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2. **Title**

   Role of Nicotine-induced Hippo Signal Pathway in Osteoblasts and Chondrocytes

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4. **Summary**

Cigarette smoking is one of the causal factors for osteoporosis, periodontal disease and impaired enchondral ossification. Nicotine has been suggested to disrupt osteoblast and chondrocyte function, particularly in cell differentiation and maturation, thereby causing the aforementioned dysfunction. However, the underlying molecular mechanism for nicotine action remains largely unknown. In this study, we focus on nicotine action on the Hippo signaling pathway in osteoblast and chondrocyte in order to figure out how nicotine affects osteogenesis and chondrogenesis *in vivo* and *in vitro*. Nicotine repressed YAP activity in osteoblast and promoted osteoblast differentiation. The decrease in YAP activity was associated with and required for osteoblast differentiation. In addition, hyperactivation of YAP *in vivo* resulted in a bone hardening of limbs and dome-like malformation of the skull, resulting from increased osteogenesis. On the other hand, nicotine treatment resulted in increased YAP activity and repressed chondrocyte proliferation. Hyperactivation of YAP in chondrocytes *in vivo* resulted in impaired chondrocyte proliferation and differentiation/maturation, leading to chondroplasia. These defects were linked to repression of SOX9, a master regulator of chondrogenesis. These observations, taken together, suggest that the Hippo-YAP signaling pathway is a promising target of nicotine action on osteogenesis and chondrogenesis.