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BMP signaling controls limb muscle development and maintenance

par

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Abstract

Bone morphogenetic proteins (BMPs) regulate the activity of skeletal muscle precursors as well as the trophic state of differentiated muscle. Here, the role of BMP signaling was explored at different stages of limb muscle development by overexpressing an inhibitory Smad protein (Smad6) to abrogate the BMP signaling cascade at cell autonomous level. Overexpression of Smad6 in limb muscle precursors during development (crossing Rosa26-Lox-Stop-Lox-Smad6-IRES-GFP mice, termed RS6, with $Lbx1^{Cre/+}$ transgenic mice) disturbed limb muscle myogenesis: early myogenic markers Pax3 and MyoD were strongly downregulated, fetal limb muscles were smaller, consisted of fewer myofibers and displayed a disturbed muscle patterning. Overexpression of Smad6 in postnatal muscle precursors (using RS6:$Pax7^{CreERT2/+}$ mice) caused decreased cell proliferation resulting in smaller myofibers containing less myonuclei and in decreased generation of satellite cells. Overexpression of Smad6 in differentiated muscle resulted in a different phenotype (using RS6:HSA-Cre mice): limb muscles were only modestly smaller, however, consisted of fewer but larger myofibers with increased myonuclear number. Overexpression of the BMP antagonist Noggin in adult muscle (loss-of-function) resulted in muscle fiber atrophy, whereas overexpression of the BMP receptor Alk3 (gain-of-function) caused muscle fiber hypertrophy. These latter effects were likely muscle precursor independent, as overexpression of Smad6 in differentiated fibers (using RS6:$Pax7^{CreERT2/+}$ mice) had no effect on satellite cell number and muscle size in the adult. In conclusion, the role of BMP signaling in skeletal muscle is stage and context specific.

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