ISSN No: 2455-7803

REVIEW ARTICLE

REVISITING THE PATHOGENESIS OF ODONTOGENIC TUMORS: A MINI REVIEW

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ABSTRACT:

Odontogenic tumors contain a heterogeneous collection of lesions that are categorized from hamartomas to benign and malignant neoplasms of inconstant aggressiveness. Odontogenic tumors are usually extraordinary with assessed frequency of short of 0.5 cases/100,000 population for every year. The lesions such as odontogenic tumors are inferred from the components of the tooth-structuring contraption. They are discovered solely inside the maxillary and mandibular bones. This audit speaks to experiences and cooperation of the molecular and genetic variations connected to the development and movement of odontogenic tumors which incorporate oncogenes, tumor-silencer genes, APC gene, retinoblastoma genes, DNA repair genes, onco-viruses, development components, telomerase, cell cycle controllers, apoptosis-related elements, and regulators/controllers of tooth development. Hence; in this review, we tend to summarize the pathogenesis of some of the odontogenic tumors.

Key words: Odontogenic, Pathogenesis, Tumors.

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This article may be cited as: Choudhary A, Bhushan A, Narain P, Rana S, Verma A, Butolia H. Revisiting The Pathogenesis Of Odontogenic Tumors: A Mini Review. Int J Res Health Allied Sci 2017;3(2):29-31.

INTRODUCTION

In humans, the evidence of tooth development is initially observed at the sixth week of intrauterine life. At the same time basal cell layer of stomatodeum epithelium begins to proliferate and give rise to dental lamina which later on could have given rise to deciduous and permanent teeth. Odontogenic tumours (OTs) are derived from epithelial or mesenchymal elements, or both, that are part of the tooth forming apparatus. They are therefore exclusively found in the mandible and maxilla and must be considered in differential diagnosis of tumours involving these sites. Thus odontogenic tumours may be epithelial, mesenchymal, or mixed and they may be non–calcifying or may contain hard structures that mimic enamel, dentin, cementum, or bone.[1]

Molecular and genetic alterations are also associated with the development and progression of odontogenic tumours, including oncogenes, tumour-suppressor genes, oncoviruses, growth factors, telomerase, cell cycle regulators, apoptosis-related factors, regulators of tooth development, hard tissue-related proteins, cell adhesion molecules, matrix-degrading proteinases, angiogenic factors, and osteolytic cytokines.[2]

AMELOBLASTOMA

Ameloblastomas are benign odontogenic tumours, of epithelial origin. Their histological appearance resembles that of developing tooth. The tumour islands are lined by cuboidal or columnar epithelium, resembling pre ameloblast and centrally loosely connected cells, which resembles stellate reticulum cells. Currently the theory of defective cell interaction is believed to play a role in the pathogenesis of ameloblastomas.[3] With the above evidences it can be hypothesized that ameloblastomas represent derangement in the reciprocal exchange of instructive signalling, which normally operates in developing tooth organ. Epidermal growth factor is one such signalling molecule contributing to odontogenic tumorigenesis.[4]

Various signaling pathways have been identified to explain the pathogenesis of ameloblastoma. Sonic Hedgehog (SHH), a mammalian homolog of drosophila segment polarity gene Hedgehog, encodes a secreted protein that activates a membrane receptor complex formed by patched 1 (PCTH 1) and smoothened (SMO). In the absence of SHH, PCTH inhibits SMO. When PCTH-SHH binding occurs, SMO is released, glioma-associated (GLi 1) family transcription factor gene is activated and SHH signaling is mediated from cytoplasm to nucleas. High expression of SHH, SMO and GLi 1 was reported in ameloblastoma. The benign and metastasizing types of ameloblastoma showed stronger PCTH 1 expression in neoplastic cells than stromal cells. Studies suggested that SHH signaling molecules may play a role in epithelial-mesenchymal interaction and cell proliferation in ameloblastoma.[5, 6]

WNT genes encode a family of 38–43 kDa glycoproteins, first identified in mammals as proto-oncogenic integration site for mouse mammary tumor virus. These proteins activate a number of signaling pathways that are divided into two categories: Canonical β-catenin pathway and noncanonical β-catenin independent pathway. WNT 5a signaling was found to have a crucial role in modulating tumorigenesis and behaviors of enamel epithelial cells in ameloblastoma. Overexpression of WNT 5a increases enamel epithelial cell migration while suppression impairs their migration and fails to form actin re-organization. Canonical WNT pathway is associated with the accumulation and translocation of adherens junction-associated protein β catenin into

nucleus. Therefore, the main action is stabilization of β catenin and its translocation into nucleus, where it exerts its effect on gene transcription. This mechanism was demonstrated in ameloblastomas.[5, 7]

Bone morphogenetic protein (BMP) is a mesenchymal cell differentiation factor and a morphogen. It plays a crucial role in cell proliferation, differentiation, chemotaxis, extracellular matrix (ECM) production and apoptosis during the development process. Kumamoto examined tooth germs, ameloblastomas, malignant ameloblastomas and adenomatoid odontogenic tumors by reverse transcription polymerase chain reaction and immunohistochemistry for BMP-2, -4, -7, BMP receptors I and II (BMPR I and II), core-binding factor alpha 1 (CBFA 1) and osterix. They found that mRNA expression of BMPs, BMPRs, CBFA 1 and osterix was detected in all odontogenic tissues. BMPs and BMPRs was evidently expressed in odontogenic epithelial cells in tooth germs and epithelial odontogenic tumors. Acanthomatous ameloblastomas showed an increased BMP-7 reactivity in keratinizing cells. Ameloblastic carcinomas showed low reactivity for BMPs, BMPRs and CBFA1.[5, 8]

Number of cytokines such as interleukin 1α, interleukin 1 β, interleukin 6 and TNF α possess osteolystic activity and they are been implicated in the growth and expansion of the ameloblastoma. Ooya detected the expression of parathyroid hormone-related protein (PTHrP), osteoclast differentiation factor (ODF)/receptor activator of nuclear factor-kappaB ligand (RANKL) and osteoclastogenesis inhibitory factor (OCIF)/osteoprotegerin (OPG) mRNA in all tooth germs and ameloblastoma samples. In ameloblastomas, PTHrP, reactivity in peripheral columnar cells was stronger than central polyhedral cells, and keratinizing cells showed increased PTHrP reactivity. ODF/RANKL and OCIF/OPG were expressed predominantly in mesenchymal cells rather than in odontogenic cells in both tooth germs and ameloblastomas. Epithelial ODF/RANKL and OCIF/OPG expression was slightly lower in ameloblastomas than in tooth germs. Tumor cells in plexiform ameloblastomas showed higher reactivity for PTHrH and ODF/RANK L than tumor cells in follicular ameloblastomas.[5]

CALCIFYING EPITHELIAL ODONTOGENIC TUMOUR (CEOT)

The role of the Sonic hedgehog pathway in the pathogenesis of CEOT has been investigated. Immunoreactivity for Sonic hedgehog pathway proteins was evaluated using antibodies to the receptor PTCH as well as to the transcription factors Gli1 and Gli2. PTCH gene sequencing was completed using PCR. The study implicated that the Sonic hedgehog pathway in the pathogenesis of the CEOT through sequencing. Similar to other odontogenic neoplasms, gene mutations in PTCH1 are present in the CEOT.[9]

ODONTOMAS

The odontogenic tissues are laid down and proliferate. In the beginning, there is a resorption of the bone showing a radiolucent image on the radiograph followed by an intermediate stage in which there is partial calcification of the odontogenic tissues characterized by a radiolucent–radio opaque image. Then calcification of the dental tissues is completed which is the most radio opaque stage.[10]

CALCIFYING ODONTOGENIC CYSTS (COC)

Although the true nature of the lesion, whether cyst or tumour remains controversial, even though majority of them seem to be non neoplastic. WHO describes calcifying odontogenic cyst as a neoplasm rather than cyst, but then states that most of the lesions appear to be non neoplastic. This explains the mystery surrounding this lesion.[11] Because of the wide histologic variations of calcifying odontogenic cyst (especially some are cystic, while others are solid or neoplastic), there has been confusion and disagreement in the terminology and classification of this lesion. Some authors have regarded COC as a neoplasm with marked tendency towards cyst formation. Based on this monistic concept, the terms 'calcifying ghost cell tumour' and 'cystic calcifying odontogenic tumour' were proposed to substitute for the term calcifying odontogenic cyst. Other authors classify COC into two entities, a cyst and a neoplasm. Based on this dualistic concept, Praetorius et al proposed the term 'dentinogenic ghost cell tumour' for the neoplastic counterpart of COC. Other proposed terms for the same lesion are 'epithelial odontogenic ghost cell tumour' and 'odontogenic ghost cell tumour'.[12]

There has been general agreement on the odontogenic origin of COC, since Gorlin et al suggested it. They pointed out the histologic similarities of basal cells to ameloblast- like cells and upper layers resemble stellate reticulum. These facts in addition to production of dentinoid and the exclusive occurrence in the locations with close relationship to dental structures, favour odontogenic origin.[88] Further COC is frequently found in association with, or shows areas histologically similar to, some odontogenic tumours like odontomas, ameloblastic fibromas, and fibro odontomas, ameloblastomas and AOT.[12] In pathogenesis of peripheral COC, lesions located entirely within connective tissue of gingiva and separated by band of connective tissue probably arise from surface epithelium.[13]

MALIGNANT AMELOBLASTOMA

In malignant ameloblastomas, about 80% of tumours are pure plexiform type or mixed type. There are several factors that appear to be contributory to the development of metastatic disease including extensive local disease, duration of the primary tumour, frequent surgical problems, radiotherapy and chemotherapies, and mandibular focus of the disease. In case of metastases from ameloblastoma, following three routes are suggested which include haematogenous and/ or lymphatic route, and by aspiration.[14]

Cases of malignant ameloblastomas with pulmonary metastases are generally considered to be of haematogenous spread. The fact that lung metastases are most often found bilaterally and with multiple nodules

lends support to the idea of haematogenous spread. This is also supported by the fact that diffusely scattered tumour foci are often found bilaterally, and clusters of tumour cells are commonly observed in the surrounding blood vessels.[15] On the other hand, based on the fact that tumour casts are often found in the bronchi and bronchioles, some authors support the theory that metastatic spread occurs through aspiration of tumour contents.[16] A rare complication of malignant ameloblastoma is association with hypercalcaemia. It has been postulated that the release of parathyroid hormone like substance is responsible for hypercalcaemia. The presence of eosinophilic crystal like substances, electron dense bodies, and elevated levels of prostaglandin E_2 in ameloblastomas metastatic in lung has led some authors to speculate that prostaglandin E_2 is a PTH like substance which results in pseudo hyperparathyroidism.[17- 22]

AMELOBLASTIC FIBROSARCOMA (AFS)

Histogenesis of ameloblastic fibrosarcoma is by primitive mesenchymal cells. It is speculated that the odontogenic epithelial component in these tumours induces the proliferation of mesenchymal cells. These cells subsequently are transformed into neoplastic cells without formation of dental papilla or odontoblasts.[22] Further it has been noted that greatest density of sarcomatous cells occurs in the zones surrounding the benign ameloblastomatous islands. Closely packed mitotically active polygonal cells are also seen. These cells show scanty cytoplasm with hyperchromatic nuclei, exhibiting moderate variation in nuclear size and shape. Bone like collagenous matrix has been observed in the lesional connective tissue which is remote from any epithelium.[23]

CONCLUSION

Odontogenic tumors have been largely the domain of oral and maxillofacial surgeons and pathologists, the former relying upon the latter for guidance on treatment. Research on odontogenic tumors is limited to what can be performed on relatively small numbers of fixed and processed excision specimens. The knowledge about the origin of particular tumour, and the cells or tissues involved in it, will not only refine the treatment, but may also help to prevent development of such lesions.

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Source of support: Nil **Conflict of interest:** None declared