The Identification of ACVR1 Phosphorylation Sites Critical to Activation of the ACVR1 Signaling Pathway in Fibrodysplasia Ossificans Progressiva (FOP)

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Fibrodysplasia Ossificans Progressiva(FOP) is an extremely rare and debilitating bone disorder that affects 0.00005% of the population. The defining characteristic of FOP is severe heterotopic ossification(HO), a condition in which bone forms outside the regular skeleton, particularly in areas of soft tissue or skeletal muscle. A mutation in the ACVR1 gene leads to FOP by over activating BMP signaling, causing HO. In this signaling pathway, SMAD 1/5/8, the mutated ACVR1 signaling complex gets phosphorylated causing downstream signal activation, resulting in excessive bone growth. Inhibition of a phosphorylation site on the ACVR1 receptor could potentially inhibit downstream signaling and prevent of HO in FOP patients. In this study, 4 different phosphorylation sites in the GS domain of ACVR1 were mutated individually as well as in combination to determine which sites are critical for ACVR1 downstream signaling to occur. Plasmids with these mutations were introduced into E. coli through transformations, and then lentiviruses were given it to insert the mutations into a Hek293 cell line. Ligands were used to stimulate signaling and signaling output was measured with luciferase assays. Remarkably, three phosphorylation sites were demonstrated to be significant in the ACVR1 signaling cascade – the S190, S192 and T189 sites. This study indicated that drug development to target the S190, S192, and T189 phosphorylation sites could prove to be a viable therapeutic option for FOP patients. Additionally, this deepened understanding of the ACVRI pathway could be exploited to regulate bone growth in relevant diseases that are characterized by lack of bone growth.

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