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Abstract

BACKGROUND:

Abnormal activation of endochondral bone formation in soft tissues causes significant medical diseases associated with disability and pain. Hyperactive mutations in the bone morphogenetic protein (BMP) type 1 receptor ACVR1 lead to fibrodysplasia ossificans progressiva (FOP), a rare genetic disorder characterized by progressive ossification in soft tissues. However, the pathological mechanisms are unclear. In addition, the difficulty obtaining tissue samples from FOP patients and the limitations in mouse models of FOP hamper our ability to dissect the pathogenesis of FOP.

METHODS:

To address these challenges and develop a "disease model in a dish", we created human iPS cells derived from normal and FOP dermal fibroblasts by two separate methods, retroviral integration or integration-free episomal vectors. We tested if the ability to contribute to different steps of endochondral bone formation was different in FOP vs. control iPS cells.

RESULTS:

Remarkably, FOP iPS cells showed increased mineralization and enhanced chondrogenesis in vitro. The mineralization phenotypes could be suppressed with a small-molecule inhibitor of BMP signaling, DMH1. Our results indicate that the FOP ACVR1 R206H mutation favors chondrogenesis and increases mineral deposition in vitro.

CONCLUSIONS:

Our findings establish a FOP disease cell model for in vitro experimentation and provide a proof-of-concept for using human iPS cell models to understand human skeletal disorders.