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Molecular Pathogenesis of Odontogenic Cysts and Tumors: Recent Advances

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Abstract
Odontogenic tumors and cysts represent a varied collection of lesions that originate from odontogenic epithelium and ectomesenchyme displaying a range of clinical behaviors and biological potentials. Recent advances in molecular biology have elucidated several genetic and epigenetic alterations that play critical roles in their pathogenesis. This review highlights the key molecular mechanisms, including mutations in tumor suppressor genes, oncogenes, signaling pathways, and epigenetic modifications contributing to the development and progression of odontogenic cysts and tumors. Understanding these molecular events not only aids in precise diagnosis and prognostication but also opens avenues for targeted therapy in aggressive lesions.

Keywords: Odontogenic tumors, Odontogenic cysts, Molecular pathogenesis, BRAF V600E, PTCH1, SHH pathway, Epigenetics

Introduction

Rare malignancies called odontogenic tumors and cysts develop from the cells and tissues that are engaged in odontogenesis as well as from their byproducts. This group of tumors comprises a wide variety of lesions, including benign and malignant neoplasms as well as hamartomatous forms.[1]. Depending on the type of odontogenic tissue they mimic, odontogenic tumors are classified as epithelial, mesenchymal, or mixed epithelial and mesenchymal tumors [1]. Reciprocal signaling between the epithelium and ectomesenchyme, which is mostly dependent on signals from Wnt, BMP, FGF, Shh, and Eda, guides the formation of embryonic teeth.[2] Modifications to the elements of these signaling pathways are associated with the formation of odontogenic tumors. For instance, studies over the last decade have found harmful mutations in extracellular signal-regulated proteins and mitogen-activated protein kinases. The elements of the MAPK/ERK pathway cascade in odontogenic tumors, both benign and malignant, are examined.[3] One intracellular signaling system that heavily depends on intracellular protein kinases is MAPK/ERK. The activity of the route is closely related to the control of vital cellular processes, such as growth, migration, metabolism, differentiation, survival, and proliferation. This route may be disrupted, which could help neoplastic cells thrive [4]. Although MAPK/ERK is commonly dysregulated in a variety of human malignancies, each mutation's predictive and prognostic significance depends on the particular situation[4]. Crucially, mutations in some of the pathway's components, like the KRAS proto-oncogene GTPase (KRAS) and B-Raf proto-oncogene serine/threonine kinase (BRAF) genes, can be found in healthy tissues [7,8] as well as benign and possibly malignant conditions [3,5,6]. It is

recognized that the MAPK/ERK signaling pathway has a role in the molecular pathogenesis of multiple forms of odontogenic cancers, even if the molecular pathogenesis of these tumors is still not fully understood. Ameloblastoma, adenomatoid odontogenic tumor, ameloblastic fibroma, ameloblastic fibrodentinoma, ameloblastic fibro-odontoma, ameloblastic carcinoma, clear cell odontogenic carcinoma, and ameloblastic fibrosarcoma have all been shown to have mutations in the genes linked to the MAPK/ERK pathway [9,10,11,12,13]. A thorough comprehension of the basic genetic changes found in odontogenic tumors may improve their categorization, aid in the diagnosis of intricate lesions, and guide the creation of innovative targeted treatments for aggressive and/or malignant instances. Therefore, the purpose of this study is to analyze the changes in MAPK/ERK components that have been documented for odontogenic tumors that are benign or malignant. We will also look at MAPK signaling, talk about the genetic changes in MAPK/ERK that have been found and how they relate to carcinogenesis, biological behavior, entity classification, and future prospects for targeted therapy. The current discoveries are reviewed in this article.

Molecular Pathogenesis

Odontogenic Keratocyst (OKC)

Gene mutation: PTCH1 (9q22.3) mutation in both sporadic and syndromic (Gorlin-Goltz syndrome) cases. Pathway involved: Sonic Hedgehog (SHH) signaling pathway. Other alterations: SMO, SUFU mutations in a minority of cases.
Clinical implication: Suggests neoplastic behavior, hence its reclassification by WHO as a tumor and then back as a cyst with neoplastic features.

Ameloblastoma

Gene mutations: BRAF V600E mutation (40-80%) most frequent, especially in unicystic and conventional types. SMO mutations predominantly in maxillary ameloblastomas.
Signaling pathways: MAPK/ERK and Hedgehog pathways.
Epigenetic changes: Aberrant methylation of tumor suppressor genes (e.g., p16INK4A).
Clinical implication: Targeted BRAF inhibitors (vemurafenib, dabrafenib) are under clinical evaluation.

Adenomatoid Odontogenic Tumor (AOT)

Genetic alterations: Not thoroughly defined.

Possible mechanisms: Activation of the WNT/β-catenin pathway.

Clinical characteristics: Less aggressive; molecular investigations are currently in progress.

Calcifying Odontogenic Cyst (COC) / Calcifying Cystic Odontogenic Tumor

CTNNB1 (β-catenin) gene mutations identified in many cases.
Activates the WNT signaling pathway leading to cellular proliferation.

Odontogenic Myxoma

Limited molecular data.

Some studies suggest involvement of WNT and MAPK pathways.

Ameloblastic Carcinoma

Mutations: BRAF V600E, HRAS, KRAS, FGFR2, and SMO mutations.

High proliferative index: Increased Ki-67 and p53 expression.
Clinical implication: Potential for molecularly targeted therapies in high-grade tumors.

Epigenetic Alterations in Odontogenic Lesions

DNA methylation, histone modifications, and miRNA dysregulation influence tumor suppressor gene silencing.
Promoter methylation of p16INK4A, MGMT, and DAPK genes seen in aggressive odontogenic tumors.

Recent Advances in Molecular Techniques in Odontogenic Cysts and Tumors

Molecular pathology has revolutionized the diagnostic, prognostic, and therapeutic landscape of head and neck lesions, including odontogenic cysts and tumors. Several advanced molecular techniques have been adopted in recent years for detecting genetic alterations, epigenetic changes, and protein expression profiles associated with these lesions. Below is a detailed elaboration of some key techniques:

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Molecular Diagnostic Techniques in Odontogenic Lesions

1. Next-Generation Sequencing (NGS)

Next-Generation Sequencing (NGS) is a high-throughput technology that allows for the simultaneous sequencing of millions of DNA fragments. This provides comprehensive data on gene mutations, copy number variations, insertions, deletions, and translocations.

Applications:

- **Ameloblastoma:** Identified recurrent $BRAF$ $V600E$ mutations in conventional/unicystic variants and SMO mutations in maxillary cases.
- **Odontogenic Keratocyst (OKC):** Characterized mutations in the $PTCH1$ gene within the Sonic Hedgehog pathway.

Advantages:

- Simultaneous multi-gene analysis.
- High sensitivity and specificity.
- Ability to detect low-frequency mutations.

The workflow step of DNA sequencing with Next Generation sequencing technique in sample of liquid biopsy that represent in three simple step: Sample collection (blood), Extraction and Analyzing.

2. Droplet Digital PCR (ddPCR)

Droplet Digital PCR is a highly sensitive quantitative technique that partitions a DNA sample into thousands of nanoliter-sized droplets. Each droplet undergoes independent PCR amplification.

Applications:

- **Mutation Quantification:** Detecting specific mutations like $BRAF$ $V600E$ in tumor tissue or circulating DNA.
- **Clinical Monitoring:** Tracking minimal residual disease (MRD) or recurrence via ctDNA analysis.

Advantages:

- Ultra-sensitive detection of low-abundance mutations.
- Absolute quantification (no standard curves required).
- Highly effective for Formalin-Fixed Paraffin-Embedded (FFPE) samples.

3. Fluorescence In Situ Hybridization (FISH)

FISH is a cytogenetic method that uses fluorescently labeled DNA probes to locate and identify specific DNA sequences or chromosomal aberrations within tissue slices.

- **Applications:**
  - **Aggressive Tumors:** Detecting gene amplifications, translocations, and deletions.
  - **Malignancies:** Identifying chromosomal imbalances or gene rearrangements in rare malignant odontogenic tumors.

Advantages:

- Applicable to FFPE tissue sections.
- Provides spatial context within the histological architecture.
- Highly specific for targeted genetic aberrations.

4. Immunohistochemistry (IHC)

IHC utilizes specific antibodies to detect proteins in tissue slices, visualizing their location through chromogenic or fluorescent markers. It remains a cornerstone for protein expression analysis.

- **Common IHC Markers:** Used to differentiate various odontogenic tumors and assess proliferative activity (e.g., Ki-67, cytokeratins)

Marker	Significance

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BRAF V600E		Detects mutated BRAF protein, predominantly in ameloblastomas
β-catenin		Aberrant nuclear localization in Calcifying Odontogenic Cyst indicating WNT pathway activation
p53		Overexpression linked with malignant transformation and aggressive behavior in ameloblastic carcinoma
Ki-67		Proliferation index aiding in grading and prognosis

Conclusion

Advancements in molecular pathology have transformed our understanding of odontogenic cysts and tumors. Identifying key genetic mutations and signaling pathways not only refines diagnostic accuracy but also opens avenues for precision medicine in managing aggressive odontogenic lesions. The integration of these advanced molecular techniques has significantly enhanced the diagnostic accuracy, risk stratification, and therapeutic targeting of odontogenic cysts and tumors. As technology advances, future research should focus on the combined application of these modalities and the development of liquid biopsy-based molecular diagnostics for early detection and monitoring of aggressive odontogenic lesions.

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