A molecular insight in the prevalence of odontogenic tumor

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Abstract

Odontogenic tumors (OT) encompass a diverse collection of lesions that range from hamartomas to benign and malignant neoplastic lesions of erratic aggressiveness. The progress and development of OT are influenced by variation of many kinds of genes and molecules. Genetic instability is a hallmark of cancer. This review illustrate a concurrent sketch of the recent updating of the molecular and genetic alterations linked with the growth and development of OT, including oncogenes, tumor-suppressor genes, oncoviruses, growth factors cell cycle regulators, apoptosis-related factors, regulators of tooth development, hard tissue-related proteins, matrix-degrading proteinases, factors of angiogenesis, and osteolytic cytokines. The logical and enhanced understanding of the molecular mechanism may provide newer thoughts for their recognition and administrate an improved prognosis of OT.

Keywords
Ameloblastoma, genes, odontogenic tumors

Introduction

Odontogenic tumors (OT) are neoplasms that are originated from the odontogenic tissues or their remnants. Some of these lesions might resemble hemartomas which reveal varying degrees of differentiation, whereas the rest are benign or malignant with a variable aggressive behavior and the potential to induce metastatic growth.[1]

Genetic and molecular alterations emerge to endorse the expansion and progression of tumors through multiple steps. The etiology and pathology behind the OT stay unidentified, recent studies have identified various molecular alterations accountable for their growth and evolution.[2] The aim of this review is to provide a current sketch in knowing and considering of the molecular and genetic events linked with OT.

Molecules Implicated in Tumor Genesis

Oncogenes

Oncogenes are usual cellular genes that participate in neoplastic alteration by functions stimulated by gene amplification, translocation, or mutation. Abundant oncogenes have been recognized, and their genetic material function as growth factors, growth factor receptors, serine/threonine kinases (Mos), non-receptor tyrosine kinases (Src, Abl), transcription factors (Myc, Fos), and signal transducers (Ras) which contribute in cellular functions related to propagation and differentiation.[3]

Activated ras oncogene is the acutely transforming component of Harvey sarcoma virus 15. There are three cellular homologs: K-ras, H-ras, and N-ras. The ras superfamily is part of the large family of G-proteins and is a component of the growth-prompting signal transduction pathway. Therefore, activating ras mutations in cancer have been extensively studied. ras mutation in codons 12, 13, and 61 of K-ras, H-ras, and N-ras are mutational hot spots in a wide variety of premalignant and malignant lesions.[3]

C-Myc protein is a nuclear transcription factor which centrally regulates cell proliferation, arrest, differentiation, and death. It plays a role in cell cycle by transition from G1 to S phase of the cell cycle and is mediated by a succession of sequential regulatory events. c-Myc ultimately renders genomic instability to the cells. c-Myc has an important role in the early stages of embryonic tooth development and their appearance here has been linked to the proliferation of odontogenic epithelial cells and its degree of differentiation.[4]

Fos oncogene encodes a transcription factor which contributes in the control of cell proliferation and differentiation. Its overexpression was seen in ameloblastoma which suggest that these oncogenes play a role in the pathogenesis of OT through impairment of cell proliferation.[2]
Tumor suppressor gene

Tumor suppressor genes (for example, p53, patched [PTC], WT-1, adenomatous polyposis coli [APC], and retinoblastoma [RB] genes) play a key role in the progression of tumors by participating in the developing cells or genes inactivation by altering and loss of heterozygosity in alleles. P53 gene also known as TP53 gene has been describes as “the guardian of the genome” is the key gene altered in tumors. It plays a role genomic destruction by persuading apoptosis or arresting the cell cycle. Overexpression of p53 gene is seen in ameloblastomas, p53 mutations are infrequent in ameloblastomas. Mouse double minute 2 homolog (MDM2) is a protein which inhibits p53 mediated cell cycle arrest by starting its degradation; it is a negative regulator of p53 or an inhibitor of tumor suppressor function of p53. MDM2 overexpression has been reported in ameloblastoma.

APC gene a multifunctional cancer suppressor gene, is involved not only in Wnt signal pathway to regulate β-catenin degradation, but also regulating cytoskeleton movement, managing cell cycle and influencing cell migration and division. APC mutation holds a major role in monitoring the tumor malignancy degree as it might mark the transition process of ameloblastoma malignant phenotype.

Mitogen-activated protein kinase (MAPK) pathway activation plays a prominent role in the pathologic process of ameloblastoma. Several studies have demonstrated activation of components of the MAPK pathway in an ameloblastoma cell line (AM-1) under various circumstances, including stimulation with tumor necrosis factor α and fibroblast growth factors-7 (FGF-7) and 10. The presence of activating BRAF mutations indicates the role of a hyperactive RAS–RAF–MAPK pathway in the pathogenesis of ameloblastomas. ERBB receptors are a receptor tyrosine kinase subfamily that includes the epidermal growth factor receptor (EGFR), ERBB2, ERBB3, and ERBB4. ERBB receptors are essential for development and frequently dysregulated in human malignancies. EGFR, its ligands, EGF, transforming growth factor-α (TGF-α) are all expressed in the odontogenic epithelium of normal developing teeth, and strong expression of EGFR has also been found in ameloblastoma.

Oncovirus

In cancer cells, multiple copies of oncopogenes are expressed. In hematologic cancer, chromosomal translocation is a common oncogene amplification mechanism. Chromosomal translocation T (9;22) activates the Abelson mouse leukemia implicated in oncogene abl. Epstein-Barr virus plays a potent role in Burkitt’s lymphoma. A distinct involvement has been recognized between human papillomavirus (HPV) infection and the development of neoplastic lesions from the squamous epithelium which lines the oral cavity in the last decade. It is assumed HPV may also hold a significant position in the pathological process of ameloblastoma.

Growth Factors

In few OT certain growth factors (EGF, TGF-α, TGF-β, FGF) and their receptors have been found. TGF-β is a multifunctional growth factor that has several biological effects in vivo, including control of cell growth and differentiation, cell migration, and production and degeneration of extracellular matrix (ECM). Impaired TGF-β signaling can also lead to tumor formation. TGF-β2 participates in epithelial growth and differentiation, epithelial-mesenchymal interactions, and matrix formation in odontogenic tissues.

Vascular endothelial growth factor (VEGF) also known as vascular permeability factor, is a heparin-binding, dimeric glycoprotein and has a selective mitogenic effect on vascular endothelial cells. It is the most important and specific agent among the many molecules initiating angiogenesis. VEGF has various actions such as enhancement of both angiogenesis and permeability of blood vessels. Elevated expressions of VEGF was seen in benign and malignant ameloblastomas which suggests that production of VEGF by odontogenic epithelial cells was up regulated along with neoplastic changes, malignant transformation or both.

EGFR is the most important growth factor ligand on the cell surface. Overexpression of EGFR-related genes is seen in many neoplasms, which causes the over sensitivity of cells to the normal level of growth factor. Nowadays, EGFR is known as an effective growth factor in many human cancers. EGFR signaling is associated with malignancy transformation. EGFR expression is seen in ameloblastoma. EGFR is mostly found in the epithelial component of human tooth germ, cystic odontogenic lesions, and OT, which signifies its potential role in the normal osteogenesis and development of these lesions. Hepatocyte growth factor and TGF-β expressions were collectively found in epithelial and mesenchymal cells of germs of tooth origin in addition to OT of epithelial origin, and their reactivity was seen in epithelium which is close to the basement membrane.

Fibroblastic growth factor signaling has strategic roles in embryonic development and differentiation. Expression of FGF-3, -4, -7, -8, -9, -10, and -20 have been identified in the tooth (Tompkins, 2006). FGFs regulate pattern and growth, as they are potent stimulators of cell proliferation. They also stimulate cell division in both dental mesenchyme and epithelium at several stages of tooth morphogenesis (Thesleff and Sharpe, 1997). Immunolocalization of FGF-1 and FGF-2 in cultured ameloblastoma epithelial cells revealed intense reactivity in the cytoplasm.

Cell Cycle Regulators

Cell proliferation trails expansion by the cell cycle in arranged mode, which is synchronized by different rudiments containing cyclin-dependent kinases (CDKs), cyclins, CDK inhibitors (CKIs), and other critical controller. Proliferating cell nuclear antigen (PCNA) is a nuclear protein linked to DNA synthesis in S phase with proliferation of cells. In odontogenic epithelium,
especially in case of ameloblastic fibroma (AF), odontogenic ameloblastoma, and mesenchymal tissue which resembles dental papilla we can see positive PCNA. The reactivity of cyclin D1, p16 INK4a, p21 WAF1/CipL, and p27KipL is usually protected in ameloblastomas advocating that proliferation of epithelial cells of odontogenic origin has been decisively synchronized using cell cycle regulators.[5]

**OT markers**

Bone morphogenetic protein (BMP), a component of the TGF superfamily, is defined as a mesenchymal cell differentiation factor and is classified as a morphogen. It is considered to play a significant role in cell proliferation, differentiation, chemotaxis, production of ECM, and apoptosis during developmental processes. Two types of receptors have been thought to act in this signaling cascade, the BMP receptors (BMPR) Type I and Type II (BMPRI and BMPRII). Members of the BMP family have been identified to participate in the normal process of tooth development, especially concerning epithelial-mesenchymal interactions.[15]

Matrix metalloproteinases (MMPs) comprise a family of calcium and zinc dependent endopeptidases which can degrade elements of ECM and basal layer and takes part in both physiological and pathologic processes. MMPs 1, 2, 3, and 9 participate in early tooth development. According to numerous studies; MMPs 1, 2 and 9 were expressed in calcifying cystic OT, adenomatoid OT, and ameloblastoma.[16]

Cytokeratins (CK) are intermediate filaments. Odontogenic epithelium exhibits positivity for CK14, but it is gradually replaced by CK19 in pre-ameloblasts and secreting ameloblasts. OT with epithelial component frequently express CK 14 and 19. 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. Amelogenin expression is seen in ameloblastoma, AOT, calcifying epithelial OT, AF, malignant ameloblastoma and ameloblastic carcinoma.[16]

Integrins are transmembrane receptors that modulate cell-cell and cell-matrix binding. Integrin α5β1 is the classic receptor for fibronectin, a protein that has a significant function in the epithelial-mesenchymal interactions in OT. Receptor activator of nuclear factor-kappaB (RANK), RANK ligand and osteoprotegerin, members of tumor necrosis factor ligand and receptor super family, regulate formation, differentiation, and activity of osteoclasts.[16]

**Conclusion**

The growth and sequence of OT are exaggerated by variations of numerous kinds of genes and molecules which affect the expansion and succession of OT. Relative study enables us to find out the mechanisms behind the differentiation of physiological odontogenesis and also the pathological tumors. Precise analysis of pathological lesions is the crucial aim of every pathologist and one of the valuable tools for this principle are tumor markers.

### References
