

Tumor markers in oral cancer: A review

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ABSTRACT

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. These markers are useful in differentiating primary or secondary tumors. In few noncancerous conditions, these markers are often found to be elevated. For these reasons, the knowledge regarding these biomarkers has increased tremendously. This article classifies the different types of tumor markers and implicates their role in some diseases.

Keywords: Biomarkers, cancer, tumor

Introduction

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 (noncancerous) conditions that can aid in the diagnosis of cancer and in the assessment of tumor burden.^[1,2] Tumor markers have been used to predict the recurrence of a particular disease. Few markers are specific for a single individual tumor (tumor-specific marker); most are found with different tumors of the same tissue type (tumor-associated markers). They are present in higher quantities in cancer tissue or in blood drawn from cancer patients than in benign tumors or in the blood of normal subjects.^[3]

A quick diagnosis is crucial to control a possible malignant transformation of oral premalignant diseases and for increasing the overall survival rate of the patients. Numerous techniques and methods like scraping the surface of the lesion analyzing the cytological characteristics of the oral premalignant lesions are essential for doing the right diagnosis. Nowadays, though the current standard of performing diagnosis in oral pathology is related to incisional biopsy with histology, this method is painful for patients and involves a delay in the diagnosis, although histology is fully done. A new technique for doing noninvasive analysis of a soft tissue lesion is the autofluorescence. It can be used as a helpful method useful to find oral precursor malignant lesions and the correct location for taking biopsies within the altered mucosa.^[4,5]

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Use of Markers in Screening for Cancer

Screening involves the detection of early disease or a preclinical state in subjects without signs or symptoms of the disease.

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Instead of the screening tests such as mammography for breast cancer, the Papanicolaou test for cervical cancer, the use of tumor markers serves greater practical advantages in cancer screening.^[6]

These advantages include:

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.^[7]

Classification

I. According to *Spiegth and Morgan* (1993)^[8]

- A. Proliferative markers: PCNA, Ki67, BrU, Histones and AgNORs
- B. Genetic markers: Ploidy
- C. Oncogene: C-myc
- D. Tumor suppressor markers: P53 mutations
- E. Cytokines
- F. Blood group antigens
- G. Integrins ECM ligands

2. According to *Schliephake H*^[9]

A. Tumor growth markers

1. Epithelial growth (EGF)
2. Cyclin
3. Nuclear cell proliferation antigens
4. AgNORs (Agryophilic nucleolar organizer region)
5. Skp2 (S-phase kinase-interacting protein 2)
6. HSP 27 and 70 (Heat shock protein)
7. Telomerase

B. Markers of tumor suppression and anti-tumor response

1. Retinoblastoma protein (pRb)
2. Cyclin-dependent kinase inhibitors
3. p53

4. bax
5. Fas/FasL

C. Angiogenesis markers

1. VEGF/VEGF-R (Vascular endothelial growth factor/receptor)
2. PD-ECGF (Platelet-derived endothelial cell growth factor)
3. FGFs (Fibroblast growth factor)

D. Markers of tumor invasion and metastatic potential

1. MMPs (matrix-metallo proteases)
2. Cathepsins
3. Cadherins and catenins
4. Desmoplakin

E. Cell surface markers

1. Carbohydrates
2. Histocompatibility antigen
3. CD57 antigen

F. Intracellular markers

1. Cytokeratins

G. Markers of anomalous keratinization

2. Filagrins
3. Invoulcryn
4. Desmosomal proteins
5. Intercellular substances antigen
6. Nuclear analysis

H. Arachidonic acid products

1. Prostaglandin E2
2. Hydroxyecosatetraenoic acid
3. Leukotriene B4

I. Enzymes

1. Glutathione S-transferase

Epithelial Markers

- a. Cytokeratins (CK)
- b. Epithelial membrane antigen (EMA)
- c. Oncofetal antigens
- d. Alpha-fetoprotein (AFP)
- e. Carcinoembryonic antigen (CEA)
- f. Desmoplakin

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

Prognostic Markers

Cell adhesion molecules

- Cadherins
- Integrins
- Selectins

Proliferation markers

- PCNA
- Ki67
- AgNORs

Biochemical Markers

Enzymes and isoenzymes

- Prostatic acid phosphatase (PAP)
- Prostate-Specific Antigen (PSA)
- Placental Alkaline Phosphatase (PALP)
- Lysozyme

Protein

- Ferritin
- Glycoprotein
- Beta protein
- Immuno globulins

Hormone Receptors

- Estrogen receptor (ER)
- Progesterone receptor (PR)

Epithelial Markers

Cytokeratin

Cytokeratins are the intermediate filament proteins present in the cytoplasm of all epithelial cells. Cytokeratins are a family of 20 members who are present in normal epithelial cells and their

tumors.^[10] Based on their isoelectric point, the cytokeratins are divided into two types:^[11]

- I. The acidic group includes keratins 10 to 19. They have a molecular weight ranging from 40 to 56.5 kD.
- II. The basic group contains keratins from 1 to 8. They have a molecular weight ranging from 52 to 67 kD.

Cytokeratin expression in normal oral mucosa

Keratins are usually found in pairs, with one type I (9–20) coexisting with one type II (1–8), each encoded by its own gene. K5 and K14 are expressed by the basal cells of oral mucosa and in “noncornifying” sites K19 is usually found. Suprabasal cells in the “noncornifying” regions, e.g. buccal mucosa, ventral tongue, express K4 and K13. In cornifying sites e.g. hard palate, dorsal tongue, K1 and K10 are largely found. In regions of increased proliferation, K6 and K16 are found. The so-called “simple” epithelial keratins K8 and K18 are not normally found in the stratified squamous epithelium but rather in single cells such as glandular tissue (e.g. salivary glands).^[10]

Cytokeratin expression in pathology

Low molecular weight keratins are seen in simpler nonstratified epithelia and tumors derived from them (i.e. breast carcinomas or gastrointestinal carcinomas derived from cuboidal or simple columnar epithelia). The higher molecular weight keratins are seen in more complex stratified squamous epithelia and their corresponding tumors (i.e. squamous cell carcinomas).^[10,11]

Desmoplakin

Desmoplakins are the proteins present within the epithelial attachments i.e. the desmosomal plaques of epithelial cells. Desmoplakin may be expressed by epithelial cells, meningeal cells, and the mesothelium. Desmoplakins can also be identified within the glandular component of synovial sarcomas but not in other sarcomas.^[12,13]

Thus, desmoplakins represent an additional marker of epithelial differentiation independent of keratin.^[13] Mutations in the gene encoding for these proteins lead to several cardiomyopathies and keratodermas as well as the autoimmune disease paraneoplastic pemphigus.

Alfa fetoprotein

Human alpha-fetoprotein (HAFP) is a tumor-associated fetal glycoprotein involved with both ontogenic and oncogenic growth. The fetal protein is a 69-kDa single-polypeptide chain that contains 3–5% carbohydrate and is produced in the yolk sac and fetal liver.^[14] The levels of HAFP during pregnancy can serve as a biomarker for detecting multiple congenital malformations of the embryo and fetus. The abnormal AFP levels are indicative of neural tube defects and brain/spinal cord malformations.

The role of alpha-fetoprotein in malignancy

Serum AFP levels help in the diagnosis of primary hepatocellular carcinoma, hepatoblastoma, nonseminomatous testicular germ

cell tumors the embryonal carcinoma, teratoma, choriocarcinoma, and yolk sac carcinoma, and so on germ cell tumors of ovary and extragonadal germ cell tumors.

Alpha fetoprotein is a more sensitive and more specific marker for hepatoma than CA 19–9. Increased alpha-fetoprotein concentrations are found in 80% of patients with liver cell cancer and substantially increased values are rarely found in patients with benign liver disease or other gastrointestinal malignancies.^[10]

Carcinoembryonic antigen

Carcinoembryonic antigen (CEA), a glycosylated protein of MW 180 kDa, is overexpressed in a wide range of human carcinomas including colorectal, gastric, pancreatic, nonsmall cell lung, and breast carcinomas.^[15] CEA measurement is mainly used as a tumor marker to identify recurrences after surgical resection or localize cancer spread through the dosage of biological fluids. The CEA blood test is not reliable for diagnosing cancer or as a screening test for early detection of cancer. Most types of cancer do not produce high CEA. Elevated CEA levels should return to normal after successful surgical resection or within 6 weeks of starting treatment if cancer treatment is successful. CEA levels may also be raised in some non-neoplastic conditions such as ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease as well as in smokers.^[1]

Mesenchymal Markers

Desmin and vimentin

Desmin and Vimentin are members of intermediate filament family of proteins.^[16] Desmin levels are elevated in cases such as Rhabdomyosarcomas, Leiomyosarcomas and in other spindle cell lesions such as fibromatosis, malignant fibrous histiocytoma, and myofibroblastoma of the breast.

Desmin positivity can also be observed in malignant peripheral nerve sheath tumor, epithelioid sarcoma, liposarcoma, and angiomatoid fibrous histiocytoma. Desmin is mainly used as a diagnostic marker.^[10]

Actin

Actins are a family of contractile proteins. They are composed of molecular weight of about 42 kD. They are seen distributed in mammalian cells. It can be divided into alpha, beta, and gamma subtypes depending on electrophoretic mobility. This protein is seen in cardiac, skeletal, and smooth muscle cells. It also recognizes pericytes, myoepithelial cells, and myofibroblasts. This can be used for immunostaining of myofibroblastic cells within granulation tissue, scar tissue, nodular fasciitis, and fibromatosis. It is positive for rhabdomyosarcoma but negative for other round cell sarcomas such as neuroblastoma and Ewing's sarcoma. Thus, it acts as a marker for Rhabdomyosarcoma. It is mainly used as a diagnostic marker.^[17]

Myoglobin

Myoglobin is the oxygen-binding heme protein. It is a protein present in humans. It is encoded by the MB gene. It has a molecular weight of 17,800 daltons. It is found exclusively in skeletal and

cardiac muscle. It acts as a marker for Rhabdomyosarcomas. Myoglobin is used as a diagnostic marker.

AgNORs

The nucleolar organizer regions (NORs) are loops of DNA which transcribe ribosomal RNA.^[18] They are associated with proteins, which are required for RNA transcription. The AgNOR number is directly proportional to the speed of the cell cycle. For this reason, cell proliferation has a prognostic value, since the high proliferative activity is associated with poor prognosis.^[19]

NORs are located on each of the short arms of acrocentric chromosomes 13, 14, 15, 21, and 22. NORs can be detected by staining with silver nitrate and the structures thus demonstrated are termed AgNORs. Simple silver staining technique can recognize these argyrophil associated proteins. They appear as black dots after silver staining in nucleolar and extranucleolar regions. In a normal cell 20 black dots of AgNORs can be seen (2 per arm of chromosome i.e. $2 \times 10 = 20$) but only one or two dots are the dots are tightly packed. In the dysplastic cells and malignant cells, as the amount of DNA increases, the number of AgNOR dots (AgNOR count) also increases.^[10]

P53 mutations

p53 (the product of the human TP53 and mouse TRP53 genes) is best known and most extensively studied as a pivotal signaling node that converts diverse upstream stress signals into downstream responses including cell cycle arrest, senescence, DNA repair, and programmed cell death.^[20] An emerging role for p53 in regulating cellular differentiation, self-renewal, and plasticity has generated intense interest, particularly among cancer researchers. p53 loss is almost exclusively associated with poorly differentiated thyroid cancers. In breast cancer, p53 mutations are most frequent.

Neural antigens

S100 protein

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 led to the hypothesis that it plays a role in ionic regulation in the brain.^[21] 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).^[21]

Neuron-specific enolase

Neuron-specific enolase (NSE) is a member of the family of enolase dimeric isoenzymes. These are formed of three types of subunits: Alpha, beta, and gamma. NSE is the gamma subunit of enolase enzyme. It is present predominantly in neurons and

neuroendocrine cells.^[22] NSE has been detected in patients with neuroblastoma, small cell lung cancer (SCLC), Wilms' tumor, melanoma, and cancers of the thyroid, kidney, testicle, and pancreas.

Synaptophysin

It is a membrane protein found in the presynaptic vesicles of nerve cells. It can be identified within the nerve cells of the peripheral, central nervous system, and neuroendocrine cells. Neuroblastic tumors (neuroblastoma, ganglioneuroblastoma, ganglioneuroma) and paragangliomas also contain this membrane protein.

Implications for clinical practice

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.^[23,24]

Conclusion

Tumor markers that are the biochemical substances thus not only help in detecting the malignancy but also differentiate the nature of malignancy involved. The amount of their production depends on the growth of tumor cells. Tumor markers also serve as a biomarker to determine the prognosis of the disease. Many molecular markers are associated with the occurrence, progression, and prognosis of carcinoma. Markers of increased proliferation in oral cancer have been identified and explored for more than a decade. 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 that there are only a few markers that have an impact on prognosis.

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Conflicts of interest

There are no conflicts of interest.

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