Investigating cellular processes that drive skeletal muscle wasting

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Our understanding of the intracellular signaling pathways which drive muscle wasting continues to grow. Data from our lab and others show that activation of the Forkhead boxO (FoxO) transcription factors is sufficient to cause muscle atrophy and necessary for muscle wasting and contractile dysfunction in response to numerous pathophysiological conditions, including cast immobilization, denervation, starvation, sepsis and cancer cachexia. Interestingly, recent work from our lab demonstrated that FoxO-dependent transcription is a central node controlling diverse gene networks in skeletal muscle of tumor bearing mice. Included in these networks were a multitude of repressed genes related to the structural and functional integrity of skeletal muscle. Promoter analysis of these repressed genes using Gene Set Enrichment Analysis (GSEA) to identify consensus motifs identified a conserved motif for the Myocyte Enhancer Factor 2 (MEF2) transcription factors as one of the most highly enriched motifs. Moreover MEF2c, which is known to regulate muscle contractile genes and is necessary for the maintenance of muscle structural integrity, was also identified as a FoxO target gene downregulated in response to tumor burden. Importantly, we further demonstrate that MEF2c and bona fide MEF2c target genes are also downregulated in muscle of cancer patients. Recently acquired data have demonstrated the consequences of preventing MEF2c downregulation in the skeletal muscle of tumor bearing mice and propose a mechanism by which FoxO1 represses MEF2c. Our data also demonstrate the biological significance of select structural genes regulated by MEF2c that are downregulated in response to tumor burden.