted form of S100A7 protein could act as a potential OSCC marker. However, it is important to interpret these findings with caution.[5]

S100A2 in cell nuclei may play an inhibitory role in preventing primary oral cancer from recurring, and loss of nuclear S100A2 may serve as an adjuvant prognostic marker for earlystage oral cancer patients with a higher

risk of recurrence. Because a high rate of loco-regional recurrence is often accompanied by high mortality in early-stage oral cancer patients, more aggressive therapeutic regimens and intensive follow-up may be used for early-stage oral cancer patients with fewer than 50% of nuclei staining positive for S100A2. Although we only included a small group of patients primarily treated with complete surgical resection, one effective treatment regimen for oral SCC,3 this study draws attention to a promising prognostic factor that may define a more appropriate disease management for individual patients.[3]

With the findings of the included studies, the threshold for diagnostic levels of S100 proteins cannot be proposed. In addition, a moderate risk of bias and poor quality studies was found in almost 60% of the included studies mainly in: (i) selection and (ii) exposure of the disease. The overall sample sizes in the included studies were small. These methodological shortcomings should be considered when interpreting the findings of the study.[5]

S100 proteins show variation in structure, expression in different cancer tissue/cell, metal ion binding and dimer formation ability.[6]

It remains debatable whether up-regulation or down-regulation of specific S100 protein members serves as diagnostic marker in OSCC. From the present systematic review the threshold for diagnostic levels of S100 proteins cannot be proposed. Further case-control studies with larger sample sizes are required to obtain strong conclusions in this regard.[5]

Conclusion

The tumor markers can serve as an important diagnostic tool in clinical practice. The level of these markers may reflect the extent of the disease, indicating the level of progression and prognosis of the disease. Tumor markers cannot be considered alone as primary modalities for the diagnosis of cancer, but they can be used as an adjunct to routine histopathology using hematoxylin and eosin stain. These markers can also be used in combination with the diagnostic methods to confirm the malignancy and help in grading them. Their main utility in clinical medicine has been a laboratory test to support the diagnosis. New investigative techniques at the cellular and molecular level show great promise at defining potentially malignant lesions but further prospective, in-depth studies are required to determine their practical usefulness.[4]

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