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“Unlocking the Future: Cutting-Edge Molecular Markers and Biomarkers in Odontogenic Tumor Diagnosis”

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Abstract

Pathology is currently experiencing substantial changes due to advancements in molecular pathology. Tumor markers play a crucial role in aiding pathologists with the confirmatory diagnosis of lesions that are challenging to identify histopathologically. Odontogenic tumors consist of complex, heterogeneous lesions that range from hamartomas to malignant tumors, each with distinct behaviors and histological characteristics. The exact etiology of odontogenic tumors remains unclear, making diagnosis challenging for pathologists. Odontogenic tumors are relatively uncommon, with an estimated incidence of fewer than 0.5 cases per 100,000 people annually. Their rarity, overlapping histologic features and limited experience available for evaluation further complicate the diagnostic process. However, accurate diagnosis is vital, as treatment approaches and prognosis differ considerably. Tumor markers can be useful in these situations, but the absence of extensive literature on specific markers for odontogenic tumors often forces pathologists to explore various markers without clear guidance to reach the correct diagnosis. With this in mind, we aim to describe diagnostically significant immunohistochemical and molecular markers for odontogenic tumors.

Keywords: tumor markers, odontogenic tumors, hamartomas, malignant tumors, molecular pathology

Introduction:

Odontogenic tumors are diverse and complex lesions that originate from the ectomesenchymal and/or epithelial tissues involved in tooth development. They can range from benign hamartomas to malignant tumors, exhibiting varying behaviors, histologies, and even differing geographical distributions [1]. Odontogenic tumors are categorized into three groups—epithelial, mesenchymal, and mixed epithelial and mesenchymal—based on the type of odontogenic tissue they resemble [2]. While radiological findings and histological features of odontogenic tumors are useful for clinical diagnosis, challenges remain with small biopsies and the identification of malignant changes [3]. Markers are molecules, genes, or molecular features involved in the pathogenesis of diseases that play a crucial role in diagnosing and managing patients, particularly in tumorigenic cases [4]. Specific markers assist in accurately diagnosing particular types of odontogenic tumors and enhance our understanding of their pathogenesis and molecular genetic characteristics. As tumor markers have become essential in modern pathology, this article reviews the importance of immunohistochemical and molecular markers in the diagnosis and prognostic evaluation of odontogenic tumors.

Diagnostic markers in odontogenic tumors**Cytokeratin**

Cytokeratins (CK) are a type of intermediate filament. In odontogenic epithelium, CK14 is initially expressed but is gradually replaced by CK19 in pre-ameloblasts and secreting ameloblasts. Odontogenic tumors with an epithelial component commonly express CK14 and CK19. Numerous studies have demonstrated that adenomatoid odontogenic tumors (AOTs) and ameloblastomas express CK5, CK14, and CK19 [5-8].

Amelogenin

Amelogenin is a low-molecular-weight protein found in the enamel matrix, and it is believed to play a role in the organization of enamel rods and the mineralization of enamel. Amelogenin

expression has been observed in several odontogenic tumors, including ameloblastoma, AOT, calcifying epithelial odontogenic tumor (CEOT), ameloblastic fibroma (AF), malignant ameloblastoma, and ameloblastic carcinoma. Notably, reduced ameloblasts in odontomas exhibit highest amelogenin expression. Therefore, this marker is a significant tool for distinguishing other types of epithelial lesions that may arise in the oral and maxillofacial regions [6,9,10].

Ameloblastin

Ameloblastin (AMBN) functions as a cell adhesion molecule that is crucial for amelogenesis. The proteins AMBN, enamelin, and sheathlin are not expressed in ameloblastoma, indicating that the tumor cells do not reach functional maturation as secretory phase ameloblasts. Mutations in the AMBN gene are linked to the development of ameloblastoma, AOT, squamous odontogenic tumor (SOT), and CEOT [11-13].

Calretinin

Calretinin is a mediator of signalling intra-cellular calcium ions that intervene in cellular proliferation and differentiation. It is the diagnostic marker for malignant mesotheliomas as it primarily expressed in neurons of central and peripheral nervous system. Calretinin is considered to be the specific immunohistochemical marker for neoplastic ameloblastic epithelium as it is expressed only in solid and unicystic ameloblastomas and not in any other odontogenic cysts/tumors [14].

Bone morphogenetic proteins

Bone morphogenetic proteins (BMPs) belong to the transforming growth factor (TGF) superfamily and are associated with both pathological mineralization and tumor development as they are expressed in several neoplasms such as ovarian tumors, osteosarcoma and chondrosarcoma. BMP positivity was noticed in cementoblastoma, dentinoma, odontogenic fibroma and odontoma while ameloblastoma, AOT, CEOT showed negativity. BMP therefore play an important role in the development of odontogenic tumors containing calcified tissues [15,16].

Tenascin

Tenascin is a versatile glycoprotein that plays a role in interactions between cells and between cells and the extracellular matrix. Tumors that form calcifying masses, such as CEOT, ameloblastic fibro-odontomas (AFO), and odontomas, show extensive stromal immunoreactivity for tenascin. Therefore, tenascin serves as a valuable marker for distinguishing odontogenic tumors that form calcifying masses from other non-calcifying odontogenic tumors [17].

Nestin

Nestin is an intermediate filament that forms part of the cytoskeleton. It is expressed in the ectomesenchymal tissue of odontogenic tumors due to its neural crest origin. While almost all ameloblastomas and malignant ameloblastomas are negative for nestin, the odontogenic ectomesenchyme in mixed tumors, such as AF, AFO, ameloblastic fibrodentinoma (AFD), and ameloblastic fibrosarcoma (AFS), shows strong expression, particularly around the neoplastic follicular odontogenic epithelium. Therefore, nestin is a valuable marker for tumors with odontogenic ectomesenchyme [18].

High-mobility group A protein 2 (HMGA2)

HMGA2 is a non-histone chromatin factor mainly expressed in undifferentiated tissues and tumors of mesenchymal origin. The rearrangement of the HMGA2 gene and overexpression of the HMGA2 protein may be linked to the tumorigenesis of odontogenic tumors, such as odontogenic myxoma (OM) and odontogenic myxofibroma (OMF). Therefore, HMGA2 gene rearrangement and protein overexpression are characteristic features of odontogenic mesenchymal tumors [19,20].

Basement membrane proteins

The basement membrane (BM) is a structured extracellular matrix (ECM) that separates the epithelium from the adjacent connective tissue stroma. It is composed of various components, including collagens (types I, III, IV, V, VII, and XVII), laminins 1, 5, and 6, fibronectin,

nidogen, and heparan sulfate. The formation of odontogenic tumors from remnants of odontogenesis is regulated by a series of reciprocal epithelial-mesenchymal interactions through integrin-BM protein communication. Laminins 1 and 5, collagen type IV, and fibronectin are expressed in ameloblastomas, calcifying cystic odontogenic tumors (CCOT), and AOTs. Laminin 1 expression is observed in odontogenic epithelium, but not in mucosal epithelium, making it a potential marker for odontogenic epithelium [21].

The localized absence of laminin and type VII collagen in the basement membrane, along with the presence of fibronectin containing an oncofetal domain in the ECM of ameloblastomas, could be related to their aggressive nature. Specific antibodies targeting basement membrane components can help distinguish ameloblastomas from malignant lesions. Consequently, the absence or disruption of basement membrane proteins, such as type IV collagen and laminin, may correlate with the aggressive behavior of tumors [22,23].

Cytoskeleton remodeling protein (moesin and RhoA)

Cytoskeleton remodeling protein connects the plasma membrane and cytoskeleton along with maintaining and remodeling them. Moesin and RhoA strongly express in odontogenic epithelial cells and are involved in development of benign odontogenic lesions [24,25].

Vimentin and S-100

Vimentin is an intermediate filament and a structural cytoskeleton protein that expresses in mesenchymal cell of primordial odontogenic tumor and central odontogenic fibroma. S-100 belongs to a family of calcium binding proteins and is involved in the expression of OM [24,25].

CD138 (syndecan-1) and Matrix Metalloproteinase (MMP)-9

CD138 is a heparin sulphate proteoglycan that controls tumor cell growth, adhesion and differentiation. MMP9 is involved in the degradation of the extracellular matrix. Both CD138 and MMP9 express in tumor and stromal cell of dentinogenic ghost cell tumor [24,25].

CD68, lysozyme

CD68 and lysozyme are present within the macrophages and are involved in cell lysis. They show expression in COF [24,25].

P63, epithelial membrane antigen (EMA), Filaggrin

P63 is a transcription factor for teeth and mammary glands development. EMA is a transmembrane mucin expressed on epithelial cells and filaggrin is a filament-associated protein that binds to keratin fibers. P63, EMA and filaggrin are expressed in clear cell odontogenic carcinoma [24,25].

RANK, RANKL and OPG

Receptor activator of nuclear factor κ B (RANK), RANK ligand (RANKL), and osteoprotegerin (OPG) are components of the tumor necrosis factor ligand and receptor superfamily, which regulate the formation, differentiation, and activity of osteoclasts. The RANK-RANKL-OPG system plays a role in odontogenic cysts and tumor-induced osteolysis. A higher level of RANKL expression compared to OPG in the mesenchymal cells of OM, AF, and CEOT indicates increased bone resorptive activity [26].

Integrins

Integrins are transmembrane receptors that regulate cell-cell and cell-matrix interactions. Integrin $\alpha 5 \beta 1$ is the primary receptor for fibronectin, a protein crucial for epithelial-mesenchymal interactions in odontogenic tumors. Ameloblastomas exhibit a significantly stronger expression of $\alpha 5 \beta 1$ integrin. Additionally, $\alpha 5 \beta 1$ integrin's interaction with fibronectin is linked to increased secretion and expression of metalloproteinases, which play a role in tumor invasion. Focal expression of $\alpha 3 \beta 1$ integrin may cause disorganization of the basement membrane in certain

areas, contributing to the infiltrative behavior of ameloblastomas. The presence of these enzymes in ameloblastomas has been associated with enhanced local invasiveness of these tumors [27].

MMPs

MMPs are a group of calcium- and zinc-dependent endopeptidases that degrade components of the extracellular matrix (ECM) and the basal layer, contributing to both normal physiological functions and pathological processes. Studies have found that MMPs 1, 2, and 9 are expressed in CCOT, AOT, and ameloblastoma, with increased levels of these MMPs being associated with the invasive behavior of OM [28-30].

Syndecan

Syndecan (SDC1), also known as CD138, is a transmembrane heparan sulfate. Lower expression of SDC1 has been observed in solid ameloblastoma (SA) compared to unicystic ameloblastoma (UA), suggesting that the reduced SDC1 expression in SA is indicative of its more aggressive biological behavior. Additionally, SDC1 expression has been studied in desmoplastic ameloblastomas, peripheral ameloblastomas, and ameloblastic carcinomas, with lower levels of SDC1 noted in ameloblastic carcinomas compared to other types of ameloblastoma [31,32].

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. Primary conventional ameloblastomas demonstrated strong Wnt1 immunoreactivity compared to 42.9% of primary unicystic ameloblastoma. 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 [33,34].

Podoplanin

Podoplanin, a transmembrane sialomucin-like glycoprotein, serves as a specific marker for lymphatic vessels and is believed to be involved in tooth development and tumor invasion. Its expression is associated with neoplastic odontogenic tissues. In ameloblastomas, podoplanin is strongly expressed in peripheral columnar cells and to a lesser extent in central stellate reticulum-like cells. The migration and invasion of podoplanin in different ameloblastoma variants, including parakeratinized and orthokeratinized types, may be linked to cytoskeletal reorganization [35,36].

Conclusion

The ultimate goal for every pathologist is to accurately diagnose pathological lesions, and tumor markers are valuable tools in this process. Presently, there are only a few tumor markers available for diagnosing odontogenic tumors, although many potential markers are under development. While histopathology remains the mainstay for diagnosing odontogenic tumors, tumor markers are anticipated to play a growing role as supplementary diagnostic aids.

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