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Mitochondrial and skeletal muscle health with advancing age

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ABSTRACT

With increasing age there is a temporal relationship between the decline of mitochondrial and skeletal muscle volume, quality and function (i.e., health). Reduced mitochondrial mRNA expression, protein abundance, and protein synthesis rates appear to promote the decline of mitochondrial protein quality and function. Decreased mitochondrial function is suspected to impede energy demanding processes such as skeletal muscle protein turnover, which is critical for maintaining protein quality and thus skeletal muscle health with advancing age. The focus of this review was to discuss promising human physiological systems underpinning the decline of mitochondrial and skeletal muscle health with advancing age while highlighting therapeutic strategies such as aerobic exercise and caloric restriction for combating age-related functional impairments.

1. Introduction

Reports of skeletal muscle atrophy that accompany advancing age (i.e., sarcopenia) and the associated reductions in skeletal muscle function and quality have been observed for several decades (Critchley, 1931; Rosenberg, 1989, 1997). Recently, panels of leading scientists and physicians associated with large-scale epidemiological studies have created specific, objective criteria based on lean tissue mass and functional capacity to improve the diagnosis and treatment of sarcopenia (Delmonico et al., 2007; Fielding et al., 2011; Goodpaster et al., 2006; Morley et al., 2011; Newman et al., 2003). Human aging starts after the third decade and the progression of skeletal muscle atrophy with age is a slow process (~1% per year), but accelerates as humans approach 80 years of age (Baumgartner et al., 1998). With expansion in human lifespan, the elevated rate of muscle loss becomes more problematic since skeletal muscle is critical for functionality and substrate metabolism. When the substrate reservoir deteriorates with age, the associated cardiometabolic disease states (i.e. insulin resistance, diabetes, cardiovascular disease, obesity) become more prevalent (Atlantis et al., 2009). Many studies have observed reduced skeletal muscle mass and infiltration of adipose tissue depots within or between skeletal muscle groups that are associated with reduced muscle function, insulin resistance and obesity (Delmonico et al., 2009; Goodpaster et al., 2005, 2000). A key link between a reduction in skeletal muscle health and prevalence of metabolic disorders with advancing age may be related to impaired mitochondrial function. A reduction in mitochondrial abundance and function with age has been observed across various species (c elegans, drosphilla, mice, humans) and tissues (skin, nerve, brain, skeletal muscle). Moreover, perturbations in skeletal muscle mitochondrial energetics have been correlated with reduced aerobic capacity (Short et al., 2005a), walking capacity (Coen et al., 2012) and skeletal muscle function (Safdar et al., 2010) in older adults. The mechanisms of age-related changes in skeletal muscle are multifactorial but the purpose of this review is to highlight the apparent temporal and functional connection between the decline of mitochondrial and skeletal muscle health (Fig. 1).

2. Reduced mitochondrial content and function with age

Electron microscopic assessment of skeletal muscle biopsy samples revealed lower mitochondrial volume density in older adults (Conley et al., 2000). A decline in mitochondrial content, as represented by mitochondrial DNA copy number, has also been demonstrated in rodents (Barazzoni et al., 2000) and humans (Short et al., 2005a). These findings, coupled with investigations that observed reduced levels of mitochondrial protein synthesis (Rooyackers et al., 1996) and expression of proteins encoded by both mitochondrial and nuclear DNA (Lanza et al., 2008; Short et al., 2005a), are expected to alter mitochondrial function. Semi-quantitative analyses, such as immunoblotting or maximal enzyme activity, support the notion that aging skeletal muscle contains less abundance of enzymes in oxidative metabolism (i.e. Krebs Cycle, beta-oxidation) and/or proteins involved in the electron transport chain (ETC) (Cooper et al., 1992; Ghosh et al., 2011; Lanza et al., 2008; Rooyackers et al., 1996; Tonkonogi et al., 2003; Trounce et al., 1989). Collectively, reductions in mitochondrial proteins and volume may

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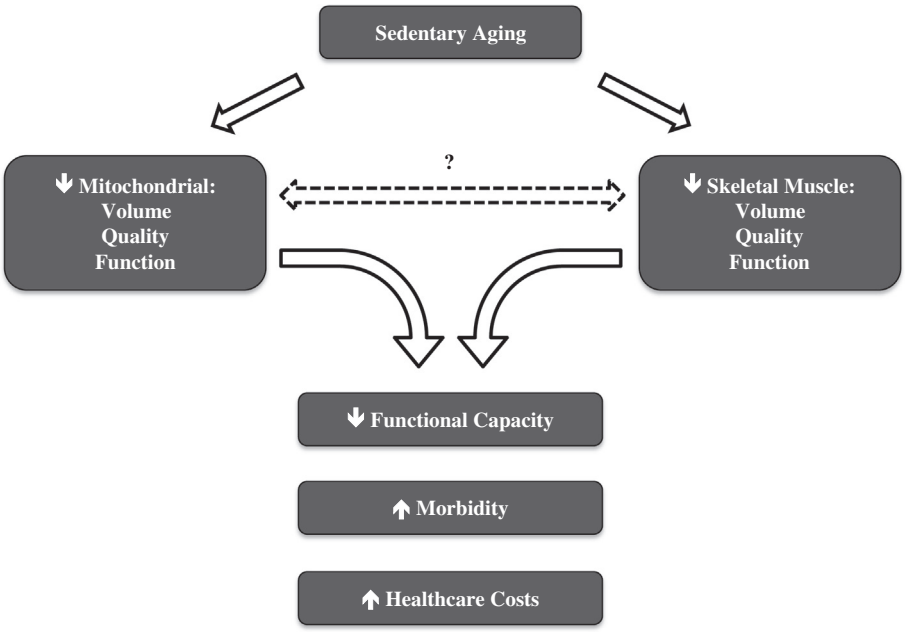

Fig. 1. Reduced mitochondrial and skeletal volume, quality and function with sedentary aging. Sedentary aging is associated with the decline of mitochondrial and skeletal muscle volume, quality and function. The casual link between the loss of mitochondrial homeostasis and sarcopenia is unknown, however, both appear with advancing age and are associated with the loss of functional capacity and corresponding increases in comorbidities and annual healthcare costs. Exercise and physical activity are effective prescriptions to attenuate the negative consequences of sedentary aging illustrated in Fig. 1.

limit ATP production for energy demanding processes such as myocellular remodeling to maintain protein quality.

Advancements of *in vitro* and *ex vivo* measures of mitochondrial energetics have detected diminished capacity for basal (Petersen et al., 2003) and maximal (Conley et al., 2000; Kent-Braun and Ng, 2000; Short et al., 2005a) mitochondrial ATP synthesis in older adults. When expressing the rate of mitochondrial ATP synthesis relative to mitochondrial content there remains a deficit in older adults suggesting that there is not only a reduction in mitochondrial protein content but also mitochondrial protein quality. These findings appear to be related to physical activity, as sedentary individuals had lower *in vivo* mitochondrial function compared to active individuals (Kent-Braun and Ng, 2000; Larsen et al., 2012). It is important to acknowledge that in aging human skeletal muscle, findings of mitochondrial dysfunction are highly equivocal and the disparity between studies is not well discussed. In Table 1 we provide potential confounding variables related to the characteristics of research participants (column A) as well as the use of various measurements of mitochondrial abundance or function (column B). Key differences exist when interpreting data since each measurement in Table 1 assesses different constituents of mitochondrial abundance or function and each method presents key strengths and weaknesses as has been reviewed in detail previously (Lanza and Nair, 2010; Perry et al., 2013). One difference could be comparisons between content or maximal activities of enzymes in the mitochondrial matrix (e.g., citrate synthase, βHAD) which are completely encoded by nuclear DNA vs. proteins involved in oxidative phosphorylation (e.g., cytochrome c oxidase, NADH) that are encoded by both nuclear and mitochondrial genomes. Although analysis of maximal mitochondrial energetics *in vivo* (i.e., ^{31}P-MRS) and *ex vivo* (i.e., high-resolution respirometry) are highly correlated (Lanza et al., 2011), subtle discrepancies still exist between different approaches for measuring mitochondrial function *in vivo* (basal vs. maximally stimulated) and *ex vivo* (ATP production vs. oxygen respiration; permeabilized fibers vs. isolated mitochondria). Also, sampling of human muscle tissue from various muscle groups consisting of different recruitment patterns and fiber type composition can create conflicting results between studies. These variables need to be recognized and addressed to properly assess the true age-related phenotype. Globally, when investigations utilize large sample sizes and rigorous control to avoid many of the confounding variables there appears to be an age-related decline in mitochondrial protein content, quality and function in the quadriceps femoris muscles. These data provide well-founded evidence for perturbations in mitochondrial health and connections to impaired functional capacity during sedentary aging.

Aerobic training is an effective exercise prescription to stimulate markers of oxidative capacity as established in the 1960s (Holloszy, 1967), when it was revealed that aerobic exercise of sufficient intensity increased mitochondrial enzyme activity in animal models. Numerous other investigations have confirmed these results, however, few studies in humans have directly investigated if age influences exercise induced mitochondrial adaptations after the same exercise training program. From the few available studies, it appears that mitochondrial molecular regulation and protein content are increased after 12–16 weeks of exercise training, independent of age, suggesting older individuals (<80 y) adapt favorably to exercise training (Ghosh et al., 2011; Short et al., 2003). However, the influence of various exercise training programs (i.e., aerobic vs. resistance vs. concurrent training) on mitochondrial and skeletal muscle function (*ex vivo* or *in vivo*) has yet to be determined and warrants investigation. Collectively, these data suggest that exercise can improve or prevent the loss of mitochondrial health during sedentary aging (Fig. 2).

3. Molecular Regulation of Aging Mitochondria

The mitochondria consist of proteins encoded from both mitochondrial (mtDNA) and nuclear DNA (nDNA). Although mtDNA contains just 27 genes that encode 13 proteins (all within the electron transport chain), 2 ribosomal and 22 translational RNA, proper organelle biogenesis and function require input from both gen-

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