SHP2 Deficiency in the *Prrx1+* Osteoprogenitors Hinders Odontoblast Development and Function

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Objective: SHP2 is a ubiquitously expressed protein-tyrosine phosphatase that is required for the RAS/ERK pathway activation down stream of multiple receptor protein-tyrosine kinases (RTK) as well as cytokine and integrin receptors. In a study focused on head and limb development, SHP2 was specifically ablated in *Prrx1+* osteochondroprogenitors (OCPs) in mice, and affected SHP2 mutants were found to have skeletal dysplasia, impaired ossification of cranial facial bones, and hindered teeth development. Understanding how SHP2 functions in dental mesenchymal progenitors and mature odontoblasts can shed light on and contribute to regenerative dental medicine.

METHODS: *Ptpn11* floxed (*Ptpn11^{fl}*), *Tg(Prrx1-Cre)*, and *Tg(Rosa26-LSL-ZsGreen) (R26^{ZSG})* mice, all on the C57BL/6 background, were bred to yield *Tg(Prrx1-Cre;Ptpn11$^{fl/+}$;R26^{ZSG})* **(SHP2CTR ^{Prrx1};R26^{ZSG})** and *Tg(Prrx1-Cre;Ptpn11$^{fl/fl}$;R26^{ZSG})* **(SHP2KO ^{Prrx1};R26^{ZSG})** mice (short-hand nomenclature in bold). To examine the effect of SHP2 deletion on tooth development, skull from 1 week old control and SHP2 mutants were fixed in 4% PFA overnight at 4°C, imaged via x-ray, microcomputed tomography, scanning electron microscopy (SEM) and sectioned and stained with Hematoxylin and Eosin (H&E).

RESULTS: SHP2 ablation in *Prrx1+* OCPs cause impaired mineralization of dentin, enamel, and alveolar bone. Radiograph and µ-CT images unveiled under-developed enamel and root, and missing 3rd molar in SHP2 deficient mice. This is further confirmed by the SEM and H&E studies where the thickness of polarized odontoblast and dentin is significantly reduced. The disrupted enamel structure also suggests that SHP2 deficiency affects ameloblast differentiation and/or function.

Conclusion: The results provide strong evidence that the *Prrx1+* cell population is a common progenitor of both odontoblast and osteoblast, and their odontoblastic and osteoblastic differentiation are regulated by SHP2. SHP2 ablation causes tooth development defects. While it's known that PRRX1 plays a critical role in orofacial development, our findings revealed the SHP2's involvement in odontoblast differentiation and/or proliferation and raise the possibility of promoting dentine and alveolar bone formation by manipulating SHP2-associated signaling pathway(s).