Mitochondrial Recycling and the Path to Exercise Adaptation
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Endurance exercise is a potent stimulus for improving whole-body metabolism within skeletal muscle. Exercise does this, in part, by promoting the removal of damaged cellular components, like mitochondria, via lysosomes through a process known as mitophagy. Thus, the maintenance of lysosomal content is important to support mitophagy, and the process is regulated by the transcription factors TFEB and TFE3. Acute exercise is known to promote improvements in mitochondria by initiating signaling events that drive mitochondrial biogenesis, as well as mitophagy. To support this, exercise also stimulates lysosomal biogenesis. Interestingly with repeated exercise, increases in lysosomal content precede changes in mitochondria. This highlights a link between lysosomes and mitophagy in mediating exercise-induced mitochondrial adaptations. The purpose of my study is to evaluate how TFEB and TFE3 mediate exercise-induced lysosomal and mitochondrial adaptations. We hypothesize that the absence of TFEB or TFE3 will negatively impact the mitochondrial adaptation to repeated bouts of contractile activity. To assess this, we stimulate mature mouse muscle cells to contract in cell culture (3hr/day; CCA) in the presence or absence of TFEB or TFE3, thus providing an effective in vitro model to study exercise adaptations. In the absence of TFEB, PGC-1a the master regulator of mitochondrial biogenesis was reduced both basally and in response to CCA. This decrease was not observed in the absence of TFE3. In contrast, mitochondrially-encoded COX-I was increased basally and with CCA in the absence of TFEB, while this adaptation was blunted in the absence of TFE3. However, nuclear-encoded COX IV increased by 2.4-fold in response to CCA, regardless of the presence or absence of TFEB and TFE3. The reduced exercise response following the loss of TFE3, but not TFEB, likely indicates a distinct and more direct role for TFE3 in mediating exercise-induced adaptations, in comparison to TFEB. Thus, the significance of this work is that it is beginning to define the overlap between the regulation of mitochondrial synthesis and degradation, suggesting a co-operative interaction between the two pathways in order to produce a healthy mitochondrial pool within muscle.