

The mitochondrial biogenesis signaling pathway is a potential therapeutic target for myasthenia gravis via energy metabolism (Review)

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Abstract. Myasthenia gravis (MG) is an autoantibody-mediated autoimmune disease that is characterized by muscle weakness and fatigue. Traditional treatments for MG target the neuromuscular junction (NMJ) or the immune system. However, the efficacy of such treatments is limited, and novel therapeutic options for MG are urgently required. In the current review, a new therapeutic strategy is proposed based on the mitochondrial biogenesis and energy metabolism pathway, as stimulating mitochondrial biogenesis and the energy metabolism might alleviate myasthenia gravis. A number of cellular sensors of the energy metabolism were investigated, including AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1). AMPK and SIRT1 are sensors that regulate cellular energy homeostasis and maintain energy metabolism by balancing anabolism and catabolism. Peroxisome proliferator-activated receptor γ coactivator 1 α and its downstream transcription factors nuclear respiratory factors 1, nuclear respiratory factors 2, and transcription factor A are key sensors of mitochondrial biogenesis, which can restore mitochondrial DNA and produce new mitochondria. These processes help to control muscle contraction and relieve the symptoms of MG, including muscle weakness caused by dysfunctional NMJ transmission. Therefore, the present review

provides evidence for the therapeutic potential of targeting mitochondrial biogenesis for the treatment of MG.

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1. Introduction

Myasthenia gravis (MG) is an autoimmune disease that is mediated by autoantibodies targeting acetylcholine receptors (AChRs) at the neuromuscular junction (NMJ), ultimately causing damage to skeletal muscles (1). The clinical symptoms of MG include blepharoptosis, muscle weakness, slurred speech and dysphagia, and may also include paralysis of respiratory muscles in severe cases (2-4). Globally, the prevalence of MG is 15-30 per 100,000, with an annual incidence of >1 per 100,000 (5). The mean duration of the myasthenia crisis course is 42 days and, if left untreated, fatality rates may reach 80% (6,7). However, with the advances in medical knowledge, MG-associated worldwide mortality has been reduced from 70% in the 1930s to 30% by 1955, and is currently <10% (8).

To date, treatments for MG are limited to the NMJ or the immune system, and acetylcholinesterase inhibitors are the first-line treatment of MG (9). Neostigmine and pyridostigmine are the most commonly used anticholinesterase drugs in the clinical setting (10). Acetylcholinesterase inhibitors compensate for the degradation of acetylcholine (ACh) and pernicious effects on the NMJ by increasing the concentration of ACh in the synaptic cleft (11). However, this class of drugs can only alleviate symptoms in a minority of the patients, and cannot

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further modify the autoimmune response (12). Therefore, the majority of the patients require adjuvant and synergistic therapy. At present, glucocorticoids are the most effective immunosuppressant adjuvant for the treatment of MG (5). However, due to serious adverse reactions caused by high-dose shock therapy over a short period of time, transient myasthenia aggravation may occur (13). Occasionally, chemical immunosuppressants, including azathioprine, are used in combination therapy, which not only enhance the curative effect, but also help to reduce hormone dosage (14). Although most patients exhibit good tolerance to azathioprine, the effect of the drug is slow and, due to the immunosuppression, patients may be at an increased risk of liver damage and bone marrow suppression, amongst other adverse effects (15). Moreover, it has been demonstrated that the levels of choline acetyltransferase in the thymus of patients with MG and thymic hyperplasia were higher compared with those in control subjects (16), which suggested that an abnormal immune tolerance in the thymus serves an important role in the pathogenesis of MG. Therefore, thymectomy or thymic radiotherapy is a common therapy used for patients with MG, and a previous study reported that ~30% of patients achieved complete and stable remission or pharmacological remission following this surgery (12). However, thymectomy may also disrupt self-tolerance and further lead to immune system dysfunction. Immunomodulatory treatments are promising for the reduction or elimination of MG symptoms (14). Plasma exchange can alleviate symptoms by removing the pathogenic substances in the plasma and reducing the concentration of autoantibodies (17). Effects may be observed from 2 to 5 days following treatment (18,19), but plasma exchange only alleviates MG temporarily by removing harmful substances from the blood. Additionally, plasma exchange may be associated with various complications, such as plasma anaphylaxis (20). Intravenous immune globulin (IVIG) is often used in the emergency treatment of severe myasthenia, and has the advantages of being rapid, effective and relatively low-cost (21). However, IVIG is associated with potential risks of infection and thrombosis (22) (Table I).

Although there are a number of treatment options for MG, ~10% of patients are treatment-intolerant, and up to 80% of patients do not achieve complete stabilization (23). The onset of MG is associated with AChR antibody (AChR-Ab), but there is no clear association between disease severity and antibody titer (24). Moreover, it has been demonstrated that both neuronal and muscular cells in MG are highly sensitive to energy deprivation, which significantly affects signal transmission and the normal physiological function of the NMJ. Therefore, by investigating mitochondrial biogenesis and energy metabolism pathways, the current review puts forward the hypothesis that modulation of mitochondrial biogenesis may represent a viable therapeutic option for MG by regulating energy metabolism, as well as the dysfunctional NMJ transmission.

2. Mitochondrial dysfunction disorders

Previous studies investigating neuromuscular diseases mainly focused on immune responses and synapses of the NMJ (25,26). MG is considered to be a neuromuscular disease, and dysfunctional transmission at the NMJ and autoantibody binding appear to be the initial mechanisms of MG (27). The

NMJ is composed of Schwann cells, which are a highly specialized skeletal muscle cell membrane, and the axon terminal of the motor nerve (28). Damaging any part of this system may cause signal transmission disorders (29,30). The NMJ can be targeted by a variety of autoimmune antibodies, including AChR-Ab, ryanodine receptor antibody, muscle-specific receptor tyrosine kinase antibody (MuSK-Ab) and low-density lipoprotein receptor-related protein 4 antibody (31). These antibodies bind to the postsynaptic membrane, and attack and destroy postsynaptic molecules. This damage to postsynaptic structures occurs by activation of the complement system, enhancing the binding capacity of the AChR or inhibition of the function of ACh, and subsequently induces clinical MG symptoms by reducing AChR numbers and disrupting clustering at muscle tubules (5).

Although the immune mechanisms underlying neuromuscular diseases, such as MG, has been extensively investigated, there are relatively few studies on muscle cell damage and mitochondrial dysfunction. MG autoantibodies do not only induce AChR destruction directly, but also cause intracellular mitochondrial changes (32). In a previous experimental autoimmune MG (EAMG) rat study, it was observed that both mitochondrial structure and skeletal muscle function were compromised to varying degrees (15). Mitochondria are the core source of cellular energy and are essential for the daily activities of hypermetabolic tissues, such as muscle contraction and utilization (33). Mitochondrial dysfunction may affect the normal energy metabolism and, in combination with specific autoantibodies, aggravate neuromuscular disorders (34). Kordas *et al* (24) demonstrated that the mitochondrial protein CHCHD10 is required for ATP production, which facilitates AChR expression and promotes agrin-induced AChR clustering.

Mitochondrial dysfunction and sensitivity of muscle cells to energy deprivation are major characteristics of neuromuscular diseases (35). It has been demonstrated that mitochondrial dysfunction serves an important role in muscular dystrophy muscle consumption (36). Excessive reactive oxygen species (ROS) produced by mitochondrial dysfunction may trigger autophagy, which results in muscle atrophy from an enhanced catabolism and decreased protein synthesis in the skeletal muscle (37). Blocking the extracellular ATP/P2X axis results in enhancement of muscle T regulatory cells and accelerates the muscular dystrophic process in mdx mice (38). Similarly, mitochondrial dysfunction has also been indicated to be one of the important pathogenetic mechanisms involved in amyotrophic lateral sclerosis (ALS) (39). Abnormal mitochondrial morphology and dysfunction have been previously identified in patients with ALS (40). In addition, it has been reported that resting energy consumption in patients with ALS was lower compared with that in healthy individuals using indirect calorimetry (41). Recently, a number of studies have demonstrated that MG is closely associated with dysfunction of mitochondria and muscle cells (42,43). The muscle tissue of patients with MG display abnormal mitochondrial morphology and function, and the energy levels are often significantly lower than normal (44,45). Similarly, abnormally shaped and structured mitochondria on muscle biopsy, ragged-red fibers, loss of mitochondrial respiratory chain complexes-1 and muscle aerobic dysfunction were observed in MG (46,47). These previous findings suggest the

Table I. Most frequently used treatments for myasthenia gravis.

Therapy	Drugs or methods	Typical side effects
Symptomatic therapy	Acetylcholinesterase inhibitors (Neostigmine, pyridostigmine)	Gastrointestinal illnesses
Immunosuppressive therapy	Immunosuppressive drugs (glucocorticoid, azathioprine)	Transient myasthenia aggravation
Thymectomy therapy	Thymectomy	Immune impairment
Supportive therapy	Physical activity and systematic training	Overwork aggravates illness
Immunomodulating therapy	Intravenous immune globulin	Allergic reactions
Plasma exchange	Plasma exchange	Plasma allergy

Table II. A selected list of neuromuscular diseases that exhibit mitochondrial dysfunction.

Diseases	Mitochondrial dysfunction	(Refs.)
MD	Increased ROS and oxidative stress, increased catabolism of muscle and protein degradation, triggering autophagy and decreased ATP	(24-26)
ALS	Increased nutrition and fat mass, decreased respiratory parameters, motor neuron involvement, and decreased metabolism	(27,28)
MG	Decreased metabolism and energy level, mitochondrial respiratory chain complex-1 loss, muscular atrophy, and increased inflammatory responses	(15,29-31)

MD, muscular dystrophy; ALS, amyotrophic lateral sclerosis; MG, Myasthenia gravis; ROS, reactive oxygen species.

presence of mitochondrial abnormalities in neuromuscular diseases, such as MG, which may lead to muscular weakness. Therefore, it is of great significance to further explore the mitochondrial biogenesis signaling pathway and its link to the energy metabolism as a potential target for the treatment of MG (Table II).

3. Regulatory mechanism of mitochondrial biogenesis on MG through energy metabolism

As aforementioned, mitochondrial dysfunction can damage the normal function of muscle, leading to the development of MG. However, the specific role of mitochondria in the pathogenesis of MG remains unclear. Herein, the current review discusses the potential mechanisms regulating mitochondrial function in MG from the perspective of biogenesis and energy metabolism.

The term 'energy metabolism' refers to a series of continuous, cyclic processes in which the energy substance ATP is produced, transported and utilized by the action of ATP synthase or ATP hydrolase, respectively (48). AMP-activated protein kinase (AMPK) is one of the key enzymes of the mitochondrial energy metabolism (49). AMPK can phosphorylate a variety of transcription factors included in the energy metabolism and biogenesis pathways, providing necessary cellular mechanisms for skeletal muscle plasticity (50).

AMPK: A key mitochondrial energy metabolism molecule. AMPK is a serine/threonine protein kinase that regulates

cellular energy metabolism and serves a key role in maintaining the cellular energy balance (51). AMPK is an allo-trimer that is composed of a catalytic α and regulatory β and γ subunits, which are assembled into a total of 12 possible AMPK complexes (52). In general, AMPK is activated by upstream kinases, including liver kinase B1, Ca^{2+} /calmodulin-dependent protein kinase 2 and transforming growth factor- β -activated kinase 1 (53). An increase in the cellular AMP:ATP and ADP:ATP ratio during low energy state activates AMPK by inhibiting the synthesis process that consumes ATP to restore energy balance, while promoting the decomposition process that produces ATP (Fig. 1) (15). The activation of AMPK triggers a cellular metabolic transformation, promoting an uptake of lipids and glucose to balance the energy metabolism of skeletal muscle (54). The mechanism is that AMPK inhibits glycogen synthesis by inhibiting the translation of TBC1 domain family member 1 and glucose transporter type 4 (GLUT4), and fatty acid (FA) synthesis by inhibiting acetyl-coenzyme A carboxylase and sterol regulatory element-binding protein-1c (51). 5-Aminoimidazole-4-carboxamide 1- β -D-ribofuranoside (AICAR) acts as an AMP analogue and has been widely used as an AMPK activator and stimulant for mitochondrial biogenesis (55). Activating the AMPK signaling pathway through muscle training or using pharmacological AICAR treatment may increase the mitochondrial content in cells and tissues (56). Metformin exerts anti-inflammatory effects via AMPK. In an EAMG rat model, it was demonstrated that the oral administration of metformin attenuated MG severity by correcting the imbalance of different T-cell groups (57).

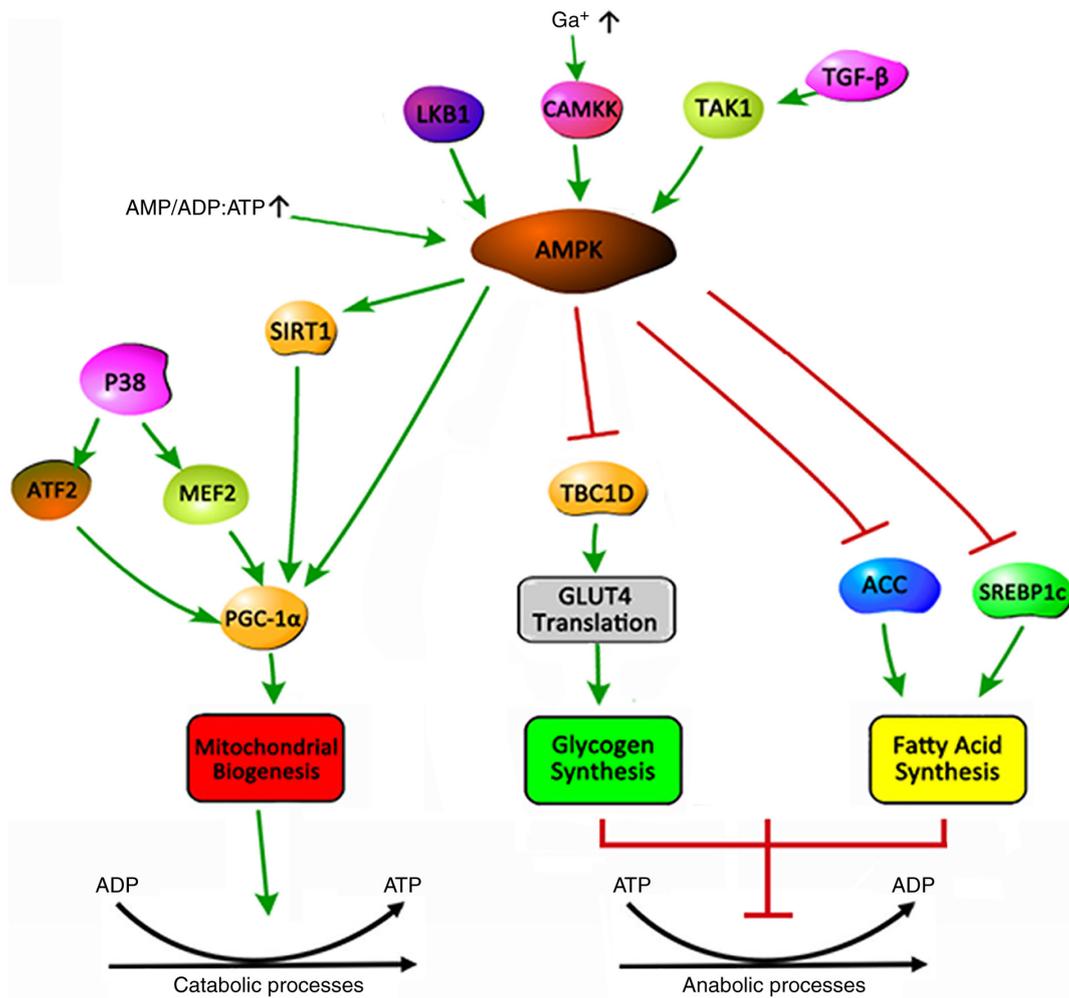


Figure 1. Balance of the energy metabolism triggered by activation of AMPK. AMPK can be activated by the upstream kinases LKB1, CAMKK2, TAK1 and high AMP/ADP:ATP ratios, which maintain the body's energy balance by promoting catabolism and inhibiting anabolism. (1) Promoting catabolism: AMPK controls the biogenesis through phosphorylation of SIRT1 to activate PGC-1 α , thereby affecting the energy metabolism of the body. P38 can also activate PGC-1 α by phosphorylating ATF2 and MEF2. (2) Inhibition of anabolism: AMPK inhibits glycogen synthesis by inhibiting TBC1D1 to control the translation of GLUT4. AMPK inhibits fatty acid synthesis by suppressing ACC and SREBP1C. Arrow, activation. Bar-headed line, inhibition. AMPK, AMP-activated protein kinase; LKB1, Liver Kinase B1; CAMKK2, calcium/calmodulin dependent protein kinase kinase 2; TAK1, TGF-beta-activated kinase 1; SIRT1, sirtuin 1; PGC-1 α , proliferator-activated receptor γ coactivator 1 α ; ATF2, activating transcription factor 2; MEF2, myocyte enhancer factor 2; GLUT4, glucose transporter type 4; TBC1D1, Tre-2/BUB2/cdc1 domain family 1; ACC, acetyl-CoA carboxylase; SREBP1C, sterol-regulatory element binding protein 1C.

Sirtuin 1 (SIRT1): A mitochondrial energy metabolism sensor. SIRT1 is a member of the NAD⁺-dependent histone deacetylase family and is widely considered to be a cellular energy sensor (58). SIRT1 has received widespread attention as it is positively regulated by the oxidized coenzyme NAD⁺, and due to its ability to regulate peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1 α) and other mitochondrial-related genes (59). SIRT1 activation is triggered by an increased NAD⁺/NADH ratio (60). The overexpression of brain-specific SIRT1 in aged mice results in more youthful NMJ morphological characteristics (distinct terminal Schwann cells, clear innervation, and pretzel-shaped motor endplates), with increased AChR numbers and NMJ innervation (61). It has also been reported that SIRT1 exerts protective effects during metabolic syndrome (62). Deletion of SIRT1 reduces mitochondrial biogenesis and ATP production, while SIRT1 overexpression increases the expression of PGC-1, which is a regulatory factor of mitochondrial biogenesis (63).

Association between AMPK and SIRT1. The process of mitochondrial biogenesis is strictly regulated by a series of upstream energy metabolism pathways, including AMPK and SIRT1, and the regulation of PGC-1 α , nuclear respiratory factors (Nrfs) and transcription factor A (TFAM) via downstream effectors (Fig. 2) (64). AMPK promotes mitochondrial biogenesis in three ways: i) It increases the activity or expression of the transcriptional coactivator PGC-1 α ; ii) it enhances the deacetylation of AMPK through SIRT; or iii) it directly phosphorylates itself, which has a positive effect on its expression levels (65). Recently, the activation of AMPK has been demonstrated to activate and facilitate the deacetylation of PGC-1 by phosphorylating Thr177/Ser538 of PGC-1 α (48). P38-MAPK can directly activate the upstream transcription factors of the PGC-1 α gene, such as activating transcription factor 2 and myocyte enhancer-binding factor 2, and promote the transcription and activity of the PGC-1 α protein (66). In addition to PGC-1 α and SIRT1, AMPK can phosphory-

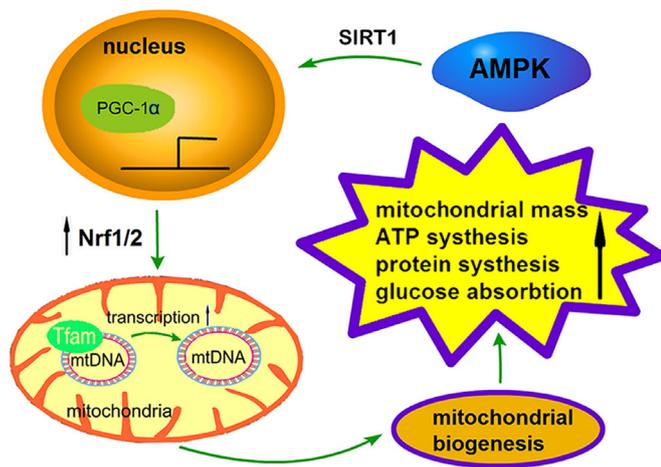


Figure 2. A sensor network regulating mitochondrial biogenesis. AMPK activation promotes the expression of PGC-1 α and its downstream signals and serves a key role in mitochondrial biogenesis. The activation of AMPK by phosphorylation of SIRT1 enhances PGC-1 α dependent transcription. PGC-1 α interacts with nuclear receptors and stimulates Nrf1/2 to participate in the expression of various nuclear coding genes and TFAM, leading to an increase of mtDNA replication transcribed on TFAM. These processes ultimately affect mitochondrial biogenesis, promoting mitochondrial mass, ATP synthesis, protein synthesis and glucose absorption. AMPK, AMP-activated protein kinase; SIRT1, sirtuin 1; PGC-1 α , proliferator-activated receptor γ coactivator 1 α ; TFAM, transcription factor A; mtDNA, mitochondrial DNA.

late a number of different transcription factors, including Nrf1/2 and TFAM (67). The synergistic expression of these transcriptional regulators under AMPK stimulation provides the necessary support for the metabolism and biogenesis of skeletal muscle.

PGC-1 α : A major mitochondrial biogenesis regulator. PGC-1 α is a major regulator of diverse metabolic pathways and mitochondrial biogenesis, and serves an important role in mitochondrial biogenesis and gene expression (68). As a co-activator with low transcriptional activation activity, the activity of PGC-1 α is significantly enhanced by its interaction with nuclear receptors, which can regulate the expression of target genes (69). PGC-1 α controls several aspects of the muscular metabolism during exercise, and it is generally hypothesized that PGC-1 α regulates respiratory function, controls muscle aerobic metabolism and mitochondrial biogenesis, and responds to environmental and physiological changes (70,71). PGC-1 α has been identified to serve a key role in regulating mitochondrial function, and is specialized for the thermogenesis and differentiation of cell type in brown adipose tissue (72,73). Forced overexpression of PGC-1 α in cardiac myocytes in culture has been indicated to induce the expression of nuclear and mitochondrial genes that are involved in multiple mitochondrial energy transduction/production pathways, increase the number of cellular mitochondria and stimulate coupled respiration (74). In addition, PGC-1 α is the detoxified cation of ROS that is generated during the mitochondrial respiration process (75). PGC-1 α knockout mice display marked hyperactivity accompanied by neuronal degeneration (76). Similarly, the expression of PGC-1 α was also found to be decreased in spinal muscular atrophy mouse models (77). PGC-1 α is expressed at high levels

in tissues with an abundance of mitochondria and an active oxidative metabolism, allowing for a response to increased energy needs. In muscle, PGC-1 α activates mitochondrial biogenesis, increases FA oxidation and GLUT4 expression, which, in turn, reduces fat accumulation and increases insulin sensitivity (75).

Nrfs: Regulation of downstream transcription factors in mitochondrial biogenesis. Nrfs, which are the downstream nuclear receptors of PGC-1 α , contain the recognition sites of mitochondrial DNA (mtDNA) promoter and serve a key role in biogenesis (78). As a mtDNA transcription factor, Nrfs can alleviate MG by regulating the mitochondrial respiratory chain function and alleviating antioxidant damage (79). Nrf-1 and Nrf-2 belong to the CNC basic leucine zipper (bZIP) regulatory protein family, are the major transcription factors in the human genome and powerful stimulators of the expression of nuclear genes required for mitochondrial respiratory function (80-82). Nrf-1 was initially indicated to be associated with the regulation of genes, serving a role in a wide range of biological functions, including signal transduction, organelle biogenesis, protein synthesis and cell growth (83). Nrf-1 also coordinates synaptic activity and energy metabolism by regulating excitatory neurotransmission via genes that code for subunits of the N-methyl-D-aspartate receptor (84). Nrf-1 directly regulates the expression of nuclear encoded genes related to respiratory chain expression, assembly and function, or indirectly regulates the cytochrome oxidase subunit genes that are encoded by mitochondria, and is associated with the generation of ROS and oxidative stress (85). Recently, Nrf-2 was demonstrated to serve an important role in cellular bioenergetics by controlling substrate availability for mitochondrial respiration (46). In addition, Nrf-2 regulates mitochondrial biogenesis through co-activation with PGC-1 α and the expression of the TFAM gene (86). Nrf-1 and Nrf-2 are involved in the regulation of inflammatory processes and antioxidant pathways, acting protectively against ROS-induced toxicity (87). Nrf-2 has been reported to control oxidative stress or exercise-induced mitochondrial biogenesis by promoting Nrf-1 transcription following its binding to the antioxidant response element of the Nrf-1 promoter (88).

TFAM: Promoting mitochondrial biogenesis by regulating mtDNA. TFAM is a high mobility family protein factor that is located in mitochondria but encoded by nuclear genes (89). TFAM can be activated by PGC-1 α and Nrfs to transcribe and regulate mtDNA (90). In a study investigating mtDNA in patients with MG, mtDNA amplification was performed in 20 muscle samples of patients with muscle-specific kinase MG, and multiple mtDNA deletions were identified in 13 patients (91).

The function of TFAM in the maintenance and transcription initiation of mtDNA can be summarized by the following three aspects: i) TFAM regulates mtDNA copy number. As a major regulator of the mtDNA transcriptional machinery, TFAM directly promotes transcription utilizing the mitochondrial RNA polymerase (92). In a previous study, both the mRNA and protein levels of TFAM were assessed during muscle differentiation, and it was observed that TFAM protein and mRNA increased two-fold in parallel, corresponding to

a two- to three-fold increase of mitochondrial content (93). Therefore, increasing levels of TFAM may promote the transcription of mtDNA and the production of proteins; ii) TFAM maintains mtDNA structural stability. Although mtDNA is a short molecule, mistakes often occur during replication, transcription and translation as mitochondria lack a DNA proofreading and repair system (94). TFAM avoids these errors to a certain extent. It has been demonstrated that TFAM binds to damaged DNA and regulates TFAM/DNA affinity by interacting with proteins, leading to tighter compression of mtDNA and reduced accessibility to transcription, replication or repair factors (83,95). TFAM can shape DNA and compensate for the unstable phenotype of mtDNA, which is the key to maintaining the structure and stability of mtDNA. iii) TFAM prevents mtDNA damage. The mutation rate of mtDNA is 10-20 times higher compared with that of nuclear DNA (96); this is due to its high superoxide environment, lack of protective histone-like proteins and poor reparative activity in response to damage. It has been revealed that TFAM binds and coats mtDNA to protect it from ROS and degradation, while increasing mitochondrial function (92). The ratio of mtDNA molecules to TFAM protein molecule in cells is ~1:1,000 (97). Furthermore, TFAM acts as a packaging protein to bind mtDNA, forming mtDNA-protein complexes and compressing a number of mtDNAs into the nucleoid (86).

Mitochondrial biogenesis based on energy metabolism is a tightly controlled process (98). When mitochondrial biogenesis is disrupted, the number of mitochondria and energy metabolism will be reduced, and mitochondrial gene and protein expression will be inhibited (99). It has been demonstrated that deletion of AMPK- α 1 and AMPK- α 2 in mouse skeletal muscle can affect FA utilization (100). Overexpression of TFAM in astrocytes induces mtDNA protection against A β 1-42 peptide, ultimately protecting neurons (101), while tissue-specific or partial deletion of the TFAM protein leads to respiratory chain defects (102). A previous study of miR-133a-deficient mice have suggested that the transcription of the mitochondrial biogenesis regulators PGC-1 α , Nrf-1 and TFAM was reduced in miR-133a-deficient muscle, which was consistent with lower mitochondrial mass and impaired exercise capacity (103). In summary, these studies indicated that mitochondrial biogenesis is an indispensable process for maintaining mitochondrial function and normal muscular activity by regulating the stability of involved proteins and mtDNA.

4. Effect of mitochondrial biogenesis on MG is based on energy metabolism

It is known that mitochondrial biogenesis, which is regulated by energy metabolism, is the foundation for maintaining mitochondrial function and a normal muscular metabolism (104). When failure of mitochondrial biogenesis and energy metabolism occurs, individuals are prone to tissue dysfunction and degeneration (105,106). Mitochondrial biogenesis or energy metabolism disorders have been observed in a number of diseases [such as epilepsy and Parkinson's disease (PD) involving nerve or muscle dysfunction (107,108).

Effect of mitochondrial energy metabolism on MG. The adaptation of mitochondria to exercise is generally referred

to as mitochondrial energy metabolism (109). The physiological function of mitochondria is to improve metabolic efficiency through oxidative phosphorylation of ATP, in order to supply energy for the contraction of muscle cells (104). Muscle contraction utilizes energy supplied by cells due to ATP decomposition to overcome resistance, converting chemical energy to mechanical energy (110). However, the mitochondrial energy metabolism is inevitably accompanied by ROS generation. Excessive ROS accumulation can cause irreversible oxidative stress damage to mitochondria and muscles (111).

In recent years, there has been accumulating evidence that the mitochondrial energy metabolism is crucial for the maintenance and plasticity of motor neurons, the NMJ and skeletal muscles (112). A variety of neurodegenerative diseases, including Alzheimer's disease (AD), PD and Huntington's disease, are associated with increased ROS production, mitochondrial dysfunction and apoptosis activation (113). Mitochondrial dysfunction and elevated ROS levels are common results in a number of neurodegenerative diseases and axonopathies, such as multiple sclerosis (114) and Charcot-Marie-Tooth disease (115). It is well known that excessive ROS induces inflammatory cytokine production and T-cell activation (116). In patients with MG, the levels of pro-inflammatory cytokines, including interleukin (IL)-6, IL-17 and interferon- γ , which are secreted by T effector cells, are increased (117). During the early stages of MG, exercise intolerance, muscular and nervous system dysfunction are commonly observed, amongst other clinical symptoms, which are similar to the clinical observations of mitochondrial myopathy, respiratory chain and energy metabolism disorders (118). A disruption of integrity of the energy metabolism at the NMJ is associated with the occurrence and development of MG (119). Neurite outgrowth is an energy consuming process: The energy metabolism provides enough energy to support protein and membrane synthesis at the NMJ, as well as intracellular transport (120). Aging NMJs exhibit abnormal morphology and decreased numbers of mitochondria, oxidative damage and reduced ATP synthesis (28).

Effect of mitochondrial biogenesis on MG. Biogenesis is the general term used to indicate an assimilation reaction in organisms, and it is a vital regulatory process of protein synthesis (121). As a semi-autonomous organelle, mitochondria serve an indispensable role in protein biogenesis (122). Proteins are the major effectors of cellular activities, and promote metabolism, maintain the composition of all cells, including muscle and nerves, and regulate the physiological functions of the body (123).

Misfolded, conformationally modified proteins can cause neurodegenerative diseases, such as AD and PD (considered as protein conformation disorders) (124). It has been demonstrated that insufficient protein levels make it difficult to maintain normal motor neuron function and survival (125). Loss of axonal domain proteins in nerve conduction may have a severe impact on neuromuscular integrity and health. For example, compromised axonal structural integrity may lead to pathological changes of peripheral nervous system myelinated fibers and muscle pathology (126). It has been demonstrated that impaired mitochondrial function of presynaptic and postsynaptic cells at the NMJ may cause neuromuscular dysfunction,

mainly by reducing the production of presynaptic ACh and the number of postsynaptic AChRs (127). Caveolin-3 is an integral membrane protein that is essential for the repair of muscle membrane damage and is expressed in skeletal, cardiac and smooth muscle cells. It has been demonstrated that partial loss of caveolin-3 expression is a relatively common occurrence in the muscles of patients with MG. Caveolin-3 overexpression induced after NMJ defects in MG muscles exerts a protective effect on skeletal myotubes (128). It has been indicated that complement-dependent lysis of the post-synaptic membrane, receptor internalization, as well as direct interference with the binding capacity of ACh to the AChR, may cause muscular damage in patients with MG (129). The normal function of the low-density lipoprotein receptor-related protein 4 and clustering of proteins serve a key role in the proper formation and maintenance of the NMJ (130).

These findings suggest that the abnormalities of mitochondrial biogenesis and the energy metabolism are closely associated with the pathogenesis of MG. Regulation of mitochondrial function and the restoration of the function of related targets in the mitochondrial biogenesis pathway may represent a novel therapeutic approach to MG and similar muscle contraction disorders.

5. Conclusions

Although recent studies have investigated MG, the majority of these studies have focused on immunity (22,131), while relatively few studies to date assessed the link between MG and mitochondrial function. As the powerhouse of the cell, mitochondria are the main energy source for skeletal muscle cells, enabling various biological processes and providing muscle movement support, and are key organelles for the maintenance of signal transmission and normal physiological function. Mitochondrial dysfunction directly affects the energy metabolism of skeletal muscle, impairing ACh biogenesis and NMJ signal transmission, ultimately accelerating the progression of MG. Therefore, it may be inferred that the mitochondrial function pathway may represent a promising target for the development of neuromuscular drugs for the treatment of MG.

Mitochondria and bioenergetic dysfunction are increasingly considered to be key components of neuromuscular diseases. In a number of neuromuscular diseases, it has been demonstrated that nerves and muscles are highly sensitive to energy deprivation, which has an adverse impact on recovery (35,132). The mitochondrial biogenesis pathway involves multiple targets, including AMPK, SIRT1, PGC-1 α , NRFs and TFAM, each of which serves an important regulatory role in neuromuscular function (133). Dysfunction of these factors may be involved in the development of neuromuscular diseases, such as MG, which are sensitive to energy deprivation and motor dysfunction.

Although the mitochondrial biogenesis pathway exhibits potential for the treatment of neuromuscular diseases, no specific pharmacological activator has yet been developed for the treatment of related diseases. A large number of researchers are currently investigating this approach in order to identify more effective treatment strategies. In summary, the biogenesis pathway represents a reasonable and feasible potential therapeutic target for neuromuscular diseases.

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Availability of data and materials

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Authors' contributions

LK, HP and YS designed the present study. LK, QL and TC prepared the draft of the manuscript; JS and WJ reviewed and edited the manuscript; AJ produced the figures; QL, HP and YS are responsible for text layout. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Conflicting interests

The authors declare that they have no competing interests.

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