Role of PPR Signaling in CXCL12+ Apical Papilla Mesenchymal Progenitor Cells

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Objectives: Apical papilla (AP), a unique cell rich tissue located at the base of the developing tooth root, contains multipotent mesenchymal stem cells of the AP (SCAPs) and guides tooth root elongation and maturation. However, the fundamental properties of SCAPs *in vivo* remain largely unknown. We previously demonstrated that MSCs in the dental follicle regulate tooth root formation and tooth eruption via parathyroid hormone (PTH)/PTH-related peptide type 1 receptor (PPR) signaling. Dental pulp cells express a diverse array of chemokines, particularly chemokine C-X-C motif ligand 12 (CXCL12). In this study, we tested if $CXCL12^{+}$ mesenchymal progenitor cells in the AP orchestrate tooth eruption and tooth root formation via PPR signaling.

Experimental Methods: We manipulate PPR signaling *in vivo* specifically among $CXCL12^{+}$ AP cells at the onset of tooth root formation using a *Cxcl12-iCreER* transgenic line. PPR signaling is conditionally inactivated by deleting PPR using its floxed allele. PPR-deficient AP cells are simultaneously traced using an R26R-tdTomato reporter allele. *Cxcl12-iCreER*; $PPR^{fl/fl}$; $R26R^{tdTomato}$ (cKO) and *Cxcl12-iCreER*; $PPR^{fl/+}$; $R26R^{tdTomato}$ (cHet; Control) littermate mice are pulsed with tamoxifen at P3 and analyzed at various time points using fluorescent microscopy. Three-dimensional micro computed tomography (micro-CT) images obtained at 3 months.

Results: $tdTomato^{+}$ cells were present in the dental pulp and the root surface in both cKO and cHet at 25, however, excessive deposition of cellular cementum and delayed tooth eruption were observed in cKO. MicroCT analysis revealed that the root lengths and eruption heights of the mandibular molars in cKO were significantly decreased compared to those in cHet.

Conclusion: Our data demonstrated that the lack of PPR signaling leads to failure of tooth root formation and tooth eruption. These results suggested that PPR signaling plays an important role in regulating the differentiation of $CXCL12^{+}$ mesenchymal cells into odontoblasts and cementoblasts.

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