E3 ligase substrate receptor ASB2 is a negative regulator of skeletal muscle size

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The TGF-β signaling network in skeletal muscle regulates muscle size and function primarily through control of a gene expression program that modulates biosynthesis and metabolic processes. Inhibition of TGF-β ligands myostatin and activin modifies gene expression to promote muscle hypertrophy characterized by increased protein synthesis, deposition of contractile apparatus, and decreased protein catabolism. Analysis of differential gene and protein expression during this growth has identified ASB2, an E3 ubiquitin ligase substrate receptor, as a novel regulator of muscle hypertrophy. Suppression of ASB2 is required to achieve maximal growth *via* myostatin and activin inhibition, however its broader function in skeletal muscle biology is unknown.

We show that ASB2 resides in a Cullin5/ElonginBC/Rbx2 complex in skeletal muscle and overexpression of ASB2 in the *tibialis anterior via* recombinant Adeno-Associated Virus (rAAV) delivery results in a progressive muscle atrophy. Knockdown in skeletal muscle using rAAV delivered ASB2 mIRs stimulated a mild hypertrophy suggesting that ASB2 negatively regulates muscle size. Quantitative proteomic analysis of the transduced muscle identified changes in ubiquitination at 1066 sites on 411 proteins, and was accompanied by differential expression of 859 proteins. Gene ontology, cellular component and protein-protein interaction mapping identified an enrichment in these datasets of proteins that comprise the contractile apparatus and regulate mitochondrial function. Further analysis demonstrated changes in energy sensing and regulation of mitochondrial fission that was accompanied by an activation of discrete atrogenes.

These observations suggest that Asb2 function is linked to the regulation of mitochondria and energy sensing which results in skeletal muscle atrophy and weakness.