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Regulation of mitochondrial dynamic equilibrium by physical exercise in sarcopenia: A systematic review

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ABSTRACT

Background: Sarcopenia is a hallmark of the ageing process, which is characterized by the decline in muscle mass and strength. Growing evidence indicates that mitochondria dysfunction play core roles in this process. Meanwhile, physical exercise is regarded as one of the efficiency therapies to attenuate sarcopenia via regulating mitochondrial function during ageing. However, the specific mechanisms among exercise, mitochondrial function and sarcopenia are still unclear. The aim of this systematic review is to delineate the effects of physical exercise on mitochondria during ageing in order to explore potential target for rescuing sarcopenia.

Methods: A systematic literature search was performed in PubMed, Embase and Web of Science. Information was extracted from the included studies for review.

Results: In this review, 16 pre-clinical studies were included and 105 clinical studies that were not mechanistic research were excluded. 16 pre-clinical studies provided evidence that physical exercise could affect mitochondrial quality control to attenuate sarcopenia. Most of the included studies described the important role of mitochondrial dynamic equilibrium in sarcopenia and showed that effective physical exercise could influence mitochondrial biogenesis, fusion, fission and mitophagy to attenuate sarcopenia in aged animal.

Conclusions: This systematic review provides an up-to-date sequential overview and highlights the link in the potential mitochondria-related target and physical exercise in aged animal.

Translation of this article: Currently, there is no standard treatment method for sarcopenia. This systematic review revealed the underlying mechanisms for how physical exercise improved muscle performance via regulating mitochondrial dynamic equilibrium, which could provide scientific support for using exercise as a timely intervention for sarcopenia. Additionally, this systematic review allows a better understanding of mitochondrial dynamic equilibrium and exercise for future development of new therapeutic interventions to attenuate sarcopenia.

1. Introduction

With increasing life expectancy and growing elderly population, people over age of 65 in the world will increase to 1.5 billion by 2050 and the number of elderly patients with ageing-related diseases is increasing as well [1]. Ageing and related diseases have become one of the most serious problems in public health.

Skeletal muscle is a plastic tissue that can adapt to different stimuli from daily physical activities, which accounts for approximately 40% of body weight and is the largest metabolic organ in the human body [2]. Skeletal muscle tissue is prominently affected by ageing with the characteristics of loss of muscle mass and strength. It is reported that loss of muscle mass and strength begins at the age of 40 in human [3]. In addition, the loss of muscle function would increase the risk of frailty and number of falls, thus resulting in a high risk of fracture. Besides, decreased mobility will markedly affect the quality of life with an impaired ability to perform daily tasks or engage in social interactions [4].

According to the definition of Asian Working Group for Sarcopenia (AWGS 2019), sarcopenia is defined as a geriatric syndrome characterized by progressive and generalized skeletal muscle disorder. Accelerated loss of muscle mass and function with increased risk of falls will increase

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adverse outcomes including functional decline, poor quality of life, and even death [5–7]. The prevalence of sarcopenia will certainly escalate in the upcoming decades, which is a significant social healthcare challenge. There is a pressing need to investigate and dissect the pathological mechanisms of sarcopenia for developing effective preventive and therapeutic strategies [8]. Mitochondrial dysfunction is one of the main factors causing sarcopenia, while ageing is a major factor that leads to mitochondrial dysfunction and accumulation of impaired mitochondria [9,10].

Mitochondria are ubiquitous cellular organelles and crucial integrators of intermediary metabolism in various cellular metabolic pathways, including oxidative phosphorylation, fatty acid oxidation, etc [10]. Normally, mitochondrial quality control (Fig. 2) by means of mitochondrial biogenesis, fusion, fission, and mitophagy the processes taken by cells for eliminating impaired mitochondria caused by high levels of reactive oxygen species (ROS) to prevent mitochondrial dysfunction and apoptosis [9,11,12].

Physical exercise is generally accepted as a kind of effective and safe approach for relieving age-related diseases. To reduce the risk of the age-related chronic conditions, World Health Organization (WHO) encourages adults aged 18–64 years to take more than 150 min of moderate-intensity physical activity each week [13].

Since skeletal muscle is highly enriched with mitochondria for the production of energy required for its normal function. Mitochondria are critical organelles responsible for regulating the metabolic status of skeletal muscle [14]. Previous studies observed that decreasing mitochondrial function such as mitochondrial quality control, ATP production, as well as morphological deterioration are associated with the progression of sarcopenia [15–19]. Therefore, more studies focus on how exercise are effective in maintaining mitochondria function and morphology (Table 2). Additionally, it is well reported that regular physical exercise is an important approach to combat sarcopenia through regulating mitochondrial biogenesis [20,21], which will lead to the enhancement of mitochondrial mass, morphology, and density in skeletal muscle [22]. However, the specific mechanism for how exercise attenuates sarcopenia through regulating mitochondrial homeostasis is still uncertain. Muscle mass and muscle performance are essential parameters for sarcopenia definition, and decreasing muscle fiber type II is one of the important features of sarcopenia. Additionally, mitochondrial dysfunction is a known cause of sarcopenia, and mitochondrial morphology and function are major readouts for evaluating mitochondrial status. In this context, many studies investigated specific parameters including muscle mass, myofiber morphology, and functional performance to evaluate muscle changes in relations to changes of mitochondrial morphology and functions. In addition, the effects of exercise vary among different kinds of exercise, such as aerobic exercise and anaerobic exercise, etc.

This systematic review aims to summarize the mechanisms of mitochondrial dynamic equilibrium under normal condition and perform a comprehensive analysis of ageing-associated mitochondrial dysfunction, including mitochondrial quality control related factors and their relative changes before and after exercise training in aged animals.

2. Methods

2.1. Search strategy

Literature search was performed on PubMed, Embase and Web of Science (last accessed on 27th October 2021). The keywords used were sarcopeni*, mitochondri*, muscle, ageing, ageing, and senescence. We combined the keywords as (sarcopeni* AND mitochondri* AND muscle AND (ageing OR aging OR senescence)) and searched in all fields. This search strategy was used in the three databases. PRISMA guidelines were followed.

2.2. Search criteria

Inclusion criteria were: (1) pre-clinical and clinical studies related to morphological and functional changes in mitochondria during ageing; (2) studies that investigated the mechanisms of ageing-related changes of mitochondria before and/or after exercise; (3) full-text literature published in English.

Exclusion criteria were: (1) non-English-language papers; (2) without full-text access; (3) not mitochondria-related; (4) without comparisons among different ages; (6) not rodent animal models or myocyte research; (7) not mechanistic research; (8) review articles, comments; (9) conference abstracts.

2.3. Evidence synthesis

The following information was extracted by reviewers: species, gender, age range, exercise type and protocol, muscle type, testing methods, results of muscle (muscle mass or strength) and mitochondria, as well as other major results. 16 pre-clinical studies and 105 clinical studies fulfilled the predefined inclusion criteria and were included in the final analysis (Fig. 1).

2.4. Study risk of bias assessment

Data from the included studies were extracted and summarized independently by three authors. Any differences were resolved by adjudicating senior authors. Study selection was conducted by two independent reviewers. First screening excluded obviously irrelevant papers based on titles and abstracts. The remaining potentially relevant articles were reviewed according to the inclusion and exclusion criteria. Disagreements were resolved by discussion and consensus.

2.5. Data analysis

The studies included in this review adopted various animal models and different methodologies. There were also discrepancies in assessment outcomes and statistical methodologies, therefore meta-analysis was not suitable to be conducted. A qualitative review was performed on the muscle and mitochondria.

3. Results

3.1. Results of the search

After the initial search, the total number of papers was 469 from PubMed, 699 from Embase and 678 from Web of Science. 902 papers in English with full text and without duplication were sorted out for further selection. 634 papers were excluded based on the selection criteria, in which 83 were comments, letters, conference abstracts, and books; 317 were review papers; 30 were papers using non-rodent animal models; 204 were not ageing-related sarcopenia research in conjunction with mitochondria. 268 of them were identified as potentially relevant for further examination. After further screening of the remaining articles, 105 clinical studies were excluded because they did not refer to mechanistic research, and 163 were pre-clinical papers. Finally, 16 pre-clinical papers were included in the systematic review which studied the relationship between exercise and mitochondria in ageing animals. The flow chart presenting the selection process is shown in Fig. 1.

3.2. Topics of study

Table 1 showed a summary of the included studies. 12 papers investigated mitochondrial biogenesis [19,23–33]; 7 studies investigated

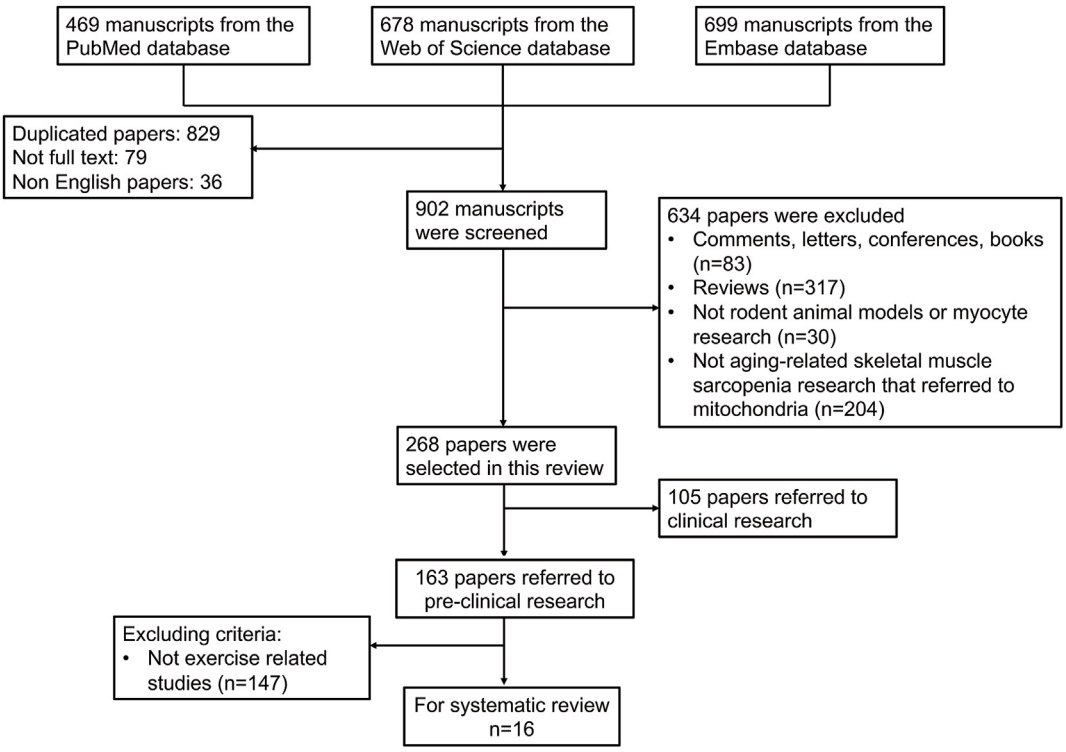

Fig. 1. Flow chart for selection process.

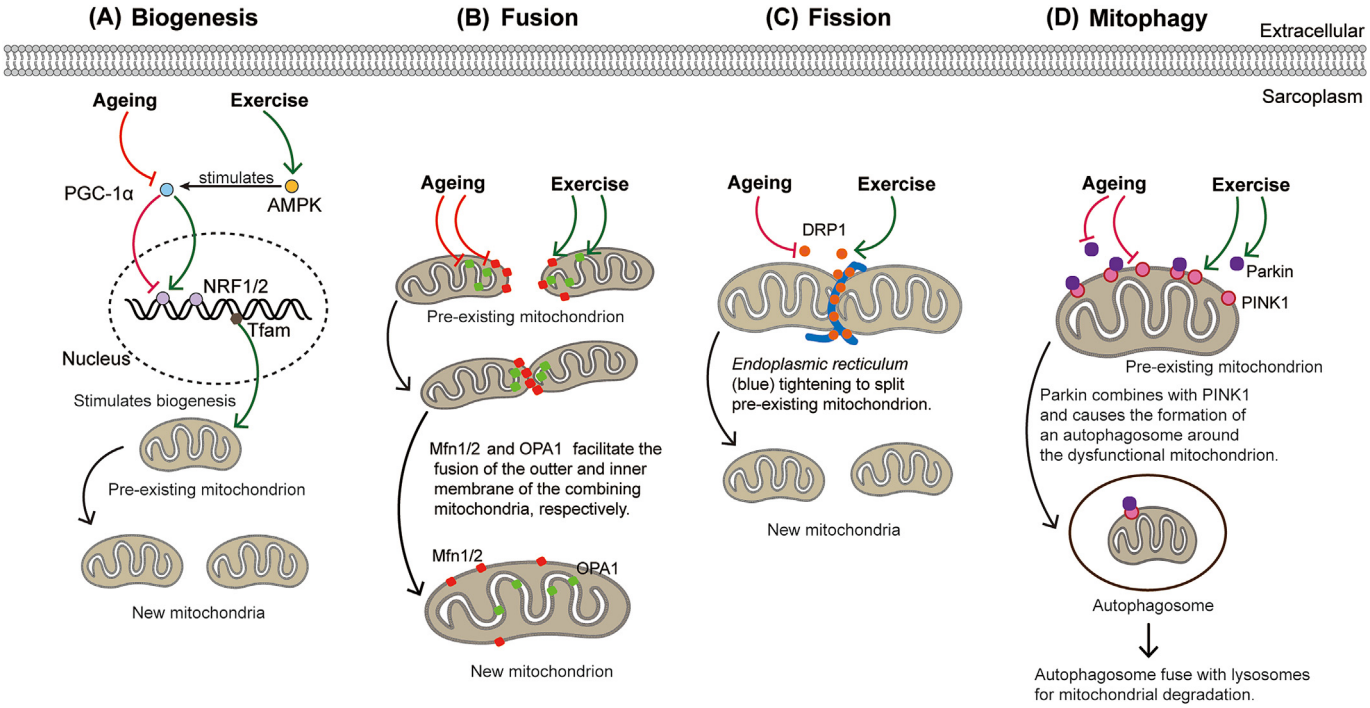

Fig. 2. Mitochondrial quality control includes mitochondrial biogenesis, fission, fusion and mitophagy. (A) Expression level of PGC-1α is decreased during ageing, which causes decreased activation of NRF1/2 and decreased expression of Tfam. Thus decreased level of biogenesis. Exercise was shown to stimulate AMPK pathway to stimulate expression of PGC1 to reverse the ageing effect. (B) Expression level of DRP1 is decreased during ageing, which causes decreased level of fission. Exercise was shown to increase the expression of DRP1 to reverse the ageing effect. (C) Expression level of Mfn1/2 and OPA1 are decreased during ageing, which causes decreased level of fusion. Exercise was shown to increase the expression of Mfn1/2 and OPA1 to reverse the ageing effect. (D) Expression level of PINK1 and Parkin are decreased during ageing, which causes decreased level of mitophagy. Exercise was shown to increase the expression of PINK1 and Parkin to reverse the ageing effect. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Characteristics of the included studies.

Study	Strain, species	Gender	Age range	Exercise-related intervention	Exercise protocol (beginning age, frequency and intensity)	Muscle	Testing for muscle properties/Function/or morphology	Testing for mitochondria	Results summary related to muscle and mitochondria
Zoe White et al. [28]	C57BL/6J mice	Male and female	15–23 months	Voluntary resistance wheel exercise	Voluntary resistance wheel exercise began at 15 months and lasted for 34 weeks, until mice reached 23 months.	1. QUA 2. GA 3. TA 4. SOL 5. EDL 6. TB	1. Muscle mass; 2. Muscle performance; -Values for distance run and speed were recorded every hour, for each mouse. 3. Muscle morphology: -Laminin-stained sections were used to measure myofiber CSA and determine myofiber size distribution -soleus muscle were stained with H&E to assess general tissue architecture, and to quantify myofiber number and percentage of myofibers with centralized nuclei.	Mitochondrial density: -Citrate synthase (CS) activity was investigated to measure the density: the quadriceps muscles stained with NADHTR were used to quantify changes in the oxidative state of whole muscle sections, which can be used as a complementary measure of mitochondrial density. Mitochondrial autophagy: -Via Western blot, LC3II/LCI was determined.	1.Exercise increased intramuscular mitochondrial density and oxidative capacity (measured by citrate synthase and NADH-TR) and increased LC3II/I ratios (a marker of autophagy) in exercised mice of both sexes. 2. long-term resistance wheel exercise initiated from 15 month of age significantly improved some markers of the mitochondrial and autophagosomal pathways and prevented age-related muscle wasting.
Frederic Derbré [23]	1. PGC-1α KO mice 2. Wistar rats	Male	Rat: 3–24 months Mice: 5–6 months	Treadmill running	1. For rat, endurance-trained young and aged rats were exercised 5 day/week on an animal treadmill with different running speed and time. Young animals were running for 1 h at a speed of 30 m × min^{-1}; aged ones were running for 45 min at a speed of 18 m × min^{-1}. During the experiment, the grade of the treadmill corresponded to 15% for young rats and 5% for aged rats. 2. For mice, they were running to exhaustion at 20 m × min−1 at a grade of 10%	1. GA 2. SOL 3. FDB	Muscle maximal endurance time.	1. Mitochondrial morphology. 2. Mitochondrial biogenesis (Western Blotting: PGC-1a, NRF1, Cytochrome.c). 3. Mitochondrial oxidative status (immunoblot detection of protein carbonyl groups.	PGC-1α in the loss of mitochondrial biogenesis was associated with ageing.
Marwa Hassan Muhammad [24]	Mice	Male	12–18 months	Swimming	Swimming for 30 min daily for 4 weeks in a tank (30 × 30 × 40 cm) filled with warm water and to a depth of 25 cm.	GA	1. Swimming-until-exhaustion exercise test was carried out at the end of the 4 weeks' swimming to evaluate the anti-fatigue effects.	/	Exercise trained for 4 weeks showed significant longer time to exhaustion showed significant decreased blood lactate and free fatty acids levels associated with improved oxidative stress evidenced by decreased gastrocnemius muscle lipid peroxidation and increased antioxidant enzymes activities, catalase and superoxide dismutase, when compared to aged mice control group. These changes were accompanied by overexpression of skeletal muscle PGC-1α mRNA.

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Table 1 (*continued*)

Study	Strain, species	Gender	Age range	Exercise-related intervention	Exercise protocol (beginning age, frequency and intensity)	Muscle	Testing for muscle properties/Function/or morphology	Testing for mitochondria	Results summary related to muscle and mitochondria
Stine Ringholma [29]	PGC-1α KO mice Wild type mice	Female	3–15 months	Treadmill running	Mice were determined on a treadmill with an incremental exercise test up to 40 min.	1.Qua 2.EDL	1. Running duration in minutes of WT and PGC-1α KO mice was determined on a treadmill with an incremental exercise test up to 40 min. 2. Glucose tolerance of WT and PGC-1α KO mice was determined by injecting 2 g of glucose/kg mouse intraperitoneally and blood glucose was determined before and 15, 30, 45, 60, 90 and 120 min after injection.	1.Mitochondrial DNA content: -The isolated DNA from quadriceps muscle tissue was to determine the ratio between mtDNA and nuclear DNA (nDNA) content by real-time PCR. 2.Mitochondrial oxidative status: -Citrate synthase activity assessment was determined spectrophotometrically; -PDH-E1α protein content was determined by western blotting.	Lifelong exercise increased activity/content of oxidative proteins (PDH-E1α protein),mtDNA in skeletal muscle through PGC-1α.
Thais Ceresér Vilela [36]	Wistar rats	/	24–26 months	Treadmill running	Ageing Wistar rats performed treadmill or strength training for 50 min 3 to 4 times a week for 8 weeks. -Treadmill running: The exercise groups performed an incremental running program to obtain progressive levels of intensity (13–17mmin−1, no inclination) for 3 or 4 days/ week for 8 weeks and a total period of 60 days. Each session lasted 50 min, and there was a 48-h interval between sessions.	GA	Levels of blood lactate were used as indicators of exercise intensity and glycolytic metabolism. Absence of analysis on lean mass/body composition.	Mitochondrial oxidative capacity: -Enzymatic activity of SOD was estimated by adrenaline auto-oxidation inhibition and read at 480 nm using a spectrophotometer. -CAT activity was measured using the rate of decrease in hydrogen peroxide (H2O2) absorbance at 240 nm and expressed as U/mg protein. -For the determination of ROS, the DCFH levels were monitored in samples incubated with 2′,7′-dichlorodihydrofluorescein diacetate (DCFH-DA).	Oxidative parameters showed that skeletal muscle adapt to increased ROS levels, reducing the risk of free radical damage to the tissue after exercise in aged Rats.
Mohammad-Ali Bahreinipour [25]	Wistar rats	Male	23–24 months	Treadmill running + blood flow restriction	Animals walked for 10 weeks and 5 days per week, at a speed of 7.5 m per minute every day for 15 min on a treadmill designed for rodents. The treadmill speed and duration of exercise sessions gradually increased. At the last week, treadmill speed was 15 m per minute and its duration was 60 min. Blood flow restriction: -a steel wire with diameter 0.014 in. was put on the femoral artery and was tied tightly with silk suture (4–0) at the level of bottom of inguinal ligaments.	1.SOL 2.EDL	1. Muscle phenotype: -The percent of the total muscle contractile protein was estimated in relation to total muscle proteins, and it was considered as muscle hypertrophy index (100 * (contractile protein/total protein).	Mitochondrial biogenesis -Western Blotting: PGC-1a.	Low endurance exercise improved the muscle hypertrophy index of both slow and fast muscles of elderly rats probably through the rise of PGC-1α expression.
Jonathan F. Gill [30]	PGC-1α KO mice PGC-1α overexpression mice	Male	21–24 months	Treadmill running	At 21 months, mice were trained on a treadmill during 12 weeks, 3 times per week, for 30 min. Maximal speed was determined prior to the beginning of the endurance	1. GA 2. TA	1. Balance performance -Time required to cross the beam and number of foot slips made during the crossing were recorded during the 3 following days with 3 trials per day.	1. Mitochondria DNA copy number: -DNA was analyzed by qPCR to measure mitochondrial DNA copy numbers. 2. Mitochondrial OXPHOS level -Determined by western blot: CV-ATP5A, CIII-UQRC2, CIV-MTCO1.	1. Exercise-associated mitochondrial improvement in old muscle is dependent on muscle PGC-1a: -oxidative phosphorylation (OXPHOS) protein levels were elevated by PGC-1a

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Table 1 (*continued*)

Study	Strain, species	Gender	Age range	Exercise-related intervention	Exercise protocol (beginning age, frequency and intensity)	Muscle	Testing for muscle properties/Function/or morphology	Testing for mitochondria	Results summary related to muscle and mitochondria
					exercise training by an exhaustion test.		2. Motor coordination and planning -The time the mice spend on the rod before falling was recorded and averaged over the 5 days. 3. Maximal grip strength and four limbs hanging time -Maximal grip strength was recorded using a grip strength meter; Four limbs hanging time was measured by placing mice on an elevated inverted grid and measuring the maximum time until the mice released and fell. 4. Endurance exercise capacity -The exhaustion test was performed one day after acclimatization, starting at a speed of 4.8 m/min and a subsequent an increased by 1.6 m/min every 3 min until a speed of 29 m/min was reached. When mice reached exhaustion, the maximal running distance was recorded. 5. Muscle phenotype -Fiber type percentages and diameters were quantified after immunostaining.		and exercise. 2. Muscle PGC-1a affects endurance capacity of untrained and trained skeletal muscle in old mice; 3. Ageing, exercise and muscle PGC-1a modulate muscle mass.
Sarah Stolle [34]	C57BL6/JOlaHsd mice	Male	6–24 months	Voluntary running-wheel	Mice were given a lifelong ad libitum low-fat or high-fat sucrose diet and were further divided into sedentary and running-wheel groups.	1. Qua 2. GA 3. TA	1. Muscle weight. 2. Muscle fiber type. -According to the composition of the myosin heavy chain (MHC) isoforms.	1. Mitochondrial respiratory capacity -Estimating the total respiratory capacity of intact muscle by multiplying the state 3 flux of isolated mitochondria to the mitochondrial protein content of the muscle. 2. Mitochondrial function and quantity -Muscle energy metabolism: the maximal ADP-stimulated O2 flux in isolated skeletal muscle mitochondria oxidizing pyruvate plus malate was determined. 3. Mitochondrial content: Relative mtDNA copy number via qPCR.	Endurance exercise did not prevent the decline of skeletal muscle mass with age, but it did increase the mitochondrial content as well as the mitochondrial respiratory capacity.
Eloi F. Rosa [27]	C57BL/6 mice	Male	3–18 months	Treadmill running	60-min endurance run at speeds between 13 and 21 m/min, according to the tolerance of each animal; and 3-min warm-down at 5 m/min.	GA	1. Physical performance: -this test consisted of 3 min of warm-up at 5 m/min, initial speed set at 10 m/min, followed by progressive increases of 1 m/min every min until animal exhaustion,	1. Mitochondrial oxidative status -Lipid peroxidation assay. Peroxidative damage to membrane lipid constituents from gastrocnemius muscle, was determined by measuring the chromogen reaction product of 2-thiobarbituricacid (TBA) with one of	The beneficial effects of this kind of exercise are also the reversion of the well-known effects of ageing, such as impairment of the physical performance in ageing.

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Table 1 (*continued*)

Study	Strain, species	Gender	Age range	Exercise-related intervention	Exercise protocol (beginning age, frequency and intensity)	Muscle	Testing for muscle properties/Function/or morphology	Testing for mitochondria	Results summary related to muscle and mitochondria
							and 3 min of cooling down at 5 m/min 2. Muscle morphology -tissue sections were appropriately isolated and stained with hematoxylin and eosin.	the products of membrane lipid peroxidation, malondialdehyde (MDA).	
C. Andreani [19]	SAMP8 mice	Male	5–7 months	Treadmill running	physical exercise: at 0.5 km/h, on a 5% inclination, for 30 min, 5 days per week, for 2 months up to 7 months of age	1. GA, 2. TA 3. SOL	1. Muscle morphology -hypertrophy, fiber diameter was measured	1. Mitochondrial morphology: electron microscope analysis 2. Mitochondrial biogenesis -Via western blot assay, Mitochondrial DNA content and PGC-1α, Tfam, and SIRT5 protein levels of TA muscles were analyzed to evaluate the mitochondrial biogenesis. 3. Mitochondrial membrane depolarization - via flow cytometry analysis, mitochondrial membrane potential was evaluated in dissociated skeletal muscle cells by flow cytometry using a Nernstian fluorescent probe 4. Mitochondrial DNA (mtDNA) quantification -DNA was extracted from GA muscle and then used for quantitative real-time PCR (qRT-PCR) 5. Mitophagy -To determine whether apoptosis was also modulated, cleaved caspase-3 level was also examined via Western blot assay.	1. Physical exercise alone was able to induce muscle fiber hypertrophy 2. Physical exercise alone did not induce any changes in markers that are related to mitochondrial biogenesis, with the exception of a significant downregulation of SIRT5 in the trained mice. 3.muscle mitochondria of the trained mice appeared even compromised presenting typical matrix swelling and poorly organized or absent cristae In conclusion, 2 months physical exercise significantly increased mitochondrial damage in the muscles of exercised mice when compared to wild type mice.
Zhengzhong Zeng [17]	Rats	Male	6–24 months	Voluntary running wheel	1. Treadmill: at speed of 12 m/min at a speed increment of 1 m/min every 30 s, and then maintained this speed for exercise training for 12 weeks with 60 min during each training time. 2. Ladder climbing(resistance exercise): consisted of two sets with three repetitions, followed by 1 min rest between each repetition and 2 min rest between each set.	GA	1. Muscle mass 2. Muscle morphology -The cross-sectional areas (CSA) of gastrocnemius muscle fibers were gauged 3. Muscle atrophy - -Via Western blot, E3 ubiquitin ligases including Atrogin-1 (atrophy gene-1) and MuRF1 (muscle ring finger protein 1) were determined.	1. Mitochondrial biogenesis and quality control -Via western blot assay, PGC-1α, Mfn2, Drp1, AMPK and PINK1 protein level were determined 2. Mitochondrial morphology -via transmission electron microscopic examination	1. Exercise Interventions Rescued the Atrophy of Skeletal Muscle in Aged Rats 2. Exercise Suppressed E3 Ubiquitin Ligase in Skeletal Muscle of Aged Rats 3. Exercise Induced Autophagy and Inhibited Excessive Apoptosis in the Skeletal Muscle of Aged Rats 4. Exercise Regulated Akt/mTOR and Akt/FoxO3a Signal Pathways in Skeletal Muscle of Aged Rats to suppress sarcopenia. In conclusion, exercise-induced autophagy was beneficial for remedying sarcopenia by modulating Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control, and

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Table 1 (*continued*)

Study	Strain, species	Gender	Age range	Exercise-related intervention	Exercise protocol (beginning age, frequency and intensity)	Muscle	Testing for muscle properties/Function/or morphology	Testing for mitochondria	Results summary related to muscle and mitochondria
									resistance exercise exhibits the best interventional efficiency.
Kai Aoki [35]	SAMP8 mice	Male	7–11 months	Treadmill running	Running at 15 m/min for 30 min a day in light cycle, 5 days per week, from 7-month to 11-month of age	1. SOL 2. Plantaris muscles 3. GA	1. Grip Strength, 2. Muscle phenotype 3. muscle protein synthesis -via Western blot, The phosphorylation levels of Akt and p70S6K as a protein synthesis marker of muscle protein synthesis were determined	1. mitochondrial function -Via real-time PCR and Western blot, PGC1-1a, Atp5a1, Cox IV were determined	1. Exercise prevented the decreasing of muscle weight and grip strength Long-term habitual exercise attenuates muscle mass and strength decline, possibly through maintenance of muscle protein synthesis and mitochondrial maintenance.
Haoen GAO [31]	Sprague–Dawley rats	/	8–26 months	Treadmill running	1. 1 min of warm-up at a constant running speed of 10 m·min−1, 2.followed by 45min at a constant running speed of 17 m·min−1 3. cool-down at a constant running speed of 10 m·min−1 for 1 min.	Vastus lateralis muscle	1. Expression of muscle atrophy, apoptosis: Caspase-3, BAX, Bcl2, LC3II/LC3I	1. Expression of muscle mitochondrial function markers:PGC-1α, SDHA, SIRT3, COX-IV	Exercise leaded to a greater enhancement of mitochondrial function, anti-apoptosis events, and autophagy and also increased protein synthesis and reduced skeletal muscle atrophy in age skeletal muscle.
Jiling Liang [32]	ICR mice	Male	3–17 months	Treadmill running	The running duration and intensity were progressively increased at the increment of 4.2 m/min until the running duration of 60 min/day at the speed of 12 m/min.	GA	The skeletal muscle atrophy in aged mice -by CSA of skeletal muscle fibers -by estimating the expression level of Caspase-3, BAX, Bcl2, LC3II/LC3I	1. Morphology of mitochondria in skeletal muscle 2. Mitochondrial function: - the activity of citrate synthase -the function of enzyme in mitochondria	Lifelong Aerobic Exercise Alleviates Sarcopenia by Activating Autophagy and Inhibiting Protein Degradation via the AMPK/PGC-1 Signaling Pathway
Sujuan Liu [33]	C57BL/6 mice	Male	8–23 months	Treadmill running	1. Mice underwent 8-month aerobic exercise training on a motor-driven rodent treadmill for 5 days per week (60 min/day) at 75% VO2max intensity (12 m/min).	GA	1. Muscle mass 2. Muscle performance -Running distance and time -The grip strength 3. Muscle morphology –H&E staining of muscle section	1. Morphology of mitochondria in skeletal muscle 2. Mitochondrial function: - the activity of citrate synthase -the function of enzyme in mitochondria - the expression level of PGC-1α, Mfn2, Pink1,COX4	1. Aerobic exercise alleviated the negative effects resulting from sarcopenia via the Sesn2/AMPKα2 pathway 2. Sesn2/AMPKα2 signaling axis mediates the beneficial impact of exercise on sarcopenia

Table 2
The changes of skeletal muscle and mitochondria during ageing and after exercise.

	Muscle weight/ Body weight	Skeletal muscle			Mitochondria				
		Muscle weight	Muscle morphology	Performance	Biogenesis	Fusion/ Fission	Mitophagy	Performance	Morphology
During ageingr	1. The ratio of gastrocnemius muscle weight (GMW)/body weight (BW) decreased in aged rats [26]. 2. Body weight increased during ageing mice [28,33]. 3. Body weight had no significant change during ageing in mice [34,37].	1. Muscle weight decreased in aged mice [28,32,33,35,37]. 2. Muscle mass decreased during ageing in mice [30]. 3. The weight of quadriceps had no significant change during ageing in mice [34].	Muscle fiber intensity decreased during ageing in mice [28,31,32,37].	1. Endurance capacity decreased in aged rats and mice [23,24,34]. 2. The grip strength decreased in aged mice [30,35,37]. 3.Running distance decreased in aged mice [28]. 4. Running speed decreased in aged mice [28]. 5. Compared with young mice, running duration had no significant change in aged mice [29].	The expression of PGC-1α decreased in aged rats and mice [23,24,26,29,31,32,35].	The expression of Mfn2 and DRP1 decreased in aged rats [26,33].	The expression of PINK1 decreased in aged rats [26] and mice [33].	1. The expression level of ATP5A1 decreased in aged mice [35]. 2. The content of mitochondrial DNA decreased in aged mice [29,32]. 3. The content of cytochrome C had no significant change during ageing in mice [29,37]. 4. The citrate synthases activity decreased in aged mice [32]. 5. The SOD activity decreased in aged mice [32,37]	Mitochondria were swollen and vacuous in aged rats [23,26,32,33].
Endurance exercise	Endurance exercise had no significant effects on aged mice [27].	Endurance exercise improved muscle mass in aged mice [30].	1. Endurance exercise Improved the soleus muscle fiber size in aged mice [19]. 2. Endurance exercise Improved the gastrocnemius muscle fiber size in aged rats [26]. 3. Endurance exercise decreased myocyte cross-sectional area in aged mice [27].	1. Endurance exercise Improved the endurance capacity in aged rats and mice [23,24]. 2. Endurance exercise improved running distance in aged mice [30]. 3. Endurance improved running speed in aged mice [27]. 4. Endurance exercise improved grip strength in aged mice [30].	Endurance exercise Improved the expression level of PGC-1α in aged mice and rats [19,23–26,29–33,35].	Endurance exercise improved the expression level of Mfn2 and Drp1 [26,33].	Endurance exercise improved the expression level of PINK1 [26,33].	1. Endurance exercise Improved the capacity to handle oxidative stress in aged mice [19,30]. 2. Endurance exercise improved the activities of catalase and superoxide dismutase in aged mice [24]. 3. Endurance exercise improved the activities of catalase, superoxide dismutase, and glutathione in aged rats [36]. 4. Endurance exercise improved the expression level of ATP5A1 decreased in aged mice [35]. 5. Endurance exercise improved citrate synthase in quadriceps in aged mice [29] 6. Endurance exercise had no effects on cytochrome C in aged mice [29] 7. Endurance	Endurance exercise Improved the mitochondrial ultrastructure in aged rats [19,26,32,33]

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Table 2 (*continued*)

	Muscle weight/ Body weight	Skeletal muscle			Mitochondria				
		Muscle weight	Muscle morphology	Performance	Biogenesis	Fusion/ Fission	Mitophagy	Performance	Morphology
								exercise improved the expression level of cytochrome C in aged mice [30]. 8. Endurance exercise improved the citrate synthases activity in aged mice [32]. 9. Endurance exercise improved the SOD activity in aged mice [32,37].	
Resistance exercise			1. Resistance exercise improved the gastrocnemius muscle fiber size in aged rats [26]. 2. Resistance exercise improved soleus muscle fiber size in aged mice [28]. 3. Residence exercise improved the quadriceps muscle fiber in aged mice [28].		Resistance exercise improved the expression level of PGC-1α [26].	Resistance exercise improved the expression level of Mfn2 and DRP1 [26].	Resistance exercise improved the expression level of PINK1 [26].	Resistance exercise improved citrate synthase in GA and QUA in aged mice [28].	Resistance exercise Improved the mitochondrial ultrastructure in aged rats [26].

Abbreviations: 1. QUA, quadriceps; GA, gastrocnemius; TA, tibialis anterior; EDL, extensor digitorum longus; SOL, soleus; and quadriceps; TB, Triceps brachii; FDB, Flexor digitorum brevis (FDB); PGC-1α, peroxisome proliferative activated receptor gamma coactivator 1 alpha; Mfn2: Mitofusin 2; DRP1: dynamin related protein 1; Tfam, mitochondrial transcription factor A.

mitochondrial quality control [26–28,31–34]; 6 papers investigated autophagy [26–28,32,33,35]; 9 papers investigated the oxidative stress of mitochondria [19,23,24,27,29,33,34,36,37]; 14 studies investigated muscle performance [23–30,32–37]; 7 papers studied muscle morphology [19,26–28,30,33,37]; 4 papers investigated the mitochondrial morphology [23,26,32,33].

In addition, the exercise protocols and animal model in the included studies are different. 4 studies used the volunteer running wheel exercise [26,28,34,37], 11 studies used the treadmill running exercise [19,23,25,27,29–33,35,36], and swimming was conducted in 1 study [24]. 12 studies used mice [19,23,24,27–30,32–35,37] and 5 papers used rats [23,25,26,31,36] as the animal model.

3.3. Body weight and muscle weight

As an index to reflect the animals' metabolism level, the changes in animals' body weight and muscle weight during ageing [26–28,30,32–35,37] were reported in 9 papers. 1 paper used rats [26] while 8 papers used mice as the animal model [27,28,30,32–35,37]. 1 paper showed that the body weight decreased during ageing in rats [26]. 5 papers showed no significant change of body weight during ageing in mice [27,32,34,35,37], and 2 paper showed increased body weight during ageing in mice [28,33]. For muscle weight, 4 papers reported that the weight of gastrocnemius (GA), tibialis anterior (TA), extensor digitorum longus (EDL), soleus (SOL), and quadriceps (QUA) decreased during ageing [28,32,33,35]. In contrast, Gill et al. showed that the muscle weight of TA, quadriceps, and soleus decreased significantly during ageing in mice [30]. Also, Zeng et al. reported that the muscle weight of gastrocnemius in rats decreased significantly [26]. 3 paper reported that the muscle weight of quadriceps between young and aged had no significant difference in mice [32,34,37]. These results demonstrated the contradictory results of body weights in rats and mice during ageing, which might be influenced by the measurement bias.

In addition, 4 papers evaluated the effects of exercise on body weight [26,28,33,35], while 5 papers studied on muscle weight [26,28,30,33,35]. 1 paper used aged rats [26], while 4 papers used aged mice [28,30,33,35]. For body weight, 1 paper reported that both endurance exercise and resistance exercise improved the body weight of aged rats [26], but 3 papers reported that endurance exercise had no effect on body weight of aged mice [28,33,35]. For muscle weight, 4 papers showed that exercise increased the muscle weight in aged rats [26] and mice [28,30,33]. Meanwhile, resistance exercise improved the muscle weight of gastrocnemius in aged rats [26]. 1 paper showed that the muscle weight of TA, EDL, gastrocnemius, soleus, and quadriceps were increased significantly after the voluntary resistance wheel exercise [28]. In addition, Gill et al. showed that treadmill running increased the muscle weight of quadriceps significantly, yet had no effects on the weight of TA and soleus [30]. 1 paper showed that the weight of gastrocnemius of aged mice had no significant change after the treadmill running [35].

3.4. Muscle fiber morphology

6 papers evaluated the change of muscle fibers during ageing [19,26,28,32,33,37]. 1 paper showed that the fiber size of gastrocnemius decreased during ageing in rats [26]. 5 papers compared the fiber size between young and aged mice, whereas the results showed that the fiber size decreased during ageing [19,28,32,33], while 1 paper showed no significant difference [37]. For fiber typing, 1 paper indicated that both type IIA and IIB in quadriceps showed decreasing trend during ageing in mice, yet without statistical significance [28]. In summary, the size of muscle fibers should decrease during ageing in rats and mice.

To study the effect of exercise on muscle fibers, 7 papers analyzed the change of muscle fibers after exercise in aged animal [19,26–28,32,33]. 4 papers reported that exercise improved the fiber size of soleus in aged mice [19,28,32,33], meanwhile, 1 paper also indicated that both endurance and resistance exercise increased the fiber size of gastrocnemius in aged rats [26]. Regarding the muscle typing, 1 paper showed that exercise improved the proportion of type IIB and decreased type IIA in quadriceps of aged mice [28]. In addition, 1 paper indicated that swimming decreased the cross-sectional area of gastrocnemius in aged mice [27]. Taken together, exercise may increase the muscle fiber size in aged mice and rats, and influence the proportion of muscle type IIA and IIB.

3.5. Muscle performance

To investigate muscle performance during ageing and after exercise training, the grip strength, running speed, running time, and distance were evaluated in 9 papers [23,24,27–30,33–35]. 3 papers showed that the grip strength decreased during ageing in mice [30,33,35]. 3 papers showed that the maximal running speed decreased during ageing in mice [27,28,34]. For the maximal running time, 2 papers showed a decrease during ageing in rats and mice [23,24]. However, 1 paper reported that the maximal running time in aged mice had no significant change [29]. For the maximal running distance, 1 paper reported that the maximal distance had no significant difference between young and aged mice [28].

7 papers evaluated the muscle function after exercise [23,24,27,29,30,33,35]. 1 paper used rats [23] while 6 papers used mice [24,27,29,30,33,35] as the animal model. 1 paper reported the increase of grip strength after exercise in aged mice [33], while 2 papers showed that exercise had no significant effect on the grip strength in aged mice [30,35]. 1 paper showed that the maximal running speed was improved after exercise in aged mice [27]. For the maximal running time, 1 paper reported an improvement by exercise in aged rats [23] and mice [24]. However, 1 paper showed that the maximal running time of aged mice had no significant change after exercise [29]. Meanwhile, 1 paper reported that exercise improved the maximal running distance of aged mice [30].

3.6. Mitochondria morphology

Mitochondria is known as one of the key factors in ageing and mitochondrial morphologic changes such as mitochondrial number, size and density are important parameters to evaluate mitochondria status. 4 papers evaluated the morphological change of mitochondria during ageing [19,26,32,33]. These papers showed that the content of mitochondria decreased, which changed into swollen and vacuous in mice [19,32,33] and rats during ageing [26]. In summary, mitochondria may change into abnormal morphology, and the mitochondrial content decrease during ageing. Mitochondrial biogenesis promotes a development in mitochondrial content to fulfill cellular energy needed. Additionally, PGC-1α, the master regulating factor in mitochondrial biogenesis, can be regulated by phosphorylation of adenosine monophosphate kinase (AMPK). 4 papers studied the effects of exercise on the mitochondrial morphology, which showed that the mitochondrial contents were improved after exercise in aged mice and rats [19,26,32,33]. Derbré et al. showed that fewer and smaller mitochondria in SOL muscle of PGC-1α KO mice [23]. The expression level of PGC-1α and AMPK were increased after exercise, which suggested that exercise could activate the AMPK/PGC-1α signal pathway and promote mitochondrial synthesis in aged skeletal muscle [26,32,33]. In addition, compared to WT mice, the content of mitochondria significantly reduced in AMPKα2$^{-/-}$ mice, suggesting that AMPK knockout damaged the mitochondrial morphology and synthesis [32,33]. Based on these results, it suggests that exercise can improve mitochondrial morphology and content via AMPK/PGC-1α signaling pathway.

3.7. Mitochondrial function

Mitochondria are the well-known organelle to generate ATP for biological processes. To evaluate the changes of mitochondrial functions during ageing, 6 papers compared the differences of mitochondrial ATP generation between young and aged animals [23,28,29,34,35,37]. 1 paper used rats as the animal model [23], while 5 papers used mice for the experiments [28,29,34,35,37].

4 papers indicated that the production of ATP decreased during ageing [23,28,29,35], while 1 paper showed no significant change in mice during ageing [37]. Specifically, 2 papers indicated that the expression level of cytochrome c (a hemeprotein involved in electron transport in mitochondria and initiation of apoptosis) decreased during ageing in rats [23] and mice [35]. However, 1 paper indicated that the cytochrome c expression had no significant change during ageing in quadriceps of mice during ageing [29]. Regarding the activity of citrate synthase (CS) which is used as a quantitative enzyme marker for the presence of intact mitochondria. 2 paper showed the activity decreased in the quadriceps of mice during ageing [29,32], while another paper reported that the activity of CS had no significant change in both the quadriceps and gastrocnemius of mice during ageing [28].

For anti-oxidative ability, 2 papers indicated that the anti-oxidative capacity of mitochondria decreased in mice during ageing [24,34], and 1 paper showed that the copy number of mitochondrial DNA (mtDNA) decreased during ageing [34]. In summary, the functions of mitochondria, including ATP generation, the copy number of mtDNA, anti-oxidative capacity, decreased in rats and mice during ageing.

8 papers compared the relative index before and after the exercise [19,23,24,28–30,35,36] in aged animal. 2 papers used rats [23,36], while 6 papers used mice [19,24,28–30,35] as the animal model. 4 papers indicated that the production of ATP was improved after exercise in age mice [28–30,35] but 1 paper showed that the expression level of cytochrome c decreased after exercsse [23] in aged rats. For anti-oxidative ability, 3 papers indicated that the anti-oxidative capacity of mitochondria was improved after the exercise in aged rats and mice [19,24,36]. These results suggest that exercise can promote ATP generation in aged mice, and also improve the anti-oxidative capacity in aged rats and mice.

3.8. Mitochondrial biogenesis

Mitochondrial biogenesis is an important biological process to maintain the homeostasis of mitochondria, and peroxisome proliferative activated receptor gamma coactivator 1 alpha (PGC-1α) is a major factor to regulate the mitochondrial biogenesis.

7 papers investigated the change of PGC-1α expression level during ageing [23,24,26,31–33,35]. 3 papers showed that PGC-1α level decreased in the skeletal muscle of rats during ageing [23,26,31]. Similarly, 4 papers indicated that the expression level of PGC-1α decreased in skeletal muscle of mice during ageing [24,32,33,35]. These results substantiate that the expression level of PGC-1α decreased in skeletal muscle of rats and mice during ageing.

9 papers reported the effects of exercise on the expression level of PGC-1α in skeletal muscle of aged animal [19,23–26,30,32,33,35]. 8

papers showed that exercise improved the expression level of PGC-1α in skeletal muscle of aged mice [24,30,32,33,35] and rats [23,25,26]. However, 1 paper showed that the expression level of PGC-1α in soleus and TA of aged mice had no significant change after exercise [19]. By knocking out Sesn2 protein (a protein involved in cellular response to different stress conditions), Liu et al. showed that the expression level of PGC-1α was lower than the wild-type group, and exercise could attenuate the expression level of PGC-1α in Sesn2$^{-/-}$ mice [33]. It suggested that mitochondrial biogenesis was damaged after Sen2 knockout and could be rescued by exercise. In addition, Liang et al. showed that the expression level of phosphorylated-adenosine monophosphate kinase (p-AMPK) and PGC-1α decreased during ageing and could be attenuated by exercise [32], which indicated that exercise could enhance mitochondrial biogenesis via AMPK/PGC-1α signaling pathway.

3.9. Mitochondrial fusion and fission

Mitochondrial fusion and fission are two critical processes to maintain mitochondrial dynamic balance, and prevent the mitochondrial dysfunction due to the damaged mitochondria or mis-translated protein in mitochondria. Mitofusin 2 (Mfn2) is a key mitochondrial membrane protein involved in fusion, while dynamin related protein 1 (DRP1) is for mitochondrial fission. 2 paper showed that the expression level of Mfn2 and DRP1 in skeletal muscle of rats decreased during [26,33].

2 paper investigated the influence of exercise on mitochondrial fusion and fission in aged rats, which showed that endurance exercise and resistance exercise improved the expression level of Mfn2 and DRP1 [26,33]. Compared to wide type (WT) mice, the protein expression of Mfn2 and DRP1 was significantly reduced in gastrocnemius of AMPKα$^{2-/-}$ mice, suggesting that AMPK knockout damaged the mitochondrial fusion and fission [33].

3.10. Mitophagy

Mitophagy is a specific autophagic elimination of mitochondria that is an important mechanism in preserving mitochondria when severe mitochondrial damage emerges. PINK1-Parkin-mediated mitophagy pathway is one of the most significant pathways to maintain mitochondrial homeostasis. 3 papers evaluated the mitophagy during ageing, which showed that the expression levels of PINK1 and Parkin decreased during ageing [26,32,33].

3 papers evaluated the expression levels of PINK1 and Parkin in skeletal muscle after exercises, which showed that exercise improved the expression levels of PINK1 and Parkin during ageing [26,32,33]. Furthermore, by using AMPK knockout mice, 2 papers showed that the expression level of PINK1 and Parkin were decreased, while exercise could attenuate the expression level [32,33], suggesting that exercise can improve mitophagy via AMPK.

3.11. Potential signaling pathways

As mentioned before, mitochondrial quality control plays an essential function in regulating muscle performances, while exercise improves muscle mitochondrial quality control effectively. Furthermore, 2 papers elucidated the potential pathways for how physical exercise affected mitochondrial quality control. Liang et al. suggested that exercise improved mitochondrial biogenesis by promoting PGC-1α through improving the expression level of AMPK [32]. Liu et al. showed that decreasing AMPK led to a lower level of Mfn2 and DRP1 simultaneously, which indicated that mitochondrial fusion and fission could be regulated by AMPK [33]. Furthermore, 2 studies showed that decreasing AMPK caused a lower level of PINK1; while exercise could attenuate the expression level of PINK1, which suggested exercise attenuated mitophagy by promoting the level of PINK1 through increasing the level of AMPK [32,33].

4. Discussion

Sarcopenia is a geriatric syndrome characterized by progressive and generalized skeletal muscle disorder, including the loss of muscle mass and strength during ageing. This systematic review showed that the fiber size of skeletal muscle and muscle performance decreased during ageing [19,26,28], while exercise interventions improved the size of muscle fibers and muscle function in aged mice and rats [19,23,24,26–28,30]. Mitochondria dysfunction plays a major role in sarcopenia. ROS are kinds of metabolite produced by mitochondria during oxidative phosphorylation when it utilizes oxygen to generate ATP [38] that is regarded as one of the factors leading to sarcopenia during ageing via disrupting mitochondrial function [39,40]. In the process of ATP generation, Complex I, II, III in mitochondria contributed to the production of mitochondrial ROS (mtROS) [38,41] that in turns affect the expression of nuclear genes to influence the normal functions of mitochondia [38]. This systematic review revealed that oxidative capacity and ATP production of mitochondria in skeletal muscle decreased during ageing [23,24,28,29,34,35], while exercise interventions showed positive effects on improving mitochondrial functions [28,30,35,36].

To prevent the damage from daily produced mtROS, mitochondria have developed a mechanism of quality control to maintain mitochondrial dynamics (Fig. 1.). The mitochondrial quality control involves the dynamic process of fission, fusion, mitophagy, and biogenesis [42–44]. These processes are two opposing ways which constitute mitochondrial turnover: mitochondrial biogenesis and fission, which respectively refer to the growth and division of pre-existing mitochondria; and mitochondrial fusion and mitophagy, which respectively refer to the merging of pre-existing mitochondrial or removal of damaged mitochondria or their components [42,43]. Therefore, the rates of the two opposing processes regulated mtROS [43]. Once the balance of these processes is impaired, mtROS will accumulate and leads to further mitochondrial dysfunction in muscle leading to sarcopenia [9,10].

PGC-1α is a main factor in mitochondrial biogenesis and the expression level of PGC-1α is prominently enhanced in organs/tissues with high energy demands such as skeletal muscle [45]. In these organs/tissues, PGC-1α can be activated by specific stimuli (such as physical exercise). The activated PGC-1α can lead to the activation of several transcription factors, such as nuclear respiratory factors (NRF-1 and 2), and mitochondrial transcription factor A (Tfam) [46]. Previous findings showed a decrease of PGC-1α in rats and mice during ageing [23,24,26,31–33,35], meanwhile, physical exercise improved the expression level of PGC-1α in aged rats and mice [23–26,30,32,33,35] and muscle endurance in aged mice. By using PGC-1α KO mice, Derbré et al. observed a significant decrease of NRF and muscle performance, meanwhile, the morphology of mitochondria changed into swollen. In addition, exercise had no significant effect on improving muscle performance [23]. These results provided evidence supporting that exercise might improve the mitochondrial function through improving the expression level of PGC-1α for the activation of NRF-1 and NRF-2 which in turns improves muscle performance in aged animal. Meanwhile, NRF-1 and 2 could also interact with Tfam to increase the replication and transcription of mtDNA [47] in order to activate tissue-specific gene programs for adjusted exercise adaption in skeletal muscle, inducing a transcriptional network to regulate mitochondrial biogenesis (Fig. 1.) [20].

Mitochondrial fusion and fission are two important biological mechanisms for the constant elongation and division, respectively (Fig. 1.). Longer and fused mitochondria are optimal for ATP generation, whereas the fission of mitochondria promotes mitophagy and cell division [48]. Mfn1 and Mfn2 are two mitochondrial membrane proteins that control the mitochondrial fusion of the outer mitochondrial membrane, while fusion of the inner mitochondrial membrane requires the membrane bound protein of optic atrophy 1 (OPA1) [48]. Furthermore, Mfn2 plays a key role in the regulation of mitochondrial dysfunction in skeletal muscle and the progressive reduction in Mfn2 is reported to associate with ageing [49]. Previous reports showed that once the process of

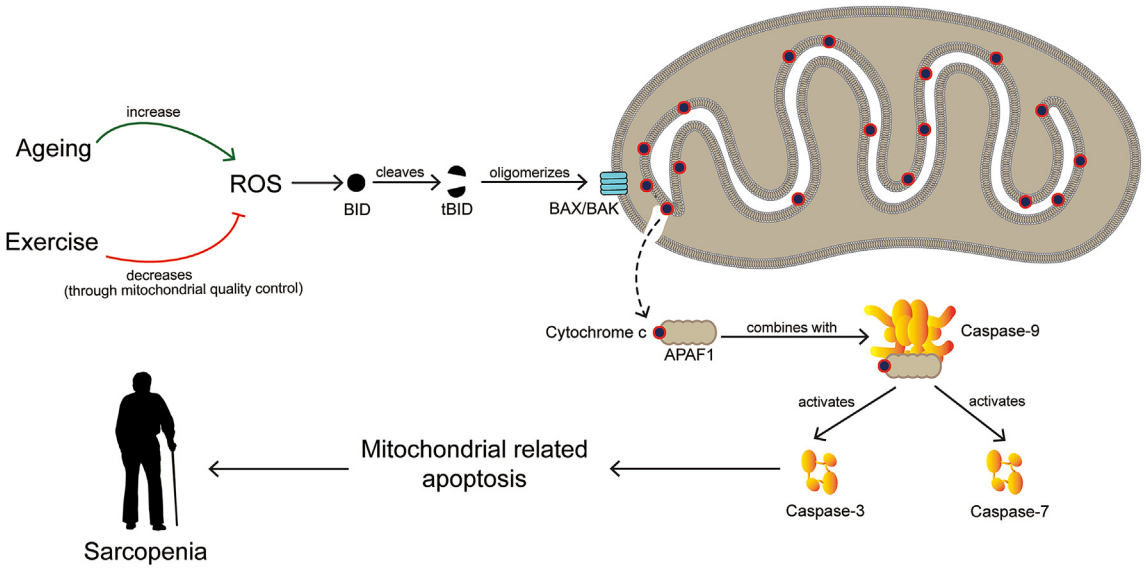

Fig. 3. During ageing, ROS increases because of the imbalance of mitochondrial quality control while exercise can decrease excessive ROS through mitochondrial quality control processes. Excessive ROS causes BID to be cleaved into truncated tBID. Then, tBID activates the oligomerization of BAX and BAK to form pores in the outer mitochondrial membrane. Cytochrome c are released to the cytoplasm via the openings in the mitochondrial membrane. Once in the cytoplasm, cytochrome c can bind to apoptotic protease activating factor-1 (APAF1) to enable its heptamerization and binding to the procaspase-9. Activated caspase-9 then activates the executioner caspases-3 and -7 which in turns lead to mitochondrial related apoptosis in skeletal muscles.

mitochondrial fusion was blocked, the generation of ATP and the transfer of both mitochondrial mtDNA and protein would be impaired that ultimately resulting in the accumulation of mtDNA mutation and hence mitochondria-related disease such as sarcopenia [50,51]. Mitochondrial fission mainly plays a role in segregating dysfunctional mitochondria that contain damaged proteins, destabilized membranes, mutated or damaged mtDNA for mitochondrial remodeling to keep mitochondrial dynamic equilibrium [42,52]. DRP1 is one of the core roles in mitochondrial fission [52,53]. DRP1 in the cytoplasm can be recruited by the DRP1 receptor on mitochondrial membrane, and then forms oligomers around the constricted site, which will constrict the "marked" mitochondrial membrane. Furthermore, there are two functionally and mechanistically distinct types of fission. Both types are mediated by DRP1: one is the division at the periphery, which enables damaged or mistranslated protein in mitochondria to be shelled into smaller mitochondria for mitophagy; another is the division at the middle of mitochondria, which is regarded as one of the ways to increase mitochondrial mass [54]. It was reported that the expression of Mfn2 and DRP1 decreased during ageing, while both endurance and resistance exercises improved their expression levels [26]. These results suggested that exercise could attenuate sarcopenia by regulating the membrane in mitochondria via improving the mitochondrial function and preventing the damage from mtROS. Hu et al. revealed that a proportion of AMPK was distributed in the outer mitochondrial membrane and interacted with Mfn2 under normal conditions, however, a large amount of AMPK was translocated to the fragmented mitochondria under energy stress condition [55]. One study showed that DRP1 deficient mitochondria were morphologically bigger and functionally abnormal, thus causing sarcopenia via increasing mitochondrial Ca^{2+} uptake and myofiber death [56].

Mitophagy is another important mechanism for the mitochondrial quality control that is responsible for the degradation and recycling of damaged mitochondria. Previous reports showed that the elimination of whole mitochondria was accomplished by a selective form of mitophagy [43]. PINK1/Parkin-mediated mitophagy is the most well-known pathway for detecting dysfunctional mitochondria and recruiting autophagosomes for degradation mainly regulated by PTEN-induced putative protein kinase 1 (PINK1) [42] that is a mitochondrial serine/threonine kinase. Normally, PINK1 is easily cleaved in mitochondria [57], and Parkin is a kind of cytosolic E3 ubiquitin ligase in cytoplasm [58]. During ageing, PINK1 is stabilized on the outer membrane of damaged mitochondria, where it recruits cytosolic Parkin [59,60]. Then PINK1 directly phosphorylates Parkin to promote Parkin E3 ligase activity to trigger mitophagy and facilitate the clearance of damaged mitochondria: Parkin ubiquitylates mitochondrial proteins and causes mitochondria to become autophagosome by isolation membranes that then fuse with lysosomes for mitochondrial degradation (Fig. 1.) [58,59]. The expression level of PINK1 decreases during ageing indicating the function or capacity of mitophagy in skeletal muscle decreases with age [26] thus contributing to the increased mtROS in ageing. In addition, both endurance and resistance exercise were shown to improve the expression level of PINK1 in aged rats [26] suggesting that exercise might prevent mitochondrial dysfunction by promoting mitophagy via maintaining the expression level of PINK1. Zhao et al. reported that physical exercise might rescue mitochondrial dysfunction via SIRT1-FOXO1/3-PINK1-Parkin–mediated mitophagy [18] suggesting a potential research direction for the treatment of sarcopenia.

The continuously produced mtROS must be decomposed or will lead to the mitochondrial dysfunction. Therefore, mitochondrial quality control plays an important role in maintaining homeostasis to prevent mitochondrial dysfunction due to excessive mtROS. Mitochondrial biogenesis and fusion are vital to increasing mitochondrial mass and function to meet the energy requirements from the cells. Meanwhile, fission and mitophagy are important processes for eliminating dysfunctional mitochondria. If mitochondrial biogenesis and/or fusion are impaired, apoptosis will occur due to the insufficient ATP supply. On the other hand, if fission and/or mitophagy are inhibited, mitochondrial content will be maintained but damaged mitochondria cannot be eliminated. This would result in the accumulated mitochondrial dysfunction and exacerbate the damage to the entire mitochondrial network. Therefore, mitochondrial dynamic equilibrium between keeping adequate mitochondrial mass for sufficient ATP production and removing damaged mitochondria is important for cells.

Once ROS cannot be eliminated in time due to the mitochondrial dysfunction during ageing, accumulated ROS will increase the permeability of mitochondrial membrane and promote the release of proteins in the mitochondrial inner membrane (such as cytochrome c) to trigger mitochondria-related apoptosis (Fig. 3.) [61,62]. At present, some studies indicated that the mitochondria-related apoptosis was the main

pathway of sarcopenia via mediating skeletal muscle fiber loss in aged-induced mitochondrial dysfunction [63,64]. Pardo et al. showed that miR-434-3p was an anti-apoptotic miRNA that could attenuate sarcopenia via suppressing eukaryotic translation initiation factor 5A1 (eIF5A1) during ageing [65]. In addition, several studies showed that exercise and certain chemicals (such as coenzyme Q10, resveratrol, spermidine) might have positive effects on attenuating sarcopenia through reducing mitochondria-related apoptosis [19,66,67]. Luo et al. showed that chronic resistance exercise reduced apoptosis by modulating IGF-1 and its receptors, the Akt/mTOR and Akt/FOXO3a signaling pathways in aged skeletal muscles [68], while Fan et al. showed that spermidine coupled with exercise rescued skeletal muscle atrophy through enhanced autophagy and reduced apoptosis via AMPK-FOXO3a signal [67]. Furthermore, compared to WT mice, the expression levels of PGC-1α, Mfn2, DRP1, PINK1, Parkin were significantly reduced in $AMPK^{-/-}$ mice and could be attenuated by exercise [32,33]. It suggested that AMPK knockout damaged the mitochondrial biogenesis, fusion, fission and mitophagy and exercise could improve the expression level of these proteins directly.

With the increasing ageing population, sarcopenia is increasingly recognized not only as an age-related problem, but also a social health problem [6]. During ageing, the balance of skeletal muscle between atrophy and regeneration was impaired [19,28]. Sarcopenia resulted in the decrease of muscle weight in both mice and rats [26,28,35], accompanied by the decrease of grip strength and muscle performance in mice and rats during ageing [23,30,35]. Meanwhile, the proportion of skeletal muscle fiber type I and type II changed due to the myofiber changes during ageing, with a decrease of type II fibers and an increase of type I fibers [6,19,26,28]. This was partly due to the imbalance between muscle protein anabolism and catabolism [6]. Regarding the mechanism resulting in the sarcopenia, the mitochondrial dysfunction during ageing has been indicated as the major contributor [10,69]. The increased mtROS during ageing that could not be decomposed in time in the mitochondria would disturb mitochondrial function and eventually mitochondrial dysfunction [38]. By comparing the young and aged mice and rats, the morphology of mitochondria was observed to be swollen, accompanied by a low level of ATP production [23,28,29,34,35]. Normally, the rate of decomposing mtROS could be regulated by the ability of cells to carry out mitochondrial quality control under normal condition. However, this biological function decreased during ageing, which indicated the ability of improving mitochondrial content and eliminating damaged mitochondria were decreased [23,24,26,35].

Regular physical exercise is the clinically recommended gold standard for preventing sarcopenia among the old population [70]. Recently, evidence for the benefits of exercise in improving both skeletal muscle strength and mass were compelling, and the positive effects of exercise on attenuating sarcopenia were growing [6]. Exercise could induce AMPK activation, which in turn induced mitochondrial biogenesis via increasing the expression level of PGC-1α [71]. A study reported that prolonged exercise training attenuated the ageing-associated decline in mitochondrial biogenesis in skeletal muscle partly and improved muscle performance via upregulating the expression level of PGC-1α [72]. Also, the increase of mitochondrial mass [19,26], ATP production [28–30,35], and the oxidative capacity [19,24,36] were also shown after exercise in aged animal as well as the performances of skeletal muscle [23,24,27,28,30,34,35]. These results showed the positive effects of exercise on influencing myofiber and mitochondria in skeletal muscle during the ageing process. However, some contradictory results of the exercise's effects on muscle mass, performance and mitochondrial biogenesis were reported. The results showed an increased muscle weight of TA, EDL, gastrocnemius, and quadriceps after the endurance or resistance exercise in aged animal [26,28,30,35], but 2 studies showed that the treadmill running exercise had no effects on improving the mass of TA, soleus, and gastrocnemius [30,35]. 4 out of 6 studies showed an increased running performance in age mice and rats [23,24,27,30], but 3 out of 6 studies indicated no significant effects of exercise on grip strength and the running time in aged mice [29,30,35]. In addition, 6 out of 7 studies reported mitochondrial biogenesis showed increased PGC-1α after exercise [23–26,30,35] while 1 paper showed no effects of exercise on PGC-1α [19]. Some researchers revealed that exercise training attenuated muscle atrophy and function via improving mitochondrial function while others indicated that exercise had no significant effects on improving the function of muscle and mitochondria. The contradictory results may be caused by several factors, including the difference in exercise protocols and muscle samples collected in these studies. Different skeletal muscles have different proportion of fast-twitch and slow-twitch muscles, thus leading to different expression levels of certain factors. It would be more comparable to investigate the effects of exercises on the same skeletal muscle by using a uniform protocol. In addition, several studies investigated the effects of exercise combined with some nutriments (such as resveratrol, spermidine, or restricting diet), which showed positive results in improving muscle performance through regulating mitochondrial function [34,73,74]. These results indicated that exercise coupled with certain nutriments could attenuate sarcopenia via improving mitochondrial function, including mitochondrial respiratory flux and quality control.

There are few limitations in this review. Firstly, the included papers only reported the change of mitochondria and/or related proteins after exercise in aged animal model, which cannot reveal the specific role in the link between exercise and mitochondria. Secondly, this review only included pre-clinical research, which may have bias in explaining the effects of exercise on humans. In addition, only English articles were included, which may miss other available evidence.

In conclusion, this systematic review has summarized the current knowledge of possible factors and pathways involved in sarcopenia and mitochondrial dysfunction in aged rodents, as well as revealed the potential mechanisms for how physical exercise attenuated the decline of muscle mass and muscle function by regulating mitochondrial dynamic equilibrium. During ageing, muscle mass, physical performance and mitochondrial function decrease simultaneously that is accompanied by the activated mitochondria associated apoptosis. Exercise is generally shown to attenuate the deterioration of muscle function and mass and improve mitochondrial function through maintaining mitochondrial quality control and inhibiting mitochondria associated apoptosis. However, there are some inconsistent results in the effects of exercise on mitochondria and skeletal muscle. Furthermore, the molecules regulating the mitochondrial function and mitochondria associated apoptosis after exercise can be targeted for further investigation in aged animals. Meanwhile, few evidence can explain how exercise and/or nutriments attenuate sarcopenia through suppressing mitochondria-related apoptosis by regulating mitochondrial function via certain pathways. Exploring the potential pathways is worthy for the further studies, which may promote the development of new therapeutic interventions for treating sarcopenia.

Declaration of competing interest

The authors declare that they have no conflict of interest.

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References

[1] Maiese K. Sirtuins: developing innovative treatments for aged-related memory loss and Alzheimer's disease. Curr Neurovascular Res 2018;15(4):367–71 [eng].
[2] Iizuka K, Machida T, Hirafuji M. Skeletal muscle is an endocrine organ. J Pharmacol Sci 2014;125(2):125–31 [eng].
[3] Nair KS. Aging muscle. Am J Clin Nutr 2005;81(5):953–63 [eng].
[4] Landi F, Cesari M, Calvani R, Cherubini A, Di Bari M, Bejuit R, et al. The "Sarcopenia and Physical fRailty IN older people: multi-componenT Treatment strategies"

(SPRINTT) randomized controlled trial: design and methods. Aging Clin Exp Res 2017;29(1):89–100 [eng].
[5] Zhang N, Chow SKH, Leung KS, Lee HH, Cheung WH. An animal model of co-existing sarcopenia and osteoporotic fracture in senescence accelerated mouse prone 8 (SAMP8). Exp Gerontol 2017;97:1–8 [eng].
[6] Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet (London, England) 2019; 393(10191):2636–46 [eng].
[7] Chen LK, Woo J, Assantachai P, Auyeung TW, Chou MY, Iijima K, et al. Asian working group for sarcopenia: 2019 consensus update on sarcopenia diagnosis and treatment. J Am Med Dir Assoc 2020;21(3):300–7. e2. [eng].
[8] Wiedmer P, Jung T, Castro JP, Pomatto LCD, Sun PY, Davies KJA, et al. Sarcopenia - molecular mechanisms and open questions. Ageing Res Rev 2020;65:101200 [eng].
[9] Ferri E, Marzetti E, Calvani R, Picca A, Cesari M, Arosio B. Role of age-related mitochondrial dysfunction in sarcopenia. Int J Mol Sci 2020;21(15) [eng].
[10] Gorman GS, Chinnery PF, DiMauro S, Hirano M, Koga Y, McFarland R, et al. Mitochondrial diseases. Nat Rev Dis Prim 2016;2:16080 [eng].
[11] Sebastián D, Hernández-Alvarez MI, Segalés J, Sorianello E, Muñoz JP, Sala D, et al. Mitofusin 2 (Mfn2) links mitochondrial and endoplasmic reticulum function with insulin signaling and is essential for normal glucose homeostasis. Proc Natl Acad Sci U S A 2012;109(14):5523–8 [eng].
[12] Zorov DB, Juhaszova M, Sollott SJ. Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. Physiol Rev 2014;94(3):909–50 [eng].
[13] Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med 2020;54(24):1451–62 [eng].
[14] Hood DA, Memme JM, Oliveira AN, Triolo M. Maintenance of skeletal muscle mitochondria in health, exercise, and aging. Annu Rev Physiol 2019;81:19–41 [eng].
[15] Distefano G, Standley RA, Dubé JJ, Carnero EA, Ritov VB, Stefanovic-Racic M, et al. Chronological age does not influence ex-vivo mitochondrial respiration and quality control in skeletal muscle. J Gerontol Seri A Biol Sci Med Sci 2017;72(4):535–42 [eng].
[16] Liu HW, Chang YC, Chan YC, Hu SH, Liu MY, Chang SJ. Dysregulations of mitochondrial quality control and autophagic flux at an early age lead to progression of sarcopenia in SAMP8 mice. Biogerontology 2020;21(3):367–80 [eng].
[17] Zeng Z, Liang J, Wu L, Zhang H, Lv J, Chen N. Exercise-induced autophagy suppresses sarcopenia through Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control. Front Physiol 2020;11:583478 [eng].
[18] Zhao N, Xia J, Xu B. Physical exercise may exert its therapeutic influence on Alzheimer's disease through the reversal of mitochondrial dysfunction via SIRT1-FOXO1/3-PINK1-Parkin-mediated mitophagy. J Sport Health Sci 2021;10(1):1–3 [eng].
[19] Andreani C, Bartolacci C, Guescini M, Battistelli M, Stocchi V, Orlando F, et al. Combination of coenzyme Q(10) intake and moderate physical activity counteracts mitochondrial dysfunctions in a SAMP8 mouse model. Oxid Med Cell Longev 2018; 2018:15. 8936251.
[20] Rius-Pérez S, Torres-Cuevas I, Millán I, Ortega Á L, Pérez S. PGC-1α, inflammation, and oxidative stress: an integrative view in metabolism. Oxid Med Cell Longev 2020;2020:1452696 [eng].
[21] Arribat Y, Broskey NT, Greggio C, Boutant M, Conde Alonso S, Kulkarni SS, et al. Distinct patterns of skeletal muscle mitochondria fusion, fission and mitophagy upon duration of exercise training. Acta Physiol 2019;225(2):e13179 [eng].
[22] Axelrod CL, Fealy CE, Mulya A, Kirwan JP. Exercise training remodels human skeletal muscle mitochondrial fission and fusion machinery towards a pro-elongation phenotype. Acta Physiol 2019;225(4):e13216 [eng].
[23] Derbré F, Gomez-Cabrera MC, Nascimento AL, Sanchis-Gomar F, Martinez-Bello VE, Tresguerres JA, et al. Age associated low mitochondrial biogenesis may be explained by lack of response of PGC-1α to exercise training. Age (Dordrecht, Netherlands) 2012;34(3):669–79 [eng].
[24] Muhammad MH, Allam MM. Resveratrol and/or exercise training counteract aging-associated decline of physical endurance in aged mice; targeting mitochondrial biogenesis and function. J Physiol Sci 2018;68(5):681–8.
[25] Bahreinipour MA, Joukar S, Hovanloo F, Najafipour H, Naderi V, Rajiamirhasani A, et al. Mild aerobic training with blood flow restriction increases the hypertrophy index and MuSK in both slow and fast muscles of old rats: role of PGC-1α. Life Sci 2018;202:103–9 [eng].
[26] Zeng ZZ, Liang JL, Wu LW, Zhang H, Lv J, Chen N. Exercise-induced autophagy suppresses sarcopenia through Akt/mTOR and Akt/FoxO3a signal pathways and AMPK-mediated mitochondrial quality control. Front Physiol 2020:11.
[27] Rosa EF, Silva AC, Ihara SS, Mora OA, Aboulafia J, Nouailhetas VL. Habitual exercise program protects murine intestinal, skeletal, and cardiac muscles against aging. J Appl Physiol (Bethesda, Md : 1985) 2005;99(4):1569–75 [eng].
[28] White Z, Terrill J, White RB, McMahon C, Sheard P, Grounds MD, et al. Voluntary resistance wheel exercise from mid-life prevents sarcopenia and increases markers of mitochondrial function and autophagy in muscles of old male and female C57BL/6J mice. Skeletal Muscle 2016;6(1):45 [eng].
[29] Ringholm S, Olesen J, Pedersen JT, Brandt CT, Halling JF, Hellsten Y, et al. Effect of lifelong resveratrol supplementation and exercise training on skeletal muscle oxidative capacity in aging mice; impact of PGC-1 alpha. Exp Gerontol 2013;48(11): 1311–8.
[30] Gill JF, Santos G, Schnyder S, Handschin C. PGC-1α affects aging-related changes in muscle and motor function by modulating specific exercise-mediated changes in old mice. Aging Cell 2018;17(1) [eng].
[31] Gao HE, Li FH, Xie T, Ma S, Qiao YB, Wu DAS, et al. Lifelong exercise in age rats improves skeletal muscle function and MicroRNA profile. Med Sci Sports Exerc 2021;53(9):1873–82 [English].
[32] Liang J, Zhang H, Zeng Z, Wu L, Zhang Y, Guo Y, et al. Lifelong aerobic exercise alleviates sarcopenia by activating autophagy and inhibiting protein degradation via the AMPK/PGC-1α signaling pathway. Metabolites 2021;11(5) [eng].
[33] Liu S, Yu C, Xie L, Niu Y, Fu L. Aerobic exercise improves mitochondrial function in sarcopenia mice through Sestrin2 in an AMPKα2-dependent manner. J Gerontol Seri A Biol Sci Med Sci 2021;76(7):1161–8 [eng].
[34] Stolle S, Ciapaite J, Reijne AC, Talarovicova A, Wolters JC, Aguirre-Gamboa R, et al. Running-wheel activity delays mitochondrial respiratory flux decline in aging mouse muscle via a post-transcriptional mechanism. Aging Cell 2018;17(1).
[35] Aoki K, Konno M, Honda K, Abe T, Nagata T, Takehara M, et al. Habitual aerobic exercise diminishes the effects of sarcopenia in senescence-accelerated mice Prone8 model. Geriatrics 2020;5(3) [eng].
[36] Vilela TC, Effting PS, Pedroso GD, Farias H, Paganini L, Sorato HR, et al. Aerobic and strength training induce changes in oxidative stress parameters and elicit modifications of various cellular components in skeletal muscle of aged rats. Exp Gerontol 2018;106:21–7.
[37] Anwar M, Mallick S, Paliwal D, Shekhar S, Panda SK, Dey S, et al. Impact of physical activity on mitochondrial enzymes, muscle stem cell and anti-oxidant protein Sestrins in Sarcopenic mice. Exp Gerontol 2021;150:111358 [eng].
[38] Shadel GS, Horvath TL. Mitochondrial ROS signaling in organismal homeostasis. Cell 2015;163(3):560–9 [eng].
[39] Alway SE, Mohamed JS, Myers MJ. Mitochondria initiate and regulate sarcopenia. Exerc Sport Sci Rev 2017;45(2):58–69 [eng].
[40] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell 2012; 148(6):1145–59 [eng].
[41] Quinlan CL, Perevoshchikova IV, Hey-Mogensen M, Orr AL, Brand MD. Sites of reactive oxygen species generation by mitochondria oxidizing different substrates. Redox Biol 2013;1(1):304–12 [eng].
[42] Anzell AR, Maizy R, Przyklenk K, Sanderson TH. Mitochondrial quality control and disease: insights into ischemia-reperfusion injury. Mol Neurobiol 2018;55(3): 2547–64 [eng].
[43] Pickles S, Vigié P, Youle RJ. Mitophagy and quality control mechanisms in mitochondrial maintenance. R170-r85 Curr Biol : CB 2018;28(4) [eng].
[44] Song J, Herrmann JM, Becker T. Quality control of the mitochondrial proteome. Nat Rev Mol Cell Biol 2021;22(1):54–70 [eng].
[45] Wenz T. PGC-1alpha activation as a therapeutic approach in mitochondrial disease. IUBMB Life 2009;61(11):1051–62 [eng].
[46] Bhatti JS, Bhatti GK, Reddy PH. Mitochondrial dysfunction and oxidative stress in metabolic disorders - a step towards mitochondria based therapeutic strategies. Biochim Biophys Acta, Mol Basis Dis 2017;1863(5):1066–77 [eng].
[47] Virbasius JV, Scarpulla RC. Activation of the human mitochondrial transcription factor A gene by nuclear respiratory factors: a potential regulatory link between nuclear and mitochondrial gene expression in organelle biogenesis. Proc Natl Acad Sci U S A 1994;91(4):1309–13 [eng].
[48] Farmer T, Naslavsky N, Caplan S. Tying trafficking to fusion and fission at the mighty mitochondria. Traffic (Copenhagen, Denmark) 2018;19(8):569–77 [eng].
[49] Sebastián D, Sorianello E, Segalés J, Irazoki A, Ruiz-Bonilla V, Sala D, et al. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. EMBO J 2016;35(15):1677–93 [eng].
[50] Twig G, Shirihai OS. The interplay between mitochondrial dynamics and mitophagy. Antioxidants Redox Signal 2011;14(10):1939–51 [eng].
[51] Chen H, Detmer SA, Ewald AJ, Griffin EE, Fraser SE, Chan DC. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J Cell Biol 2003;160(2):189–200 [eng].
[52] Pagliuso A, Cossart P, Stavru F. The ever-growing complexity of the mitochondrial fission machinery. Cell Mol Life Sci : CMLS 2018;75(3):355–74 [eng].
[53] Lee JE, Westrate LM, Wu H, Page C, Voeltz GK. Multiple dynamin family members collaborate to drive mitochondrial division. Nature 2016;540(7631):139–43 [eng].
[54] Kleele T, Rey T, Winter J, Zaganelli S, Mahecic D, Perreten Lambert H, et al. Distinct fission signatures predict mitochondrial degradation or biogenesis. Nature 2021 [eng].
[55] Hu Y, Chen H, Zhang L, Lin X, Li X, Zhuang H, et al. The AMPK-MFN2 axis regulates MAM dynamics and autophagy induced by energy stresses. Autophagy 2021;17(5): 1142–56 [eng].
[56] Favaro G, Romanello V, Varanita T, Andrea Desbats M, Morbidoni V, Tezze C, et al. DRP1-mediated mitochondrial shape controls calcium homeostasis and muscle mass. Nat Commun 2019;10(1):2576.
[57] Jin SM, Lazarou M, Wang C, Kane LA, Narendra DP, Youle RJ. Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. J Cell Biol 2010;191(5):933–42 [eng].
[58] Ni HM, Williams JA, Ding WX. Mitochondrial dynamics and mitochondrial quality control. Redox Biol 2015;4:6–13 [eng].
[59] Ashrafi G, Schwarz TL. The pathways of mitophagy for quality control and clearance of mitochondria. Cell Death Differ 2013;20(1):31–42 [eng].
[60] Onishi M, Yamano K, Sato M, Matsuda N, Okamoto K. Molecular mechanisms and physiological functions of mitophagy. EMBO J 2021;40(3):e104705 [eng].
[61] Schapira AH. Mitochondrial diseases. Lancet (London, England) 2012;379(9828): 1825–34 [eng].
[62] Ow YP, Green DR, Hao Z, Mak TW. Cytochrome c: functions beyond respiration. Nat Rev Mol Cell Biol 2008;9(7):532–42 [eng].
[63] Wang D, Yang Y, Zou X, Zhang J, Zheng Z, Wang Z. Antioxidant Apigenin relieves age-related muscle atrophy by inhibiting oxidative stress and hyperactive

mitophagy and apoptosis in skeletal muscle of mice. J Gerontol Seri A Biol Sci Med Sci 2020;75(11):2081–8 [eng].
[64] Cheema N, Herbst A, McKenzie D, Aiken JM. Apoptosis and necrosis mediate skeletal muscle fiber loss in age-induced mitochondrial enzymatic abnormalities. Aging Cell 2015;14(6):1085–93 [eng].
[65] Pardo PS, Hajira A, Boriek AM, Mohamed JS. MicroRNA-434-3p regulates age-related apoptosis through eIF5A1 in the skeletal muscle. Aging 2017;9(3):1012–29 [eng].
[66] Muhammad MH, Allam MM. Resveratrol and/or exercise training counteract aging-associated decline of physical endurance in aged mice; targeting mitochondrial biogenesis and function. J Physiol Sci : JPS 2018;68(5):681–8 [eng].
[67] Fan J, Yang X, Li J, Shu Z, Dai J, Liu X, et al. Spermidine coupled with exercise rescues skeletal muscle atrophy from D-gal-induced aging rats through enhanced autophagy and reduced apoptosis via AMPK-FOXO3a signal pathway. Oncotarget 2017;8(11):17475–90 [eng].
[68] Luo L, Lu AM, Wang Y, Hong A, Chen Y, Hu J, et al. Chronic resistance training activates autophagy and reduces apoptosis of muscle cells by modulating IGF-1 and its receptors, Akt/mTOR and Akt/FOXO3a signaling in aged rats. Exp Gerontol 2013;48(4):427–36 [eng].
[69] Russell OM, Gorman GS, Lightowlers RN, Turnbull DM. Mitochondrial diseases: hope for the future. Cell 2020;181(1):168–88 [eng].
[70] Nascimento CM, Ingles M, Salvador-Pascual A, Cominetti MR, Gomez-Cabrera MC, Viña J. Sarcopenia, frailty and their prevention by exercise. Free Radic Biol Med 2019;132:42–9 [eng].
[71] Melouane A, Yoshioka M, St-Amand J. Extracellular matrix/mitochondria pathway: a novel potential target for sarcopenia. Mitochondrion 2020;50:63–70 [eng].
[72] Kang C, Chung E, Diffee G, Ji LL. Exercise training attenuates aging-associated mitochondrial dysfunction in rat skeletal muscle: role of PGC-1α. Exp Gerontol 2013;48(11):1343–50 [eng].
[73] Joseph AM, Malamo AG, Silvestre J, Wawrzyniak N, Carey-Love S, Nguyen LM, et al. Short-term caloric restriction, resveratrol, or combined treatment regimens initiated in late-life alter mitochondrial protein expression profiles in a fiber-type specific manner in aged animals. Exp Gerontol 2013;48(9):858–68 [eng].
[74] Fan JJ, Yang XQ, Li J, Shu ZY, Dai J, Liu XR, et al. Spermidine coupled with exercise rescues skeletal muscle atrophy from D-gal-induced aging rats through enhanced autophagy and reduced apoptosis via AMPK-FOXO3a signal. Oncotarget 2017; 8(11):17475–90.