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An overview of tumour marker in oral cancer

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Abstract

Essential understanding and knowledge about the development of oral cancer, transformation of precancerous lesion to malignant lesion is very essential for making early diagnosis leading to success and prognosis of the treatment. Complete awareness of Tumor marker can aid in earlier detection of oral cancer. In combination with other diagnostic modalities, tumor marker can support in staging, assess tumor volume and to ascertain tumour metastasis.

Keywords: Biomarker; Proliferation markers; salivary tumor markers; Tumor associated antigen.

INTRODUCTION

Oral cancer is a dreadful condition affecting a lot of humankind and serves to report the lowest survival rate all over the world. Among the cancers, oral cancer is a common malignancy affecting the individual[1]. Among the cancers in head and neck region oral squamous cell carcinoma (OSCC) is the fifth most common cancer seen worldwide[2]. The most common malignant Head and neck OSCC reported may include leukoplakia or oral submucous fibrosis (OSF). Inspite the oral cavity is visible, it is unfortunate that the patient always report when they have noticeable changes in the mucosa and almost all the condition precede to malignancies in the reporting stage of the patients to the hospital. Delayed diagnosis presents a challenge not only for treatment planning, but also significantly adds to the expenditure. This may consequently result in disfigurement, higher morbidity rate and reduced cure rates. Detection of oral cancer at the initial stages can thus directly impact the survival rate of an individual.

The process of development of oral cancer usually occurs in 2-steps i.e., the presence of a precursor (potentially malignant) lesion and its subsequent transformation into cancer. Studies have shown that between 1 and 18% of oral pre-malignant lesions will develop into oral cancer[3,4]. Clinically, the distinction between a potentially malignant lesion and an early malignancy cannot be ascertained, thus posing a problem in diagnosis. Advances in the molecular analysis of cell alterations leading to malignant transformation have revealed the mechanisms that lead to the occurrence and progression of malignancies. Malignant cells show alterations in the histologic appearance and biochemical behaviour as compared to their normal counterparts. These malignant cells synthesize endogenous products or several abnormal cellular products in excess. They can be detected in the various body fluids such as blood, serum or saliva and on the surface of the cancer cells either by biochemical methods or by immunochemistry. These products which are synthesized by the tumour cells or by the body in such abnormal situation are known as 'tumour markers'. These tumour markers can be used for early screening and detection of cancer.

HISTORY:

The first tumour marker was identified incidentally by Bence-Jones in 1846 from patients suffering from "Mollities ossium"[5]. In 1930, Zondek identified the first modern tumour marker Human Chorionic Gonadotropin (HCG). Generally, HCG is used to detect pregnancy, but presence of high level of HCG in the blood in non-pregnant women may be the sign of a cancer of the placenta called Gestational Trophoblastic Disease (GTD) [6]. In 1965, Gold et al. discovered the first "tumour antigen" from specimens of human colonic cancer, which was later identified as carcino-embryonic antigen (CEA) [7]. Till date, numerous tumour markers are identified.

CLASSIFICATION OF TUMOUR MARKERS

Tumour markers have been classified by Malathi (2007)[8] as:

1. Oncofetal antigens e.g. Alphafetoprotein (AFP), Carcinoembryonic antigen (CEA).
2. Tumour associated antigens/Cancer antigens (CA) e.g. CAl25, CA19-9.
3. Hormones e.g. Beta human chorionic gonadotropin, Placental lactogen, Calcitonin.
4. Hormone receptors e.g. Estrogen & progesterone receptors.
5. Enzymes and isoenzymes eg: Prostate specific antigen (PSA), Neuron specific enolase (NSE).

6. Serum and tissue proteins e.g. Beta2 microglobulin, protein S-100.
7. Other biomolecules e.g. Polyamines.

BROAD CLASSIFICATION OF TUMOUR MARKERS[9]:

1. Proliferation markers- Ki-67, PCNA (proliferation Cell Nuclear Antigen) , DNA polymerase alpha, protein- p105, p120, statin
2. Oncogenes- c-erbB2 gene, ras gene, myc gene, Bcl-2 gene (B-cell lymphoma)
3. Growth factors and receptors- EGFR (Epidermal Growth Factor Receptor), Transforming growth factor, β-HCC (β-Hepatocellular carcinoma), Fibroblast growth factor (FGF) receptor, Insulin and insulin like growth factor receptor
4. Tumour suppressor genes- protein53, Retinoblastoma susceptibility suppressor gene
5. Serological tumour markers

a. Markers associated with cell proliferation
b. Markers related to cell differentiation: (Carcinoembryonic proteins like Carcinoembryonic antigen, α- Feto protein)
c. Markers related to metastasis
d. Related to other tumour-associated events
e. Related to malignant transformation
f. Inherited mutations
g. Monoclonal Antibody-defined tumour markers

MECHANISM OF BIOMARKER IN CANCER

Cancer is a cluster of diseases involving alterations in the status and expression of multiple genes that confer a survival advantage and undiminished proliferative potential to somatic or germinal cells[10]. Alterations occur primarily in 3 main classes of genes viz., (proto) oncogenes, tumour suppressor genes and DNA repair genes results in the development of cancer cell, which will resists the natural and inherent death mechanism(s) embedded in cells (apoptosis and like processes), coupled with dysregulation of cell proliferation events[11,12]. This conversion of normal cells to cancer cells includes gene rearrangement, point mutations, and gene amplifications resulting in changes in molecular pathways[13, 14]. Biomarkers are therefore invaluable tools for early cancer detection at molecular level.

IDEAL TUMOUR MARKER

Criteria for Ideal tumour markers[8] are

1. High sensitivity and low false negatives
2. High specificity and low false positive
3. High positive and negative predictive value
4. 100% accuracy in differentiating between healthy individuals and tumour patients. If present in the plasma of healthy individuals, it should exist in a much lower concentration than that found in association with all stages of cancer.
5. Be able to differentiate between neoplastic and non-neoplastic disease and show positive correlation with tumour volume and extent. They should change as the current status of the tumour changes over time.
6. Precede and predict early recurrence before they are clinically detectable.
7. Predict the risk for eventual development of recurrence.
8. Be clinically sensitive i.e., detectable at early stage of tumour
9. Be either a universal marker for all types of malignancies or specific to one type of malignancy
10. Be easily assayable and be able to indicate all changes in cancer patients receiving treatment.
11. Its levels should precede the neoplastic process, so that it can be useful for screening early cancer. It should have an abnormal plasma level, urine level or both in the presence of micro metastases.

USES OF TUMOUR MARKERS[15] (Summarized by Chan and Sell in 1994)

1. Screening in general population
2. Diagnosis of primary tumour
3. Differential diagnosis of suspicious lesions
4. Clinical staging of cancer
5. To identify the undetected tumour metastasis
6. Estimating tumour volume
7. To indicate the prognosis of disease progression
8. Evaluating the success of treatment
9. Detecting the recurrence of cancer
10. Monitoring responses to therapy
11. Radioimmunolocalization of tumour masses
12. Determining direction for immunotherapy

TESTS USED IN TUMOUR MARKER DETECTION[16]:

- EIA: Enzyme immunoassay
- FISH: Fluorescence in-situ hybridization
- ICC: Immunocytochemistry
- ICMA: Immunochemiluminometric assay
- IHC: Immunohistochemistry
- IRMA: Immunoradiometric assay
- MEIA: Micro particle enzyme immunoassay
- PCR: Polymerase chain reaction
- RIA: Radioimmunoassay
- RT-PCR: Reverse transcriptase polymerase chain reaction

TUMOUR MARKERS IN ORAL LESIONS

1. Giant cell lesions of the oral cavity

Alpha-1 chymotrypsin and Factor XIIIa antibodies are specific markers for histiocyte and macrophages and are used for giant cell lesions, since they have been found to arise from precursors cells that express these markers[17]. p53 inactivation by MDM2 (Murine Double Minute) expression may occur in the pathogenesis of giant lesions of the jaws and long bones [18].

2. Oral Squamous Cell Carcinoma (OSCC)

Bcl-2 is used as a prognostic indicator in early oral squamous cell carcinoma[19]. Decrease in CD-80 expression serves as marker for increased tumorigenicity during early OSCC[20]. Decreased expression of CD44 indicates decreased survival rate[21]. Expression of C-erbB2 predicts higher risk of recurrence for tongue SCC[22]. Cyclin D1,

Ki67[23], CKD2[24] over expression were positively correlated in OSCC. VEGF is an important angiogenic factors seen in endothelial and cancer cells in head and neck SCC[25,26].

3. Potentially malignant diseases and malignant transformation

Cytokeratins- CK19 and CK8 are markers of progressive premalignant changes in head and neck carcinomas[27, 28]. The aberrations of C-erb-1 and C-erb-2 are indicators of early changes during carcinogenesis process in oral premalignant lesions[29]. Expression of cell cycle proteins p16 and p53 along with Ki-67 can be used as markers to identify evolution of oral precancerous disease and improves the identification of the degree of dysplasia. Immunohistochemical p53 overexpression is valuable marker for early malignant transformation. Overexpression of p53 along with PCNA is presumed predictors for malignant transformation of oral papilloma. Beta-2 microglobulin was increased in oral submucous fibrosis (OSF) and oral cancer[30]. Survivin expression levels were higher in OSCC transformed from OSF[31].

4. Salivary gland tumours

Differences in the expression of HA (Hyaluronic) and CD44 antigen was seen among different types of salivary gland tumours [32].

5. Solid malignancies

Endoglin (CD105) is a powerful marker for neovascularisation in solid malignancies[33].

6. Adenoid cystic carcinomas

Positive CD105 indicates increased risk of metastasis[34].

7. Metastatic tumours

Cathepsin D is the predictor of cervical lymph node metastasis in SCC of head and neck region[35]. VEGF-C (Vascular Endothelial Growth Factor- C) or LVD (Lymphatic vessel density) can effectively predict lymphatic metastasis of OSCC[36]. Preoperative serum p53 antibody is a significant prognostic marker for nodal metastasis of SCC in head and neck region[37].

8. Prognosis and Overall survival rate

C-erbB2 expression denotes significantly decreased overall survival rate in recurrent head and neck cancers[38]. Cyclin A activity predicts clinical outcome in oral pre-cancer and cancer[39]. EGFR, TGF- α (transforming growth factor-α), FGF (Fibroblast Growth Factor), Cyclin D1 and p53 are some of the molecular markers that can provide independent prognostic information in head and neck SCC[40]. Preoperative serum p53 antibody may act as an important prognostic marker[41]. Several HSPs (Heat Shock Protein) are implicated in the prognosis of specific cancers, for example, HSP70 expression predicts predicts the response to chemotherapy in osteosarcomas.

9. Recurrence and second primary tumour

P53 expression may be a significant tumour marker for diagnosing the risk of recurrence of primary disease as well as second primary tumours of head and neck SCC[42-46]

10. Odontogenic tumours

Cytokeratins- CK 14 and 19 are frequently expressed in odontogenic tumours with epithelial origin[47, 48]. Development of the odontogenic tumours from the remnants of the odontogenic process is regulated by series of reciprocal epithelial –mesenchymal interactions via integrin-Basement membrane (BM) protein communications. BM proteins like Laminins 1 and 5, collagen type IV and fibronectin expression was reported in ameloblastomas, calcifying cystic odontogenic tumours (CCOT), and Adenomatoid Odontogenic Tumours (AOTs) [49]. EMA (Epithelial membrane antigen), CEA, CK 10, CK13, Ki-67[50], IPO-38 (Monoclonal antibody of IPO)[51] , gp38 (glycoprotein)[52], Podoplanin[53] expression were reported in KCOT (Keratocytic odontogenic tumor), indicating the aggressive behaviour, proliferative potential, and neoplastic potential of KCOT.

Ameloblastin (AMBN) gene mutations are responsible for the tumorigenesis of epithelial odontogenic tumours without Odontogenic ectomesenchyme[54]. Reduced ameloblasts in the odontoma displayed most intense amelogenin expression[55].

Calretinin is a calcium binding protein and is primarily expressed in central and peripheral nervous system and it is used as the diagnostic marker for malignant mesotheliomas[56]. Calretinin can be used as the specific marker for neoplastic ameloblastic epithelium which is expressed only in solid and unicystic ameloblastomas and not in any other Odontogenic cysts/tumours[57]. Thus, Calretinin can be used as a diagnostic marker to differentiate unicystic ameloblastoma from other cystic lesions[58].

Bone morphogenetic proteins (BMP) might play an important role in the formation of calcified dental tissues and the development of odontogenic tumours containing such tissues[59]. Expression of tenascin in the stromal tissue of odontogenic tumours differs according to their potential to form calcified masses. Thus, tenascin is a useful marker to differentiate odontogenic tumours forming calcifying masses from other non-calcifying odontogenic tumours[60].

Nestin is a useful marker for tumours with Odontogenic ectomesenchyme[61]. Rearrangement of the HMGA2 (High Mobility Group A2) gene and HMGA2 protein over expression are features of Odontogenic mesenchymal tumours[62].

Enzymes: Lysozyme is an enzyme primarily found in monocytes and neutrophils. Serum lysozyme levels are elevated in acute granulocytic leukaemia, acute myelomonocytic leukaemia, and acute myeloid leukemia[63]. Serum amylase level was found to be highly sensitive for small cell lung cancer[64]. LDH in serum and saliva was found to be increased in premalignant conditions like leukoplakia and OSF.

Salivary tumor markers: Saliva has been used as diagnostic tools in various conditions. Protein MRP14 (calcium binding protein) [65], CD59[66], p53[67], HA[68], Interleukin- IL-1-6 & 8[69], sialic acid[70] and statherin[71] was significantly increased in OSCC patients. Polymeric immunoglobulin receptor (PIGR), Clusterin and EGF[72] was significantly down regulated in saliva of OSCC patients. Salivary epithelial marker[73] like CA125, CA19-9, tissue polypeptide antigen (TPA), CEA, and Cyfra21-1 were increased in the cancer patients.

Salivary oxidant[74] and anti-oxidant levels[75] may be helpful in early detection, treatment planning and prevention of tumor recurrence. Salivary oxidants like salivary reactive

nitrogen species was increased and salivary anti-oxidants were reduced significantly[76] .

Tumor specific genomic markers consisting of DNA and RNA markers can be identified in saliva for detection of oral cancer. Microsatellite inability has been successfully used as molecular markers for head and neck cancer[77]. Aberrant methylation of genes like tissue inhibitors of metalloproteinase (TIMP), ECAD, O-methyl guanine-DNA-methyltransferase (MGMT), p16, DAPK, and RASSF1A in exfoliated malignant cells of the saliva reflects tumor status. Reactivation of telomerase is a pre-requisite for development of malignant cells.

The role of bacteria in oral cancer is under investigation to determine whether the bacteria is the causative agent or just an co-incidental finding. Organisms like P.gingivalis, T. forsythia, C.albicans, P.melaninogenica and S. mitis in saliva was higher in patients with head and neck cancer[76]. Increased Candidal carriage in saliva might be used as diagnostic and prognostic indicator of oral premalignant and malignant conditions[77].

CONCLUSION:

Recent advances in molecular biology have resulted in mind boggling array of tumour markers being developed, each with its characteristic sensitivity and specificity. It is therefore imperative on the part of the clinicians to tap into this pool and utilize the task-specific marker in various orofacial diseases in order to be able to contribute towards early diagnosis and prompt management, which will go a long way in reducing morbidity and improving survival. This paper has highlighted some of the commonly used tumour markers in benign and malignant conditions that are frequently encountered by dental surgeons. It is therefore important for us to continuously update our knowledge regarding the effective usage of tumour markers in day-to-day practice in order to do justice to our patients.

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