

The Role of Tooth Matrix Proteins in Biomineralization: Lessons from Genetic Studies.

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The tooth is a unique mineralized organ in that both the epithelial-derived ameloblasts (enamel forming) and ectomesenchymal-derived odontoblasts (dentin forming) produce a mineralized extracellular matrix in juxtaposition. Our understanding of the process of tooth matrix formation and biomineralization has dramatically increased through the identification of tooth-specific enamel and dentin extracellular matrix proteins, the molecular characterization of human genetic diseases affecting tooth matrix mineralization, and the establishment of various protein knock-out models.

Gene mapping studies have identified an enamel and dentin/bone gene cluster on the long arm of human chromosome at 4q21. The enamel cluster contains the matrix proteins enamelin and ameloblastin. The dentin/bone gene cluster includes matrix proteins expressed in common to both dentin and bone but at different levels such as osteopontin, MEPE (matrix extracellular phosphoglycoprotein) also known as osteoblastic factor 45 (OF45 renamed osteoregulin), bone sialoprotein, dentin matrix protein 1, and dentin sialophosphoprotein. Genetic linkage studies using large informative families with structural tooth defects have identified critical disease loci for the autosomal dominant forms of amelogenesis imperfecta, dentinogenesis imperfecta types II and III, and dentin dysplasia type II. Various mutations in the largest enamel protein enamelin have been shown to cause both local and smooth hypoplastic forms of amelogenesis imperfecta. Heterogeneous mutations in the acidic phosphoprotein dentin sialophosphoprotein, which is expressed at high levels in dentin and very low levels in bone, have been associated with dentinogenesis imperfecta type II and III and dentin dysplasia type II. These naturally occurring alterations in tooth matrix proteins are beginning to shed light as to significant functional domains of key tooth proteins.

Additional *in vivo* models to explore the biological function of critical tooth proteins are just beginning to be production. These include mice carrying null mutations or overexpressing specific tooth matrix protein. Initial studies have demonstrated that these null mutations in most cases mimic the phenotypes of human genetic diseases affecting enamel and dentin providing much needed viable animal model systems. Furthermore, *in vitro* models are being developed through the establishment of immortalized human cell lines derived from normal teeth and teeth affected by enamel or dentin structural diseases. These stable cell lines, with well characterized and defined gene mutations, will serve as models to explore the ramifications of precise protein modifications on normal tooth mineralization.

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