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Review

Skeletal muscle mitochondria: A major player in exercise, health and disease☆

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ABSTRACT

Background: Maintaining skeletal muscle mitochondrial content and function is important for sustained health throughout the lifespan. Exercise stimulates important key stress signals that control skeletal mitochondrial biogenesis and function. Perturbations in mitochondrial content and function can directly or indirectly impact skeletal muscle function and consequently whole-body health and wellbeing.

Scope of review: This review will describe the exercise-stimulated stress signals and molecular mechanisms positively regulating mitochondrial biogenesis and function. It will then discuss the major myopathies, neuromuscular diseases and conditions such as diabetes and ageing that have dysregulated mitochondrial function. Finally, the impact of exercise and potential pharmacological approaches to improve mitochondrial function in diseased populations will be discussed.

Major conclusions: Exercise activates key stress signals that positively impact major transcriptional pathways that transcribe genes involved in skeletal muscle mitochondrial biogenesis, fusion and metabolism. The positive impact of exercise is not limited to younger healthy adults but also benefits skeletal muscle from diseased populations and the elderly. Impaired mitochondrial function can directly influence skeletal muscle atrophy and contribute to the risk or severity of disease conditions. Pharmacological manipulation of exercise-induced pathways that increase skeletal muscle mitochondrial biogenesis and function in critically ill patients, where exercise may not be possible, may assist in the treatment of chronic disease.

General significance: This review highlights our understanding of how exercise positively impacts skeletal muscle mitochondrial biogenesis and function. Exercise not only improves skeletal muscle mitochondrial health but also enables us to identify molecular mechanisms that may be attractive targets for therapeutic manipulation. This article is part of a Special Issue entitled Frontiers of mitochondrial research.

1. Introduction

1.1. Benefits of exercise in diseased conditions

There is a plethora of research demonstrating that regular physical exercise has major health benefits for apparently healthy individuals (for reviews see [1,2]). Exercise training is known to positively affect most organ systems including the cardiovascular, neuroendocrine, respiratory and musculoskeletal systems. Epidemiological data clearly demonstrate that physical inactivity markedly increases the relative risk of several chronic diseases such as coronary artery disease, stroke, type 2 diabetes, osteoporosis and some cancers [3]. In addition, physical inactivity is associated with an increase in falls in the elderly, depression, anxiety and obesity [2,4]. Life-long physical activity is also associated with an increased median lifespan [5].

Perhaps unsurprisingly, regular exercise can also be beneficial for either alleviating or slowing the progression of many pre-existing diseases. For example, exercise training interventions reduce adipose tissue mass, improve glycaemic control and increase whole-body oxygen uptake capacity in obesity, metabolic syndrome, type 2 diabetes and heart disease patients [6,7]. Furthermore, aerobic exercise training

Abbreviations: AICAR, 5′aminoimidazole-4-carboxyamide-ribonucleoside; AD, Alzheimer's disease; ATF-2, activating transcription factor-2; AMPK, AMP-activated protein kinase; Bnip3, BCL2/adenovirus E1B 19 kDa interacting protein 3; BnipL/Nix, BCL2/adenovirus E1B 19 kDa interacting protein 3-like; CAMK, Ca^{2+}-calmodulin kinase; CREB, cAMP-response element-binding protein; coQ, coenzyme Q; COX1, cytochrome c-oxidase subunit 1; COX4, cytochrome c-oxidase subunit 4; COX2, cytochrome c-oxidase subunit 2; DMD, Duchenne muscular dystrophy; Drp1, dynamin related-protein 1; ERRα, oestrogen-related receptor alpha; FoXO3a, Forkhead-box protein O3a; Foxj3, Forkhead box j3; HDAC, histone deacetylase; htt, huntingtin; HD, Huntington's disease; IBM, inclusion-body myositis; miRNAs, microRNAs; mtDNA, mitochondrial DNA; Tfam, mitochondrial transcription factor A; Mef2c, myocyte enhancer factor 2c; MFN1, mitofusin 1; MFN2, mitofusin 2; mRNA, messenger RNA; Mul1, mitochondrial E3 ubiquitin-ligase 1; NO, nitric oxide; NF90, nuclear factor 90; NRF-1, nuclear respiratory factor 1; NRF-2, nuclear respiratory factor 2; OPA1, optic atrophy 1; PPAR, peroxisome proliferator-activated receptor; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha; PGC-1β, peroxisome proliferator-activated receptor-gamma coactivator-1 beta; p38 MAPK, p38 mitogen-activated protein kinase; Parkin, Parkinson protein 2, E3 ubiquitin protein ligase; PD, Parkinson's disease; PINK1, PTEN-induced putative kinase 1; PDK4, pyruvate dehydrogenase kinase, isoenzyme 4; rRNA, ribosomal RNA; ROS, reactive oxygen species; p62/SQSTM1, sequestosome 1; SIRT-1, sirtuin-1; SOD1, superoxide dismutase [Cu–Zn]; T2D, type 2 diabetes; tRNA, transfer RNA; TNFα, tumour necrosis factor alpha; 3'-UTR, three prime untranslated region

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improves endurance exercise capacity in patients with mitochondrial myopathies [8] and resistance exercise training can help attenuate sarcopenia [9]. Exercise may also be efficacious in lowering both the recurrence of some cancers and the associated cardiovascular disease risk in cancer patients [10]. It is well accepted that regular exercise can act to help prevent the onset of, or aid in the treatment of, many human diseases.

Given endurance training has positive health effects for most organ systems within the body, it's not surprising that beneficial adaptations to training, such as improved mitochondrial content are not confined to skeletal muscle, but also observed in several highly metabolic tissues such as the liver, brain, adipose tissue and kidney; for review see [11]. However, given skeletal muscle comprises ~40% of our body mass and is a highly metabolic tissue [12] this review will focus on skeletal muscle.

2. Exercise and mitochondrial biogenesis

Mitochondria are the primary controllers of cellular metabolism and form a reticular network within mammalian skeletal muscle [13]. This network is dynamic in nature, with the mitochondria joining and separating the network in processes termed fusion and fission, respectively. This dynamic process allows the mitochondria to share components, such as mitochondrial DNA (mtDNA), and to also degrade and remove damaged components, through a process called mitophagy. The mitochondrial content within the cell at any one time is a balance between mitochondrial biogenesis (synthesis) and its degradation via mitophagy [14]. Importantly, endurance training regulates many of these processes to ultimately increase or maintain a high level of mitochondrial content within skeletal muscle.

2.1. Exercise and transcriptional control

Endurance exercise potently stimulates increases in skeletal muscle mitochondrial content [15,16] and the increased mitochondrial biogenesis following exercise training is thought to be largely attributed to the cumulative effects of each acute bout of exercise [17,18]. Key steps in the exercise-induced mitochondrial biogenesis pathway in skeletal muscle following acute exercise (Fig. 1) involve p38 MAPK phosphorylating and activating transcription factor-2 (ATF-2), allowing the latter to bind to the cAMP-response element-binding protein (CREB) site on the peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1α (PGC-1α) promoter and induce PGC-1α gene expression [19]. Several hours following acute exercise the gene expression of skeletal muscle PGC-1α, nuclear respiratory factors 1 and 2 (NRF-1 and NRF-2) and mitochondrial transcription factor A (Tfam) is increased, as is NRF-1 and 2 DNA binding which are also involved in coordinating the exercise training response [19,20]. Acute exercise also activates AMP-activated protein kinase (AMPK) [20], which is known to phosphorylate and activate PGC-1α [21]. Additional regulation by PGC-1α also appears to involve its subcellular localisation. In skeletal muscle under resting conditions, most PGC-1α protein is localised in the cytosol, however following endurance exercise nuclear PGC-1α protein content increases, probably by translocation from the cytosol [22,23]. Recent evidence also suggests that following endurance exercise there is a translocation of PGC-1α to the mitochondria for co-activation of Tfam [22]. Further post-translational modification of PGC-1α can be achieved following its deacetylation by sirtuin-1 (SIRT-1), which is activated by increased NAD^+ levels [24]. However SIRT-1 is not necessary for exercise-induced mitochondrial biogenesis since muscle specific SIRT-1 knockout mice have normal increases in mitochondrial content following endurance training [25,26]. Although the mitochondria specific sirtuin-3 (SIRT-3) isoform is implicated in mitochondrial biogenesis, it doesn't appear to act directly on PGC-1α [27]. However, during acute exercise SIRT-3 is thought to reduce the energy consuming process of mitochondrial protein synthesis [28] and aid energy production via the deacetylation and activation of mitochondrial enzymes including ATP synthase [29], malate dehydrogenase [27] and isocitrate dehydrogenase [30].

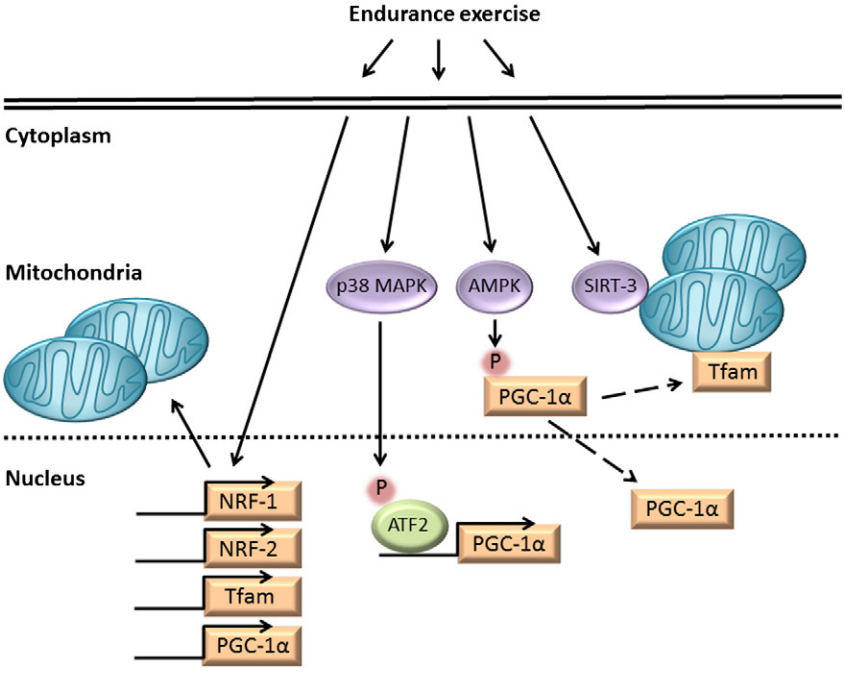

Fig. 1. Endurance exercise leads to mitochondrial biogenesis through transcriptional control. Endurance exercise training stimulates modifying factors (purple ovals) and transcription factors (green oval) to activate specific transcriptional regulators (orange rectangles) resulting in an increase in mitochondrial volume and biogenesis. Activation may occur via increased transcription (bent arrows) or via post-translational events such as phosphorylation (P). Exercise-induced PGC-1α activation can cause PGC-1α translocation (dashed arrows) into the nucleus and to the mitochondria to co-activate Tfam. p38 MAPK, p38 mitogen-activated protein kinase; AMPK, AMP-activated protein kinase; SIRT-3, sirtuin 3; ATF-2, activating transcription factor-2; NRF-1 and NRF-2, nuclear respiratory factors 1 and 2; Tfam, mitochondrial transcription factor A; and PGC-1α, peroxisome proliferator-activated receptor (PPAR)-gamma coactivator-1 alpha.

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