Advances in Mitochondrial Transplantation for the Treatment of Sarcopenia

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Abstract

Sarcopenia is a comprehensive disease characterized by age-related decline in skeletal muscle mass and strength, representing a major health challenge for the elderly. Accumulating evidence demonstrates that mitochondrial dysfunction plays a pivotal role in the pathogenesis of sarcopenia. Lifestyle interventions, such as exercise, nutrition, and pharmacological treatments, have limited efficacy in treating sarcopenia, necessitating urgent solutions to maintain and improve skeletal muscle health. Mitochondrial transplantation (MTP) is an emerging therapeutic modality for treating tissue damage resulting from mitochondrial dysfunction. Given the critical role of mitochondria in skeletal muscle function and metabolism, mitochondrial transplantation may represent a novel therapeutic strategy for sarcopenia. In this review, we summarize the mitochondrial-related molecular mechanisms underlying sarcopenia and discuss mitochondrial transplantation as a potential therapeutic option.

Full Text

Advances in Mitochondrial Transplantation Therapy for Sarcopenia

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Abstract

Sarcopenia is a comprehensive disease characterized by aging-induced decline in skeletal muscle mass and strength, representing a major health challenge for the elderly. Accumulating evidence demonstrates that mitochondrial dysfunction plays a pivotal role in the pathogenesis of sarcopenia. Lifestyle interventions such as exercise, nutrition, and pharmacological treatments have shown limited efficacy, necessitating urgent development of solutions to maintain and improve skeletal muscle health. Mitochondrial transplantation (MTP) is an emerging therapeutic approach for treating tissue damage caused by mitochondrial dysfunction. Given the critical role of mitochondria in skeletal muscle function and metabolism, mitochondrial transplantation may represent a novel strategy for sarcopenia treatment. This review summarizes the mitochondrial-related molecular mechanisms underlying sarcopenia and discusses mitochondrial transplantation as a potential therapeutic option.

Keywords: Sarcopenia; Mitochondrial dysfunction; Mitochondrial quality control; Mitochondrial transplantation; Limitations

Sarcopenia is a disease associated with age-related loss of skeletal muscle mass, decreased muscle strength, and/or reduced muscle function. It significantly impacts quality of life in older adults and increases the risk of falls and fractures. The prevalence of sarcopenia is approximately 19.8%, with severe sarcopenia affecting 7.9% of the population, leading to substantially increased healthcare costs [1]. These statistics underscore that sarcopenia will become a major challenge in aging societies. The molecular mechanisms underlying sarcopenia involve multiple complex biological processes, including altered signaling pathways regulating protein synthesis and degradation, diminished satellite cell function, dysregulated inflammatory responses, and mitochondrial dysfunction [2]. Research has identified mitochondrial dysfunction as a critical factor in the progression of age-related sarcopenia.

Mitochondrial dysfunction leads to reduced adenosine triphosphate (ATP) synthesis, impaired bioenergetics, and mitochondrial DNA (mtDNA) mutations, all of which are associated with skeletal muscle mass loss and functional decline. Furthermore, dysfunctional mitochondria initiate the release of reactive oxygen species (ROS), resulting in impaired mitochondrial quality control (MQC), decreased protein synthesis, and apoptosis [3]. Mitochondrial quality control encompasses biogenesis, fusion, fission, and autophagy, with multiple cytokines and molecular signals participating to maintain mitochondrial integrity. Failure of mitochondrial quality control can lead to mitochondrial dysfunction and muscle functional deterioration.

Given the important role of mitochondrial dysfunction in sarcopenia development, mitochondrial transplantation may serve as a potential therapeutic strategy by improving mitochondrial bioenergetics and modulating mitochondrial-related signaling pathways [4]. While mitochondrial transplantation for various diseases has garnered significant attention, studies evaluating its therapeutic

efficacy in preventing skeletal muscle atrophy remain limited [4,5]. Therefore, further exploration of mitochondrial transplantation' s potential for sarcopenia treatment is warranted. This review emphasizes the critical role of mitochondria in skeletal muscle, examines the mechanisms by which MQC contributes to sarcopenia, summarizes current preclinical and clinical studies on mitochondrial transplantation, and proposes that mitochondrial transplantation may represent a viable therapeutic strategy for sarcopenia.

1. Sarcopenia and Mitochondrial Dysfunction

Although the precise mechanisms of sarcopenia remain incompletely understood, mitochondrial dysfunction has been recognized as a crucial mechanism of skeletal muscle aging [2,6]. Mounting evidence indicates the presence of damaged and dysfunctional mitochondria in skeletal muscle of both aged rodents and humans [6]. Using ^{31}P magnetic resonance spectroscopy, researchers have demonstrated reduced oxidative phosphorylation activity in older adults compared to younger controls [7]. Impaired redox status is also associated with increased mtDNA mutations and accumulation of damaged mitochondria [8]. Coen et al. [9] found that the ratio of ATP synthesis to oxygen consumption correlates with gait speed, which the Asian Working Group for Sarcopenia has proposed as a screening indicator for sarcopenia. Additional studies have linked mitochondrial apoptotic signaling with slower walking speed and reduced muscle volume in older adults [10]. These findings suggest that age-related disruption of skeletal muscle mitochondria may be associated with sarcopenia progression. However, Inci et al. [11] discovered that in a biological model of cellular senescence, naked mole-rats with lifespans up to 32 years maintain skeletal muscle mitochondrial function and structure into late life without developing age-related diseases. The molecular basis of interactions between mitochondria and sarcopenia is complex, making it essential to understand the multiple signaling pathways activated by mitochondria to effectively intervene in sarcopenia.

2. Mitochondrial Quality Control

Mitochondrial quality control (MQC) involves mitochondrial biogenesis, mitochondrial dynamics (fusion-fission), and mitophagy, with multiple cytokines and molecular signals participating to maintain mitochondrial integrity. MQC is essential for regulating mitochondrial morphology, quality, and function.

2.1 Mitochondrial Biogenesis

Mitochondrial biogenesis refers to the process of mitochondrial proliferation and systematic synthesis. This process is tightly regulated by peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α). PGC-1α can activate and promote the expression of various transcription factors in mitochondrial biogenesis pathways [12]. Recent rodent model studies have revealed connections between PGC-1α-centered biosynthesis-related gene expression

and skeletal muscle aging. In sarcopenia development, researchers have found reduced expression levels of PGC-1α, nuclear respiratory factor 1 (NRF1), and mitochondrial transcription factor A (TFAM) in skeletal muscle of the senescence-accelerated mouse prone 8 (SAMP8) model [13]. Yang et al. [14] observed decreased PGC-1α expression in aged rodents, accompanied by reduced skeletal muscle mitochondrial mass. However, compared to controls, PGC-1α overexpression increased skeletal muscle cross-sectional area and mass in aged mice by increasing mitochondrial protein content, antioxidant enzyme activity, and altering gene expression [14,15]. Based on these findings, PGC-1α-mediated mitochondrial biogenesis may represent a promising therapeutic target for sarcopenia.

2.2 Mitochondrial Dynamics (Fusion-Fission)

Mitochondrial dynamics regulation depends on the dynamic balance between fusion and fission. This process enables mitochondria, as dynamic organelles, to form network structures in cells, allowing rapid response to different physiological demands in skeletal muscle. It plays a critical role in mitochondrial function and quality control and is strictly regulated by highly complex protein factors.

The mitochondrial fusion process is primarily regulated by guanosine triphosphatases (GTPases), including mitofusin 1 (Mfn1) and Mfn2 on the outer mitochondrial membrane, and optic atrophy 1 (OPA1) on the inner mitochondrial membrane. These fusion mechanisms facilitate component distribution from damaged mitochondria to healthy ones, preventing accumulation of damaged mitochondria [16]. In animal models, mice lacking Mfn1 and Mfn2 exhibit reduced exercise capacity associated with impaired mitochondrial bioenergetics [17]; OPA1 deletion in mice leads to growth retardation, reduced muscle fiber volume, and increased inflammation, resulting in skeletal muscle atrophy [18]. Therefore, failed mitochondrial fusion leads to skeletal muscle atrophy, decreased physical function, and increased lethality.

Conversely, mitochondrial fission is mainly controlled by dynamin-related protein 1 (Drp1) and mitochondrial fission protein 1 (Fis1). In a recent study, Dulac et al. [19] demonstrated that low Drp1 expression in mouse skeletal muscle causes mitochondrial dysfunction, impaired autophagy, and denervation, inducing severe muscle atrophy. On the other hand, muscle-specific Drp1 overexpression in transgenic mice reduces mtDNA levels and weakens protein synthesis [20]. Collectively, these data indicate that mitochondrial fission must be maintained within physiological ranges, and stable Drp1 levels are necessary for preserving mitochondrial function. Additionally, other studies have shown that loss of Fis1 impairs mitochondrial function and muscle protein homeostasis, reducing flight ability and lifespan in Fis1-mutant Drosophila [21].

2.3 Mitophagy

Another major cause of mitochondrial dysfunction in aging muscle is impaired mitophagy mechanisms. Mitophagy selectively removes dysfunctional and damaged mitochondria to maintain mitochondrial homeostasis. Recently, the PINK1/Parkin pathway has been recognized as one of the most important signaling pathways regulating ubiquitin-dependent mitophagy [22]. Briefly, after mitochondrial membrane potential damage, PTEN-induced kinase 1 (PINK1) recognizes damaged mitochondria and accumulates on the outer mitochondrial membrane, then activates the E3 ubiquitin ligase Parkin protein to promote mitochondrial ubiquitination and initiate mitophagy.

Accumulation of damaged mitochondria leads to skeletal muscle cell dysfunction. In the SAMP8 model of accelerated aging, impaired mitophagy has been observed in sarcopenic mice [13]. Animal studies show that Parkin-deficient mice exhibit decreased muscle contractile function and damaged skeletal muscle mitochondria [23]. Conversely, rodent studies indicate that Parkin overexpression alleviates aging-related loss of muscle mass and strength while improving mitochondrial biogenesis and enzyme activity [24]. These findings demonstrate a close relationship between reduced mitophagy during aging and skeletal muscle function. Recent research suggests that mitochondrial-derived vesicles (MDVs) may also represent a novel method for eliminating damaged mitochondria or alternative mitophagy [25]. Notably, a recent study identified MDV-derived NADH:ubiquinone oxidoreductase subunit S3 (NDUFS3) as a potential new predictor of sarcopenia [26].

3. Mitochondrial Transplantation

Exercise, nutrition, and pharmacotherapy are the most effective strategies for preventing and treating sarcopenia. However, some older adults cannot benefit from exercise due to chronic conditions such as osteoarthritis, heart disease, or stroke. The optimal dosage, frequency, and duration of high-quality protein intake for affecting muscle mass or function remain unclear [27]. While selective androgen receptor modulators (SARMs) have been shown to enhance skeletal muscle function and increase lean body mass, potential side effects have prevented FDA approval to date [28]. Mitochondrial transplantation has attracted scientific attention as a potential therapeutic method for diseases associated with mitochondrial or mtDNA dysfunction. Transplanted mitochondria can enter cells, induce mitochondrial gene transfer, alter bioenergetics, and reprogram metabolism [29].

3.1 Preclinical Studies of Mitochondrial Transplantation

Numerous studies have demonstrated the therapeutic potential of mitochondrial transplantation for various diseases, primarily focusing on ischemia models of neurological, cardiac, renal, and hepatic disorders. Zhang et al. [30] employed a rat middle cerebral artery occlusion model, transplanting autologous mito-

chondria isolated from the pectoralis major muscle into the lateral ventricle of the cerebral ischemic injury model. They observed increased viable mitochondria in cerebrospinal fluid, reduced cellular oxidative stress and apoptosis, and participation in neuroprotection following ischemia-reperfusion injury. Guariento et al. [31] investigated the efficacy of mitochondrial transplantation for myocardial protection in a cardiac ischemia-reperfusion model, finding that mitochondrial transplantation significantly increased coronary blood flow and ejection fraction while reducing infarct size. In a renal ischemia model, Jabbari et al. [32] demonstrated the effectiveness of mitochondrial transplantation by injecting mitochondria isolated from skeletal muscle tissue into the renal artery, showing that mitochondrial transplantation could prevent renal tubular cell death, improve renal function, enhance tubular regenerative potential, and reduce apoptosis. Lin et al. [33] reported that mitochondrial transplantation ameliorates hepatic ischemia-reperfusion injury by administering mitochondria isolated from rabbit left ventricle via splenic injection, resulting in reduced ROS levels and apoptotic cells. Lee et al. [34] injected isolated mitochondria into the knee joints of osteoarthritis rats, finding decreased pro-inflammatory cytokine levels, improved mitochondrial function, ameliorated cartilage destruction and bone loss, and pain relief. Furthermore, recent animal studies have found that mitochondrial transplantation can improve anxiety and depression behaviors in aged rats [35] and produce anti-aging effects [36], with reparative effects on neurodegenerative diseases such as Parkinson' s disease [37] and hippocampal damage following epilepsy [38].

3.2 Sarcopenia and Mitochondrial Transplantation

Given the critical role of mitochondrial dysfunction in sarcopenia pathogenesis, mitochondria represent a potential therapeutic target for preventing or treating this age-related disease. Mitochondrial transplantation has been successfully used to treat muscle atrophy, myopathy, and ischemic muscle injury, laying the groundwork for subsequent research in sarcopenia treatment. In a dexamethasone-induced skeletal muscle atrophy model, Kim et al. [4] found that mitochondrial transplantation increased muscle mass and enhanced expression of the muscle regeneration marker desmin. Importantly, mitochondrial transplantation significantly reduced expression of muscle-specific ubiquitin E3 ligases MAFbx (muscle atrophy F-box protein) and MuRF-1 (muscle-specific RING finger protein 1) through the Akt-FoxO (protein kinase B-forkhead box protein O) signaling pathway. These results demonstrate the therapeutic potential of mitochondrial transplantation in atrophic muscle diseases [4]. Orfany et al. [39] transplanted different proportions of mitochondria directly into limb muscles two hours after limb ischemia, showing reduced apoptosis and infarct area in the soleus, gastrocnemius, and vastus medialis muscles. Similarly, Alway and colleagues found that systemically administered mitochondria promoted muscle regeneration and improved muscle function in mice with barium chloride-induced muscle injury [5]. They also observed differential regeneration across skeletal muscle fiber types, with the most pronounced regeneration in type

II muscle fibers [5]. While these studies suggest that mitochondrial transplantation may have therapeutic effects on sarcopenia and represents a promising target for age-related diseases, further research is needed to fully elucidate its mechanisms and effects.

3.3 Limitations of Mitochondrial Transplantation

Despite its potential as a therapeutic approach for sarcopenia and promising results in animal experiments, numerous challenges must be addressed before clinical application.

First, the source of transplanted mitochondria is a critical factor in clinical application. Most previous mitochondrial transplantation studies have used mitochondria isolated from autologous tissues, which effectively avoids immune reactions post-transplantation but limits mitochondrial sources, particularly for patients with congenital dysfunction or multiple chronic conditions in old age. Studies have found that bone marrow mesenchymal stem cells as a source of mitochondria for transplantation show promising potential and may provide a novel approach for sarcopenia treatment [40].

Second, mitochondrial isolation can be achieved using techniques such as differential centrifugation and density gradient centrifugation. McCully' s team proposed using differential filtration instead of differential centrifugation to more rapidly isolate highly purified, activated, and intact mitochondria [41]. The narrow time window for mitochondrial isolation also limits clinical application; if storage conditions could be improved to stabilize mitochondrial function without requiring fresh preparation each time, clinical applications of mitochondrial transplantation would be greatly expanded.

Third, isolated mitochondria require proper storage. Both freezing and refrigeration can damage the inner and outer mitochondrial membranes, impairing ATP synthesis capacity, reducing energy production, and inevitably leading to cell apoptosis. Therefore, establishing a method for long-term mitochondrial storage represents a crucial challenge.

Fourth, several pathways mediate intercellular mitochondrial transfer, including tunneling nanotubes (TNTs), extracellular vesicles (EVs), and gap junction channels. Each pathway involves different signaling mechanisms, and it remains unclear whether cells can simultaneously transfer mitochondria through multiple pathways. Zhu et al. [42] found that photobiomodulation (PBM) can promote mitochondrial transfer through connexin 36, enhancing the therapeutic effects of mitochondrial transplantation. As understanding of mitochondrial transfer mechanisms increases and more preclinical studies are conducted, the gap between basic research and clinical application will continue to narrow.

Fifth, the timing and frequency of mitochondrial transplantation require consideration. Current studies indicate that single administration of mitochondria produces non-persistent therapeutic effects, necessitating repeated long-term

dosing. Furthermore, the timing, cycle, and frequency of administration require further experimental research and rigorous clinical investigation.

Sixth, whether mitochondrial transplantation can be combined with other drugs warrants consideration. Maeda et al. [43] found that transactivators of transcription-dextran complexes significantly enhance cellular uptake of exogenous mitochondria and improve mitochondrial protection against oxidative stress in neonatal rat cardiomyocytes.

Additionally, mitochondrial transplantation methods, signals triggering mitochondrial transfer, immune rejection post-transplantation, and ethical issues all represent future challenges and urgent problems to be solved for mitochondrial transplantation therapy in sarcopenia.

As society ages, sarcopenia has become one of the major diseases affecting older adult health. Mitochondrial dysfunction is considered a key factor in sarcopenia pathogenesis, with mitochondrial quality control being critically important for delaying aging-related muscle loss. Mitochondrial transplantation may provide a novel approach for sarcopenia treatment by restoring ATP, reducing inflammation and oxidative stress, inhibiting protein degradation, and preventing apoptosis to maintain muscle health. However, clinical studies on the therapeutic effects of mitochondrial transplantation for preventing skeletal muscle atrophy remain limited. Therefore, further research is needed to explore the potential of mitochondrial transplantation for sarcopenia treatment in both animal models and human clinical trials. Meanwhile, several unresolved questions in mitochondrial transplantation require answers. Once these issues are addressed, mitochondrial transplantation therapy for sarcopenia may achieve widespread clinical application.

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