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Advances in the Effects of Aerobic Exercise on Mitochondrial Function and Anti-aging of Muscles

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Abstract: *The aging of skeletal muscle is associated with the change of mitochondrial function. In increasingly aging society, exercise has been an important factor for health. Recent research showed that the decrease of proteins related to mitochondrial dynamics and the loss of skeletal muscle mass were only associated with protein OPA1. Aerobic exercise could increase the level of OPA1 in skeletal muscle, increase the amount of mitochondria and the secretion of cytokines in skeletal muscle, inhibit the generation of reactive oxygen species (ROS), thus regulate donwstream effectors, inhibit skeletal muscle atrophy and influence systemic metabolism and aging.*

Keywords: *aerobic exercise, skeletal muscle, signing, mitochondrial dynamics*

1. Introduction

Keletal muscle aging is a risk factor of age-associated diseases, such as metabolic syndrome, cancer, Alzheimer's disease and Parkinson's disease [1]. During the aging process, the aging and atrophy of skeletal muscle would accelerate the aging and decrease physical functions. Recent study showed that the change of mitochondrial dynamics may be involved in the degeneration of muscle mass and function over time. Scientific exercise can prevent and improve muscle complications, thus have been interested in scientific community. It can delay aging and extend long lifespan as well as achieve healthy aging through exercise intervention.

The decrease of mitochondrial function and activity is closely associated with normal aging. Mitochondia shall be considered as the platform of intracellulr signal transduction and the regulator of innate immunity and stem cell activity, rather than simple bio-energy factory. Mitochondrial function was decreased with increasing age, thus the respiration was decreased. Mitochondrial dynamics was a major factor of mitochondrial function and mass, and was involved in mitochondrial autophagy and the stability of mitochondrial DNA. The adenosine triphosphates (ATPs) in most cells are produced in mitochondroia, especially, muscle cells need a large amount of ATPs for mechanical and energetic demand, including muscle contraction, ion transportation, protein synthsis and other metabolism. The relationship between mitochondrial function and aging was mostly manifested by the change of skeletal muscle in aging. Most studies indicated that aging was accompanied by accelearated loss of both muscle mass and strength. Goodpaster B, et al demonstrated that the mean annual decrease of mascle mass was approximately 1% in the lefetime, and for patients ≥ 70 years old, the decrease may be accelearated by 2-4 fold [2]. It was reported that regular exercise and aerobic exercise were benefical to a series of age-associated diseases (such as sarcopenia) and age-associated decrease of cardiac and cognitive function.

2. Aerobic exercise and anti-aging of skeletal muscle

2.1 Aerobic exercise and skeletal muscle stress

Aerobic exercise can rescue the aging of skeletal muscle mitochondria, repair damaged skeletal muscle mitochondria and decrease the fragmentation of skeletal muscle mitochondria. Skeletal muscle is the main site of metabolism and the most aboudant tissues in human body, accounting for approximately 50% of body weight. As the largest protein reservoir, muscle was the source of amino acids, and could produce energy in the catabolism in organs. Skeletal muscle satellite cells are specific precursors and can be activated in the case of muscle regeneration or muscle damage. For the elderly, the activation of skeletal muscle satellite cells in muscle damage or muscle regeneration is less and

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positively related to the telomere length of cells. This cell reservoir was normally decreased during aging, yet aerobic exercise could stimulate the satellite cells, thus balance the aging. Moderate aerobic exercise could increase the methylation level of apoptosis-associated speck-like protein caspase gene in proinflammatory cells. This gene regulated the interleukine 18 (IL-18) and IL -1b in the leukocytes in the elderly, thus decreased the age-associated proinflammatory cytokines [3].

IGF-1/Akt/mTOR is a key signal pathway of skeletal muscle development and regeneration. The damage of skeletal muscle autophagy will disrupt the balance between synthesis and degradation of skeletal muscle proteins, leading to skeletal muscleatrophy. Aerobic exercise could increase autophagy activity, influence Akt/mTOR and Akt/FOXO3 signal pathways through regulating IGF-1 and its receptor, thus decrease the apoptosis of muscle cells and cardiovascular risk as well as eliminate the injury leading to neurodegeneration[4]. Skeletal muscle could activate CaMK through repeated contraction. CaMK could induce the expression of Peroxisome Proliferator-Activated Receptor Gamma Activated Factor 1 (PGC-1), which was a major modulator of skeletal muscle mitochondrial synthesis. Long-time aerobic exercise could result in significant metabolic change, including the effects on Ca2+-CaMK-calcineurin pathway, cAMP-PKA-P38MAPK pathway and AMPK-SIRT-mTOR pathway, to regulate downstream effectors. AMPK is linked to multiple signal pathways and can reflect the lack of cellular energy. Once being activeted, AMPK can trigger metabolism pathway to compensate the defect, such as increasing mitochondiral bio-synthesis and inhibiting the anabolic pathways that consume ATP. Mice lacking AMPK activity in skeletasl muscle showed approximately 50 % less of mitochondria content in skeletasl muscle. Moderate aerobic exercise could promote the activation of AMPK, improve muscular function and decrease the side effect of doxorubicin (DOX).

Importantly, aerobic exercise could counteract physical deterioration through maintaining and improving muscular metabolism and various organ functions. It was reported that caloric restriction and low calorie intake could delay cellular aging, sedentary lifestyle and sharp increase of caloric intake caused damage to human body, long-time aerobic exercise required heat dissipitation, which was beneficical to body hair loss and sweat gland diffusion, these changed the metabolic level in human body significantly, thus delay the aging.

2.2 Aerobic exercise and the secretory regulatory function of skeletal muscle

Skeletal muscle was considered as the effector in human body conventionally, yet it was also the largest secretory organ. The cytokines and growth factors that were secreted by muscles were called actins, which were predominantly expressed in muscular tissues, some actins were also expressed in other tissues. Many actins secreted by muscles, such as MSTN, IGF1, Irisin, FGF21 and IL-6, could influence the metabolism significantly [5]. Among others, myostatin (MSTN) was a key regulator of the homeostasis of skeletal muscle mass, and could influence the synthesis of fat. MSTN could promote the generation of immature adipocytes with increased insulin sensitivity and capacity of glucose oxidation. Exercise could up-regulate the expression of brain-derived neurotrophic factor (BDNF) and promote the remodeling of chromatin containing BDNF gene.

Muscle contraction and exercise could increase the expression of IL-6 in muscles and circulating level of IL-6 by 100 fold. IL-6 was closely associated with immunity, and the regulation of the expression level of IL-6 could increase immunity. IL-6 also played important roles in glucose intake, degradation of fat and regulation of insulin. Aerobic exercise could increase the expression level of IL-15 in muscles, yet overexpression of IL-15 could enhance the oxidation of fatty acid and increase insulin sensitivity. Both IL-8 and CXCR2 were involved in neovascularization. Exercise (and other metabolic stimuli) could stimulate the secretion of proteins and small molecules, which combined the systemic adapation that exercise required to regulate systemic metabolism. In future, further studies are needed to investigate various proteins secreted by skeletal muscle and complement the list of actins secreted by muscles.

3. The regulation of mitochondrial dynamics by aerobic exercise

Aerobic exercise can significantly enlarge the network of mitochondria and vessels, and partially change the content of myofibril in muscle fibers. The morphological change of mitochondria is influenced by the balance between mitochondrial fusion and fission. Aerobic exercise can regulate the balance between mitochondrial fusion and fission through regulating the expression of Mfn1\Mfn2, OPA1 and DRP1.

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3.1 The effects on key proteins of mitochondrial dynamics in skeletal muscle and anti-aging of skeletal muscle by aerobic exercise

Optic nerve atrophy protein 1 (OPA1) is located on the mitochondrial inner membrane and facing the intermembrance space, and plays important roles in the mitochondrial inner membrane fusion and the fomation of cristae. The decreased expression level of OPA1, which is related to mitochondrial fusion, can change the trend of the balance between mitochondrial fusion and fission toward fission. Therefore, OPA1 can be considered as both the effector of fusion and the inhibitor of fission. It was reported that the expression levels of OPA1, Mfn1 and DRP1 were decreased in individuals with sedentary lifestyle, and regular exercise could counteract the decrease [6]. In addition to the role in fusion, OPA1 played direct role in regulating the diameter of the cristae joint during apoptosis. The deficiency of OPA1 resulted in decreased mitochondrial fusion, increased mitochondrial fragmentation and other cellualr deficiency, including the decrease of cristae, significantly decrease of respiratory capacity and sensitivity as well as apoptosis.

Aerobic exercise could upregulate the expression level of Mfn1 mRNA. Zhang L, et al showed that after ischemia of the brain before exercise, treadmill exercise could increase the levels of OPA1 and COXII / III / IV in mitochondria [7]. Zhao Fei, et al showed that after 8 weeks of aerobic exercise, the levels of Mfn2, Opa1 and Drp1 in the mitochondria of skeletal muscle in exercise group was not higher than those in non-exercise group, indicating that mitochondrial fusion and fission were closely associated with aerobic exercise, and aerobic exercise could increase mitochondrial fusion and fission.

Seungmin Lee, et al found aging-associated phenotype change in those cells with knock-out hFis1 gene, and transfection of hFis1 gene in those cells could repair mitochondrial fragmentation, and further inhibit the acitivity of aging-associated β-lactase. A large amount of fission was seen in those mitochondria with simultaneous konck-out of OPA1 and hFis1, leading to change of aging-associated phenotypes. Persistent elongation of mitochondria could result in decreased membrane potential, increased generation of ROS and DNA damage. Thus, an important function of mitochondrial fission was to inhibit cell aging due to persistent elongation of mitochondria.

However, Chen H observed complete non-fission in mitochondria with knock-out Mfns resulted in decreased membrane potential and respiration as well as unhealthy cell proliferation, yet fragmented mitochondria could not cause these injuries. Mitochondrial fusion, rather than fission, dominated the maintenance of cell function and aging.

Caterina Tezze, et al reported the test results in 24 persons [8]: the levels of OPA1, Mfn1 and DRP1 in the mitochondria of elderly persons were decreased than those in youngster and elderly athletes, incicating that these factors were decreased with increasing age. Long-time regular exercise could counteract the decrease of these factors and decreased skeletal mass and strength. They found that the decrease of mitochondrial morphogenetic proteins was only related to OPA1, rather than Drp1 or Mfn1. Similarly, decreased muscle strength was significantly related to decreased expression level of OPA1, rather than Drp1 or Mfn1. Mouse experiment showed the same results. Unexpectedly, the level of OPA1 was significantly increased in the gastrocnemius muscles in elderly mice after 1 week of exercise intervention. These studies of elderly mice with knock-out OPA1 gene found that the absence of OPA1 could result in compensatory up-regalution of PGC1α and Mfn1 in mitochondria, while the level of fission-related Drp1 was not increased. Interestingly, Klotho (KLB) and FGF receptor (FGFR) were expressed in skeletal muscle, FGF21 was significantly up-regulated in a time-dependent manner, leading to increased level of circulating FGF21. Many studies found that the regulator of mitochondrial morphology - fusioin/fission protein was involved in the regulation of cell aging, yet the role of fusioin/fission protein in aging was controversial

3.2 The effects on mitochondrial DNA in skeletal muscle and anti-aging of skeletal muscle by aerobic exercise

Aerobic exercise can influence many regulators of gene expression through various signal pathways. Most signal pathways, including calcineurin, p38, adrenaline signal and SIRT, were associated with PGC-1. The aging of human body can result in accumulation of ROS. When accumulation of ROS is higher than threshold, mitochondrial respiration will be decreased. Accumulation of ROS is the main reason of DNA oxidative damage and mutation. The mutation of mitochondrial DNA in skeletal muscle can decrease the activity of key complex in mitochondrial respiratory chain, such as complex protein I (COXI) and complex protein IV (COXIV). It was reported that long-time aerobic exercise could enable the expression of mitochondrial fusion/fission genes respond rapidly to increased

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metabolic demand, indicating that long-time aerobic exercise could regulate mitochondrial fusion and fission.

The interruption of the balance between mitochondrial fusion and fission increases mitochondrial fragmentation. Mitochondrial fragmentation can activate AMPK-FoxO3 axis, which can induce the expression of atrophy-related genes, protein degradation and loss of muscles. It was reported that aerobic exercise could increase the expression of PGC-1α proteins, over-expression of PGC-1α could prevent the decrease of pro-fusion proteins (MFN1, Mfn2 and OPA1), meanwhile, PGC-1α could attenuate the up-regulation of MuRF-1, atrogin-1, beclin1 and p62 to regulate muscular atrophy.

In general, aerobic exercise could increase the expression of mitochondrial fusion protein OPA1 in skeletal muscle, decrease endoplasmic reticulum (ER) stress, increase antioxidant capacity, activate mitochondrial autophagy, decrease mitochondrial fragmentation and maintain mitochondrial function, thus could prevent skeletal muscle aging. The stable balance between mitochondrial fusion and fission inhibited the production of ROS, thus inhibited FoxO-related signal pathways to decrease skeletal muscle atrophy.

4. Aerobic exercise and other mitochondrial functions

Mitochondria is a regulator of innate immune response. A marker of aging is mild, chronic and aseptic inflammatory state, which is usually considered as “inflammation”. The development of this state was partially attributed to increased circulating inflammatory factors, such as IL-6 and C-reactive protein, and a known risk factor of increasing elderly morbidity and mortality [9]. Both mitochondrial DNA and formylated peptide were considered as mitochondria derived damage associated molecular mode (DAMP), which could stimulate innate immune system. The importance of TLR9 responses caused by mitochondria could be seen in many important medical inflammatory state, including trauma and heart failure.

Mitochondria is the main hub of cellular metabolism and generation of ROS. Mitochondrial injury and decreased mitochondrial function can accelerate the leakage of electrons in mitochondrial respiratory chain and the decrease of ATP. Loss of skeletal muscle and cell aging are usually related to the generation rate of mitochondria ROS. Interestingly, increased level of ROS could entend the life of both yeast and caenorhabditis elegans [10]. However, ROS predominantly prevents the damage of aging compensatively. When the level of ROS is higher than specific threshold, aging will be accelerated, leading to further mitochondrial injury and cell damage. The balance between oxidants and antioxidants may be interrupted during exercise, this was characterized by the fact that long-time exercise could produce antioxidant response, resistance and adapatation to exercise in elderly skeletal muscle [11].

5. Conclusion

The interruption of the dynamic balance in the mitochondria of skeletal muscle is a reason for muscle atrophy. We emphasized the key evidences that aerobic exercise and mitochondrial dynamics in skeletal muscle played regulatory roles in aging and age-associated diseases. Aerobic exercise significantly increased the level of mitochondrial fusion protein OPA1, over-expression of OPA1 could decrease endoplasmic reticulum stress (ER), repair injured mitochondria and delay body aging. Possible mechanism included: aerobic exercise could inhibit the generation of ROS, induce mitochondrial autophagy and the expression of various actins, decrease mitochondrial fragmentation through increasing the expression of mitochondrial fusion protein OPA1 and mitochondrial function, so as to increase antioxidant capacity, inhibit skeletal muscle atrophy and delay body aging.

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