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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.
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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].

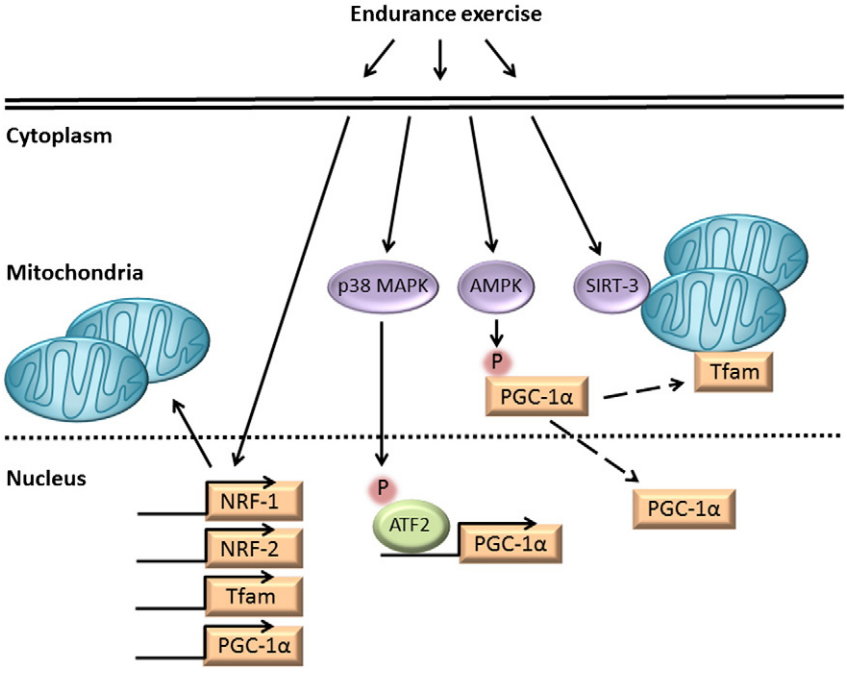

Fig. 1. Endurance exercise leads to mitochondrial biogenesis through transcriptional control. Endurance exercise training stimulates modifying factors (purple ovals) and transcription factors (green oval) to activate specific transcriptional regulators (orange rectangles) resulting in an increase in 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.

2.2. Exercise-induced stress signals controlling mitochondrial biogenesis

During exercise there is an increase in several molecular "stress" signals in skeletal muscle that appear to be responsible, at least in part, for the initial activation of mitochondrial biogenesis after exercise. These molecular signals include elevated levels of cytosolic Ca^{2+} [20,31], AMP [20], reactive oxygen species (ROS) [32] and possibly NAD^+ [24]. Increasing cytosolic Ca^{2+} levels in L6 muscle cells via caffeine treatment activates Ca^{2+}-calmodulin kinase (CAMK) and increases mitochondrial biogenesis markers including PGC-1α, Tfam, cytochrome c-oxidase (COX) and citrate synthase [20,31], whilst inhibitors of Ca^{2+} release abolish these caffeine effects [33]. The activation of muscle AMPK by 5′aminoimidazole-4-carboxyamide-ribonucleoside (AICAR) in L6 muscle cells also increases many of these mitochondrial biogenesis markers [20,34]. Increasing the ROS levels in skeletal muscle cells activates the redox sensitive kinases, AMPK and p38 MAPK, resulting in elevated PGC-1α with these ROS effects being blocked by co-treatment with antioxidant [32]. The role of NAD^+ as a molecular signal to activate skeletal muscle mitochondrial biogenesis during contraction is less clear with human studies being equivocal for whether skeletal muscle free NAD^+ levels increase or decrease during exercise (reviewed in [35]). Nitric oxide (NO) levels also increase in skeletal muscle during contraction [36] and NO donors increase skeletal muscle mitochondrial biogenesis [20,34,37], partly by activation of AMPK [20,34] and perhaps Ca^{2+}/CAMK [20]. However NO is not necessary for exercise-induced mitochondrial biogenesis, since pharmacological inhibition of NO synthase (NOS) during exercise does not attenuate PGC-1α mRNA following exercise [38]. Furthermore, the increase in mitochondrial biogenesis markers in response to acute exercise and exercise training is intact in neuronal NOS and endothelial NOS knock-out mice [39].

3. Mitophagy and mitochondrial health

3.1. Factors regulating mitophagy

Maintaining mitochondrial shape, size and networking and function requires the autophagic degradation and removal of damaged mitochondria via the process of mitophagy. Mitophagy is active in the basal state, during development and under stress conditions [40]. It is controlled by the balance between fission and fusion that involve mitofusin 1 (MFN1) and 2 (MFN2), optic atrophy 1 (OPA1), and dynamin related-protein 1 (Drp1), as well as established mitophagy proteins such as BCL2/adenovirus E1B 19 kDa interacting protein 3-like (BnipL/Nix), BCL2/adenovirus E1B 19 kDa interacting protein 3 (Bnip3), Parkinson protein 2, E3 ubiquitin protein ligase (Parkin), sequestosome 1 (p62/SQSTM1) and PTEN-induced putative kinase 1 (PINK1). The roles of these proteins have been reviewed recently [41]. Mitochondrial fission and the associated loss in membrane potential play a key role in orchestrating mitophagy [42,43]. The disruption in fission leads to an accumulation of damaged and dysfunctional mitochondria and is lethal in newborn humans [44] and mice [45]. MFN1 and MFN2 are located on the outer mitochondrial membrane. They are able to form homo- and hetero-oligomers that stimulate the tethering and the fusion of outer mitochondrial membranes from different mitochondria [46]. Recently, studies have shown that disruption of the mitochondrial network, a general term describing the content, shape and localisation of the mitochondria, plays a role in activating skeletal muscle atrophy programmes [47]. Deletion of both MFN1 and MFN2 in mouse skeletal muscle causes mitochondrial dysfunction, compensatory mitochondrial proliferation, mtDNA depletion, high levels of mtDNA mutations and muscle atrophy [48]. It has also been shown that mitochondrial fission activates an AMPK–Forkhead box O3a (FoXO3a) axis that induces muscle atrophy genes and muscle loss [47]. This may seem contradictory as exercise stimulates AMPK and the activation of PGC-1α [21]; the latter a known positive regulator of mitochondrial biogenesis and an inhibitor of FoXO3a and autophagic activity [49]. It appears that the type of upstream signal that activates AMPK may direct the downstream pathway it will target.

PGC-1α and PGC-1β regulate MFN1 and MFN2 in an ERRα-dependent manner in C2C12 myotubes [50,51]. In mice, the double deletion of skeletal muscle PGC-1α and PGC-1β results in a 60–70% reduction in *Mfn1* and *Mfn2* mRNA levels and mitochondrial dysfunction [52]. Skeletal muscle wasting is also associated with an increase in the mitochondrial E3 ubiquitin-ligase 1 (Mul1). Mul1 is a FoXO-regulated gene that increases mitochondrial fission via the ubiquitination and degradation of MFN2. The suppression of Mul1 protects against mitochondrial fission and partially rescues muscle wasting [53]. Nuclear factor 90 (NF90) participates in DNA/RNA binding and mice overexpressing NF90 have skeletal muscle atrophy and mitochondrial vacuolation caused by autophagocytosis [54]. This is accompanied by reduced expression levels of PGC-1α, PGC-1β and NRF-1 protein levels. Additionally, COX4, and COX2 mRNA levels are reduced. Whether NF90 acts as a direct transcriptional suppressor of PGC-1α/β remains to be established.

3.2. Exercise and mitophagy

Endurance exercise increases *MFN2* mRNA [55] and the phosphorylation of DRP1 [56] in human skeletal muscle. In contrast, reducing physical activity in rats by 3 weeks of hindlimb unloading decreases *Drp1* and *Mfn2* mRNA levels [57]. These results suggest that the level of muscle contraction controls not only mitochondrial biogenesis but also mitophagy.

4. Conditions with perturbations in mitochondrial content and function

4.1. Myopathies and neuromuscular disease

Mitochondrial diseases often manifest in skeletal muscle as an outcome of defects in the respiratory chain from enzyme deficiencies and structural alterations. These mitochondrial myopathies arise from inherited genetic mutations in the mtDNA or nuclear DNA (nDNA). For example, mutations may arise in the transfer RNA (tRNA) and ribosomal RNA (rRNA) genes, respiratory chain complexes and their subunits, COX proteins, and coenzyme Q (coQ) 10 impairing their enzyme activities. Defects may also occur in support or ancillary proteins such as cardiolipin, an acidic phospholipid in the inner mitochondrial membrane linked to individuals with Barth syndrome [58,59]. Finally, intergenomic signalling involving mutations in nDNA causing depletion and/or deletion of mtDNA, also contribute to mitochondrial myopathies. Comprehensive reviews of inherited genetic mutations are discussed elsewhere [60,61].

In addition to the aforementioned genetic mutations, mitochondrial myopathies may arise as secondary outcomes to other diseases and conditions; many of which are age-related including cancer cachexia, type 2 diabetes and sarcopenia. The latter two conditions will be discussed later in the review. Reduced mitochondrial biogenesis, remodelling and translation, altered homeostasis, disrupted mitochondrial unfolded protein response and impaired mitophagy may all be linked to mitochondrial dysfunction (reviewed in [62,63]). Such changes in the mitochondria manifest as reduced uncoupling and ATP production, oxidative stress, elevated cytosolic calcium levels and/or increased susceptibility to calcium signalling and enhanced apoptosis. These perturbations may be the consequence, or a stimulator of, altered mitochondrial fusion, fission and mitophagy that ultimately results in the breakdown and removal of mitochondrial, nuclear and cytoplasmic proteins.

Neuromuscular disorders, muscular dystrophies and the neurodegenerative diseases, Parkinson's (PD), Alzheimer's (AD) and Huntington's disease (HD) often display reduced mitochondrial functionality in skeletal muscle. Mutant huntingtin (htt) protein affects complex II/III function [64] and causes inadequate ATP production and oxidative respiration [65]. Decreased levels of PGC-1α, PGC-1β and oxidative muscle fibres

have been measured in HD subjects [66]. The mechanisms by which mutant htt affect mitochondrial function have not been clearly defined. However, animal studies have shown that mutant htt can interfere with mitochondrial trafficking proteins, reducing their transport and distribution. This occurs prior to htt aggregates forming in neuronal cells [67]. In skeletal muscle from individuals with PD, reduced complex I, and sometimes complexes II, III and IV activities have been detected [68–70]. Sporadic inclusion-body myositis (IBM) is a common age-related, degenerative muscle disease linked with mitochondrial abnormalities including COX-deficient muscle fibres and large-scale mtDNA deletions [71]. Its phenotype also bears strong resemblance to PD and AD pathologies with β amyloid protein, phosphorylated tau, α-synuclein and Parkin accumulation in the skeletal muscle (reviewed in [72]). Direct overexpression of the β amyloid precursor in IBM muscle results in mitochondrial structural abnormalities and reduced COX activity [73] whilst increased levels of Parkin can help protect against β amyloid effects and other mitochondrial toxins [74]. Other neuromuscular disorders and dystrophies linked to mitochondrial myopathies include collagen VI dystrophies [75,76], the autosomal recessive limb girdle muscular dystrophy, which arises through the cysteine protease calpain 3 deficiency [77], and Duchenne muscular dystrophy (DMD) [78–80]. The motor neuron disease amyotrophic lateral sclerosis (ALS), featuring neuromuscular junction deterioration, altered mitochondrial membrane potential and calcium signalling, decreased ATP levels and higher oxygen consumption as well as respiratory uncoupling in skeletal muscle [81–83] will be discussed in greater detail below. Disuse muscle atrophy from prolonged bed-rest, spaceflight, denervation and mechanical ventilation may lead to dysfunctional mitochondria [84–88]. Nutritional changes such as vitamin D deficiency [89] or drug-related side effects such as prolonged statin use [90] are other causative agents that also can result in mitochondrial myopathy. An overview of direct and secondary effects leading to mitochondrial myopathies and skeletal muscle wasting can be viewed in Fig. 2.

4.2. Motor neuron disease: amyotrophic lateral sclerosis (ALS)

ALS is a severe motor neuron disorder resulting in the progressive degeneration of upper and lower motor neurons, a decline in strength, severe muscle atrophy and respiratory insufficiency. It is the most common of the 5 motor neuron diseases. There is no cure for ALS and death occurs within 3–5 years after diagnosis [91]. The general consensus is that ALS is caused by motor neuron death, however the precise factor/s causing motor neuron degeneration in ALS remains equivocal [92–94]. Mitochondrial dysfunction is an important component in ALS pathogenesis [95]. Skeletal muscle of ALS patients and ALS G93A SOD1 mice presents severe atrophy [96] and has considerable mitochondrial disruption and dysfunction, indicated by NADH:CoQ oxidoreductase and COX deficiency [97,98], reduced mitochondrial DNA and reduced levels of the mitochondria manganese superoxide dismutase [97]. Neuronal degeneration in ALS G93A SOD1 mice is preceded by the degeneration of the neuromuscular junction [93] and muscle atrophy and degeneration [99]. This suggests that skeletal muscle degeneration and mitochondrial dysfunction may either occur more rapidly than in the brain or that a negative feedback may occur that contributes to neurodegeneration. Therefore, the pathogenesis and progression of ALS may involve perturbations in signalling molecules that are normally required for the healthy maintenance of skeletal muscle mitochondrial biogenesis and function as well as muscle mass. A significant reduction in PGC-1α and PGC-1β as well as key downstream targets such as ERRα, NRF-1, MFN1, MFN2 and COX4 has been observed in ALS patients [50], suggesting that perturbations in these molecular signalling proteins may play a role in the on-set or severity of the disease.

4.3. Type 2 diabetes

Skeletal muscle accounts for approximately 80% of insulin-stimulated glucose uptake and a key defect in the aetiology of type 2 diabetes (T2D) is the development of skeletal muscle insulin resistance

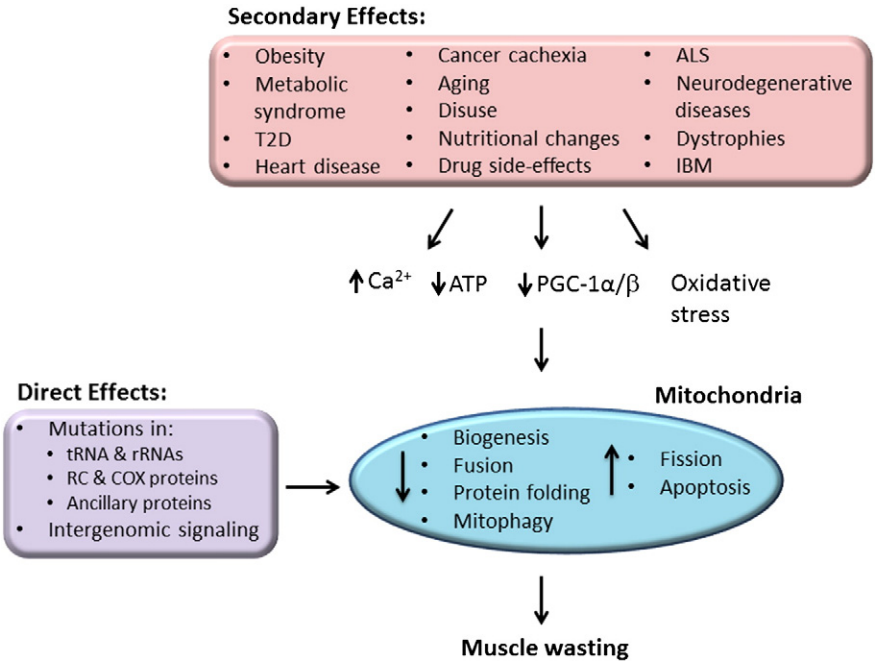

Fig. 2. Causes of mitochondrial myopathies leading to skeletal muscle wasting. Defects in the mitochondria (blue oval) can result in skeletal muscle wasting. These defects may arise directly from inherited genetic mutations (purple box) or potentially as secondary effects from multiple chronic and age-related diseases and conditions (pink box). Typically, elevated calcium and oxidative stress are evident along with reduced ATP levels and reduced PGC-1α and PGC-1β expressions and activities. T2D, type 2 diabetes; ALS, amyotrophic lateral sclerosis; IBM, inclusion body myositis; ATP, adenosine triphosphate; tRNA, transfer RNA; rRNA, ribosomal RNA; RC; respiratory chain.

[100]. It has been well documented that skeletal muscle of people with T2D has impaired mitochondrial function, with this being due to reduced mitochondrial content [101]. Furthermore, many of the regulatory components involved in mitochondrial biogenesis, such as PGC-1α and NRF-1 are also reduced in the skeletal muscle of people with T2D [101,102]. This led to the popular hypothesis that the reduction in mitochondrial content in T2D was causative in the development of skeletal insulin resistance, via the reduced capacity for lipid oxidation and subsequent accumulation of lipids that may impair insulin-stimulated glucose uptake [102,103]. However, it has been shown that the majority of studies which find reduced mitochondrial content in T2D are confounded by several factors, such as not controlling for reduced physical activity, which strongly impacts mitochondrial content [103,104]. Therefore, it appears that mitochondrial dysfunction, at least in humans with T2D, is secondary to the development of skeletal muscle insulin resistance.

Although mitochondrial dysfunction may not be causative in the development of skeletal muscle insulin resistance, it is still quite likely that improving skeletal muscle mitochondrial content and function could be causative in improving insulin resistance. Indeed, people with T2D respond to endurance training with normal increases in insulin sensitivity and skeletal muscle mitochondrial proteins [15,103,104]. Furthermore, studies that mimic the exercise training response via electrotransfection of PGC-1α into rat skeletal muscle result in increased PGC-1α protein content, mtDNA and mitochondrial enzyme activities with concomitant improvements in skeletal muscle insulin sensitivity [105].

Mitochondria are responsible for the majority of ROS production under basal (non-contraction) conditions [106], particularly in skeletal muscle [107], and it appears that mitochondrial ROS is responsible for the majority of excessive chronic ROS production in diabetes [108–111]. Inducing insulin resistance in human hepatoma cells with TNFα increases mitochondrial ROS levels [111], and high glucose levels in endothelial cells increase mitochondrial ROS levels in a dose dependent manner [112]. Furthermore, rats treated with the highly specific mitochondrial ROS inhibitor, SS31, and mice that overexpress the antioxidant enzyme, catalase, that is targeted specifically to the mitochondria do not develop insulin resistance when fed a high fat diet [113]. Skeletal muscle insulin resistance can also be reversed in rodent models by treatment with mitochondria specific antioxidants in vitro and in vivo [114].

The mechanism for reduced ROS levels following increased mitochondrial content (e.g. after exercise training) is thought to be due to the elevated mitochondrial content per unit of tissue (i.e. more efficient respiration) [108,109]. Indeed, increased mitochondrial content reduces oxygen consumption and mitochondrial membrane potential for an equivalent amount of ATP production and results in lower overall mitochondrial ROS production [108,109]. Importantly, high glucose levels in skeletal muscle cells [109] and endothelial cells [115], treatments known to induce insulin resistance, increase mitochondrial ROS levels and this can be reversed by increasing mitochondrial biogenesis and mitochondrial content [109,115]. Therefore, it is possible that a similar process may occur in diabetic skeletal muscle in response to exercise training. However, the aforementioned studies were performed in cell culture and it is not known if this also occurs in human or animal skeletal muscle.

4.4. Ageing

In old age, mitochondria appear abnormally rounded [116]. They are lower in density and a reduced mitochondrial DNA content is evident [117,118]. They have reduced activities of some enzymes, impaired respiration and demonstrate increased oxidative stress. It has been suggested that the increased production in ROS is a key factor contributing to the perturbations in mitochondrial morphology and DNA content and is a major contributor to the ageing process. Correlations between mitochondrial DNA mutations, impaired biogenetics and muscle wasting have been observed [119]. From a molecular perspective, AMPK activation as well as PGC-1α and MFN2 levels are reduced [120], whilst Fis1 [121] is increased in muscle from the elderly. A reduction in these signalling molecules would support impaired mitochondrial biogenesis, remodelling and function as well as contribute to the age-related decline in muscle mass. As exercise increases mitochondrial biogenesis and function in young and older subjects, maintaining physical activity through the lifespan may delay the on-set of age-related mitochondrial decline.

5. microRNAs and mitochondrial biogenesis and function

microRNAs (miRNAs) are small (~20–30 nucleotides) noncoding ribonucleic acids (RNAs) that inhibit protein translation or enhance messenger RNA (mRNA) degradation [122,123]. They have been observed to play a role in regulating numerous diseases including cancers, hepatitis C, heart disease, neurodegenerative disease and myopathies [124]. Recently, miRNAs have been observed to be present in the mitochondria and regulate mitochondrial biogenesis in the muscle tissue and cells.

A decrease in miR-494 occurs in C2C12 myoblasts during differentiation and is paralleled by an increase in mtDNA [125]. Reporter assay experiments revealed that the knockdown of miR-494 increased the activity and protein content of Tfam and Forkhead box j3 (Foxj3), a transcriptional regulator of Myocyte enhancer factor 2c (Mef2c) [126]. These observations were reversed following the overexpression of miR-494.

miRNAs are also able to translocate into the mitochondrial to regulate mitochondrial encoded genes. The nuclear encoded miR-181c is translocated to the mitochondria in cardiac myocytes [127]. miR-181c binds to the three prime untranslated region (3′UTR) of mt-COX1 and the overexpression of a miR-181c precursor results in a decrease in COX1 protein but not mRNA, suggesting that it acts as a translational regulator. The overexpression of miR-181c also increases mRNA and protein levels of COX1 and COX2 and alters mitochondrial function as shown by an elevation in oxygen consumption that is related to increased ROS production [127].

miR-484 represses Fis1 translation resulting in an inhibition of mitochondrial fission and apoptosis in cardiomyocytes and cancer cells [128]. It was also established that miR-484 is transactivated by Foxo3a. These results show that FoXo3a can have a cardioprotective role that is mediated via its increase in miR-484, which functions to attenuate mitochondrial fission and apoptosis. The role of miR-484 is yet to be established in skeletal muscle.

As mentioned earlier, PGC-1α positively regulates mitochondrial biogenesis and function via the induction and activation of several nuclear transcription factors, such as NRF-1 [129] and ERRα [130–132]. Using reporter assays we have recently demonstrated that miR-23a binds to the PGC-1α 3'-UTR to reduce PGC-1α reporter activity [50]. Additionally, transgenic overexpression of miR-23a in mice results in reduction in PGC-1α, cytochrome c and COX4 protein levels. Similarly, it was shown in C2C12 cells that overexpression and inhibition of miR-696 reduced and increased, respectively, PGC-1α protein levels [133]. This was also paralleled by the respective attenuation and increases in fatty acid oxidation and pyruvate dehydrogenase kinase, isoenzyme 4 (PDK4) and COX2 mRNA levels. However, whether miR-696 directly regulates PGC-1α, via binding to the PGC-1α 3′ UTR, has not yet been confirmed. The role of miRNAs in the control of mitochondrial biogenesis and function in health and disease is still emerging. As the field evolves it will significantly contribute to our understanding of mitochondrial function and potentially identify new potential therapeutic targets.

6. Current and potential approaches to restore mitochondrial function

As discussed earlier, the benefits of regular endurance exercise to reduce disease effects, particularly those associated with chronic diseases

may in part be due to positive effects on mitochondrial biogenesis and function. Whilst individuals with mitochondrial myopathies can display exercise intolerance [134], endurance training appears to help alleviate the ROS levels and oxidative stress associated with the myopathy [135]. The meta-analyses of microarray datasets revealed, for example, in both aged individuals and young DMD individuals, an enrichment of genes down-regulated by the PGC-1α transcription factor-binding partner ERRα [136]. Gene-replacement studies involving PGC-1α [137,138] and antioxidant enzymes such as catalase [139] in animal models of DMD improve mitochondrial function in muscle. Studies using mouse models of ALS demonstrate that enhanced PGC-1α levels sustain mitochondrial content and generation but were unable to extend life-span [140]. In vitro, higher mitochondrial content achieved through nitric oxide donor and AMPK agonist agents protects against apoptosis in myoblasts [141]. Pharmacological agents such as resveratrol, PPAR agonists, class I histone deacetylase (HDAC) inhibitors can, or are expected, to improve muscle mitochondrial function within chronic disease conditions through enhanced PGC-1α activity and signalling either alone or in combination with exercise [26]. Such studies highlight the importance and clinical interest to restore mitochondrial mass and oxidative capability in many of these muscle-related mitochondrial diseases and conditions. An overview of interventions currently being pursued is indicated in Fig. 3.

7. Conclusion

Mitochondria play a vital role in maintaining health through their regulation of substrate metabolism and energy production as well as their involvement in influencing skeletal muscle size and function. Perturbations in muscle mitochondrial biogenesis significantly contribute to the on-set and/or severity of various chronic diseases and to the numerous health issues that our ageing population faces. As mitochondria are highly sensitivity to contractile-initiated signals, physical activity and exercise play important roles in promoting the biogenesis and function of the mitochondria and as a consequence help maintain cellular and whole body health. For patients, where exercise is not possible due to extreme muscle wasting and dysfunction, pharmacological interventions that mimic exercise-induced muscle mitochondrial adaptations will play important roles in potentially returning muscle function to a level which enables exercise to be performed.

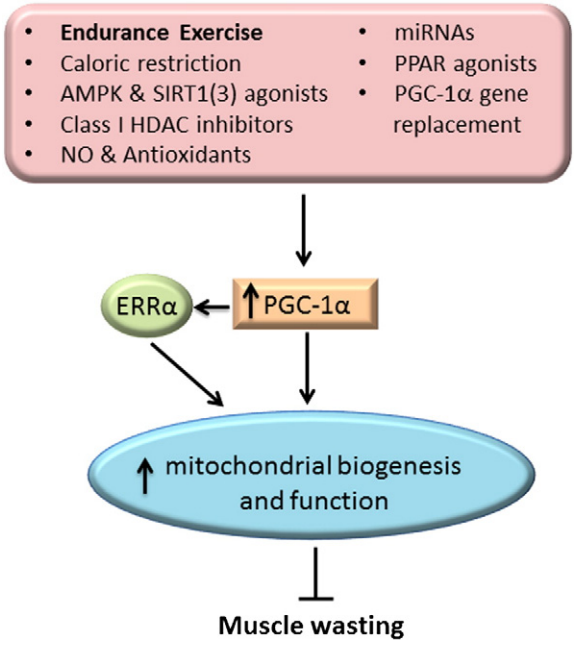

Fig. 3. Known and potential modes of intervention (pink box) to enhance PGC-1α (orange rectangle) and ERRα (green oval) functions to help increase mitochondrial biogenesis (blue oval) and block skeletal muscle wasting. HDAC, histone deacetylase; NO, nitric oxide; miRNAs, miroRNAs.

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