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REVIEW ARTICLE

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Adenomatoid odontogenic tumor molecular pathogenesis: focusing on *KRAS* oncogenic mutations

Abstract:

Adenomatoid odontogenic tumor is a rare benign odontogenic tumor, accounting for less than 10% of odontogenic tumors. It primarily affects young females and typically grows slowly, often in association with an unerupted permanent maxillary canine. Histologically, it contains rosette- or duct-like structures. A monoclonal tumor origin has been suggested and more recently *KRAS* mutations, particularly at codon 12, have been reported in a high proportion of cases. The occurrence of such mutations in adenomatoid odontogenic tumors is the focus of the present narrative review. The MAPK/ERK pathway is activated in adenomatoid odontogenic tumor, even in *KRAS* wild-type cases, suggesting that other mechanisms may lead to the activation of this pathway. Considering that the tumor usually exhibits an indolent clinical course with almost no risk of recurrence after conservative surgical treatment, the value of targeted therapies is unclear. The rarity of adenomatoid odontogenic tumor limits large-scale studies, but future research may reveal additional mutations and their role on its pathogenesis.

Keywords: Adenomatoid tumor; *KRAS*; Genetics; MAPK/ERK; Molecular pathology.

INTRODUCTION

The adenomatoid odontogenic tumor is a benign tumor that accounts for less than 10% of odontogenic tumors[1]. In 2019, a systematic review of 436 publications identified 1,558 cases of adenomatoid odontogenic tumor in the literature[2]. This epithelial tumor has an indolent clinical course, showing a slow, self-limiting growth pattern, and it is often associated with an unerupted tooth, typically the permanent maxillary canine. Over 80% of cases are diagnosed in the second and third decades of life and show a higher prevalence in females[1,2].

Statement of Clinical Significance
KRAS mutations are highly prevalent in adenomatoid odontogenic tumors and these tumors also exhibit MAPK/ERK pathway activation. Such molecular characterization deepens our understanding of their pathogenesis. While the tumor is benign with an excellent prognosis following conservative surgery, its genetic profile may provide insights into RAS-driven mechanisms in benign tumors.

Adenomatoid odontogenic tumor can present as central or peripheral lesions[1]. It may occur as a single tumor or as multiple lesions in patients with Schimmelpenning syndrome (OMIM #163200), a condition marked by postzygotic *RAS* mutations[3,4].

Adenomatoid odontogenic tumor essential diagnostic criteria include the location in alveolar processes of the maxilla or mandible, the epithelial nodular structure, the presence of rosettes of spindled/columnar epithelial cells, as well as the duct-like structures, with minimal stroma[1]. Additionally, other features such as encapsulation and association with tooth follicle are desirable diagnostic features[1].

Recently, it has been shown that the presence of pathogenic mutations, once thought to be exclusive of malignant tumors, is a common feature of benign tumors as well[5]. In line with that, a high proportion of adenomatoid odontogenic tumors have been shown to harbor *KRAS* oncogenic mutations[6,7]. The occurrence of such mutations in adenomatoid odontogenic tumors will be the focus of the present narrative review.

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LITERATURE REVIEW

A limited number of studies have explored the genetic basis of the adenomatoid odontogenic tumor. *HUMARA* gene polymorphism assay results showed a monoclonal inactivation pattern in adenomatoid odontogenic tumors, suggesting a monoclonal origin for this tumor[8]. Such monoclonal pattern strengthens the notion that there is a founder mutation for adenomatoid odontogenic tumors.

In 2004, a somatic mutation at the *AMBN* gene has been detected in a single case of adenomatoid odontogenic tumor in which this gene was sequenced[9]. This gene codes for the nonamelogenin enamel matrix protein, ameloblastin, which participates in the differentiation of ameloblasts and epithelium-mesenchyme signaling during odontogenesis. β-catenin immunoexpression in one case of adenomatoid odontogenic tumor was not associated with mutations in *CTNNB1*[10]. *SMO* variants (p.Y394S and p.Y399S) have been reported in a case of adenomatoid odontogenic tumor[11]. The presence of two alterations in nearby regions of the same gene needs careful interpretation of the results, though.

Considering that the most important genetic alterations reported in adenomatoid odontogenic tumors so far are the highly prevalent *KRAS* genetic variants, this narrative review employed a search strategy using the terms "adenomatoid odontogenic tumor", "molecular", "genetics", "mutation", "variants", "KRAS", "MAPK", "MAPK/ERK pathway" and "oncogenic signaling" combined with appropriate Boolean operators "AND" and "OR". Additionally, key studies from the background literature and reference lists were also included. All studies using molecular techniques and/or immunohistochemistry to assess *KRAS* mutations or related signaling pathways in adenomatoid odontogenic tumor were considered.

In 2016, our group sequenced one adenomatoid odontogenic tumor sample from a patient with Schimmelpenning syndrome and two sporadic adenomatoid odontogenic tumors using a next-generation sequencing panel of 50 oncogenes and tumor suppressor genes commonly mutated in human cancers[6]. The *KRAS* p.G12V mutation was detected in all three samples, and further confirmed by qPCR allele-specific assay in these cases and in four out of six additional cases (n=7/9, 78%)[6]. Copy number alterations were also detected, more specifically losses at 6p15 and 7p15.3, the latter encompassing the *IGF2BP3* gene. These alterations were observed in 1 of 2 sporadic adenomatoid odontogenic tumor samples evaluated[6].

Subsequently, an investigation of *KRAS* codon 12 mutations was performed on a larger cohort of 38 adenomatoid odontogenic tumor cases. *KRAS* codon 12 mutations were detected in 27 cases (n=27/38, 71%), specifically *KRAS* p.G12V in 15 cases and p.G12R in 12 cases[7]. No statistically significant association was observed between the presence of *KRAS* mutations and clinicopathological parameters including tumor size, capsule thickness and age[7]. Strong pERK1/2 immunopositivity was observed in all the tested cases, suggesting MAPK/ERK pathway activation even in *KRAS* wild-type cases, raising the possibility of other mechanisms leading to MAPK activation in these tumors[7].

Bologna-Molina et al. studied nine cases of adenomatoid odontogenic tumor by immunohistochemistry for KRAS, BRAF, CRAF, BRAFV600E, EGFR, ERK1/2, MEK1/2. All cases showed positive immunostaining for EGFR, KRAS, BRAF and CRAF. Only one case showed negative ERK and MEK immunoexpression, and all were negative for BRAFV600E. One sample underwent next-generation sequencing with a panel for 50 oncogenes and tumor suppressor genes and eight others underwent PCR-rSSO for *RAS* mutations, including *KRAS* and *NRAS* codons 12, 13, 59, 61, 117 and 146[12]. They detected *KRAS* mutations at codon 12 in seven out of nine cases (p.G12D n=1, p.G12V n=2, and p.G12R n=4)[12]. More recently, another group has further reported *KRAS* p.G12V (n=4/11) and p.G12R (n=3/11) in adenomatoid odontogenic tumors[13].

The *RAS* oncogene family, composed of *KRAS*, *NRAS* and *HRAS*, plays a critical role in normal development and cancer progression[14]. Activating point mutations in *RAS* are common across many human cancers. *KRAS* is the most frequently mutated oncogene in human cancers, with mutations at codon 12 frequently observed in cancers such as pancreatic, colorectal, lung adenocarcinomas, and urogenital cancers[15]. Notably, there are biological differences between the distinct *KRAS* activating mutations, and the effect of such mutations seem to be context-dependent[16]. KRAS functions as a small GTPase, transmitting extracellular signals to intracellular signaling pathways[17]. Activation of RAS/GTP complexes can initiate several downstream signaling pathways, such as Raf-MEK-ERK and PI3K-AKT-mTOR[17]. This is depicted in Figure 1, which provides a

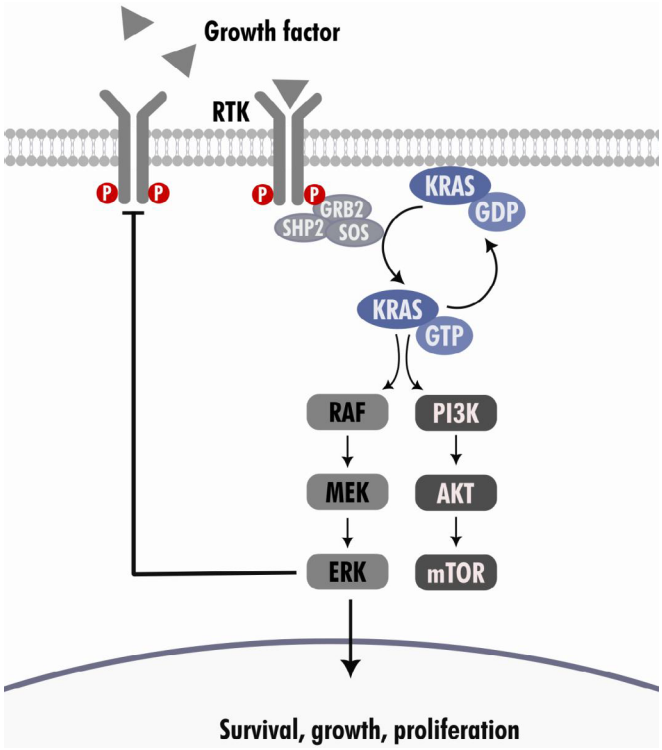

Figure 1. Schematic representation of RAS-mediated signaling pathways. Activation of receptor tyrosine kinases (RTKs) by growth factors triggers downstream signaling cascades. *KRAS,* in its active GTP-bound form, drives key pathways such as the RAF-MEK-ERK and PI3K-AKT-mTOR. These pathways regulate critical cellular processes, including survival, growth, and proliferation.

schematic representation of the MAPK/ERK and AKT/mTOR pathways and their key components.

The molecular features currently known for adenomatoid odontogenic tumors represent initial steps toward the understanding of the pathogenesis of these tumors and may aid in the differential diagnosis of challenging cases[1,7]. Given the tumor's indolent behavior, conservative surgical treatment is typically effective, with minimal risk of recurrence[1]. A systematic review of 1,558 cases showed only one case with strong evidence of recurrence[2]. Thus, targeted therapy is unlikely to be beneficial for most, if not all, cases of adenomatoid odontogenic tumors.

The limited number of studies on the genetic background of adenomatoid odontogenic tumor does not yet provide enough evidence to draw conclusions about the relationship between genomic alterations and clinical behavior. The rarity of adenomatoid odontogenic tumors is a significant limitation. Therefore, the existence of other mutational signatures, either co-occurring with *KRAS* mutations or occurring in wild-type *KRAS* cases, cannot be ruled out.

Whole-exome sequencing of *KRAS* wild-type cases may potentially elucidate whether there are other mutational signatures. The prognostic significance of codon 12 mutations is context-dependent, and it remains unclear why different codon 12 alleles occur in different diseases. The study of benign lesions should be encouraged, as these investigations can bring valuable insights into their biological behavior and molecular pathway. The results can enhance the understanding of the tumorigenic process and also contribute to improved diagnostic accuracy[5].

CONCLUSION

Recent studies have revealed adenomatoid odontogenic tumors genetic alterations, specifically *KRAS* p.G12V and p.G12R mutations, providing valuable insights into the molecular pathogenesis of this tumor. These findings highlight the role of the MAPK/ERK pathway in the pathogenesis of adenomatoid odontogenic tumor and call for further research to assess the functional impact of these mutations on adenomatoid odontogenic tumor cellular behavior and tumor development. Such studies may enhance our understanding of the biological mechanisms underlying the pathogenesis of odontogenic tumors.

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AUTHORS' CONTRIBUTIONS

IPG: investigation, methodology, writing – original draft, writing – review & editing. CCG: investigation, project administration, supervision, writing – review & editing.

CONFLICT OF INTEREST STATEMENT

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