Exploration of ACVR1's Signaling Mechanisms in Relation to Fibrodysplasia Ossificans Progressiva (FOP) Using ACVR1/ACVR1B Chimera Receptors

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Fibrodysplasia Ossificans Progressiva (FOP) is a rare bone disorder caused by a mutation in the ACVR1 receptor, whose downstream signaling leads to excessive bone growth. The defining characteristic of FOP is severe heterotopic ossification, where bone forms outside the skeleton, progressively immobilizing patients. Currently, there are no effective FDA-approved treatments beyond Palovarotene, which is costly and has adverse effects. No drugs directly target the ACVR1 receptor, which could stop symptoms at the source and be more effective. Recently, a novel non-signaling complex was discovered between ACVR1 and activin A. The mechanisms of this complex must be explored before it can become a drug target. This project investigates the role of activin A in ACVR1 signaling, particularly in its internalization and non-signaling complex, which may play a key role in FOP. Chimera receptors combining different domains from ACVR1 and ACVR1B, an established signaling receptor, were integrated into HEK293 cell lines. Six sub-cell lines were established. Western blots and confocal microscopy were used to measure phosphorylation and internalization, identifying which domains drive internalization. Results showed that the ACVR1B transmembrane chimera lacked active internalization, while a construct with the ACVR1 transmembrane domain exhibited a significant increase in internalization. This study is the first to establish the crucial role of the ACVR1 transmembrane in activin A-driven internalization, showing the viability of using chimera receptors to study receptors. This study provides new evidence highlighting the importance of the ACVR1 transmembrane domain in signaling, which may also be critical in FOP pathology and a potential therapeutic target

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