Craniopharyngiomas and odontogenic tumors mimic normal odontogenesis and share genetic mutations, histopathologic features, and molecular pathways activation

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Odontogenic tumors bear some histopathologic and molecular resemblance to craniopharyngiomas. Specifically, adamantinomatous craniopharyngioma shares morphologic features and CTNNB1 (the gene encoding β-catenin) mutations with calcifying odontogenic cyst, whereas papillary craniopharyngioma and ameloblastoma are driven by BRAF mutations. Recently, important similarities between adamantinomatous craniopharyngioma and the cell signaling pathways involved in tooth formation have been described. Here, we expand the interpretation of these data in the context of odontogenic tumors. We discuss some morphologic and molecular features that are shared by tumors from these 2 distinct sites (i.e., craniopharyngiomas and odontogenic tumors). Current conservative surgical treatment is effective in most cases of benign odontogenic tumors, but in the future, the understanding of the molecular pathogenesis could impact the treatment of aggressive and/or malignant cases. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;127:231–236)

Craniopharyngiomas are benign but locally invasive tumors of the sellar region, occurring as 2 subtypes: adamantinomatous craniopharyngioma (ACP) and papillary craniopharyngioma (PCP). A recent study has demonstrated similar expression profiles of β-catenin-accumulating clusters in ACP and the enamel knots of tooth enamel organ. The mentioned work studied ACP molecular signature and RNA-Seq data from ACP mouse models and human tumors and described the presence of cell clusters molecularly analogous to the enamel knot, which is a critical control center of tooth morphogenesis. These findings show important similarities between ACP and the cell signaling pathways involved in tooth morphogenesis. The analogy between craniopharyngioma and odontogenesis can be extrapolated to the context of odontogenic tumors, which originate from aberrant odontogenesis.

In this mini-review, we explore the similarities between odontogenic tumors and craniopharyngiomas. Specifically, we focus on 2 odontogenic lesions: calcifying odontogenic cyst (COC) and ameloblastoma. COC is a benign developmental odontogenic cyst that displays locally destructive behavior, and ameloblastoma is a benign locally infiltrative tumor of the jaws. Craniopharyngiomas and these odontogenic tumors share a genetic background, with CTNNB1 (the gene encoding β-catenin) mutations occurring in COC and ACP, and BRAF mutations being the driver event in ameloblastoma and PCP.

CRANIOPHARYNGIOMA MIMICS TOOTH DEVELOPMENT

The molecular aspects of tooth development and ACP include reciprocal inductive epithelial–mesenchymal interactions regulated by several growth factors, such as fibroblast growth factors and bone morphogenetic proteins. Apps et al. showed that human β-catenin accumulating cell clusters of ACP express high levels of fibroblast growth factors, transforming growth factor-beta and bone morphogenetic protein, and these secreted factors signal to neighboring cells to express the phosphorylated proteins pERK1/2, pSMAD3, and pSMAD1/5/9. Interestingly, compared with fetal pituitary tumors, human ACP tumors showed higher expression of genes expressed in both ameloblasts and their precursors, but the genes specifically expressed in dental mesenchyme were not upregulated. Laser capture microdissection further identified molecular similarities between ACP β-catenin-accumulating cell clusters and odontogenic tumors. Therefore, it is plausible to hypothesize that similar mechanisms might be involved in the development of both ACP and odontogenic tumors.

Statement of Clinical Relevance

Similarities between odontogenic tumors and craniopharyngiomas go beyond histopathology, with both groups showing activation of the same cell signaling pathways. In the future, therapies targeting these activated pathways may result in better options for treating aggressive or malignant odontogenic tumors.

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Fig. 1. Histopathologic aspects of odontogenic lesions and craniopharyngioma subtypes. Calcifying odontogenic cyst (A, B) and adamantinomatous craniopharyngioma (C, D) epithelia consist of loosely cohesive cells showing a stellate reticulum-like appearance and a basal layer of palisading cuboidal cells, interposed by numerous ghost cells. Ameloblastoma (E, F) is composed of islands of epithelium with columnar peripheral cells and fusiform to polyhedral central cells loosely connected. Papillary craniopharyngioma (G, H) displays solid sheets of well-differentiated, nonkeratinizing squamous epithelium in a slightly papillary architecture. (Hematoxylin and eosin (H&E) stain; original magnifications × 20 (A, C, E, and G) and × 200 (B, D, F, and H).
and the enamel knot of tooth enamel organ. As indicated by these results, β-catenin-accumulating clusters in ACP and the enamel knots act as signaling hubs through the secretion of growth factors on the surrounding cells in both tissues. Collectively, the results of this study suggest that ACP tumorigenesis can be interpreted as aberrant mimics of natural tooth development.

Similarities between craniopharyngioma and odontogenic tumors go beyond histopathology

The histopathologic resemblance of ACP and COC was described more than 3 decades ago, and both tumors show the presence of peripheral columnar epithelium accompanied by an inner zone of loose stellate cells resembling enamel organ during tooth formation, ghost cells, and sometimes dentinoid (Figure 1).1 PCP presents in solid sheets of squamous epithelium with (pseudo)papillary areas.2 Ameloblastoma is composed of islands of epithelium with columnar to cuboidal peripheral cells with hyperchromatic nuclei arranged in a palisading pattern and fusiform to polygonal central cells loosely connected.3 In contrast to COC and ACP, ameloblastoma and PCP do not show ghost cell formation.1,4 Also, PCP does not express odontogenic markers, such as enamelin and amelogenin.1,4 Figure 1 presents representative images of the histopathologic features of these 4 tumors.

Genomic characterization of PCP and ACP has revealed that each subtype harbors recurrent activating mutations, and similarly, COC and ameloblastoma share the same pattern of recurrent mutations with these brain tumors.3,5 Specifically, CTNNB1 and BRAFV600E mutations drive COC and ameloblastoma, respectively.3,11 Although ameloblastoma does not show great histologic resemblance to PCP, it also presents BRAFV600E mutation and MAPK/ERK pathway activation.5,6 BRAFV600E mutation occurs at high frequency in both tumors, with PCP showing this mutation in up to 95% of cases investigated2 and in 46% to 82% of ameloblastoma cases.5,12,14,15 Over 90% of ACP and COC show mutations in CTNNB1.3,11,16

ACP and COC share CTNNB1 mutations at the same mutational hotspots (Figure 2),3,4,11,13,17-19 together with strong nuclear and cytoplasmic β-catenin expression,20 and this confirms a genotype-phenotype correlation in these 2 different tumor contexts. Because β-catenin enhances odontoblastic differentiation,21 the occasional presence of dentinoid deposits in both lesions is not surprising. Besides CTNNB1 mutations, in a similar fashion to ACP, COC shows immunoeexpression of pERK1/2 consistent with MAPK/ERK pathway activation.22 This is not surprising because there is crosstalk between WNT/β-catenin and MAPK/ERK cell signaling pathways in normal development and in cancer (Figure 3).23 The main secreted molecules and activated transmembrane receptors that trigger the downstream signaling cascade of both pathways are illustrated in Figure 3.

Fig. 2. β-Catenin (CTNNB1) mutations are the main genetic drivers of adamantinomatous craniopharyngioma (ACP) and calcifying odontogenic cyst (COC). A, β-Catenin protein (UniProtKB, P35222, CTNNB1_Human), showing localization of shared mutations between ACP and COC; Ser33, Ser37, and Thr41 residues are phosphorylation sites. B, Venn diagram representing exclusive and shared CTNNB1 mutation codons in ACP and COC.
Although BRAFV600E mutation has been reported in a few cases of ACP,\textsuperscript{18,24} CTNNB1 mutations have never been reported in PCP. Considering that CTNNB1 and BRAF mutations are almost mutually exclusive in ACP and PCP, the detection of these mutations has implications for the diagnosis and clinical management of some patients. This is especially relevant because precision medicine is gaining importance in cancer research and treatment. Although the high frequency of
these mutations could generate some enthusiasm, it is important to highlight that in a total of 1123 cases of craniopharyngioma evaluated in 27 studies, no currently identified marker was a reliable predictor of lesion behavior or possible recurrence.16

In line with the current view about WNT/B-catenin and RAS-ERK pathways interaction and cooperation in tumorigenesis (see Figure 3), MAPK/ERK pathway activation around β-catenin accumulating cell clusters has been demonstrated in ACP.2 The inhibition of MAPK/ERK pathway with trametinib, a clinically approved MEK inhibitor, was tested in explant cultures of human and mouse ACP, and the cells treated with the drug showed reduced proliferation and increased apoptosis.2 Several MEK inhibitors have been used in the clinical context, and others are in different stages of clinical development.26 Single-agent therapy using trametinib,26 cobimetinib,27 or a combination of MEK and RAF inhibitors, as dabrafenib and vemurafenib, are currently ongoing in various cancers, such as melanoma and non–small cell lung carcinoma.26,27 Clinically, recurrent and residual ACPs have shown significant reduction with use of a dual BRAF and MEK inhibitor.28,29 Unsuccessful MEK inhibition has been attributed to MAPK activation via several feedback mechanisms.27

Taking into consideration the fact that ACP mimics odontogenesis and shares morphologic and molecular features with COC, including pERK1/2 immunorepression,2,22 MEK inhibitors could also be useful in the management of patients with rare aggressive COC or malignant variants. COC and ameloblastomas show different biologic behaviors. COC is a locally destructive cyst, but because it is not usually infiltrative, it can be treated with enucleation and has a low recurrence rate. Conversely, ameloblastoma is an aggressive benign neoplasm, characterized by high local infiltrative potential, with frequent recurrences, and therefore, it usually needs wide surgical resection. Similar to craniopharyngiomas, for which there are no biologic markers to predict behavior and recurrence,16 the association between BRAFV600E mutation and the aggressive behavior of ameloblastoma needs further validation because this association has only been reported by 1 group using immunohistochemistry.30 BRAFV600E mutation leads to MAPK/ERK activation, and there are reports of successful use of BRAF-inhibitors in aggressive and malignant BRAFV600E ameloblastoma cases.31-33 Given the side effects associated with the use of BRAF-inhibitors and also the possibility of tumor resistance to therapy, along with the fact that surgical treatment is highly effective in most cases of ameloblastomas, targeted therapy should be reserved for highly aggressive and destructive cases.

CONCLUSIONS

The modulation of MAPK/ERK and WNT/β-catenin pathways is a new area in research on craniopharyngiomas, but the results could also impact the development of new strategies for patients with aggressive odontogenic tumors. This is particularly relevant for specific groups of patients with aggressive lesions, where surgery is associated with important morbidities. However, more experimental data need to be acquired before performing any tests in humans because targeted therapy with drugs is associated with several adverse effects and conventional conservative surgical treatment is effective in most cases of odontogenic tumors. The crosstalk between the MAPK/ERK and WNT/B-catenin pathways in the odontogenic tumor pathogenesis is an interesting area that needs to be further explored.

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