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The FOP R206H Acvr1 Mutation is Sufficient to Cause Heterotopic Ossification in Mouse Limbs and is Inhibited by a Selective RARγ Agonist Treatment

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Introduction

Fibrodysplasia ossificans progressive (FOP) is a rare autosomal dominant genetic disorder characterized by extensive heterotopic ossification (HO). Most cases of FOP are caused by the same gain-of-function mutation of the ACVR1/ALK2 type I BMP receptor (R206H).

Methods

In the present study, we conditionally-activated the Acvr1 R206H mutation in skeletal mesenchymal progenitor (Prrx1$^+$) cells in mice to examine the effects of this cell population on HO and skeletal development. We also tested palovarotene, a phase II selective RARγ agonist, as an inhibitor of Acvr1 R206H-induced heterotopic ossification.

Results

Heterozygous Prrx1-Cre;Acvr1 R206H (Prrx1;R206H) mice are viable, but show reduced body length at birth. Histology revealed shorter growth plates with increased proliferative cells and a decreased hypertrophic chondrocyte zone. Consistent with FOP patients, Prrx1;R206H mice at P0 had hind-limb specific great toe malformations and no HO. Soft x-ray and microCT analyses showed that all Prrx1;R206H mice spontaneously developed HO within 2 weeks, with most occurring in the hind limbs. By 4 weeks, HO formation occurs in both hind limbs and fore limbs where Prrx1 is most highly expressed, then progressed to severely impair movement over time. Histological examination confirmed that the HO occurs through endochondral ossification, as in FOP patients. Of note, when the Acvr1 R206H mutation was globally expressed post-natally by a doxycycline-inducible system beginning at P5, all mice developed HO, however the onset and progression were substantially delayed compared to mice with embryonic expression of Acvr1 R206H in Prrx1$^+$ cells. Palovarotene, a RARγ agonist that inhibits chondrogenesis, was administered to Prrx1;R206H mice from P3-P14 and significantly reduced spontaneous HO in a dose dependent manner, rescued longitudinal bone growth, and improved limb movement.

Discussion

Our data demonstrate that Acvr1 R206H expression in skeletal progenitor cells supports the induction and progression of heterotopic endochondral ossification as well as being sufficient to induce the characteristic great toe malformations that are characteristic of FOP. While Prrx1$^+$ cells appear to be major contributors to HO formation, given the localized expression of Prrx1, additional cell populations likely also contribute to HO in patients. Palovarotene was able to inhibit both the skeletal and HO effects of Acvr1 R206H, providing strong preclinical data for RARγ agonists in clinical trials for FOP.