Regulation of Mitochondrial Quality Control by P53 in Denervated Skeletal Muscle

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Persistent muscle disuse, as with aging or immobilization, promotes progressive weakness and atrophy of skeletal muscle along with reductions in mitochondrial content, the metabolic powerhouses of the cell. This in turn has considerable consequences on strength, mobility, and overall health. Mitochondria being critical organelles for health are maintained by a series of processes, collectively referred to as mitochondrial quality control (MQC), that work in conjunction to maintain organelle function. p53 is a transcription factor that is well-known to respond to disturbances in the cellular environment to restore homeostasis through many targets. Previous studies from our lab and others have determined a role for p53 in regulating skeletal muscle mitochondria, while additional studies have shown that p53 may also contribute to muscle atrophy following prolonged disuse. We investigated whether p53 is necessary for mediating MQC and muscle atrophy following muscle disuse by subjecting p53 muscle-specific knockout (mKO) and wild-type (WT) mice to unilateral denervation-induced disuse for 7 days. Hindlimb muscles were collected to assess the extent of muscle atrophy, changes in mitochondrial content and function, and the protein expression of markers of MQC. Reductions in hindlimb mass of denervated muscle corresponded with reductions in the signaling for mitochondrial biogenesis, leading to reduced content and function. Similarly, denervation induced increases in MQC markers involved in mitophagy (mitochondrial degradation), and the mitochondrial unfolded protein response (UPR^{mt}), an intermediary responder to cellular stress, in both WT and mKO animals. However, the lack of p53 contributed to a blunted response in almost all markers observed. This suggests a dysregulation of MQC in the absence of p53 within skeletal muscle subjected to denervation and indicates a potential role of p53 in contributing to organelle maintenance during muscle atrophy.