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Review article

Mitochondrial biogenesis and fragmentation as regulators of protein degradation in striated muscles

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ABSTRACT

Mitochondria are dynamic organelles which adapt their morphology by fusion and fission events to the bioenergetic requirements of the cell. Cardiac and skeletal muscles are tissues with high energy demand and mitochondrial plasticity plays a key role in the homeostasis of these cells. Indeed, alterations in mitochondrial morphology, distribution and function are common features in catabolic conditions. Moreover, dysregulation of mitochondrial dynamics affects the signaling pathways that regulate muscle mass. This review discusses the recent findings of the role of mitochondrial fusion/fission and mitophagy in the control of proteolytic pathways. This article is part of a special issue entitled "Focus on Cardiac Metabolism".

Contents

1. Introduction

The mammalian heart is a hotspot of metabolic activity which consumes each day 100 times its own weight in ATP [1]. In contrast, skeletal muscle, accounts for almost 40% of total body mass and is a major site of metabolic activity. Mitochondria provide most of the ATP required for metabolic cell processes via oxidative phosphorylation. Striated muscles rapidly respond to metabolic challenges like exercise or inactivity, and the plasticity of mitochondria is one of the key factors in cellular metabolic adaptation [2]. Both, cardiac and skeletal muscles have a limited proliferative capacity, thus the regulation of their size is mostly based on protein turnover. Muscle atrophy is the result of an increase in protein breakdown causing a decrease in cell size mainly due to loss of organelles, cytoplasm and proteins. Muscle protein degradation is achieved mainly by two ATP-dependent proteolytic systems. The ubiquitin-proteasome system degrades predominantly myofibrillar proteins, whereas the autophagy-lysosome system removes dysfunctional organelles, protein aggregates as well

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as unfolded and toxic proteins [2]. Cardiac atrophy takes place under prolonged best rest, in patients suffering from anorexia or in patients with mechanical unloading of the heart. Similarly, skeletal muscle atrophy occurs in many conditions like disuse, denervation and immobilization as well as sepsis in debilitating diseases, like burn injury, cancer, AIDS, diabetes, heart and renal failure. Different signaling pathways regulate protein content and energy production in adult myofibers [2]. Cardiac and skeletal muscle growth is both regulated by the IGF/insulin/PI3K/AKT signaling pathway. The key mediators of the catabolic response during atrophy are the FoxO family of transcription factors, whose activity is suppressed during growth by AKT. Activation of FoxOs in cardiac and skeletal muscle promotes the expression of atrophy-related genes which include atrogin-1 [3,4] and MuRF-1 [3], two muscle-specific ubiquitin ligases, [5–7] and several autophagy-related genes such as LC3, GABARAP, Bnip3 and Ulk1 [7,8]. Therefore, FoxOs coordinate both major proteolytic systems of the cell, the autophagy–lysosome and the ubiquitin–proteasome. More than 10% of the atrophy-related genes are directly involved in energy production, amongst which various genes coding for enzymes important in glycolysis and oxidative phosphorylation are coordinately suppressed in atrophying muscles [9].

2. Cardiac and skeletal muscles have two distinct mitochondrial populations

A unique characteristic of the striated muscle, cardiac and skeletal, is the presence of two distinct populations of mitochondria that exist as a dynamic network. Mitochondria differ in their subcellular localization, morphology and biochemical properties and they constantly adapt to cellular needs. Subsarcolemmal (SS) mitochondria are located just underneath the sarcolemma and have a large, lamellar shape. In contrast, the intermyofibrillar (IMF) mitochondria are smaller, more compact, and located between the contractile filaments. These two spatially distinct mitochondrial populations possess precise functional and biochemical properties. SS mitochondria represent 20% of mitochondria within skeletal muscle, whereas IMF mitochondria account for the remaining 80% [10]. It has been suggested that SS mitochondria provide energy for membrane-related events like signaling and transport of ions and other substrates, while IMF mitochondria supply ATP for the interaction of myosin with actin leading to muscle contraction. The two populations show different biochemical properties of mitochondrial enzymes. In cardiac muscle the specific activity of many mitochondrial enzymes like succinate dehydrogenase and citrate synthase is greater in IMF than in SS mitochondria [11]. Both cardiac and skeletal muscle SS and IMF mitochondria have specific energetic requirements. In the heart, the rate of oxidative phosphorylation is 1.5 times higher in IMF mitochondria [11] with increased oxidative phosphorylation (OXPHOS) activity, compared to SS mitochondria [12]. In addition, cardiac IMF mitochondria present higher ATP synthase activity suggesting an increased ATP production capacity of IMF mitochondria supporting the ATP synthesis needed for muscle contraction [13]. Similarly, in skeletal muscles, state III respiration (ADP-stimulated respiration) is 2.3 to 2.8 fold greater in IMF than in SS mitochondria and IMF mitochondria show 3 fold greater ATP synthesis rates. Besides the bioenergetic differences, cardiac mitochondria have different cristae morphology that characterize each population. SS mitochondria present lamelliform cristae and IMF mitochondria have predominantly tubular cristae [14]. Mitochondrial populations are not only characterized by specific biochemical and functional properties but also by compositional differences between IMF and SS mitochondria. In skeletal muscle endogenous mitochondrial protein synthesis is 1.8-fold higher in IMF than in SS mitochondria. Moreover, lipid composition differs among mitochondrial types, with 60% higher cardiolipin content in SS, than in IMF mitochondria. IMF mitochondria compared to SS mitochondria have 3–4-fold greater protein import rates of the precursor proteins malate dehydrogenase (MDH) and ornithine-carbamyltransferase [15]. Furthermore, there are higher amounts of mitofilin, the mitochondrial-associated protein involved in the regulation of cristae morphology, in IMF mitochondria compared to SS mitochondria. This difference is more pronounced in cardiac tissue than in gastrocnemius muscle [13].

Cardiac SS and IMF mitochondria respond differently to disease. SS mitochondria are more prone to be susceptible to ischemia damage, due to an increased loss of cardiolipin, reduced oxidative phosphorylation and more ROS production. In contrast, cardiac IMF mitochondria have an increased susceptibility to aging and heart failure with a significant increase in oxidative stress markers [16]. In conclusion, SS and IMF mitochondria present a distribution-dependent phenotype with distinct biochemical and functional properties. For these reasons, the analyses of both mitochondrial populations should be considered in order to properly understand the contribution of mitochondrial dysfunction to atrophy/hypertrophy.

3. PGC1, the master gene of mitochondrial biogenesis, controls metabolic adaptations to energy status of muscle cells

Mitochondrial fusion, fission and mitochondrial turnover (the balance between mitochondrial biogenesis and degradation) are interconnected processes essential for mitochondrial quality control. Mitochondrial biogenesis is controlled by a family of coactivators including PGC-1α and PGC-1 β (peroxisome proliferator-activated receptor-γ coactivator-1α and β). PGC-1α interacts directly with transcriptional factors, recruits the histone acetyl transferase (HATs) and interacts with the transcriptional machinery [17]. Different transcription factors, including PPARs, nuclear respiratory factors (NRFs), myocyte enhancing factors (MEFs), estrogen-related receptor (ERR), forkhead box (FoxOs) and yin-yang (YY1) [18] are modulated by PGC1α. PGC1 family members are preferentially expressed in tissues with high-capacity mitochondrial function like heart, adipose tissue and slow-twitch skeletal muscle. PGC-1 α co-ordinately increases mitochondrial biogenesis as well as the uptake and utilization of substrates for energy production, being crucial in the maintenance of energy homeostasis. PGC-1α is a powerful coactivator of NRF-1and NRF-2 enhancing the expression of mitochondrial transcription factor A (Tfam), mitofusins and of different nuclear genes encoding mitochondrial proteins. Both Tfam and nuclear gene products are imported into mitochondria where they regulate the expression of mitochondrial proteins required for ATP synthesis [18]. It is well accepted that alterations in mitochondrial biogenesis contribute to cardiac pathologies. Accordingly, PGC-1α and PGC-1 β double knockout mice die shortly after birth due to heart failure. Interestingly, loss of function studies of single PGC-1α or PGC-1 β in mice showed no profound alterations in basal cardiac phenotype. Taken together, these results suggest that at least in the heart these two coactivators partially compensate for each other's loss in vivo and share a subset of target genes and functions [19]. In skeletal muscle, there is compelling evidence that PGC-1α is a key regulator of multiple pathways coordinating tissue adaptation to exercise. Transgenic mice that expressed PGC-1α specifically in fast glycolytic muscles show a switch to oxidative metabolism, increased mitochondrial content and improvements in endurance exercise [20]. However, muscle mass is not particularly affected in these transgenic animals, suggesting that mitochondrial biogenesis per se does not affect protein synthesis and muscle mass. Accordingly, PGC-1α/β overexpression does not affect protein synthesis in cultured myotube [21]. Skeletal muscles are composed of myofibers which differ in mitochondrial content, physiological properties and myosin composition. The relative distribution of the different myofiber types account for the functional properties of muscles. Muscles that rapidly generate a great force for a short time are mainly composed of glycolytic fibers, while muscles that produce discrete (lesser) force for prolonged periods are constituted mainly of