Mechanisms controlling skeletal muscle mitochondrial function and metabolic health

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USA

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Mechanisms controlling skeletal muscle mitochondrial function and metabolic health

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

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parkin gene, , , ,

Research Abstract

? DESCRIPTION (provided by applicant): Metabolic dysfunction, manifested clinically as the metabolic syndrome (MetSyn), constitutes a major health crisis in the US due to the high

incidence and links of its defining features including obesity, glucose intolerance, and insulin resistance, with the pathogenesis of type 2 diabetes, atherosclerosis, certain cancers, and idiopathic Parkinson’s disease. Considering that skeletal muscle is a primary contributor to whole body oxidative metabolism and insulin-stimulated glucose disposal, and that mitochondria are an important organelle in regulating these processes, our research efforts are focused on mechanisms impacting mitochondrial function in skeletal muscle. Since mitochondria are a highly dynamic organelle undergoing rapid fusion-fission and subsequent autophagic turnover (mitophagy) to maintain a healthy network, we propose that perturbations reducing the efficiency or balance of mitochondrial fission-mitophagy flux will lead to mitochondrial dysfunction and impairments in muscle metabolism and insulin action. In this application we will test this notion using loss- and gain-of-function approaches targeting the fission-mitophagy related E3 ubiquitin ligase Parkin in myocytes and mouse muscle. In Aim 1 we will use wild-type mice and a mitochondrial mutator mouse line (heterozygous for the D257A mutation in polymerase gamma) to investigate the impact of ablating Parkin protein, blocking its kinase (PINK1)-induced translocation, or increasing its expression on mitochondrial morphology, mtDNA integrity, autophagic flux, oxidative metabolism, and insulin sensitivity. In Aim 2 we will determine whether Parkin protein expression and phosphorylation activation at Ser65 is essential for acute exercise tolerance and adaptations in mitochondrial function and muscle metabolism in response to endurance training. Our compelling preliminary findings support the hypothesis that fission-mitophagy incompetence causes mitochondrial dysfunction and insulin resistance, and blunts muscle mitochondrial adaptations to exercise training. The proposed studies are of important translational relevance as our research will elucidate a novel mechanism underlying mitochondrial dysfunction in skeletal muscle and link defective mitochondrial dynamics with features of MetSyn, common underpinnings of chronic diseases responsible for significant mortality in the US.

Lay Summary

PUBLIC HEALTH RELEVANCE: The incidence of metabolic dysfunction is rising dramatically in the US and is associated with elevated morbidity and mortality secondary to type 2 diabetes, cardiovascular disease, and certain forms of cancer. In this application we propose to investigate the role of the E3 ubiquitin ligase Parkin on mitochondrial health, muscle metabolism, and insulin sensitivity in sedentary and exercise trained rodents. These studies may bring to light novel strategies for the treatment of metabolic dysfunction and enhance our understanding of mechanisms underlying the health benefit of physical activity.

Further information available at:

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