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Review

Molecular concepts in the pathogenesis of ameloblastoma: Implications for therapeutics

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ABSTRACT

Ameloblastoma is a benign odontogenic neoplasm that may exhibit aggressive biological behavior as evidenced by its rapid growth and significance recurrence rates following initial surgical resection. Currently, the only therapy for ameloblastoma is surgical, and adjunctive treatment modalities are needed to mitigate tumor growth and to reduce the need for extensive and disfiguring surgeries. Many studies have identified markers expressed by ameloblastoma and these lend insight to our understanding of tumor progression. This review provides a summary of the specific molecular pathways implicated in tumor pathogenesis, including those involved in bone remodeling, apoptosis, cell signaling, and tumor suppression. Based on these data, we identify several prognostic or therapeutic markers that have been used successfully in the treatment of other neoplastic processes that may also have diagnostic and prognostic utility for ameloblastoma. Thus, it is important to determine which markers hold the greatest promise for clinical management of this benign neoplasm in order to improve treatment options, particularly in patients with aggressive forms of ameloblastoma.

Contents

Abbreviations: EGFR, epidermal growth factor receptor; EMT, epithelial–mesenchymal transition; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; FasL, Fas ligand; ICE, interleukin-1β converting enzyme; NF-κB, nuclear factor κB; OPG, osteoprotegerin; PI3K, phosphatidylinositol 3-kinase; PTEN, phosphatase and tensin homolog deleted on chromosome 10; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB Ligand; Ras/MAPK, Ras/mitogen activated protein kinase; sFas, soluble Fas; ssDNA, single stranded DNA; TCC, transitional cell carcinoma; TNF, tumor necrosis factor.

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1. Introduction

In the past decade, several studies have sought to identify factors responsible for ameloblastoma development and growth. Though there have been several proteins implicated in the tumoral progression of ameloblastoma, there are no data identifying the underlying cause of

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this lesion. This review focuses on markers that might be useful prognostically or as targets in the treatment of ameloblastoma. While the vast majority of studies demonstrate preliminary data related to the tumorigenesis of ameloblastoma, these initial studies provide a framework for understanding tumor etiology. Although ameloblastoma is a benign tumor, it may be very aggressive in its clinical presentation. Current treatment of ameloblastoma involves extensive surgical excision because the tumor has a high recurrence rate. For large lesions that destroy crucial anatomic structures in the jaw, the surgical procedures often lead to high morbidity and difficult rehabilitation. Targeted adjunctive therapeutics might be useful to limit the surrounding bone destruction and tumor progression leading to better surgical or treatment outcomes. The purpose of the review is to summarize the results from studies that identify molecules implicated in tumor growth and progression, and discuss the possible therapeutic value of such in the treatment of ameloblastoma.

1.1. Features of Ameloblastoma

Ameloblastoma is a locally aggressive, epithelial odontogenic benign neoplasm that has close histologic resemblance to the enamel organ seen in developing teeth. It is usually present within the bone, however, it can also be found in the soft tissues (peripheral ameloblastoma). It is classified into solid and cystic or multicystic variants. In the solid variant, there are a variety of histopathologic patterns seen such as follicular, plexiform, desmoplastic, basal cell, acanthomatous, and granular cell (Neville, 2009). Ameloblastoma comprises of 1% of all oral tumors and about 11–18% of odontogenic tumors (Sciubba et al., 2000).

Clinically, it often presents as a painless, slow growing mass, and if untreated it can become large, loosen or displace teeth, and expand the cortices. Due to its destructive nature, some authors advocate designation of ameloblastoma as a low-grade malignancy (Gold, 1991), although this lesion is considered benign according to the World Health Organization classification of odontogenic neoplasms (Neville, 2009). In the solid variant, the follicular histopathologic pattern is the most common and recognizable, where islands of epithelium resemble enamel organ epithelium in a mature fibrous connective tissue stroma. A single layer of tall columnar ameloblast-like cells outlines the epithelial nests and shows reversed polarity. The epithelial nests consist of central loosely arranged angular cells resembling the stellate reticulum of an enamel organ. In other areas, the peripheral cells may be more cuboidal and resemble basal cells (Fig. 1). There are several other histologic variants of solid ameloblastoma. The plexiform variant consists of anastomosing cords of epithelial cells which surround loosely arranged stellate reticulum-like cells. The granular cell variant exhibits granular cells (cells containing eosinophilic granules) in the central portion of the epithelial nests, whereas the acanthomatous variant shows squamous differentiation of the central epithelial cells. The desmoplastic variant contains epithelial islands with surrounding dense fibrous stroma. Finally, the basal cell variant consists of nests of basoloid cells with peripheral palisading with no central stellate reticulum-like cells.

For solid or multicystic ameloblastomas, recurrence rates of 50 to 90% have been reported after curettage (Neville, 2009; Sciubba et al., 2000). Recurrence often takes many years, and 5-year disease-free periods do not indicate a cure. Marginal resection is the most widely used treatment, but recurrence rates of up to 15% have been reported after marginal or block resection (Neville, 2009). In the case of unicystic ameloblastoma, 30% of these lesions recur after enucleation (Neville, 2009). Thus, ameloblastomas may behave aggressively and there is evidence to suggest that different types of ameloblastoma carry varied prognoses and may warrant special therapeutic considerations.

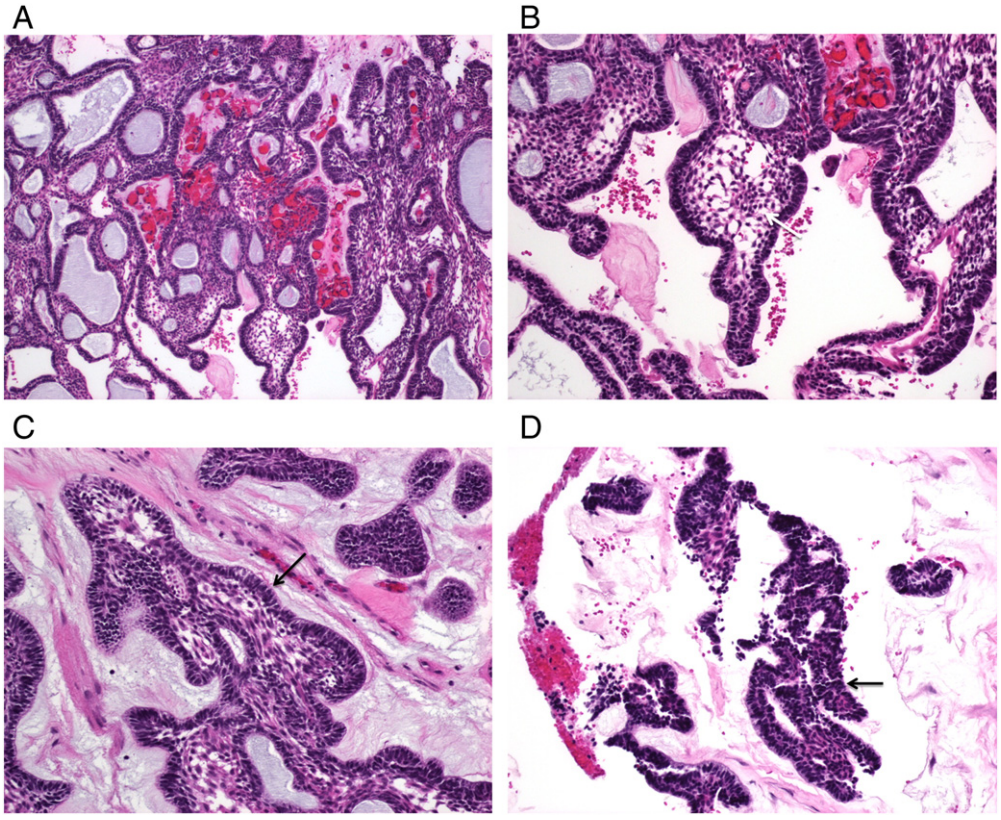

Fig. 1. Histological characteristics of ameloblastoma. The follicular variant of ameloblastoma is characterized by islands of epithelium in a mature fibrous connective tissue stroma. A. Tall columnar ameloblast-like cells surround the epithelial nests. Original magnification 100×. B. The epithelial nests consist of central loosely arranged angular cells resembling the stellate reticulum of an enamel organ (white arrow). C. Epithelial cells exhibit reversed polarity (black arrow). Original magnification 200×. D. In other areas, the peripheral cells may be more cuboidal and resemble basal cells (black arrow). Original magnification 200×.