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Anti-Aging Medicine: Mitochondria-Targeted Antioxidants and Physical Activity

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Abstract—Mitochondria are an important source of reactive oxygen species in skeletal muscles. Mitochondrial dysfunction accompanies the development of age-related human diseases. An increased production of reactive oxygen species contributes to the muscle atrophy caused, for example, by the absence of physical activity. Many regulatory pathways involved in the mitochondrial biogenesis are targets of anti-aging therapy. An active lifestyle and physical exercise prevent age-related damage to mitochondria in skeletal muscles. The use of antioxidants aimed directly at mitochondria is another way to correct the effect of reactive oxygen species. The treatment with mitochondria-targeted antioxidants weakens the mitochondrial degeneration, improves the age-related function of skeletal muscles, and protects the muscles from atrophy. Data are presented on the use of mitochondria-targeted antioxidants and physical exercises to maintain the structural and functional state of mitochondria and on the protection of muscles from sarcopenia.

Keywords: reactive oxygen species, aging, bioenergetics, physical exercises, mitochondria, sarcopenia, oxidative stress

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INTRODUCTION

A disdainful (usually unconscious) attitude to a healthy (necessary) lifestyle is often one of the circumstances contributing to the acceleration of aging in elderly individuals. Most often, we are talking about pathological (pathogenic) behavioral stereotypes, including the exposure to prolonged emotional stresses and irrational nutrition, as well as an insufficient level of physical activity (Yarygin, 2010).

Mitochondria are not only the main source but also a target of reactive oxygen species (ROS) that cause the oxidative damage to these cellular structures. Namely these damages underlie many degenerative diseases and age-related pathologies (Feniouk and Skulachev, 2017). Since the 1970s, mitochondria are considered to be a machine causing cell death and determining (by regulating the rate of respiration and oxygen consumption) the life expectancy and rate of aging of the body (Harman, 1972). Changes in energy metabolism associated with mitochondrial dysfunction are central events in aging (Javadov et al., 2015).

Skeletal muscles have the ability to adapt to mechanical and physiological loads by changing their phenotype in terms of the size and type of muscle fibers, capillarization level, and aerobic capacity. Prolonged periods of muscle inactivity (for example when the limbs are immobilized) cause the atrophy of muscle fibers and a decrease in the muscle strength owing to a loss of muscle protein as a result of its increased degradation and decreased synthesis (Talbert et al., 2013). The production of ROS increases with age; their higher content leads to damage to macromolecules and dysfunction of signaling pathways, which together becomes one of the leading factors in aging of the cells, tissues, and the body as a whole (Powers et al., 2012). The oxidative stress is associated with muscle atrophy and muscle weakness caused by the absence of physical activity (Zorov et al., 2007; Min et al., 2011).

The absence of physical activity is an actual reason for many pathological conditions, including most of the leading causes of death in the United States (Booth et al., 2017). In this work, some ways to affect the mechanisms of development of muscle pathologies, including age-related ones (sarcopenia), are considered.

The review discusses a concept according to which ROS play an important role in the regulation of skeletal muscle atrophy caused by the absence of physical activity. Special attention is paid to the work of mitochondria in connection with the cellular respiration, generation of ROS, and cell death.

AGE-RELATED CHANGES IN MITOCHONDRIAL HOMEOSTASIS

As well as a number of neurodegenerative diseases (including Alzheimer's and Parkinson's diseases), aging is accompanied by a chronic inflammatory response, an increase in the level of ROS in the tissues, and progressive mitochondrial dysfunction. All this leads to a decrease in the level of ATP synthesis, an increase in the level of ROS, and cell death.

Mitochondrial DNA

Mitochondrial DNA (mtDNA) copy number, which reflects the number of mitochondria in the cell, can change with different energy requirements and different physiological or environmental conditions. With aging, there is a decrease in the rate of transcription, a decrease in the oxidative capacity of different substrates, and an increase in mitochondrial membrane lipid peroxidation. These data demonstrate that, although structural changes in mtDNA with human aging are insignificant, changes in the mitochondrial homeostasis (ultimately leading to changes in the rate of mitochondrial biogenesis) play an important role in the aging process. It was noted that a decrease in the content of mtDNA and the number of mitochondria occurs in the cell with age (Hebert et al., 2015; Zhang et al., 2017). On average, an individual loses about 4 mtDNA copies every 10 years. A decrease in mtDNA copy number is also associated with age-related physiological parameters (Zhang et al., 2017). A low mtDNA copy number is associated with a senile phenotype and is a predictor of mortality from all causes in the population (Ashar et al., 2015; Eshima et al., 2020).

Changes observed in mitochondria with aging also include a high level of mtROS formation, which leads to an increase in the level of damage to proteins, lipids, and mtDNA, activation of stress response pathways and a decrease in the level of expression of mtDNA-encoded proteins, and a decrease in the respiratory function of mitochondria (Conley et al., 2007). It was demonstrated that the level of oxidative damage to mtDNA in the heart and brain is inversely proportional to a maximal lifespan of mammals (Barja and Herrero, 2000). In addition, mitochondria, being the organelles that produce the largest amount of ATP and ROS (mtROS) in living cells, are also equipped with a universal mechanism which can completely prevent the production of mtROS. This mechanism consists in a gentle depolarization of the inner mitochondrial membrane in order to decrease the membrane potential to a level sufficient for ATP production, but insufficient for the generation of mtROS. In short-lived animals (mice), aging is accompanied by inactivation of the mild depolarization mechanism, which leads to a chronic poisoning of the body with mtROS. However, a moderate depolarization persists for many years in the long-living naked mole-rat (life span of 32 years) and *Carollia perspicillata* bat (life span of 17 years) (Vyssokikh et al., 2020).

In humans, age-related decrease in O_2 consumption (Coen et al., 2013) and ATP synthesis (Short et al., 2005) correlate with a decrease in mitochondrial mass and level of oxidative phosphorylation (Petersen et al., 2003). Mice with increased level of mtDNA mutations exhibit the traits of premature aging (Trifunovic and Larsson, 2008). As a result, mitochondria of older muscles generate less ATP and are unable to provide an adequate energy for muscle movement, thus contributing to the development of sarcopenia. In addition, it is known that mitochondrial dysfunction is associated with the development of age-related human diseases, including loss of muscle mass and function (Gouspillou and Hepple, 2016), muscle atrophy caused by a lack of physical activity (Min et al., 2011), Duchenne muscular dystrophy and collagen muscular dystrophy, long-term muscle dysfunction caused by chemotherapy, and development of insulin resistance (Gouspillou and Hepple, 2016). Age-related muscle dysfunction is accompanied by disturbances in morphology, signaling pathways, and protein interactions in mitochondria.

Mitochondrial Reactive Oxygen Species

Long periods of the absence of mechanical load lead to muscle weakness and atrophy (Feng et al., 2016). A loss of contractile function in the skeletal muscle is accompanied by an increase in the oxidative stress and mtROS production. It is considered that mtROS induces signaling events that contribute to the muscle atrophy in different animal models (Johnson et al., 2018). In particular, increased ROS production in the muscle fibers can contribute to an increase in proteolysis, as well as suppress the protein synthesis during the periods of skeletal muscle inactivity (Powers et al., 2012). Muscle atrophy is apparently based on age-related dysregulation of redox signaling and misalignment of mitochondrial homeostasis, including the signaling pathways that control the metabolic and functional integrity of muscles (protein metabolism, cell death and regeneration, inflammation, damage to the body, and metabolic functions). A decrease in the muscle mass and strength (sarcopenia) is a distinguishing feature of the aging process. Consequently, a decrease in the level of mtROS is important for potential therapeutic strategies for delaying sarcopenia (Eshima et al., 2020). Being one of the main sources of ROS production, mitochondria are a key player in the field of oxidative stress.

However, although reactive oxygen and nitrogen species (ROS and RNS) were initially considered only harmful to the muscle cells, it is now recognized that they are required for normal skeletal muscle physiology (Sohal and Orr, 2012), mainly owing to reversible

redox post-translational modifications that they can cause.

Mitochondrial metabolism is very sensitive to the degree of physical load, and its absence contributes to an acceleration of age-related mitochondrial dysfunction (Powers et al., 2012). Using a method of simultaneous determination of mitochondrial respiration and H_2O_2 release in the skeletal muscle tissue in the range of biologically significant ADP concentrations, it was demonstrated that the ability of mitochondria to emit H_2O_2 does not increase with age, while the sensitivity of mitochondria to ADP worsens. This leads to an increase in the level of mitochondrial H_2O_2 and electron leakage fraction in H_2O_2 (Holloway et al., 2018).

An increased ROS generation (and/or loss of mtDNA repair) and an increase in the lipid peroxidation products can increase mtDNA damage, which can lead to mtDNA mutations and possible heteroplasmy, causing a mitochondrial dysfunction and potentially leading to a pathology and organ disease (van Houten et al., 2016). With the oxidative stress caused by the absence of physical activity, mitochondria are responsible for the production of a significant amount of superoxide anion formed as a result of leakage of electrons from the electron transport chain (Turrens, 2003).

It is assumed that an increase in mtROS production triggers proteolysis (due to autophagy) and reduces the protein synthesis in the absence of physical activity (Zhang et al., 2018). The mechanism by which the autophagy increases after an increase in the level of ROS appears to include both the mammalian target of rapamycin (mTOR) protein (this is a key protein kinase, which controls cellular metabolism and growth) and adenosine monophosphate-activated protein kinase (AMPK). Active mTOR usually suppresses autophagy by inhibiting the activity of Unc-51-like kinase 1 (ULK1), while AMPK accelerates the autophagy by phosphorylating ULK1 and inhibiting mammalian target of rapamycin complex 1 (mTORC1) (Rodney et al., 2016; Morgunova and Klebanov, 2019). It was demonstrated that the oxidative stress caused by muscle immobilization activates the proteolytic pathways and inhibits mTOR (Talbert et al., 2013).

MITOCHONDRIA-TARGETED ANTIOXIDANTS

The preparations for mitochondria-targeted therapy (mitoceutics), including antioxidants, as well as a number of genetic manipulations, are used to protect the skeletal muscles from atrophy (Williamson and Davison, 2020). Efficient mitotherapy should provide the maintenance of an efficient mitochondrial pool, ATP production, ability to cope with stress, and maintain homeostasis and cell viability. Consequently, the most efficient strategies should be aimed at biogenesis or at the removal of dysfunctional mitochondria (through mitophagy) and at eliminating the consequences of mitochondrial dysfunction. Thus, the development of mitochondria-targeted substances capable of reaching mitochondria not only in vitro but also in vivo is the most important direction of anti-aging medicine.

Neutralization of ROS Using Superoxide Dismutase and Catalase

The level of superoxide dismutase (SOD) in the muscles is stable and does not change with overexpression of catalase targeted to mitochondria (mCAT) or hindlimb unloading (HU) (Kondo et al., 1993; Lee et al., 2017). The previous studies suggest that the skeletal muscles contain an excess of mitochondrial SOD (Hsu et al., 1996). At the same time, it was demonstrated that susceptibility to denervation-induced muscle atrophy is not increased in mice with tissue-specific SOD knockout in muscles (Ahn et al., 2019). In another study, the SOD and catalase mimetic EUK-134 weakened HU-induced muscle atrophy (Lawler et al., 2014). Electroporation of mCAT in vivo also weakened the muscle atrophy in rats (Dodd et al., 2010). A different effect of the above-listed preparations is probably caused by differences in the selected model, in the method of restricting physical activity, and in the method of overexpression. Thus, neutralization of mtROS by mitochondria-targeted expression of SOD was insufficient to cancel the pathological state caused by the absence of physical load. This can be explained by the fact that SOD catalyzes the reaction of converting superoxide anion into hydrogen peroxide, which is also an oxidizer (Eshima et al., 2020).

Targeted expression of mCAT preserves the structure and functions of mitochondria and increases the life span, which is associated with a decrease in the muscle dysfunction, as well as insulin resistance in mice (Lee et al., 2010). Unexpectedly, neutralization of mtROS (in particular, H_2O_2) through the mCAT expression did not change the trends toward HU-induced loss of mass or contractile function by skeletal muscles. After HU, the muscles of mCAT and wild-type mice did not differ in cross-sectional area of the fibers or the mass of individual muscles (Umanskaya et al., 2014). Despite this, these observations demonstrate that neutralization of mtROS does not protect against the loss of muscle mass even at a microscopic level (Egawa et al., 2018). It can be assumed that the suppression of mtROS by catalase expression protects the muscles from the loss of muscle mass or contractile function caused by immobilization of the hind limbs in mice (Lawler at al., 2003). These data indicate that the formation of skeletal muscle mtROS is not a mechanism by means of which a low mobility contributes to skeletal muscle atrophy and weakness (Lustgarten et al., 2011). However, the study of muscle force in

mice with selective overexpression of catalase and wild-type mice also found no differences after 7 days of HU (McClung et al., 2010). Similar results were also observed with other antioxidants acting on different components of cellular ROS (Watanabe et al., 2019). In total, these studies demonstrate that the involvement of oxidative stress in the loss of muscle contractile function probably depends on the type of intervention. An increase in the oxidative stress in skeletal muscle can be incidental, but not the cause of atrophy. Overexpression of mCAT probably neutralizes only mtROS (in particular, H_2O_2), but not ROS that are produced by cytosolic proteins (Eshima et al., 2020).

PHYSICAL EXERCISES AS A METHOD OF ANTI-AGING PROTECTION

It is paradoxical, but the absence of physical activity leads not to a decrease, but to an increase in the formation of ROS and other adverse consequences, including a decrease in muscle strength, a decrease in the number of myofibrils, and the development of pathologies (Austad, 2018). Similar results are observed in age-related muscle atrophy (Javadov et al., 2015). Regular physical training is one of the fairly efficient measures to counteract the muscle weakening (including age-related). Despite the fact that physical exercises contribute to an increase in the production of ROS (Egawa et al., 2018), however, according to the principle of hormesis, moderately intense exercises cause the induction of cell protection systems, which leads to a decrease in the number of defects.

Regular physical exercises have many health advantages, primarily by preventing chronic diseases (Booth et al., 2017). Exercises can reverse harmful consequences of the lack of physical activity and neutralize age-related changes (Gries et al., 2018). In addition to obvious beneficial effect on a person's physical condition and health in general, such training decreases the probability of heart pathologies (Ascensão et al., 2011), Alzheimer's disease (Marques-Aleixo et al., 2012), and a number of chronic diseases, including those associated with inflammatory responses (Austin and St-Pierre, 2012), and also accelerates the healing of wounds. This effect was confirmed in the experiments on mice: in older (18 months) animals exposed to the physical activity, the wounds healed faster, and also there was a decrease in the inflammatory response as compared with the control group (Emery et al., 2005).

A clarification of the molecular mechanism determining a positive effect of prolonged physical activity is one of the actively developing fields of physiology. A central role in this mechanism is played by the stimulation of mitochondrial biogenesis (Steiner et al., 2011) and mitochondrial functions in general, as well as an increase in the efficiency of ROS level control (Marques-Aleixo et al., 2012). An increase in the production of ROS and damage to macromolecules (including DNA) caused by regular exercises of moderate intensity can trigger the activation of transcription factors and activate redox signaling, which leads to the induction of antioxidant enzymes and DNA repair. These load-stimulated phenotypic adaptations are a consequence of the responses regulated by redox triggers (for example, ROS and RNS, sarcoplasmic calcium, and the ATP : ADP and NAD^+ : NADH ratios) (Margaritelis et al., 2020). Nuclear factor erythroid 2-related factor 2 (Nrf2 factor) is the main regulator of the transcription of antioxidant enzymes. This factor is activated by oxidative stressors and electrophilic agents and provides the adaptation to stress through a positive regulation of cellular antioxidant protection and other metabolic processes (Shilovsky et al., 2021). Physical exercises are one of the types of hormetic stress, which leads to the activation of Nrf2 cell protection systems. The synthesis of small peptides (including mitoregulin) in mitochondria on open reading frames and their transport into the nucleus is another regulatory pathway that connects antioxidant enzymes in the nucleus (Shilovsky and Ashapkin, 2022; Averina et al., 2023).

Although regular exercises of moderate intensity induce a favorable adaptation, irregular and excessive physical exercises provoke the oxidative stress owing to increased production of ROS and RNS (Williamson and Davison, 2020).

Most studies on the consequences of physical activity focused on nDNA damage with insufficient understanding of the relationship between the exercises and mitochondrial redox dynamics in vivo (Tryfidou et al., 2020). However, there is an association between mitochondrial dysfunction and progression of diseases (Druzhyna et al., 2008; Chakrabarty et al., 2018).

A cross-sectional analysis of mitochondria from older individuals leading a sedentary lifestyle (as compared with both active older ones and younger adults) demonstrated that regular physical activity slows down the age-related decrease in mitochondrial function in the skeletal muscles. It was also demonstrated that progeria of mutator mice with a defect in the corrector region of mtDNA polymerase is sharply weakened by physical exercises, beginning from the age of three months (Safdar et al., 2011). An increased load for five months extended the life of progeria mice by more than a factor of two. At the same time, almost all defects accompanying the accelerated aging were leveled: early graying and baldness, fatigue; sarcopenia; a decrease in the total body weight and skin thickness; an increase in the weight of the heart muscle and spleen; a decrease in the size of ovaries and testes; a drop in the level of hemoglobin, red blood cells, and leukocytes; a change in the number, shape, and size of mitochondria; sharp stimulation of apoptosis in different tissues; a decrease in the number of mtDNA; an

increase in the number of mtDNA mutations; a decrease in the number of complexes I–IV of the respiratory chain and the PGC-1α factor regulating mitochondrial biogenesis. It should be noted that all these changes are also typical normal aging of mice, but they appear much earlier in mutator mice (Chow et al., 2007). It was demonstrated that, in mice subjected to regular endurance training (running from the age of three months), the level of mitochondrial transcription factors, the number of mtDNA, and ATP production by muscle mitochondria increase; glucose tolerance increases and the total level of physical activity increases; three-month maximal physical activity also eliminates many pathological changes in mouse cardiomyocytes in such age-related disease as diabetes (Stølen et al., 2009). It was also established that, in adult (twenty-month-old) and old (thirty-month-old) rats, regular physical exercises (for 8 weeks) led to a decrease in the level of DNA damage, activation of repair systems, an increase in resistance to the oxidative stress, and a decrease in the age-dependent increase in the level of 8-oxy-2'-deoxyguanosine in muscles (Radák et al., 2002).

Daily physical load (1 h per day, for 8 weeks) stimulates the biogenesis of brain mitochondria: in young (2 months) mice, the amount of mtDNA in the brain tissues noticeably increases, and also the level of expression of a number of protein markers of mitochondrial biogenesis increases (Steiner et al., 2011). It is possible that namely this phenomenon causes a favorable effect of exercises in the development of age-related neurodegenerative diseases (Marques-Aleixo et al., 2012). The molecular mechanism of muscle loading includes a number of events triggered by muscle contraction and regulating mitochondrial biogenesis and functions. During muscle contraction, calcium is released from the sarcoplasmic reticulum. This affects the activity of calcium-dependent enzymes, including calcium/calmodulin-dependent kinases. As a result, the phosphorylation profile of a number of transcription factors and their co-activators (including PGC-1α, which regulates the plasticity of skeletal muscle cells in normal condition and in the case of pathology) changes (Handschin and Spiegelman, 2008; Kupr and Handschin, 2015). The factors stimulating the formation of PGC-1α include not only cold but also the physical load and starvation (Kelly and Scarpulla, 2004). In addition to the control of thermogenesis, PGC-1α is involved in the regulation of the expression of many genes, including those responsible for the formation of mitochondria (Austin and St-Pierre, 2012), for fat and glucose metabolism (Fan et al., 2023), and for the control of circadian rhythms (biological clock genes) (Liu et al., 2007).

This protein interacts with a variety of transcription factors and is involved in the regulation of mitochondrial function, and its expression increases during regular endurance exercises (Wenz, 2011). PGC-1α is a co-activator of the nuclear receptor PPAR-γ, which controls the development and metabolism of adipose tissue and muscles (Chen et al., 2022).

The regulation of transcription is the main function of PPAR-γ. By binding low molecular weight compounds, PPAR-γ changes its affinity for promoter regions of DNA. PGC-1α regulates the plasticity of skeletal muscle cells in normal condition and in the case of pathology, mediating both short-term and long-term organism responses to the physical load. Its level increases quite quickly in working muscles and drops during relaxation, but regular endurance exercises lead to its steady increase. Overexpression of PGC-1α leads to an increase in the portion of slow oxidative fibers (Kupr and Handschin, 2015).

A submaximal ADP-supported mitochondrial respiration and/or ROS release change depending on different physiological situations, including brief high-intensity loads, regular low-intensity loads, HU, blood flow restriction, aging, and development of high-fat diet-induced insulin resistance; their differences in men and women were demonstrated (Petrick and Holloway, 2020). The content and functions of mitochondria, as well as mitochondrial sensitivity to ADP, decrease with age in the skeletal muscles, which leads to an increase in the level of mtROS. This provokes impaired utilization of glucose and lipids, insulin resistance, and obesity.

Long-term training with weights in older individuals increases the muscle mass, strength, and maximal mitochondrial respiration, but has no effect on redox balance, including the rate of H_2O_2 formation in the presence of ADP and the portion of electron leakage in H_2O_2 (Holloway et al., 2018).

CONCLUSIONS

In the concept of aging proposed back in the 1970s, mitochondria play a decisive role in aging and cell death (Harman, 1972). The oxidative stress arising as a result of increased mtROS production and impaired antioxidant protection is associated with muscle atrophy. The protective strategies in this model are associated with a geroprotective effect of mitochondria-targeted antioxidants, dietary restriction, and regular physical load, leading to the activation of the body's own antioxidant system. The treatment with mitochondria-targeted antioxidants (as well as targeted delivery of antioxidant enzymes to mitochondria) decreases the formation of mtROS (including H_2O_2) and prevents the muscle atrophy caused by the absence of physical activity (Javadov et al., 2015). All these effects are pleiotropic in nature; that is, they affect a large group of parameters that are different traits of aging. These effects not only slow down the aging of muscles but also to a certain extent reverse some of its manifestations. The physical load and delivery of antioxidant enzymes to mitochondria in animal models are also efficient in slowing down pro-

geria caused by a mutation in the corrector domain of mitochondrial DNA polymerase. Thus, the methods of anti-aging therapy, including physical exercises of moderate intensity, are efficient in reducing the degree of age-related mitochondrial dysfunction and associated pathologies.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

REFERENCES

Ahn, B., Ranjit, R., Premkumar, P., et al., Mitochondrial oxidative stress impairs contractile function but paradoxically increases muscle mass via fibre branching, *J. Cachexia, Sarcopenia Muscle*, 2019, vol. 10, pp. 411–428. https://doi.org/10.1002/jcsm.12375

Ascensão, A., Lumini-Oliveira, J., Oliveira, P.J., and Magalhães, J., Mitochondria as a target for exercise-induced cardioprotection, *Curr. Drug Targets*, 2011, vol. 12, pp. 860–871. https://doi.org/10.2174/138945011795529001

Ashar, F.N., Moes, A., Moore, A.Z., et al., Association of mitochondrial DNA levels with frailty and all-cause mortality, *J. Mol. Med.*, 2015, vol. 93, pp. 177–186. https://doi.org/10.1007/s00109-014-1233-3

Austad, S.N., The comparative biology of mitochondrial function and the rate of aging, *Integr. Comp. Biol.*, 2018, vol. 58, pp. 559–566. https://doi.org/10.1093/icb/icy068

Austin, S. and St-Pierre, J., PGC1α and mitochondrial metabolism-emerging concepts and relevance in ageing and neurodegenerative disorders, *J. Cell Sci.*, 2012, vol. 125, pp. 4963–4971. https://doi.org/10.1242/jcs.113662

Averina, O.A., Permyakov, O.A., Emelianova, M.A., et al., Kidney-related function of mitochondrial protein mitoregulin, *Int. J. Mol. Sci.*, 2023, vol. 24, p. 9106.

Barja, G. and Herrero, A., Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals, *FASEB J.*, 2000, vol. 14, pp. 312–318. https://doi.org/10.1096/fasebj.14.2.312

Booth, F.W., Roberts, C.K., Thyfault, J.P., et al., Role of inactivity in chronic diseases: Evolutionary insight and pathophysiological mechanisms, *Physiol. Rev.*, 2017, vol. 97, pp. 1351–1402. https://doi.org/10.1152/physrev.00019.2016

Chakrabarty, S., Kabekkodu, S.P., Singh, R.P., et al., Mitochondria in health and disease, *Mitochondrion*, 2018, vol. 43, pp. 25–29. https://doi.org/10.1016/j.mito.2018.06.006

Chen, L., Qin, Y., Liu, B., et al., PGC-1α-mediated mitochondrial quality control: molecular mechanisms and implications for heart failure, *Front. Cell Dev. Biol.*, 2022, vol. 10, p. 871357. https://doi.org/10.3389/fcell.2022.871357

Chow, L.S., Greenlund, L.J., Asmann, Y.W., et al., Impact of endurance training on murine spontaneous activity, muscle mitochondrial DNA abundance, gene transcripts, and function, *J. Appl. Physiol. (1985)*, 2007, vol. 102, pp. 1078–1089. https://doi.org/10.1152/japplphysiol.00791.2006

Coen, P.M., Jubrias, S.A., Distefano, G., et al., Skeletal muscle mitochondrial energetics are associated with maximal aerobic capacity and walking speed in older adults, *J. Gerontol., Ser. A*, 2013, vol. 68, pp. 447–455. https://doi.org/10.1093/gerona/gls196

Conley, K.E., Amara, C.E., Jubrias, S.A., and Marcinek, L.J., Mitochondrial function, fibre types and ageing: New insights from human muscle in vivo, *Exp. Physiol.*, 2007, vol. 92, pp. 333–339. https://doi.org/10.1113/expphysiol.2006.034330

Dodd, S.L., Gagnon, B.J., Senf, S.M., et al., Ros-mediated activation of NF-κB and Foxo during muscle disuse, *Muscle Nerve*, 2010, vol. 41, pp. 110–113. https://doi.org/10.1002/mus.21526

Druzhyna, N.M., Wilson, G.L., and LeDoux, S.P., Mitochondrial DNA repair in aging and disease, *Mech. Ageing Dev.*, 2008, vol. 129, pp. 383–390. https://doi.org/10.1016/j.mad.2008.03.002

Egawa, T., Ohno, Y., Goto, A., et al., AMPK mediates muscle mass change but not the transition of myosin heavy chain isoforms during unloading and reloading of skeletal muscles in mice, *Int. J. Mol. Sci.*, 2018, vol. 19, p. 2954. https://doi.org/10.3390/ijms19102954

Emery, C.F., Kiecolt-Glaser, J.K., and Glaser, R., et al., Exercise accelerates wound healing among healthy older adults: a preliminary investigation, *J. Gerontol., Ser. A*, 2005, vol. 60, pp. 1432–1436. https://doi.org/10.1093/gerona/60.11.1432

Eshima, H., Siripoksup, P., Mahmassani, Z.S., et al., Neutralizing mitochondrial ROS does not rescue muscle atrophy induced by hindlimb unloading in female mice, *J. Appl. Physiol. (1985)*, 2020, vol. 129, pp. 124–132. https://doi.org/10.1152/japplphysiol.00456.2019

Fan, D., Pan, K., Guo, J., et al., Exercise ameliorates fine particulate matter-induced metabolic damage through the SIRT1/AMPKα/PGC1-α/NRF1 signaling pathway, *Environ. Res.*, 2023, vol. 245, p. 117973. https://doi.org/10.1016/j.envres.2023.117973

Feng, H.Z., Chen, X., Malek, M.H., and Jin, J.-P., Slow recovery of the impaired fatigue resistance in postunloading mouse soleus muscle corresponding to decreased mitochondrial function and a compensatory increase in type I slow fibers, *Am. J. Physiol.: Cell Physiol.*, 2016, vol. 310, pp. C27–C40. https://doi.org/10.1152/ajpcell.00173.2015

Feniouk, B.A. and Skulachev, V.P., Cellular and molecular mechanisms of action of mitochondria-targeted antioxidants, *Curr. Aging Sci.*, 2017, vol. 10, pp. 41–48. https://doi.org/10.2174/1874609809666160921113706

Gouspillou, G. and Hepple, R.T., Editorial: Mitochondria in skeletal muscle health, aging and diseases, *Front. Physiol.*, 2016, vol. 7, p. 446. https://doi.org/10.3389/fphys.2016.00446

Gries, K.J., Raue, U., Perkins, R.K., et al., Cardiovascular and skeletal muscle health with lifelong exercise, *J. Appl. Physiol. (1985)*, 2018, vol. 125, pp. 1636–1645. https://doi.org/10.1152/japplphysiol.00174.2018

Handschin, C. and Spiegelman, B.M., The role of exercise and PGC1alpha in inflammation and chronic disease, *Nature*, 2008, vol. 454, pp. 463–469. https://doi.org/10.1038/nature07206

Harman, D., The biologic clock: The mitochondria?, *J. Am. Geriatr. Soc.*, 1972, vol. 20, pp. 145–147.

Hebert, S.L., Marquet de Rougé, P., Lanza, I.R., et al., Mitochondrial aging and physical decline: Insights from three generations of women, *J. Gerontol., Ser. A*, 2015, vol. 70, pp. 1409–1417. https://doi.org/10.1093/gerona/glv086

Holloway, G.P., Holwerda, A.M., Miotto, P.M., et al., Age-associated impairments in mitochondrial ADP sensitivity contribute to redox stress in senescent human skeletal muscle, *Cell Rep.*, 2018, vol. 22, pp. 2837–2848. https://doi.org/10.1016/j.celrep.2018.02.069

Hsu, J.L., Hsieh, Y., Tu, C., et al., Catalytic properties of human manganese superoxide dismutase, *J. Biol. Chem.*, 1996, vol. 271, pp. 17687–17691. https://doi.org/10.1074/jbc.271.30.17687

Javadov, S., Jang, S., Rodriguez-Reyes, N., et al., Mitochondria-targeted antioxidant preserves contractile properties and mitochondrial function of skeletal muscle in aged rats, *Oncotarget*, 2015, vol. 6, pp. 39469–39481. https://doi.org/10.18632/oncotarget.5783

Johnson, J.M., Ferrara, P.J., Verkerke, A.R.P., et al., Targeted overexpression of catalase to mitochondria does not prevent cardioskeletal myopathy in Barth syndrome, *J. Mol. Cell. Cardiol.*, 2018, vol. 121, pp. 94–102. https://doi.org/10.1016/j.yjmcc.2018.07.001

Kelly, D.P. and Scarpulla, R.C., Transcriptional regulatory circuits controlling mitochondrial biogenesis and function, *Genes Dev.*, 2004, vol. 18, pp. 357–368. https://doi.org/10.1101/gad.1177604

Kondo, H., Nakagaki, I., Sasaki, S., et al., Mechanism of oxidative stress in skeletal muscle atrophied by immobilization, *Am. J. Physiol.*, 1993, vol. 265, pp. E839–E844. https://doi.org/10.1152/ajpendo.1993.265.6.E839

Kupr, B. and Handschin, C., Complex coordination of cell plasticity by a PGC-1α-controlled transcriptional network in skeletal muscle, *Front. Physiol.*, 2015, vol. 6, p. 325. https://doi.org/10.3389/fphys.2015.00325

Lawler, J.M., Song, W., and Demaree, S.R., Hindlimb unloading increases oxidative stress and disrupts antioxidant capacity in skeletal muscle, *Free Radical Biol. Med.*, 2003, vol. 35, pp. 9–16. https://doi.org/10.1016/S0891-5849(03)00186-2

Lawler, J.M., Kunst, M., Hord, J.M., et al., EUK-134 ameliorates nNOSμ translocation and skeletal muscle fiber atrophy during short-term mechanical unloading, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2014, vol. 306, pp. R470–R482. https://doi.org/10.1152/ajpregu.00371.2013

Lee, H.Y., Choi, C.S., Birkenfeld, A.L., et al., Targeted expression of catalase to mitochondria prevents age-associated reductions in mitochondrial function and insulin resistance, *Cell Metab.*, 2010, vol. 12, pp. 668–674. https://doi.org/10.1016/j.cmet.2010.11.004

Lee, H.Y., Lee, J.S., Alves, T., et al., Mitochondrial-targeted catalase protects against high-fat diet-induced muscle insulin resistance by decreasing intramuscular lipid accumulation, *Diabetes*, 2017, vol. 66, pp. 2072–2081. https://doi.org/10.2337/db16-1334

Liu, C., Li, S., Liu, T., et al., Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism, *Nature*, 2007, vol. 447, pp. 477–481. https://doi.org/10.1038/nature05767

Lustgarten, M.S., Jang, Y.C., Liu, Y., et al., MnSOD deficiency results in elevated oxidative stress and decreased mitochondrial function but does not lead to muscle atrophy during aging, *Aging Cell*, 2011, pp. 493–505. https://doi.org/10.1111/j.1474-9726.2011.00695.x

Margaritelis, N.V., Paschalis, V., Theodorou, A.A., et al., Redox basis of exercise physiology, *Redox Biol.*, 2020, vol. 35, p. 101499. https://doi.org/10.1016/j.redox.2020.101499

Marques-Aleixo, I., Oliveira, P.J., Moreira, P.I., et al., Physical exercise as a possible strategy for brain protection: Evidence from mitochondrial-mediated mechanisms, *Prog. Neurobiol.*, 2012, vol. 99, pp. 149–162. https://doi.org/10.1016/j.pneurobio.2012.08.002

McClung, J.M., Deruisseau, K.C., Whidden, M.A., et al., Overexpression of antioxidant enzymes in diaphragm muscle does not alter contraction-induced fatigue or recovery, *Exp. Physiol.*, 2010, vol. 95, pp. 222–231. https://doi.org/10.1113/expphysiol.2009.049650

Min, K., Smuder, A.J., Kwon, O.S., et al., Mitochondrial-targeted antioxidants protect skeletal muscle against immobilization-induced muscle atrophy, *J. Appl. Physiol. (1985)*, 2011, vol. 111, pp. 1459–1466. https://doi.org/10.1152/japplphysiol.00591.2011

Morgunova, G.V. and Klebanov, A.A., Age-related AMP-activated protein kinase alterations: from cellular energetics to longevity, *Cell Biochem. Funct.*, 2019, vol. 37, pp. 169–176. https://doi.org/10.1002/cbf.3384

Petersen, K.F., Befroy, D., Dufour, S., et al., Mitochondrial dysfunction in the elderly: possible role in insulin resistance, *Science*, 2003, vol. 300, pp. 1140–1142. https://doi.org/10.1126/science.1082889

Petrick, H.L. and Holloway, G.P., Revisiting mitochondrial bioenergetics: experimental considerations for biological interpretation, *Function*, 2020, vol. 2, p. zqaa044. https://doi.org/10.1093/function/zqaa044

Powers, S.K., Smuder, A.J., and Judge, A.R., Oxidative stress and disuse muscle atrophy: Cause or conse-

quence?, *Curr. Opin. Clin. Nutr. Metab. Care*, 2012, vol. 15, pp. 240–245. https://doi.org/10.1097/MCO.0b013e328352b4c2

Radák, Z., Naito, H., Kaneko, T., et al., Exercise training decreases DNA damage and increases DNA repair and resistance against oxidative stress of proteins in aged rat skeletal muscle, *Pflügers Archiv*, 2002, vol. 445, pp. 273–278. https://doi.org/10.1007/s00424-002-0918-6

Rodney, G.G., Pal, R., and Abo-Zahrah, R., Redox regulation of autophagy in skeletal muscle, *Free Radical Biol. Med.*, 2016, vol. 98, pp. 103–112. https://doi.org/10.1016/j.freeradbiomed.2016.05.010

Safdar, A., Bourgeois, J.M., Ogborn, D.I., et al., Endurance exercise rescues progeroid aging and induces systemic mitochondrial rejuvenation in mtDNA mutator mice, *PNAS USA*, 2011, vol. 108, pp. 4135–4140. https://doi.org/10.1073/pnas.1019581108

Shilovsky, G.A. and Ashapkin, V.V., Transcription factor Nrf2 and mitochondria—friends or foes in the regulation of aging rate, *Biochemistry*, 2022, vol. 87, pp. 1477–1486.

Shilovsky, G.A., Putyatina, T.S., Morgunova, G.V., et al., A crosstalk between the biorhythms and gatekeepers of longevity: Dual role of glycogen synthase kinase-3, *Biochemistry*, 2021, vol. 86, pp. 433–448.

Short, K.R., Bigelow, M.L., Kahl, J., et al., Decline in skeletal muscle mitochondrial function with aging in humans, *PNAS USA*, 2005, vol. 102, pp. 5618–5623. https://doi.org/10.1073/pnas.0501559102

Sohal, R.S. and Orr, W.C., The redox stress hypothesis of aging, *Free Radical Biol. Med.*, 2012, vol. 52, pp. 539–555. https://doi.org/10.1016/j.freeradbiomed.2011.10.445

Steiner, J.L., Murphy, E.A., McClellan, J.L., et al., Exercise training increases mitochondrial biogenesis in the brain, *J. Appl. Physiol. (1985)*, 2011, vol. 111, pp. 1066–1071. https://doi.org/10.1152/japplphysiol.00343.2011

Stølen, T.O., Høydal, M.A., Kemi, O.J., et al., Interval training normalizes cardiomyocyte function, diastolic Ca^{2+} control, and SR Ca^{2+} release synchronicity in a mouse model of diabetic cardiomyopathy, *Circ. Res.*, 2009, vol. 105, pp. 527–536. https://doi.org/10.1161/CIRCRESAHA.109.199810

Talbert, E.E., Smuder, A.J., Min, K., et al., Immobilization-induced activation of key proteolytic systems in skeletal muscles is prevented by a mitochondria-targeted antioxidant, *J. Appl. Physiol. (1985)*, 2013, vol. 115, pp. 529–538. https://doi.org/10.1152/japplphysiol.00471.2013

Trifunovic, A. and Larsson, N.G., Mitochondrial dysfunction as a cause of ageing, *J. Intern. Med.*, 2008, vol. 263, pp. 167–178. https://doi.org/10.1111/j.1365-2796.2007.01905.x

Tryfidou, D.V., McClean, C., Nikolaidis, M.G., and Davison, G.W., DNA damage following acute aerobic exercise: A systematic review and meta-analysis, *Sports Med.*, 2020, vol. 50, pp. 103–127. https://doi.org/10.1007/s40279-019-01181-y

Turrens, J.F., Mitochondrial formation of reactive oxygen species, *J. Physiol.*, 2003, vol. 552, pp. 335–344. https://doi.org/10.1113/jphysiol.2003.049478

Umanskaya, A., Santulli, G., Xie, W., et al., Genetically enhancing mitochondrial antioxidant activity improves muscle function in aging, *PNAS USA*, 2014, vol. 111, pp. 15250–15255. https://doi.org/10.1073/pnas.1412754111

van Houten, B., Hunter, S.E., and Meyer, J.N., Mitochondrial DNA damage induced autophagy, cell death, and disease, *Front. Biosci.*, 2016, vol. 21, pp. 42–54. https://doi.org/10.2741/4375

Vyssokikh, M.Y., Holtze, S., Averina, O.A., et al., Mild depolarization of the inner mitochondrial membrane is a crucial component of an anti-aging program, *PNAS USA*, 2020, vol. 117, pp. 6491–6501. https://doi.org/10.1073/pnas.1916414117

Watanabe, D., Aibara, C., and Wada, M., Treatment with EUK-134 improves sarcoplasmic reticulum Ca^{2+} release but not myofibrillar Ca^{2+} sensitivity after fatiguing contraction of rat fast-twitch muscle, *Am. J. Physiol.: Regul., Integr. Comp. Physiol.*, 2019, vol. 316, pp. R543–R551. https://doi.org/10.1152/ajpregu.00387.2018

Wenz, T., Mitochondria and PGC-1α in aging and age-associated diseases, *J. Aging Res.*, 2011, vol. 2011, p. 810619. https://doi.org/10.4061/2011/810619

Williamson, J. and Davison, G., Targeted antioxidants in exercise-induced mitochondrial oxidative stress: Emphasis on DNA damage, *Antioxidants*, 2020, vol. 9, p. 1142. https://doi.org/10.3390/antiox9111142

Yarygin, V.N., *Rukovodstvo po gerontologii i geriatrii* (Guide to Gerontology and Geriatrics), vol. 1: *Osnovy gerontologii. Obshchaya geriatriya* (Fundamentals of Gerontology. General Geriatrics), Yarygin, V.N. and Melent'ev, A.S., Eds., Moscow: GEOTAR-Media, 2010.

Zhang, R., Wang, Y., Ye, K., et al., Independent impacts of aging on mitochondrial DNA quantity and quality in humans, *BMC Genomics*, 2017, vol. 18, p. 890. https://doi.org/10.1186/s12864-017-4287-0

Zhang, X., Trevino, M.B., Wang, M., et al., Impaired mitochondrial energetics characterize poor early recovery of muscle mass following hind limb unloading in old mice, *J. Gerontol., Ser. A*, 2018, vol. 73, pp. 1313–1322. https://doi.org/10.1093/gerona/gly051

Zorov, D.B., Isaev, N.K., Plotnikov, E.Y., et al., The mitochondrion as janus bifrons, *Biochemistry*, 2007, vol. 72, pp. 1115–1126. https://doi.org/10.1134/s0006297907100094

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