Review Article

Markers in oropharyngeal cancer

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ABSTRACT

Tumor markers are substances that can be found in the body when cancer starts to proliferate inside the body. The classic tumor marker is a protein that can be found in the blood in higher than normal levels when a certain type of cancer starts to kick in, but not all tumor markers are like that. Some types of markers are found in urine or other body fluids, and others are found in tumors and other tissue. They may be made by the cancer cells themselves, or by the body in response to cancer or other conditions. Most tumor markers are proteins, but some newer markers are made up of genes or other substances. There are many different tumor markers. Some are directly linked to only one type of cancer, while others can be found in other types of cancer. A perfect tumor marker would be one that could be used as a cancer screening blood test for all people suffering with cancer. It would tell doctors the type of cancer, how much cancer spread is present, and which treatment would work best when put forth to the patients. At present, there are no tumor marker tests that work like this. If a cancer is already widespread when it is found, tumor markers can help to figure out what is the reason behind it. None of the tumor markers are considered accurate until today and so several researches are going on to find a tumor marker which is most sensitive and reliable.

KEY WORDS: Canonical Wnt pathway, Cyclin D1, Human papillomavirus type 16-related tumor markers, Novel tumor markers, Periostin

INTRODUCTION

Cancers of the oropharynx are usually so-called squamous cell carcinomas, which originate from cells of the mucous membranes. Known risk factors for this disease include alcohol and cigarettes.[1] However, there are patients who have been found to have cancer who neither drink nor smoke. Oncologists are very interested in a marker that reliably identifies tumors with a favorable prognosis and diagnose them at early stages. These patients could be treated with less intensively and side effects and could be reduced considerably.[2]

Classification of Tumor Markers

According to Schliephake,

a. Tumor growth markers
   - Epithelial growth
   - Cyclin
   - Nuclear cell proliferation
   - Antigens argyrophilic nucleolar organizer region
   - S-phase kinase-interacting protein 2
   - HSP27 and 70 (heat shock protein)
   - Telomerase.

b. Markers of tumor suppression and antitumor response
   - Retinoblastoma protein
   - Cyclin-dependent kinase
   - Inhibitors p53
   - Bax
   - Fas/Fas1.

c. Angiogenesis markers
   - Vascular endothelial growth factor (VEGF)/ VEGF-R
   - Platelet-derived endothelial cell growth factor
   - Fibroblast gf.

d. Markers of tumor invasion and metastatic potential
   - Matrix metalloproteases
   - Cathepsin
   - Cadherins
   - Catenins desmoplakin.

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e. Cell surface markers carbohydrates
   - Histocompatibility antigen
   - CD57 antigen.

f. Intracellular markers
   - Cytokeratins.

g. Markers of anomalous keratinization
   - Filagrins
   - Involucrin
   - Desmosomal proteins
   - Intercellular substances
   - Antigen nuclear analysis.

h. Arachidonic acid products
   - Prostaglandin E2
   - Acid leukotriene.

i. Enzymes
   - Glutathione S-transferase.

NOVEL TUMOR MARKERS

Novel tumor markers which are useful in diagnosing oropharyngeal tumors are as follows:

Trophoblast Cell-Surface Antigen 2 (TROP2)

It is an independent prognostic marker. The human TROP2 also termed GA733-1, M1S1, and EGP-1 was encoded by the TACSTD2 gene which is mapped to chromosome 1 p32. It was highly expressed in majority of human carcinomas.[2]

Periostin

Periostin was originally identified from osteoblasts and functions as a cell adhesion molecule for preosteoblast and to participate in osteoblast recruitment, attachment, and spreading. Studies showed that Periostin in oral squamous cell carcinoma (OSCC) which shows significant correlation with tumor metastasis and its prognosis.[3] It was useful only as a predictive marker and had no role as a therapeutic target.[4]

SENP5

SUMOylation was a most important post-translational modification. The small ubiquitin-like modifiers (SUMOs) were ubiquitin proteins conjugated by a series of enzymes to cellular regulators.[5] This can be reversed by SUMO-specific proteases. It is not a therapeutic target.

Metabotropic Glutamate Receptor (MGluR5)

MGluR5 was a multifunctional G protein-coupled receptor which acts as excitatory neurotransmitter. It played an important role in tumor progression.[6]

Septin 1

Septins are GTP- binding proteins that are evolutionarily and structurally related to the RAS oncogenes. Septin 1 plays an important role in tumor differentiation in OSCC. It regulates cytokinesis by phosphorylation of Aurora B (chromosomal passenger protein) and chromosome segregation and cytokinesis.[7]

Stathmin

Kouzu *et al*. (2006) examined stathmin in OSCC and found its correlation to clinical staging, thereby playing a crucial role in tumor progression and aggressiveness.[8]

Insulin-Like Growth Factor II mRNA-Binding Protein 3 (IMP3)

IMP3 regulates tumor cell proliferation, migration, and metastasis. Shengjin demonstrated that IMP3 expression was correlated with several clinicopathologic factors including high histopathologic grade, presence of lymph node metastasis, advanced tumor, and clinical stages. In OSCC, IMP3 was associated with poor patient prognosis.[9]

Tapasin

Tapasin surface antigen absence has been reported in number of cancers and many represent a mechanism of tumor escape from control of immune system such as head and neck cancer. Qian Jiang described that lack of tapasin was associated with overall poor survival in OSCC.

Stromal Versican

It is a large chondroitin sulfate proteoglycan which plays a role in ECM assembly, anti-adhesion, cell proliferation, migration, and extracellular matrix remodeling. In oropharyngeal and hypopharyngeal tumors, stronger versican expression was associated with lower stage.[10] It had good clinical and pathological correlation with OSCC and is an independent prognostic marker.

STAT1

The signal transducer and activator of transcription 1 trigger apoptosis therapy by making it a prognostic marker in head and neck tumors.

Cyr61

Cysteine-rich 61 was associated with angiogenesis, cell proliferation, adhesion, migration, and differentiation. Kang *et al*. found that overexpression of Cyr61 was associated with invasive phenotype of oral squamous cell carcinoma *in vitro* and was an independent prognostic marker.[11]

MUC4

Mucins promote tumor progression by repressing apoptosis multiple mechanisms, both Erb B2 dependent and independent. In poor prognosis of Oral squamous cell carcinoma, MUC4 is used to determine the tumour size and metastasis.[12]

Human Papilloma Virus Type 16 (HPV 16)-Related Oral Tumor Biomarkers and Inflammatory Biomarkers

HPV-16 was recognized as a cause of most cancers of the cervix and substantial portion of anogenital and oropharyngeal cancers. E6 and E7 oncoproteins were correlated malignant transformation of affected cervical tissues.[13] The p16INK 4a marker had been used in identifying OSCC and resulted in identifying OSCC and HPV-related oral cancers.

Cyclin D1

Cyclin d1 is a vital prognostic marker in oropharyngeal squamous cell carcinoma. The protein expression levels of cyclin D1 on a tissue microarray composed of 63 OSCCs with long-term follow-up data were studied. Protein expression was analyzed with automated *in situ* quantitative method which allows preservation of tissue morphology in paraffin-embedded tissue. Automated *in situ* quantitative analysis is a strong predictor for outcome in OSCC.[14]

Cyclin D1, a potential target for molecular, intervention in patients, who are suffering from oropharyngeal squamous cell cancer. Matted nodes are a marker of poor prognosis in oropharyngeal SCC. Matted nodes may identify patients at risk for developing distant metastasis and could be cured by systemic therapy, whereas patients without matted nodes may be candidates for deescalation of therapy.[15]

Today, there is a subgroup of the HPV-positive oropharyngeal cancers that have worse clinical outcome, and do not respond well to given treatment, and have a higher rate of relapses and worse survival than most of the tumors in this group. A question for the future is how to separate the HPV-positive oropharyngeal tumors in this relatively small group. Several potential clinical markers have been suggested, cyclin D1 and EGFR. p53 and p21 and maybe a combination of these and other not yet known markers may provide additional prognostic information and thus guide us to select the right patients for the right combination of treatment.[16-18]

Canonical Wnt Pathway

It is also known as Wnt/beta-catenin pathway which regulates cell proliferation, migration, and apoptosis and was downregulated in several cancers. The present study expresses the pattern of selected canonical pathway genes including ligand,[19] inhibitors, and target genes such as Wnt-3a, Dickkopf-1, Wnt inhibitory factor 1, secreted frizzled-related protein (sFRP) 1, sFRP4, sFRP5, c-Myc, cyclin D1, and beta-catenin. Among these, sFRPs act as negative regulators of Wnt pathway and are downregulated during carcinogenesis through hypermethylation. Clinical analysis with the above said genes from cancer and normal tissue samples showed sFRP-1, sFRP-2, and sFRP-5 in control samples and c-Myc and cyclin D1 in cancer samples with quantitative reverse transcriptase polymerase chain reaction. Wnt3a was seen in patients with recurrence and deceased.[20]

CONCLUSION

Even though Wnt 3a, beta-catenin, and cyclin D1 are recognized as key components of Wnt/beta-catenin signaling, numerous researches were going onto find a reliable tumor marker which fits in all criteria and that show an accurate diagnosis of location and extension of tumor. None of the markers were found to be perfectly sensitive and accurate, and new researches including gene, HPV markers, and other biomolecular markers are thoroughly studied to understand their role in prognosis and therapy of numerous oropharyngeal tumors.

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