Regulation of Mitochondrial Biogenesis in Muscle by Endurance Exercise

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Abstract

Behavioural and hereditary conditions are known to decrease mitochondrial volume and function within skeletal muscle. This reduces endurance performance, and is manifest both at high- and low-intensity levels of exertion. A programme of regular endurance exercise, undertaken over a number of weeks, produces significant adaptations within skeletal muscle such that noticeable improvements in oxidative capacity are evident, and the related decline in endurance performance can be attenuated. Notwithstanding the important implications that this has for the highly trained endurance athlete, an improvement in mitochondrial volume and function through regular physical activity also endows the previously sedentary and/or aging population with an improved quality of life, and a greater functional independence. An understanding of the molecular and cellular mechanisms that govern the increases in mitochondrial volume with repeated bouts of exercise can provide insights into possible therapeutic interventions to care for those with mitochondrially-based diseases, and those unable to withstand regular physical activity. This review focuses on the recent developments in the molecular aspects of mitochondrial biogenesis in chronically exercising muscle. Specifically, we discuss the initial signalling events triggered by muscle contraction, the activation of transcription factors involved in both nuclear and mitochondrial DNA transcription, as well as the post-translational import mechanisms required for mitochondrial biogenesis. We consider the importance and relevance of chronic physical activity in the induction of mitochondrial biogenesis, with particular emphasis on how an endurance training programme could positively affect the age-related decline in mitochondrial content and delay the progression of age- and physical inactivity-related diseases.
It is a very interesting time to be studying mitochondrial structure and function, particularly in skeletal muscle. Mitochondria are not only vital for cellular energy production, but they are also known to participate in cell signalling events leading to apoptosis (programmed cell death). Moreover, it is now also established that mitochondrial dysfunction, brought about by either nuclear or mitochondrial DNA (mtDNA) mutations, can lead to a wide variety of pathophysiological conditions affecting the nervous system, the heart and/or skeletal muscle. Furthermore, under conditions of skeletal muscle disuse (e.g. microgravity, denervation, immobilisation, sedentary lifestyle, aging), mitochondrial content is diminished. This compromises energy production. Fortunately, skeletal muscle is highly ‘plastic’, a term popularised by Dirk Pette\(^1\) to describe the remarkable capability of this tissue to alter its gene expression profile and phenotype in response to changes in functional demand imposed by muscle use, disuse, and to developmental or neural influences. This adaptability permits us to be optimistic about the role of training in ameliorating the processes which lead to cell death, and myonuclear decay, or in reversing the pathophysiology of mitochondrial disease in skeletal muscle. To date, however, this still remains to be established. This review will focus on the cellular mechanisms involved in mitochondrial biogenesis as produced by experimental models of endurance exercise. An appreciation of these mechanisms will help us understand the basis for the use of exercise in improving the quality of life in patients with mitochondrial disease.

### 1. Muscle Fibre Types and Mitochondrial Content

Skeletal muscle is categorised into three classes of fibres on the basis of their metabolic and contractile properties. In humans, the most common method of classification is based on the myosin heavy chain isoform, and consists of the slow-twitch type I fibres, and the fast-twitch type IIA and IIX (formerly classified as type IIb) fibres. Each of these muscle fibre types has varying steady-state mitochondrial contents, which contribute to their endurance capacity. In humans, the type I fibres have the largest volume fraction of mitochondria, followed by the type IIA and type IIX fibres, respectively,\(^2\) although considerable overlap exists.\(^3\) This wide range of mitochondrial content among fibre types clearly indicates the independent regulation of myosin heavy chain expression and mitochondrial biogenesis. Provided that these different muscle fibres are recruited, repeated bouts of exercise in the form of endurance training can induce increases in the mitochondrial content in all three muscle fibres,\(^2,4,5\) resulting in the major functional adaptation which is an improvement in fatigue resistance (figure 1). This occurs without any substantial change in myosin heavy chain composition within the trained muscle.

### 2. Obligatory Events in Mitochondrial Biogenesis

The expansion of the mitochondrial reticulum in muscle cells as a result of endurance training involves a complex series of events that begins with the first bout of exercise within a given training programme. The morphological manifestation of the accumulation of multiple acute exercise bouts, performed 3–4 times per week over 4–8 weeks, is mitochondrial biogenesis. This can be visualised by electron microscopy as an increase in mitochondrial content in both subsarcolemmal and intermyofibrillar regions of each muscle fibre that has been recruited during the exercise bouts.\(^6,8\) The intervening time between the onset of the first exercise bout and mitochondrial biogenesis is filled with intermittent, contraction-induced signalling events, which may be attenuated in amplitude\(^9\) as the training period extends. These signals are known to activate protein kinases and phosphatases that modify the activity of transcription factors acting in the nucleus, as well as...
mRNA stability factors acting within the cytosol resulting in an increase in the mRNA expression of nuclear-encoded mitochondrial proteins (NEMPs). The translated NEMPs are then appropriately chaperoned to the mitochondria and imported into the different organelle compartments, such as the matrix space, the inner or outer membranes.

A small subgroup of NEMPs comprises transcription factors that act directly on mtDNA to increase the mRNA expression of mitochondrial gene products, as well as mtDNA copy number. mtDNA is small by genomic standards (16kb), but it is essential because it encodes 13 proteins that are vital for the function of the electron transport chain. Since there are no introns and few non-coding regions in mtDNA, point mutations in mtDNA have severe consequences, leading to a dysfunctional protein (or proteins) involved in mitochondrial respiration.[10]

One of the most fascinating aspects of mitochondrial physiology is the fact that biogenesis requires: (i) the integration of a multitude of contraction-induced cellular signals; and (ii) the cooperative and timely interaction between the nuclear and mitochondrial genomes to produce an organelle that is functional in cellular adenosine triphosphate (ATP) provision.

2.1 Contraction-Induced Cell Signalling

The initial cellular signals associated with the onset of muscle activity that ultimately lead to mitochondrial biogenesis are beginning to be defined. These signals are triggered with each bout of contractile activity, and they activate transcription factors that promote the transcription of nuclear and mitochondrial genes (figure 2). There is strong evidence for the participation of intracellular Ca\textsuperscript{2+} and ATP turnover as the initial triggers brought about by exercise. However, the evidence for this is indirect, as the experimental models used to produce mitochondrial biogenesis do not typically involve exercise, but rather utilise other experimental models in which changes in ATP turnover or Ca\textsuperscript{2+} levels can be elicited in a dramatic fashion.

2.1.1 Adenosine Triphosphate Turnover

Exercise increases the rate of ATP turnover within muscle cells. This alters the ATP/free adenosine

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**Fig. 1.** Relationship of changes in mitochondrial content to alterations in endurance performance. Increases in mitochondrial enzyme activity due to chronic muscle use (e.g. chronic stimulation, endurance training) lead to improvements in endurance performance. Decrements in mitochondrial enzyme activity brought about by chronic disuse (e.g. denervation, immobilisation, physical inactivity) result in decreases in endurance performance. The data indicate that a strong relationship exists over an approximate 6-fold range in enzyme activity.[6,7]
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Mitochondrial diphosphate ratio and stimulates muscle metabolic rate. A similar change in energy status can also be achieved through the uncoupling of the mitochondrial respiratory chain,[11] by mtDNA depletion,[12] with iron deficiency,[13] by disruption of the creatine phosphokinase system,[14] or with prolonged use of the agent β-guanidinopropionic acid (β-GPA).[15]

Changes in cellular energy status associated with these adaptations have been linked to the activation of adenosine monophosphate-activated protein kinase (AMPK).[16] AMPK can be activated physiologically by decreases in phosphocreatine and ATP, and pharmacologically using the adenosine analog 5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside (AICAR), which is frequently used to mimic the effects of chronic exercise. AMPK activation via AICAR treatment of animals led to an increase in mitochondrial enzyme activities,[17] while AMPK activation using chronic β-GPA was shown to increase the expression of downstream targets, including cytochrome C and δ-aminolevulinic acid synthase (ALAS).[16] Cytochrome C is an important component of the electron transport chain, while ALAS is the rate-limiting enzyme in the synthesis of heme. This effect was likely mediated by an increase in the binding of the transcription factor nuclear respiratory factor-1 (NRF-1; see section 2.2) to a DNA sequence located within the promoter regions of these genes. Interestingly, increases in NRF-1 DNA binding and its downstream effects were also shown to occur in cells overexpressing uncoupling protein-1.[11] Finally, mtDNA depletion also leads to a reduction in cellular energy status similar to the conditions described above. This provoked an increase in intracellular Ca2+, ultimately leading to the upregulation of nuclear genes including cytochrome C oxidase subunit Vb mRNA.[12]

2.1.2 Calcium

As a result of α-motoneuron-induced depolarisation, Ca2+ is released from the sarcoplasmic reticulum. Ca2+ then plays a crucial role in mediating

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Fig. 2. Mitochondrial content within skeletal muscle can be reduced in mitochondrial myopathies, aging, or by low physical activity. This leads to decreases in endurance performance (see text and figure 1). Time- and intensity-dependent increases in daily physical activity influence mitochondrial volume and function such that deficiencies in energy production can be ameliorated, and increases in endurance performance can be re-established. At the molecular level, the signals that are triggered with each bout of exercise likely arise from a combination of rapid ATP turnover and altered calcium levels that, when sustained for sufficient durations and amplitude result in mitochondrial proliferation. These signals activate signal transduction cascades, resulting in changes in TF activity and the upregulation of diverse genes, including those involved in organelle synthesis and oxidative phosphorylation. The recent identification of PGC-1 has enhanced our understanding of the mechanisms underlying the formation of the organelle. The precise role of PGC-1 in coordinating contractile activity-induced mitochondrial biogenesis is currently under investigation. This enhanced organelle biogenesis provides a negative feedback mechanism to reverse the initial deficit in mitochondrial function and content. ADP = adenosine diphosphate; ATP = adenosine triphosphate; PGC-1 = PPAR-γ coactivator-1; PPAR = peroxisome proliferator-activated receptor; TF = transcription factor.
muscle contraction, and it also acts as an important second messenger to couple the initial electrical event to subsequent alterations in gene expression. Changes in intracellular Ca\(^{2+}\) levels modify the activities of calcium-dependent protein kinases and phosphatases. These include Ca\(^{2+}\)/calmodulin-dependent protein kinases, protein kinase C, and calcineurin, among others. An increase in the mRNA and protein expression of mitochondrial enzymes, as well as the electron transport chain component cytochrome C can be produced in muscle cells using continuous exposure of cells to the calcium ionophore A23187 to artificially elevate intracellular Ca\(^{2+}\) concentrations. In addition, the intermittent exposure of muscle cells to the Ca\(^{2+}\) ionophore ionomycin, or to caffeine, which stimulates the release of Ca\(^{2+}\) from the sarcoplasmic reticulum, also produces mitochondrial biogenesis. Finally, in transgenic mice, selectively expressing a constitutively active form of Ca\(^{2+}\)/calmodulin-dependent protein kinase IV in muscle, an increase in mtDNA copy number as well as the expression of a wide variety of genes involved in mitochondrial biogenesis occurred. These included gene products directly involved in oxidative phosphorylation, fatty acid metabolism, and also the important coactivator termed peroxisome proliferator-activated receptor (PPAR)-γ coactivator-1 (PGC-1). These data imply that Ca\(^{2+}\) released from the sarcoplasmic reticulum during each action potential could serve as an important second messenger leading to mitochondrial biogenesis. However, the amplitude, duration and temporal pattern of the Ca\(^{2+}\) signals needed to provoke such changes need to be established in the physiological setting of muscle contraction.

In summary, the work to date suggests that alterations in the energy status of the cell brought about by contractile activity can simultaneously activate AMPK, as well as modify intracellular Ca\(^{2+}\) levels. It seems likely that both of these signalling pathways are instrumental in producing mitochondrial biogenesis.

2.2 Transcription Factors Involved in Mitochondrial Biogenesis

A subsequent effect of the contractile activity-mediated activation of signal transduction cascades involves the post-translational phosphorylation/dephosphorylation of transcription factors. This can then mediate the upregulation of nuclear and mitochondrial gene expression (figure 2). A number of transcription factors have been implicated in mitochondrial biogenesis. These include NRF-1 and -2, PPAR-α and -γ, specificity protein-1 (Sp1) and the products of the immediate early genes, c-jun and c-fos. This variety of transcription factors is important given the large differences in regulatory DNA sequences that are found within the promoter regions of nuclear genes encoding mitochondrial proteins. It therefore stands to reason that a single transcription factor could not function unilaterally to induce mitochondrial biogenesis. Nonetheless, evidence to date has implicated NRF-1 as a particularly important component in the process of contractile activity-induced mitochondrial biogenesis. This is mainly because NRF-1 expression increases in response to contractile activity in cell culture and as a result of exercise in vivo. Moreover, its induction precedes the expression of cytochrome C, an NRF-1 target gene. Finally, NRF-1 also transcriptionally activates mitochondrial transcription factor A (Tfam), a DNA binding protein largely responsible for regulating mtDNA transcription and replication (see next paragraph). However, while NRF-1 appears to play an important role, not all nuclear genes encoding mitochondrial proteins contain putative NRF-1 DNA binding sites. Thus, further work led to the discovery of PGC-1. This protein has emerged as an important regulator of fibre type determination and mitochondrial biogenesis in skeletal muscle (figure 2). PGC-1 mRNA
is increased in muscle by swimming exercise, and PGC-1 protein is increased by contractile activity, as well as thyroid hormone treatment, consistent with a role for this coactivator in mediating mitochondrial biogenesis.

Overexpression studies in animals and in cell culture have shown that PGC-1 induces the expression of a variety of genes within the nuclear genome. This effect appears to be mediated by its strong coactivation of NRF-1, and possibly other transcription factors, which leads to increased levels of several NEMPs, including Tfam. The effect on Tfam is important, since this protein regulates the transcription and replication of mtDNA, leading to mitochondrial biogenesis and an increase in cellular oxygen consumption in muscle, heart and adipocytes. However, this function of Tfam on mtDNA transcription and replication is also dependent on its import into the mitochondrion, another important step in the regulation of mitochondrial biogenesis.

2.3 Mitochondrial Protein Import

Given the limited coding capacity of mtDNA (i.e. 13 proteins), most of the proteins found within mitochondria are derived from the nuclear genome. Mitochondrial biogenesis, therefore, is dependent not only on the import of Tfam, but also on the incorporation of many nuclear-encoded matrix and membrane precursor proteins into the organelle. This occurs via the multi-subunit complex known as the protein import machinery, which is comprised of the translocases of the outer membrane (Toms) and the translocases of the inner membrane (Tims) [figure 3]. Mitochondrially-destined proteins are targeted to the organelle import site via the molecular chaperones cytosolic heat shock protein 70 (HSP70), mitochondrial import stimulation factor and possibly Tom34. Protein import into the mitochondria is initiated by receptors found in the Tom complex, which then transfers the precursor protein to the Tim proteins. The precursor protein is then

![Fig. 3. Overview of the mitochondrial protein import pathway and the targeting of a matrix protein.](image-url)
Skeletal muscle contains distinct subfractions of mitochondria that are found within different cellular compartments. Subsarcolemmal mitochondria are located immediately below the surface of the sarcolemma, while intermyofibrillar mitochondria are found intermingled within the myofibrils.\(^{[8,36]}\) It is surmised that these subfractions have different functional roles within the muscle cell, likely due to differences in subcellular location, and also due to their distinct biochemical differences. These can be attributed, in part, to differential rates of protein import.\(^{[37]}\) Protein import into mitochondrial subfractions is closely related to their distinct rates of oxygen consumption and ATP synthesis, the latter of which is important for protein unfolding in the cytosol, translocation across the membrane, and the final refolding of the protein within the matrix.

Chronic exercise affects the rate of import into mitochondria (figure 3). Using a model of chronic electrical stimulation, it has been shown that contractile activity induces increases in the expression of multiple protein import machinery components.\(^{[6,38,39]}\) Most importantly, these include the outer membrane receptor Tom20, the inner membrane phospholipid cardiolipin, the matrix mtHSP70, which pulls the precursor protein inside, and the cytosolic chaperones HSP70 and mitochondrial import stimulation factor. Accelerations in the rate of protein import into the matrix occurred coincident with these changes. Thus, the adaptive response of protein import machinery components appears to be an important aspect of mitochondrial biogenesis that occurs with contractile activity. This is physiologically relevant, because it implies that the import process will exhibit a greater sensitivity for import at any given concentration of cytosolic precursor protein produced by translation. A similar adaptation in protein import occurs with thyroid hormone-induced mitochondrial biogenesis in the heart.\(^{[40]}\) These adaptations are particularly relevant now, given recent studies demonstrating that defects in protein import can lead to a number of pathological conditions.\(^{[41,42]}\) Therefore, these studies indicate the potential of regular exercise (or thyroid hormone treatment) to ameliorate defects that may arise in the protein import process.

### 2.4 mtDNA and Chronic Contractile Activity

As noted at the beginning of section 2, mitochondria contain their own circular 16 kilobase mtDNA encoding 13 protein, 22 tRNA and two rRNA genes. In order to transcribe and replicate this genome, a process that is vital for mitochondrial biogenesis, the import of nuclear-encoded mtDNA maintenance proteins is required. These proteins include Tfam, as well as mtRNA polymerase, DNA polymerase, single-stranded binding protein (mtSSB), RNA processing enzymes\(^{[43]}\) and mitochondrial transcription factor B.\(^{[44]}\) Chronic contractile activity is known to induce an increase in mtDNA copy number, as well as an increase in the transcription of mtDNA genes.\(^{[45,46]}\) This is facilitated by the rapid and early increase in Tfam mRNA and protein expression, followed by an accelerated rate of import and Tfam/mtDNA binding.\(^{[47]}\) An increase in Tfam protein has also been observed in response to endurance training in humans.\(^{[48]}\) In addition, contractile activity also increases the expression of RNA processing enzyme subunits\(^{[49]}\) and mtSSB, but not DNA polymerase.\(^{[50]}\) These changes are likely responsible for the observed coordination between nuclear and mitochondrial mRNA responses to chronic contractile activity.\(^{[46,51]}\) This may be important to maintain the correct stoichiometry between nuclear- and mitochondrially-encoded subunits during the assembly of protein complexes within mitochondria. These changes may conceivably represent the most important contractile activity-induced adaptations within the organelle, since no effect on intramitochondrial protein synthesis or degradation have been observed,\(^{[52]}\) although protein...
synthesis is a definite requirement for the mitochondrial adaptations to contractile activity.[53]

The extent to which mitochondrial biogenesis will occur in human muscle depends on the intensity, duration and frequency of the training programme, and perhaps the initial mitochondrial content within the muscle, leading to significant improvements in endurance capacity. The functional consequences of physical activity become even more important when we consider: (i) the societal tendency towards inactivity; (ii) the age-related decline in oxidative capacity; and (iii) the involvement of mitochondria in the progression of disease.

3. Mitochondrial Biogenesis, Aging and Disease

A significant loss in the number of muscle fibres occurs with age. This is defined as sarcopenia, and along with significant muscle atrophy, demonstrable biochemical and morphological abnormalities also occur.[54] Some of these age-related alterations could be attributable to mitochondrial dysfunction. Mitochondrial enzyme activities and rates of intra-organellar protein synthesis are known to decline with age.[55,56] Aged skeletal muscle tissue from a variety of species show a greater number of fibres with cytochrome C oxidase deficiency, along with increased succinate dehydrogenase activity.[57-60] These histological changes are similar to the 'ragged red fibres' typically observed in mitochondrial myopathy patients,[61,62] which result from an abnormal proliferation of subsarcolemmal mitochondria. This represents the most common morphological change associated with impaired oxidative phosphorylation[63,64] as a result of mtDNA defects. While it is known that endurance training can ameliorate the decline in enzyme activities evident in older individuals,[65-67] the effect of exercise-induced mitochondrial biogenesis on age-related changes in mtDNA content, mitochondrial protein synthesis, reactive oxygen species (ROS) production or apoptosis, is currently unknown.

A decline in the oxidative capacity of muscle with age could be related to the augmented production of ROS. Approximately 1–2% of the oxygen within a cell is converted to ROS, the basal production of which increases with aging in tissues of many mammals and humans.[68] ROS compromise the integrity of macromolecules such as mtDNA housed within the mitochondria, and lead to organelle dysfunction. mtDNA is particularly vulnerable to ROS because: (i) mtDNA is located in close proximity to the electron transport chain; (ii) mtDNA lacks the protective sheath of histones compared with nuclear DNA; and (iii) mitochondria have an insufficient repair system for mtDNA mutations. This can develop into a feed-forward cycle of progressive deterioration, since defects of oxidative phosphorylation brought about by mtDNA mutations will further exacerbate ROS production. Interestingly, coincident increases in mtDNA content, the frequency of mtDNA mutations, and elevated levels of Tfam have been reported as a function of age in healthy humans.[69,70]

The age-related increases in ROS production have the potential to activate programmed cell death, or apoptosis,[71,72] a process that results from a cascade of events initiated by the release of cytochrome C and other pro-apoptotic factors from mitochondria. An increased incidence of apoptosis within aged rat skeletal muscle has recently been documented,[73] although it remains to be determined whether this is ROS-mediated. In addition, while it is established that various forms of exercise training can produce an increase in mitochondrial content in aged individuals,[65-67,74] it is not known whether this can exert a beneficial, or detrimental effect on the progression of aged muscle toward apoptosis or myonuclear destruction.

Very limited research has involved studying the effect of training in patients with known mitochon-
drial diseases; however, the results are promising. Noticeable improvements in levels of respiratory enzymes in mitochondrial myopathy patients with mtDNA defects were a consequence of aerobic training.[75] This change led to an improvement in work capacity. Further, increases in the relative proportion of wild type mtDNA copy number were observed in a case study as a result of resistance training.[76] These promising outcomes warrant further investigation, particularly when corrected for age. However, the compensatory events involved in the training adaptation, in the face of a mutant mtDNA fraction, remain to be determined. Studies using different training regimens in a variety of patients are required to establish regular exercise as a valuable approach to the treatment of patients with mitochondrial disorders.

4. Conclusions

Initial cellular disturbances that are triggered by contractile activity appear to involve changes in intracellular Ca²⁺ concentrations and accelerations of ATP turnover. These changes result in the activation of signal transduction cascades, the activation of important transcription factors, followed by the increased expression of nuclear and mitochondrial gene expression. The coordination of these responses results in mitochondrial biogenesis. While the precise details of the specific pathways involved in mitochondrial biogenesis in skeletal muscle are not yet clearly understood, the benefits of regular exercise are undisputed.

Chronic exercise is known to induce increases in mitochondrial volume and function, from which we derive a greater work capacity and an improved resistance to fatigue. Furthermore, chronic muscle use can also be used to reverse the trend toward the decrease in mitochondrial content brought about by disuse (figure 1 and figure 2). Thus, under circumstances in which mitochondrial content is compromised, such as in some mitochondrial myopathies or in age- and physical inactivity-related diseases, the plasticity of mitochondrial phenotype and content within muscle by exercise can likely be viewed as a highly favourable consequence. Further elucidation of the molecular mechanisms involved in mitochondrial biogenesis may be important in the future to identify potential alternative therapeutic interventions in patients in which even small amounts of physical activity cannot be tolerated. It is clear, however, that the full spectrum of exercise-associated physiological (i.e. central and peripheral cardiovascular, metabolic, muscular and hormonal) and psychological benefits will never be acquired via treatments other than exercise itself.

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