


REVIEW

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# Mitochondrial dysfunction: roles in skeletal muscle atrophy

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## Abstract

Mitochondria play important roles in maintaining cellular homeostasis and skeletal muscle health, and damage to mitochondria can lead to a series of pathophysiological changes. Mitochondrial dysfunction can lead to skeletal muscle atrophy, and its molecular mechanism leading to skeletal muscle atrophy is complex. Understanding the pathogenesis of mitochondrial dysfunction is useful for the prevention and treatment of skeletal muscle atrophy, and finding drugs and methods to target and modulate mitochondrial function are urgent tasks in the prevention and treatment of skeletal muscle atrophy. In this review, we first discussed the roles of normal mitochondria in skeletal muscle. Importantly, we described the effect of mitochondrial dysfunction on skeletal muscle atrophy and the molecular mechanisms involved. Furthermore, the regulatory roles of different signaling pathways (AMPK-SIRT1-PGC-1 $\alpha$ , IGF-1-PI3K-Akt-mTOR, FoxOs, JAK-STAT3, TGF- $\beta$ -Smad2/3 and NF- $\kappa$ B pathways, etc.) and the roles of mitochondrial factors were investigated in mitochondrial dysfunction. Next, we analyzed the manifestations of mitochondrial dysfunction in muscle atrophy caused by different diseases. Finally, we summarized the preventive and therapeutic effects of targeted regulation of mitochondrial function on skeletal muscle atrophy, including drug therapy, exercise and diet, gene therapy, stem cell therapy and physical therapy. This review is of great significance for the holistic understanding of the important role of mitochondria in skeletal muscle, which is helpful for researchers to further understanding the molecular regulatory mechanism of skeletal muscle atrophy, and has an important inspiring role for the development of therapeutic strategies for muscle atrophy targeting mitochondria in the future.

**Keywords** Mitochondrial dysfunction, Muscle atrophy, Therapy, Antioxidants

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## Introduction

Skeletal muscle is a highly adaptable tissue that comprises approximately 40% of total body mass and is essential for maintaining limb posture and body movement. Skeletal muscle is also an endocrine organ that secretes myokines that have an effect on the whole-body organs [1–3]. Skeletal muscle atrophy is closely associated with some conditions such as sedentary, physical inactivity and cachexia [4, 5]. Skeletal muscle atrophy can seriously impact the quality of life of patients and increase the morbidity and mortality of many diseases. Muscle atrophy usually leads to the loss of muscle mass and function and is characterized by a reduction in muscle fiber size and mass, a conversion of muscle fiber type and an imbalance between protein synthesis and degradation in the muscle [6]. Under pathological conditions, skeletal muscle proteolysis is mainly mediated by the ubiquitin–proteasome system (UPS) and the autophagy-lysosome pathway (ALP). Muscle atrophy F-box (MAFbx) and muscle RING-finger protein-1 (MuRF1) are two muscle-specific E3 ubiquitin ligases in the UPS. During muscle atrophy, they are specifically expressed and target specific protein substrates for degradation in the UPS [7, 8]. The ALP is another important proteolysis system that removes misfolded or other harmful proteins, but its overactivation can lead to muscle atrophy [9]. Protein synthesis in skeletal muscle is mainly regulated by the IGF-1/PI3K/Akt/mTOR signaling axis, and activation of the mTOR pathway inhibits UPS and ALP in skeletal muscle [6, 10]. In addition, inflammation, oxidative stress and myofiber regeneration pathways also play a very important role in the process of muscle atrophy [11–14]. Overall, numerous molecules and complex signaling pathways have been involved in muscle atrophy; therefore, it is a major challenge for us to treat and prevent muscle atrophy.

Mitochondria are the site of ATP production and are involved in key metabolic pathways. Mitochondrial defects or dysregulation play a key role in the cytopathological mechanisms of aging, cancer, and neurodegenerative diseases [2, 15, 16]. During muscle atrophy, mitochondrial degradation influences the reduction of mitochondrial quality and quantity, which is controlled by mitochondrial autophagy as well as mitochondrial fusion and fission kinetics [17]. These mitochondrial quality-control systems are essential for the maintenance of skeletal muscle mass by recognizing and correcting mitochondrial dysfunction. Mitochondrial dysfunction triggers catabolic signaling pathways, which then will feed back to the nucleus to promote the expression of muscle atrophy genes [18]. As early as 1964, it was reported that mitochondrial dysfunction causes skeletal muscle atrophy [19]. Studies have indicated the effect of mitochondrial dysfunction on skeletal muscle atrophy.

For example, in cisplatin-induced muscle atrophy, mitochondrial mass, membrane potential and reactive oxygen species (ROS) levels are abnormal. Therefore, reducing ROS production, rather than promoting ATP production, may be a therapeutic strategy to prevent cisplatin-induced muscle atrophy [20]. During muscle atrophy, denervation exacerbates mitochondrial dysregulation in muscle-specific knockout p53 tissues, suggesting that p53 promotes organ maintenance during muscle atrophy by regulating the mitochondrial quality-control process [21]. Furthermore, a clinical trial showed impaired mitochondrial function and significantly reduced level and activity of mitochondrial respiratory complex protein in pre-frail elderly (>60 years of age) [22]. Therefore, it is an urgent task to provide an experimental basis for the treatment of muscle atrophy by targeting mitochondria.

Mitochondrial dysfunction has been recognized as an important sign of skeletal muscle atrophy, but its specific molecular mechanisms are unknown. Here, we review the role of normal mitochondria in skeletal muscle and the effects of mitochondrial dysfunction on skeletal muscle atrophy. Recent studies have also indicated that targeted modulation of mitochondrial function is an effective measure to treat and prevent skeletal muscle atrophy, which will provide an important target for developing new drugs for muscle atrophy [2, 23, 24].

## Literature search

This review focuses on a comprehensive review of the literature on mitochondria in skeletal muscle, as well as to review and analysis of the current evidences for mitochondrial dysregulation associated with skeletal muscle atrophy. The information related to the mitochondrial dysfunction were obtained from different databases and platforms, mainly PubMed, Scopus, Wiley Online Library, Springer Link, Web of Science, and Science Direct. The articles were from 1964 to 2023. After a thorough study and investigation of all the searched articles, 286 manuscripts were finally selected to complete this review based on the exclusion and inclusion criteria. More precisely, for this review, inclusion criteria included articles published in indexed and non-indexed journals, year of publication, and in vitro and in vivo investigations of mitochondria in skeletal muscle. Exclusion criteria included duplicate similar studies, poor statistical analyses, poorly written articles, poorly organized studies, and manuscripts of studies that did not meet the above inclusion criteria.

## Molecular mechanism of skeletal muscle atrophy

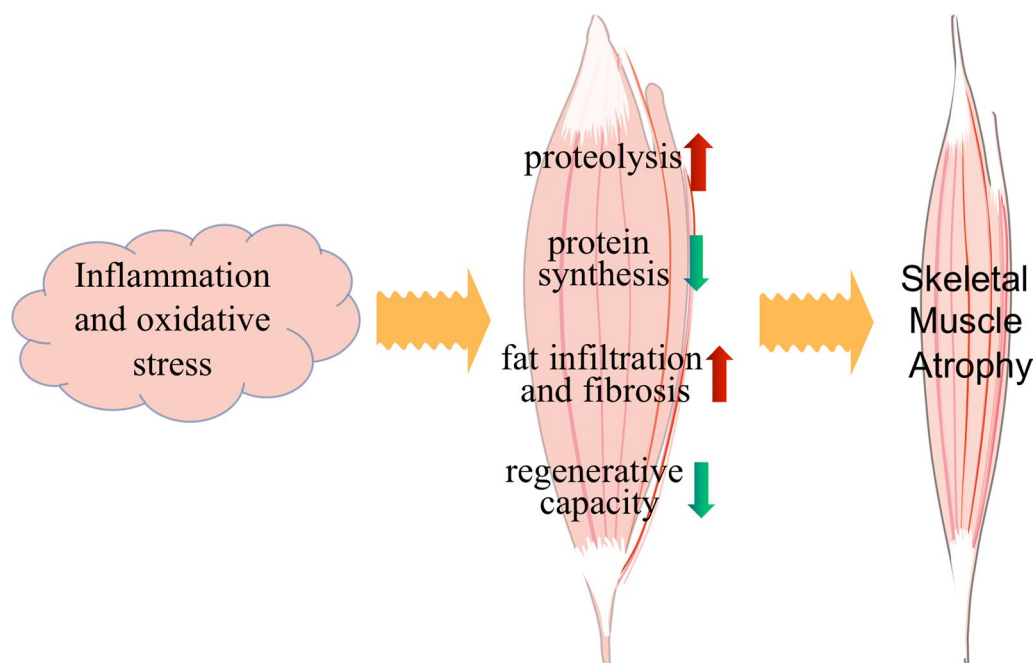
More and more studies have shown that inflammation and oxidative stress play a crucial triggering role in the process of muscle atrophy [1, 24]. Inflammation

and oxidative stress lead to increased proteolysis (ubiquitin–proteasome system, autophagic-lysosomal pathway, calpain and caspase-3), reduced protein synthesis, decreased regenerative capacity and increased fat infiltration and fibrosis (Fig. 1).

### Inflammation and oxidative stress

Skeletal muscle atrophy is a state of uncontrolled inflammation and oxidative stress, which exacerbates proteolytic metabolism [25–27]. Inflammation induces skeletal muscle atrophy. During skeletal muscle injury, many key inflammatory mediators, especially inflammatory cytokines, are involved in repair process, including interferon- $\gamma$  (IFN- $\gamma$ ), interleukin-6 (IL-6), transforming growth factor- $\beta$  (TGF- $\beta$ ), and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) [1, 28]. Oxidative stress is a regulator of cellular signaling pathways, which influences energy metabolism, protein degradation and apoptosis in muscle through transcriptional and post-translational regulation of key proteins, leading to muscle mass loss and metabolic dysfunction [29, 30]. A transient elevation in oxidative stress levels may indicate an underlying health-promoting process, while uncontrolled accumulation of oxidative stress may have pathological implications [6, 31, 32]. Cyclooxygenase-2 (COX-2) is considered to be a positive regulator of pathophysiological processes, such as inflammation and oxidative stress, and silencing COX-2 blocks

PDK1/TRAF4-induced activation of protein kinase B (AKT), which subsequently inhibits fibrogenesis after skeletal muscle atrophy [5, 33]. An anti-inflammatory drug, Triptolide, has been shown to prevent lipopolysaccharide-induced skeletal muscle atrophy by inhibiting the NF- $\kappa$ B/TNF- $\alpha$  pathway [34]. ROS, a by-product of mitochondrial metabolism, causes progressive damage to key cellular macromolecules (lipids, proteins and DNAs), and skeletal muscle is particularly susceptible due to its high metabolic rate [35]. During contractile activity, membrane-localized nicotinamide adenine dinucleotide phosphate oxidases (NAPDH) are a source of superoxide in skeletal muscle, which play an important role in redox signaling. In aging muscle, redox signaling dysregulation may lead to the loss of muscle fibers [36]. In addition, activation of toll-like receptor 2 induces oxidative stress and inflammation, while inhibition of toll-like receptor 2 attenuates skeletal muscle atrophy in a mouse model [37]. Salidroside and *Tinospora cordifolia* alleviate denervation-induced muscle atrophy by inhibiting oxidative stress and inflammation [12, 38, 39]. In the meantime, chronic inflammation can activate NAPDH oxidase and other inducible enzyme families that periodically promote the production of ROS and trigger further inflammation in skeletal muscle [40]. Therefore, inflammation and oxidative stress play an important regulatory role in the process of skeletal muscle atrophy, where inflammatory responses



**Fig. 1** Molecular mechanism of skeletal muscle atrophy. Inflammation and oxidative stress lead to increased proteolysis, reduced protein synthesis, decreased regenerative capacity and increased fat infiltration and fibrosis

trigger oxidative stress responses and conversely, oxidative stress responses activate inflammatory responses.

### Increased proteolysis

During skeletal muscle atrophy, the main proteolysis systems include UPS, ALP, calpain and caspase-3 [6, 41–43]. The UPS is responsible for the degradation of most misfolded or defective proteins in cells, which are modified through ubiquitination, that is, covalent binding to small proteins called ubiquitins. The ubiquitination process involves three enzymes, E1 ubiquitin activating enzyme, E2 ubiquitin coupling enzyme and E3 ubiquitin ligase, ultimately leading to the rapid degradation of muscle mass [44, 45]. MAFbx and MuRF1 were the first identified E3 ubiquitin ligases that play an important role in muscle atrophy, both of which are identified as the landmarks of muscle atrophy [46, 47]. They mediate the polyubiquitination of proteins and are eventually degraded by the 26S proteasome [48]. Under the condition of aging, injury and chronic disease, UPS is significantly activated, which destroys the homeostasis of protein and causes the accumulation of protein aggregates and the imbalance of redox [1, 5, 6, 49]. The ALP is an important proteolysis system in muscle atrophy [5, 7, 33, 50]. Autophagy can be divided into chaperone-mediated autophagy, microautophagy and macroautophagy (hereinafter referred to as autophagy). The ALP is mainly involved in two processes, where autophagosomes deliver cytoplasmic components that are then degraded by lysosomal hydrolases [51]. FoxO3 is a key factor in the regulation of autophagy during skeletal muscle atrophy and controls the expression of several autophagy-related genes, the most important of which is BCL2/adenovirus E1B interacting protein 3 (BNIP3) [52]. In denervated skeletal muscle, lysosomal dysfunction may limit degradation capacity, leading to an inability to clear dysfunctional mitochondria and increased ROS signaling, thus accelerating muscle atrophy [53]. Both ALP and UPS are important pathways that regulate protein degradation in muscles and complement each other to play an important regulatory role in the control of muscle mass [54]. Calpain and caspase-3 act on the upstream of UPS to aid in the complete proteolysis of myofibrillar proteins [55]. Inhibition of calpain activity prevents caspase-3 activation, and inhibition of caspase-3 activity also prevents calpain activation. There is regulatory crosstalk between these proteases, which are required for fixation-induced muscle atrophy [56]. Increased protein oxidation triggers a progressive increase in the degradation of myofibrillar proteins using calpain and caspase-3, which may link oxidative stress to the accelerated proteolysis of myofibrillar protein during disuse atrophy [57]. After aspiration pneumonia, pro-inflammatory cytokines induce muscle proteolysis

through activation of calpain and caspase-3, thereby causing skeletal muscle atrophy [58]. Superoxide-mediated oxidative stress leads to overall protein degradation and accelerates skeletal muscle atrophy through the activation of UPS and ALP, accompanied by the upregulation of calpain and caspase-3 [59]. Calpain and caspase-3 act synergistically to induce skeletal muscle proteolysis, with the potential to cause oxidative stress, thereby exacerbating skeletal muscle atrophy.

### Reduced protein synthesis

Protein synthesis in skeletal muscle is a highly complex process that can be influenced by nutritional status, mechanical stimuli, repair procedures, hormones and growth factors [60]. Protein synthesis is controlled by the translation efficiency and capacity (the number of ribosomes) of mRNA into peptides [61]. Insulin-like growth factor-1 (IGF-1) is a key growth factor that regulates anabolic and catabolic pathways in skeletal muscle, and it promotes protein synthesis through the PI3K/Akt/mTOR pathway [48]. mTORC1 activation leads to protein and lipid synthesis, and cellular growth [62]. In the skeletal muscle immobilized or disused state, mTORC1 and Akt signaling decreases, thus reducing muscle protein synthesis [63]. Hindlimb suspension-induced muscle atrophy results in increased protein synthesis and decreased protein degradation, and MAFbx and MuRF1 expression is also elevated in muscle [64]. Compared with wild-type mice, renalase-deficient mice could delay denervation-induced muscle atrophy via increased protein synthesis (Akt and p70S6K) [65]. In addition, both aerobic and resistance exercise can safely and effectively alleviate skeletal muscle atrophy by regulating myogenesis, protein synthesis and degradation, and apoptosis through the IGF-1/PI3K/Akt pathway in a mouse model of myocardial infarction [66]. Muscles play an important role in systemic protein metabolism, and promoting protein synthesis will inhibit the onset of muscle atrophy. Therefore, balancing protein synthesis and degradation is necessary to maintain a healthy state of skeletal muscle.

### Decreased regenerative capacity

Skeletal muscle is a dynamic tissue that has two unique abilities: one is the regenerative capacity, which is due to the activity of muscle satellite cells (MuSCs) unique to the skeletal muscle; the other is the adaptation of myofiber size to external stimuli, intrinsic factors or physical activity, which is known as plasticity [67]. Muscle regeneration depends on several variables, for example, MuSCs number, activation and proliferation, myogenesis and fusion all contribute to skeletal muscle regeneration [68]. The activation and differentiation processes of MuSCs

are finely controlled by genetic reaction cascades involving Pax7 and myogenic regulatory factors (Myf5, MyoD, myogenin and MRF4) [69]. These factors drive each step of skeletal muscle regeneration until the formation of new myofibers [69]. Fibroadipogenic progenitors are essential for skeletal muscle regeneration and are required for the long-term homeostatic maintenance and growth of skeletal muscle [70]. It has been shown that chronic denervation leads to a reduction in muscle stem cell populations, thereby negatively influencing the regenerative ability of muscles following innervation [71]. Although MuSCs depleted mice exhibit no sign of increased muscle loss, MuSCs depletion leads to environmental disturbance of the surrounding muscle, resulting in increased fibrosis and decreased muscle mass and function [72]. Clearly, MuSCs are important in the development and regeneration of skeletal muscle. Predictably, muscle stem cell therapy will be a major challenge in skeletal muscle regeneration and repair.

#### Increased fat infiltration and fibrosis

Myosteatosis (pathological fat accumulation in muscle) is defined by lower mean skeletal muscle radiodensity in computed tomography (CT) [73]. Skeletal muscle fibrosis is a common hallmark of chronic injury, such as injury caused by sarcopenia or denervation [74]. Skeletal muscle fat infiltration is associated with inflammation and fibrosis. An increase in muscle fat deposition, adipocyte infiltration and myofibrosis may play an additional role in the pathogenesis of sarcopenia in aging skeletal muscle [75–77]. TGF- $\beta$  is a regulator of fibrosis and inflammation in many tissues and can trigger skeletal muscle atrophy and fibrosis by inducing atrogen-1 and scleraxis [78]. Fat infiltration into muscle and bone, as well as the redistribution of subcutaneous fat into the intra-abdominal region (visceral fat), can lead to a decrease in overall strength and function, an increase in risk of falls and fractures, and a possible increase in morbidity following sarcopenia [79]. Inhibition of Toll-like receptor 9 attenuates skeletal muscle fibrosis in aged mice with sarcopenia via the p53/SIRT1 pathway [80]. Increased secretion of complement component 1q with aging results in muscle fibrosis and atrophy, while resistance training can reduce muscle fibrosis and atrophy via downregulating the C1q-induced Wnt signaling in aging mice [81]. In addition, radiothione prevents radiation-induced muscle fibrosis by modulating Nrf2-mediated antioxidant activity and downregulating the TGF- $\beta$ 1/Smad pathway [82]. In summary, increased muscle fat infiltration and fibrosis are the hallmarks of muscle atrophy. Increased muscle fat infiltration and fibrosis, as well as increased proteolysis and decreased protein synthesis and regeneration, are influenced by inflammation and oxidative stress.

#### Structure and function of mitochondria

Skeletal muscle is crucial for body movement, energy metabolism and substance metabolism, and directly affects the quality of human life [83]. Skeletal muscle fibers have two mitochondrial populations with different subcellular locations: subsarcolemmal mitochondria (about 20%) gather under the myolemma and intermyofibrillar mitochondria (about 80%) arrange in an order pattern between the myofibrils [84, 85]. Mitochondria have two layers of membranes (outer membrane and inner membrane) and two compartments. The two compartments are the innermost matrix and the intermembrane space between the outer membrane and inner membrane. Mitochondria are composed of about 1000 different proteins and about 400 different lipids, including fatty acids, glycerophospholipids, glycerolipids, sphingolipids and aryl alcohols [86]. Mitochondria play a central role in cellular metabolism, cell proliferation, cell death, and the redox state of the cell [87]. To maintain adequate mitochondrial homeostasis, cells have many mitochondrial quality-control processes and protective compensatory pathways that can be activated in response to a certain level of mitochondrial dysfunction [88]. Mitochondria are essential organelles that are responsible for regulating the metabolic state of skeletal muscle, and the preservation of mitochondrial structure and function is an important determinant for maintaining skeletal muscle fitness.

#### Role of mitochondria in muscle atrophy

##### The role of normal mitochondria in skeletal muscle

##### *Mitochondrial dynamics*

Mitochondria are highly dynamic organelles that undergo a coordinated cycle of fission and fusion, called “**Mitochondrial dynamics**.” Mitochondrial fission and fusion are considered to be key processes related to mitochondrial and cellular health [89]. Mitochondrial fusion and fission dynamically control the cell cycle, metabolism and survival, which are associated with a variety of physiological and pathological conditions. Mitochondrial fusion occurs in two steps, starting with the outer mitochondrial membrane fusion mediated by mitofusin 1 (MFN1) and mitofusin 2 (MFN2), followed by the inner mitochondrial membrane fusion mediated by optic atrophy 1 protein (OPA1). In contrast, mitochondrial fission produces a large number of small fragments, mainly mediated by dynamin-related protein 1 (Drp1), fission protein 1 (Fis1), mitochondrial fission factor (Mff) and mitochondrial dynamics protein of 49 and 51 (Mif49/51) [90, 91]. During the mitochondrial life cycle, fission leads to both the biogenesis of new mitochondria and the removal of dysfunctional mitochondria through mitochagy [92]. Thus, mitochondrial dynamics plays a very important role in

maintaining skeletal muscle and mitochondrial integrity and function.

### **Mitochondrial biogenesis**

Mitochondrial biogenesis is a process that generates new mitochondria from existing mitochondria. The biogenesis process is regulated by PPAR-gamma coactivator-1 alpha (PGC-1 $\alpha$ ). Once activated by phosphorylation or deacetylation, PGC-1 $\alpha$  activates nuclear respiratory factor 1 and 2 (NRF1 and NRF2) and subsequently activates mitochondrial transcription factor A (TFAM) [93, 94]. Mitochondrial biogenesis is driven with three main steps: transcription of nuclear genes, import of nuclear encoded mitochondrial protein, and transcription and replication of mitochondrial DNA (mtDNA) [95]. Although the coordinated control of mitochondrial biogenesis is mainly achieved through nuclear genome-encoded factors, mitochondria-related mechanisms, such as mitochondrial protein import and mtDNA replication, transcription, and translation, are also indispensable to mitochondrial biogenesis [96]. In yeast and mammalian cells, ROS regulate mitochondrial biogenesis through the regulation of Hap4p and PGC-1 $\alpha$  [97]. Mitochondrial biogenesis regulates the homeostasis of mitochondrial mass and function. Exploring the coordinated role of signaling pathways involved in mitochondrial biogenesis and mitochondrial dynamics should be the focus of future work.

### **Mitophagy**

Autophagy is essential for muscle quality control, contributing to the degradation of damaged or aggregated proteins and the turnover of basal proteins [98]. Mitophagy is a mitochondria-specific autophagy regulated by PINK1-Parkin-dependent and PINK1-Parkin-independent pathways [99]. To specifically remove damaged or redundant mitochondria, dysfunctional mitochondria recruit PINK1 and subsequently activate parkin, leading to ubiquitination of outer membrane proteins. This mitochondrial ubiquitination complex is wrapped by autophagosomes and then degraded in the lysosome [100, 101]. Mitochondrial fission and fusion regulate their size, number, morphology and distribution in cells. Mitochondrial fission and fusion controls autophagic degradation of dysfunctional mitochondria to maintain a healthy physiological state [102]. Bcl2 has been found to be a key regulator of exercise-induced autophagy in vivo, and autophagy may contribute to the beneficial effects of exercise on metabolism [103]. Mitophagy is coordinated with mitochondrial fission and fusion to maintain the mitochondrial quality control, required for normal metabolism and growth and development of skeletal muscle.

### **The role of mitochondrial dysfunction in skeletal muscle atrophy**

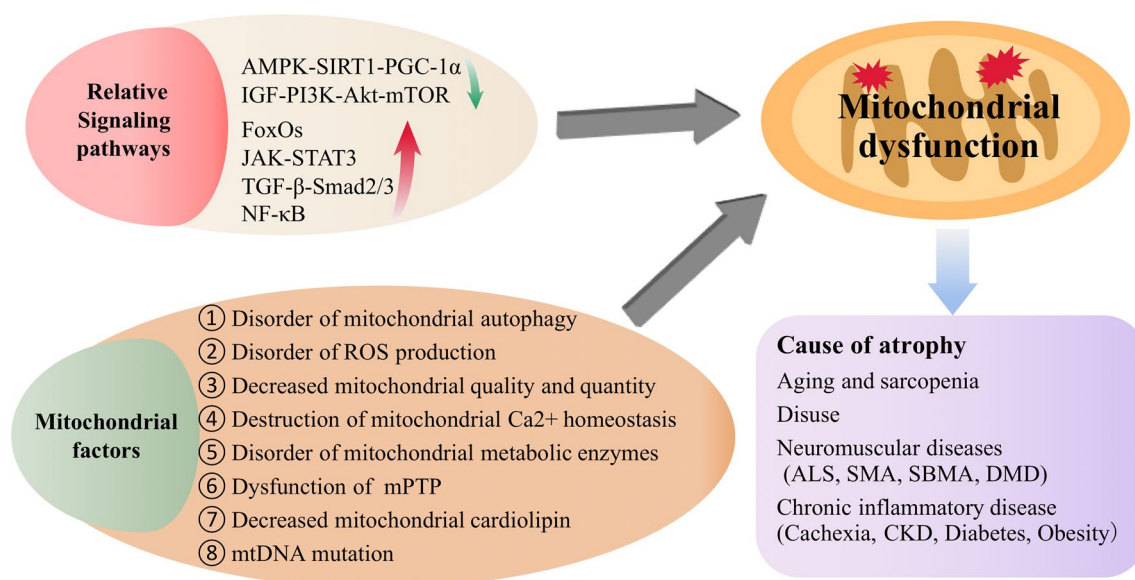
Mitochondria are the key organelles regulating the metabolic state of skeletal muscle. Mitochondrial dysfunction will directly affect the normal state of skeletal muscle. In the context, we will outline the signaling pathways involved in regulating mitochondrial function and the role and mechanisms of mitochondrial factors in mitochondrial dysfunction, and discuss the role of mitochondrial dysfunction in skeletal muscle atrophy caused by different diseases, including aging and sarcopenia, disuse muscle atrophy, neuromuscular diseases and chronic inflammatory disease (Fig. 2).

### **Signaling pathways involved in mitochondrial dysfunction**

Signaling pathways involved in mitochondrial dysfunction are very complex and includes AMPK-SIRT1-PGC-1 $\alpha$ , IGF-1-PI3K-Akt-mTOR, FoxOs, JAK-STAT3, TGF- $\beta$ -Smad2/3, NF- $\kappa$ B signaling pathways and so on (Fig. 3, Table 1).

**AMPK-SIRT1-PGC-1 $\alpha$  signaling pathway** The AMP-activated protein kinase (AMPK)/silent information regulator 1 (SIRT1)/PGC-1 $\alpha$  signaling pathway acts as an energy sensing network that is crucial for mitochondrial biosynthesis, energy metabolism and oxidative stress [104]. AMPK is a core component of the AMPK-SIRT1-PGC-1 $\alpha$  signaling pathway that regulates the switch between anabolic and catabolic metabolism [2, 105]. AMPK controls the expression of genes involved in energy metabolism in mouse skeletal muscle by synergizing with another metabolic sensor, SIRT1, leading to deacetylation of downstream SIRT1 targets (e.g., PGC-1 $\alpha$ ) [106]. In obesity-induced muscle atrophy, fibroblast growth factor 19 may promote mitochondrial biogenesis and antioxidant responses via the AMPK/PGC-1 $\alpha$  pathway, thereby attenuating the effects of palmitate on mitochondrial dysfunction and oxidative stress [107]. Ampelopsin attenuates d-gal-induced skeletal muscle atrophy in aged rats by activating the AMPK/SIRT1/PGC-1 $\alpha$  pathway [108]. Considering the AMPK-SIRT1-PGC-1 $\alpha$  signaling pathway directly regulates mitochondrial biosynthesis, the activation of this pathway can reduce the negative effects of oxidative stress on skeletal muscle.

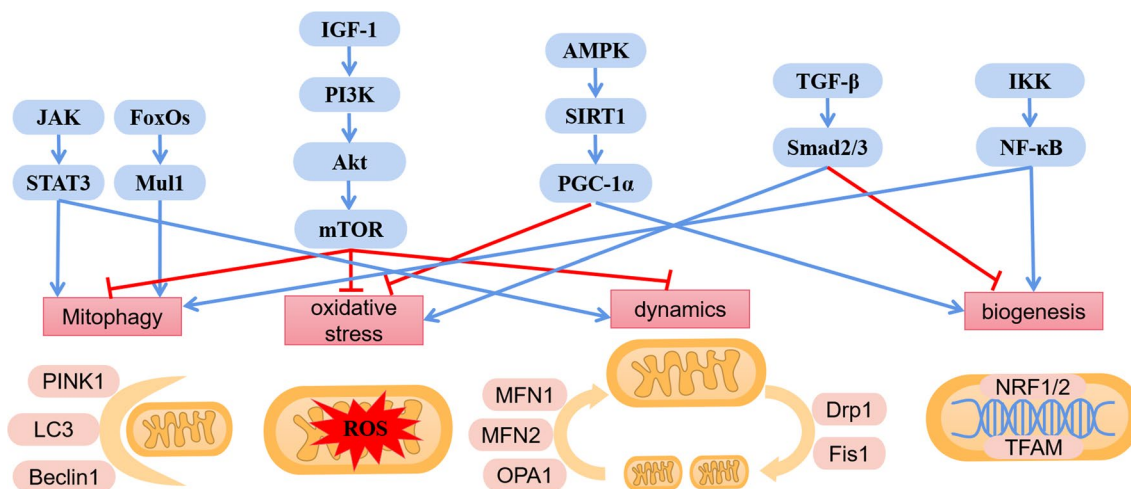
**IGF-1-PI3K-Akt-mTOR signaling pathway** IGF-1-PI3K-Akt-mTOR is a well-characterized anabolic pathway that plays an important role in the regulation of protein degradation [109]. IGF-1, binding to the IGF-1 receptors on the surface of myocytes, phosphorylates insulin receptor substrate-1 (IRS1) and then activates PI3K. PI3K accelerates the adhesion of Akt to the cell



**Fig. 2** The role of mitochondrial dysfunction in skeletal muscle atrophy

membrane where it is phosphorylated. Akt then activates mTORC1 to regulate autophagy [110, 111]. Insulin-deficient diabetes or loss of insulin/IGF-1 action in muscle reduces complex I-driven mitochondrial respiration and supercomplex assembly, in part due to FoxO-mediated inhibition of complex I subunit expression [112]. The IGF-1 signaling system has been found to increase sensory protection by regulating the balance between mitochondrial fusion and fission, thereby improving the functional status of chronically denervated skeletal muscle cells [113]. During skeletal muscle hypertrophy, the relative reduction in mitochondrial

function or content is complemented by enhanced mitochondrial fusion, and this complementary response may be regulated by mTORC1 [114]. In addition, butyrate ameliorates skeletal muscle atrophy in a db/db mouse model of diabetic nephropathy by enhancing activation of the PI3K/Akt/mTOR pathway to inhibit oxidative stress and autophagy [115]. Neuromodulin-1β alleviates sepsis-induced skeletal muscle atrophy in rats by inhibiting autophagy through the Akt/mTOR signaling pathway [116]. Once this pathway is dysregulated, protein synthesis, protein hydrolysis and mitochondrial



**Fig. 3** The related proteins involved in the mitochondrial dysfunction

**Table 1** Roles of signaling pathways involved in regulating mitochondrial function in mitochondrial dysfunction

Signaling pathways	Roles in mitochondrial dysfunction	References
FoxOs	Activate UPS and ALP; upregulate Mul1, influence mitochondrial dynamics (increased mitochondrial fission, accelerated mitochondrial fusion protein degradation), and induce excessive autophagy	[83, 102]
AMPK/SIRT1/PGC-1 $\alpha$	Promote mitochondrial biosynthesis; involve in the regulation of energy metabolism-related genes; reduce oxidative stress	[103, 105, 106]
IGF-1/PI3K/Akt/mTOR	Promote complex I-driven mitochondrial respiration and supercomplex assembly; regulate the balance between mitochondrial fusion and fission; inhibit oxidative stress and autophagy	[111–114]
JAK/STAT3	Induce mitochondrial respiration; promote mitochondrial apoptosis and autophagy; increase the expression of mitochondria-related proteins (PGC-1 $\alpha$ , OPA1, MFN2, cytochrome C)	[14, 117–119]
TGF- $\beta$ /Smad2/3	Disrupt redox signaling and result in the accumulation of ROS; inhibit mitochondrial biogenesis; downregulate the abundance of PGC-1 $\alpha$ , AMPK- $\alpha$ 2, TFAM, and mitochondrial enzymes	[121–124]
IKK/NF- $\kappa$ B	Inhibit differentiation and promotes mitochondrial biogenesis; increase the expression of autophagy-related Beclin1; disrupt mitochondrial respiratory function/morphology, induce ROS production, and increase the expression of key mitochondrial genes (SDHA, ANT-1, UCP3, and MFN2)	[125, 126, 128]

function are all affected, and then the homeostasis of the skeletal muscle is bound to be disrupted.

**FoxOs signaling pathway** FoxOs regulate the expression of atrophy-related genes (MuRF1 and MAFbx) and autophagy-related genes in skeletal muscle cells, and coordinate the two major proteolysis systems (UPS and ALP) [12, 46, 117, 118]. FoxO activates UPS and ALP simultaneously, ensuring that the loss of different cellular components such as proteins and organelles during muscle atrophy is coordinated [85]. Mitochondrial E3 ubiquitin protein ligase 1 (Mul1) is a mitochondrial ubiquitin ligase that plays an important role in the remodeling of the mitochondrial network. Under catabolic conditions, the FoxOs family upregulates Mul1, induces autophagy, and increases mitochondrial fission, leading to MFN2 ubiquitination and degradation [119]. The FoxOs family may induce mitochondrial dysfunction by triggering mitochondrial dynamics and excessive autophagy.

**JAK-STAT3 signaling pathway** The IL-6 cytokine family activates the JAK/STAT3 signaling pathway and regulates MuSCs-dependent myogenesis [120]. Fam3a is a STAT3-regulated secretory factor, and the STAT3-Fam3a axis has been found to promote myogenic differentiation of muscle stem cells by inducing mitochondrial respiration [121]. In response to skeletal muscle injury, deletion of MAPK phosphatase-5 reduces the activation of the mitochondrial apoptotic pathway involving STAT3 and increases the expression of Bcl-2 [122]. A microarray analysis of differentially expressed genes revealed that the IL-6/JAK/STAT3 signaling pathway was strongly activated in denervation-induced skeletal muscle atrophy, while inhibition of the JAK/STAT3 signaling pathway suppressed mitochondrial phagocytosis and muscle atrophy [14]. Furthermore, inhibition of the JAK/STAT3 signaling pathway

was found to be sufficient to rescue HCT116 cell-induced myotube atrophy and inhibit the reduction of mitochondrial proteins PGC-1 $\alpha$ , OPA1, MFN2, and Cytochrome C in a mouse model of colorectal cancer cachexia [123]. Therefore, therapeutic strategies targeting the JAK-STAT3 pathway may have the potential to delay muscle atrophy.

**TGF- $\beta$ -Smad2/3 signaling pathway** TGF- $\beta$  signals through the activation of classical Smad-dependent and non-classical signaling pathways (e.g. ERK1/2, JNK1/2 and p38 MAPK) and induces muscle atrophy dependent on ROS mechanisms [124]. Targeted inactivation of TGF- $\beta$  activated kinase 1 (TAK1) can disrupt redox signaling, leading to ROS accumulation, mitochondrial dysfunction and skeletal muscle loss [125, 126]. In a rat model of emphysema, ursolic acid reduces cigarette smoke-induced oxidative stress and muscle atrophy by upregulating IGF-1 and inhibiting the TGF- $\beta$ 1-Smad2/3 signaling pathway [127]. Smad3 deficiency promotes mitochondrial biogenesis and function in white adipose tissue of diabetic and obese mice, as evidenced by increased expression of PGC-1 $\alpha$  and increased mitochondrial DNA copy number [128]. Furthermore, in middle-aged adults at high risk of type 2 diabetes, activated TGF- $\beta$ 1 signaling can promote impaired motor responses by downregulating the abundance of PGC-1 $\alpha$ , AMPK $\alpha$ 2, TFAM, and mitochondrial enzymes [129]. Therefore, the TGF- $\beta$ -Smad2/3 signaling pathway has the potential to induce several types of muscle atrophy, accompanied by mitochondrial dysfunction.

**NF- $\kappa$ B signaling pathway** Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is a transcription factor that can be rapidly activated by inflammatory cytokines such as TNF- $\alpha$  and is then involved in a range of biological processes, including inflammation and immune response [61]. TWEAK has been shown to enhance Beclin1 expression in C2C12



myotubes by activating NF- $\kappa$ B transcription factors [130]. MiR-155 in exosomes from M1 polarized macrophages promotes endothelial-to-mesenchymal transition and impair mitochondrial function following traumatic spinal cord injury via activating the NF- $\kappa$ B signaling pathway in vascular endothelial cells [131]. In case of obesity and diabetes, inhibition of the NF- $\kappa$ B signaling pathway ameliorates disturbances in mitochondrial respiratory function/morphology, decreases the expression of key mitochondrial genes such as SDHA, ANT-1, UCP3, and MFN2, and attenuates the increase of ROS and the decrease of insulin sensitivity of myotubes [132]. Furthermore, the extent to which NF- $\kappa$ B inhibition alters mitochondrial function depends on age and muscle specificity, and targeted inhibition of the activity of NF- $\kappa$ B in skeletal muscle at the early stage of life to prevent aging related pathology may be detrimental [133]. Inflammation is an important trigger of muscle atrophy and pro-inflammatory cytokines are important precipitating factors of muscle atrophy. The pro-inflammatory signaling pathway NF- $\kappa$ B can be involved in muscle atrophy due to multiple causes via the regulation of mitochondrial function, which also provides new potential targets for the treatment of muscle atrophy.

#### **Mitochondrial factors participate in mitochondrial dysfunction**

**Decreased mitochondrial quality and quantity** Mitochondria in aged skeletal muscle appear larger, rounder in shape, vacuolated in matrix, and shorter in cristae compared with young skeletal muscle mitochondria. Also older muscles lose mitochondria, which may lead to loss of skeletal muscle [134]. Drp1-deficient mitochondria are morphologically large and functionally abnormal, which leads to increased mitochondrial Ca<sup>2+</sup> uptake, and induces the activation of UPS and unfolded protein reaction (UPR), thereby inducing muscle atrophy [135]. Opa1 deficiency can also change mitochondrial morphology and function and lead to endoplasmic reticulum stress, which then affects muscle mass and metabolic homeostasis [136]. Alterations in mitochondrial morphology, quality and quantity are direct factors causing mitochondrial dysfunction.

**Mitochondrial DNA (mtDNA) mutation** mtDNA consists of light (L) and heavy (H) strands, carries 16,569 base pairs and contains 37 genes (9 in the L strand and 28 in the H strand), encoding 13 subunits of the electron transfer chain complex I, III, IV and V [137, 138]. Somatic mtDNA deletion mutations expand clonally within individual fibers until a phenotypic threshold is exceeded, leading to the loss of cellular respiration, myofiber atrophy, apoptosis, and necrosis, accompanied by fiber breakage and loss [139]. In muscle fibers, the process begins with an

mtDNA replication error that results in 25–80% loss of the mitochondrial genome [140]. In aging skeletal muscle, mtDNA replication damage leads to increased ROS production [141]. The involvement of mtDNA is required for the synthesis of new mitochondria and therefore mtDNA is essential for the maintenance of normal mitochondrial state and biogenesis.

**Disorder of mitochondrial autophagy** Both excessive autophagy (excessive catabolism) and insufficient autophagy (protein accumulation, oxidative stress, and apoptosis) may lead to muscle atrophy [142]. There is an increase in autophagy in laminin  $\alpha$ 2 chains deficient muscles, suggesting that excessive autophagy leads to muscle atrophy [143]. Muscle-specific deletion of autophagy-related 7 (Atg7) results in abnormal mitochondrial accumulation, sarcoplasmic reticulum expansion, disorganized sarcomere and formation of abnormal concentric membrane structures, leading to muscle atrophy and impaired muscle function [144]. Furthermore, AMPK activation promotes mitophagy by enhancing mitochondrial fission (via MFF phosphorylation) and autophagosome phagocytosis (via TBK1 activation) in a PINK1-Parkin-independent manner [145]. In X-linked myopathies, mutations in the VMA21 gene reduce lysosomal degradation and result in increased autophagy, leading to autophagic vacuolar myopathy [146, 147]. In a mouse model of diabetic muscular atrophy, there was a 20–30% reduction in muscle mass and myofiber area, characterized by increased microtubule-associated protein light chain 3 (LC3)-containing vesicles and elevated LC3-II levels [148]. NRF2-deficient aged mice showed increased expression of LC3-II, P62, and BNIP3, and excessive autophagy due to AMPK and ROS signaling in skeletal muscle, which may be a potential mechanism for sarcopenia [149]. Under normal physiological conditions, mitophagy is necessary for skeletal muscle growth and development, while under the above pathological conditions mitophagy can cause skeletal muscle atrophy.

**Disorder of ROS production** Nicotinamide adenine dinucleotide phosphate oxidase and mitochondria are two major sources of ROS production in skeletal muscle. ROS is an important cell signal sensor that controls autophagy through a cascade of different signals localized based on its signaling [150]. It has long been proposed that denervation-induced skeletal muscle atrophy is associated with increased mitochondrial ROS generation [151]. IL-6 deficiency has been found to inhibit mitochondrial ROS production by up-regulating PGC-1 $\alpha$  expression in sepsis mice, thus alleviating skeletal muscle atrophy [152]. In addition, aberrant levels of ROS can disrupt the redox environment in older muscles, possibly disrupting cellular

signaling and in some cases weakening adaptive responses to exercise [153]. ROS level is closely related to the activation of autophagy, and abnormal ROS production will lead to mitochondrial dysfunction.

*Disorder of mitochondrial metabolic enzymes* Cytochrome oxidase is the terminal oxidase of the electron transport chain, and citrate synthase activity is closely related to mitochondrial content and is involved in mitochondrial substrate oxidation, which is one of the most commonly used markers of mitochondrial content [154, 155]. With aging, expression of mitophagy protein increases in skeletal muscle, while citrate synthase activity and cytochrome c oxidase subunit IV protein content are considerably reduced [156]. In cancerous cachectic mice, citrate synthase and cytochrome c oxidase activities in skeletal muscle were decreased, damaged mitochondrial content was increased, and Drp1 and MFN2 expression was reduced [157]. Alterations in either mitophagy or mitochondrial dynamics are accompanied by abnormal expression of mitochondrial metabolic enzymes, thereby inducing skeletal muscle atrophy.

*Destruction of mitochondrial Ca<sup>2+</sup> homeostasis* Ca<sup>2+</sup> as ubiquitous signaling second messenger is a key player in the regulation of skeletal muscle cell functions. Ca<sup>2+</sup> regulates mitochondrial functions, while mitochondria shape Ca<sup>2+</sup> dynamics [158]. Mitochondrial Ca<sup>2+</sup> homeostasis plays a pivotal role to maintain muscle homeostasis and to sustain muscle function. The regulation of the mitochondrial Ca<sup>2+</sup> controls skeletal muscle size, force, and nutrient utilization [159]. Mitochondria capture Ca<sup>2+</sup> through the mitochondrial calcium uniporter complex, to regulate energy production, cytoplasmic Ca<sup>2+</sup> signaling, and cell death [160]. The uniporter complex is composed of pore-forming MCU, gatekeeper MICU1 and MICU2, and an auxiliary EMRE subunit essential for Ca<sup>2+</sup> transport [161]. MICUs sense the changes in cytosolic Ca<sup>2+</sup> concentrations to switch MCU on and off. When Ca<sup>2+</sup> levels rise above ~ 1 μM, the uniporter complex is activated [160]. MICUs prevent excessive Ca<sup>2+</sup> influx that can increase mitochondrial oxidative stress [162]. Reduced MCU activity impedes the autophagic flux, and loss of autophagy further impairs mitochondrial Ca<sup>2+</sup> signaling, thereby disrupting muscle homeostasis and function [159]. MCU overexpression can prevent denervation-induced skeletal muscle atrophy [163]. Moreover, MCU expression triggers hypertrophy by controlling protein synthesis through the PGC-1α and IGF1-Akt/PKB pathways [163]. Mutations of MICU1 were related to debilitating neuromuscular diseases in patients [164]. In HEK293 cells, removing MICU1 allows mitochondria to more readily take up Ca<sup>2+</sup>. However, the trade-off is elevated ROS, impaired

basal metabolism, and higher susceptibility to death [165]. EMRE deletion blocks mitochondrial Ca<sup>2+</sup> uptake, however, EMRE protein expression is upregulated in a mouse model of muscular dystrophy [166]. Therefore, regulation of mitochondrial Ca<sup>2+</sup> homeostasis may be a new therapeutic intervention for muscle atrophy.

*Dysfunction of mitochondrial permeability transition pore (mPTP)* Disruption of mitochondrial membrane potential is the main sign of mitochondrial dysfunction. Mitochondrial membrane potential reduction is associated with an impaired mitochondrial electron transport chain, reduced metabolic oxygen consumption, ATP depletion, and low energy metabolism [167]. The mPTP is a large conductive pore in the inner mitochondrial membrane that is predominantly closed under non-stress conditions. The mPTP is permeable to solutes up to 1.5 kDa in size, and sustained pore opening leads to the dissipation of the mitochondrial membrane potential, organelle swelling, and eventual rupture [168]. The mPTP opening can be induced by increased ROS and Ca<sup>2+</sup> or mitochondrial depolarization, and it can be further exacerbated by an imbalanced Ca<sup>2+</sup> homeostasis [169]. Cyclophilin D is involved in the regulation of mPTP. Although loss or inhibition of cyclophilin D confirmed that it was an activator of mPTP opening, with higher levels of Ca<sup>2+</sup>, mPTP opening was cyclophilin D independent [168]. Cyclophilin D was upregulated in skeletal muscle of SMNKO mice (skeletal muscle-specific nicotinamide phosphoribosyl transferase KO) from 2 weeks of age, with associated increased sensitivity of mitochondria to the Ca<sup>2+</sup>-stimulated mPTP opening [170]. Cyclophilin D can bind to adenine nucleotide translocator (ANT), which suggested that the ANT might be the pore-forming unit [168]. Moreover, the expression of pro-apoptotic Bcl-2 family members, Bax and Bak localization to the outer mitochondrial membrane is required for MPTP-dependent mitochondrial dysfunction and subsequent necrotic cell death. Mitochondrial Ca<sup>2+</sup> retention capacity and MPTP sensitivity are influenced by Bax/Bak activation/oligomerization on the outer mitochondrial membrane [171]. Sporadic denervation in mouse muscle has been shown to reduce mitochondrial respiratory capacity and increase sensitivity to mPTP opening [172]. Furthermore, mitochondrial permeability shift has been identified as a new pathogenesis of skeletal muscle atrophy, which acts through mitochondrial ROS emission and Caspase-3 activation [173]. It is worth noting that the mPTP activation is associated with mitochondrial Ca<sup>2+</sup> homeostasis and mitochondrial ROS, which together influence mitochondrial function.

*Decreased mitochondrial cardiolipin* Cardiolipin is the representative phospholipid of the inner mitochondrial

membrane and affects the stability of many inner membrane protein complexes, including respiratory chain complexes and metabolite carriers [174]. Cardiolipin that is externalized to the outer mitochondrial membrane may mediate targeted autophagy of mitochondria in primary and transformed neuronal cells by interacting with the autophagy protein LC3 [175]. During long-term muscle inactivity, a decrease in cardiolipin abundance and the relative composition of its fatty acid chains can directly influence mitochondrial function and cause disuse muscle atrophy [23]. Cardiolipin is essential for mitochondrial function and cardiolipin-targeted treatments have significant implications for the prevention of mitochondrial dysfunction.

#### **Mitochondrial dysfunction in different disease states**

**Aging and sarcopenia** Sarcopenia is an age-related debilitating skeletal muscle atrophy syndrome. Sarcopenia is one of the main causes that limit daily activities in the elderly, characterized by loss of skeletal muscle mass, decreased muscle strength and decreased physical performance [176]. A hallmark of aging is the loss of protein homeostasis, which is partly due to alterations in the UPS and ALP that lead to impaired function and maintenance of mass in tissues such as skeletal muscle [177]. Sarcopenia patients have reduced expression and activity of mitochondrial respiratory complexes and down-regulated oxidative phosphorylation and mitochondrial protein homeostasis genes in skeletal muscle [178]. In an mtDNA mutant mouse model, mtDNA mutations are determinants of mitochondrial electron transport chain function and therefore mitochondrial bioenergetics and ATP homeostasis are impaired, thereby inducing skeletal muscle apoptosis and sarcopenia [179]. During aging, the morphology, quality and quantity of mitochondria are altered, mitochondrial function is also impaired, and skeletal muscle function is lost.

**Disuse muscle atrophy** Disuse muscle atrophy indicates a temporary condition of unused muscles, such as limb immobilization (i.e., plaster immobilization) due to fracture, bed rest, hindlimb unloading, denervation, and heart failure. Disuse muscle atrophy promotes significant mitochondrial alterations, leading to impaired metabolic homeostasis and an increased degree of muscle atrophy [180]. However, a study indicated that during the progression of disuse muscle atrophy, mitochondrial aberrations exert different effects on male and female mice, and females may give up muscle mass to maintain mitochondrial mass compared with males, which may lead to different clinical manifestations of atrophy [181]. Chronic muscle inactivity can lead to major disturbances in intracellular calcium homeostasis, resulting in impaired

mitochondrial calcium handling and increased oxidant production [182]. It has been demonstrated that denervation induces a reduction in mitochondrial biogenesis in response to changes in mitochondrial translation factors in mouse skeletal muscle, which provides new molecular-level insights into the effects of muscle denervation on mitochondrial translation processes [183]. In addition, miR-142a-5p is an important regulator of denervation-induced skeletal muscle atrophy, which can induce mitochondrial dysfunction, mitophagy and apoptosis by targeting MFN1 [184]. Spinal cord injury is a unique form of disuse atrophy in which paralysis and disruption of the central nervous system leads to a rapid decline in skeletal muscle function and metabolic status, as well as disruption of the activity of PGC-1 $\alpha$  and calcium-regulated neurophosphatase that are key regulators of mitochondrial health and function [185]. Obvious mitochondrial dysfunction is a very important mechanism in the process of disuse muscle atrophy.

**Cachexia** The progression of cachexia is associated with metabolic changes, mainly including excessive energy expenditure, increased proteolysis and mitochondrial dysfunction [186]. Muscle atrophy associated with mitochondrial dysfunction can be observed in cachectic rodents, including impaired mitochondrial dynamics (increased fission (Fis1) and reduced fusion (MFN1 and MFN2)), reduced activity of respiratory chain complexes, and an increase in the suspected indicators of mitochondrial energy coupling (UCP-2 and UCP-3) [187]. The ALP and UPS are simultaneously activated in skeletal muscle of patients with cachectic gastric cancer and may play a coordinated role in cachexia-induced muscle loss [188]. A genome-wide transcriptome analysis of a cancer-induced cachexia rodent model indicated that the expression of genes involved in mitochondrial fusion and fission, ATP production and mitochondrial density was reduced, while the expression of genes involved in ROS detoxification and mitochondrial phagocytosis was increased [189]. In addition, autophagy exacerbated muscle atrophy and impaired mitochondrial function in a C26 mouse model of cancer cachexia [190]. Therefore, mitochondrial dynamics, mitophagy and oxidative stress disorder are the main causal factors for cachexia.

**Chronic kidney disease (CKD)** CKD has multiple causative factors, commonly characterized by a recurrent cycle of glomerular or tubular epithelial injury, and elevated intracellular ROS levels play a major role in the pathogenesis of CKD [191]. CKD predisposes to acute kidney injury (AKI), while AKI facilitates CKD progression [192]. Dysregulation of mitochondrial homeostasis, bioenergetics alterations and organelle stress cross-

talk also contribute to the transition from AKI to CKD [193]. Following CKD, there is a reduction in mitochondrial copy number, expression of biogenesis markers (PGC-1 $\alpha$  and TFAM) and mitochondrial fusion marker (Mfn2) while an increase in BNIP3, Beclin-1 and LC3II at protein and mRNA levels, indicating the formation of autophagosome [194]. Both mitochondrial dysfunction and reduced antioxidant enzyme levels can increase ROS production, which often cause oxidative stress and lead to CKD-induced muscle atrophy [4, 195]. In addition, FoxO3 can activate autophagy in skeletal muscle of CKD patients, which may be a novel intervention for muscle atrophy in CKD [196]. Mitochondrial bioenergetics plays a central role in CKD, and targeting metabolic pathways involved in mitochondrial bioenergetics is a promising therapeutic strategy.

**Diabetes** Diabetes can reduce skeletal muscle function, leading to myasthenia and muscle atrophy and causing structural changes such as metabolic disturbances characterized by reduced cellular glucose uptake and fatty acid oxidation, impaired mitochondrial function, and muscle fiber conversion [6]. Oxidative stress can induce insulin deficiency and produce large amounts of ROS to block insulin signaling, thus triggering insulin resistance, which may help the malignant progression of diabetic muscular atrophy [6]. In addition, in diabetic mice, mitochondrial number and quality were decreased, and mitophagy and biogenesis-related proteins were significantly reduced [197]. However, there are not many drugs targeting mitochondria for treatment of diabetic muscular atrophy. So, the search for biological targets based on the molecular mechanisms of diabetic muscular atrophy is required for the purpose of developing new drugs.

**Obesity** Obesity causes structural and functional changes in skeletal muscle, leading to the accumulation of intramuscular lipids, which is associated with impaired mitochondrial content and function in skeletal muscle [198]. Obesity also leads to renal mitochondrial dysfunction and energy imbalance, accelerating the progression of CKD and worsening CKD-dependent sarcopenia in mice [199]. Compared with sarcopenia or obesity alone, myopenic obesity is more likely to increase the risk of death, and patients with myopenic obesity have significantly lower expression of mitochondria-related proteins PGC-1 $\alpha$ , MFN1, MFN2 and DRP1 than normal controls [200]. Furthermore, mitochondrial uncoupling may provide protection against myopenic obesity via enhancing skeletal muscle mitophagy and quality control to attenuate age-related decline in muscle mass and function [201]. Targeted regulation of mitochondrial dynamics,

mitochondrial biogenesis and mitophagy seems to be an attractive treatment strategy for muscle atrophy caused by Obesity.

**Amyotrophic lateral sclerosis (ALS)** ALS is a neurodegenerative disease accompanied by progressive loss of motor neurons, eventually leading to fatal paralysis [202, 203]. ALS was initially thought to be associated with oxidative stress, as it was first shown to be associated with the mutant SOD1, TDP-43 or other ALS-related mutant proteins that can all lead to mitochondrial imbalance in ALS and affect mitochondrial respiration as well as ATP production, calcium handling, mitochondrial dynamics and apoptotic signaling [204, 205]. ROS can lead to mitochondrial DNA mutations, membrane permeability and calcium homeostasis, as well as enhanced lipid oxidation and protein carbonylation, which will lead to various neurodegenerative diseases, including ALS [206]. Furthermore, a serum lipid analysis revealed a significant decrease in Cardiolipin content in the spinal cord of ALS rats, along with the loss of mitochondrial integrity [207]. Mitochondria are directly involved in the pathogenesis of ALS, but the causal relationship between mitochondrial dysfunction and ALS pathogenesis remains to be confirmed.

**Spinal muscular atrophy (SMA)** SMA is caused by loss of function of survival motor neuron (SMN) protein, resulting in structural and functional alterations of the cytoskeleton in motor neurons and other cells [208]. SMN has been shown to affect mitochondrial and bioenergetic pathways and regulate the UPS function [209]. Impaired mitochondrial biogenesis can be observed both in the muscles of SMA patients and in the motor neurons of SMA mice, while the expression of the mitochondria-related genes TFAM, NRF1 and NRF2 is downregulated in the muscles of SMA patients [210]. In addition, SMA can increase the levels of oxidative stress and impair mitochondrial membrane potential in motor neurons, and fragmentation of mitochondrial networks in primary motor neurons of SMA mice is significantly increased [211]. The pathogenesis of SMA involves the proteolysis system and mitochondrial dysfunction, and their effects on SMN are required for further exploration.

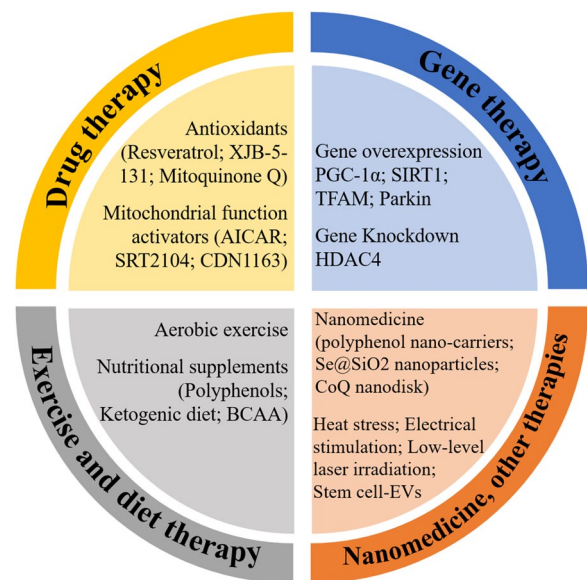
**Spinal and bulbar muscular atrophy (SBMA)** SBMA is an inherited neuromuscular disease characterized by motor neuron deficiency and skeletal muscle atrophy caused by polyglutamine expansion in the androgen receptor gene. Altered autophagy and mitochondrial defects underlie SBMA neuromuscular degeneration [212, 213]. In impaired motor neurons, an elevated synaptojanin 2 binding protein (SYNJ2BP) level (an outer

mitochondrial membrane protein) alters the cellular distribution of mitochondria and increases mitochondrial-endoplasmic reticulum membrane contact sites, while lowering the SYNJ2BP level improves mitochondrial oxidative function [214]. Molecular links between epigenetic dysregulation of SBMA motor neurons and mitochondrial damage and metabolic dysfunction have been identified using gene expression analysis and ChIP sequencing [215]. These findings highlight the impact of mitochondrial dysfunction on SBMA and the search for potential biological targets is an urgent task for us.

**Duchenne muscular dystrophy (DMD)** DMD is one of the most common and severe forms of muscle atrophy caused by mutations in the DMD gene encoding different isoforms of antimitotrophic proteins [216, 217]. DMD protein deficiency leads to intracellular  $Ca^{2+}$  dysregulation, mitochondrial dysfunction and increased ROS production [218]. Mitochondrial dysfunction is one of the first cellular changes in myofibers following DMD, as evidenced by mitochondrial dysfunction, abnormal mitochondrial morphology and mitophagy impairment (degradation of damaged mitochondria) [219]. In an mdx mouse model at 10–12 weeks of age, functional mitochondrial oxidative capacity was found to be disturbed, suggesting that mild oxidative stress reduces oxidative phosphorylation and thus declines ATP production [220]. In the future, we should pay attention to the impact of mitochondria-related pathways on DMD, which will lead to further understanding of the molecular mechanisms of DMD and potentially facilitate the discovery of DMD-targeted mitochondrial therapies.

### Therapeutic strategies targeting mitochondria for skeletal muscle atrophy

Mitochondria can provide sufficient energy for the life activities in cells. Mitochondrial dysfunction has been shown to play a very important role in the process of skeletal muscle atrophy. Targeted mitochondrial therapy has become an effective strategy, can directly regulate mitochondria, and improve treatment efficiency in skeletal muscle atrophy. At the same time, direct targeting of mitochondria may lead to fewer side effects on normal tissues. Targeted mitochondrial therapy has good biomedical prospects and is expected to provide new directions for clinical diagnosis and treatment. Strategies for improving mitochondrial function and delaying muscle atrophy mainly include mitochondria-targeted drug therapy (Mitochondria-targeted antioxidants, mitochondrial function activators, etc.), exercise and diet therapy,



**Fig. 4** Therapeutic strategies targeting mitochondria for muscle atrophy. Strategies mainly include drug therapy, exercise and diet therapy, gene therapy and other therapies

mitochondria-targeted gene therapy and other therapies (Fig. 4).

### Mitochondria-targeted drug therapy

#### Mitochondria-targeted antioxidants

So far, more and more mitochondrial targeting drugs have been reported. Meanwhile, the effective way to deliver drugs specifically to mitochondria is by covalent linking a lipophilic cation such as an alkyltriphenylphosphonium moiety to a pharmacophore of interest [221]. The combination of metformin and exercise improves mitochondrial bioenergetics and has beneficial effects against muscle loss and fat accumulation by regulating redox status [222]. Moreover, Mito-Met (metformin conjugated with TPP<sup>+</sup>) can enhance the targeting of metformin [221]. Resveratrol prevents high-fat diet-induced muscle atrophy in aged rats by reversing mitochondrial dysfunction and oxidative stress via the PKA/LKB1/AMPK pathway [223]. The mitochondria-targeted antioxidant XJB-5-131 increases the activity of electron transfer chain complexes in skeletal muscle mitochondria, reversing age-related alterations in mitochondrial function and improving contractility of skeletal muscles [224]. Mitoquinone Q improves mitochondrial homeostasis and metabolism, promotes  $\beta$ -oxidation in muscle tissue, and facilitates the glycolytic-oxidative transition in muscle metabolism and fiber composition [225]. Mitochondrial cardiolipid-targeted peptide, SS peptide, restores mitochondrial function, remodels mitochondria, repairs cellular structure, and promotes tissue regeneration

during aging [226]. Szeto-Schiller 31, a mitochondria-targeted antioxidant peptide, prevents inactivity-induced decreased mitochondrial coupling and increased ROS emission to protect mitochondrial function and prevent muscle atrophy due to prolonged inactivity [23]. Szeto-Schiller 31 has shown promise in restoring mitochondrial bioenergetics viability in a phase I-II trial targeting heart failure and primary mitochondrial myopathy [227]. Astaxanthin, a red lutein carotenoid, promotes muscle health by reducing oxidative stress, myogenic apoptosis, and proteolysis pathways, and promoting mitochondrial regeneration and angiogenesis [228]. Trimetazidine, a partial inhibitor of lipid oxidation, prevents high-fat diet-induced muscle dysfunction by improving mitochondrial quality-control and mitochondrial function [229]. In addition, edaravone reverses oxidative stress-induced apoptosis and inhibits upregulation of mitochondrial ROS in induced pluripotent stem cell-derived spinal motor neurons from SMA patients. Therefore, it may be a therapeutic target for SMA [230]. Dysregulation of oxidative stress levels has been shown to be involved in the progression of skeletal muscle atrophy, so the specific use of antioxidants to target and modulate mitochondrial function would be a very effective intervention for muscle atrophy.

#### **Mitochondrial function activators**

5-Aminoimidazole-4-carboxamide ribonucleoside (AICAR) is an activator of AMPK that effectively improves mitochondrial and muscle function while maintaining the size of skeletal muscle in models of sarcopenia and cancer cachexia [2]. The age-related decreases in NRF2 signaling activity and mitochondrial dysfunction may be associated with the development of age-related diseases. Sulforaphane is a natural NRF2 activator. Cohorts of 2 month-old and 21- to 22 month-old mice were administered regular rodent diet or diet supplemented with Sulforaphane for 12 weeks. Sulforaphane restored Nrf2 activity, mitochondrial function, exercise capacity, glucose tolerance, and activation/differentiation of skeletal muscle satellite cells [231]. Furthermore, sulforaphane improves muscle function and pathology and protects dystrophic muscle from oxidative damage related to the NRF2 signaling pathway in mdx mice, with clinical implications for the treatment of patients with sarcopenia [232]. SRT2104 is a synthetic small molecule activator of SIRT1, and SRT2104 treatment improves systemic metabolic function, increases mitochondrial content, and preserves bone and muscle mass in an experimental model of atrophy [233]. CDN1163 is a novel small molecule allosteric activator of sarcoplasmic reticulum  $\text{Ca}^{2+}$  ATPase (SERCA) that reverses increased mitochondrial ROS generation and increased oxidative

damage in muscle tissue in SOD1 mice, preventing oxidative stress-related muscle atrophy and weakness [234]. These activators can directly target molecules involved in mitochondrial dysfunction, providing potential targets for the development of new drugs to prevent and treat skeletal muscle atrophy.

#### **Other drugs**

During skeletal muscle aging, *Lactobacillus paracasei* PS23 protects mitochondrial function by reducing age-associated inflammation and ROS emission, thereby slowing age-related muscle loss [235]. In a mouse model of disuse muscle atrophy, Gomisin G (a lignan component of *S. chinensis*) enhances mitochondrial biogenesis and function through the SIRT1/PGC-1 $\alpha$  signaling pathway to improve muscle strength [236]. Ginsenoside Rg3 protects against glucocorticoid-induced muscle atrophy by improving mitochondrial biogenesis and myotubular growth through the activation of PGC-1 $\alpha$  [237]. Geranylgeraniol attenuates muscle atrophy in the flounder muscle of diabetic rats by altering mitochondrial mass [238]. Myricanol prevents against dexamethasone-induced muscle atrophy and myasthenia, reduces muscle protein degradation, enhances autophagy, and promotes mitochondrial biogenesis and function by activating SIRT1 in mice [239]. Dihydromyricetin reverses mitochondrial dysfunction via PGC-1 $\alpha$ /TFAM and PGC-1 $\alpha$ /MFN2 signaling pathways to attenuate dexamethasone-induced muscle atrophy [240]. Chrysanthemi Zawadskii var. Latilobum attenuates mitochondrial dysfunction in skeletal muscle of obese mice by modulating protein arginine methyltransferases, thereby alleviating obesity-induced skeletal muscle atrophy [241]. Paeoniflorin increases the activity of electron transport chain complexes and mitochondrial membrane potential, and improves skeletal muscle atrophy in CKD through AMPK/SIRT1/PGC-1 $\alpha$ -mediated oxidative stress and mitochondrial dysfunction [242]. Urolithin A alleviates the symptoms of DMD by inducing mitophagy, increases skeletal muscle respiratory capacity, and improves muscle regeneration, which may have potential therapeutic applications in sarcopenia [243]. Olesoxime, a mitochondria-targeted drug for SMA, has been in phase III clinical trials. Olesoxime exerts its neuroprotective effects through modulation of mPTP to improve cell survival in multiple in vitro and in vivo models [244]. Oyster hydrolysate is a valuable natural material to inhibit skeletal muscle atrophy by regulating protein turnover and mitochondrial biogenesis [245]. Celecoxib alleviates denervation-induced muscle atrophy by reducing mitophagy and inhibiting oxidative stress [5]. Aspirin alleviates denervation-induced muscle atrophy and inhibits the shift from type I to type II muscle fiber and mitophagy

via the SIRT1/PGC-1 $\alpha$  axis and STAT3 signaling [246]. Levetiracetam is neuroprotective against SMA by ameliorating mitochondrial dysfunction in spinal motor neurons differentiated from SMA patient-derived induced pluripotent stem cells [247]. Mitochondria-targeted interventions using L-carnitine or teneligliptin can be used to treat CKD-induced muscle atrophy and decreased exercise tolerance [248]. Furthermore, ATG-125 is a phytochemical-rich herbal formulation that hinders sucrose-induced gastrocnemius muscle atrophy via rescuing Akt signaling and improving mitochondrial dysfunction in young adult mice [249]. Treatments with the pro-appetitive hormone ghrelin significantly increase mitochondrial respiratory capacity of C2C12 cells enhance muscle anabolism, and play an important role in preserving aging muscle [250]. In addition to antioxidants and activators, many other drugs such as Chinese herbs, anti-inflammatory drugs, and hormones can alleviate skeletal muscle atrophy by improving mitochondrial function. So, we need to focus on their long-term efficacy and safety.

#### Nanomedicine

In recent years, nanomedicine technology targeting mitochondria or cells has attracted increasing attention. Compared to conventional approaches, drug targeting with nanomaterials improves biocompatibility, safety, and specificity [251]. For example, nanomaterials have been used to enhance and mediate the functions of vascular cells (such as vascular endothelium and smooth muscle cells) and to prevent thrombosis and inflammation on stents in cardiovascular disease [251]. The polyphenols show protective antioxidant role in neurodegenerative disease at least partially due to their capacity to stimulate mitochondrial biogenesis and improve their function, which elevates mitochondrial efficiency resulting in diminished ROS production [252]. However, polyphenol compounds possess weak pharmacokinetics properties such as low bioavailability and solubility. The targeted polyphenol delivery by drug carriers created using nanotechnology that guarantees target specificity can overcome the drawbacks, and boost the bioavailability and stability of the therapeutic molecules in vivo [251]. Moreover, researches show that porous Se@SiO<sub>2</sub> nanoparticles which would slowly release selenium could improve oxidative injury to promote muscle regeneration via modulating mitochondria [253]. CoQ's lack of aqueous solubility and poor oral bioavailability contribute to suboptimal results observed with respect to the effect of CoQ supplements on statin-induced myopathy. Importantly, the nanodisk enhances CoQ bioavailability that represent a water-soluble vehicle capable of delivering CoQ to cultured myotubes [254]. However, there are still

many challenges, such as the fabrication and toxicity of nanomaterials. Such as, copper nanoclusters are increasingly being used in nanomedicine owing to their utility in cellular imaging and as catalysts. Additionally, exposure to CuNCs may be a risk factor for the skeletal muscle system [255]. More thorough studies of nanomedicine are still needed.

#### Exercise and diet

Exercise triggers an increase in key regulatory components of mitochondrial biogenesis (e.g., PGC-1, NRF1, and NRF2), and PGC-1 mediates a coordinated increase in GLUT4 and mitochondria [256]. Moreover, exercise attenuates UPS activity and increases the expression of mitophagy-related genes in skeletal muscle of patients with inflammatory myopathies [257]. It has been reported that exercise may inhibit muscle apoptosis, stimulate mitochondrial oxidative capacity and increase muscle blood flow by activating mTOR signaling and decreasing local TNF- $\alpha$  levels, thereby reversing sarcopenia in patients with cirrhosis [258]. In addition, aerobic exercise may help to inhibit the loss of mitochondrial content in skeletal muscle and forestall aging-induced complications of skeletal muscle, such as sarcopenia and insulin resistance [259]. Aerobic exercise can not only increase SIRT3 and PGC-1 $\alpha$  expression levels in sedentary, overweight or obese adolescents, but it also enhances amino acid and carbohydrate intake in healthy older adults, which may prevent against muscle loss with age [260, 261]. Aerobic exercise has also been reported to improve mitochondrial function via Sestrin2 in an AMPK $\alpha$ 2-dependent manner in sarcopenia mice [262]. Sedentary individuals present with decreased expression of skeletal muscle catabolism-related proteins (e.g., FoxO3a and MSTN), improved mitochondrial dynamics, and significant activation of signaling pathways associated with proliferation after aerobic exercise training, thereby favoring an increase in muscle fiber and overall muscle size, which may be associated with skeletal muscle hypertrophy [263]. Although endurance exercise training has long been thought to elevate aerobic capacity of skeletal muscle by enhancing mitochondrial quality-control and mitochondrial function, alternative exercise training that can induce similar improvements in mitochondria is gaining increasing attention as a viable intervention [264]. However frequent unaccustomed exercise can alter the structure and function of skeletal muscle fibers, which is called exercise-induced muscle damage. Exercise-induced muscle damage can lead to a temporary muscle damage and soreness that negatively affects muscle function [265]. In addition to exercise, attention to diet can also have a therapeutic effect on muscle atrophy. As nutritional supplements, polyphenols are plant-based

compounds with antioxidant and anti-inflammatory properties, many of which are beneficial to human health and may delay skeletal muscle loss and functional impairment [266]. Long-term ketogenic diet slows aging-related muscle mass loss and increases mitochondrial content in aging skeletal muscle [267]. A ketogenic diet enhances mitochondrial biogenesis, oxidative metabolism, and antioxidant capacity in mice, and may protect skeletal muscle mass and function in aged mice [268]. Ketogenic diets combined with exercise alter mitochondrial function in human skeletal muscle while improving metabolic health [269]. In addition, branched-chain amino acids (BCAA: leucine, valine, isoleucine) have been shown to maintain body mass and cardiac function and prolong survival in rats with heart failure, possibly by increasing the expression of genes involved in mitochondrial biogenesis and skeletal muscle function [270]. Leucine is a branched-chain amino acid supplement that activates mTORC1, promotes protein synthesis and inhibits autophagy in muscle [271, 272]. Whereas drug therapy may carry risks such as side effects, exercise and diet seem to be relatively healthy treatments that will benefit the body from all aspects if adhered to over time.

#### **Mitochondria-targeted gene therapy**

Mitochondria belong to semi-automatic organelles, which have their own genome different from nuclear genome. Targeting genes involved in mitochondrial regulation and mitochondrial genes are of great significance for the treatment of skeletal muscle atrophy. PGC-1 $\alpha$  overexpression preserves muscle size by inhibiting ALP and UPS and alleviating mitochondrial dysfunction, indicating that compounds that induce PGC-1 $\alpha$  expression may benefit the treatment of muscle atrophy [273]. Overexpression of TFAM reduces skeletal muscle atrophy after hindlimb suspension in mice, which is correlated with the increased expression of antioxidants [274]. Parkin overexpression may prevent sepsis-induced skeletal muscle atrophy by improving mitochondrial mass and content [275]. Elevated SIRT1 expression leads to an increase in oxidative metabolism and mitochondrial biogenesis markers, thereby improving pathophysiological manifestations in a mouse model of DMD [276]. Histone deacetylase 4 (HDAC4) may inhibit mitophagy in denervated skeletal muscle and improve mitochondrial function through the direct regulation of myogenin, and therefore, the histone deacetylase 4-myogenin axis may function as a new target for the prevention and treatment of muscle atrophy [9]. Inhibition of the IL-6/JAK/STAT3 signaling pathway inhibits muscle atrophy and mitophagy, accompanied by a reduction in the expression of atrophy-related and autophagy-related genes, so the IL-6/JAK/STAT3 pathway can be used as a targeted

strategy for skeletal muscle atrophy [14]. Furthermore, restoration of miR-181a levels in aged mice can prevent the accumulation of p62, DJ-1 and PARK2 and improve mitochondrial mass and muscle function [277]. lncRNA EDCH1 may improve mitochondrial function through SERCA2-mediated activation of the AMPK pathway to diminish muscle atrophy [278]. Early activation of lncRNA Pvt1 following muscle atrophy affects mitochondrial respiration and morphology and influences autophagy and apoptosis related to mitochondrial conformation and myofiber size, and thus targeting lncRNA Pvt1 may be a viable therapeutic target for muscle atrophy [279]. lncRNA Gm20743 may be involved in regulating mitochondrial function, oxidative stress, cell proliferation and myotube differentiation in skeletal muscle cells, and may be a potential therapeutic target for diabetes-induced sarcopenia [280]. Taken together, these genes and non-coding RNAs would be novel targets for targeting mitochondrial dysfunction in the treatment of muscle atrophy.

#### **Other treatments**

Extracellular vesicles are thought to be involved in many physiological and pathological processes, such as cancer progression, immune regulation, neurodegenerative diseases, and tissue regeneration [13]. Extracellular vesicles derived from skin precursor-derived Schwann cells can reduce mitochondrial vacuolar degeneration and autophagy in denervated muscles by inhibiting autophagy-associated proteins and alleviate muscle atrophy by suppressing oxidative stress and inflammatory responses [50]. Human umbilical cord-derived mesenchymal stromal cells ameliorate sarcopenia-associated skeletal muscle atrophy and dysfunction through AMPK-PGC-1 $\alpha$  axis-mediated anti-apoptotic, anti-inflammatory, and mitochondrial biogenesis mechanisms [281]. Mesenchymal stem cell can mediate the transplantation of mitochondria into aging cells. This can restore the function of mitochondria in aging muscle cells and neurons, and then achieve the therapeutic purpose [282]. In addition, heat stress has been shown to trigger a stress response that leads to increased heat shock protein expression and improved mitochondrial function, while attenuating the reduction in human skeletal muscle mass and metabolic function due to immobilization [283]. Electrical stimulation can prevent against doxorubicin-induced muscle atrophy and mitochondrial loss in C2C12 myotubes [284]. Low-level laser irradiation prevents doxorubicin-induced skeletal muscle atrophy by preserving mitochondrial homeostasis and alleviating oxidative stress and apoptosis through the AMPK/SIRT1/PCG-1 $\alpha$  pathway [285]. It has also been proposed that



caloric restriction can delay sarcopenia by reducing oxygen radical production, decreasing oxidative stress damage, enhancing mitochondrial function, improving protein homeostasis, reducing iron overload, increasing autophagy and apoptosis, and reducing inflammation [286]. In conclusion, there are many ways to target mitochondria for the treatment of sarcopenia, and their mechanism is more worthy of our attention. In the future, the combined therapeutic modalities may be an alternative.

## Prospects

Our understanding of the role of mitochondria in skeletal muscle atrophy has progressed considerably over the last few years. Mitochondria play a very important role in skeletal muscle growth and development, and mitochondrial dysfunction is an important cause of skeletal muscle atrophy. Therefore, the molecular mechanisms by which mitochondrial dysfunction induces skeletal muscle atrophy have attracted the interest of scientists. An understanding of these mechanisms could benefit the development of clinical treatment options for skeletal muscle atrophy, and future therapeutic strategies targeting mitochondria may be a key measure to prevent or treat different types of skeletal muscle atrophy. Currently the common therapeutic approaches are drug therapy, gene therapy, stem cell therapy and physiotherapy, and if additional combination therapeutic strategies can be developed or the feasibility of mitochondrial transplantation can be increased, the quality of life would be greatly improved in patients with muscle atrophy.

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## Author contributions

XC, YJ and RL drafted the manuscript; XC, YJ, XZ, KW, XY, BL, ZG and YH contributed to the analysis of the results, YS, HL and HS reviewed and modified the manuscript. All authors agreed on the final version. All authors read and approved the final manuscript.

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## Availability of data and materials

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## Declarations

## Ethics approval and consent to participate

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## Competing interests

The authors declare that they have no competing interests.

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