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Review Article

New insights into the functions of enamel matrices in calcified tissues

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Summary Ameloblasts secrete enamel matrix proteins, including amelogenin, ameloblastin, enamelin, amelotin, and Apin/odontogenic ameloblast-associated protein (Apin/ODAM). Amelogenin is the major protein component of the enamel matrix. Amelogenin, ameloblastin, and enamelin are expressed during the secretory stage of ameloblast, while amelotin and Apin/ODAM are expressed during the maturation. Amelogenin and ameloblastin are also expressed in osteoblasts, and they regulate bone formation. In addition, recent studies show the importance of protein—protein interactions between enamel matrix components for enamel formation. In a mouse model mimicking a mutation of the amelogenin gene in amelogenesis imperfect (AI) in humans, the mutated amelogenin forms a complex with ameloblastin, which accumulates in the endoplasmic reticulum/Golgi apparatus and causes ameloblast dysfunction resulting in AI phenotypes. Ameloblastin is a cell adhesion molecule that regulates cell proliferation. It inhibits odontogenic tumor formation and regulates osteoblast differentiation through binding to CD63. Amelotin interacts with Apin/ODAM, but not ameloblastin, while Apin/ODAM binds to ameloblastin. These interactions may be important for enamel mineralization during amelogenesis. The enamel matrix genes are clustered on human chromosome 4 except for the amelogenin genes located on the sex chromosomes. Genes for these enamel matrix proteins evolved from a common ancestral gene encoding secretory calcium-binding phosphoprotein.

Contents

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1. Introduction

Dental enamel, known as the hardest tissue in vertebrates, is formed by ameloblasts derived from the oral epithelium. In the initial stage of the enamel organ's development, the oral epithelium invades the dental mesenchyme, followed by differentiation into four types of epithelial cells, including the inner enamel epithelium, the stratum intermedium, the stellate reticulum, and the outer enamel epithelium. Among these cell types, the inner enamel epithelium differentiates into enamel matrix-secreting ameloblasts. The formation of dental enamel is a prototype of functional organ development through a matrix mineralization process (Fig. 1). Unlike dentin and bone matrices, in which collagen I is the major matrix protein, enamel matrices consist of a distinct set of matrix molecules with amelogenin being the major component. The different matrix components in enamel contribute to its larger and more rigid hydroxyapatite crystal structures than dentin and bone. Enamel matrix proteins are produced at their highest levels by ameloblasts during the secretory and transition stages of amelogenesis and collectively orchestrate the proper assembly and growth of crystals within mineralized enamel. These proteins are nearly completely degraded by specific proteases such as MMP-20, mainly produced during the secretory/transition stage, and KLK4, mainly produced during the transition/maturation stage, resulting in a highly ordered and purposefully designed meshwork of carbonated hydroxyapatite crystals with astonishing mechanical properties [1].

Cell adhesion to the extracellular matrix is of fundamental importance for a wide range of cellular functions, including cell differentiation, proliferation, and survival [2]. Inner and outer enamel epithelial cells interact with the basement membrane, of which major constituents are type IV collagen, laminin, and heparan-sulfate proteoglycan perlecan. For example, laminin α5 (Lama5)-deficient mice show small tooth germs without a cusp [3]. In addition, proliferation and polarization of the dental epithelium are inhibited in these mice, indicating that interactions between the dental epithelium and the basement membrane are important to determine tooth sizes and dental epithelial cell differentiation.

Ameloblasts are polarized in the secretory stage and secrete enamel matrix components, including amelogenin (AMEL), ameloblastin (AMBN), and enamelin (ENAM). Furthermore, amelotin (AMTN) and Apin/odontogenic ameloblast-associated (ODAM) are secreted from those in the

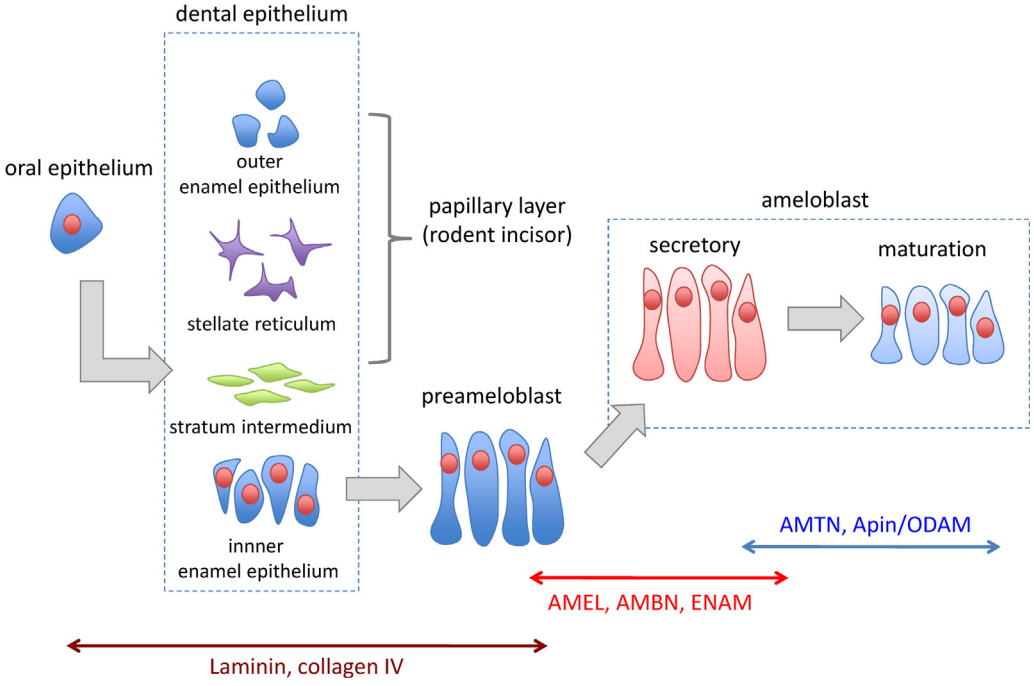

Figure 1 Oral epithelium differentiates into four types of dental epithelium: inner and outer enamel epithelium, stratum intermedium, and stellate reticulum. Inner enamel epithelium differentiates into pre-ameloblast and ameloblast. Inner enamel epithelium and pre-ameloblast secrete and bind to basement membrane. Secretory-stage ameloblasts secrete enamel matrices AMEL, AMBN, and ENAM. Maturation-stage ameloblasts secrete AMTN and Apin/ODAM.