Investigating the role of the transcription factor ATF5 in the regulation of the mitochondrial unfolded protein response during exercise in skeletal muscle

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Skeletal muscle health is critical in the maintenance of whole-body metabolism, locomotion and for the prevention of metabolic diseases, thus, greatly contributing to quality of life. The functional state of this organ heavily relies on mitochondria, primarily known as ‘the powerhouses of the cell’, to produce energy for muscle contractions and cell signaling processes. Interestingly, these organelles are also imperative in the homeostatic regulation of skeletal muscle cells by continuously monitoring stress levels and triggering an appropriate response. An imbalance in mitochondrial protein homeostasis or ‘proteostasis’ occurs wherein the amount of misfolded proteins exceeds the number of regulatory enzymes that work to refold or degrade them. A variety of external stimuli, including unaccustomed exercise, can invoke an accumulation of these misfolded proteins and cause mitochondrial dysfunction. Although exercise is beneficial for long-term muscle health, the acute cellular stress that is induced by muscle contractions must be handled accordingly to produce an adaptation. The associated proteotoxicity activates a pathway called the Mitochondrial Unfolded Protein Response (UPRmt), a protective cellular mechanism, to improve the protein folding capacity of the mitochondrion and confer resistance to subsequent stressors. The activating transcription factor 5 (ATF5) is an important inducer of this pathway, responsible for the transcription of genes involved in the UPRmt. However, the regulation of the UPRmt and whether ATF5 could have a role in the maintenance of mitochondria during exercise-induced stress is not known. Thus, my objectives are to: 1) investigate the role of ATF5 in basal mitochondrial maintenance, 2) study the impact of ATF5 on the UPRmt gene expression response to acute exercise, and 3) evaluate the function of ATF5 in mediating mitochondrial adaptations from exercise training. Wild-type (WT) and ATF5 knockout (KO) mice will be subjected to six weeks of aerobic exercise training on the treadmill to observe the effects of chronic exercise. From there, half of the animals will additionally complete a bout of acute exercise to observe the response of trained muscle to contractile activity. Biochemical analyses will be performed on the skeletal muscle of the rodents to measure indicators of mitochondrial content, function, and activation of the UPRmt.

We hypothesize that ATF5 is necessary for basal mitochondrial maintenance and the induction of UPRmt genes following acute exercise. Furthermore, we hypothesize that ATF5 is necessary in promoting mitochondrial adaptations from exercise training via its regulation of the UPRmt. This research will help us understand the mechanisms by which the cell adapts to exercise-induced mitochondrial stress and how they can lead to lead to beneficial mitochondrial adaptations, thereby promoting long-term muscle health.