CHEST

Contribution of the Mitochondria to Locomotor Muscle Dysfunction in Patients With COPD

Tanja Taivassalo, PhD; and Sabah N. A. Hussain, MD, PhD

COPD is a significant public health challenge, notably set to become the third leading cause of death and fifth leading cause of chronic disability worldwide by the next decade. Skeletal muscle impairment is now recognized as a disabling, extrapulmonary consequence of COPD that is associated with reduced quality of life and premature mortality. Because COPD typically manifests in older individuals, these clinical features may overlie normal age-associated declines in muscle function and performance. Although physical inactivity, oxidative stress, inflammation, hypoxia, malnutrition, and medications all likely contribute to this comorbidity, a better understanding of the underlying mechanism is needed to develop effective therapies. Mitochondrial alterations have been described; these alterations include reductions in density and oxidative enzyme activity, increased mitochondrial reactive oxygen species production, and induction of muscle proteolysis including autophagy. This review focuses on the perspective that mitochondrial alterations contribute to impaired locomotor muscle performance in patients with COPD by reducing oxidative capacity and thus endurance, as well as by triggering proteolysis and thus contributing to atrophy and weakness. We discuss how the potential underlying mechanisms converge on mitochondria by targeting the peroxisome proliferator-activated receptor γ-coactivator-1α signaling pathway (thereby reducing mitochondrial biogenesis and muscle oxidative capacity and potentially increasing fiber atrophy) and how taking advantage of normal muscle plasticity and mitochondrial biogenesis may reverse this pathophysiology. We propose recent therapeutic strategies aimed at increasing peroxisome proliferator-activated receptor γ-coactivator-1α levels, such as endurance training and exercise mimetic drugs, with the strong rationale for increasing mitochondrial biogenesis and function and thus improving the muscle phenotype in COPD. CHEST 2016; 149(5):1302-1312

KEY WORDS: atrophy; COPD; exercise; mitochondria; skeletal muscle

Skeletal muscle impairment is a disabling, systemic consequence of COPD.[1] It is most commonly described in locomotor muscles, occurs even at mild stages of the disease, is highly prevalent (affecting 20%-40% of patients with moderate to severe COPD[2]),

ABBREVIATIONS: COX = complex IV activity; FoxO = forkhead box class O; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mPTP = mitochondrial permeability transition pore; mtDNA = mitochondrial DNA; mtROS = mitochondrial reactive oxygen species; MuRF1 = muscle RING finger 1; NFκB = nuclear factor kappa-light-chain-enhancer of activated B cells; PGC-1α = peroxisome proliferator-activated receptor γ-coactivator-1α; PPAR = peroxisome proliferator-activated receptor; ROS = reactive oxygen species; SDH = succinate dehydrogenase; TFAM = transcription factor A; TNF-α = tumor necrosis factor-α

AFFILIATIONS: From the Department of Kinesiology (Dr Taivassalo), McGill University, Montreal, QC, Canada; and the Department of Critical Care (Dr Hussain), McGill University Health Centre and Meakins-Christie Laboratories, Department of Medicine, McGill University, Montreal, QC, Canada.

CORRESPONDENCE TO: Sabah N.A. Hussain, MD, PhD, Room EM2.2224, Block E, 1001 Decarie Blvd, Montreal, QC H4A 3J1, Canada; e-mail: sabah.hussain@muhc.mcgill.ca

DOI: http://dx.doi.org/10.1016/j.chest.2015.11.021

and is strongly related to diminished quality of life and premature mortality.[3] Functional manifestations of locomotor muscle impairment include exercise intolerance, weakness, poor endurance, and increased fatigability.[1] Numerous structural and metabolic alterations account for COPD-compromised muscle performance. Fiber atrophy, a shift in fiber-type distribution from type I to type II/IIx, and mitochondrial abnormalities all contribute to losses in muscle oxidative capacity and endurance.[1,4,5] The present review, however, focuses on alterations in mitochondrial content and/or function that reduce oxidative capacity and thus endurance, and then trigger proteolysis, thereby contributing to muscle atrophy and weakness in patients with clinically stable COPD.

Mitochondria and Muscle Homeostasis

Mitochondria play a central role in adenosine 5′-triphosphate production through oxidative phosphorylation and cellular Ca^{2+} dynamics due to their capacity to take up and release Ca^{2+}. Moreover, they are one of the main sources of the reactive oxygen species (ROS) that affect cell signaling and dysfunction. In all cell types, mitochondria can trigger apoptosis through opening of the mitochondrial permeability transition pore (mPTP). Apoptotic nuclei and activated caspases have been detected inside skeletal muscle fibers of several neuromuscular pathologies.[6-8] However, the issue of apoptosis has a particular connotation in skeletal muscles because these are multinucleated cells, and there is evidence that not all nuclei of a skeletal muscle fiber undergo DNA fragmentation at the same time.[9] These observations led to the proposal that apoptosis of individual nuclei in skeletal muscle fiber does not lead to loss of the entire muscle fiber but to degradation of associated cytoplasmic segments and thereby contributes to muscle fiber atrophy.[10] The strong correlation between the degree of muscle atrophy and the number of apoptotic nuclei seems to support this proposal.[6,11] In summary, by virtue of their involvement in apoptosis and ROS production, mitochondria may play an important role in the development of muscle atrophy.

In healthy skeletal muscle, the quantity and function of mitochondria vary according to fiber type and change in response to physiological cues such as exercise or physical inactivity. For example, mitochondrial density and enzymatic activity significantly increase in response to endurance training.[12] Conversely, muscle disuse has the opposite effects on mitochondria, ultimately compromising cellular energy production and increasing fatigability. As such, mitochondrial density determines muscle oxidative capacity and is determined by the balance between mitochondrial synthesis (biogenesis) and degradation (mitophagy).

Mitochondria are unique organelles that contain multiple copies of extranuclear DNA in the form of double-stranded circular molecules comprising 16,569 nucleotides. Although the majority of mitochondrial proteins (approximately 1,500) are encoded by nuclear DNA, 13 proteins are encoded by mitochondrial DNA (mtDNA), all of which are essential components of the electron transport chain (complexes I, III, IV, and V). Thus, maintaining the integrity of mtDNA is essential for normal cell homeostasis. Mitochondrial biogenesis involves expansion of the mitochondrial reticular network through a complex series of signaling events orchestrated by peroxisome proliferator-activated receptor γ-coactivator-1α (PGC-1α), resulting in the formation of protein complexes encoded by both nuclear and mtDNA. An important downstream effector of PGC-1α is mitochondrial transcription factor A (TFAM), which maintains the mtDNA copy number by regulating mtDNA replication and transcription in proportion to muscle oxidative capacity.[13]

Selective degradation of mitochondria occurs through mitoptosis (mitochondrial suicide) and mitophagy. Mitoptosis is a cellular process in which the mitochondria is selectively degraded through a mitochondria-specific program, usually triggered by increased ROS production and involves the release of cytochrome c from mPTP.[14,15] Mitoptosis takes various forms and is manifested as a degradation of internal matrix and cristae (inner membrane mitoptosis) or degradation of the outer membrane with swollen cristae as remnants.[16] Dysfunctional mitochondria exhibiting abnormal membrane potential and those undergoing mitoptosis are removed through mitophagy, a process of the autophagy-lysosome degradation pathway in which mitochondria are targeted through specific signaling mechanisms and delivered to lysosomes for proteolytic degradation. Mitophagy is important for normal cellular turnover of mitochondria. In skeletal muscles, mitophagy is upregulated in response to denervation-induced muscle disuse and acute aerobic exercise-induced muscle activation.[17,18] Therefore, normal mitochondrial function and turnover are essential for maintaining tissue homeostasis.