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Review Article

Sonic Hedgehog and Other Molecular Pathways in Odontogenic Cysts and Tumours: A Review Based on WHO 2022 Classification

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Abstract

Molecular signalling pathways, including Sonic Hedgehog (SHH), MAPK/ERK, Wnt/β-catenin, and PI3K/mTOR, play critical role in embryonic development and odontogenesis, and its dysregulation contributes to the development of certain odontogenic cysts and tumours. A review of current evidence, aligned with the WHO 2022 classification, shows that aberrant SHH activity is particularly prominent in odontogenic keratocysts and ameloblastomas, where it promotes epithelial proliferation, survival, and lesion expansion. In contrast, other developmental cysts such as dentigerous, glandular, and orthokeratinized cysts demonstrate minimal SHH involvement, with their pathogenesis more strongly linked to mechanical, inflammatory, or differentiation-related factors. Benign odontogenic tumours exhibit distinct molecular profiles, with MAPK/ERK signalling common in mixed epithelial–mesenchymal lesions, Wnt/β-catenin alterations in adenoid ameloblastoma and odontomas, and PI3K/mTOR activation in mesenchymal tumours. Overall, SHH plays a lesion-specific role, within a broader network of molecular pathways and most significant in odontogenic keratocysts and ameloblastomas, and integrating these molecular insights with the WHO 2022 framework improves understanding of pathogenesis, diagnostic accuracy, and identification of potential therapeutic targets.

Keywords: Sonic Hedgehog pathway; Molecular signalling pathways; Odontogenic cysts and tumours; WHO 2022 classification.

Statement of Clinical Significance:

Sonic Hedgehog pathway dysregulation drives odontogenic keratocysts and ameloblastomas; identifying lesion-specific molecular patterns enhances diagnosis, prognosis, and targeted treatment.

Introduction

The Sonic Hedgehog (SHH) signalling pathway is a conserved molecular network essential for embryonic development, particularly in cell differentiation and tissue patterning (1). SHH functions as a morphogen, with concentration-dependent effects on cell fate, and requires post-translational processing for proper secretion and gradient formation. Activation occurs when SHH binds to the Patched (PTCH) receptor, releasing Smoothened (SMO) inhibition and triggering GLI-mediated gene regulation (2). Tight control of this pathway is crucial, as its dysregulation is linked to developmental disorders and cancer (3).

Odontogenic cysts and tumors comprise a diverse group of lesions arising from epithelial and/or ectomesenchymal remnants involved in tooth development. Among the epithelial remnants, the dental lamina, the enamel organ epithelium, and the epithelial rests of Malassez have the potential to give rise to these pathologies (4). The fifth edition of the World Health Organization (WHO) classification of odontogenic cysts and tumours (2022) provides a refined taxonomic framework incorporating clinical, histopathological, and molecular characteristics (4).

The SHH signalling pathway has been widely investigated in odontogenic cysts and tumours due to its crucial role in tooth embryogenesis (5). Despite extensive research, the pathogenesis of odontogenic lesions remains controversial, prompting numerous studies to explore the molecular mechanisms involved in their development and progression. Genetic and epigenetic investigations have particularly focused on signalling pathways such as the SHH pathway (5). While SHH signalling has been extensively studied, odontogenic lesions are increasingly understood as being driven by multiple interacting molecular pathways, necessitating a broader integrative perspective (6-8).

Among developmental odontogenic cysts, the odontogenic keratocyst (OKC) is of special interest because of its aggressive behaviour, high recurrence rate, distinctive histopathological features, and occasional association with naevoid basal cell carcinoma syndrome (8). With respect to odontogenic tumours, ameloblastoma is especially significant due to its high prevalence, locally aggressive nature, and tendency to recur, making it a frequent subject of research (6). In contrast, calcifying epithelial odontogenic tumour (CEOT, or Pindborg tumour) is an uncommon benign odontogenic neoplasm characterized by local aggressiveness with PTCH1 mutation (7).

While this review focuses on the molecular landscape of odontogenic cysts and benign tumours, the most prevalent of these pathologies, it is important to note that malignant transformation involves distinct genomic shifts and increased genomic instability, which are beyond the current scope. This review summarizes evidence on the SHH pathway alongside other key molecular networks, providing an updated overview of genetic alterations and expression patterns within the WHO 2022 framework.

Methodology

A literature search was conducted using PubMed, Scopus, and Web of Science for studies published up to 2026, with the WHO Classification of Head and Neck Tumours (5th edition, 2022) used as a reference framework. Keywords included "Sonic Hedgehog pathway," "SHH," "odontogenic cysts," "odontogenic tumours," "ameloblastoma," and "odontogenic keratocyst." Studies addressing molecular mechanisms in odontogenic lesions were included, while non-English articles, case reports, and studies lacking molecular data were excluded. Screening was performed by title/abstract and full-text review, with additional articles identified through manual reference searches.

Literature review

1. **WHO 2022 Classification of Odontogenic Cysts and Tumours**

The WHO 2022 classification recognizes the following odontogenic cysts of the jaws entities (9):

- Calcifying odontogenic cyst
- Dentigerous cyst
- Gingival cysts
- Glandular odontogenic cyst
- Inflammatory collateral cysts
- Lateral periodontal cyst and botryoid odontogenic cyst
- Odontogenic keratocyst
- Orthokeratinized odontogenic cyst
- Radicular cyst

The WHO 2022 classification recognizes the following benign odontogenic tumours entities (9):

- Benign epithelial odontogenic tumours
    i. Adenomatoid odontogenic tumour
    ii. Squamous odontogenic tumour
    iii. Calcifying epithelial odontogenic tumour
    iv. Ameloblastoma, unicystic
    v. Ameloblastoma, extraosseous
    vi. Ameloblastoma, conventional
    vii. Adenoid ameloblastoma
    viii. Metastasizing ameloblastoma

- Benign mixed epithelial and mesenchymal odontogenic tumours
    i. Odontoma
    ii. Primordial odontogenic tumour
    iii. Ameloblastic fibroma
    iv. Dentinogenic ghost cell tumour

- Benign mesenchymal odontogenic tumours
    i. Odontogenic fibroma
    ii. Cementoblastoma
    iii. Cemento-ossifying fibroma
    iv. Odontogenic myxoma

This updated framework provides a basis for evaluating molecular associations within defined diagnostic categories.

2. The Sonic Hedgehog Pathway

The SHH signalling pathway is a highly conserved molecular network essential for embryonic development, tissue patterning, and odontogenesis (1). In its inactive state, the transmembrane receptor PTCH1 constitutively inhibits SMO, a G-protein-coupled receptor-like protein, preventing downstream signalling. Activation occurs when the SHH ligand binds to PTCH1, relieving this inhibition and allowing SMO to trigger a cytoplasmic cascade that protects GLI transcription factors (GLI1, GLI2, and GLI3) from proteolytic cleavage. The resulting active GLI proteins translocate to the nucleus to regulate genes involved in cell proliferation and survival (1).

To evaluate SHH-related pathogenesis in odontogenic lesions, specific molecular markers serve as critical indicators of pathway activity (5). SHH ligand overexpression often marks the initiation of autocrine or paracrine signalling, while PTCH1 and SMO expression levels provide insight into receptor-level dysregulation, such as the loss-of-function mutations typical in odontogenic keratocysts (10). Crucially, the nuclear localization of GLI1 and GLI2 is considered the definitive evidence of an "on" state, as these effectors directly drive the transcription of oncogenic targets. Functional activation is further confirmed by the presence of downstream proteins like Bcl-2, which provides anti-apoptotic signals, and Cyclin D1, which accelerates the cell cycle, collectively contributing to the aggressive expansion and survival of lesions such as ameloblastomas and odontogenic keratocysts (10).

3. SHH and Other Molecular Pathways in Odontogenic Cysts

3.1 Odontogenic Keratocyst (OKC)

The pathogenesis of the OKC is inexorably linked to the aberrant activation of the SHH signaling pathway, primarily driven by PTCH1 mutations. This molecular signature is so profound that it has historically dictated the lesion's taxonomic status, fuelling the WHO's 2005 reclassification of the OKC as a neoplasm before its 2017/2022 reversion to a cystic entity, a shift that acknowledges its "neoplastic-like" driver yet recognizes its clinical behaviour (8). Beyond taxonomy, SHH pathway components like SMO and nuclear GLI1/2 serve as critical diagnostic pivots; their absence in Orthokeratinized Odontogenic Cysts (OOC) provides a definitive molecular demarcation between these mimics (10). Furthermore, the ubiquitous overexpression of these markers in NBCCS-associated OKCs underscores the pathway's dual role as a hallmark of aggressive epithelial proliferation and a vital sentinel for systemic genetic screening (11). Ultimately, the successful pharmacologic suppression of OKC growth via SMO antagonists like cyclopamine solidifies SHH dysregulation as the central engine of its expansion and a prime target for precision therapeutics (10).

3.2 Other Odontogenic Cysts

Although several odontogenic cyst types show expression of SHH protein or downstream effectors in immunohistochemical studies, no direct genetic mutation of the SHH pathway has been established.

- **Calcifying odontogenic cyst**

Calcifying odontogenic cyst is a WNT/β-catenin–driven odontogenic epithelial lesion arising from odontogenic remnants, with recurrent CTNNB1 and related pathway mutations leading to nuclear β-catenin accumulation (9). Aberrant WNT signalling promotes epithelial proliferation and altered differentiation, resulting in ghost cell formation, dystrophic calcification, and induction of adjacent dentinoid-like matrix through epithelial–mesenchymal interaction. This mechanism underlies the cystic–neoplastic spectrum of the lesion and explains its frequent intraluminal and mural proliferative features (12).

- **Dentigerous cyst**

The dentigerous cyst is a developmental odontogenic cyst arising from reduced enamel epithelium around an unerupted tooth. It develops mainly due to mechanical pressure from the erupting tooth, leading to fluid accumulation, epithelial separation from the enamel surface, and progressive cyst expansion (13). Secondary inflammation, often originating from an infected overlying deciduous tooth, can further stimulate epithelial proliferation and cyst enlargement through cytokine- and prostaglandin-mediated pathways (i.e., IL-1, TNF-α, COX-2/PGE_2), as well as growth factor signalling (i.e., EGFR, TGF-β) (14).

- **Glandular odontogenic cyst**

Glandular odontogenic cyst (GOC) is a developmental odontogenic cyst arising from dental lamina remnants that undergo glandular and mucous metaplasia, forming a lining with mucous cells, microcysts, and duct-like structures (9). Immunohistochemistry confirms odontogenic epithelial origin, while low proliferative activity and occasional expression of invasiveness-associated proteins (i.e., MT1-MMP, cortactin) explain its locally aggressive behaviour and recurrence. GOC lacks consistent oncogenic mutations, indicating that its pathogenesis is driven primarily by epithelial differentiation and reactive invasive potential rather than classical neoplastic pathways (15).

- **Orthokeratinized odontogenic cyst**

The OOC is a developmental odontogenic cyst arising from rests of dental lamina (9). Its pathogenesis is primarily epithelial differentiation-driven, where the cyst lining undergoes orthokeratinization with a prominent granular layer, unlike the parakeratinized lining of keratocystic odontogenic tumours (9). OOC exhibits low proliferative activity, minimal inflammation, and lacks consistent mutations in oncogenic pathways such as PTCH1 or WNT, distinguishing it from neoplastic keratocysts. Expansion is largely due to cystic fluid accumulation and epithelial growth, indicating that OOC represents a benign developmental cyst with limited proliferative and invasive potential (16).

- **Radicular cyst**

Radicular cysts are inflammatory odontogenic cysts that develop as a chronic consequence of periapical inflammation following pulpal necrosis (9). Persistent microbial antigens stimulate epithelial rests of Malassez within a periapical granuloma, leading to cyst formation lined by stratified squamous epithelium and surrounded by an inflamed fibrous capsule (9). Pro-inflammatory cytokines and growth factors drive lesion expansion and bone resorption, while metabolic mediators further amplify inflammation and tissue remodelling within the cyst microenvironment (17).

Table 1 highlights the involvement of SHH and principal molecular signalling networks in odontogenic cyst pathogenesis and progression.

Table 1: Molecular Signalling Pathways and SHH Involvement in Odontogenic Cysts

Odontogenic Cyst	SHH Expression / Involvement	Dominant Signalling / Molecular Alterations	Reference
Odontogenic keratocyst (OKC)	◍ Dominant	◍ SHH pathway: SHH, PTCH1, SMO, GLI1/2 → promotes epithelial proliferation; targetable by SMO antagonists	(4,8)
Calcifying odontogenic cyst (COC)	◍ Modulatory	◍ WNT/β-catenin pathway: CTNNB1 mutations → nuclear β-catenin → epithelial proliferation, ghost cell formation, dentinoid induction	(9)
Dentigerous cyst	◍ Not involved	◍ Mechanical/fluid-driven; inflammatory cytokines (IL-1, TNF-α), prostaglandins (COX-2/PGE_2), growth factors (EGFR, TGF-β) → epithelial proliferation and cyst expansion	(10,11)
Glandular odontogenic cyst (GOC)	◍ Not involved	◍ Epithelial differentiation and reactive invasive potential; mucous metaplasia, microcysts, duct-like structures; invasiveness proteins (MT1-MMP, cortactin)	(12,13)
Orthokeratinized odontogenic cyst (OOC)	◍ Not involved	◍ Epithelial differentiation-driven; orthokeratinized lining with granular layer; low proliferation; no consistent oncogenic mutations (PTCH1/WNT); expansion via fluid accumulation	(14)
Radicular cyst	◍ Not involved	◍ Inflammation-driven; epithelial rests of Malassez proliferation; cytokines (IL-1β, IL-6, IL-12A), growth factors (PDGFα), metabolites (1-nonadecene, L-lactic acid) → chronic inflammation, EMT modulation, collagen deposition, cyst expansion and bone resorption	(15,16)
Other cysts of the jaws	◍ Not involved	Lacks defined molecular alterations	(7)

◍: Dominant/driver pathway; ◍: Modulatory/minor involvement; ◍: No involvement.

4. SHH and Other Molecular Pathways in Benign Odontogenic Tumours

4.1 Ameloblastoma

The SHH signalling pathway is actively involved in the pathogenesis of ameloblastoma (6). Components of the pathway including SHH, PTCH1, SMO, and GLI family transcription factors (GLI1–3) are expressed in ameloblastoma tissues, with overexpression of PTCH1 and GLI1 frequently observed, suggesting constitutive activation of the pathway in tumour cells (6). This activation likely promotes neoplastic cell proliferation via epithelial–mesenchymal interactions, similar to its role in normal tooth development, and may contribute to the aggressive growth characteristic of ameloblastoma. Additionally, SHH signalling appears to exert an anti-apoptotic effect by regulating apoptosis-related proteins such as Bcl-2 and BAX, further supporting tumour survival and expansion (18). Because of its central role in tumour growth and survival, the SHH pathway represents a potential therapeutic target, with several small-molecule inhibitors under investigation to modulate SHH activity in ameloblastoma management (6).

4.2 Calcifying epithelial odontogenic tumour

Calcifying epithelial odontogenic tumour (CEOT) is a rare benign odontogenic neoplasm with locally aggressive behaviour, but its molecular pathogenesis remains incompletely defined (9). Immunohistochemical studies have demonstrated expression of key SHH pathway components, including PTCH1, GLI1, and GLI2, in the majority of CEOT cases, and sequencing analyses have identified PTCH1 mutations in some tumours, implicating dysregulated SHH signalling in CEOT development alongside other odontogenic neoplasms (7). However, broader genomic profiling has also revealed sporadic mutations in tumour suppressor genes (e.g., PTEN, CDKN2A) and oncogenes (e.g., MET, JAK3) in isolated CEOT cases, although these alterations do not appear to be consistent drivers (19). Unlike other odontogenic tumours where MAPK or Wnt pathways predominate, the evidence for canonical signalling pathway activation in CEOT is currently limited to variable SHH involvement, with further comprehensive molecular characterization needed to clarify the dominant pathways and potential therapeutic targets in CEOT pathogenesis (20).

4.3 Other Benign Odontogenic Tumours

- **Adenomatoid odontogenic tumour**

Current evidence indicates that the SHH signalling pathway does not play a central role in the pathogenesis of AOT. Unlike ameloblastoma, where SHH pathway components such as SMO may contribute to tumour proliferation and survival (6), AOTs are predominantly driven by activating mutations in the MAPK pathway, particularly KRAS (G12V/R), which are present in the majority of cases (~76%) (21). Mutations in canonical SHH pathway genes, including PTCH1 and SMO, are largely absent, and SHH signalling activity appears minimal (21). These findings suggest that AOT tumorigenesis is primarily mediated through RAS/MAPK signalling rather than SHH dysregulation, underscoring distinct molecular mechanisms between AOT and other odontogenic tumours (21).

- **Squamous odontogenic tumour**

Squamous odontogenic tumour (SOT) is a rare benign odontogenic neoplasm arising from epithelial remnants, such as the rests of Malassez or dental lamina, characterized by local invasiveness and epithelial proliferation (9). Unlike other odontogenic tumours, the molecular

pathogenesis of SOT remains poorly defined, with no consistently implicated signalling pathway, including SHH, Wnt, or MAPK, established as a driver of tumour development. Limited genomic analyses from isolated or aggressive cases suggest occasional alterations in cell cycle–related genes, such as MAP2K1 and CDKN1B, hinting at potential involvement of MAPK signalling in rare instances, but these findings are not representative of typical SOT (20). Overall, SOT pathogenesis appears largely independent of canonical oncogenic pathways described in other odontogenic tumours (20), underscoring the need for comprehensive molecular studies to elucidate its regulatory mechanisms and identify potential therapeutic targets.

- **Adenoid ameloblastoma**

Adenoid ameloblastoma is a distinct odontogenic tumour recently recognized as a separate entity, whose molecular pathogenesis is driven predominantly by dysregulation of the canonical Wnt/β-catenin signalling pathway rather than by the MAPK or SHH cascades typical of conventional ameloblastoma and related tumours (2). Somatic CTNNB1 mutations disrupt regulatory phosphorylation, leading to β-catenin stabilization and nuclear accumulation. This triggers transcriptional programs that drive neoplastic growth in adenoid ameloblastoma. Similar aberrant Wnt signalling in wild-type cases suggests that alternative disruptions in pathway regulation or destruction complex components also contribute to constitutive activation (22). Emerging evidence positions Wnt/β-catenin dysregulation as the central driver of adenoid ameloblastoma, molecularly distinguishing it from other odontogenic tumours dominated by different signalling alterations (20).

- **Primordial odontogenic tumour**

Primordial odontogenic tumour (POT) is a benign mixed odontogenic neoplasm that mimics early tooth development (9). Unlike other odontogenic tumours, POT shows no activating mutations in major pathways such as MAPK, SHH, or Wnt. Its pathogenesis appears driven by arrested odontogenic differentiation, with expression of early dental epithelial and mesenchymal markers (e.g., AMELX, AMBN, ENAM, DSPP) but limited odontoblastic maturation. This suggests POT arises from developmental perturbations rather than classical oncogenic signalling, explaining its slow growth and benign behaviour (23).

- **Ameloblastic fibroma**

Ameloblastic fibroma (AF), ameloblastic fibrodentinoma (AFD), and ameloblastic fibro-odontoma (AFO) are mixed odontogenic tumours that recapitulate early odontogenesis and are increasingly understood within the context of MAPK/ERK pathway dysregulation (9). Molecular analyses have revealed that a substantial subset of these lesions harbour activating BRAF p.V600E mutations, implicating constitutive MAPK signalling in their pathogenesis and distinguishing them from odontomas, which lack this mutation (24). BRAF or FGFR1-driven MAPK activation promotes survival in AF, AFD, and AFO, confirming that these subsets are true neoplasms rather than hamartomas. This kinase-driven profile aligns them with other odontogenic neoplasms, offering new avenues for targeted diagnostics and therapeutics (24).

- **Dentinogenic ghost cell tumour and odontoma**

Wnt/β-catenin dysregulation is central to both odontomas and dentinogenic ghost cell tumours (DGCT). In odontomas, nuclear and cytoplasmic β-catenin accumulation reactivates

postnatal tooth development programs and disrupts epithelial–mesenchymal interactions, driving the formation of supernumerary tooth-like structures (25). In DGCT, activating CTNNB1 mutations stabilize β-catenin, triggering tumorigenesis and ghost cell formation. While BMP/TGF-β, Notch, and SHH may modulate this, Wnt/β-catenin remains the primary driver, governing differentiation in odontomas and neoplastic growth with potential malignancy in DGCT (26, 27).

- **Odontogenic fibroma**

Odontogenic fibroma (OF) is a rare benign mesenchymal odontogenic tumour with poorly understood molecular pathogenesis. Unlike other odontogenic neoplasms, no recurrent oncogenic mutations or dominant signalling pathways have been identified. Its growth is thought to result from aberrant epithelial–mesenchymal interactions, with limited evidence suggesting a role for EMT-related signalling in stromal expansion. Overall, major pathways such as MAPK, Wnt/β-catenin, or SHH have not been definitively implicated, and further molecular studies are needed to clarify OF pathogenesis (28).

- **Cementoblastoma**

Cementoblastoma is a benign mesenchymal odontogenic tumour arising from cementoblasts, with pathogenesis primarily driven by c-FOS overexpression and AP-1 transcriptional dysregulation, which promotes proliferation and matrix production (29). Although canonical pathways are not directly implicated, c-FOS–driven transcription is central to cementoblastoma pathogenesis. Its molecular profile mirrors osteogenic tumours, likely utilizing Wnt/β-catenin, TGF-β/Smad, MAPK, and NF-κB pathways to modulate proliferation, differentiation, and matrix mineralization (29).

- **Cemento-ossifying fibroma**

Cemento-ossifying fibroma (COF) is a benign mesenchymal odontogenic tumour arising from periodontal ligament cells, characterized by dysregulated Wnt/β-catenin signalling that drives proliferation and aberrant differentiation into fibrous, bone, and cementum-like tissues. Additional pathways, including Notch and regulators such as CDC73/parafibromin, may modulate this process, but no consistent oncogenic mutation has been identified, indicating that abnormal osteogenic differentiation rather than classical tumorigenic signalling underlies COF pathogenesis (27).

- **Odontogenic myxoma**

Odontogenic myxoma (OM) is a benign mesenchymal odontogenic tumor whose pathogenesis is primarily driven by MAPK/ERK and PI3K/mTOR pathway activation, promoting proliferation and survival (9). Unlike other odontogenic tumors, Wnt/β-catenin and Notch signalling are not major contributors, highlighting a distinct mesenchymal signalling–driven mechanism underlying OM growth and invasiveness (30).

Table 2 summarizes the involvement of SHH and other principal molecular signalling pathways in the development and progression of benign odontogenic tumours.

Table 2: Molecular Signalling Pathways and SHH Involvement in Benign Odontogenic Tumours

Odontogenic Tumour	SHH Expression / Involvement	Dominant Signalling / Molecular Alterations	Reference
Ameloblastoma	◍ Dominant	◍ SHH, PTCH1, SMO, GLI1–3 → SHH pathway; promotes proliferation, anti-apoptotic effects (BCL-2/BAX)	(5,17)
Calcifying epithelial odontogenic tumour (CEOT)	◍ Modulatory	◍ SHH pathway (PTCH1, GLI1/2); sporadic mutations in PTEN, CDKN2A, MET, JAK3; broader molecular drivers unclear	(6,18,19)
Adenomatoid odontogenic tumour (AOT)	◍ Minimal	◍ KRAS (G12V/R) → MAPK pathway	(20)
Squamous odontogenic tumour (SOT)	◍ Not involved	◍ Occasional MAP2K1 / CDKN1B, otherwise undefined	(19)
Adenoid ameloblastoma	◍ Minimal	◍ CTNNB1 exon 3 → Wnt/β-catenin pathway	(21)
Primordial odontogenic tumour	◍ Not involved	◍ Developmental; early dental markers (AMELX, AMBN, ENAM, DSPP)	(22,23)
Ameloblastic fibroma / AFO / AFD	◍ Minimal	◍ BRAF p.V600E / FGFR1 → MAPK/ERK pathway	(24,25)
Dentinogenic ghost cell tumour (DGCT) / Odontoma	◍ Modulatory	◍ CTNNB1 → Wnt/β-catenin pathway; BMP/TGF-β, Notch cross-talk	(24,26,27)
Odontogenic fibroma (OF)	◍ Not involved	◍ Possible EMT-related stromal signalling	(28)
Cementoblastoma	◍ Minimal	◍ c-FOS / AP-1 dysregulation; Wnt/β-catenin, TGF-β/Smad, MAPK, NF-κB	(29)
Cemento-ossifying fibroma (COF)	◍ Minimal	◍ Dysregulated Wnt/β-catenin, plus Notch / CDC73-parafibromin	(24)
Odontogenic myxoma (OM)	◍ Not involved	◍ MAPK/ERK and PI3K/mTOR pathway activation	(30)

◍: Dominant/driver pathway; ◍: Modulatory/minor involvement; ◍: No involvement.

Conclusion

While SHH signalling is the primary engine of proliferation in odontogenic keratocysts and ameloblastomas, it represents only one facet of a complex landscape. Lesion-specific molecular signatures, including Wnt/β-catenin, MAPK/ERK, and PI3K/mTOR pathways, underpin the molecular heterogeneity of odontogenic lesions, highlighting that their pathogenesis cannot be explained by SHH signalling alone. Integrating these signatures with the WHO 2022 classification not only refines diagnostic accuracy and targeted therapeutics but also establishes a critical baseline for decoding the malignant transition, where developmental pathways inevitably intersect with cell-cycle escape mechanisms.

AUTHORS' CONTRIBUTIONS

Vinesh Raj.S: Conceptualization, literature review, manuscript drafting, data synthesis, and figure/table preparation.

Dr. Nur Syahirah Binti Mohd Nazar: Critical review, manuscript editing, figure/table preparation and final approval of the submitted version.

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