## Genetic over-expression of a dominant negative activin receptor preserves muscle mass in a model of muscle wasting

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Skeletal muscle wasting is a serious feature of multiple diseases including cancer, HIV (AIDS), chronic obstructive pulmonary disease, sepsis, aging and the muscular dystrophies (Lynch *et al.*, 2007). Characterised by a loss of muscle mass and strength, muscle wasting not only reduces a patients' quality of life and response to treatment, but also places a great burden on primary carers, the public health system and the wider population (Janssen *et al.*, 2004). Investigations into the aetiology of muscle wasting have identified the canonical TGF-β signalling pathway as one of the central drivers of this condition. Additionally, the therapeutic potential of TGF-β antagonism as a means to counter muscle catabolism has been well characterised. The majority of research in this field has focused on the systemic administration of inhibitory proteins such as soluble activin receptors to sequester TGF-β ligands and thus prevent downstream signalling (Zhou *et al.*, 2010). However, deleterious off-target effects have proven a significant limitation of these approaches in clinical evaluation. Modern molecular techniques could enable muscle specific inhibition of TGF-β signalling to enhance the morphological and functional properties of muscle with reduced risk of off-target effects. Here we test the hypothesis that muscle specific expression of a truncated type II B activin receptor (dnActRIIB) will inhibit TGF-β signalling and promote anabolism in a model of muscle wasting.

To test our hypothesis male C57/BL6 mice were anaesthetised with isoflurane before being administered an intramuscular injection of recombinant adeno-associated viral (rAAV) vectors rAAV:dnActRIIB, rAAV:activin-A or AAV:dnActRIIB and AAV:activin-A in combination. Mice were then aged appropriately and humanely culled for analysis. All testing was carried out in accordance with the NHMRC code of practice for the care and use of animals for scientific purposes. We have identified that muscle-specific expression of dnActRIIB causes muscle hypertrophy in mice. Furthermore, rAAV:dnActRIIB administration was capable of entirely preventing muscle atrophy caused by over-expression of activin A, one of the key TGF-β ligands associated with muscle wasting disease. Biochemical analysis indicates that the muscle hypertrophy and subsequent preservation of muscle mass were due to inhibition of the catabolic TGF-β signalling cascade; as indicated by reduced phosphorylation of intracellular Smad proteins. In compliment to this, we have observed an up-regulation of anabolic pathways in treated muscles. These results support the hypothesis that muscle specific inhibition of TGF-β signalling can prevent catabolism and could provide a new strategy for achieving therapeutic amelioration of muscle wasting with reduced risk of off target effects.

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