Odontogenic Tumor Markers - An Overview

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ABSTRACT

The practice of pathology is currently undergoing significant change, due to advances in the field of molecular pathology. Tumor markers are molecules that help the pathologists for confirmatory diagnosis of histopathologically confounding lesions. Odontogenic tumors are relatively rare with estimated incidence of less than 0.5 cases/100,000 population per year. Odontogenic tumors can pose diagnostic challenges because of overlapping histology. But, appropriate diagnosis is crucial as their treatment modality and prognosis differ; in these situations tumor markers can be helpful. But lack of comprehensive literature on specific markers for odontogenic tumors imposes pathologists to think aimlessly about various markers to arrive at an appropriate diagnosis. With this background, it is our attempt at compiling diagnostically important odontogenic tumor markers. Also, a note is added on tumor behaviour studies in common clinically important odontogenic tumors: Ameloblastoma and Keratoctyic odontogenic tumor.

Key words: Tumor markers, Odontogenic tumors, Ameloblastoma, Keratoctyic odontogenic tumor.


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Introduction

Tumor markers are substances present in or produced by a tumor itself or by the host that can be utilized to differentiate a tumor from normal tissue or to determine the presence of a tumor based on its measurement in blood or secretions.¹ Tumor marker can also be defined as a molecule, a process or a substance that is altered quantitatively or qualitatively in precancerous or cancerous conditions, the alteration being detectable by an assay. ² Odontogenic tumors represent a spectrum of lesions ranging from malignant and benign neoplasms to dental hamartomas, all arising from the odontogenic residues. As tumor markers have become an integral part of modern pathology, this article reviews significance of markers in diagnosis and prognostic assessment of odontogenic tumors.

Odontogenic Tumors Markers

Cytokeratin
Cytokeratins (CK) are intermediate filaments. Odontogenic epithelium shows positivity for CK14 but, it is gradually replaced by CK19 in pre- ameloblasts and secreting ameloblasts.
Odontogenic tumors with epithelial component frequently express CK 14 and 19. Numerous studies have shown that adenomatoid odontogenic tumors (AOTs) and ameloblastomas express CKs 5, 14 and 19.\textsuperscript{3,4,5,6} Immunohistochemical (IHC) studies by Martínez-Mata et al. proved that most of tumors of mesenchymal origin like odontogenic myxoma (OM) do not express CK 14 and 19.\textsuperscript{7} Thus, CK 14 and 19 can be used as markers for tumors of odontogenic epithelial origin.\textsuperscript{3,4,8}

**Amelogenin**
Amelogenin is a low-molecular-weight enamel matrix protein. It has been consistently demonstrated in reduced enamel epithelium, stratum intermedium and stellate reticulum of enamel organ. The function is believed to be organization of enamel rods and mineralization of enamel. In a study by M Mori et al, amelogenin expression was positive in ameloblastoma, AOT, calcifying epithelial odontogenic tumor (CEOT), ameloblastic fibroma (AF), malignant ameloblastoma and ameloblastic carcinoma. Reduced ameloblasts in the odontoma displayed most intense amelogenin expression.\textsuperscript{9} Therefore, the use of this marker is a valuable tool to segregate other types of epithelial lesions that may develop within the oral and maxillofacial regions.\textsuperscript{4,8,9}

**Ameloblastin**
Ameloblastin (AMBN) acts as a cell adhesion molecule essential for amelogenesis. This protein plays an important role in maintaining the ameloblasts in secretory stage of differentiation by binding to them and inhibiting their proliferation.\textsuperscript{10} Ameloblastin, enamelin and sheathlin proteins were not expressed in ameloblastoma, suggesting that the tumour cells do not attain functional maturation as secretory phase ameloblasts.\textsuperscript{11} Perdigao et al (2004) demonstrated that AMBN gene mutations are associated with the development of ameloblastoma, AOT, squamous odontogenic tumor (SOT)\textsuperscript{12} and CEOT.\textsuperscript{10} Mutations in the AMBN gene are responsible for the tumorigenesis of epithelial odontogenic tumors without odontogenic ectomesenchyme.\textsuperscript{10}

**Calretinin**
Calretinin (calbindin-2) is a 29-kDa calcium-binding protein (CaBP). CaBP acts as a mediator of signalling intra-cellular calcium ions which are considered to be important second messengers intervening in cellular proliferation and differentiation. Calretinin is primarily expressed in neurons of central and peripheral nervous system and it is the diagnostic marker for malignant mesotheliomas.\textsuperscript{13} In a study by Alaeddini et al, in 55 odontogenic tumors including ameloblastoma, AOT, CEOT, AF and OM; calretinin was expressed only in ameloblastomas.\textsuperscript{14} According to another study by Sireesha K et al, in keratocystic odontogenic tumor (KCOT), dentigerous cyst and ameloblastoma, only stellate reticulum-like cells of solid multicystic and unicystic ameloblastomas expressed calretinin.\textsuperscript{13} Thus, calretinin can be considered as the specific IHC marker for neoplastic ameloblastic epithelium which is expressed only in solid and unicystic ameloblastomas and not in any other odontogenic cysts/tumors.\textsuperscript{13} Also calretinin can be used as a diagnostic marker to differentiate unicystic ameloblastoma from other cystic lesions.\textsuperscript{13,15}

**Bone morphogenetic proteins**
Bone morphogenetic proteins (BMPs) belong to the transforming growth factor (TGF) superfamily and play an important role in cell proliferation,
differentiation, chemotaxis, extracellular matrix production, apoptosis and mesenchymal cell differentiation. Furthermore, recognition of BMPs in several neoplasms such as ovarian tumors, osteosarcoma and chondrosarcoma suggest that they may be associated with both pathological mineralization and tumor development. BMP 2, 4 and 7 are expressed in dental epithelium in the initial stages of tooth formation and their expression was found to shift between epithelium and mesenchyme during the subsequent steps of morphogenesis, suggesting a potential role in the mechanisms of induction. Moreover, BMPs are recognized in several neoplasms such as ovarian tumors, osteosarcoma and chondrosarcoma suggesting that they may be associated with both pathological mineralization and tumor development. BMP 2, 4 and 7 are expressed in dental epithelium in the initial stages of tooth formation and their expression was found to shift between epithelium and mesenchyme during the subsequent steps of morphogenesis, suggesting a potential role in the mechanisms of induction. According to Gao YH et al; cementoblastoma, dentinoma, odontogenic fibroma and odontoma showed BMP positivity while ameloblastoma, AOT, CEOT showed negativity. Therefore, BMP might play an important role in the formation of calcified dental tissues and the development of odontogenic tumors containing such tissues.

**Tenascin**

Tenascin is a multifunctional glycoprotein involved in cell-cell and cell-extracellular matrix interactions and is expressed at epithelial-mesenchymal interface during embryonic development. Expression of tenascin in the stromal tissue of odontogenic tumours differs according to their potential to form calcified masses. M. Mori et al reported that tumours forming calcifying masses i.e. CEOT, ameloblastic fibro-odontoma (AFO) and odontoma, have widespread stromal immunoreactivity of tenascin. Thus, tenascin is a useful marker to differentiate odontogenic tumors forming calcifying masses from other non-calcifying odontogenic tumors.

**Nestin**

Nestin is an intermediate filament constituting the cytoskeleton. It is known as a neural stem cell marker. Ectomesenchymal tissue of odontogenic tumors express nestin because of it’s origin from the neural crest. According to a study by Fujita S et al, almost all ameloblastomas and malignant ameloblastomas were negative for nestin whereas, odontogenic ectomesenchyme in mixed tumours such as AF, AFO, ameloblastic fibrodentinoma (AFD) and ameloblastic fibrosarcoma (AFS) demonstrated intense expression particularly around the neoplastic follicular odontogenic epithelium. Hence, nestin is a useful marker for tumours with odontogenic ectomesenchyme.

**High-mobility group A protein 2 (HMGA2)**

HMGA2 is a non-histone chromatin factor that is primarily expressed in undifferentiated tissues and tumors of mesenchymal origin. Sato et al. suggested that HMGA2 rearrangement and HMGA2 protein over expression might be associated with the tumorigenesis of odontogenic tumors like OM, odontogenic myxofibroma. Hence, rearrangement of the HMGA2 gene and HMGA2 protein over expression are features of odontogenic mesenchymal tumors.

**Basement membrane proteins**

Basement membrane (BM) is the organized extracellular matrix (ECM) that separates epithelium and adjacent connective tissue stroma. Its components are collagens (type I, III, IV, V, VII, and XVII); laminins 1, 5, and 6; fibronectin; nidogen and heparan sulfate. Formation of odontogenic tumors from tissue remnants of odontogenesis is controlled by series of reciprocal epithelial-mesenchymal interactions via integrin-BM protein communications. Poonsawat et al reported expression of laminins 1 and 5, collagen type IV and fibronectin in ameloblastomas, calcifying cystic odontogenic tumors (CCOT), and AOTs. The expression of laminin 1 is seen in odontogenic epithelium, but not in mucosal epithelium. Thus, laminin 1 can be a marker for odontogenic epithelium.
Markers for Odontogenic Tumor Behaviour

Basement membrane proteins
According to Heikinheimo K, focal absence of laminin and type VII collagen from the basement membrane and the presence of fibronectin containing an oncofetal domain in the ECM of ameloblastomas may correlate with their aggressive behavior. 23 J. J. Sauk noticed that use of specific antibodies to basement membrane components may differentiate ameloblastomas from malignant lesions. In their study, tumor islands of ameloblastomas are circumferentially delineated by a linear staining to both type IV collagen and laminin (i.e. ameloblastomas spread into tissue spaces by expanding their compartmental volumes rather than by secreting proteinases that disrupt their basement membranes compartmental barriers). In contrast, malignant ameloblastoma was not continuously delineated by circumferential linear basement membrane components. 24 Thus, absence or discontinuity in expression of basement membrane proteins like type IV collagen, laminin can be correlated with aggressive behavior of tumors.

RANK, RANKL and OPG
Receptor activator of nuclear factor κB (RANK), RANK ligand (RANKL) and osteoprotegerin (OPG) are members of tumor necrosis factor ligand and receptor super family. They regulate osteoclast formation, differentiation and activity. Ligation of RANKL to its receptor RANK results in the fusion and differentiation of osteoclasts while OPG inhibits the interaction between RANKL and RANK. RANK-RANKL-OPG system is involved in odontogenic cysts and tumor-induced osteolysis. According to Andrade et al higher intensity of RANKL expression than that of OPG in mesenchymal cells of OM, AF and CEOT is suggestive of greater bone resorptive activity. 25 Higher the expression of RANKL in a tumor, greater will be the bone resorption.

Integrins
Integrins are transmembrane receptors that modulate cell-cell and cell-matrix binding. Integrin α5β1 is the classic receptor for fibronectin, a protein that plays an important role in the epithelial-mesenchymal interactions in odontogenic tumors. According to Andrade ESS et al, intensity for α5β1 integrin was significantly stronger in ameloblastomas. Another role attributed to α5β1 integrin in the mechanism of tumor invasion is that its binding to fibronectin increases the secretion and expression of metalloproteinases. Focal expression of α3β1 may lead to basement membrane disorganization in some regions, thus contributing to infiltrative behaviour of ameloblastomas. Presence of these enzymes in ameloblastomas has been reported to increase local invasiveness of these tumors. 26

Matrix metalloproteinases
Matrix metalloproteinases (MMPs) comprise a family of calcium and zinc dependent endopeptidases that are capable of degrading components of extracellular matrix (ECM) and basal layer and participate in both physiological events and pathologic processes. 27 MMPs 1, 2, 3, and 9 participate in early tooth development. 28 According to numerous studies; MMPs 1, 2 and 9 were expressed in CCOT, AOT and ameloblastoma. 27, 29 Gomes et al reported that increased expression of MMP- 1, 2 and 9 is responsible for the invasive behaviour of odontogenic myxoma. MMP-2 and 9 degrade type IV collagen, component of the basement membrane.30 Thus, lesions with intense expression of MMPs show more invasive behaviour.
Table 1: Tumor markers in KCOT and OOC

<table>
<thead>
<tr>
<th>Markers</th>
<th>KCOT</th>
<th>OOC</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EMA, CEA</strong> 39 (Cell surface carbohydrates)</td>
<td>Present in the surface parakeratin layer</td>
<td>Absent</td>
<td>Increased aggressiveness of KCOT</td>
</tr>
<tr>
<td><strong>CK 10, CK 13</strong> 39 (CK 10: Early marker of keratin differentiation)</td>
<td>In upper and surface parakeratin layers</td>
<td>All the layers of the epithelium except basal layer.</td>
<td>Related to epithelial cell maturation and proliferation. 39</td>
</tr>
<tr>
<td>(CK 13: Expressed in dental lamina, enamel organ, non-keratinized stratified squamous epithelium)</td>
<td></td>
<td></td>
<td>OOC presents a well formed cystic envelope whereas the KCOT profile is compatible with more aggressive biologic behaviour 41</td>
</tr>
<tr>
<td><strong>Ki-67</strong> (Proliferative marker) 39</td>
<td>Intense expression</td>
<td>Low expression</td>
<td>Higher proliferative potential of KCOT</td>
</tr>
<tr>
<td><strong>IPO-38</strong> (Proliferative marker) 42</td>
<td>Intense expression</td>
<td>Low expression</td>
<td>Higher proliferative potential of KCOT</td>
</tr>
<tr>
<td><strong>gp38</strong> 43 (Cell surface glycoprotein)</td>
<td>In basal &amp; parabasal layers</td>
<td>Negative</td>
<td>Neoplastic potential of KCOT 44</td>
</tr>
<tr>
<td><strong>Podoplanin</strong> 45 (Cell migration and tumor invasion)</td>
<td>Intense expression</td>
<td>Low expression</td>
<td>Neoplastic potential of KCOT</td>
</tr>
</tbody>
</table>

(EMA - Epithelial membrane antigen, CEA – Carcinoembryonic antigen, CK- cytokeratin, IPO - monoclonal antibody of IPO (Institute of Problems of Oncology, Kiev) directed against the nuclear antigen of proliferative cells; gp 38 – 38 kDa cell surface glycoprotein)

**Syndecan**

Syndecan (SDC1) also known as CD 138 is a transmembrane heparan sulphate. It has important role in cell adhesion and cohesion and inhibit invasion of cells into type 1 collagen gels. Bologna-Molina R et al (2008) noted low expression of SDC1 in solid ameloblastoma (SA) than in unicystic ameloblastoma (UA). Reduced expression of syndecan-1 supports the view that SA has a more aggressive biological behavior than the UA. In another study, Bologna-Molina et al. (2009) studied SDC1 expression in desmoplastic ameloblastomas, peripheral ameloblastomas and ameloblastic carcinomas and observed lower expression levels of SDC1 in ameloblastic carcinomas when compared to other types of ameloblastoma. Thus, SDC1 mediates intercellular and cell to matrix adhesion and its expression appears to be inversely correlated with tumor aggressiveness and invasiveness.
Table 2: Tumor behaviour studies in Ameloblastoma

| Role of Markers          | Markers                                      | a. Expression in Ameloblastoma | b. is Suggestive of-
|--------------------------|----------------------------------------------|--------------------------------|--------------------------
| ECM matrix degradation   | MMPs –1, 2,7,9,14,26 47,48                   | a. Increased                  | b. More aggressiveness   |
|                          | TIMP-2 47                                    |                                |                          |
|                          | Heparanase, CD 147 47                        |                                |                          |
| Cell adhesion            | Syndecan -I 32,33                            | a. Decreased                  | b. More invasiveness     |
|                          | Cadherins 47                                 |                                |                          |
|                          | Integrins α5β1 26                            | a. Increased                  | b. More invasiveness     |
| Cell migration           | WNT5A 47                                     | a. Increased                  | b. Cell migration        |
|                          | Podoplanin 38                                 |                                |                          |
| Bone resorption          | IL -1, IL-6, TNF α, RANKL, PTHrP 48          | a. Increased                  | b. Increased osteolysis  |
| Cell proliferation       | Cyclin E 47                                   | a. Increased                  | b. Increased cell proliferation |
|                          | p21,p27 47                                   | a. Decreased                  | b. Increased cell proliferation |

(MMP – Matrix metalloproteinase, TIMP – Tissue inhibitor of matrix metalloproteinase, WNT5A- Wingless integration family- member 5A , TNF- Tumor necrosis factor, IL- Interleukin, RANKL- receptor activator of nuclear factor kappa B ligand, PTHrP- Parathyroid hormone–related protein, p 21,27- Cyclin dependent kinase inhibitors)

Wingless type 1 glycoprotein (Wnt 1)

Wnt is a family of 19 glycoproteins that function as signal transducers for cell-cell interaction, cell growth and differentiation. Wnt signaling is also essential for odontogenesis. Kee Chuah et al reported that 76.9% of primary conventional ameloblastomas demonstrated strong Wnt1 immunoreactivity compared to 42.9% of primary unicystic ameloblastoma. According to Siar CH et al, altered expressions of Wnts-1, 2, 5a, and 10a are detected in ameloblastomas and Wnt-1 might be the key signaling molecule involved in ameloblastoma tumorigenesis. Thus, aberrations of the Wnt signaling pathway play a role in oncogenesis and cytodifferentiation of odontogenic epithelium via deregulation of cell proliferation.

Podoplanin

Podoplanin, a transmembrane sialomucin-like glycoprotein, is a specific marker of lymphatic vessels and its expression is also considered to be associated with tooth development and tumor invasion. Expression of podoplanin is considered to be associated with neoplastic odontogenic tissues. According to Patricia González-Alva, podoplanin was expressed strongly in peripheral columnar cells and slightly in central stellate reticulum-like cells of ameloblastomas. The migration and invasion...
mediated by podoplanin in ameloblastomas variants: parakeratinized and orthokeratinized.

### Table 3: Summary of odontogenic tumor markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK 14,19</td>
<td>Differentiates odontogenic epithelial tumors from other epithelial tumors</td>
</tr>
<tr>
<td>Amelogenin</td>
<td>Expressed in odontogenic tumors with odontogenic epithelial component</td>
</tr>
<tr>
<td>Ameloblastin</td>
<td>Mutated in odontogenic tumors with odontogenic epithelial component</td>
</tr>
<tr>
<td>Nestin</td>
<td>Marker for odontogenic ectomesenchyme</td>
</tr>
<tr>
<td>Calretinin</td>
<td>Differentiates ameloblastoma from other tumors</td>
</tr>
<tr>
<td></td>
<td>Differentiates unicystic ameloblastoma from odontogenic cysts</td>
</tr>
<tr>
<td>Bone Morphogenic Protein</td>
<td>Expressed in odontogenic tumors with dental hard tissue formation</td>
</tr>
<tr>
<td>Tenascin</td>
<td>Expressed in tumors forming calcified masses</td>
</tr>
<tr>
<td>HMG A2</td>
<td>Over expression in odontogenic mesenchymal tumors</td>
</tr>
<tr>
<td>Basement membrane proteins: Laminin 1</td>
<td>Marker for odontogenic epithelium</td>
</tr>
</tbody>
</table>

### Table 4: Summary of odontogenic tumor behaviour markers

<table>
<thead>
<tr>
<th>Markers</th>
<th>Strongly Positive in</th>
<th>Clinical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>RANKL</td>
<td>Ameloblastoma, OM, AF and CEOT</td>
<td>Bone resorption</td>
</tr>
<tr>
<td>Integrins</td>
<td>Ameloblastoma</td>
<td>Invasive behaviour</td>
</tr>
<tr>
<td>MMPs</td>
<td>AOT, CCOT, Ameloblastoma, OM</td>
<td>Invasive behaviour</td>
</tr>
<tr>
<td>Syndecan</td>
<td>Desmoplastic &amp; unicystic ameloblastoma compared to conventional ameloblastoma</td>
<td>Intense expression is suggestive of less aggressiveness.</td>
</tr>
<tr>
<td>Wnt-1</td>
<td>Ameloblastoma</td>
<td>Increased cell proliferation</td>
</tr>
<tr>
<td>Podoplanin</td>
<td>Ameloblastoma, CCOT, KCOT</td>
<td>Invasive behaviour</td>
</tr>
<tr>
<td>Basement membrane proteins: Laminin</td>
<td>Ameloblastoma when compared to malignant ameloblastoma.</td>
<td>Absence or discontinuity in expression correlates with aggressive behavior of tumors.</td>
</tr>
</tbody>
</table>

could be related to cytoskeletal reorganization. Thus it plays a role in the collective cell migration and thereby indicates tumor invasion. 

**Tumor Markers in KCOT**

KCOT was previously grouped under odontogenic cystic lesions with two histological variants: parakeratinized and orthokeratinized. Considering the biological behavior & genetic abnormalities, WHO working group 2005 grouped parakeratinized OKC as a benign neoplasm and orthokeratinised variant as a separate entity- orthokeratinised odontogenic cyst (OOC). KCOT is an important neoplasm because of its high recurrence rate and aggressive behaviour. Clinical basis for separation between
KCOT and OOC is aggressiveness of the later. Various studies evaluating the behavioural differences between KCOT and OOC are collated in Table 1.

**Tumor Markers in Ameloblastoma**
Ameloblastoma is the second most common odontogenic tumor which is benign and locally infiltrative. Since the treatment is radical surgical intervention and long term follow up, diagnosis and assessment of prognosis is very important. Various tumor behaviour studies using tumor markers in ameloblastoma are compiled in Table 2.

**Conclusion**
Accurate diagnosis of pathological lesions is the ultimate goal of every pathologist and tumor markers are useful tools for this purpose. There are only a handful of tumor markers that can be used by pathologists for diagnosis of odontogenic tumors. Many other potential markers are constantly under development. Even though histopathology continues to be staple in the diagnosis of odontogenic tumors, tumor markers will play an increasingly important role as adjuvant tools. The odontogenic tumor markers are summarized in Table 3 and 4.

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