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Tumor Markers : A Review

Abstract
Tumor markers are molecules occurring in blood or tissue that are associated with cancer and whose measurement or identification is useful in patient diagnosis or clinical management. The ideal marker would be a "blood test" for cancer in which a positive result would occur only in patients with malignancy, one that would correlate with stage and response to treatment and that was easily and reproducibly measured.

Key Words
Metastasis, Circulation, Serum, Screening, Hormones.

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Quick Response Code

Introduction

Oral cavity cancer constitutes 30-40% of all cancers in India and the best cure is its early detection. Unfortunately, these are symptom less till they become large and start undergoing metastasis. Screening for early diagnosis has also led to lower mortality for various cancers especially in breast cancer and cervical cancer; many malignancies, however, are still diagnosed after the metastatic process has already started, indicating a poor prognosis. Thus, broadly these aid to detect cancer/tumor at an early stage and help in caring for cancer patients.[1]

Definition

A tumor marker is a substance present in or produced by a tumor or by the tumor's host in response to the tumors 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.

Markers classified according to the site:

The appearance of tumor marker and their concentration are related to the genesis and growth of malignant tumors in patients.They may be present as intracellular substances in tissues or may be released into the circulation and appear in serum.[2]

1. Biochemical /serological markers

There are a large number of tumor markers present in the blood circulation. Markers which can be detected in the blood or body fluids of patients harboring an underlying malignancy are thus called as serological markers.

2. Histochemical /tissue markers

Markers that can be detected in the tissue and are thus, detected by immunological tests

Identification of tumor markers:

- Associated with Cell Proliferation
- Related to Cell Differentiation
- Related to Malignant Transformation
- Inherited Mutations
- Related to Metastases
- Related to Other Tumor-Associated Event

There are two major processes involved in cell growth: differentiation and proliferation. When anyone or both of these processes loses regulation, the risk increases for normal cells to turn into tumor cells. Tumors are composed of heterogeneous cells. Each type of cell may produce a different tumor marker.[3]

Tumor cells shedding these markers:

1. Cell membrane constituents or secretory products may be shed from viable cells
2. Intracellular constituents could be released on loose of viability
3. Some markers are released in appreciable quantities only after invasion of blood vessels [4]

Detection of tumor markers:

Blood circulation:

1. Radio –immuno assay
2. Enzyme immune assay
3. Immunochemical reactions

Tissues:

1. Immunofluorescence
2. Immuno peroxidase
3. Monoclonal antibody technology

Significance of tumor markers:

- Screening
- Diagnosis
- Adjunct to clinical staging
- Monitoring
- Prognosis
- Relapse

Ideal characteristic of tumor markers:

- Analytical criteria
- High sensitivity
- High specificity
- High accuracy
- High precision
- Simple and easy to measure
- Not very costly
- Result must be reproducible

Clinical criteria:

- Should be disease sensitive
- Positive in all patients with particular cancer
- No false negative results
- Able to detect relapse and recurrences
- Should have high disease specificity
- Should not be detectable in normal healthy persons
- Stable

- Positive correlation with tumor volume and extent

Limitations:

a. None of the tumor markers have ideal characteristics.
b. Not specific to single malignancy
c. Every tumor marker is specific to a group of malignancies
d. Malignant process is known to elaborate a group of markers

Classifications of tumor markers: [5]

1) 5 eras of tumor markers:
1st era:Bence - Jones protein (1847)
Helped in diagnosis of multiple myeloma
2nd era(1928-1963): Hormones, enzymes, isoenzymes and proteins
Occasionally, used for diagnosis of individual tumors
3rd era- Onco developmental markers: AFP (1963) and CEA (1965)
Used for monitoring cancer patients
4th era: Monoclonal Ab (1975)
Detection of oncofetal Ag and other carbohydrate Ag on cancer cell lines
5th era: Molecular probes and monoclonal Ab to detect chromosomal abnormalities e.g., oncogenes

2) Another broad classification:

Proliferation markers: Ki-67, PCNA, P27 Kip/gene, DNA polymerase alpha, P105, P120, Statin
Oncogenes: C-erbB-2 gene, Ras gene,Myc gene,Bcl-2 gene
Growth factors and receptors: EGFR, TGF, FGFR, Insulin growth factor receptor
Tumor suppressor genes: p53, Retinoblastoma susceptibility suppressor gene
Serological markers: Blood level of serum tumor markers usually reflects cellular tumor volume and tumor activities, the measurement of serologic tumor markers has become an attractive means for the detection and diagnosis of neoplastic diseases, as well as the monitoring of their course, especially during treatment.[6] The ease of blood sampling and the sensitivity of these noninvasive tumor marker assays also make the serologic tests far superior to other clinicalexaminations based on physical methods.

1. Enzymes and isoenzymes
2. Hormones
3. Oncofetal antigens
4. Carbohydrate markers
5. Proteins

The first four markers are non-specific and show considerable overlap.

1. Enzymes and isoenzymes[7]

These enzymes and isoenzymes give an easy detection method of the underlying pathogenesis. Since an elevation is an indication of the presence of carcinoma.
Disadvantage:Non specific/sensitive,
Use:Monitoring carcinoma patients
E.g.: Alkaline phosphatase, Neuron specific enolase, Prostate acid phosphatase, Lactase dehydrogenase

2. Hormones

Hormones are also used for the detection and monitoring of treatment.
E.g.Calcitonin, Human Chorionic Gonadotropin, Parathyroid Hormone-Related Peptide

3. Oncodevlopmental markers/ Oncofetal antigens

Alpha fetoprotein, Carcino-embyrionic antigen, Human chorionic gonadotropin

4. Carbohydrate markers[8]

CA 19-9, CA 125, CA 15-3
CA 19-9 is the first tumor marker of a group of new epitopes including CA 125, CA 15-3, and CEA, defined by monoclonal antibodies. These new monoclonal kits detect newly discovered epitopes and were designed to replace polyclonal CEA measurements for various carcinomas.

5. Proteins

There are numerous proteins unfolded or crop-up which can be used to detect malignancies.
E.g.: Squamous Cell Carcinoma Antigen, Estrogen Receptors and Progesterone Receptors, Tissue Polypeptide Antigen
Biological markers in body fluids: [9]

Tumor-derived
Tumor-associated

3) Tumor markers are divided into four groups according to their function:
(i) Enhancement of Tumor Growth: Cell cycle acceleration and, proliferation,
(ii) Tumor Suppression and Anti-Tumor Defense: Immune response and apoptosis,
(iii) Angiogenesis,
(iv) Tumor Invasion and Metastatic Potential: Adhesion molecules and matrix degradation.

Commonly used tumor markers:

Squamous: Pancytokeratin, CEA, EMA
Melanocytic:S-100 protein, HMB-45 Mart-1,
Odontogenic: Cytokeratin 5, 13, 14, 19, Enamelin, Amelogenin
Odontogenic markers: [10]
CK5/6:dental follicles, dentigerous cysts, odontogenic keratocyst, radicular cysts
CK7: Normal tissues: Stellate reticulum, Dental lamina, Outer enamel epithelium, Her twig root sheath. Pathological situations: CEOTs, ameloblastic fibroma, odontome, GOCs.
Ameloblastoma: CK 13, 14, and 19, few cases CK18 and CK8, p53 and Bcl-2 proteins positive, isoforms of p63 /p73
Fragile histidine triad (FHIT) and p53/p63 protein
FHIT: Tumor suppressor gene and induces apoptosis
1. Keratocystic odontogenic tumor
2. Dentigerous cyst
3. Radicular cyst
Glandular: S-100 protein, Actin, Calponin, Cytokeratin 14, CEA, EMA
General connective tissue marker:Vimentin
Skeletal muscle: Desmin, Muscle actin, Myoglobin, Myogenin, Skeletal muscle actin
Smooth muscle: Desmin, Muscle actin, Smooth muscle-αactin
Endothelial markers: Factor VIII, VEGF, CD31, CD34, ULEX Lectins, Podoplanin.
Salivary gland tumors: CK 7, 8, 13, 14, Vimentin, Smooth muscle actin, S-100, Calponin.
Lymphoid markers: [11]
1. T-cell lymphomas: CD 3, CD 43, CD 45-RO
2. B-cell lymphomas: CD 20, CD 79a, CD 15, CD 20, CD 30, CD 45 RA
3. Anaplastic large cell lymphoma: CD 30, ALK 1
Neural markers: S-100 protein, CD-57, Neuron specific enolase
Neuroendocrine markers: Synatophysin, chromogranin, Germ cell tumors, AFP
Bone markers: CD 99, Osteocalcin
Proliferative markers:
1. up regulation of oncogenes: TGFα, RAS, Cyclin D, PCNA
2. down regulation of TSG: RB, P53, TGFβ
3. Anti-apoptotic markers: BCL-2 family, p53
4. Adhesion molecules E-cadherin, B-catenin, Laminin
5. Metastatic epithelial tumor markers: Cytokeratin 7.

PROGNOSTIC MARKERS IN ESTABLISHED MALIGNANCY: [12]

Characterization of a malignant disease

by molecular markers is expected to improve understanding of variations in the clinical course of individual patients and help to estimate their prognosis. This will help determine the prognostic value of tumor marker in the treatment of oral squamous cell, carcinoma (OSCC).

New in Tumor Marker Research

1. Genomics

The study of patterns of DNA changes is likely to prove more useful than looking for single DNA changes. DNA changes in blood, stool, or urine can help determine cancers very early.

2. Proteomics

It examines the pattern of all the proteins in the blood (instead of looking at individual protein levels) and narrow down which protein levels are important in a particular type of cancer.

This information could then be used to develop a blood test that might look only at these important proteins.

Conclusion:

Advances in the analysis of molecular alterations in cells undergoing malignant transformation have increasingly revealed the mechanisms that led to the occurrence and progression of malignancies.

It has improved our understanding of variations in the clinical course of individual patients and help to estimate their prognosis.

But, there is far less knowledge on the prognostic and therapeutic value of these markers in the diagnosis and treatment of oral cancer.

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