Integrated expression analysis of follistatin treatment identifies a novel E3 ubiquitin ligase in the regulation of muscle hypertrophy and sarcopenia

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The TGF-β signaling network is a critical regulator of skeletal muscle mass and function in health and disease. Member ligands of the TGF-β family that regulate skeletal muscle and are associated with muscle wasting in disease include myostatin, activin A and B, and GDF11. Manipulation of these ligands may hold the potential to address muscle wasting associated with a variety of conditions and with advancing age. We sought to evaluate the impact of inhibiting these ligands by follistatin treatment in sarcopenia. We report that follistatin-based interventions can promote growth in sarcopenic muscle but to a lesser degree than in healthy muscle. This disparity highlights the importance of revealing the mechanisms of TGF-β mediated muscle adaptation. To this end, we combined quantitative analyses of proteomic and transcriptomic changes associated with growth of muscles exposed to follistatin. We identified a combined expression signature elicited by acute and chronic follistatin treatment. This data-set provides the first insight into the program of transcription and translation events governing follistatin-induced adaptation of skeletal muscle attributes.

Amongst the features in this analysis was repression of a novel E3 ubiquitin ligase. This ligase is acutely down-regulated by follistatin expression. AAV mediated over-expression of the E3 ligase in skeletal muscle potently induced muscle atrophy. Although follistatin treatment represses expression of this protein in healthy adult mice, we found that the response was specifically lost in sarcopenia. Expression of this ligase in combination with follistatin treatment potently diminished muscle hypertrophy in young mice demonstrating that its regulation is critical for normal growth response during TGF-β inhibition. We propose that specific elements of the genetic response to TGF-β inhibition which account for muscle hypertrophy are no longer preserved in sarcopenia and this dysfunction contributes to amelioration of hypertrophy in sarcopenic muscle.