Implications of exercise training in mtDNA defects—use it or lose it?

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Abstract

Whether regular exercise is beneficial or should be avoided is a question currently unsettled in patients with heteroplasmic mitochondrial DNA (mtDNA) disorders of skeletal muscle. Detrimental effects of habitual physical inactivity superimposed upon impaired mitochondrial oxidative phosphorylation may contribute to varying degrees of exercise intolerance in these patients. Endurance exercise training is widely known to improve exercise capacity in healthy subjects and various chronic-disease patient populations. Although we have shown that beneficial physiological and biochemical responses to training increase exercise tolerance in patients with mtDNA defects, knowledge of the muscle adaptive response to endurance training within the setting of mitochondrial heteroplasmy remains limited. In order to determine advisability of endurance training as therapy, it remains to be established whether potential endurance training-induced increases in mutant mtDNA levels may be offset by increases in absolute wild-type mtDNA levels, and whether chronic inactivity leads to a selective down-regulation of wild-type mtDNA. Resistance training utilizes a different adaptive exercise approach to induce the transfer of normal mitochondrial templates from satellite cells to mature muscle fibers of patients with sporadic mtDNA disorders. The efficacy and safety of this approach needs to be further established. Our current inability to clearly advise patients to “use it or lose it” underscores the immediate urgency of studying the effects of exercise on skeletal muscle of patients with heteroplasmic mtDNA defects.

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1. Introduction

Mitochondrial electron transport chain defects due to heteroplasmic, mitochondrial DNA (mtDNA) mutations are common and becoming increasingly recognized with advances in molecular diagnostics. Exercise intolerance is a common and often disabling manifestation of muscle involvement in mitochondrial disease. With the current lack of effective treatment for mitochondrial myopathies, we have focused on the possibility that muscle adaptation to chronic exercise (i.e. exercise training) might improve mitochondrial respiratory chain function and hence, overall exercise capacity in adult patients with mtDNA mutations. This review will cover the rationale underlying the use of two different modes of exercise training, endurance and resistance, as treatment approaches for patients with mtDNA disorders and present studies in support of their efficacy.

Significant physiological benefits of endurance training have been detected in mitochondrial myopathy including consistent improvement in work and oxidative capacity. However, the possibility that endurance training may result in an increased proportion of mutant relative to wild-type mtDNA in patients with heteroplasmic mtDNA mutations has raised the specter that, despite significant functional improvements, training might have long-term deleterious effects [1]. This consideration, combined with a complete absence of information on the effects of physical inactivity...
upon relative levels of mutant versus wild-type mtDNA, has resulted in a management crisis for mitochondrial myopathy patients in which the basic question of whether exercise should be encouraged or avoided cannot currently be answered.

The exciting potential of physiological gene-shifting through resistance exercise training in patients with sporadic mtDNA mutations will also be reviewed. The aim in the very near future is to provide centers managing patients with mitochondrial disease with practical guidelines relating the type and degree of exercise to the nature of mtDNA mutation.

2. mtDNA mutations—effects on exercise capacity

Exercise intolerance is characterized by the development of undue fatigue at relatively low levels of exertion and can be associated with fatigue and weakness of active muscles, lactic acidosis, tachycardia, and dyspnea. Clinically, the degree of exercise intolerance in patients with mtDNA defects can vary from mild to debilitating, but in most instances, the performance of many activities of daily living (i.e. climbing stairs, grocery shopping, vacuuming, walking) is limited by low endurance. Loss of muscle mass and fixed weakness may also contribute to functional limitations in patients with mtDNA mutations.

Exercise-related symptoms may cause patients with mtDNA defects to adopt a sedentary lifestyle. Habitual physical inactivity in healthy humans results in deconditioning which is associated with decreases in mitochondrial numbers and respiratory chain activity in skeletal muscle as well as reduced cardiovascular capacity. We have postulated that habitual inactivity in mitochondrial myopathy patients may also lead to a decrease in levels of functional mitochondria with a further restriction of the capacity of muscle for oxidative phosphorylation. Thus, habitual inactivity and resulting deconditioning could magnify functional limitations and set in motion a vicious cycle of progressively worsening exercise intolerance (Fig. 1).

3. Physiological measures of exercise capacity

The degree of exercise intolerance as well as the potential contribution of deconditioning versus mitochondrial oxidative impairment to reduced endurance can be quantified in an exercise laboratory by measuring peak oxygen utilization and the physiological components of oxygen utilization, i.e. oxygen delivery (cardiac output, Q) and oxygen extraction (systemic arterio-venous oxygen difference, a-vO2 diff). Aerobic fitness is typically measured as maximal oxygen uptake (VO2 max) and used to reflect peak capacity for aerobic energy production during dynamic exercise. According to the Fick equation, VO2=Q×a-vO2 diff. This signifies that VO2 is the product of, and determined by, the cardiovascular capacity to deliver oxygen (ultimately dependent upon peak cardiac output, Q) and muscle metabolic capacity for extraction of available oxygen (dependent primarily upon muscle mitochondrial capacity for oxidative phosphorylation) [2]. In healthy individuals, maximal VO2 and hence aerobic performance during large muscle exercise (e.g. running, cycling), is limited by the capacity of the circulation to deliver oxygen to contracting muscles. Cardiac output is tightly coupled to the level of oxygen use during exercise, normally increasing by 5 l per liter of increase in oxygen utilization. This 5:1 relationship is attributable to the fact that, assuming normal O2 carrying capacity, arterial blood contains about 200 ml O2 per liter of blood [3]. Thus 5 l of cardiac output corresponds to 1 l of oxygen delivery. Maximal cardiac output is dependent on the level of aerobic conditioning. Thus peak cardiac output represents an independent measure of aerobic fitness. Systemic a-vO2 difference represents the level of extraction of available O2 from arterial blood. Systemic a-vO2 diff increases from 5 mlO2/dlQ at rest to about 15 mlO2/dlQ at peak exercise, with relatively minor increases as a function of aerobic fitness [4].

Several studies assessing exercise capacity in mitochondrial myopathies have demonstrated that peak VO2 is markedly low (on average about one-third of age-matched healthy sedentary individuals) [1,5,6], but the range of impaired oxygen utilization is broad. The differentiation of healthy subjects who are severely impaired, in whom O2 utilization in exercise is limited by a low peak cardiac output, from patients in whom VO2 is limited by mitochondrial function can be defined by measuring exercise cardiac output and determining peak systemic a-vO2 diff. In the absence of significant cardiac disease, oxygen delivery by
The circulation is preserved and peak cardiac output is comparable to healthy subjects. In contrast, muscle capacity for extraction of available oxygen (systemic a-vO₂ difference) is markedly limited, relating to the block in oxidative phosphorylation within skeletal muscle. In relation to oxygen utilization during exercise, O₂ delivery is high and the circulation is "hyperkinetic", i.e., the increase in cardiac output, ΔQ, relative to the increase in oxygen uptake, ΔVO₂, from rest to exercise is abnormally high in mitochondrial myopathy patients, oxygen delivery relative to oxygen utilization is exaggerated (ΔQ/ΔVO₂>5). The measurement of cardiac output and determination of systemic a-vO₂ difference are therefore critically important in the assessment of muscle oxidative capacity in patients with suspected mitochondrial myopathy.

In a recent analysis of exercise tolerance in a group of 40 patients with characterized mitochondrial defects, the range of exercise capacity was broad. Peak VO₂ ranged from a level barely above resting metabolic rate to one comparable to healthy conditioned individuals, with the majority of patients demonstrating low aerobic fitness. Moreover, this variability correlated directly with the degree of impaired muscle extraction of available oxygen, enabling us to use systemic a-vO₂ difference as a surrogate marker of mitochondrial capacity for oxidative phosphorylation. The finding that the level of mutation (% mutant mtDNA) governed the ability of muscle to increase systemic a-vO₂ difference with exercise further supports the notion that impaired muscle oxidative phosphorylation determines the degree of exercise intolerance in patients with respiratory chain defects (Fig. 3).

4. Normal physiological changes with endurance training and detraining

Human beings are subjected to cycles of increased and decreased physical activity throughout life, and accordingly, the cardiovascular and skeletal muscle systems adapt to these changes in oxidative demand. This review is not able to address the numerous changes in physiology and metabolism that normally occur in response to endurance training and detraining, but rather, will focus on the changes most pertinent to the exercise response in patients with mtDNA disorders.

4.1. Use it

Increases in oxidative capacity are brought about through endurance exercise training, which is generally defined as...
any regularly performed aerobic activity involving the use of large muscle groups for sufficient intensity and duration (30 min, 50–85% VO2 max) [2]. Endurance (or aerobic) training induces adaptations in the heart and peripheral circulation, and skeletal muscle systems that increase exercise capacity by enhancing the delivery of oxygen (O2) to exercising muscle and by increasing muscle capacity for O2 utilization in oxidative phosphorylation. Greater oxygen delivery is achieved through increases in cardiac output (due to increases in cardiac stroke volume rather than to changes in maximal heart rate), whereas greater oxygen extraction from blood by trained skeletal muscle (resulting in a greater a-vO2 difference) is attributable to increases in capillary density, vascular conductance, and mitochondrial oxidative capacity [9]. A key feature of enhanced muscle oxidative capacity is increased mitochondrial biogenesis, which is associated with increases in respiratory chain enzyme levels, resulting in an increased capacity to generate energy via oxidative phosphorylation. Mitochondrial biogenesis (proliferation) is associated with an increase in mtDNA copy number as demonstrated by the proportionality between mtDNA content and muscle oxidative capacity [10]. Increased mtDNA replication and mtDNA copy numbers support increased rates of synthesis of mitochondrially encoded proteins. This is in contrast to the increased rate of transcription of nuclear-encoded genes that occurs with mitochondrial biogenesis [11]. Endurance training is also known to promote the expression of slow type myosins, resulting in greater proportions of Type IIa and I fibers [12]. These peripheral adaptive responses are local in nature, evident only in those muscles that are trained.

The magnitude of these physiological adaptations is dependent on duration, intensity and frequency of training as well as initial level of fitness [2]. In previously sedentary individuals, regularly performed aerobic exercise results in significant improvements in exercise capacity, whereas the development of peak exercise performance typified by competitive endurance athletes depends upon several months to years of training. Two to three months of training in sedentary individuals is known to induce moderate increases in VO2, muscle blood flow and capillary density (all between 15% and 20%) with greater changes in mitochondrial volume and enzyme levels (30–40%) [9,13]. Important to note is that a constant proportionality or stoichiometry is retained with respect to increases in mitochondrial respiratory chain and related enzymes, i.e. changes in nuclear encoded and mitochondrially encoded enzymes occur to the same extent. Further increases in cardiovascular and metabolic capacity accompany more prolonged periods of training.

Another notable training adaptation relates to the fact that trained individuals have lower blood and muscle lactate levels than untrained individuals at the same absolute level of submaximal exercise, reflecting a greater metabolic efficiency of skeletal muscle. Elevations in mitochondrial enzyme levels in trained muscle result in greater fatty acid oxidation and reduced carbohydrate oxidation (and lactate production), thereby allowing oxidative metabolism to provide a greater contribution to the total energy demand, with lesser increase in ADP and decrease in phosphocreatine and reduced activation of glycolysis [14]. These changes in muscle oxidative capacity are thought to play a major role in the capacity to perform submaximal work with less effort and for longer durations. Furthermore, the point during submaximal exercise at which ventilation increases disproportionately to oxygen uptake (ventilatory threshold) is delayed with endurance training, related to the delayed onset of lactate accumulation within trained muscle.

4.2. Lose it

Inherent to the concept of training adaptation is the notion of training reversibility, or detraining, since the physiological and metabolic changes responsible for improved exercise capacity are not permanent. Complete cessation or marked reduction of endurance training leads to complete or partial reversal of training-induced adaptations, throughout the cardiopulmonary and skeletal muscle systems that decrease maximal and submaximal exercise performance. Detraining leads to decreases in maximal work capacity, VO2 and cardiac output that are associated with marked reductions in muscle capillary density, mitochondrial volume and oxidative enzymes (for review, see Ref. [14]).

As with training gains, both the time course and magnitude of loss of these various adaptations are influenced by the degree and duration of detraining as well as by the initial fitness level of the individual before detraining [15]. In recently trained subjects, training-induced gains in VO2 max are typically completely reversed within 4–8 weeks of stopping training [15–17]. This loss in the maximal capacity for oxygen utilization is thought to be due to a decline in maximal cardiac output initially, with decreases in arterial-venous oxygen difference accounting for declines after more prolonged cessation of training [9]. Rapid and progressive reductions in mitochondrial content and oxidative enzyme activities occur, resulting in decreased peak rates of mitochondrial ATP production within 3–6 weeks. The time course of these oxidative enzymatic losses appears to be non-linear, with an initial rapid decline followed by a gradual slowing in rate of loss until a new steady-state is reached [18]. Declines in oxidative enzyme levels following detraining occur faster than decreases in VO2 max, and are therefore thought not to be causally linked to maximal performance but rather to be of functional significance during submaximal exercise [19,20]. Exercise performed at the same absolute intensity after detraining results in higher lactate accumulation, increased muscle glycogen utilization, and carbohydrate oxidation, leading to reduced exercise time to fatigue. These data are taken to support the notion that it is the mitochondrial content of
working muscle that is an important determinant of substrate utilization during submaximal exercise. In contrast to completely stopping training, a reduction in training frequency and duration may prevent the loss of adaptation, whereas a reduction in training intensity will lead to decrements in VO2 max and performance. Exercise intensity therefore seems to be the key variable for maintenance of training-induced adaptations [14].

5. Endurance training in mtDNA defects

Endurance training has been used to combat the effects of deconditioning in various chronically ill patient populations. However, little consideration had been given to the possibility that exercise training might be applied as therapy for muscle mitochondrial disorders.

5.1. Previous studies

Initial studies indicated that exercise training was well tolerated and improved exercise capacity in mitochondrial myopathy patients suggesting that such training had the potential to induce physiological adaptations to reverse the effects of deconditioning and ameliorate the underlying mitochondrial defect [21,22]. Although the physiological and metabolic mechanisms of improvement were not directly assessed in these studies, a particularly important question arose with respect to the normal adaptive training response of mitochondrial proliferation. In the distinctive setting of heteroplasmic muscle mtDNA disorders, would the training stimulus induce expansion of wild-type and mutant mtDNA populations equally or selectively?

A study was subsequently designed to assess training effects upon the overall proportion of mutant versus wild-type mtDNA as well as to more clearly define the physiological and biochemical basis of previously demonstrated improvements [1]. This study of 10 patients with various heteroplasmic mtDNA defects confirmed previous findings that exercise training increased exercise capacity and improved patient assessment of quality of life: the study further showed that enhanced exercise capacity was attributable to a 20% increase in peak oxygen utilization and that the physiological basis of improved O2 utilization was an enhanced capacity of skeletal muscle to extract available oxygen (Fig. 4) with no increase in peak O2 delivery by the circulation (which is the dominant physiological mechanism by which endurance training increases oxygen utilization in healthy subjects). Correspondingly, mitochondrial volume (as monitored by levels of citrate synthase) increased by 50%. In most patients, enzymatic activity of respiratory chain complexes affected by the mutation also increased albeit by a lesser extent (20% on average). These muscle mitochondrial adaptations imply that the biochemical basis of improved systemic a-VO2 difference during exercise is an increased level of functional mitochondria. Interestingly, although the magnitude of increase in peak VO2 was consistent for the training program, the increase in mitochondrial volume was approximately 10–20% greater than that observed in healthy, sedentary individuals undergoing similar training.

Analysis of muscle mutation load revealed an increase in the relative proportion of mutant mtDNA in muscle homogenates of six of nine patients and no change in three patients. In no case was a decrease in mutant mtDNA detected. These findings have raised concern regarding the advisability and safety of endurance training in mitochondrial patients with heteroplasmic mutations. The particular question is, despite substantial physiological and biochemical benefits, can endurance training promote a progressive expansion of mutant mtDNA with potentially long-term deleterious effects? This concern relates to the view that clinical progression of mtDNA diseases is attributable to a progressive accumulation of mutant mtDNA with resulting...
increases in the proportion of respiration-incompetent fibers in clinically affected tissues [23]. Furthermore, increases in skeletal muscle mutation levels over time have been reported in heteroplasmic mtDNA disorders [24,25], although the number of patients in whom longitudinal data on mutation load is available is small. The mechanism(s) responsible for accumulations of the mutation within muscle fiber segments and for possible net increases in muscle mutation load over time are not known. Possible mechanisms include selective replication (replicative advantage) of mutant mtDNA [26], random genetic drift of mutant mtDNA [27,28] and compensatory increases in mitochondrial replication in response to biochemical deficiency [29]. In light of findings from this endurance training study, physical activity-related preferential increases in mutant mtDNA could also contribute to a drift toward higher proportions of mutant mtDNA with time. Physical inactivity and resulting deconditioning reduces mitochondrial numbers in healthy humans; and it is possible that deconditioning could decrease wild-type relative to mutant mitochondrial genomes and promote a shift toward a higher percentage of mutant mtDNA.

The biochemical benefit of exercise training (Fig. 5) in mitochondrial myopathy (i.e. increased COX activity in patients with mtDNA defects that impaired COX synthesis) suggests, that increases in _absolute_ levels of wild-type mtDNA occurred in response to training. These data imply that the overall volume of wild-type mtDNA increased despite a trend toward disproportionate expansion of mutant mtDNA. Such a response could relate to the distribution of mutant and wild-type genomes within single fibers and their proliferative response to metabolic feedback within normal and deficient fiber segments. For example, within segments that are oxidatively compromised (i.e. contain higher percentages of mutant mtDNA), the exercise-related metabolic stimulus for mitochondrial proliferation may be magnified. In other words, relating to the concept of the nuclear domain theory [30], the nucleus of a cytoplasmic domain within a myofiber which is functionally compromised by the presence of mutant mtDNA attempts to compensate for reduced oxidative capacity and added metabolic stress of training by stimulating replication of mtDNA in that domain, thereby stimulating expansion of mutant genomes. Alternatively, in segments containing predominantly wild-type mtDNA, the training stimulus would result in an increase in total numbers of wild-type mtDNA. Thus both the pattern of muscle activation in exercise and the distribution of mtDNA genomes within active muscle may determine regional and overall patterns of expansion.

Our inability to interpret the paradoxical molecular and biochemical findings reflects our lack of knowledge of factors that control copy number of wild-type and mutant mtDNA molecules within skeletal muscle containing heteroplasmic mitochondria. In fact, the regulatory mechanisms controlling mitochondrial biogenesis in response to contractile activity in normal muscle still remain unclear [31,32]. That mitochondrial content varies to meet the energy demands of the cell has been well-established, and the coordinated expression of nuclear and mitochondrial genes necessary for mitochondrial biogenesis makes a well-orchestrated regulation of genes likely. More than 95% of the genes necessary for mitochondrial biogenesis are encoded in the nucleus, and regulation of these genes appears to be controlled by transcriptional mechanisms [32]. Various nuclear-derived transcription factors regulating and coordinating mitochondrial gene expression have been identified: mitochondrial transcription factor A (Tfam) which binds to the D-loop regulatory region of mtDNA and is required for increasing mtDNA transcription and copy number; nuclear respiratory factor (NRF-1), which transcriptionally activates Tfam, and more recently, a co-activator peroxisome proliferator-activated receptor co-activator-1 (PGC-1), which is being considered a potential master regulator of mitochondrial biogenesis [31,33]. Tfam, NRF-1, and PGC-1 have been shown to be induced as part of the adaptation of skeletal muscle to exercise training in healthy muscle [33,34], and levels of Tfam have been found to correlate well in increased mtDNA in ragged-red fibers and decreased mtDNA levels in mtDNA-depleted cells [35].

![Fig. 5. Immunohistochemical micrograph of cytochrome oxidase (COX) activity in muscle of a patient with a mtDNA defect before and after 14 weeks of endurance training. Biochemically determined COX activity in this patient increased by 20% with training.](image-url)
5.2. Current status of endurance training in mtDNA disorders

At present, we are unable to provide definitive recommendation for or against endurance training for patients with mtDNA defects. Whether endurance training expands mutant genomes preferentially needs to be resolved before precluding patients from experiencing the numerous, established benefits of training. Also, given the likely deleterious effects of physical inactivity, we believe it would be a mistake to conclude that exercise should be entirely avoided. However, the effects of deconditioning on mitochondrial volume and mutant levels within muscle are directly relevant to the recommendation of endurance training for these patients, particularly as not all patients will continue training should they undertake an exercise training program. Physicians and patients routinely seek advice regarding endurance training as a treatment option, underscoring the immediate urgency to address its safe prescription for patients with mtDNA defects.

We believe a key to resolving the safety of endurance training is to determine the effect of cycles of training and detraining upon wild-type mtDNA copy number and that increases in wild-type copy number are responsible for improved mitochondrial oxidative capacity, exercise performance and quality of life in patients with heteroplasmic mtDNA mutations. This may be addressed by investigation of the proportion and distribution of mutant and wild-type mtDNA copies within individual muscle cells and correlating changes in wild-type mtDNA copy number with changes in biochemical enzyme activity. Single-fiber analysis techniques provide greater resolution at the cellular level than analysis of muscle homogenates (the outcome measure in Ref. [1]) and will be particularly informative with respect to the effects of training-induced proliferation and detraining-induced losses on the focal distribution of the two genomes within individual fibers containing differing levels of biochemical impairment. Given the data on wild type mtDNA copy number, perhaps the question could be re-phrased: could life-long physical activity prevent further progression of mutant mtDNA accumulation over time which has been documented thus far?

6. mtDNA mutation—effects on muscle strength

Myopathic weakness (defined as the inability to generate normal muscle contractile force) may be present with or without exercise intolerance. Apart from extraocular muscle involvement, fixed weakness usually affects predominantly proximal hip and shoulder girdle musculature and is generally mild. Weakness may be more pronounced when combined with sustained or repeated muscle contractions (i.e. with superimposed fatigable weakness). The pathophysiology of muscle weakness in patients with mtDNA defects is unclear but presumably involves mitochondrial-dependent effects upon muscle cell integrity and viability. In addition, muscle disuse related to habitual physical inactivity may play a role.

Assessment of muscle strength is most reliably done using quantitative measures of contractile force and muscle performance rather than qualitative assessment of strength obtained with manual strength testing. Computerized dynamometry permits measurement of peak isometric and isokinetic (eccentric and concentric contraction) muscle torque and can supplement information gained from measurement of isometric strength. Studies relating the degree of muscle oxidative impairment to muscle weakness in mtDNA defects are few [36], and to our knowledge, there have been no trials assessing effects of resistive strength training in patients with mitochondrial myopathies.

7. Normal physiological changes with resistance training and detraining

Resistance exercise demands low volume, highly intense contractions of muscle fibers. The lifting of weights to yield such muscle overload typically involves an eccentric component (lengthening of fiber during contact) and a concentric component (shortening of fibers during contraction). Chronic resistance training induces physiological adaptations that completely differ from those of endurance training and leads primarily to an increase in muscle strength. Although both neural and muscular factors modify the expression of human strength, enhanced neural facilitation predominates in the early phase of training, followed by physiological adaptation within skeletal muscle [37].

7.1. Use it

The most fundamental biologic adaptation to resistance training is an increase in muscle fiber cross-sectional area, allowing for increased muscular force. This is brought about by fiber hypertrophy, where increased net synthesis of myofibrillar protein is associated with enlargement of all three major fiber types, with largest increases occurring in Type II fibers [38]. A transformation in myosin heavy chain isoform expression occurs, resulting primarily in fast fiber type conversion (Type IIX→IIa) [12]. Although increases in certain glycolytic enzyme activities, such as lactate dehydrogenase and phosphofructokinase have been reported, this does not seem to be a consistent finding [39]. Furthermore, these changes are not of the same magnitude as the increases in oxidative enzymes observed after endurance training. The increases in total contractile protein generally occur without parallel increases in capillarization, total volume of mito-
The magnitude and time course of muscle strength gain, fiber hypertrophy and fiber type conversion depend on training volume (intensity, frequency and duration) and level of fitness. In studies assessing muscle adaptation to 9–10 weeks of resistance training in previously untrained individuals, increases of 20–30% in muscle strength and 10–20% in fiber cross-sectional area are typical [40,41]; however, much greater increases in cross-sectional area (100% of pre-training values) have also been reported [15]. As the muscle adapts, a progressive overload is required to continue improvements.

A vital role in the muscle adaptation process to overload is activation of muscle satellite cells, which are mononucleated, committed muscle precursor cells that are derived from the initial population of embryonic myogenic cells [42,43]. In adult muscle, they remain undifferentiated and dormant beneath the basal lamina of skeletal muscle fibers until evoked by various stimuli to re-enter the cell cycle to undergo mitotic division, proliferation and fusion. In response to muscle overload and hypertrophy, satellite cells contribute their nuclei and cytoplasmic contents (including mitochondria and mtDNA) to the existing myofiber in order to maintain the ratio of nuclear material to other cellular components at a constant level. As mature skeletal muscle is post-mitotic and multi-nucleated, the addition of these satellite cell-derived nuclei is believed to be a prerequisite for the maintenance of enlarging myofibers.

In addition to overload, acute myotrauma is a stimulus for satellite cell induction. Satellite cells typically withstand damaging influences and undergo activation, migration, and fusion and, depending on the intensity of damage, they participate in the repair of existing fibers or form new myofibers through a process equivalent to muscle histogenesis in the embryo [43]. Overload in the form of eccentric exercise, which can result in extensive muscle damage attributable to mechanical injury affecting the sarcolemma and cytoskeleton, has been proposed to stimulate satellite cell proliferation. An increase in the number of satellite cells has been reported to follow eccentric exercise in human muscle [44].

At present, the biology of satellite cells is better-characterized in animals than in humans, however, given their stem cell-like behavior and relevance to various disease states, the response of satellite cells to muscle contraction and injury is emerging as an important field of study, for review see [42]. The effects of both acute and chronic overload induced by unaccustomed or strenuous exercise, particularly damaging eccentric muscle contractions, on satellite cell activation in rats have been well described. In humans, the stimulus intensity and time course for satellite cell activation and proliferation through acute resistance overload is virtually unknown [44]. Studies of the effects of resistance training on satellite cell proportions in healthy humans is limited [41,45,46]. These studies employed high-intensity resistance exercise combining concentric and eccentric muscle contractions over a period of 8–16 weeks and demonstrated increases semi-quantitatively in the proportion of activated satellite cells within muscle after training. The authors concluded that the smaller than anticipated satellite cell response was due to the fact that peak satellite cell activation likely occurred earlier in the training period and that after 8 weeks of training, substantial differentiation of cells had already occurred.

7.2. Lose it

The cessation of resistance training inevitably leads to loss of muscle strength and hypertrophy, however, the time course for the rates of loss is variable. Muscle cross-sectional area declines more rapidly than strength performance which can be maintained for up to 4 weeks of inactivity [12,15]. Muscle strength has been found to remain above pre-training values after 12 weeks of training cessation [47]. Furthermore, a reversal in fiber type distribution with re-expression of the fast type IIX myosin heavy chain isoform accompanies cessation of resistance training.

8. “Gene-shifting” in mtDNA defects

The absence of mutant mtDNA in skeletal muscle satellite cells, despite high levels of mutant mtDNA in mature myofibers, has been demonstrated in patients with sporadic large-scale deletions and sporadic point mutations of mtDNA [48,49], in contrast to maternally inherited mtDNA defects where the mutation is present in mitotic tissue. This unanticipated finding led to the hypothesis that activation of these typically quiescent myogenic cells could result in the shifting of normal mitochondrial templates from satellite cells to mature muscle and hence, decrease the proportion of mutant mtDNA in muscle below threshold for phenotypic disease expression by restoring oxidative capacity. The feasibility of this mitochondrial gene-shifting approach has been reported in two cases of patients harboring sporadic tRNA mutations of mtDNA, both using models of muscle injury to induce satellite cell activation. Clark et al. [48] used a myotoxic agent, bupivicaine, to induce muscle fiber necrosis and found that the regenerating fibers contained undetectable levels of mutated mtDNA and were respiratory competent. Shoibridge et al. [50] described the complete restoration of wild-type mtDNA in muscle fibers regenerating from traumatic injury induced by a previous biopsy. Both groups attributed normalization of the mtDNA genotype to induction of satellite cells in the focus of regenerating muscle.
9. Resistance training in mtDNA defects

Resistance training could provide a more physiological means of mitochondrial gene-shifting than myotoxin injection or surgical trauma. In a single case report, a decrease in the proportion of mutant relative to wild-type mtDNA and an increase in respiratory-competent fibers was detected in muscle after resistance training [51]. These findings suggested that satellite cell incorporation was the basis of muscle metabolic improvement, effects of resistance training on muscle strength was not addressed, nor was the mechanism of mitochondrial gene transfer. A subsequent pilot study in a small group of patients with sporadic mtDNA mutations demonstrated improvements in muscle strength with unilateral leg training and demonstrated variable changes in mutation load and enzymatic activity assessed in muscle homogenates (Fig. 6) [52]. Analysis of wild-type and mutant mtDNA copy number in single cells, along with quantitation of satellite cell activation and proliferation may more clearly illuminate the effects of muscle overload on mitochondrial gene shifting.

Further study is essential to establish the practicality, efficacy and safety of resistance training as a non-invasive method of inducing the transfer of normal mitochondrial templates from satellite cells to mature muscle. In particular, the type of muscle contraction required to maximally induce satellite cell activation needs to be resolved. Theoretically, eccentric (damaging) exercise may provide a more potent stimulus than concentric (hypertrophy-inducing) muscle contractions, however, performing eccentric-only contractions is less practical for the patient. Also, although satellite cells demonstrate the capacity for self-renewal, the effect of such eccentric exercise training on the satellite cell pool is unknown. This question relates to the notion that a decrease in satellite cell number and proliferative capacity may account for impaired skeletal muscle regeneration with aging [43] and limited capacity for regeneration in dystrophic muscle [53]. Knowledge of the appropriate stimulus intensity for satellite cell activation is imperative, but we feel that heavy intensity muscle contractions would not compare to the constant degenerative and regenerative processes occurring in dystrophic muscle. Nevertheless, the question of whether a lifetime of intense resistance exercise (i.e. body building) depletes the satellite cell pool and influences the regenerative capacity of muscle is unresolved.

In addition to the potential therapeutic effect of resistance training on the mitochondrial disease process, normal adaptive processes increasing muscle strength are likely to occur, particularly for muscles that are weak due to disuse atrophy. Moreover, we believe that training of a large muscle mass (i.e. quadriceps) also has the potential to show a physiologically detectable effect on exercise tolerance. By improving mitochondrial oxidative metabolism in muscle groups used for daily activities (i.e. walking), resistance training may be a functionally significant approach to therapy for mitochondrial myopathy patients.

10. Conclusion

Physical activity induces numerous beneficial physiological adaptations in skeletal muscle; the lack of muscle “use” has the opposite effect in both health and disease. The effects of exercise training in mtDNA disorders are incompletely understood. Endurance training-induced mitochondrial biogenesis may increase both mutant and wild-type mitochondrial genomes within skeletal muscle; which increase is functionally dominant will determine the safety of this treatment approach. Resistance training-induced transfer of normal mitochondrial templates from satellite cells to mature muscle may lower the mutation level below phenotypic expression. Ultimately, should both endurance and resistance exercise training approaches prove to be safe and effective in inducing increases in muscle wild-type

![Fig. 6. Changes in physiological, molecular genetic and biochemical variables in four patients with sporadic mtDNA defects following 10 weeks of unilateral dynamic resistance training of upper leg (quadriceps muscles). Muscle strength increased in all patients (A), while changes in mutation load (B) were variable but was unchanged or decreased in three of four patients. The activities of cytochrome oxidase (C) are shown for the three patients in whom the mutation affected this enzyme (the fourth patient harbored a mutation in cytochrome b).](image-url)
mtDNA levels, both treatment strategies may be used in combination and in succession. A paradigm of short-term heavy resistance training to initiate incorporation of wild-type mtDNA from satellite cells to mature muscle followed by longer-term endurance training to increase and maintain their numbers may be efficacious.

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