OMPJ

10.5005/jp-journals-10037-1006

REVIEW ARTICLE

Tumor Markers: At a Glance

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ABSTRACT

Tumor markers are biochemical substances elaborated by tumor cells due to either the cause or effect of malignant process. A tumor marker can be defined as substances present in, or produced by host in response to a tumor that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurements in blood or secretions.[1] These markers can be normal endogenous products that are produced at a greater rate in cancer cells or the products of newly switched on genes that remain quiescent in the normal cells. Tumor markers can often be detected in higher than normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. Most tumor markers are proteins. This article emphasizes currently available tumor markers, their role in cancer and their current development in cancer diagnosis and prognosis.

Keywords: Tumor marker, Oral cancer, Biochemical.

How to cite this article: Manikantan NS, Balakrishnan D, Kumar ADM, Shetty B. Tumor Markers: At a Glance. Oral Maxillofac Pathol J 2014;5(1):437-440.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Head and neck squamous cell carcinoma is the fifth most common cancer worldwide. Oral cancer[12] is a disfiguring, potentially fatal disease that continues to rise in incidence among younger and older people alike. In developing countries like India, controlling the devastating, widespread consequences of oral cancer requires interventions in persons at-risk ideally before the disease becomes invasive but certainly before it becomes locally advanced or metastatic.[1,2] Once the neoplastic process sets in, it is rather difficult to control and endangers the life of the host. Therefore detection of a malignancy before it arises would be the best possible mode of preventing the dreaded disease in its earliest form or by intervening before it reaches uncontrollable proportions.

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Tumor markers[10] are substances, usually proteins, that are produced by the body in response to the cancer growth or by the cancer tissue itself and that may be detected in blood, urine or tissue samples. Most tumor markers are produced by normal cells, but their production is much increased in cancerous conditions. Measurements of tumor marker level can be useful, when used along with radiographs or other tests in the detection and diagnosis of some types of cancer.[3]

Tumor markers can be found in cells, tissues or body fluids. They can be measured quantitatively or qualitatively by chemical, immunological or molecular biological methods to determine the presence of neoplasia. Quantitative as well as qualitative evaluation of these markers is possible through modern techniques of sensitive immunoassays like radioimmuno assay (RIA) and enzyme linked immunosorbent assay (ELISA) using monoclonal or polyclonal antibodies immunoassays in majority of cases and biochemical and molecular biological techniques in other cases.[4] Few markers are specific for a single individual tumor (tumor specific markers). Most are found with different tumors of the same tissue type (tumor associated markers). They are present in higher quantities in cancer tissues or in blood from cancer patients than in benign tumors or in the blood of normal subjects. Few tumor markers are specific to the organ where the tumor resides.

The specialist comes across a variety of clinical situations where the exact demarcation between a premalignancy and malignancy cannot be ascertained, thus posing a problem in diagnosis, leading to a delay of the treatment of these dangerous lesions.[5] The tumor markers can aid the clinician greatly in such situations, if the clinicopathologic picture is not accurately suggestive or indicate, if the picture would soon change. This overview attempts to forge an understanding of these tumor markers, their interactions and clinical applications as shown relevant by the recent advances in research.

DEFINITION

'A tumor marker is a substance present in or produced by a tumor or by the tumor's host in response to the tumor's presence that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurement in the blood or secretions.'[6] Tumor markers can also be defined as 'specific, novel or structurally altered cellular macromolecules or temporarily spatially or

quantitatively altered normal molecules that are associated with malignant (and in some cases benign) neoplastic cells'.[7]

Another group of investigators have defined tumor markers as 'cellular products that are abnormally elaborated by malignancies that can he detected in various body fluids and on the surface of the cancer cells'.[8]

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Tumor markers can also be broadly defined as 'biological or molecular attributes of tumor cells that distinguish them from normal cells'.

HISTORY

- The first known attempt to find markers for malignancy was made 2000 years ago and is described in an Egyptian Papyrus where breast cancer was distinguished from mastitis.[9]
- The first tumor marker in modern medicine was identified by Bence-Jones, who in 1846 detected a heat precipitate in samples of acidified urine from patients suffering from 'Mollities ossium'.
- 1928-WH Brown—ectopic hormone syndrome
- 1930-B Zondek—HCG (human chorionic gonadotropin)
- 1932-H Cushing—ACTH
- 1949-K.oh-Uti—deletions of blood group antigens
- 1959-C Markert—isoenzymes
- 1963- GI Abelev—AFP (fetoprotein)
- 1965-P Gold and S Freeman—CEA (carcinoembryogenic antigen)
- 1969-R Heubner and G Todaro—oncogenes
- 1975-H Kohler and G Milstein—monoclonal antibodies
- 1980-G Cooper, R Weinber, M Bishop—oncogene probes and transfection
- 1985-H Harris, R Sager, and A Knudson—suppressor gene.

An ideal tumor marker theoretically should have the following criteria:[1,3]

- It should be highly sensitive and should have low false negatives.
- It should be highly specific and should have low false positive.
- It should have high positive and negative predictive value.
- 100% accuracy in differentiating between healthy individuals and tumor patients.
- It should be able to different between neoplastic and non-neoplasic disease and show positive correlation with tumor volume and extent.
- It should predict early recurrence and have prognostic value.
- It should be clinically sensitive, i.e. detectable at early stage of tumor.
- Its levels should be preceding the neoplastic process, so that is should be useful for screening early cancer.
- It should be either a universal marker for all types malignancies or specific to one type of malignancy.
- It should be easily assayable and be able to indicate all changes in cancer patients receiving treatment.

CLASSIFICATION

Classification of tumor markers can be based upon their structure or biological functions, or the class or type of marker that is in consideration.[1,11]

A comprehensive organization of the tumor markers on the basis of their type of tissue interaction was provided by Scully and Burkhardt (1993) (Table 1).

Another classification of tumor markers is as follows:

- Epithetical markers
  - Cytokeratins (CK)
  - Epitheical membrane antigen (EMA)
  - Oncofetal antigens
    - Alpa-fetoprotien (AFP)
    - Carcinoembryonic antigen (CEA)
  - Desmoplakin
- Mensenchymal markers
  - Muscle antigens
    - Desmin
    - Actin
    - Myoglobin
    - Myosin
  - Vasculator 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

Table 1: Calssification of tumor markers

1st classification	*2nd classification*	*Markers of tumor invasion and metastatic potential*
Cell surface markers	*Another way of classifying tumor markers*	
1. Carbohydrates—particularly blood group antigens	*Tumor growth markers*	1. MMPs (matrix metalloproteinases)
2. Squamous carcinoma antigens Ca-1, TA-4, SQMI and 3H-I	1. Epithelial growth factor (EGF)	2. Cathepsins
3. Histocompatibility antigens—HLA class I and HLA class II	2. Cyclins	3. Cadherins and catenins
4. Growth factors and receptors	3. Nuclear cell proliferation antigens	4. Desmoplakin
Intracellular markers	4. AgNORs (argyrophilic nucleolar organizer region)	*Cell surface markers*
1. Cytoskeletal components	5. Skp2 (S-phase kinase-interacting protein 2)	1. Carbohydrates
2. Cytokeratins	6. HSP 27 and 70 (heat shock proteins)	2. Histocompatibility antigen (HLA)
Markers of abnormal keratinization—filaggrin, involucrin, desmosomal proteins	7. Telomerase	3. CD57 antigen
3. Carcinoma antigen 17, 13	*Markers of tumor suppression and anti-tumor response*	*Intracellular markers*
4. Silver binding nucleolar organizing regions	1. Retinoblastoma protein (pRb)	Cytokeratins
5. Oncogenes	2. Cyclin dependent kinase inhibitors	*Markers of anomalous keratinization*
6. Tumor suppressor genes	3. p53	1. Filaggrins
7. Arachidonic acid products-PGE2, leukotrine B4 and 5, 12 and 15 hydroxyeicosatetraenoic acids	4. Bax	2. Involucrin
8. Enzymes-gamma-glutamyl transpeptidase—LDH	5. Fas/FasL	3. Desmosomal proteins
9. Basement membrane markers—fibronectin, laminin	*Angiogenesis markers*	4. Intercellular substance antigen
10. Matrix markers—tenascin	1. VEGF/VEGF-R (vascular endothelial growth factor/receptor)	5. Nuclear analysis
	2. PD-ECGF (platelet-derived endothelial cell growth factor)	*Arachidonic acid products*
	3. FGFs (fibroblast growth factor)	1. Prostaglandin E2
		2. Hydroxyeicosatetraenoic acid
		3. Leukotriene B4
		Enzymes
		Glutathione S-transferase

  - 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
    - Immunoglobulins
- Hormone receptors
    - Estrogen receptor (ER)
    - Progesterone receptor (PR)
- Epithelial markers.

LIMITATIONS OF TUMOR MARKER USE

Each year clinicians are faced with the discovery of a multitude of new molecular markers, often with claims that they will provide new information that is important for determining prognosis or improving cancer treatment. The clinician is then faced with the arduous task of trying to keep with the technology and sorting through the literature to determine which of these tumor markers are relevant to the care of their individual patients.[13]

Ultramicroscopy may help the diagnosis of potentially malignant lesions but its many limitations have precluded a more routine use in the lack of adequately sensitive and specific test can be attributed to a multifactorial situation.[14,15] Most tumor markers are substances produced by some types of non-neoplastic cells; although perhaps in much lower quantities than they are produced by tumor cells. Varying levels of these markers may be present at all times in different tumor free individuals and varying levels of the particular marker may be present in different individuals with a particular tumor type. Most tumor markers show some overlap between the levels seen in controls and in cancer-affected individuals. Thus it becomes necessary to choose a threshold at which level particular marker is considered abnormal and suggestive of the presence of that tumor type.[16,17] Setting the threshold lower increases sensitivity by including a higher number of patients with a particular tumor, but decreases the specificity by also including more tumor free individuals, while raising the threshold will have the reverse effect. Considering the relative prevalence of a particular tumor type, to the population at large, reveals

another factor that prevents routine screening using tumor marker. Knowledge by the patient of a rising tumor marker may cause significant anxiety, particularly, if this information does not alter the treatment plan as patient of a rising tumor marker levels with worsening disease.[13] Thus, the financial and psychological cost to the society of routine screening for early cancers using currently available tumor marker would be prohibitive.

CONCLUSION

The preceeding discussion describes our current understanding of tumor markers, which through progressive also points out the lacunae therein. The patchy perceptions of tumor marker application in clinical situations therefore point to a potential direction for research studies and furthering knowledge in that domain. This overview hopefully offered the reader and improved insight into the world of tumor markers.

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