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Review

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# Effects of exercise training on the biochemical pathways associated with sarcopenia

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**[Purpose]** Sarcopenia is considered one of the major causes of disability in the elderly population and is highly associated with aging. Exercise is an essential strategy for improving muscle health while aging and involves multiple metabolic and transcriptional adaptations. Although the beneficial effects of exercise modalities on skeletal muscle structure and function in aging are well recognized, the exact cellular and molecular mechanisms underlying the influence of exercise have not been fully elucidated.

**[Methods]** We summarize the biochemical pathways involved in the progression and pathogenesis of sarcopenia and describe the beneficial effects of exercise training on the relevant signaling pathways associated with sarcopenia.

**[Results]** This study briefly introduces current knowledge on the signaling pathways involved in the development of sarcopenia, effects of aerobic exercise on mitochondria-related parameters and mitochondrial function, and role of resistance exercise in the regulation of muscle protein synthesis against sarcopenia.

**[Conclusion]** This review suggested that the beneficial effects of exercise are still under-explored, and accelerated research will help develop better modalities for the prevention, management, and treatment of sarcopenia.

**[Key words]** aerobic exercise, resistance exercise, sarcopenia, aging, skeletal muscle, IGF-1, PI3K, AKT, mTOR, TNF-α, Atrogin, MuRF1/2, ROS

## INTRODUCTION

There is a growing body of literature that recognizes the impact of a decline in skeletal muscle mass and function associated with the progression of aging[1]. Aging is highly associated with an increased risk of developing sarcopenia[2]. Sarcopenia is a multifactorial disease that results in a gradual decline of skeletal muscle mass, strength, and functional performance[3]. Indeed, sarcopenia has proven to be a clinical relevance as a biomarker to identify the biological alterations associated with the progression of aging[4]. Despite the increasing evidence of the clinical implications of sarcopenia in the aging skeletal muscle, the exact mechanisms underlying of the sarcopenia are still unknown. It is crucial to determine the unbiased assessment methods for sarcopenia and include its diagnosis in routine clinical practice. Moreover, an incomplete pathological diagnosis of sarcopenia results in failed intervention strategies for clinical studies[5].

Physical inactivity might contribute to the development of sarcopenia[6]. Hence, current strategies for the management of sarcopenia include exercise training along with nutritional support[7]. Among the intervention strategies, exercise is well recognized to improve skeletal muscle function. Specifically, resistance exercise (RE) is a widely recommended strategy for the management of sarcopenia[8]. Recent studies have demonstrated that aerobic exercise (AE) inhibits the development of sarcopenia[9]. However, the cellular mechanisms through which RE and AE affect sarcopenia pathogenesis have not yet been determined.

Here, we briefly introduce currently available information on the signaling pathways involved in the development of sarcopenia. We also describe the beneficial effects of exercise on biochemical adaptations and discuss how this new paradigm provides a potential signal mechanism associated with the pathogenesis of sarcopenia.

## Insulin-like growth factor 1 (IGF-1)/Akt/mammalian target of rapamycin (mTOR)

Physiological maintenance of skeletal muscle tissue depends on the balance between anabolic and catabolic pathways[10]. The balance between protein synthesis and protein degradation is a decisive parameter for maintaining skeletal muscle mass during aging[11]. The activated phosphatidylinositol-3- kinase (PI3K)/Akt/mTOR signaling pathway plays a crucial role in anabolic metabolism induced by protein synthesis[12]. IGF-1 and insulin, which are representative anabolic stimuli, regulate the PI3K/Akt pathway, resulting in the control of skeletal muscle hypertrophy[13]. Increased IGF-1 and insulin levels inhibit the suppression of muscle synthesis by activating the phosphorylation of insulin receptor substrate 1 (IRS-1), resulting in the activation of the PI3K/Akt pathway and stimulation of mTOR[14]. Contraction-induced activation of mTOR depends on the phosphorylation of 70-kDa ribosomal S6 protein kinase ($p70^{S6K}$) and 4E-binding protein 1 (4E-BP1), which promote protein synthesis[15]. Furthermore, protein kinase B (Akt) is essential for the regulation of cell metabolism[16].

## Forkhead Box O (FoxO) transcription factors

Skeletal muscle protein turnover influences the levels of insulin and IGF-1, which regulate skeletal muscle FoxO isoforms[17]. FOXO proteins, members of the Forkhead family of transcription factors, are identified by a conserved DNA-binding domain and act as key growth factors in the skeletal muscle. The FoxO family, comprising FoxO1, FoxO3, and FoxO4, regulates skeletal muscle metabolism[18]. These proteins are located in the nucleus and suppress the PI-3K/Akt and mTOR signaling pathways, resulting in a decrease in satellite cell number and regeneration[19,20]. FoxO1 is associated with anabolic pathways, which regulate phosphorylation of the translational repressor protein, 4E-BP1, and mTOR and regulatory-associated protein of mTOR (RAPTOR)[21]. The myonuclear levels of FoxO1 were found to be increased in the elderly compared to younger individuals[22].

## Transforming growth factor-beta (TGFβ)

Skeletal muscle atrophy can be negatively regulated by catabolic signals, a member of the TGFβ superfamily, regulating the expression of genes involved in myogenic differentiation and muscle regeneration[23]. Additionally, myostatin, which is produced by the skeletal muscle, regulates muscle growth[24]. The transcription factors of small mothers against decapentaplegic (SMAD) 2 and 3, which induce IGF-1/Akt signaling, regulate myostatin. Myostatin upregulates the ubiquitin ligases, atrogin1 and muscle RING-finger protein-1 (MuRF1), via FoxO transcription factors[25], causing muscle atrophy. The administration of myostatin inhibits the IGF1-PI3K-Akt pathway, which results in the activation of FoxO1 and increases the expression of atrogin-1[24], whereas the inhibition of SMAD2/3 partially activates the mTOR signaling pathway that promotes skeletal muscle hypertrophy[26].

## Nuclear factor κB (NF-κB)

NF-κB is a protein complex and multifunctional regulator of DNA transcription, immune function, cell survival, and proliferation. Lower expression of myogenic differentiation 1 (MyoD) protein and MuRF1 seems to be caused by the activation of NF-κB during muscle atrophy[27]. It is well-known that NF-κB is activated in response to increased reactive oxygen species and tumor necrosis factor-alpha (TNF-α). IκB kinase is an enzyme complex associated with increased cellular inflammation and activated IkB results in a decrease in NF-κB in the cytosol[11]. Stimulation of IκB kinase induces IκBα phosphorylation, which regulates ubiquitination and subsequent proteolysis in the step of targeting IκBα, resulting in the binding of NF-κB[28].

## Mitogen-Activated Protein Kinases (MAPKs)

MAPKs, which are Ser/Thr kinases, regulate extracellular signals involved in a wide range of cellular processes, such as gene expression, apoptosis, and differentiation in eukaryotic cells[29]. Skeletal muscle myogenesis is controlled by four MAPK protein family members, including extracellular signal-regulated kinase (ERK) 1/2, p38 MAPK, c-Jun N-terminal kinases (JNKs), and ERK5. The upstream of MAPKs stimulates tyrosine and threonine residue phosphorylation after receiving signals from cytokines, growth factors, and cellular stressors, which results in the activation of MAPKs[30].

## Effects of exercise training on muscle pathophysiology

Physical inactivity and sedentary lifestyle are closely linked to a decline in muscle mass, physical fitness, and physical performance[31]. Conversely, exercise is one of the best strategies for improving the quality of life and health-related physical fitness factors and maintaining muscle mass and strength[32]. In general, physical exercise can be divided into AE, which involves low-intensity exercises for a long time, and RE, which involves powerful movements in a short time[33]. It is well known that both exercise regimes stimulate and regulate signaling pathways, such as the IGF-1/Akt/mTOR axis, FoxOs, NF-κB, MAPKs, mitochondrial function, and cell death in sarcopenia. The following paragraph summarizes the role of AE and RE in these pathways[34]. These exercises regulate the signaling pathways of the skeletal muscle in sarcopenia (Figure 1).

## AE

AE capacity contributes to the inhibition of aging[35]. It is also well known that AE improves cardiac and pulmonary function[36], which involves maximal oxygen uptake ($VO_2max$); mitochondrial function[37], which involves mitochondrial density and activity; and energy metabolism[38], which involves insulin sensitivity and energy expenditure. Furthermore, AE inhibits intra-muscular lipid accumulation and aids in the recovery from muscle dysfunction in metabolic diseases[39]. AE also contributes to an

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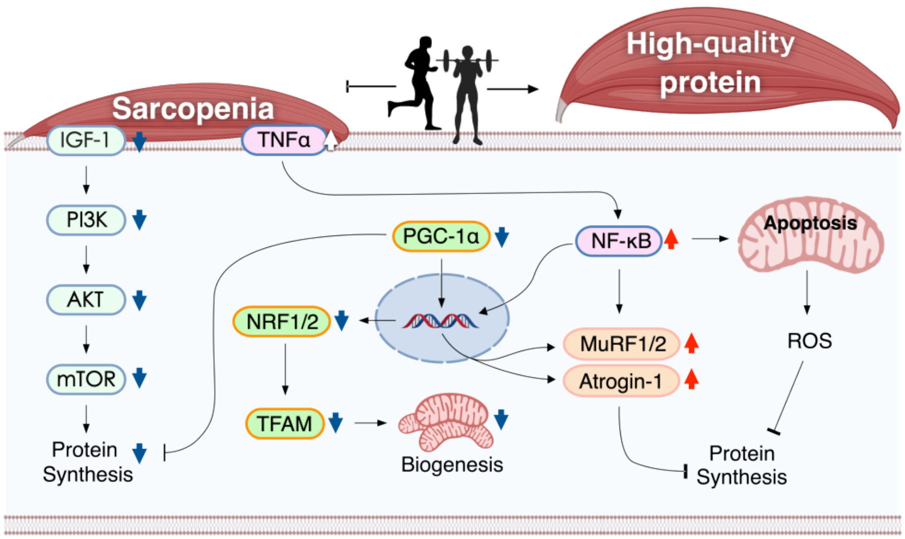


**Figure 1.** Mechanistic illustration of exercise-induced signaling pathways of the skeletal muscle in sarcopenia
IGF-1, insulin-like growth factor-1; PI3K, phosphatidylinositol-3 kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; TNF-α, tumor necrosis factor-alpha; PGC1-α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha, NRF1/2: nuclear respiratory factor 1/2, TFAM: mitochondrial transcription factor A, MuRF1/2, muscle RING-finger protein-1, NF-kB: nuclear factor kappa-light-chain-enhancer of activated B, ROS: reactive oxygen species

**Table 1. Summarizes the effect of AE on the signaling pathways of the skeletal muscle in sarcopenia**

| Subjects | Types | Duration | Significance | Reference |
|---|---|---|---|---|
| Elderly males | Cycling exercise | Acute HIT | ↑P38 MAPK/PGC1-α /COX3 | Cobley et al.[41] |
| Older adults | Walking and biking | Chronic exercise (16 weeks) | ↑ Electron transport chain complexes (I, IV, V)<br>↑ PGC1-α, TFAM | Broskey et al.[42] |
| Aged rats | Treadmill running | Chronic exercise (12 weeks) | ↑ PGC1-α, TFAM, cytochrome c<br>↑ P38 MAPK, AMPK, SIRT1 | Kang et al.[43] |
| Aged rats | Treadmill running | Chronic exercise (12 weeks) | ↓ Mitochondrial apoptotic signaling pathways | Song et al.[46] |
| Aged rats | Treadmill running | Chronic exercise (4 weeks) | ↓ TNF-α<br>↑ Exercise capacity, muscle strength | Marzetti et al.[47] |
| Older adults | Cycling exercise | Chronic exercise (8 weeks) | ↑ IGF-1, $VO_2$max | Poehlman et al.[49] |
| Aged rats | Treadmill running | Chronic exercise (8 weeks) | ↑ mTOR, insulin receptor, IRS-1 | Pasini et al.[52] |

HIT: high-intensity training, P38 MAPK: p38 mitogen-activated protein kinases, PGC1-α: peroxisome proliferator-activated receptor gamma coactivator 1-alpha; COX3, cyclooxygenase; TFAM, mitochondrial transcription factor A; AMPK, AMP-activated protein

increase in citrate synthase (CS) in muscle fibers, resulting in improved mitochondrial mass. Interestingly, acute and chronic AE contribute to the age-related decline of mitochondrial biogenesis, which is regulated by enzyme activities[40]. Table 1 summarizes the effect of AE on the signaling pathways of the skeletal muscle in sarcopenia.

To identify the beneficial effects of acute AE on mitochondrial functions of the skeletal muscle in the elderly, Cobley et al. studied the effects of acute AE on mitochondrial content, biogenesis, and mitochondria-related signaling pathways in sedentary elderly males. Their findings suggest that mitochondrial dysfunction and impairment of mitochondrial homeostasis with age-related decline in skeletal muscle are typically associated with physical inactivity. Interestingly, acute AE induced a significant increase in p38MAPK phosphorylation as well as PGC1-α and cyclooxygenase (COX)4 mRNA expression, suggesting a potential therapeutic effect of exercise on skeletal muscle adaptation to sustained skeletal muscle health in sedentary elderly individuals[41].

In contrast, chronic AE is widely considered to improve skeletal muscle function in the elderly. Broskey et al. examined the influence of exercise on mitochondrial function in older adults. They demonstrated that a 16-week AE program significantly increased the content of electron transport chain complexes, particularly that of complexes I, IV, and V in mitochondrial biogenesis (PGC-1α and mitochondrial transcription factor A, TFAM), suggesting that chronic AE may protect muscles against aging by preventing mitochondrial and metabolic dysfunction[42]. Additionally, the oxidative phosphorylation capacity was greater in trained volunteers than sedentary volunteers. Following these findings, AE for 12 weeks stimulated mitochondrial biosynthesis and energy transport in aging rats[15,43]. AE also increased the levels of COX4 and Drp1. Finally, AE contributes to the activation of ATP synthase, which increases mitochondrial energy production[44]. AE results in an increase in PGC-1α signaling in the skeletal muscle[45], as demonstrated by an increase in PGC-1α levels in aged mice during the 12 weeks of AE program[43].

**Table 2.** Summarizes the effect of RE on the signaling pathways of the skeletal muscle in sarcopenia

| Subjects | Types | Duration | Significance | Reference |
|---|---|---|---|---|
| Older adults | Leg extension (70% of 1RM) | Acute bout of RE | No significant mTOR, S6K1, 4E-BP1, ERK1/2 | Fry et al.[55] |
| Old women | Knee extension (70% of 1RM) | Acute bout of RE | ↑ MuRF-1, FOXO3A, atrogin-1 | Rau et al.[56] |
| Older adults | Combined RE (80% of 1RM) | Chronic exercise (6 months) | ↑ Skeletal muscle strength, mitochondrial function<br>↓ Senescence-related transcriptional genes | Melov et al.[57] |
| Aged rats | Ladder climbing (10 repetitions) | Chronic exercise (9 weeks) | ↑ Skeletal muscle strength and mass, IGF-1<br>↓ LC3-II/LC3-I ratio, p62 | Luo et al.[58] |

1RM: one-repetition maximum; mTOR: mammalian target of rapamycin; S6K1: ribosomal S6 kinase1; 4E-BP1: eukaryotic initiation factor 4E-binding protein1; ERK1/2: extracellular signal-regulated kinase 1/2; MuRF-1; muscle RING-finger protein-1; FOXO3A: forkhead box O3A; IGF-1: insulin-like growth factor-1; LC3: light chain 3

This mechanism is associated with a significant increase in TFAM, cytochrome c, and mtDNA content. AE also contributes to an increase in AMPK, p38MAPK, SIRT1, and p-cAMP response element-binding protein (CREB) levels. These results indicate that AE inhibits the reduction of aging-related factors and mitochondrial protein synthesis in the skeletal muscle[43]. In this regard, Broskey et al. observed an increase in electron transport complexes III, IV, and V in the skeletal muscle of elderly subjects during the 16 weeks AE program. Additionally, they reported a positive correlation between the expression of TFAM and PGC-1α.

AE also plays a role in regulating and inhibiting the development of apoptosis in aged skeletal muscle. Song et al. examined whether 12 weeks of AE reduced apoptotic DNA fragmentation and mitochondrial apoptotic signaling pathways in the skeletal muscle of aged rats. They reported the beneficial effect of AE on apoptotic signaling pathways[46]. Consistent with a similar study, AE also improved aging-induced apoptosis in the skeletal muscle of aged rats. Additionally, AE prevented the development of apoptotic signals by regulating the TNF-α signaling pathway in the extensor digitorum longus muscle of aging rats, resulting in improved exercise capacity and muscle strength[47]. Many researchers have attempted to elucidate the potential mechanisms of the beneficial effects of AE on skeletal metabolism in humans and have identified the role of IGF-1[48]. Eight weeks of AE induced the upregulation of IGF-1, suggesting a correlation between $VO_2$max and IGF-1 in males[49].

Interestingly, the basal levels of GH, IGF-1, and IGFBP-1 were higher in trained middle-aged men than sedentary individuals. Acute AE activated the GH/IGF-1 axis in middle-aged men[50]. Sakamoto et al. found that acute submaximal and maximum intensity AE activated Akt r308 and Ser473 phosphorylation[51]. Similar to these results, Pasini et al. found that 8 weeks of AE increased the anabolic pathways in the skeletal muscle of aged rats. Additionally, AE resulted in an increased expression of insulin receptor and IRS-1 in the skeletal muscle of aged rats compared to sedentary rats[52].

## RE

RE is significantly effective in treating and preventing sarcopenia and acts by regulating muscle protein synthesis (MPS), thereby resulting in improved muscle strength and skeletal muscle mass[53]. Evidence suggests that acute and chronic RE play a crucial role in regulating skeletal muscle metabolism in elderly individuals[54]. However, the exact mechanism through which acute RE regulates skeletal muscle metabolism is not clearly known. Table 2 summarizes the effect of RE on the signaling pathways of the skeletal muscle in sarcopenia.

An acute bout of RE influences the intracellular mediators of MPS in the vastus lateralis muscle of young and older adults. This study observed an increase in the phosphorylation of mTOR, S6K1, 4E-BP1, and ERK1/2 in the younger group, while no such changes were seen in the older group. Moreover, a significant increase in MPS was observed in the younger group compared to the older group[55]. However, these findings contradict those reported by Raue et al., who examined whether acute RE affects several myogenic mediators at rest and after 4 h in young and older women. Acute RE stimulates the upregulation of MyoD and myogenic regulatory factor (MRF4) along with the downregulation of myostatin. The study also showed that high-intensity RE regulated the mRNA expression of ubiquitin proteasome-related genes and elevated atrogin-1 and MuRF-1 gene expression after 4 h, resulting in skeletal muscle atrophy in the vastus lateralis[56]. In contrast to these studies, Melov et al. showed that 6 months of RE in the elderly group resulted in a significant improvement in skeletal muscle strength.

Interestingly, the RE-induced elderly group had lower levels of senescence-related transcriptional genes than the young group. They also showed an improvement in mitochondrial function and muscle atrophy and a positive relationship between skeletal muscle phenotypes and the transcriptome[57]. In a similar study, Luo et al. showed that a 9-week RE program improved mitochondrial function, autophagy, and apoptosis in the gastrocnemius muscle of aged rats. These results suggest that RE is strongly associated with the reduction of 1A/1B-light chain 3 (LC3) -II/LC3-I ratio, p62 protein, Atgs, Beclin 1, Atg 5/12, Atg 7, and lysosomal enzyme cathepsin L in the skeletal muscle of aged rats, resulting in increased skeletal muscle mass[58].

It is known that skeletal muscle stimuli lead to the activation of AMPK phosphorylation and FoxO3A expression, resulting in the enhancement of skeletal muscle function and mass in the process of aging[59]. In particular, RE reduces the activation of cytochrome c and caspase-3, which is a representative inhibitor of apoptosis. In addition, RE induces IGF-1 activation and reduction of Akt and mTOR phosphorylation, resulting in improved anti-apoptotic effects and inhibition of mitochondria-mediated apoptosis in aged skeletal muscle tissues[58]. Although RE modulates IGF-1 and its receptors as well as the Akt/mTOR and Akt/FoxO3a signaling pathways, the molecular mechanism underlying its role in protein synthesis is not fully understood. Additional studies are required to comprehensively examine the effect of RE on the IGF-1/Akt/mTOR and Akt/FoxO3a signaling pathways in the skeletal muscle.

## CONCLUSION

Sarcopenia is a multifactorial disease characterized by an age-related decline in skeletal muscle mass, strength, and function through the inhibition of protein synthesis and homeostasis. Exercise training, which regulates skeletal muscle metabolism, can promote sarcopenia prevention and delay. The benefits of exercise on sarcopenia are extensive and vary according to the exercise type, intensity, and frequency. This evidence suggests that chronic AE is recommended for enhanced maximal oxygen capacity and balanced skeletal muscle metabolism. Moreover, RE improves protein synthesis and inhibits protein degradation, resulting in the maintenance of skeletal muscle mass and improved skeletal muscle function in sarcopenia. Determining the concurrent effects of AE and RE in future studies will help clarify the pathogenesis of sarcopenia and its signaling pathways, thereby improving its treatment outcomes. Additionally, further research is needed to examine the effect of combined AE and RE on the signaling pathways of the skeletal muscle in sarcopenia.

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## REFERENCES

1. Barclay RD, Burd NA, Tyler C, Tillin NA, Mackenzie RW. The role of the IGF-1 signaling cascade in muscle protein synthesis and anabolic resistance in aging skeletal muscle. *Front Nutr*. 2019;6:146.
2. Huang DD, Yan XL, Fan SD, Chen XY, Yan JY, Dong QT, Chen WZ, Liu NX, Chen XL, Yu Z. Nrf2 deficiency promotes the increasing trend of autophagy during aging in skeletal muscle: a potential mechanism for the development of sarcopenia. *Aging (Albany NY)*. 2020;12:5977-91.
3. Hinkley JM, Cornnell HH, Standley RA, Chen EY, Narain NR, Greenwood BP, Bussberg V, Tolstikov VV, Kiebish MA, Yi F, Vega RB, Goodpaster BH. Older adults with sarcopenia have distinct skeletal muscle phosphodiester, phosphocreatine, and phospholipid profiles. *Aging Cell*. 2020;19:e13135.
4. Park HS, Kim HC, Zhang D, Yeom H, Lim SK. The novel myokine irisin: clinical implications and potential role as a biomarker for sarcopenia in postmenopausal women. *Endocrine*. 2019;64:341-8.
5. Morley JE. Treatment of sarcopenia: the road to the future. *J Cachexia Sarcopenia Muscle*. 2018;9:1196-9.
6. Fonseca H, Powers SK, Goncalves D, Santos A, Mota MP, Duarte JA. Physical inactivity is a major contributor to ovariectomy-induced sarcopenia. *Int J Sports Med*. 2012;33:268-78.
7. Yang LJ, Wu GH, Yang YL, Wu YH, Zhang L, Wang MH, Mo LY, Xue G, Wang CZ, Weng XF. Nutrition, physical exercise, and the prevalence of sarcopenia in elderly residents in nursing homes in china. *Med Sci Monit*. 2019;25:4390-9.
8. Vikberg S, Sorlen N, Branden L, Johansson Jm Nordstrom A, Hult A, Nordstrom P. Effects of resistance training on functional strength and muscle mass in 70-year-old individuals with pre-sarcopenia: a randomized controlled trial. *J Am Med Dir Assoc*. 2019;20:28-34.
9. Zhao J, Brault JJ, Schild A, Cao SP, Sandri M, Schiaffino S, Lecker SH, Goldberg AL. FoxO3 coordinately activates protein degradation by the autophagic/lysosomal and proteasomal pathways in atrophying muscle cells. *Cell Metab*. 2007;6:472-83.
10. Fielding RA, Vellas B, Evans WJ, Bhasin S, Morley JE, Newman AB, Kan AV, Andriey S, Bauer J, Breille D, Cederholm T, Candler J, Meynard CD, Donini L, Harris T,, Kannt A, Guibert FK, Onder G, Papanicolaou D, Rolland Y, Rooks D,, Sieber C, Souhami E, Verlaan S, Zamboni M. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc*. 2011;12:249-56.
11. Adams SC, Segal RJ, McKenzie DC, Vallerand JR, Morielli AR, Mackey JR, Gelmon K, Friedenreich CM, Reid RD, Courneya KS. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *Breast Cancer Res Treat*. 2016;158:497-507.
12. Bodine SC, Stitt TN, Gonzalez M, Kline WO, Stover GL, Bauerlein R, Zlotchenko E, Scrimegeour A, Lawrence JC, Glass DJ, Yancopoulos GD. Akt/mTOR pathway is a crucial regulator of skeletal muscle hypertrophy and can prevent muscle atrophy in vivo. *Nat Cell Biol*. 2001;3:1014-9.
13. Pende M. mTOR, Akt, S6 kinases and the control of skeletal muscle growth. *Bull Cancer*. 2006;93:E39-43.
14. Sandri M, Barberi L, Bijlsma AY, Blaauw B, Dyar KA, Milan G, Mammucari C, Meskers CGM, Pallafacchina G, Paoli A, Pion D, Roceri M, Romanello V, Serrano A L, Toniolo L, Larsson L, Maier AB, Muñoz-Cánoves P, Musarò A, Pende M, Reggiani C, Rizzuto R, Schiaffino S. Signalling pathways regulating muscle mass in ageing skeletal muscle: the role of the IGF1-Akt-mTOR-FoxO pathway. *Biogerontology*. 2013;14:303-23.
15. Roschel H, Ugrinowistch C, Barroso R, Batista MAB, Souza

EO, Aoki MS, Siqueira-Filho MA, Zanuto R, Carvalho CRO, Neves M, Mello MT, Valmor Tricoli. Effect of eccentric exercise velocity on akt/mtor/p70(s6k) signaling in human skeletal muscle. *Appl Physiol Nutr Metab*. 2011;36:283-90.
16. Wu M, Falasca M, Blough ER. Akt/protein kinase B in skeletal muscle physiology and pathology. *J Cell Physiol*. 2011;226:29-36.
17. O'Neill BT, Lee KY, Klaus K, Softic S, Krumpoch MT, Fentz J, Stanford KI, Robinson MM, Cai W, Kleinridders A, Pereira RO, Hirshman MF, Abel ED, Accili D, Goodyear LJ, Nair KS, Kahn CR. Insulin and IGF-1 receptors regulate FoxO-mediated signaling in muscle proteostasis. *J Clin Invest*. 2016;126:3433-46.
18. Carter ME, Brunet A. FOXO transcription factors. *Curr Biol*. 2007;17:R113-4.
19. Sandri M. Signaling in muscle atrophy and hypertrophy. *Physiology (Bethesda)*. 2008;23:160-70.
20. Bowen TS, Schuler G, Adams V. Skeletal muscle wasting in cachexia and sarcopenia: molecular pathophysiology and impact of exercise training. *J Cachexia Sarcopenia Muscle*. 2015;6:197-207.
21. Meng SJ, Yu LJ. Oxidative stress, molecular inflammation and sarcopenia. *Int J Mol Sci*. 2010;11:1509-26.
22. Giresi PG, Stevenson EJ, Theilhaber J, Koncarevic A, Parkington J, Fielding, RA, Kandarian SC. Identification of a molecular signature of sarcopenia. *Physiol Genomics*. 2005;21:253-63.
23. Yang W, Zhang Y, Li Y, Wu Z, Zhu D. Myostatin induces cyclin D1 degradation to cause cell cycle arrest through a phosphatidylinositol 3-kinase/AKT/GSK-3 beta pathway and is antagonized by insulin-like growth factor 1. *J Biol Chem*. 2007;282:3799-3808.
24. Trendelenburg AU, Meyer A, Rohner D, Boyle J, Hatakeyama S, Glass DJ. Myostatin reduces Akt/TORC1/p70S6K signaling, inhibiting myoblast differentiation and myotube size. *Am J Physiol Cell Physiol*. 2009;296:C1258-70.
25. Yoshida T, Delafontaine P. Mechanisms of IGF-1-mediated regulation of skeletal muscle hypertrophy and atrophy. *Cells*. 2020;9:E1970.
26. Nakatani M, Takehara Y, Sugino H, Matsumoto M, Hashimoto O, Hasegawa Y, Murakami T, Uezumi A, Takeda S, Noji S, Sunada Y, Tsuchida K. Transgenic expression of a myostatin inhibitor derived from follistatin increases skeletal muscle mass and ameliorates dystrophic pathology in mdx mice. *FASEB J*. 2008;22:477-87.
27. Li H, Malhotra S, Kumar A. Nuclear factor-kappa B signaling in skeletal muscle atrophy. *J Mol Med (Berl)*. 2008;86:1113-26.
28. Ashall L, Horton CA, Nelson DE, Paszek P, Harper CV, Sillitoe K, Ryan S, SDG, Unitt JF, Broomhead DS, Kell DB, Rand DA, Sée V, White MRH. Pulsatile stimulation determines timing and specificity of NF-kappaB-dependent transcription. *Science*. 2009;324:242-6.
29. Kolch W. Coordinating ERK/MAPK signalling through scaffolds and inhibitors. *Nat Rev Mol Cell Biol*. 2005;6:827-37.
30. Zhang W, Liu HT. MAPK signal pathways in the regulation of cell proliferation in mammalian cells. *Cell Res*. 2002;12:9-18.
31. Hwang H, Jung WS, Kim J, Park HY, Lim K. Comparison of association between physical activity and resting metabolic rate in young and middle-aged Korean adults. *J Exerc Nutrition Biochem*. 2019;23:16-21.
32. Jung WS, Hwang H, Kim J, Park HY, Lim K. Effect of interval exercise versus continuous exercise on excess post-exercise oxygen consumption during energy-homogenized exercise on a cycle ergometer. *J Exerc Nutrition Biochem*. 2019;23:45-50.
33. Egan B, Zierath JR. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. *Cell Metab*. 2013;17:162-84.
34. Yoo SZ, No MH, Heo JW, Park DH, Kang JH, Kim SH, Kwak HBum. Role of exercise in age-related sarcopenia. *J Exerc Rehabil*. 2018;14:551-8.
35. Seo DY, Lee SR, Kwak HB, Park Hyuntea, Seo KW, Noh YH, Song KM, Ryu JK, Ko KS, Rhee BD, Han J. Exercise training causes a partial improvement through increasing testosterone and eNOS for erectile function in middle-aged rats. *Exp Gerontol*. 2018;108:131-8.
36. Seo DY, Kwak HB, Kim AH, Park SH, Heo JW, Kim HK, Ko JR, Lee SJ, Bang HS, Sim JW, Kim M, Han J. Cardiac adaptation to exercise training in health and disease. *Pflugers Arch*. 2020;472:155-68.
37. Koo JH, Kang EB. Effects of treadmill exercise on the regulatory mechanisms of mitochondrial dynamics and oxidative stress in the brains of high-fat diet fed rats. *J Exerc Nutrition Biochem*. 2019;23:28-35.
38. Seo DY, Lee S, Figueroa A, Kwak YS, Kim N, Rhee BD, Ko KS, Bang HS, Baek YH, Han J. Aged garlic extract enhances exercise-mediated improvement of metabolic parameters in high fat diet-induced obese rats. *Nutr Res Pract*. 2012;6:513-9.
39. Kwak SE, Shin HE, Zhang DD, Lee JH, Yoon KJ, Bae JH, Moon HY, Song W. Potential role of exercise-induced glucose-6-phosphate isomerase in skeletal muscle function. *J Exerc Nutrition Biochem*. 2019;23:28-33.
40. Nilsson MI, Tarnopolsky MA. Mitochondria and aging-the role of exercise as a countermeasure. *Biology (Basel)*. 2019;8:40.
41. Cobley JN, Bartlett JD, Kayani A, Murray SW, Louhelainen J, Donovan T, Waldron S, Gregson W, Burniston JG, Morton JP, Close GL. PGC-1alpha transcriptional response and mitochondrial adaptation to acute exercise is maintained in skeletal muscle of sedentary elderly males. *Biogerontology*. 2012;13:621-31.
42. Broskey NT, Greggio C, Boss A, Boutant M, Dwyer A, Schlueter L, Hans D, Gremion G, Kreis R, Boesch C, Canto C, Amati F. Skeletal muscle mitochondria in the elderly: effects of physical fitness and exercise training. *J Clin Endocrinol Metab*. 2014;99:1852-61.
43. Li L, Muhlfeld C, Niemann B, Pan R, Li R, Hilfiker-Kleiner D, Chen Y, Rohrbach S. Mitochondrial biogenesis and PGC-1alpha deacetylation by chronic treadmill exercise: differential response in cardiac and skeletal muscle. *Basic Res Cardiol*. 2011;106:1221-34.
44. Silvennoinen M, Ahtiainen JP, Hulmi JJ, Pekkala S, Taipale RS, Nindl BC, Laine T, Häkkinen K, Selänne H, Kyröläinen H, Kainulainen H. PGC-1 isoforms and their target genes are expressed differently in human skeletal muscle following resis-

tance and endurance exercise. *Physiol Rep*. 2015;3:e12563.
45. Kang C, Chung E, Diffee G, Ji LL. Exercise training attenuates aging-associated mitochondrial dysfunction in rat skeletal muscle: role of PGC-1alpha. *Exp Gerontol*. 2013;48:1343-50.
46. Song W, Kwak HB, Kim JH, Lawler JM. Exercise training modulates the nitric oxide synthase profile in skeletal muscle from old rats. *J Gerontol A Biol Sci Med Sci*. 2009;64:540-9.
47. Marzetti E, Groban L, Wohlgemuth SE, Lees HA, Lin M, Jobe H, Giovannini S, Leeuwenburgh C, Carter CS. Effects of short-term GH supplementation and treadmill exercise training on physical performance and skeletal muscle apoptosis in old rats. *Am J Physiol Regul Integr Comp Physiol*. 2008;294:R558-67.
48. Lavin KM, Perkins RK, Jemiolo B, Raue U, Trappe SW, Trappe TA. Effects of aging and lifelong aerobic exercise on basal and exercise-induced inflammation. *J Appl Physiol (1985)*. 2020;128:87-99.
49. Poehlman ET, Rosen CJ, Copeland KC. The influence of endurance training on insulin-like growth factor-1 in older individuals. *Metabolism*. 1994;43:1401-5.
50. Manetta J, Brun JF, Maimoun L, Callis A, Prefaut C, Mercier J. Effect of training on the GH/IGF-I axis during exercise in middle-aged men: relationship to glucose homeostasis. *Am J Physiol Endocrinol Metab*. 2002;283:E929-36.
51. Sakamoto K, Arnolds DE, Ekberg I, Thorell A, Goodyear LJ. Exercise regulates Akt and glycogen synthase kinase-3 activities in human skeletal muscle. *Biochem Biophys Res Commun*. 2004;319:419-25.
52. Pasini E, Le Douairon Lahaye S, Flati V, Assanelli D, Corsetti G, Speca S, Bernabei R, Calvani R, Marzetti E. Effects of treadmill exercise and training frequency on anabolic signaling pathways in the skeletal muscle of aged rats. *Exp Gerontol*. 2012;47:23-8.
53. Endo Y, Nourmahnad A, Sinha I. Optimizing skeletal muscle anabolic response to resistance training in aging. *Front Physiol*. 2020;11:874.
54. Bolotta A, Filardo G, Abruzzo PM, Astolfi A, Sanctis PD, Martino AD, Hofer C, Indio V, Kern H, Löfler S, Marcacci M, Zampieri S, Marini M, Zucchini C. Skeletal muscle gene expression in long-term endurance and resistance trained elderly. *Int J Mol Sci*. 2020;21:3988.
55. Fry CS, Drummond MJ, Glynn EL, Dickinson JM, Gundermann DM, Timmerman KL, Walker DK, Dhanani S, Volpi E, Rasmussen BB. Aging impairs contraction-induced human skeletal muscle mTORC1 signaling and protein synthesis. *Skelet Muscle*. 2011;1:11.
56. Raue U, Slivka D, Jemiolo B, Hollon C, Trappe S. Proteolytic gene expression differs at rest and after resistance exercise between young and old women. *J Gerontol A Biol Sci Med Sci*. 2007;62:1407-12.
57. Melov S, Tarnopolsky MA, Beckman K, Felkey K, Hubbard A. Resistance exercise reverses aging in human skeletal muscle. *PLoS One*. 2007;2:e465.
58. Luo L, Lu AM, Wang Y, Hong A, Chen Y, Hu J, Li X, Qin ZH. 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;48:427-36.
59. Park SS, Seo YK, Kwon KS. Sarcopenia targeting with autophagy mechanism by exercise. *BMB Rep*. 2019;52:64-9.