SHORT COMMUNICATION

ENZYME REPLACEMENT PREVENTS ENAMEL DEFECTS IN HYPOPHOSPHATASIA MICE

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Hypophosphatasia (HPP) is the inborn error of metabolism characterized by deficiency of alkaline phosphatase activity leading to rickets or osteomalacia and to dental defects. HPP occurs from loss-of-function mutations within the gene that encodes the tissue-nonspecific isozyme of alkaline phosphatase (TNAP). TNAP knockout ($Alpl^{-/-}$, a.k.a. $Akp^{2-/-}$) mice closely phenocopy infantile HPP, including the rickets, vitamin B6-responsive seizures, improper dentin mineralization, and lack of acellular cementum. Here, we report that lack of TNAP in $Alpl^{-/-}$ mice also causes severe enamel defects, which are preventable by enzyme replacement with mineraltargeted TNAP (ENB-0040). Immunohistochemistry was used to map the spatiotemporal expression of TNAP in the tissues of the developing enamel organ of healthy mouse molars and incisors. We found strong, stage-specific expression of TNAP in ameloblasts. In the $Alpl^{-/-}$ mice, histological, μCT, and scanning electron microscopy analysis showed reduced mineralization and disrupted organization of the rods and inter-rod structures in enamel of both the molars and incisors. All of these abnormalities were corrected in mice receiving from birth daily subcutaneous injections of mineral-targeting, human TNAP (sALP-FcD10, a.k.a. ENB-0040) at 8.2 mg/kg/day for up to 44 days. These data reveal an important role for TNAP in enamel mineralization, and demonstrate the efficacy of mineral-targeted TNAP to prevent enamel defects in HPP.