

Influence of SIK Inhibitors on the Tooth Development and Eruption of a Mouse Model

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Objectives: Primary failure of eruption (PFE) is a non-syndromic, autosomal dominant condition in which posterior teeth fail to erupt properly. PFE is associated with loss-of-function mutations in the gene (*PTH1R*) encoding parathyroid hormone (PTH) receptor and parathyroid hormone-related protein (PTHrP). The expression of PTHrP within the mesenchymal progenitor cells of the dental follicle (DF) is critical in tooth eruption. These DF cells are tightly regulated by an autocrine system mediated by PTHrP and PTH1R during tooth root formation. Our previously established PFE mouse model through the deletion of the PTHR1/PPR gene within the PTHrP-expressing DF cells, exhibits failure of tooth eruption as well as tooth root formation defects. We postulate that a goal of novel therapeutics for tooth eruption disorders will be to restore functions of PTHrP-expressing DF cells by stimulating the downstream component of the PTH1R signaling pathway. Salt-Inducible Kinase (SIK) inhibitors have been shown to activate the PTHrP-PTH1R signaling pathway by mimicking the actions of PTH in bone and cartilage. This project aims to assess whether administering the SIK inhibitor YKL-05-099 in the post-eruptive stage influences tooth root development and eruption in the PFE mouse model.

Experimental Methods: MicroCT analyses of mandibular samples treated with SIK Inhibitor YKL-05-099 and PBS (control) were conducted through segmentation via ITK-SNAP, measurement of parameters and superimposition of samples via 3D Slicer. Data analyses were conducted using Excel and Prism.

Results: Compared to PBS, YKL-05-099 demonstrated no increases in parameters for 1st molars. 2nd and 3rd molars showed increases in root lengths. 3rd molars also showed increases in eruption heights. Crown width/length for all molars in both groups showed no difference.

Conclusion: SIK Inhibitor YKL-05-099 influences tooth root development in the post-eruptive stage of the PFE mouse model to a certain extent. Future studies should be conducted to analyze if YKL-05-099 has a selective influence on tooth eruption.

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