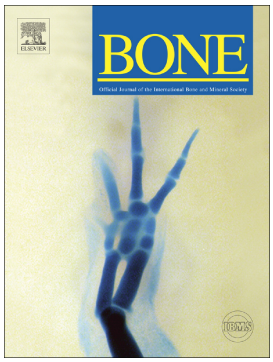

The obligatory role of Activin A in the formation of heterotopic bone in Fibrodysplasia Ossificans Progressiva

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The obligatory role of Activin A in the formation of heterotopic bone in Fibrodysplasia Ossificans Progressiva.

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Abstract

Fibrodysplasia Ossificans Progressiva (FOP) is a rare genetic disorder that presents at birth with only minor patterning defects, but manifests its debilitating pathology early in life with episodic, yet progressive and cumulative, heterotopic ossification (HO) of ligaments, tendons, and a subset of major skeletal muscles. The resulting HO lesions are endochondral in nature, and appear to be linked to inflammatory stimuli arising in association with known injuries, or from inflammation linked to normal tissue repair. FOP is caused by gain-of-function mutations in *ACVR1*, which encodes a type I BMP receptor. Initial studies on the pathogenic mechanism of FOP-causing mutations in *ACVR1* focused on the enhanced function of this receptor in response to certain BMP ligands, or independently of ligands, but did not directly address the fact that HO in FOP is episodic and inflammation-driven. Recently, we and others demonstrated that Activin A is an obligate factor for the initiation of HO in FOP, signaling aberrantly via mutant ACVR1 to transduce osteogenic signals and trigger heterotopic bone formation [1, 2]. Subsequently, we identified distinct tissue-resident mesenchymal progenitor populations residing in muscles and tendons that recognize Activin A as a pro-osteogenic signal (solely in the context of FOP-causing mutant *ACVR1*), and give rise to the cartilaginous anlagen that form heterotopic bone [3]. During the course of these studies, we also found that the activity of FOP-causing *ACVR1* mutations does not by itself explain the triggered or inflammatory nature of HO in FOP, suggesting the importance of other inflammation-introduced factors or processes. This review presents a synthesis of these findings with a focus on the role of Activin A and inflammation in HO, and lays out perspectives for future research.

Keywords: Fibrodysplasia Ossificans Progressiva, heterotopic ossification, Activin A, ACVR1, anti-Activin antibody, progenitor cells

1. Introduction