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Lessons from a rare disease: rewriting the logic of signaling mediated by Activin and its receptors

BMP/TFGß family ligands have mainly been studied as factors that initiate Smad signaling by driving the formation of heterotetrameric complexes of their corresponding type I (IR) and type II receptors (IIR). However, while exploring the molecular mechanisms underlying the pathophysiology of the genetic disorder fibrodysplasia ossificans progressiva (FOP), which is driven by missense mutation in the type I BMP receptor ACVR1 (ACVR1FOP), we made a surprising discovery regarding a particular ligand, Activin.We discovered that Activin A initiates Samd1/5/8 signaling via ACVR1FOP (with profound medical consequences) [1], whereas it forms non-signaling complexes (NSCs) with wild type ACVR1 [1, 2]. We took advantage of this discovery to develop an anti-Activin A monoclonal antibody as a therapy for FOP [3], while in parallel we explored the molecular properties and the physiological roles of ACVR1•Activin A•IIR NSCs. This was of particular interest as Activin A has been studied almost exclusively as a ligand for ACVR1B (that signals through Smad2/3). Although, ACVR1 had been initially characterized as an Activin receptor, that notion was soon considered artifactual due to inability of the ACVR1•Activin A•IIR to signal [4]. We demonstrate that ACVR1•Activin A•IIR NSCs display novel properties and are physiologically relevant. NSCs are rapidly internalized and traffic to the lysosome where their components are degraded. This results in lower Activin A levels and reduced signaling through ACVR1B, as well as reduced signaling mediated by BMPs that utilize ACVR1. To explore the physiological roles of this mechanism we generated mice in which Inhba, the gene encoding for Activin A, was mutated to encode for an Activin A mutein (F2TL) that retains its ability to signal through ACVR1B but cannot form NSCs with ACVR1 [2]. The resulting mice cannot be propagated to homozygosis due to female infertility. This phenotype arises from a block in ovarian follicle maturation which appears to be driven by excess Activin A or F2TL, as it can be corrected by inhibiting either Activin A or F2TL using blocking antibodies, but not by inhibition of ACVR1. Our results reveal a novel mechanism by which ACVR1 and Activin A coordinate to negatively regulate their own signaling and provide a first example of physiological relevance of this regulation outside of FOP.

1. Hatsell, S.J., et al., ACVR1R206H receptor mutation causes fibrodysplasia ossificans progressiva by imparting responsiveness to activin A. Sci Transl Med, 2015. 7(303): p. 303ra137.
2. Aykul, S., et al., Activin A forms a non-signaling complex with ACVR1 and type II Activin/BMP receptors via its finger 2 tip loop. Elife, 2020. 9.
3. Di Rocco, M., et al., Garetosmab in fibrodysplasia ossificans progressiva: a randomized, double-blind, placebo-controlled phase 2 trial. Nat Med, 2023.
4. Macías-Silva, M., et al., Specific Activation of Smad1 Signaling Pathways by the BMP7 Type I Receptor, ALK2. Journal of Biological Chemistry, 1998. 273(40): p. 25628-25636.

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