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Review Article

Recent advances in mitochondrial turnover during chronic muscle disuse

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ABSTRACT

Chronic muscle disuse, such as that resulting from immobilization, denervation, or prolonged physical inactivity, produces atrophy and a loss of mitochondria, yet the molecular relationship between these events is not fully understood. In this review we attempt to identify the key regulatory steps mediating the loss of muscle mass and the decline in mitochondrial content and function. An understanding of common intracellular signaling pathways may provide much-needed insight into the possible therapeutic targets for treatments that will maintain aerobic energy metabolism and preserve muscle mass during disuse conditions.

1. Introduction

Skeletal muscle is the largest tissue in the body, representing approximately 40% of the total mass of a healthy adult. This tissue is well characterized as exceptionally malleable, and a diversity of stimuli, such as prolonged inactivity,[1] denervation,[2] starvation,[3] aging,[4] or chronic disease,[3,5] can negatively impact muscle mass. Each unique stimulus yields similar, yet characteristic, molecular, functional, and phenotypic alterations in skeletal muscle. The resulting muscle atrophy is defined by an overall loss of proteins, organelles, and cytoplasm. Mitochondria are the main source of energy in skeletal muscle and they provide adenosine triphosphate by means of oxidative phosphorylation.[6] It is not surprising then that mitochondria are also quite adaptable, as their cellular content can be fine-tuned to the tissue's energy requirements. Mitochondrial content is regulated by two opposing processes, mitochondrial synthesis (biogenesis)[7] and mitochondrial degradation (mitophagy).[8] In the context of muscle disuse, a decrement in mitochondrial abundance is one of the major adaptations observed,[9] as the demand for energy is diminished. Understanding the interaction between mitochondrial biogenesis and mitophagy and their relationship to muscle atrophy during disuse is therefore invaluable for our comprehension of cellular homeostasis. The following review provides a concise summary of the mechanisms moderating muscle mass and mitochondrial content during conditions of chronic muscle disuse.

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2. Atrophy signaling during muscle disuse

Skeletal muscle mass is determined by the balance between protein synthesis and degradation. One of the most significant alterations associated with prolonged inactivity of skeletal muscle is the net loss of muscle protein, which results in myofiber atrophy.[10–14] This loss of muscle mass occurs as a consequence of enhanced activation of the cell's major proteolytic executors, the ubiquitin–proteasome system (UPS), and the autophagy–lysosome pathway (ALP), which together regulate the half-life of a majority of cellular proteins.[15] The study of the molecular pathways controlling this balance is an important area of sustained research.

Muscle mass maintenance and myofiber hypertrophy are governed, in part, by insulin-like growth factor-1 signaling. This protein can promote muscle growth partially through phosphatidylinositol 3-kinase–Akt signaling,[16–18] which stimulates myofibrillar protein synthesis via mammalian target of rapamycin complex 1 (mTORC1).[19] Thus, the direct activation of Akt is associated with muscle hypertrophy, and interestingly is sufficient to block atrophy during muscle disuse.[16] During muscle disuse, a reduction in phosphatidylinositol 3-kinase–Akt signaling is evident and could, in theory, result in reduced mammalian target of rapamycin (mTOR) activity. Notably, mTORC1 has been implicated in stimulating mitochondrial biogenesis[20–22] and in the inhibition of autophagy.[23] Thus, a decrease in mTOR activity would result in reduced protein synthesis and mitochondrial biogenesis, while stimulating autophagy. Both decreases in mitochondrial function and marked increases in autophagy are known to trigger cellular signaling events that contribute to muscle atrophy. However, several studies have noted a counter intuitive hyperactivation of mTOR during chronic muscle disuse, likely as a result of enhanced amino acid influx from the cellular degradative pathways, the UPS and ALP.[24,25] Therefore, although the exact role of mTOR-related signaling during muscle wasting is still contentious,[24–29] this complex appears to represent a critical rheostat in the control of an abundance of cellular processes during muscle growth and atrophy.

Central to the regulation of muscle mass during disuse are members of the forkhead box class O (FoxO) proteins. Although this family of transcription factors is involved in numerous intracellular processes,[30,31] these proteins also operate as critical mediators of myofiber atrophy during muscle disuse, as they orchestrate the induction of an atrophic gene program that is implicated in both UPS- and ALP-mediated catabolism.[29,32,33] In this scenario Akt is able to prevent muscle atrophy by inhibitory phosphorylation of FoxO3 on multiple residues, effectively prohibiting its nuclear entry by facilitating its sequestration in the cytoplasm though interactions with 14-3-3 proteins.[34] Indeed, Akt activity is reduced during muscle disuse,[16] allowing FoxO3 to enter the nucleus and stimulate a gene expression program that promotes an atrophic phenotype.[33] In particular, FoxO nuclear translocation has been shown to upregulate the expression of E3 ubiquitin ligases muscle RING finger 1 (MuRF1) and atrogin-1/MAFbx.[33] These E3 ligases are major effectors of the UPS, as they mediate muscle loss by targeting muscle structural proteins and components related to protein translation for degradation.[1,35–38]

Apart from Akt-mediated phosphorylation, the activity and subcellular localization of FoxO transcription factors can be fine-tuned via post-translational modifications by other upstream factors. AMP-activated protein kinase (AMPK), a metabolic sensor, has the capacity to phosphorylate FoxO on numerous residues, which positively influences its transcriptional activity.[39,40] The activation of this AMPK–FoxO axis was documented to occur with muscle disuse[41] and appears to contribute to muscle protein degradation. The increase in AMPK activation with muscle inactivity also likely inhibits protein synthesis,[42–44] further accelerating muscle protein loss. AMPK activation has also been shown to promote mitochondrial biogenesis,[45–49] however, a process that is downregulated during muscle disuse. Thus, AMPK activation at the onset of muscle disuse could serve as an early signal to mitigate energy stress, by enhancing energy substrate availability through protein breakdown and attenuating the loss of mitochondria at the early stages of muscle disuse.

FoxO3 activity can also be modulated by acetylation.[50–52] In response to muscle disuse, FoxO3 can be deacetylated by Histone deacetylase 1 (HDAC1),[50] promoting its nuclear translocation and activity. Conversely, recent research has also drawn attention to the role of SirT1, an NAD+-dependent deacetylase, in the inhibition of denervation-induced myofiber atrophy through the deacetylation of FoxO3.[53] It appears possible that the differential acetylation of lysine residues could account for the contrasting results observed between these studies. Nonetheless, the capacity of FoxO3 to be post-translationally regulated during muscle disuse represents a critical inflection point in the control of the atrophy gene program.

Another critical system contributing to disuse-induced muscle atrophy is the nuclear factor-κB (NF-κB) signaling pathway (Fig. 1). Extracellular factors, such as tumor necrosis factor α (TNFα), stimulate this pathway, activating the inhibitor of κB kinases (IKKα and IKKβ), which prompts the nuclear localization of NF-κB transcription factors. These transcription factors bind NF-κB response elements on atrophy genes, such as *MuRF1*, *FoxO3*, and *Runx1* among others,[54] and promote their transcription. Overexpression of a negative regulator of this system (inhibitor of NF-κBα) is sufficient to block disuse-induced atrophy,[55,56] and muscle-specific abolition of IKKα and IKKβ via genetic knockout (KO), or expression of a dominant negative form, is also protective of muscle mass.[57–59] Attenuation of myofiber atrophy in these models appears to result from a decrease in the activity of the NF-κB transcription factors and coactivators,[55,58,60] the most important of which are p50 and Bcl-3, which have notable roles in the expression of many genes associated with muscle atrophy.[54,61] Moreover, NF-κB signaling has also been demonstrated to impair mitochondrial biogenesis in skeletal muscle (Fig. 1).[62–64] Thus, NF-κB signaling also contributes to muscle atrophy by promoting a decline in mitochondrial content and function, increasing mitochondrial reactive oxygen species (ROS) production and stimulating nuclear apoptosis.

Recently, the cytokine TNF-like weak inducer of apoptosis (TWEAK) and its receptor Fn14 have emerged as major effectors of disuse-induced atrophy. The expression of Fn14 is upregulated during conditions of muscle disuse,[54,65] as