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Molecular pathways of odontogenic keratocysts: A systematic review.

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Abstract

Objective: This systematic review aims to identify the molecular aspects of odontogenic keratocysts that have been elucidated to date.
Methods: The odontogenic keratocyst (OKC) stands out as one of the most prevalent odontogenic tumors. Since its initial description, numerous studies have delved into various aspects of this lesion, aiming to unravel its distinctive biological behavior.
Results: Recent investigations have specifically focused on the molecular aspects of OKC, shedding light on its biological characteristics. Substantial differences at the molecular level between OKC and other odontogenic cystic lesions indicate a distinct biological origin. Genetic and molecular research in the realm of odontogenic tumors, particularly OKC, has contributed significantly to the growing knowledge and understanding of their physiopathological pathways.
Conclusion: The molecular findings may open non-surgical, pharmaceutical options for treatment.

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Introduction

Odontogenic cysts and tumors comprise a diverse range of lesions derived from components of the tooth-forming apparatus and their residual structures. As per the 2017 World Health Organization Classification of Head and Neck Tumors, odontogenic tumors are categorized into epithelial, mixed, and mesenchymal tumors, while odontogenic cysts are divided into inflammatory or developmental cysts. The predominant nature of odontogenic tumors is benign, and malignancies may either stem from a benign precursor or emerge spontaneously.[1-29]

Odontogenic lesions encompass a variety of conditions with potential shared origins but necessitate distinct treatment approaches. Dentigerous cysts (DCs) originate from the crown of teeth that are compressed, embedded, or unerupted. As the most prevalent type of odontogenic cyst, DCs result from the accumulation of fluid between the reduced enamel epithelium and the crown portion of the tooth. Ameloblastoma (AB) represents another rare odontogenic lesion. Despite its benign nature and slow growth rate, AB can invade local tissues such as the mandible and maxilla. Odontogenic keratocysts (OKC) constitute another category of odontogenic lesions. Notably, OKC and DC exhibit the highest propensity for malignant transformation among odontogenic cysts.[9,24-29]

The term "odontogenic keratocyst (OKC)" was officially coined by Philipsen in 1956. An odontogenic keratocyst is a benign intra-osseous lesion originating from odontogenic tissues, primarily affecting the posterior mandible in male patients aged between the second and fourth decades of life.[15] The majority, around 65% to 75%, of such cyst cases are observed in the mandible, with a specific predilection for the molar/ramus area.[2] These lesions can be incidentally identified through routine radiological examinations or during consultations prompted by functional and/or aesthetic concerns.[8]

The cyst has the potential to cause destruction of the jaw bones, impede the normal eruption of teeth, and result in the expansion of the typical jaw contour. In rare instances, a pathologic fracture and secondary osteomyelitis may manifest as presenting clinical signs associated with the cyst.[22]

The primary clinical approach for treating odontogenic keratocysts (OKCs) is predominantly surgical, involving procedures such as removal, decompression, application of Carnoy's solution, peripheral bone resection, and excision. However, non-surgical treatment strategies are becoming more prominent in recommendations due to the elevated recurrence rates associated with OKCs. This shift in focus acknowledges the challenges posed by the tendency of these lesions to recur and suggests the exploration of alternative non-surgical interventions to address this clinical concern.[3]

OKC may manifest sporadically or be associated with nevoid basal cell carcinoma syndrome (NBCCS)/Gorlin-Goltz syndrome.[15]

Gorlin-Goltz syndrome (GGS), also known as Nevoid Basal Cell Carcinoma

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syndrome, is an autosomal dominant inherited disorder associated with a germline mutation of the PTCH1 gene. This gene functions as a tumor-suppressor and is located on chromosome 9q22.3. Mutations in this gene can trigger a carcinogenic process by disrupting the normal cell cycle and cellular proliferation. GGS is characterized by the presence of multiple developmental anomalies and an increased predisposition to various tumor formations.[10] The presence of multiple odontogenic keratocysts (OKCs) in the jaw is a frequent manifestation of Nevoid Basal Cell Carcinoma Syndrome (NBCCS), observed in approximately 65% to 90% of affected patients.[3]

The classification of keratocystic odontogenic tumors (KCOTs) as OKC has been a topic of debate. The World Health Organization (WHO) had initially reclassified OKC from a benign cyst to a neoplastic lesion (KCOT) in 2005.

In the 2017 classification, there was a decision to reclassify KCOTs back into the cyst category as OKC. This decision was based on evidence suggesting aggressive growth, high recurrence after treatment, and mutations in the PTCH gene. This remains its current classification.[3]

Authors may categorize odontogenic keratocysts (OKCs) as tumors due to their relatively frequent mitotic activity in the epithelium, association with chromosomal aberration syndromes, mutations of the PTCH tumor suppressor gene, and their connection with Gorlin-Goltz syndrome.[5]

Recent studies have focused on the molecular aspects of OKC to further elucidate its biological characteristics. Mutations in the PTCH gene, particularly associated with Nevoid Basal Cell Carcinoma Syndrome (NBCCS), play a significant role. PTCH1 serves as a negative regulator of the Hedgehog (HH) pathway and is detected in approximately 40% to 85% of NBCCS patients. Alterations in the PTCH1 gene are also observed in sporadic odontogenic keratocysts (OKCs), often involving a single copy of the gene, leading to haploinsufficiency and reduced expression of the PTCH protein at the cell surface, ultimately activating the HH pathway. PTCH gene alterations may occur through somatic mutation, loss of heterozygosity (LOH), or gene silencing via DNA methylation.[1]

In the context of odontogenic keratocysts (OKCs), the majority of molecular studies focusing on non-syndromic single cysts or multiple syndromic cysts have been confined to the examination of the PTCH (patched) gene and a limited number of selected genes within the Hedgehog (HH) pathway. This suggests that the current understanding of the molecular basis of OKCs primarily revolves around the investigation of these specific genetic elements.[1]

As of now, the predominant clinical treatment for odontogenic keratocysts (OKCs) is primarily surgical, involving procedures such as removal, decompression, application of Carnoy's solution, peripheral bone resection, and excision. However, due to the high recurrence rates associated with surgical approaches, there is a growing trend toward recommending non-surgical treatment strategies. These alternative approaches aim to address the challenges of recurrence and may include various adjunctive therapies or medical interventions to manage and control OKCs.[3]

The molecular findings may open non-surgical, pharmaceutical options for treatment of OKCs, mainly large, destructive cysts, both sporadic and syndromic.[6]

The aim of this literature review is to identify which molecular aspects of odontogenic keratocysts have been identified to date.

Materials and Methods

The present review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The research question was about the molecular pathways of development of odontogenic keratocysts. A literature search was conducted in four electronic databases (Medline/PubMed, Scopus, Embase, and Web of Science) using the combination of the terms "odontogenic keratocyst" OR "keratocystic odontogenic tumor" and "molecular" OR "pathogenesis" OR "pathways". Articles not in English language were excluded. PICO inclusion and exclusion criteria were adopted.

Results

A total of 23 articles resulted eligible table 1. The most relevant molecular change that has been reported is the presence of PTCH1 mutations, and this data was reported in 17 articles.

Discussion

The Odontogenic keratocyst (OKC) is a cystic lesion that originates from the dental lamina epithelium and is commonly located in the mandible or maxilla. This lesion has the potential to display aggressive behavior and derves attention due to frequent recurrence and specific histopatological features. Additionally, these tumors may manifest sporadically or be associated with the nevoid basal cell carcinoma (Gorlin) syndrome.[19,23]

Gorlin syndrome is an autosomal dominant disorder predisposing affected individuals to the development of multiple OKCs, and studies on patients with Gorlin syndrome have initially shown a pivotal role for the sonic hedgehog (SHH) pathway in OKC development. Alterations, either inherited or sporadic, in the SHH signaling pathway genes might cause a number of developmental defects. Aberrant activation of the SHH signaling pathway during adult life has been shown to be related to tumor formation. The SHH signaling pathway in the development of OKC is not well known, although activation of this pathway may be related to the clinical behavior and outcome of OKC.[13,20]

The neoplastic characterization of odontogenic keratocysts (OKC) finds substantial support in molecular investigations, particularly those revealing loss of heterozygosity. Evidence of allelic loss has been prominently observed in tumor-suppression gene linked to different form of neoplasia: p16, p53, PTCH, MCC, TSLC1, LTAS2, and FHIT genes. The collective findings lend considerable credence to elucidating the inherently aggressive nature exhibited by OKCs, further substantiating their neoplastic potential.[15]

The assessment of the p53, PTCH, SHH, and GLI1 genes in odontogenic keratocyst samples is common, indicating that these genes and their signaling pathways play a significant role in the mesenchymal epithelium, as well as in cell interactions and proliferation during odontogenic tumor growth and dental development.[5] Among the mutation cited, PTCH and P53 and are the mostly assessed genes in OKC samples described in the articles analyzed.

Most of the reviewed articles describe mutations of PTCH1 gene (patched). In its normal function, PTCH1 acts to suppress the activities of the signaling effector Smoothened (SMO). When Hedgehog (HH) binds to the PTCH1-SMO complex, it releases SMO, initiating the activation of target genes through the GLI family of transcription factors.

A mutation in the PTCH1 gene results in the continuous activation of the Sonic Hedgehog (Shh) pathway, representing a significant mechanism underlying the tumorigenesis of odontogenic keratocysts (OKC). PTCH1 mutations has been found both in sporadic and sindromic OKC.[14]

The p53 protein, encoded by the tumor protein p53 (Tp53) gene, serves as a tumor suppressor and is expressed during the G1 phase of the cell cycle. Its primary role is to facilitate the repair of damaged DNA in cells, preventing them from entering the synthesis (S) phase until the repairs are completed. Indeed, p53 is a tumor suppressor gene that plays a critical role in regulating cell growth. Its functions include inducing growth arrest, initiating DNA repair processes, and triggering apoptosis if the DNA damage is irreparable. The expression of the p53 protein in the cystic epithelium of odontogenic keratocysts has not been precisely defined. However, the aggressive behavior and high recurrence rate observed in OKCs could be linked to the immunoexpression of p53. If p53 is overexpressed or mutated, it may disrupt the normal regulatory functions of the protein, potentially contributing to uncontrolled cell growth and resistance to apoptosis.[16]

GLI1 functions as a transcriptional activator downstream of the SHH signaling pathway, modulating cellular activities by either activating or inhibiting the expression of target genes.[11]

Studies on the proliferative activity in odontogenic keratocysts (OKCs) have been conducted by various investigators, comparing them to other odontogenic cysts and tumors. The majority of researchers have reported elevated immunohistochemical expression of proliferation markers such as Ki67 and PCNA in OKCs when compared to other odontogenic lesions. This heightened expression of proliferation markers suggests increased cellular activity and may contribute to the aggressive behavior and higher recurrence rates often observed in OKCs.[15]

Matrix metalloproteinases (MMPs) are pivotal enzymes that wield significant influence in the orchestration of the extracellular matrix, governing both its integrity and composition. MMPs have been associated with risk of odontogenic disorders. The intricate involvement of MMP-8 extends beyond its conventional role, as it has been elucidated to exhibit a noteworthy association with compromised bone repair mechanisms and an elevated susceptibility to the development of malignant tumors.[4,5]

The molecular interplay between RANK (Receptor Activator of Nuclear Factor κB) and RANKL (Receptor Activator of Nuclear Factor κB Ligand) has been implicated in heightened osteolytic activity, acting as a stimulant for bone resorption. Notably, the pinnacle of immunoexpression for RANKL has been discerned in odontogenic keratocysts (OKC). This finding aligns seamlessly with existing literature, reinforcing the notion that OKC is characterized as a more aggressive lesion when juxtaposed with other odontogenic cysts.[4]

DNA methylation involves the addition of a methyl group to cytosines within CpG islands, facilitated by enzymes known as DNA methyltransferases. This process serves to remodel chromatin, either activating or inactivating genes. PTCH1 methylation has been proposed as an alternative mechanism for PTCH1 inactivation in tumors linked to the Nevoid Basal Cell Carcinoma Syndrome (NBCCS), including medulloblastomas and basal cell carcinomas. However, studies examining PTCH1 methylation in basal cell carcinomas and medulloblastomas have generally indicated either no or very low levels of PTCH1 methylation. Importantly,

Table 1. Number of Articles regarding the different genetic and epigenetic mutations of OKCs.

Gene	N° of Article
PTHC	17
P16	2
P53	7
MCC	2
TSLC1	2
LTAS2	2
FHIT	3
SHH	5
CDKN2A	1
TP53	1
CADHERIN	2
GLI1	3
LOXL4	1
TCTA	1
LARP6	1
CALRETININ	1
MYC	1
PCNA	2
KI-67	2
BCL-2	3
GLUT 1	1
P63	3
COX-2	2
RANKL	2
INOS	1
MDM2	1
MCM3	1
EGFR	2
TGF-ALFA	1
VEGF	1
MMP-s	3
SURVIVIN	1
P73	1
CASPASES 3	1
V600E	2
CATK	2
SMO	3
P21	2
RB1	2
miR15a/16-1	1
LTBR	1
BCLAF1	1
P27	1
SANT	1
KAAD-CYCLOPAMINE	2
COMPOUND-5	1
COMPOUND-K	1
CUR-61414	1
GANT61	1
VDR	1

hypermethylation at the promoter region of PTCH1 was not detected in sporadic or syndromic cases of Odontogenic Keratocysts. This suggests that, at least in the context of OKCs, PTCH1 inactivation may occur through mechanisms other than DNA methylation. As of now, the methylation status of PTCH in odontogenic keratocysts lacking PTCH mutations is not yet understood or identified.[14,15]

Currently, the main therapies for odontogenic keratocysts include conservative methods, such as simple enucleation with primary closure, enucleation with open packing, decompression, or marsupialization. More aggressive techniques involve cryosurgery using liquid nitrogen, chemical destruction through the application of Carnoy's solution. Radical surgical techniques may also be employed, including bone resection.[5]

Apart from conventional surgical interventions, it is crucial to explore non-surgical treatment modalities, including molecular-targeted therapy. A deeper comprehension of odontogenic keratocyst (OKC) biology has the potential to facilitate less aggressive interventions, especially for patients with large, recurrent, or multiple lesions. Research is now focusing on small molecule selective inhibitors for SHH-related targets.[6,13,15] Among the articles reviewed, 7 articles cited the inibition of SHH as a possible molecular therapy. Other molecularly targeted therapy suggested are the inibition of COX-2 and the MiRNAs, epigenetic-targeted drugs.

Conclusion

Odontogenic keratocysts, despite their intrinsic benignity, manifest an intriguing propensity for local invasiveness and a notable frequency rate, even in the context of aggressive surgical interventions. The molecular characterization of these cysts serves a dual purpose—enabling prognostication and guiding nuanced surgical decision-making and subsequent follow-up. Consequently, pharmacological interventions have been explored to enhance the efficacy of surgical outcomes. While this avenue holds promise, the imperative for additional clinical trials is evident, underscoring the need for comprehensive research to solidify evidence and refine therapeutic strategies.

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Conflict of Interest

The author report no conflict of interest.

References

1. Van NR. The future of dental devices is digital. Dental Mater 2012;28: 3-12.
2. Barazanchi A, Li KC, Al-Amleh B, et al. Additive technology: Update on current materials and applications in dentistry. J Prosthod 2016;26: 156-163.
3. Cialy JS, Thalib B, Dharmautama M, et al. Preventive and conservative prosthodontic treatment using overdenture and richmond crown. J Dentomaxillofac Sci 2016;1: 193-195.
4. Alla R, Raghavendra KN, Vyas R, et al. Conventional and contemporary polymers for the fabrication of denture prosthesis: part I–overview, composition and properties. Int J Appl Dent Sci 2015;1: 82-89.
5. Astudillo-Rubio D, Delgado-Gaete A, Bellot-Arcís C, et al. Correction: mechanical properties of provisional dental materials: A systematic review and meta-analysis. Plos One 2018;13: e0196264.
6. Mubarak S, Dhamodharan D, Kale MB, et al. A Novel approach to enhance mechanical and thermal properties of SLA 3D printed structure by incorporation of metal-metal oxide nanoparticles. Nanomater 2020;10: 217.
7. Alshaikh AA, Khattar A, Almindil IA, et al. 3D-printed nanocomposite denture-base resins: effect of ZrO2 nanoparticles on the mechanical and surface properties in vitro. Nanomater 2022;12: 2451.
8. Totu EE, Nechifor AC, Nechifor G, et al. Poly (methyl methacrylate) with TiO2 nanoparticles inclusion for stereolitographic complete denture manufacturing– the fututre in dental care for elderly edentulous patients?. J Dentist 2017;59: 68-77.
9. Park C, Kee W, Lim HP, et al. Combining 3D-printed metal and resin for digitally fabricated dentures: A dental technique. J Prosthetic Dentist 2020;123: 389-392.
10. Chen S, Yang J, Jia YG, et al. A study of 3D-printable reinforced composite resin: PMMA modified with silver nanoparticles loaded cellulose nanocrystal. Mater 2018;11: 2444.
11. Grachev DI, Chizhmakov EA, Stepanov DY, et al. Dental material selection for the additive manufacturing of Removable Complete Dentures (RCD). Int J Molec Sci 2023;24: 6432.
12. Abduo J, Lyons K, Bennamoun M. Trends in computer-aided manufacturing in prosthodontics: a review of the available streams. Int J Dentist 2014;2014: 1-4.
13. Tian Y, Chen C, Xu X, et al. A review of 3D printing in dentistry: Technologies, affecting factors, and applications. Scan 2021;2021: 1-19.
14. Scheithauer U, Schwarzer E, Richter HJ, et al. Thermoplastic 3D printing—an additive manufacturing method for producing dense ceramics. Int J App Ceramic Technol 2015;12: 26-31.
15. Dizon JR, Espera Jr AH, Chen Q, et al. Mechanical characterization of 3D-printed polymers. Add Manufac 2018;20: 44-67.
16. Rieuwpassa IE, Rizal AM, Muis A, et al. Three in one dental mirror: Inovation of oral diagnostic instrument. J Dentomaxillofac Sci 2019;4: 75-78.

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