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Review

Exercise and nutrition benefit skeletal muscle: From influence factor and intervention strategy to molecular mechanism

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ABSTRACT

Sarcopenia is a progressive systemic skeletal muscle disease induced by various physiological and pathological factors, including aging, malnutrition, denervation, and cardiovascular diseases, manifesting as the decline of skeletal muscle mass and function. Both exercise and nutrition produce beneficial effects on skeletal muscle growth and are viewed as feasible strategies to prevent sarcopenia. Mechanisms involve regulating blood flow, oxidative stress, inflammation, apoptosis, protein synthesis and degradation, and satellite cell activation through exerkines and gut microbiomes. In this review, we summarized and discussed the latest progress and future development of the above mechanisms for providing a theoretical basis and ideas for the prevention and treatment of sarcopenia.

1. Introduction

Sarcopenia is a progressive and generalized skeletal muscle disease induced by various physiological and pathological factors,[1,2] manifesting as a decline in skeletal muscle mass and function.[3,4] Sarcopenia is commonly accompanied by profound negative effects on quality of life and is associated with clinical complications, including obesity, hypertension, diabetes, and cardiovascular diseases, which form a harmful cycle, as it could lead to frailty, fractures, disability, hospitalization, and even death.[5] Therefore, it is of great significance to summarize the risk factors and preventive strategies in patients with sarcopenia. The causes of sarcopenia could be categorized into pathological and non-pathological factors. Pathological factors include osteoarthrosis, cardiovascular diseases, and metabolic diseases, whereas non-pathological factors include aging, poor diet, and physical inactivity.

2. Pathological causes

The loss of skeletal muscle mass and function was related to the activation of inflammation and biomechanical stress signaling in patients with osteoarthritis.[6] Patients with osteoarthritis of the hip and knee were commonly accompanied by declines in muscle mass and strength, resulting in further injury to the joint and reduced physical activity ability and quality of life.[7] Clinical data showed that patients with rheumatoid arthritis (RA) were particularly susceptible to sarcopenia, with a 30% prevalence rate.[8,9] In patients with cardiovascular disease (CVD), cardiac dysfunction induces blood insufficiency and capillaries closure in skeletal muscle, thereby aggravating the ischemia and hypoxia injury of skeletal muscle cells.[10] Ischemia and hypoxia injury triggered excessive oxidative stress and inflammation, leading to mitochondrial dysfunction, protein degradation, and apoptosis in skeletal muscle, finally resulting in sarcopenia.[10,11] Metabolic syndrome (Mets) and non-alcoholic fatty liver disease (NAFLD) were prone to sarcopenia due to their similar pathogenesis, such as insulin resistance and chronic inflammation.[12,13] Decreased insulin sensitivity induced muscle metabolic dysfunction in patients with Type 2 diabetes, further leading to loss of muscle mass.[14] Mets patients were commonly accompanied by insulin resistance and metabolic dysfunction of skeletal muscle, which led to mitochondrial dysfunction, imbalance between protein synthesis and degradation, and excessive oxidative stress and inflammation (Fig. 1). In addition, cancer-induced sarcopenia, one of the major causes of death in patients, is commonly caused by medication side effects with medical therapy, malnutrition, vascular embolism, inflammation, metabolic dysfunction, protein degradation, and exceed autophagy.[15] Patients with esophageal, gastric, lung and colorectal cancer, especially pancreatic cancer, were accompanied by skeletal muscle atrophy in the progress of chemotherapy, and which would lead to poor-prognosis in patients.[16]

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Abbreviations

ADP	adenosine diphosphate
AIF	apoptosis-inducing factor
Akt	protein kinase B
ALCAT1	lysocardiolipin acyltransferase 1
ALS	autophagy-lysosomal system
AMP	adenosine monophosphate
AR	androgen receptor
ATP	adenosine triphosphate
Bax	Bcl-2-associated X protein
BCAAs	branched-chain amino acids
BMI	body mass index
CKD	chronic kidney disease
COPD	obstructive pulmonary disease
CSA	cross-sectional area
CVD	cardiovascular disease
Endo G	endonuclease G
ER	endoplasmic reticulum
ERK	extracellular regulated protein kinases
ERRα	estrogen-related receptor-α
ES	muscle electrical stimulation
FNDC5	fibronectin type III domain containing 5
GDF15	growth differentiation factor 15
GSH-Px	glutathione peroxidase
HF	heart failure
HR	heart rate
HIIT	high-intensity interval training
HFD	high-fat diet
IGF-1	insulin-like growth factor-1
IL	interleukin
iNOS	inducible nitric oxide (NO) synthase
JAK	Janus kinase
LCBE	lonicera caerulea berry extract
LBP	lipopolysaccharide-binding protein
MAPK	mitogen-activated protein kinase
Mets	metabolic syndrome
MI	myocardial infarction
mTOR	mammalian target of rapamycin
NADPH	nicotinamide adenine dinucleotide phosphate
NAFLD	non-alcoholic fatty liver disease
NO	nitric oxide
NRF	nuclear respiratory factors
PGC-1α	peroxisome proliferator-activated receptor γ coactivator-1α
PHGG	partially hydrolyzed guar gum
PI3K	phosphatidylinositol 3 kinase
PKC	protein kinase C
PPARγ	peroxisome proliferator-activated receptor γ
p70S6K	70 kDa ribosomal protein S6 kinase
REDOX	oxidation-reduction reaction
RM	repetition maximum
RNS	reactive nitrogen species
ROS	reactive oxygen species
SC	satellite cell
SCFA	short-chain fatty acids
SOCS	suppressor of cytokine signaling
SOD	superoxide dismutase
STAT	signal transducer and activator of transcription
TFAM	transcription factor A
TGF-β	transforming growth factor-β
TNF-α	tumor necrosis factor-α
TNFRI	tumor necrosis factor receptor I
UCP2	uncoupling protein 2
ULK1	uncoordinated 51-like kinase 1
UPR mt	mitochondrial unfolded protein response
UPS	ubiquitin-proteasome system
VC	vitamin C
WBV	whole-body vibration
wk	week
YAP	Yes-associated protein

3. Non-pathological causes

3.1. Aging

The prevalence of sarcopenia increased with age, manifesting as decreased muscle mass, strength, and exercise intolerance.[4,17] Studies showed that the skeletal muscle metrics decreased with increasing age, including cross-sectional area (CSA) of skeletal muscle, calf circumference, calf circumference/BMI ratio, knee extension strength, and gait speed.[18,19] Aging-induced alterations, such as denervation, chronic systemic inflammation, and insulin resistance, could disrupt the balance of protein synthesis and degradation, leading to mitochondrial dysfunction, eventually resulting in the loss of skeletal muscle mass and function (Fig. 1).

3.2. Irrational diet structure

There were associations between sarcopenia and nutrient absorption and utilization abilities as well as dietary patterns consisting of protein, fat, carbohydrates, and various micronutrients, especially vitamins.[20,21] Low protein uptake led to the loss of muscle mass and strength.[22,23] Meanwhile, a comparative study found a negative correlation between the 'mushrooms-fruits-milk' diet and sarcopenia.[24] Unhealthy long-term living habits like smoking and drinking could induce brain-gut axis dysfunction and oral diseases, resulting in nutritional deficiencies.[25] In addition, poor sleep quality disrupted the circadian rhythm and biological clock, reduced dietary intake, and ultimately inhibited muscle protein synthesis.[26] Proper nutrient supplementation, including high-protein, high-quality fat, carbohydrate, and sufficient vitamins, along with regular exercise, could effectively improve muscle mass and function. As regular exercise promotes nutritional absorption and utilization, thus preventing sarcopenia (Fig. 1).

3.3. Physical inactivity

A physically inactive lifestyle, such as sedentary and bedridden, could reduce skeletal muscle function and contribute to the increased prevalence of sarcopenia. For example, hospitalized older adults were particularly susceptible to sarcopenia due to the loss of muscle mass, strength, and mobility.[27] Sarcopenia involves both mass loss and function decline. Exercise, combined with a proper diet, could produce beneficial effects on the prevention and treatment of sarcopenia (Fig. 1).

4. Prevention of sarcopenia

Currently, there is a lack of specific drugs for treating sarcopenia. This study summarizes the pharmacological interventions based on clinical and animal research findings[28–31]: vitamin D, combined estrogen-progesterone, growth hormone, growth hormone-releasing hormone, testosterone, combined testosterone-growth hormone, insulin-like growth factor-1(IGF-1), angiotensin-converting enzyme inhibitors, dehydroepiandrosterone, and pioglitazone. However, some pharmacological treatments could induce toxic damage to the heart, liver, kidney, and other organs. Therefore, the administration route,

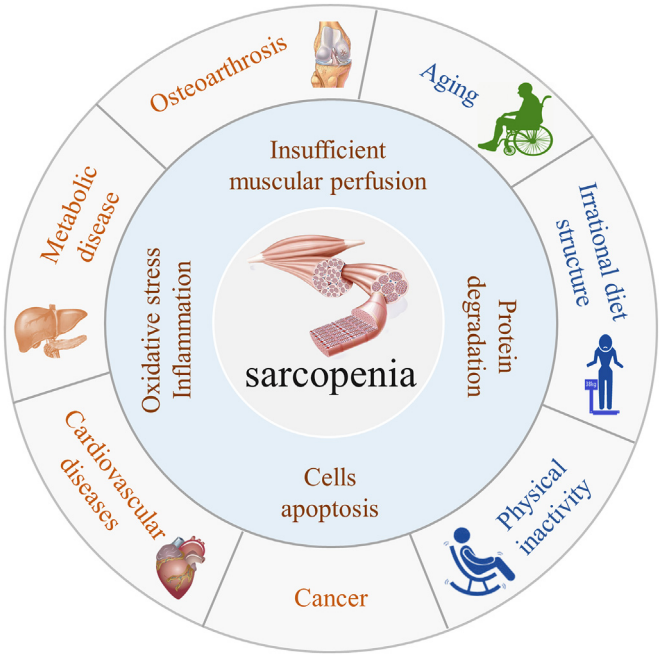

Fig. 1. Causes of sarcopenia can be categorized into pathologic and non-pathologic. Pathologic causes consist of osteoarthrosis, metabolic diseases, and cardiovascular diseases. Non-pathologic causes include aging, irrational diet structure, and physical inactivity. These causes induce low blood flow, excessive oxidative stress and inflammation, cell apoptosis, and protein degradation in skeletal muscle, leading to sarcopenia.

dosage, and duration of such treatment need to be considered and explored with circumspection, and it should be performed in a standardized and personalized manner. Compared with pharmacological therapy, non-drug methods such as exercise, muscle electrical stimulation, and nutritional supplements are safer, especially with the combination of exercise and nutrition. Moreover, exercise could decrease the side effects caused by the toxicity of drugs and promotes nutrient absorption and utilization, thereby helping to prevent and alleviate sarcopenia.

4.1. Aerobic exercise training

Aerobic exercise, as a traditional exercise form, is more acceptable among patients with sarcopenia due to its safety, effectiveness, and diversity of forms. Study demonstrated that aerobic exercise (50 min/d, 3 d/wk, 24 wk, 70% $HR_{reserve}$) alone improved endurance and aerobic fitness. Furthermore, when combined with essential amino acids supplementation, it effectively increased muscle strength and protein synthesis in older adults.[32] Combined acute aerobic training (60 min/d, 7d, 60%–65% HR_{max}) and vitamin D potentiated the metabolic benefits of exercise by reducing intramyocellular lipid and increasing $\dot{V}O_2$ level in muscle tissue.[33] Insufficient nutrition and physical inactivity are critical causes of sarcopenia, as it accelerates the loss of skeletal muscle during aging or pathological states. Aerobic exercise could mobilize whole-body muscles, increase peripheral capillary density,[34,35] improve mitochondrial function and muscle metabolism,[36] and balance oxidation-reduction reaction (REDOX),[37] ultimately alleviating sarcopenia. Therefore, combining such an approach with nutritional support could further promote muscle mass and function, which is of great significance in preventing sarcopenia.

4.2. Resistance exercise training

Resistance exercise has been well known for promoting muscle hypertrophy by activating myogenesis, increasing protein synthesis and inhibiting protein degradation-related molecular signaling.[38,39] Resistance training (3 d/wk, 12 wk, 70%–80% 1 RM) increased myonuclear and the percentage of the largest muscle fibers in older adults.[40] Progressive resistance exercise of upper and lower (2-3 d/wk, 4 month, 75% 1 RM) was effective in improving lower limb muscle strength and exercise performance in chronic obstructive pulmonary disease (COPD) patients with low muscle mass, and oral nutritional supplementation further enhanced the beneficial effects of exercise.[41] High-intensity resistance exercise (2 d/wk, 18 month) combined with protein and calcium intake significantly improved skeletal muscle mass and exercise capacity in older patients with sarcopenia.[42] Nevertheless, the effects of resistance exercise on muscle mass declined after detraining.[42] Therefore, exercise should be performed on a long-term basis, and its forms should be easy to persist.

4.3. High-intensity interval training

High-intensity interval training (HIIT) improved cardiac and pulmonary function, skeletal muscle mass and function, exercise capacity, and quality of life in older patients with systemic diseases.[43,44] After a 12-week HIIT (3 d/wk, 90% HR_{max}), muscle mass, strength, and exercise capacity were significantly increased in young and older people.[45] HIIT (25 min/d, 3 d/wk, 8 wk, 70%–85% HR_{max}) improved aerobic fitness and muscle strength. Furthermore, when combined with intermittent fasting, it effectively promoted a greater gain in fat-free mass and greater loss of body fat in women with obesity.[46] Moreover, HIIT was also found to promote protein synthesis, improve muscle metabolic capacity and insulin sensitivity, and reverse high-fat diet (HFD)-induced sarcopenia, at least partially via the modulation of mammalian target of rapamycin (mTOR) signaling.[47] Thus, HIIT could prevent and ameliorate sarcopenia under various physiological or pathological conditions.

4.4. Whole-body vibration

Whole-body vibration (WBV) is a form of passive training initiated by applying physical stimulation using vibration devices, which is suitable for older adults and mobility-limited patients with various diseases. Low-level WBV training with 6 Hz–26 Hz frequency and 2 mm–4 mm amplitude (5-10 s/d × 60 s/d, 3 d/wk, 16 wk) increased muscle mass and strength, exercise ability, and quality of life, as well as alleviated age-related sarcopenia in frail older adults.[48] Two studies demonstrated that 12-week WBV intervention (40 Hz, 4 mm, 4 s/d × 90 s/d, 3 d/wk; 12 Hz, 3 mm, 10 s/d × 60 s/d, 3 d/wk) also improved neuromuscular innervation, enhanced exercise ability, and increased skeletal muscle mass and function of older patients with sarcopenia.[49,50] Furthermore, thigh muscle CSA and strength, and exercise ability were significantly improved in older women after WBV training (20 Hz–40 Hz, 2 mm–4 mm, 3 d/wk-5 d/wk, 10 wk).[51] Thus, the prevention and treatment of WBV in sarcopenia is attributed to its effects on improving neuromuscular function and muscle mass. Importantly, it could be used as a physiotherapy technique for older adults and post-menopausal women in the community. Therefore, it is critical to establish a precise and scientifically-based WBV training program for preventing and alleviating sarcopenia in clinical practice, particularly with the appropriate frequency and amplitude.

4.5. Muscle electrical stimulation

Muscle electrical stimulation (ES) is an individual intervention to increase muscle mass and strength by external electrical pulse stimulation of local muscles, such as pectoralis, dorsal, and limb muscles. Some studies have revealed that whole-body ES with frequency of 85 Hz and impulse width of 350 μs increased skeletal muscle mass and strength, improves muscle function, promotes exercise ability, alleviates sarcopenia, and reduces sarcopenia-induced clinical complications.[52–54] It has

been gradually used as the treatment of clinical muscle diseases, which is especially suitable for patients unable or unwilling to perform conventional exercise training regularly. Further research should clarify the molecular mechanisms and combine ES with current exercise in the rehabilitation context.

4.6. Nutritional intervention

A proper dietary pattern, especially a protein-rich and antioxidant-rich diet, is essential for maintaining muscle mass and strength. In addition, vitamins, fatty acids, and antioxidants could also benefit muscle mass. A 15-year study revealed that the traditional dietary pattern increased muscle mass, and the anti-inflammatory dietary pattern containing a wide variety of vegetables, fruits, whole grains, nuts and proteins increased skeletal muscle mass and function.[55] The anti-inflammatory dietary pattern was found to be more effective than the traditional one.[55] The supplementation of vitamin E and high-quality fats like omega-3 fatty acids and oleic acid significantly aggrandized muscle mass and strength and walking speed and prevented muscle loss in older adults.[56] Branched-chain amino acids (BCAAs) such as leucine, valine and isoleucine promoted protein synthesis, increased muscle mass and strength, and improved muscle health in older adults.[57] In order to improve the dietary pattern, it is recommended to increase the proportion of BCAAs-rich foods such as meat, fish, shellfish, legumes, and cereals. Moreover, it was reported that L-glutamine products combined with exercise training improved muscle antioxidant capacity and glycemia balance, increased muscle mass, and alleviated diabetes-induced sarcopenia.[58] Thus, a rational dietary pattern combined with exercise training could reverse the sarcopenia process.

Since sarcopenia is affecting skeletal muscles in all total body, we recommend training the large muscle groups through total body approach. Evidence showed positive and significant effects of resistance training on muscle mass and strength, and physical performance.[59] Furthermore, a systematic review and meta-analysis demonstrated that among intervention methods such as aerobic, resistance, resistance with aerobic, and whole-body vibration, resistance exercise is the most effective for improving muscle mass and strength.[60,61] The load methods of resistance exercise can be divided into three types: body weight, resistance band and free weight, but there was no significant difference between the three methods.[62] Although low-intensity resistance training (50% 1 RM) is sufficient to induce gains in muscle strength, we recommend high-intensity resistance training (80% 1 RM) to promote maximal strength gains.[59] In addition, after review of evidence for multinutrient supplementation, best evidence is available to recommend leucine, which has significantly beneficial effects on muscle mass in older adults with sarcopenia.[63,64] Protein supplementation on top of resistance training is recommended to increase muscle mass and strength.[64,65]

5. Underlying mechanisms that exercise and nutrition interventions prevent sarcopenia

5.1. Exercise and nutrition increased the muscular perfusion

Aging and physical inactivity could lead to an insufficient supply of blood and nutrients to skeletal muscle, followed by a decline in skeletal muscle mass and function. Evidence has demonstrated that combining exercise with L-citrulline increased endothelial nitric oxide (NO) synthesis, improved vascular and mitochondrial function, increased blood perfusion and nutrition exchange, promoted oxygen utilization and protein synthesis, inhibited apoptosis in skeletal muscle, and ultimately contributed to reversing the process of sarcopenia.[66] In both compensatory cardiac hypertrophy rats and heart failure (HF) patients, HIIT, mechanical stretch, and voluntary wheel running were found to enhance muscle angiogenesis and perfusion as well as improving skeletal muscle performance and exercise endurance.[67,68] Exercise alone (resistance exercise and HIIT) or in combination with whey protein promoted muscle capillarization and metabolite exchange, thereby increasing protein synthesis and oxidative metabolism.[69] In addition, studies have shown that exercise increased muscle capillarization, shortened the distance between capillaries and satellite cells, and optimized the spatial distribution, which was conducive to satellite cell activation and proliferation and inhibiting aging-induced sarcopenia.[70–72] In summary, the combination of exercise and nutrition could improve muscle capillarization, vascular function, and antioxidant enzyme activation, promote nutrient exchange between blood and tissues, and further enhance muscle metabolism and protein synthesis, thereby improving muscle mass and function. Importantly, exercise could activate satellite cells to promote the remodeling and regeneration of skeletal muscle fibers.[70–72] Therefore, combining exercise with nutrition supplements is an effective strategy to maintain and improve skeletal muscle mass and function under aging and pathologic conditions.

5.2. Exercise and nutrition promoted exerkines secretion to protect skeletal muscle

Exerkines are cytokines, mRNAs, or gut microbiomes that are released in response to exercise from many different organs and tissues (including liver, skeletal muscle, heart, kidney, brain, and fat) and exert their effects via autocrine, paracrine, or endocrine pathway.[73,74] Notably, levels of exerkines are closely related to exercise intensity and amount.

5.2.1. Exerkines acted on muscle themselves or mediated organizational cross-talk

In humans and mice, the growth differentiation factor 15 (GDF15) expression in serum and muscle increased with age, whereas exercise reducing GDF15 level and improved aging muscle mass and function and.[75] It was preliminary showed that the potential use of GDF-15 as a biomarker for sarcopenia in animal models and humans. IGF-1 is a key factor in skeletal muscle growth and hypertrophy. Aerobic and resistance exercise alleviated myocardial infarction (MI)-induced loss of muscle mass by inhibiting protein degradation and apoptosis as well as promoting myogenesis via IGF-1/IGF-1R-phosphatidylinositol 3 kinase (PI3K)/protein kinase B (Akt) signaling pathway.[76] A study revealed that aerobic exercise could alleviate the levels of oxidative stress and apoptosis in skeletal muscle following MI, partly via up-regulating fibronectin type III domain containing 5 (FNDC5/Irisin) and inhibiting lysocardiolipin acyltransferase 1 (ALCAT1) expression.[77] In addition, resistance exercise combined with Leucine supplement increased IGF-1 and FNDC5/Irisin levels in muscle and serum, which promoted muscle protein synthesis.[78] Aged mice-related study revealed that γ-Oryzanol diet improved muscle antioxidant and anti-inflammation capacities by activating peroxisome proliferator-activated receptor γ (PPARγ) coactivator-1α (PGC-1α) and estrogen-related receptor-α (ERRα) signaling, and inhibiting transforming growth factor-β (TGF-β)/Smad signaling, which was conducive to skeletal muscle function and exercise ability.[79]

5.2.2. Exosomes mediated exercise-induced protection

Sarcopenia is a frequent complication of chronic kidney disease (CKD), but exercise could reverse such a process. Exosomes play a pivotal role in mediating exercise-related beneficial effects. A study revealed that resistance exercise increased miR-23a and miR-27a expressions in mice with CKD, and miR-23a/miR-27a activated Akt signaling, inhibited myostatin and downstream Smad-2/3 signaling, decreased protein degradation, reduced muscle loss, improved grip strength, and resulted in alleviated CKD-induced sarcopenia.[80] Exercise also improved PPARγ expression, reduced miR-29b level, activated Akt/mTOR pathway, inhibited protein degradation and apoptosis, increased muscle weight and CSA, and ultimately ameliorated muscle atrophy following angiotensin II-induced HF.[81] Moreover, the importance of miRNAs in mediating the effects of exercise has been shown. A study demonstrated that muscle miRNAs expressions were sensitive to carbohydrate intake during the initial phase of recovery after aerobic exercise. After aerobic exercise,

carbohydrate intake increased Let7i-5p and miR-195-5p levels, reduced activities of ubiquitin-mediated proteolysis, autophagy-lysosome system, myostatin, and caspase3 signaling, inhibited protein degradation, and ultimately facilitated muscle recovery.[82]

5.2.3. Gut microbiome was closely linked with muscle health

Gut microbiota composition and diversity might be the determinants of skeletal muscle metabolism and function.[83] Partially hydrolyzed guar gum (PHGG) contained-fiber-rich diet alleviated muscle wasting by fermenting dietary polysaccharides into short-chain fatty acids (SCFA), restoring the gut barrier function, reducing systemic inflammation lipopolysaccharide-binding protein (LBP) and interleukin (IL)-6 in serum, suppressing ubiquitin-proteasome system (UPS) and autophagy pathways, and resulting in inhibition of muscle protein degradation in cancer mice.[84]

Skeletal muscle is the main site of protein storage and metabolism, serving as an important source of cytokines, which is determined by exercise training and nutritional intake. Thus, exercise combined with nutrition could stimulate cytokine secretion in muscle or other organs (fat, liver, heart, and brain), activate downstream signaling pathways, improve muscle anti-inflammatory and antioxidant capacities, and promote muscle protein synthesis. At the same time, exercise combined with nutrients alleviate oxidative stress, inflammation, and protein degradation, as well as prevent or reverse the loss of skeletal muscle via inhibiting negative mechanisms of inflammatory mediator and protein degradation.

5.3. Exercise promoted mitochondrial homeostasis

Mitochondria play a crucial role in regulating the metabolic status of skeletal muscle, which demonstrate remarkable plasticity, adjusting its volume, structure, and function in response to chronic exercise, aging, and disease.[85] Mitochondrial biogenesis requires the coordination of multiple cellular events, including mtDNA replication, transcription from mitochondrial promoters, processing and stabilization of mitochondrial RNAs, translation, assembly of respiratory chain complexes and electron transport chain.[86] Exercise activates a large number of signaling pathways that converge to initiate mitochondrial biogenesis.[85] PGC-1α plays an important role in regulating mitochondrial biogenesis and activates multiple transcription factors, including nuclear respiratory factors (NRF) 1 and 2, mitochondrial transcription factor A (TFAM), and uncoupling protein 2 (UCP2).[87,88] PGC-1α cooperated with NRFs and promoted the expression of TFAM to regulate mitochondrial biogenesis.[89] During exercise, adenosine triphosphate (ATP) is continuously synthesized and broken down into adenosine diphosphate (ADP) and adenosine monophosphate (AMP).[90] Binding of AMP to the γ subunit of the heterotrimeric AMP-activated protein kinase (AMPK) causes AMPK conformational changes and enhances its phosphorylation.[91] AMPK activation leads to the phosphorylation of PGC-1α, further stimulating mitochondrial biogenesis.[92] Exercise promote mitophagy and remove dysfunctional mitochondria in skeletal muscle thought activating the AMPK and its representative downstream signaling molecules, such as PGC-1α and uncoordinated 51-like kinase 1 (ULK1).[93] The activation of AMPK signaling pathway promoted PGC-1α/NRFs/TAFM complex and regulated mitochondrial biogenesis in response to exercise.[87] Mitophagy is important in removing damaged or dysfunctional mitochondria and maintaining mitochondria homeostasis,[94] which can be enhanced by exercise through activating AMPK signaling in skeletal muscle.[95] The previous studies showed that running exercise promoted mitochondrial biogenesis and triggered the antioxidant defence system in muscle,[96] and skeletal muscle demonstrated a greater mitophagy drive post-exercise.[95] The mitochondrial unfolded protein response (UPR mt) is known as a conservative mechanism in response to mitochondrial dysfunction.[97] Mitophagy and UPR mt, two mitochondrial quality control mechanisms, are central to maintaining mitochondrial homeostasis in skeletal muscle and can be triggered by exercise.[87,98,99] Therefore, exercise represents a viable, nonpharmaceutical therapy with the potential to reverse and enhance the impaired mitochondrial function (Fig. 2).

5.4. Exercise and nutrition inhibited excessive oxidative stress

A study showed that both aerobic and resistance exercise increased activation of antioxidant enzymes, such as superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px), reduced reactive oxygen species (ROS) level and cell oxidative damage, inhibited UPS activation, activated satellite cells, promoted muscle fibers repair and regeneration, and ultimately alleviated HF-induced skeletal muscle atrophy.[100] It has also been reported that aerobic exercise improved mitochondrial function, reduced oxidative stress and protein ubiquitin degradation, and inhibited apoptosis via activating AMPK/PGC-1α and Akt/mTOR signaling pathways in skeletal muscle of aged mice.[101] Exercise converted ROS into

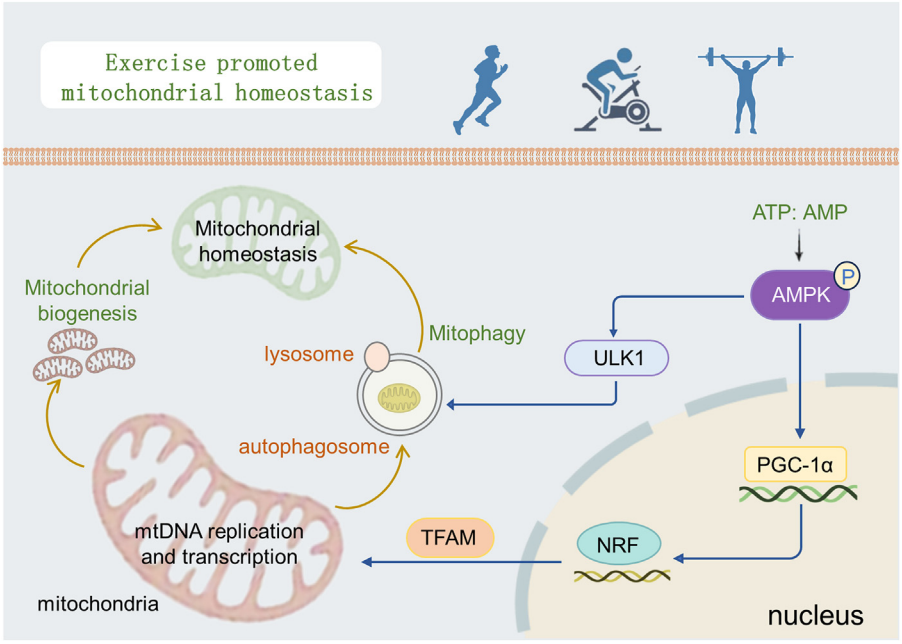

Fig. 2. Exercise-mediated mitochondrial homeostasis. Exercise activates AMPK and downstream signaling molecules such as PGC-1α and ULK1, further promotes mitochondrial biogenesis and mitophagy, partially via through NRF and TFAM signaling, results in mitochondrial homeostasis. AMP: adenosine monophosphate; AMPK: adenosine monophosphate-activated protein kinase; ATP: adenosine triphosphate; NRF: nuclear respiratory factor; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; TFAM: mitochondrial transcription factor A; ULK1: uncoordinated 51-like kinase 1.

more stable molecules (oxygen and water molecules), scavenged free radicals, regulated the production of ROS and RNS, and resulted in maintaining oxidation-reduction homeostasis; importantly, apart from exercise intervention, nutritional supplements, including vitamin E/α-tocopherol, Vitamin C (VC)/L-ascorbic acid, carotenoids, and polyphenols, were effective strategies to alleviate oxidative stress, and increase muscle mass and strength.[102] Nutraceuticals combined with exercise reduced ROS accumulation and inflammatory cytokines, improved muscle antioxidant and anti-inflammatory capacities, alleviated oxidative stress and inflammation, and inhibited skeletal muscle atrophy induced by cancer.[103] Therefore, combining exercise with nutrition is beneficial to improving skeletal muscle mass and function and preventing sarcopenia by regulating oxidative stress, inflammation, and apoptosis within the physiological range (Table 1 and Fig. 3).

5.5. Exercise and nutrition alleviated inflammation

Inflammation is a complex physiological response to stimulation, and there is an interaction between inflammation and oxidative stress. Chronic systemic inflammation induced muscle mitochondrial dysfunction, excessive oxidative stress and apoptosis, resulting in metabolic disorders and muscle loss. Exercise training has been shown to have important anti-inflammatory effects by upregulating anti-inflammatory cytokines through interlinked molecular mechanisms in skeletal muscle.[116] IL-6 is the main cytokine present in circulation during exercise, which produced by skeletal muscle depending on the mode, frequency, duration, and intensity of exercise.[116,117] IL-6 has long been regarded as a pro-inflammatory factor, but recent findings suggest that it also has anti-inflammatory effects,[118,119] manifested by inhibitory effects on pro-inflammatory cytokines (such as tumor necrosis factor-α (TNF-α) and IL-1).[116] IL-10 and IL-1Ra are well-known anti-inflammatory cytokines,[120] which is also associated with exercise.[116,121] IL-10 can inhibit the production of inflammatory cytokines IL-1α, IL-1β and TNF-α to exhibit anti-inflammatory effects.[122] IL-1Ra is an anti-inflammatory cytokine of the IL-1 family, which blocked the action of IL-1α and IL-1β by competitively ligand-specific binding to the IL-1R with higher affinity.[123,124] The appearance of circulating IL-10 and IL-1Ra following exercise contributes to mediating the anti-inflammatory effect of exercise. IL-13 is an anti-inflammatory cytokine that regulates microglia/macrophage polarization toward an anti-inflammatory phenotype and stimulates the production of IL-10,[125,126] which is also closely linked to exercise. Studies showed that exercise could increase IL-13 level in circulation,[127] adipose tissue[128] and muscle.[129]

5.6. Exercise and nutrition reduced cell apoptosis

Aging and diseases induced excessive accumulation of ROS, increased inflammatory cytokine levels, triggered oxidative stress and inflammation, and resulted in cell apoptosis in muscle, whereas exercise reduced oxidative stress and inflammation, inhibited apoptosis and protein degradation, and alleviated muscle atrophy,[130] partially via Akt and AMPK pathways.[131] Aging-related chronic systemic inflammation increased TNF-α in circulation, which was bound with tumor necrosis factor receptor I (TNFRI) to induce apoptosis, whereas exercise reduced TNF-α, TNFRI, and pro-apoptotic proteins Caspase8 and Caspase9 levels, inhibited apoptosis, maintained skeletal muscle mass.[132] Caspase12, an

Table 1
Regulation of signaling pathways and biological effects under exercise and nutrition to inhibit sarcopenia.

Signaling Pathways	Molecular and Biological effects		References
AMPK-PGC-1α	ROS↓ MDA↓ SOD↑ CAT↑ GSH-Px↑ NRF1↑ NRF2↑ TFAM↑Bax↓	improved mitochondrial function and quality control	79,101,104
	Bcl2↑ Cyt C↓ Caspase9↓ Caspase3↓	inhibited oxidative stress and cell apoptosis	
NRF2-AREs	CAT↑ SOD1↑ SOD2↑ TUNEL positive particles↑	improved antioxidant capacity	105
	Pax7↑ MyoD↑	reduced cell apoptosis promoted SC proliferation and differentiation	
HSP27 signaling	AIF↓ Endo G↓	inhibited AIF and Endo G translocation to reduce cell apoptosis	106
PKC-Nox2/Nox4	ROS↓	alleviated oxidative stress	104
iNOS-NO	TNF-α↓ MCP1↓ NF-κB↓ NQO1↑ HO-1↑	increased anti-inflammatory and antioxidant capacity decreased inflammation and oxidative stress levels	79,104
PI3K-Akt	Bax↓ Bcl2↑ Cyt C↓ Caspase3↓Atrogin-1↓ MuRF1↓ MAFbx↓ myostatin↓ mTOR↑ p70S6K↑	down-regulated UPS signaling	76,77,101,102,104, 107–112
	4-EBP1↑ Pax7↑	reduced protein ubiquitination degradation promoted synthesis reduced cell apoptosis and increased cell proliferation improved SC self-renewal and regenerative potential	
TGF-β-smad	Nox4↓ MuRF1↓	inhibited oxidative stress and protein degradation	79,102,108
	Pax7↑ MyoD↑	increased SC number and activation	
Wnt/β-catenin	Pax7↑ Myf5↑ MyoD↑	promoted SC proliferation and differentiation	113
Hippo/YAP	Pax7↑ MyoD↑	increased SC activation and myogenesis	114
JAK2-STAT3-SOCS	Pax7↑ PCNA↑ MyoD↑ Myogenin↑	increased SC proliferation and differentiation promoted myogenesis	115

AIF: apoptosis-inducing factor; AREs: antioxidant-responsive DNA elements; Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; Bax: Bcl2-associated X; Bcl-2: B-cell lymphoma-2; CAT: catalase; Cyt C: Cytochrome C; Endo G: endonuclease G; GSH: glutathione; GSH-Px: glutathione peroxidase; HO-1: heme oxygenase-1; HSP27: heat shock protein 27; iNOS: inducible NO synthase; JAK: Janus kinase; MAFbx: muscle atrophy F-box; MCP-1: monocyte chemoattractant protein-1; MDA: malondialdehyde; mTOR: mammalian target of rapamycin; MuRF1: muscle ring finger 1; Myf5: myogenic factor 5; MyoD: myogenic differentiation; NF-κB: nuclear factor-κB; NO: nitric oxide; Nox: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; NQO1: NADPH quinone oxidoreductase 1; NRF: nuclear respiratory factor; PCNA: proliferating cell nuclear antigen; PGC-1α: peroxisome proliferator activated receptor γ coactivator (PPARγ)-1α; p70S6K: 70 kDa ribosomal protein S6 kinase; PI3K: phosphatidylinositol 3 kinase; PKC protein kinase C; ROS: reactive oxygen species; SC: satellite cell; SOCS: suppressor of cytokine signaling; SOD: superoxide dismutase; STAT: transducer and activator of transcription; TFAM: mitochondrial transcription factor A; TGF-β: transforming growth factor-β; TNF-α: tumor necrosis factor-α; YAP: Yes-associated protein; 4-EBP1: 4E binding protein 1.

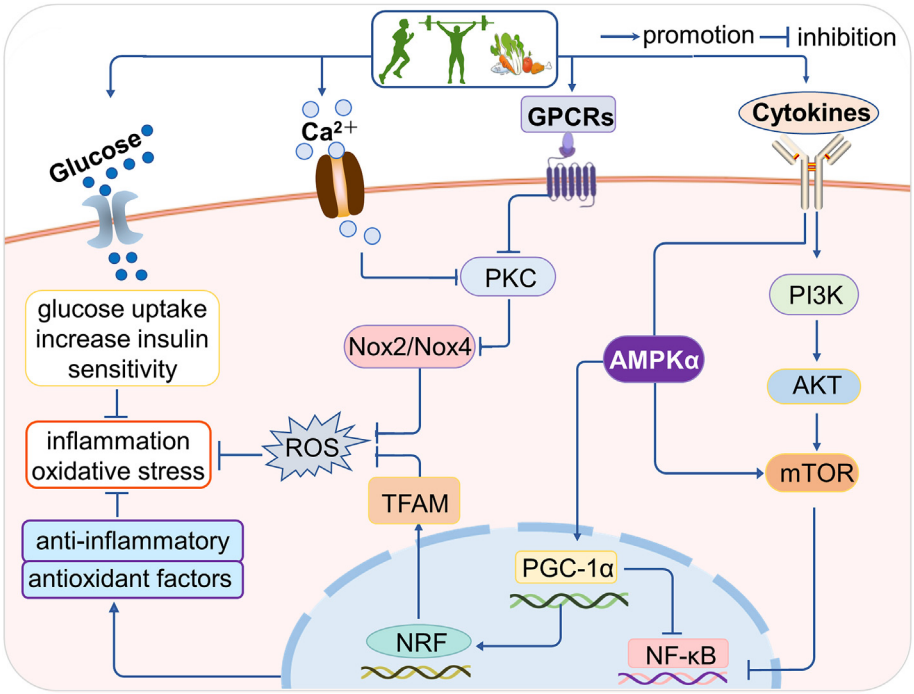

Fig. 3. Promoting anti-inflammation and antioxidant capacity of skeletal muscle by exercise and nutrition supplements. Exercise stimulates cytokine secretion and further activates PI3K-Akt and AMPK-PGC-1α pathways, to alleviate oxidative stress and inflammation by regulating NF-κB, NRF and TFAM and reducing ROS production and accumulation. Meanwhile, exercise and nutrition interventions increase glucose uptake and inhibit PKC-Nox2/Nox4 pathway to reduce ROS levels. Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; GPCRs: G protein-coupled receptors; mTOR: mammalian target of rapamycin; Nox: nicotinamide adenine dinucleotide phosphate (NADPH) oxidase; NRF: nuclear respiratory factor; PI3K: phosphatidylinositol 3 kinase; PKC protein kinase C; ROS: reactive oxygen species; TFAM: mitochondrial transcription factor A.

endoplasmic reticulum (ER) stress-specific indicator, activated Caspase9 and Caspase3, further inducing apoptosis. A study showed that six weeks of swimming reduced Caspase12 expression in the skeletal muscle of diabetic mice.[133] Therefore, exercise is viewed as an effective strategy to inhibit oxidative stress, inflammation, and cell apoptosis in skeletal muscle as well as to ameliorate sarcopenia.

However, excessive oxidative stress and inflammation are induced by fatigue after exercise. Therefore, it is important to relieve exercise fatigue to enhance exercise protective effects. A study found that lonicera caerulea berry extract (LCBE) and VC reduced apoptosis-related proteins Bax, cytochrome C (Cyt C), Caspase9, and Caspase3 levels via inducible nitric oxide (NO) synthase (iNOS)/NO and protein kinase C(PKC)-nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 2(Nox2)/Nox4 pathways in muscle following exercise fatigue; meanwhile, mitochondrial biosynthesis, antioxidant capacity, and exercise endurance were improved by long-term exercise and LCBE through activating AMPK-PGC-1α-NRF-1-TFAM pathway; and LCBE promoted cells proliferation by up-regulating miR-NA-133a/IGF-1/PI3K/Akt/mTOR signaling, which ultimately improved skeletal muscle mass and exercise capacity in mice.[104] Apoptosis-inducing factor (AIF) and endonuclease G (Endo G) are caspase-independent mediators that induced apoptosis to accelerate aging-induced muscle atrophy, whereas running exercise combined with caloric restriction decreased the translocation of AIF and Endo G from the cytoplasm to the nucleus and down-regulated pro-apoptotic signaling.[106]

In summary, the mechanisms by which exercise inhibited apoptosis to prevent muscle atrophy might be involved in the following: (1) exercise decreased oxidative stress and inflammation, and further inhibited the activation of caspase8 and caspase3; (2) exercise improved mitochondrial function, reduced AIF and Endo G levels, inhibited pro-apoptotic Bax and Cyt C release, and blocked Cyt C binding to caspase 9 to form apoptosome; (3) exercise inhibited ER-mediated caspase12 activation, further blocking the activation of caspase3 (Table 1 and Fig. 4).

5.7. Exercise and nutrition regulated protein synthesis and degradation

Skeletal muscle mass is determined by the balance between protein synthesis and degradation. Physical inactivity and insufficient nutrition decrease muscle protein synthesis and induce muscle mass and function decline. A study has demonstrated that resistance exercise improved the rate of protein synthesis, inhibited protein degradation, and increased aging muscle CSA and strength.[134] Aerobic combined with resistance exercise promoted protein synthesis, reduced muscle protein degradation by regulating inflammation, autophagy mediators, and UPS activation, and ultimately alleviated muscle atrophy in aged obese patients.[135] Moreover, resistance exercise combined with milk and vitamin D promoted protein synthesis, and increased muscle mass and strength, which were beneficial to preventing aging-induced muscle atrophy.[136] Dietary intake of protein after resistance exercise activated mTORC1 and downstream target 70 kDa ribosomal protein S6 kinase (p70S6K), improved protein synthesis, and increased aging muscle mass.[137]

Codium fragile is rich in lysophosphatidyl choline, α-tocopherol, and unsaturated fatty acids, which are important to maintain and promote skeletal muscle health.[107] PGC-1α and mTORC1 are key regulators of muscle protein synthesis, energy metabolism, and muscle mass and function via regulating UPS and autophagy-lysosomal system (ALS).[107,138] The animal experiment revealed that muscle mass and exercise endurance were increased in mice fed with Codium fragile, and the beneficial effects of Codium fragile on muscle were performed by activating PGC-1α-related signaling and Akt/mTORC1 pathway, promoting mitochondrial biogenesis and protein synthesis, and increasing muscle fibers CSA.[107] It was demonstrated that lifelong aerobic exercise also improved mitochondrial function, promoted protein synthesis, and resulted in inhibiting aging-induced muscle atrophy via AMPK/PGC-1α and Akt/mTOR pathways.[101] An imbalance of protein synthesis and degradation directly causes skeletal muscle atrophy, while inhibiting excessive activation of UPS and ALS is beneficial to protein synthesis and degradation balance. Exercise and nutrition interventions improve mitochondrial function, promote protein synthesis, and reduce UPS and ALS activation through Akt-mTORC1 and PGC-1α pathways in skeletal muscle (Table 1).

5.8. Exercise and nutrition activated satellite cells

Satellite cells (SCs) are stem cells located between the basal membrane and membrane of muscle fibers. They are activated by exercise and mechanical stimulations, leading to their proliferation and differentiation,

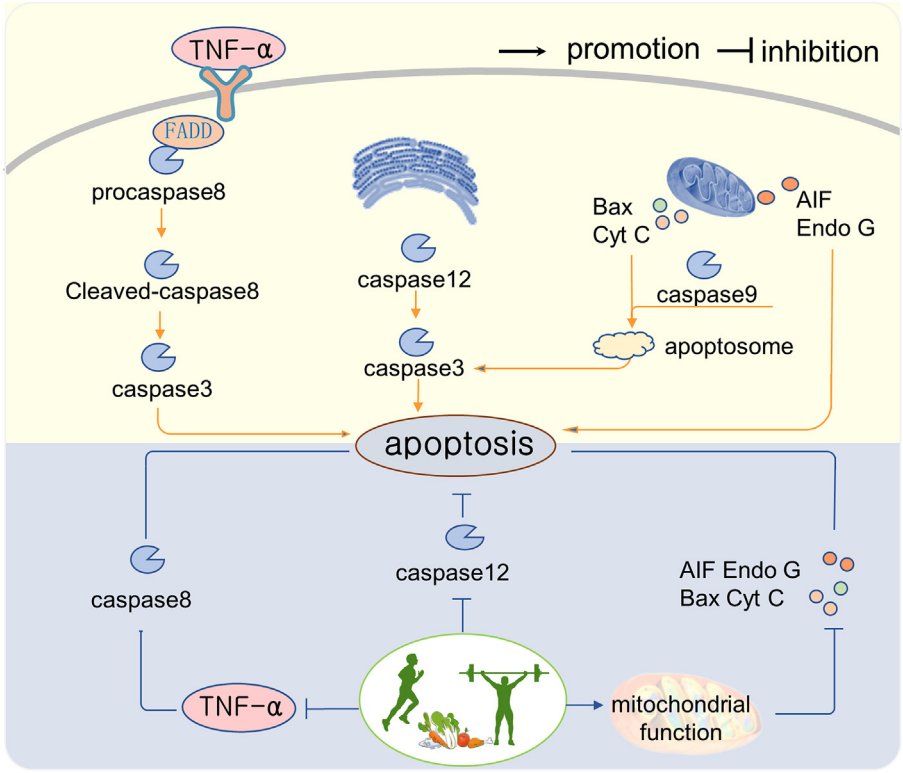

Fig. 4. Modulation of cell apoptosis pathways in skeletal muscle by exercise and nutrition intervention. TNF-α binds to TNFRI, further activates caspase8 and caspase 3, to induce apoptosis. And apoptosis executive signal-caspase3 also is activated by ER stress-specific indicator caspase 12, and Bax Cyt C is released by mitochondria. Moreover, mitochondria release AIF and Endo G to active caspase-independent apoptosis signaling. Which could be reversed by exercise and nutrition interventions. AIF: apoptosis-inducing factor; Bax: Bcl2-associated X; Bcl-2: B-cell lymphoma-2; Cyt C: Cytochrome C; Endo G: endonuclease G; FADD: Fas-associating protein with a novel death domain; TNF-α: tumor necrosis factor-α

which promotes muscle fiber repair and regeneration.[139–141] Exercise activated SC proliferation and differentiation, increased muscle capillary density in aged type II muscle fibers, improved muscle mass and strength, and resulted in preventing aging-induced sarcopenia.[142] The combinations of resistance and aerobic exercise increased SC number and pool, muscle capillarization and CSA, and inhibited muscle atrophy following bariatric surgery.[143] Endurance exercise training promoted muscle SC self-renewal and proliferation, reduced mitochondrial respiration, and inhibited inflammation and fibrosis in damaged muscle fibers.[144] Other studies have found that voluntary wheel running alleviated skeletal muscle atrophy by activating SC proliferation and differentiation and promoting myogenesis, partially via Wnt/β-catenin and Hippo/Yes-associated protein (YAP) pathways in skeletal muscle.[113,114] Importantly, exercise also inhibited muscle growth-inhibitory pathways and activated SCs to promote skeletal muscle hypertrophy. High-expression TGF-β impeded SC activation and protein synthesis, and weakened muscle hypertrophy via Smad signaling, whereas resistance exercise reversed the negative effects caused by TGF-β activation.[108] A transcriptome study found that the PI3K/Akt pathway played a key role in resistance exercise-induced SCs self-renewal and proliferation.[110] Apart from exercise, nutrients should be considered as a feasible intervention. Sulforaphane, a natural compound derived from cruciferous vegetables, activated SC proliferation and differentiation and reversed aging-related loss of muscle mass and function via NRF2 signaling.[105] A study has found that lemon myrtle extract activated SC proliferation and promoted muscle protein synthesis through interleukin-6 (IL-6).[145] It has also been reported that in IL-6-treated C2C12 cells and primary human myoblasts, high concentrations of IL-6 activated SCs and promoted cell proliferation and differentiation via activating Janus kinase (JAK)-signal transducer and activator of transcription (STAT)-suppressor of cytokine signaling (SOCS) pathway.[115] Thus, lemon myrtle could be considered as a novel nutritional intervention for preventing sarcopenia. Resistance exercise activated SC proliferation and differentiation, and promoted muscle hypertrophy through IL-6/STAT inflammatory signaling. Therefore, IL-6 and its downstream played an important role in the effects of exercise or nutrients on activating muscle SCs proliferation and differentiation. In androgen receptor (AR)-treated C2C12 cells, stretch (mimic appropriate exercise) promoted cell proliferation through the AR-IGF-1/IGF-1R-p38 and extracellular regulated protein kinases (ERK) 1/2 pathways.[111] Thus, it makes sense to explore whether exercise can activate the proliferation and differentiation of satellite cells to promote muscle fibers regeneration and hypertrophy through the AR-IGF-1/IGF-1R-mitogen-activated protein kinase (MAPK) pathway. Combining exercise with nutrient ingestion is an effective and feasible strategy for promoting SC activation and myogenic differentiation.

Activation of SCs was beneficial to muscle fibers regeneration, while excessive activation led to SC exhaustion. Thus, when SCs participated in muscle fiber repair and regeneration, treadmill training prevented excessive activation of SCs and maintained its regenerative potential by up-regulating IGF binding protein 7 (IGFBP7), blocking the binding of IGF receptor (IGFR) to its ligands, further inhibiting PI3K/Akt/mTOR pathway.[109] In conclusion, activation of SCs requires mechanical stimulation and cytokines, and capillary, as the transport channels of oxygen, nutrient and cytokines, are also critical factors in regulating the state and function of SCs. Exercise activates SC proliferation and differentiation to improve muscle fiber regeneration by promoting capillarization in skeletal muscle and up-regulating SC activation-related signaling; meanwhile, it inhibits SC excessive activation and damage by blocking activation-related signaling pathways (Table 1 and Fig. 5).

6. Conclusion and perspective

Sarcopenia is a progressive and degenerative skeletal muscle disease, and its prevention and treatment are major areas of scientific research. Advances in research on its definition, adverse outcomes, diagnosis, causes, and interventions are important to prevent and treat sarcopenia. Compelling evidence has confirmed that aging, insufficient nutrition, physical inactivity, and diseases contribute to sarcopenia. In addition, some lifestyle habits, such as smoking and excess alcohol consumption, are also conducive to sarcopenia. Therefore, it is of great significance to maintain a rational diet and regular exercise. Furthermore, sufficient

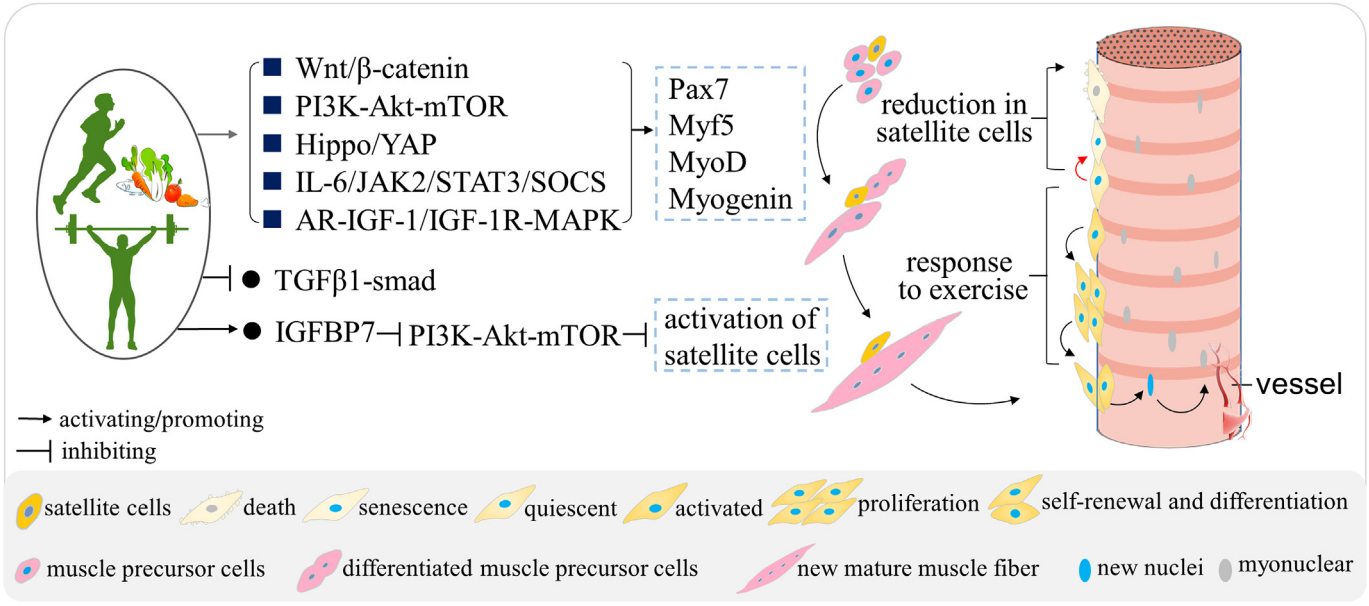

Fig. 5. Activation of satellite cells proliferation and differentiation to muscle fibers regeneration. The complex mechanisms were activated by exercise and nutrients, as shown in the picture. Satellite cell activation-related Pax7, Myf5 and MyoD were up-regulated via the above pathways to promote the proliferation and differentiation of satellite cells. Importantly, exercise could up-regulate IGFBP7 to inhibit IGF/PI3K/Akt/mTOR for preventing excessive activation of satellite cells, which was benefitial to maintaining satellite cell survival and regenerative potential. Akt: protein kinase B; AR: androgen receptor; IGF-1: insulin-like factor-1; IGF-1R: IGF-1 receptor; IL-6: interleukin-6; JAK: Janus kinase; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; Myf5: myogenic factor 5; MyoD: myogenic differentiation.

accumulation of muscle mass and strength in mid-life is beneficial in preventing age-related muscle atrophy. Maintaining regular physical activity and an optimized diet during young adulthood or middle age are effective strategies to prevent sarcopenia. Exercise and nutrition interventions regulate complex pathological or physiological mechanisms, including oxidative stress, inflammation, apoptosis, cytokines release, protein synthesis, and activation of SCs (Fig. 6), which are critical for sarcopenia prevention and treatment. Most importantly, lifelong exercise and a reasonably good diet also have practical significance.

Exerkines (including cytokines and gut microbiome-related target molecules) are involved in exercise-induced beneficial effects via exosome-mediated cross-talk between distant organs and muscle, which are new mechanisms of exercise protecting skeletal muscle. The discovery of organ-derived new exerkines and their complex network

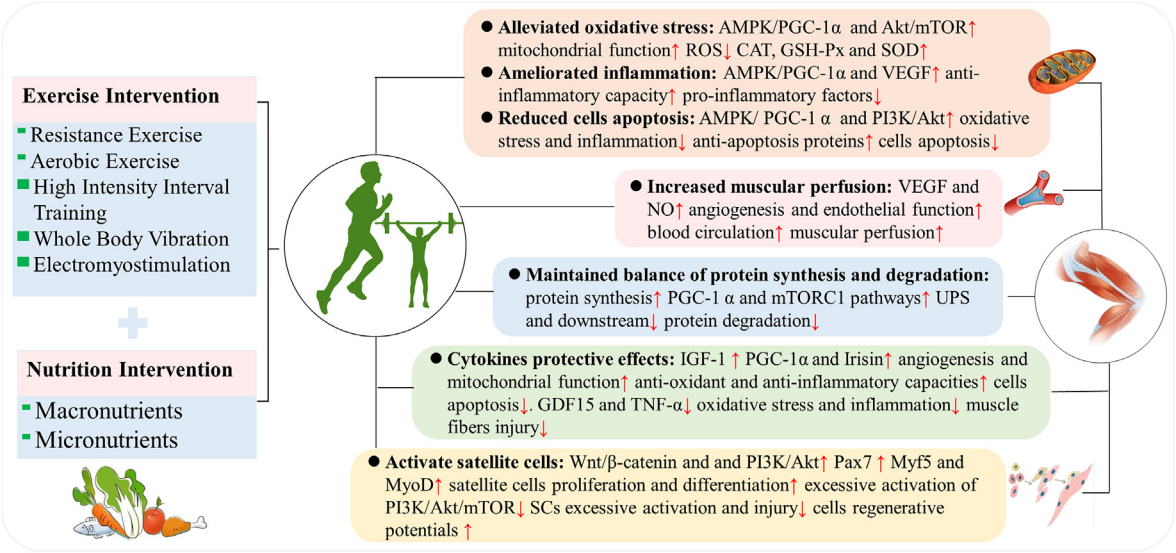

Fig. 6. Protective effects of exercise and nutrition interventions in sarcopenia. The current concerning types of exercise in improving skeletal muscle mass and function are resistance exercise, aerobic exercise, high-intensity interval training, whole-body vibration, and muscle electrical stimulation. Exercise and nutrition supplements stimulate cytokines secretion and activate mechanisms and downstream to increase muscle blood flow, ameliorate oxidative stress and inflammation, reduce cell apoptosis, promote protein synthesis, and activate satellite cells, result in preventing muscle atrophy and improving hypertrophy. Akt: protein kinase B; AMPK: adenosine monophosphate-activated protein kinase; CAT: catalase; GDF15: growth differentiation factor 15; GSH-Px: glutathione peroxidase; IGF-1: insulin-like factor-1; PGC-1α: peroxisome proliferator-activated receptor γ coactivator (PPARγ)-1α; PI3K: phosphatidylinositol 3 kinase; mTOR: mammalian target of rapamycin; MyoD: myogenic differentiation factor D; Myf5: myogenic factor 5; MyoD: myogenic differentiation; NO: nitric oxide; UPS: ubiquitin-proteasome system; VEGF: vascular endothelial growth factor; ROS: reactive oxygen species; SCs: satellite cells; SOD: superoxide dismutase; TNF-α: tumor necrosis factor-α

interaction will be conducive to comprehensively investigating the mechanisms of exercise-induced protection of muscle. With the deepening of life science, sports science and medical research, spatial transcriptomics (emerging from phenotypes and metabolomics development) and the spatial multi-omics (forming by spatial transcriptomics and spatial proteomics) will provide more possibilities to clarify the mechanisms of protection for skeletal muscle comprehensively.

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Submission statement

I would like to declare on behalf of my co-authors that the work described was original research that has not been published previously and not under consideration for publication elsewhere, in whole or in part.

Conflict of interest

Zhenjun Tian is an editorial board member for Sports Medicine and Health Science and was not involved in the editorial review or the decision to publish this article. The authors have no financial or proprietary interests in any material discussed in this article. No conflict different exists in the submission of this manuscript, and manuscript is approved by all authors for publication.

Authors' contribution

Lili Feng: Writing – original draft, Conceptualization. **Bowen Li:** Writing – review & editing, Supervision. **Su Sean Yong:** Writing – review & editing, Supervision. **Xiaonan Wu:** Writing – review & editing. **Zhenjun Tian:** Writing – review & editing, Supervision, Conceptualization.

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