

## **Exploring novel therapies for frailty and muscle disease**

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Loss of skeletal muscle mass and strength is a common and significant contributor to impaired health and premature mortality. As the Transforming Growth Factor-beta (TGF- $\beta$ ) signalling network prominently regulates skeletal muscle development and post-natal growth, manipulation of cellular events that are governed by TGF- $\beta$  signalling may provide a means to prevent or treat muscle-related disease. In mice, we have observed that local expression of follistatin (an inhibitor of the TGF- $\beta$  family ligands, myostatin and activin A) can promote a 100% increase in muscle mass and >50% increase in maximum force producing capacity concomitant with increased protein synthesis and activation of the mammalian target of rapamycin (mTOR) pathway. However, the observed follistatin-mediated hypertrophic effects also occur independently of over-expression, or knock-out of myostatin a key repressor of muscle development that inhibits mTOR signaling. We have determined that follistatin-mediated muscle hypertrophy is also associated with, and is influenced by modulation of Smad-dependent signaling, which controls an extensive program of gene expression in skeletal muscle.

These data advance our understanding of the cellular mechanisms employed to promote follistatin-mediated skeletal muscle hypertrophy. As a prospective approach for combating frailty resulting from muscle wasting and dysfunction, we have examined the effects of follistatin expression in animal models of muscle-related disease and have observed differing responsiveness to acute follistatin expression. We propose that these distinct outcomes reflect the direct and indirect involvement of the TGF- $\beta$  pathway in muscle wasting conditions of differing etiology. These data support further examination of the potential for developing TGF- $\beta$  pathway-based therapeutic interventions for muscle-related disease.

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All studies involving the use of animals were performed in accordance with federal guidelines on the appropriate conduct for care and use of animals in experimental research.

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