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Self-assembly directs enamel formation and regeneration

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SELF-ASSEMBLY DIRECTS ENAMEL FORMATION AND REGENERATION

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Enamel is a unique bioceramic tissue covering our teeth, which by improving feeding and nutrition fueled an explosion in vertebrate evolution. Enamel is also the tissue affected by the most prevalent infectious disease of humankind, caries. While enamel is the hardest tissue in the vertebrate body it develops as a soft extracellular protein matrix precursor synthesized by ameloblast cells that is composed mainly of the proteins amelogenin and ameloblastin. Amelogenins are small-, hydrophobic-, inherently disordered proteins that self-assembly to form nanospheres through the interaction of two domains located at opposite molecular ends, whereas, ameloblastin self-assembles through but a single N'-terminal domain. The assembled protein supra-structures control the deposition of calcium and phosphate to form long thin crystals that appear to be woven as a continuum by the cell secretion of protein into the extracellular matrix. The proteins of the enamel matrix are replaced to form hydroxyapatite crystallites, leaving behind only trace amounts of protein to improve the biomechanical behavior of the mineral phase. Mutations to the amelogenin self-assembly domain will alter the microstructural hierarchical organization of the enamel tissue, which in turn degrades its materials properties. Enamel matrix protein assembly is essential to enamel formation: a malformed enamel matrix must also leave behind a malformed mineral phase. This unique cell fabrication method accounts for the favorable materials properties of the bioceramic tissue, allowing the tissue to last through a lifetime of use and misuse. Recent work on the second most abundant protein of enamel, ameloblastin, shows that its only known interaction is with proteasome subunit alpha type 3 (PSMA3) at the secretory face of the ameloblast. This interaction serves to degrade ameloblastin from the C'-terminus, leaving an enriched N'-terminus that defines the lateral border of the ameloblast cell. These borders describe the smallest, repeating unit of enamel, the rod, a collection of thousands of long-, thin-, nanocrystallites of hydroxyapatite mineral. To address the loss of enamel due to caries, enamel regeneration can be achieved on demand by inducing undifferentiated cells to proliferate and differentiate as ameloblasts that create canonical enamel tissue using peptide amphiphiles that activate signals through integrin and thrombospondin pathways.