Targeting Excessive Mitophagy to Mitigate Age-Related Muscle Dysfunction
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ABSTRACT
Sarcopenia – the age-linked, involuntary decline of skeletal muscle mass and function – substantially contributes to frailty and diminished quality of life in the elderly. Decreased mitochondrial content and compromised mitochondrial function have long been linked to the development and progression of sarcopenia. Despite this strong link, few pharmacological strategies exist to bolster skeletal muscle mitochondria, creating a need for novel therapeutic approaches to maintain mitochondrial content and function in aging patients.

Our data suggest that modulating mitochondrial protein phosphorylation may be a powerful way to control mitochondrial content. Our recent data suggest that phosphorylation is a key regulator of mitophagy – the autophagy-dependent turnover of mitochondria. We found that genetic disruption of a mitochondrial phosphatase, Pptc7, causes the accumulation of phosphorylation on the mitophagy receptor Bnip3, which promotes Bnip3 overexpression. This Bnip3 overexpression leads to fewer mitochondria and substantially compromises mitochondrial function. Importantly, Bnip3 overexpression is strongly linked to the onset of skeletal muscle atrophy in both mice and humans, with Bnip3 recently classified as a bona fide atrogene. Our data suggest that dysregulated protein phosphorylation promotes Bnip3 overexpression, leading to skeletal muscle atrophy in mice and humans.

The goal of this proposal is to characterize the extent to which Bnip3 overexpression drives excessive mitophagy and skeletal muscle pathology, as well as how its phosphorylation at two specific serines modulates these phenotypes. Importantly, our data suggest that inhibiting specific kinases can promote Bnip3 turnover through disruption of this phosphorylation-based regulation. As kinases are pharmacologically tractable and have had significant clinical impact, these studies may reveal a novel therapeutic strategy to thwart the development and progression of sarcopenia.