Understanding Ameloblastomas Through Tooth Development

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Abstract
Ameloblastomas are a class of odontogenic tumors, which arise from developmental remnants in the oral tissue. Although the cellular and molecular mechanisms resulting in development of ameloblastoma are poorly understood, it is generally accepted that they exhibit an odontogenic source and originate from epithelial cells associated with tooth development. The epithelial sources in the oral tissue that can cause ameloblastomas include enamel organ, reduced enamel epithelium, rests of Malassez, and rests of Serres. These remnants originate from the stomodeal ectoderm, which give rise to the oral epithelium that initiate and guide tooth development as the embryo develops. It is of great clinical value to understand the developmental origin of these epithelial components and their histology, since the ameloblastomas display histopathological similarities to their structures.

Keywords: Ameloblastoma; Dental epithelium; Genetic regulation; Odontogenic tumors; Tooth development

Introduction
Ameloblastomas are locally invasive and slowly growing odontogenic tumors that constitute about 1% of head and neck neoplasms. They area class of highly aggressive benign tumors that has the potential to become malignant[1], and exhibit a high recurrence rate after surgical procedures[2]. Radiographically, ameloblastoma appears as radiolucency with diluted and perforated cortices. Furthermore, a tooth root resorption is a frequent radiographic observation. These characteristics are also present in renal cell carcinoma metastasis, aneurysmal bone cysts, and giant cell tumors; thus, histopathology is required for a final diagnosis.

The benign ameloblastomas can be classified into four histopathologic types, i.e. solid/multicystic, extra-ossseous/peripheral, desmoplastic, and unicystic type. The solid/multicystic types are the most common and can be subdivided into further classification according to their detailed microscopic patterns as acanthomatous, granular cell, basal cell, and desmoplastic type[3,4]. Although the biological subtypes share many common histological patterns, they are usually classified into two main types, the follicular type and the plexiform type. Both patterns may be present in the same tumor. In the follicular type of the ameloblastoma, discrete epithelial islands surrounded by a layer of cuboidal or columnar cells, can be observed. The cysts usually form within these islands. Microscopically, all ameloblastomas exhibit a fibrous stroma. In the plexiform type, the cysts formation occurs due to degeneration of this stroma rather than the cystic change within the epithelium. Here, the tumor epithelium is organized as a network rather than islands. Another typical histological characteristic is the budding of tumor cells from neoplastic foci in a pattern similar to that present in developing tooth germ.

Numerous molecular processes are believed to be involved in ameloblastoma, including those implicated in apoptosis, bone remodeling, and odontogenesis. Several investigations have also established potential prognostic markers and therapeutic targets for ameloblastoma. Although the cellular and molecular mechanisms resulting in development of ameloblastoma are uncertain, it is generally accepted that...
they exhibit an odontogenic source and originate from epithelial cells associated with tooth development[9].

The mammalian tooth develops from cells originating from stomodeal ectoderm, which forms the epithelium, and interacts with the underlying neural-crest derived ectomesenchyme[8]. Interactions between the epithelial and mesenchymal tissues constitute an essential regulatory mechanism of tooth development, in which many regulatory factors play a major role[7]. Tooth development has classically been divided into three morphologically distinct stages, the bud-, cap-, and bell stage[8]. The initiation of tooth development starts with thickening of the oral epithelium, which subsequently extends into the underlying ectomesenchyme as a dental lamina[6]. The cells of the proliferating dental lamina form a bud-like structure, and this budding of the oral epithelium causes the condensation of adjacent ectomesenchyme. The epithelium is believed to have the information required for initiation of tooth development, although the dental mesenchyme supplies many of the necessary signals[8]. Unequal growth in the different parts of the bud leads to the formation of the cap stage, characterized by a shallow invagination on the deep surface of the epithelial bud (the enamel organ)[9]. At the center of the enamel organ a group of cells form an important signaling center close to inner dental epithelium. This center is known as the enamel knot, which expresses key signaling genes.

The condensed mesenchyme is referred to as dental papilla. Subsequent folding and further growth of the epithelial cap eventually gives rise to the bell stage[10]. At this stage, the enamel organ consists of four layers of cells: outer enamel epithelium, stellate reticulum, stratum intermediate, and inner enamel epithelium. A higher amount of cells resembling stellate reticulum are usually present in the follicular type compared to the plexiform type. The inner enamel epithelium subsequently forms the enamel producing ameloblasts[11]. Further more, the dental lamina separates from the developing tooth and fragments into discrete clusters of epithelial cells that usually degenerate. However, some epithelial cells may persist and are named epithelial pearls or rests of Serres.

The inner and outer enamel epithelium fuse below the level of the crown cervical margin and is known to play an essential role in the development of the root. It is called the Hertwig’s epithelial root (HER) sheath, and as it elongates in apical direction, it induces adjacent mesenchymal cells to produce dentin and cementum. Remnants of this epithelium are a part of the normal structures within the periodontal ligament and are named epithelial rests of Malassez (ERM)[12]. Recent studies suggest that these rests may not merely be a bi-product of tooth development, but propose a role in maintaining and contributing to the normal periodontal cellular elements and function in periodontal regeneration[13].

Ameloblastomas origin from epithelium of the developing tooth, including cells of the enamel organ and dental lamina[14]. The palisading, with polarization of the nuclei in basal cells, is considered as a common characteristic of ameloblastoma and was the main histologic factor that led to identification of ameloblastoma as a neoplasm resembling the dental organ, the fetal tooth-forming structure. The differentiation level of ameloblastoma cells correspond to the differentiation level of the cells at the cap/bell stage of tooth development, and proliferation studies of ameloblastoma cells corroborate its slow growth rate[13]. Ameloblastomas are also characterized by other clinical characteristics including an infiltrative growth model, considerable tendency for recurrence, and preference for the mandibular molar area[14]. Gene expression studies have demonstrated both similarities and differences when comparing ameloblastoma with the developing human tooth.

The under-expression or over-expression of essential signaling molecules is believed to play an important role in the tumorigenesis of ameloblastomas. Using cDNA micro arrays gene expression profiling of ameloblastomas has demonstrated that more than 30 genes exhibit significant changes in levels of expression when compared to corresponding gene expression levels of developing deciduous tooth germs in the cap and bell stages[17]. Other investigation has shown that specific HER family molecules are expressed in ameloblastomas, and that they may provide predictive outcome information in patients with these benign tumors[13]. It has also been demonstrated that SOX2 is expressed in ameloblastomas, and in the dental epithelium of developing mouse and human tooth[19]. The expression of SOX2 was not detected in HER sheets and ERM cells, which are associated with root formation. Furthermore, numerous proteins that are known to be expressed in the enamel epithelium during the early stage of odontogenesis, including amelogenin, ameloblastin, and tuftelin, are distinctly expressed in ameloblastoma tumor cells. However, two other proteins, amelotin and enamelin, which are expressed in the mineralizing stage of enamel formation, are not expressed in tumor cells of ameloblastomas[20].

Future Perspectives and Conclusion

The genetic and molecular features of ameloblastomas are still poorly understood. As ameloblastomas are characterized by a slow-growth, their development may initiate in childhood. The similarities between these odontogenic tumors and the tissues found under tooth development in the childhood make it difficult to distinguish them histologically. Therefore, a better understanding of the histological structures during tooth development is warranted. The fact that the posterior end of the dental lamina proliferates continuously, and that aberrant tooth germs most often are found in this region has been proposed as the statement for why ameloblastomas occur most frequently at the angle of the mandible. This also may explain the high incidence of ameloblastomas associated with impacted lower third molar, as this region receives the significant irritation. Therefore, the stimuli and the specific kind of irritation, that cause developmental epithelium to develop into ameloblastoma, demands further investigation, as these may be the direct cause of the neoplasm. Further more, the gene expression profiling, in order to identify the candidate genes that may be involved in the origination of ameloblastoma, needs to be further studied. The expression of these genes, in relation to human tooth development, requires also further investigation.

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