Runx2 is essential for maintaining cartilage in the mandibular condyle

Amy Tran, Chiaki Tsutsumi-Arai, Noriaki Ono

Department of Diagnostic and Biomedical Sciences, School of Dentistry
The University of Texas Health Science Center at Houston, Houston, TX, 77054, USA

Objectives: We previously showed that parathyroid hormone-related protein (PTHrP) regulates Runx2$_+$ precursor cells in the mandibular condylar cartilage (MCC). Osteogenic and chondrogenic transcription factors – Runx2 and Sox9, respectively – are co-expressed in the lower polymorphic to the upper chondrocyte layer, suggesting they may coregulate chondrocyte differentiation. In long bone, Runx2 and Sox9 exhibit opposing functions in chondrocyte differentiation, as Sox9 suppresses, but Runx2 promotes hypertrophic differentiation. The aim of this study was to trace the fate of Sox9$_+$ chondrocytes and determine how Runx2 inactivation in these cells affects postnatal MCC chondrogenesis.

Experimental Methods: We studied the fates of Sox9$_+$ cells based on the *cre-lox*P system using *Sox9-creER; R26R*$_{tdTomato}$ mice carrying *Col1a1-GFP* reporter. These mice were pulsed at postnatal day 28 (P28) and chased to P30, 35, and 56. Additionally, Runx2 was specifically inactivated in Sox9$_+$ cells using *Sox9-creER; Runx2*$_{fl/fl}$*; R26R*$_{tdTomato}$ (Runx2-cKO) mice. Mandibular condyle and femur morphology were evaluated using radiographs and Safranin-O staining, along with immunohistochemistry to evaluate RUNX2 and SOX9 expression.

Results: Sox9$_+$ cells at P28 remained within the MCC and robustly differentiated into osteoblasts/cytes in the subchondral region. Radiographically, Runx2-cKO developed an underdeveloped condyle. Runx2-deficient Sox9$_+$ cells remained within the MCC; however, the Runx2-cKO MCC showed a substantial loss of Safranin-O$_+$ cartilaginous matrix and subchondral bone, associated with ectopic Col1a1-GFP$_+$ cells in the polymorphic layer. The transition of Sox9$_+$ cells to hypertrophic chondrocytes and subchondral osteoblasts were disrupted specifically in the MCC due to altered cell fates of Sox9$_+$ chondrocytes.

Conclusion: Runx2 is necessary for maintaining the cartilaginous matrix of the MCC. Runx2-deficiency causes cartilage loss in the postnatal mandibular condyle but not in long bones, leading to pathological mandibular condylar cartilage resorption. Our project reveals unique characteristics of chondroprogenitor cells in the MCC that will facilitate our understanding of the fundamental pathophysiology of temporomandibular joint disorders.

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