Review Article

Sarcopenia: Molecular pathways and potential benefits of exercise training

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Abstract

Sarcopenia, an age-associated phenomenon, is characterized by the reduced skeletal muscle mass and function. Research studies indicate that a wide range of factors can play a key role in the onset of muscle atrophy and its progression, especially during old age. However, the pathophysiology of this event is not well understood and there are many unresolved issues yet. Performing different training methods (aerobic, resistance, and concurrent) is among the strategies that may be beneficial for the prevention and improvement of sarcopenia by affecting the signaling pathways of muscle cells. On the other hand, the way in which this type of training affects the signaling pathways involved in sarcopenia has not been well understood. Even the previous research has been incapable of well introducing an effective training method for the elderly at risk for sarcopenia. Generally, in this review article, we investigate and summarize the important and key mechanisms that may contribute to sarcopenia. In the following, we have examined the effect of regular physical activity on cellular signaling pathways involved in sarcopenia, as well as the usefulness of aerobic, resistance, and concurrent activities in adaptation and prevention of the pathology of sarcopenia in the elderly.

Key Words: **Sarcopenia, Exercise activities, Aging, Skeletal muscle**

Introduction

During the two past centuries, the world has undergone a widespread demographic upheaval and the life expectancy among people has increased. Such changes have caused people to experience life beyond the age of 60 for the first time in history. In other words, with this trend, life expectancy up to the age of 80 is expected to become an ordinary expectation for all today's youth. But the consequence we probably face in the future will be an increase in the elderly population aged over 60 years from 841 million in 2013 to more than 2 billion in 2050 (Patel, 2017). Regarding the aging phenomenon, the decline in age-associated muscle mass was first introduced with the term "sarcopenia" in 1989 by a researcher named Irwin Rosenberg. But nowadays, broader definitions of this word have been presented in scientific resources. For example, sarcopenia has been characterized as an age-associated syndrome that causes a severe decline in skeletal muscle mass and strength, and finally leads to declines in physical function, decreased quality of life, and death (Nascimento et al., 2019; Yoo et al., 2018).

Researchers have for many years recognized sarcopenia as an aging-associated syndrome that is in fact a biomarker. It has been accepted for the diagnosis of aging at clinical level and in all ages (Picca et al., 2018). However, no exact theory for the cause of this syndrome has been stated given its complexity, and its pathophysiology is still not fully understood (Melouane et al., 2020; Ziaaldini et al., 2017). With the breadth of research conducted by researchers, biomarkers have thus been expressed as key tools for evaluation of age-associated diseases and interventions utilized at the preclinical and clinical levels (Cardoso et al., 2018). The study of these processes and signaling pathways is of crucial importance for a clear understanding of the cellular and molecular context of muscle atrophy during aging. However, it is important to note that the aging-induced muscle atrophy can be prevented and treated. But the multifaceted etiology of sarcopenia has led to ineffectiveness of separate pharmacological and nutritional pre-

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-vention and therapeutic methods alone. That is why paying attention to exercise programs along with other interventions can be effective in better prevention and treatment of sarcopenia (Ferri et al., 2020; Nascimento et al., 2019). The benefits of regular exercise training on the muscle cells of the elderly have been proven; however, the cellular and molecular signaling pathways of this efficacy are not fully and exactly understood. Accordingly, the study of the role of exercise and regular physical activity in relation to the health and skeletal muscle cell signaling pathways in the pathophysiology of sarcopenia is of paramount importance (Figure 1) (Oliveira & Hood, 2019; Ziaaldini et al., 2017).

In the following, the results and evidence obtained from research studies conducted on the pathways involved in the onset and progression of sarcopenia phenomenon are presented. We then describe the role of exercise activity in muscle with the aim to investigate its importance and necessity in preventing the pathophysiology of sarcopenia.

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

The balance of anabolic and catabolic pathways is of vital importance to the physiological integrity of skeletal muscle tissue. In other words, the determining factor for maintaining musculoskeletal mass during old age is the balance between protein synthesis and protein degradation (Seo & Hwang, 2020). The evidence reveals the key role of IGF-1/Akt/mTOR pathway in increasing the rate of muscular hypertrophy (Yoshida & Delafontaine, 2020). For this purpose, a study on performance

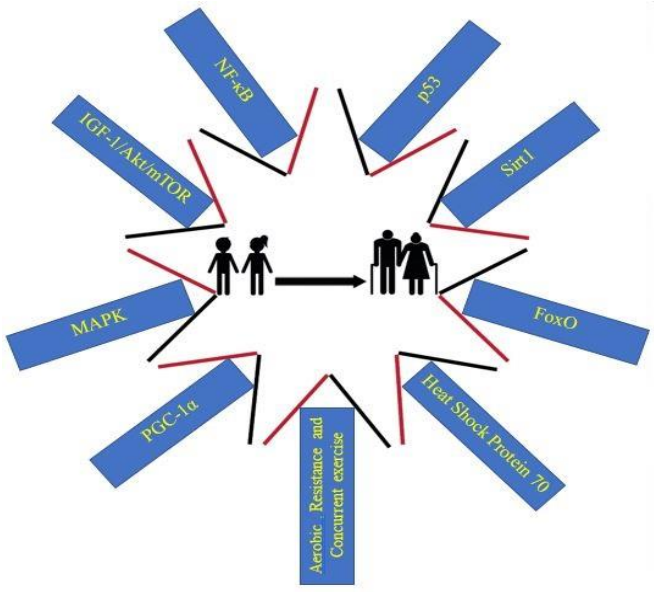

Figure 1: Different cellular and molecular signaling pathways and various types of exercise activities can play a role in the onset and progression of sarcopenia phenomenon.

enhancement showed that ectopic delivery of IGF-1 increases the size of muscle and improves muscular repair. Additionally, it reverses the effects of sarcopenia to some extent. The promyogenic effects of IGF-1 are exerted through the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) complex signaling pathway. After being activated by 3-phosphoinositidedependent protein kinase 1 (PDK1), mTORC1 is phosphorylated by AKT, which is a key driver of protein synthesis regulated by nutrients. In turn mTORC1 phosphorylates S6 kinase (S6K1), which will finally change the components of the ribosomal transporter. On the other hand, the kinase complex also phosphorylates eIF4 binding proteins (4EBP), thus eliminates their repressor preservative by increasing the translation length. In fact, the results show that the IGF-1/AKT/mTOR pathway probably slows down protein degradation signal during the process of muscle loss (Lu et al., 2017). However, research studies conducted using models of muscle atrophy in rodents have shown that IGF-1 expression prevents proteolysis and also shortens the AKT-mTOR pathway in this type of models (4 iam). Though the rate of protein synthesis is dependent upon an adequate availability of amino acids from the diet or proteolytic processes, the important point mentioned in research studies to drive anabolism is mainly related to the intracellular insulin signaling pathway and the insulin-like growth factor-1 (IGF-1) receptor signaling pathway i.e., IGF1/AKT/mTOR signaling pathway, which also inhibits proteolysis (Tournadre et al., 2019). In this vein, by studying Sprague-Dawley rats, YIN et al. stated that androgen receptor plays a key role in muscle hypertrophy resulting from both resistance training and endurance training, which occurs somewhat indirectly by the IGF-1/IGF-1R-PI3K/Akt-mTOR pathway (Yin et al., 2020). Other studies indicate that resistance training and protein consumption may be the main driver to combat sarcopenia through regulating the Akt-mTOR signaling pathway. A recent study even found that Antler Fermented with lactic acid bacteria in C57BL/6J male mice could increase training strength and endurance and elevate mitochondrial energy metabolism. Overall, this performance enhancement can be attributed to the regulation of the IGF-1/AKT/mTOR and AMPK pathway (Barclay et al., 2019; Jung et al., 2021).

The NF-κB transcription factor

NF-κB actually refers to the Rel family transcription factors. Among members of this family are p65/ relA, relB, c-rel, p52, and p50. NF-κB was discovered in 1980 and recognized as the proinflammatory factor that triggers LPS signaling. NF-κB is thus traditionally expressed as an immunological transcription factor (IRF1) that plays a role in activating inflammatory cells and regulating the gene expression of multiple cytokines and chemok-

-ines. However, the role of NF-kB in the pathology of various diseases and biological processes has been expressed over recent years (Tilstra et al., 2011). According to the previous research studies, NF-kB seems to be an important molecular target in muscle atrophy. However, further research is required to be conducted on laboratory animals to evaluate the effectiveness of NF-κB-specific molecular inhibitory interventions because such research studies provide a solid basis for further clinical trials, especially in patients with sarcopenia. But the important point is that if in vivo inhibition of NF-κB is also increased, it may be accompanied by some disorders because NF-kB has many functions in the body, including development and function of the immune system, cell proliferation and survival. This will finally be accompanied by body homeostasis (Li et al., 2008). In their study, Wen Liu and Joan Chang showed that treadmill-based moderate-intensity exercise in diabetic rats prevents the anterior tibialis and gastrocnemius muscle atrophy by inhibiting the NF-kB signaling pathway and reducing the IκBα/NF-κB pathway activity (H. W. Liu & Chang, 2018). Additionally, the evidence shows that both reactive oxygen species (ROS) and tumor necrosis factor alpha (TNF-α) contribute to the activation of NF-κB and in contrast, NF-kB also affects the ROS levels in the cell (Morgan & Liu, 2011; Ziaaldini et al., 2017). In order to keep NF-κB as an inactive form in the cytosol, NF-κB binds to inhibitors of κB (IκB). There are 7 IκB isoforms in mammals (IκBα, IκBβ, IκBγ, IκBε, Bcl-3, p 100, and P105). Each of these isoforms prevents NF-κB from functioning. In this regard, IκB prevents the incremental binding of NF-κB to DNA to the extent that the net output of the nucleus is greater than the input. In other words, NF-kB NF-κB is of cytosolic origin. By cutting the covalent bonds with IκB via the action of IκB kinase (IKK), NF-κB is activated. IKK is in fact a kinase that phosphorylates IκB and depredates IκB via the ubiquitin (Ub)-proteasome pathway (UPP) and leaves NF-kB free and active. It is finally transported to the nucleus and binds to the required promoter sequences in κB domains (Thoma & Lightfoot, 2018).

Peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α)

PGC-1 α is in fact a transcriptional coactivator with several metabolic effects. However, the important point is that it was recognized for the first time as a functional activator of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) in brown adipose tissue. Actually, PGC-1 α exhibits interaction with nuclear receptors and transcription factors for activation of their target genes transcription, and its activity leads to responding to several stimuli, namely calcium ions, ROS, insulin, thyroid hormo-ne, estrogen, hypoxia, ATP demand and cytokines. The PGC-1α activity stimulates mitochondrial proliferation. Moreover, it regulates vital cellular events, such as mitochondrial fusion and fission, and antioxidant defense (Kang & Ji, 2013). Over recent decades, PGC-1 α has been introduced as the most important activator of biogenesis and mitochondrial function. The transcriptional regulator PGC-1 α that has many functions in skeletal muscles has received lots of attention from biologists as PGC-1α helps with mitochondrial hemostasis and protein balance through interaction with other signaling pathways. Additionally, it can significantly affect the muscles' morphology and physiological function by contributing to controlling multiple genes. The obtained evidence indicates that sedentary behavior and aging are two phenomena that negatively affect the PGC-1α gene expression. On the other hand, by helping muscle contraction, the increased physical activity can enhance PGC-1α signaling activity and prevent decline in aged muscle's vital functions (Ji & Kang, 2015). In their research on old rats, Jun Ko and Gyu Ko showed that performing wheel running exercise for two months increases the expression level of VEGF in gastrocnemius muscle by activating the PGC-1α/FNDC5/AMPK signaling pathway. Moreover, they found that this exercise increases muscle mass, strength, and coordination (Ko & Ko, 2021). Investigations also showed that the stable activation of PGC-1 α in skeletal muscle of old male rats increases the endurance against muscle fatigue and prevents sarcopenia to some extent, but in contrast, no improvement was observed in the whole-body metabolism. On the other hand, it worsens the age-related trabecular bone loss. In other words, the findings show that therapeutic induction of PGC-1α in old skeletal muscle may, on balance, be contraindicated (Yang et al., 2020). However, the important point revealed by the obtained evidence is that the benefits of exercise activities, even when performed at an older age, go beyond skeletal muscle, and the exercise advantage can at least be partly attributed to PGC-1 α (Gill et al., 2018).

Transcription Factor p53

The p53 was discovered in 1979 when it was recognized as a tumor-associated antigen (TAA) that can play a role in binding to oncovirus proteins. The TP53 gene encodes the protein p53 on chromosome 17p. This protein is composed of 393 amino acids that are divided into 7 domains, including N-terminus transcription-activation domain or activation domain 1, activation domain 2, proline-rich domain, deoxyribonucleic acid (DNA)-binding core domain, nuclear localization signal, homo-oligomerization domain, and the C-terminal domain, which binds to damaged DNA. The p53 plays an important role as a tetramer by the DNA-binding core domain that binds to p53-dependent pr-

-omoters and induces the transcription of the downstream gene (Bowlus, 2014). Broad research has been conducted on the protein p53, but it is recognized more as a tumor suppressor in human and other mammals. The evidence shows that the increased sensitivity to cancer is associated with the loss or mutation of p53, and most functions mentioned for p53 are expressed given the point that how p53 can prevent the malignancy progression. However, research studies on the structural and functional level of the protein p53 show that p53 can contribute to regulation of processes and mechanisms, such as glycolysis, cell cycle, autophagy, repair of genotoxic damage, cell survival, oxidative stress, cellular aging, angiogenesis, and bone differentiation and regeneration (Vousden & Lane, 2007). The obtained results show that along with dietary restrictions, non-ionizing radiation, hypoxia and oxidizing agents that lead to low levels of oxidative stress, an increase in activation of antioxidant enzymes Nrf2, SOD2, cesterine and catalase is mediated by p53. In addition, by performing exercise activities, cell function is enhanced by p53. As a result, mitochondrial biogenesis is increased and the mtDNA maintenance is improved (Beyfuss & Hood, 2018). However, investigation of the emerging function of p53 in skeletal muscles metabolism shows a novel and controversial field of study for exercise activities and muscle physiologists. In this regard, the obtained results show that the muscle phenotypes caused by endurance and resistance exercises are very diverse. Therefore, the effect of the training method on p53 regulation is of particular importance. Accordingly, p53 with its determining role may be effective on the compatibility of various training methods performed adjacent to each other, such as concrete exercises with the probable effect of molecular interference (Bartlett et al., 2014). In their study on C57BL/6 mice, Ebert et al. showed that the activity of p53 in skeletal muscle fibers does not cause age-related skeletal muscle weakness and atrophy. Moreover, these findings indicate that in the absence of immobilization or probably other acute stress conditions, p53 expression in skeletal muscle fiber has no important cell autonomous effects on muscle mass and function (Ebert et al., 2019). On the other hand, the obtained results refer to the key role of p53 in skeletal muscle homeostasis. Additionally, the results indicate that P53 mediated upregulation of Pw1 expression and this causes an imbalance in number or function of myogenic stem cells in muscle, which will finally lead to muscle atrophy. Overall, the data show that p53 and PW1 activities contribute to the progression of cytokines induced-muscle atrophy (Schwarzkopf et al., 2008). Evidence has also been presented to show that the Id2 transcription inhibitor and p53 protein tumor suppressor are associated with hindlimb suspension induced gastrocnemius muscle atrophy in young and old rats. Actually, the expression of Id2 and p53 protein has elevated only in the cytosolic part of the suspended muscle as compared with the control muscle in young and old rats. This is while this increase in changes was not observed in the nuclear fraction of the muscle. These observations show that the hypothetical role of Id2 and p53 in mediating apoptosis-associated muscle loss during hindlimb suspension can probably be attributed to the localization of intracellular protein accumulation (Siu et al., 2006). Recently, it has been shown that telomere shortening occurs due to sarcopenia and finally leads to functional impairment during the aging process. Regular physical activity is among factors that delay telomere shortening, however, there is limited information about this effectiveness. In this regard, the study by Carvalho Cunha et al. showed that high intensity exercise attenuates the expression of p53 and shelterin telomere repeat binding 1 and 2 (Trf1/Trf2), indicating the possible effectiveness of high intensity exercise in protecting DNA (De Carvalho Cunha et al., 2018). Furthermore, performing exercise activities also reduced the increased basal cytochrome c release in isolated subsarcolemmal mitochondria, and reduced pro-apoptotic Bax expression in p53 knockout mice. Exercise training thus probably attenuates the mitochondrial defects caused by the absence of p53 in an optimal way. Accordingly, performing exercise training by patients with p53 loss-of-function mutations may effectively improve the muscle function and metabolism as in healthy individuals (Oliveira & Hood, 2019). However, further research is required to determine the role of p53 in the aged skeletal muscle and identify the therapeutic potential in targeting p53.

Sirt1

Among members of the sirtuin family we can refer to Sirt1 (mammals). Sirt1 is in fact a nicotinamide adenine dinucleotide (NAD) -dependent deacetylase, which removes acetyl groups from many histone and non-histone proteins. In addition to acetylating different types of substrates, Sirt1 can play a role in many physiological processes such as gene expression control, metabolism, and aging. Along with catalyzing the enzymatic reaction, Sirt1 generates nicotinamide and produces a new metabolite called O-acetyl-ADP ribose by transferring the acetyl substrate group to cleaved NAD. As Sirt1 substrates are growing continuously, they include the following several transcription factors: the tumor suppressor protein p53, members of the FoxO family (forkhead box factors regulated by insulin/Akt), HES1 (hairy and enhancer of split 1), HEY2 (hairy/enhancer-of-split related with YRPW motif 2), PPARg (peroxisome proliferator-activated receptor gamma), CTIP2 [chicken ovalbumin upstream promoter transcription factor (COUPTF)- interacting protein 2], p300, PGC-1a (PPARg coactivator), and NF-B (nuclear factor kappa B) (Rahman & Islam, 2011). Sirt1 responds to the NAD/NADH ratio given the role of NAD+ as a coenzyme for Sirt1. Therefore, it can be said that the energy and redox status of the cell are associated with Sirt1. Sirt1 can also activate FOXO3. FOXO3 is a transcription factor that contributes to regulating BN-

IP and LC3 genes, which are both involved in the mitophagy process. By activating the synthesis of new organelles and removal of damaged ones, Sirt1 improves the existing pool of mitochondria in the cell (Oliveira & Hood, 2019). The obtained evidence indicates that SIRT1 expression in satellite cells is of high importance for functional growth of skeletal muscles in both the initial process and complete muscle regeneration. However, despite the functional role of SIRT1 in immature skeletal muscle, it shows little benefit in improving muscle mass and function in the aged skeletal muscle of C57BL6/ jbackground mice, when it is expressed after acute cardiotoxin (CTX) -induced injury. On the other hand, SIRT1 has been reported to probably improve the effect of an important protein, such as p53, after injury through synergizing, leading to an increase in the muscles' compatibility and function. In other words, the expression of SIRT1 and p53 may contribute to the important longevity-related mechanisms, including type I fiber preservation during sarcopenia (Myers et al., 2019). Here we should refer to the role of SIRT1 as a biochemical sensor regulating the metabolic status of satellite cells. Accordingly, previous studies show that SIRT1 contributes to nutrient/energy homeostasis and cell fate signaling in skeletal muscle (Diaz-Ruiz et al., 2015). Regular physical activity has strong stimulating effects on SIRT1 and will rejuvenate the aged skeletal muscles. SIRT1 can actually be considered as an active regulator that helps muscle repair and attenuates muscle hypertrophy (Radak et al., 2020).

Forkhead Box O (FoxO) Transcription Factors

The subfamily of the class O of the large forkhead transcription factors family is the forkhead box O (FoxO). This family is characterized by a protected domain for DNA-binding (FOX) and includes more than 100 members in humans, from FOXA to FOXS. In mammals, the FOXO transcription factors mainly consist of FOXO1, FOXO3, FOXO4 and FOXO6 that are involved in the muscle physiology (Martins et al., 2016; Xie et al., 2012; Ziaaldini et al., 2017). The obtained results show that the FoxO mediated gene expression affects the final cell status caused by oxidative damage and may lead to cell death, apoptosis, stoppage of the cell cycle, and subsequent repair processes. Under physiological conditions, FoxOs regulate cell differentiation, energy metabolism and nutrient homeostasis. In contrast, they also cause skeletal muscle atrophy under pathological conditions associated with oxidative stress along with overactivation of FoxO (Klotz et al., 2015). Recent studies indicate that the transcription factor FOXO1 expression occurs under different conditions of muscle atrophy. This process is accompanied by the positive regulation of muscle atrophy-related genes, including atrogin 1 (ubiquitin ligase) and cathepsin L (lysosomal proteinase) (Hirose et al., 2018). On the other hand, the obtained evidence shows that in resistance training with muscle hypertrophy, the activities of Akt and its downstream targ-ets GSK-3β and mTOR are increased, while the activity of atrophy signaling factor, Foxo1, is reduced. The unexpected increase in atrogin-1 and MuRF1 following hypertrophy and their reduction after the atrophy phase are probably associated with maintenance of normal protein renewal in healthy muscle (Léger et al., 2006). Additionally, the investigations indicate that the activities of acetyltransferase p300/CBP play a role in regulation of FOXO signaling in skeletal muscle, and acetylation is probably the key mechanism that differently regulates FOXO homologs and determines which FOXO target genes to be activated (Senf et al., 2011).

Heat Shock Protein 70

The term "heat shock protein (HSP)" was first coined by Ritossa in 1962. He showed the heat stress response in the housefly (Musca domestica) with the study indicating that HSPs synthesis increases in houseflies after heat shock. Today, the presence of HSPs in all living organisms from bacteria to humans has been proven. However, HSPs are in fact multimolecular complexes constitutively expressed up to 5-10% under normal growth conditions. As molecular chaperones, HSPs regulate the folding of proteins, intracellular transport of proteins in cytosol, endoplasmic reticulum (ER) and mitochondria, repair or degradation of proteins, and refolding of misfolded proteins. Additionally, depending on their molecular structure, function, and weight, HSPs are divided into five main groups: HspH (Hsp110), HspC (Hsp90), HspA (Hsp70), DNAJ (Hsp40), HspB (small HSPs), and HspD/E (Hsp60/Hsp10) crystallins (Dubey et al., 2015; Milani et al., 2019). It is worth mentioning that skeletal muscle has the potential to adapt to physiological needs. In this regard, HSPs play a role in the cellular response to various types of stress, such as the elevated heat, hypoxia conditions, acidosis, low levels of glucose, or absolute mechanical stress (Folkesson et al., 2013). According to studies and obtained evidence, Hsp70 is in fact an intracellular chaperone protein with various intracellular and extracellular regulatory and protective roles. Moreover, according to the obtained results, the extracellular Hsp70 can negatively regulate the synthesis of proinflammatory cytokines and modulation of inflammatory responses (Ferat-Osorio et al., 2014; Senf, 2013). The expression of Hsp70 also causes muscular myopathy in which the muscle atrophy is more evident. Even recent data provide evidence that serum Hsp70 concentration decreases with an increase in age and sedentary lifestyle, leading to contractile dysfunction and the decline in regenerative capacity linked to these conditions in skeletal muscle. In contrast, an increase in the expression of Hsp70 is associated with inflammation and weakness in elderly patients. Today, research studies on animal models of muscle injury, muscle atrophy, aging, and muscular dystrophy, have well proven the therapeutic role of HSP70 expression in skeletal muscle, and

it is proposed as a vital solution (Yuefei Liu et al., 2006; Njemini et al., 2011; Senf et al., 2011). In this regard, the evidence shows that HSP70 induction in aged C57/BL6 mice may increase the muscular function and sensitivity to insulin (Silverstein et al., 2014). The increased expression of HSP70 in skeletal muscle of transgenic mice also improved muscle structure and function following muscle atrophy. The results of this effectiveness are probably related to the maintenance of satellite cells. These findings have significant implications for improvement of muscle atrophy-induced clinical conditions via HSP70 induction (Miyabara et al., 2012). In a study to evaluate the effect of strength training on elderly, Cumming et al. showed that 12 weeks of strength training or functional strength training lead to a reduction in the initial high levels of HSP70 in the aged muscles. In other words, regular strength training can probably avoid the increased cellular stress related to the aging process, and provide a healthier environment for aged muscle cells (Cumming et al., 2021).

Mitogen-Activated Protein Kinases (MAPKs)

There are protein kinases called mitogen-activated protein kinases (MAPKs) whose targets are activated or inactivated by autophosphorylation of serine and threonine residues. In fact, by responding to extracellular stimuli, they play a role in controlling various cellular processes, such as growth, survival, differentiation, proliferation, motility, metabolism, and apoptosis. But the transcription factors and MAPK substrates controlling these factors have not yet been fully determined and identified. Four distinct signaling cascades have been identified in skeletal muscle at present based on the components of the MAPK protein family: extracellular signal-regulated kinase 1 and 2 (ERK1/2, c-Jun N-terminal kinase (JNK), p38 MAPK, big MAPK, or ERK5 (Karin & Chang, 2001; Plotnikov et al., 2011; Soares-Silva et al., 2016; Ziaaldini et al., 2017). The research studies conducted over recent years have also referred to the role of MAPKs in regulating immune responses to the synthesis of cytokines, chemokines, and other inflammatory mediators. Investigations show that MKP proteins are also involved in this regard (Yusen Liu et al., 2007). Evidence obtained during the aging process in rats revealed the high level of the all three MAPKs activities studied, i.e., ERK, JNK, and p38 MAPK in parallel to the increased level of ROS (Kim et al., 2002). Recently a research found that with a reduction in p38α activity in mice, muscles are protected from damage and atrophy caused by denervation, which is accompanied by the reduced oxidative stress, attenuated protein damage, as well as improved clearance of damaged mitochondria by the autophagy process (Odeh et al., 2020). Additionally, research studies on MAPK p38 pathway indicate that taken together, this process leads to metabolic syndrome given that MAPK p38 increases insulin-independent glucose uptake and mitochondrial oxidative phosphorylation in the normal physical condition, and in contrast, it inhibits similar processes by insulin messaging in pathological physical conditions. In other words, this cascading path acts like a double-edged sword. Regarding this path, a study on transgenic mice showed that the proliferation rate of satellite cells decreases with hyperhomocysteinemia induction and leads to an increase in oxidative stress and p38-MAPK signaling, which is a potential hazard for mass disability and atrophy in the aged mice (Bengal et al., 2020; Veeranki et al., 2015). By studying male C57BL/6J transgenic mice, Yuasa et al. obtained evidence indicating that mutant mice lacking p38α MAPK in muscular tissues are significantly resistant to muscle atrophy induced by denervation as compared with the control group, indicating that p38 α MAPK is involved in positive regulation of muscle atrophy. They also found that the inhibition of CAMK2B as a downstream target of p38α MAPK will attenuate denervation-induced muscle atrophy. In other words, the suppression of intracellular signaling mediated by p38 α MAPK can be considered as a potential target for muscle atrophy therapy (Yuasa et al., 2018). However, in relation to c-Jun N-terminal kinase (JNK), the results indicate that this agent acts as a molecular switch and stimulates muscle mass growth when it is activated. For example, when skeletal muscle is exposed to stress caused by resistance training, the muscle mass growth is initiated via the JNK/SMAD signaling axis, leading to inhibition of myostatin. In contrast, myostatin inhibits muscle growth under conditions of muscle weakness such as cancer cachexia or pathological conditions, such as diabetes type 2 and non-alcoholic fatty liver. But these conditions are adjusted with activation of the JNK pathway (Delogu et al., 2019; Lessard et al., 2018). Studies on extracellular signal-regulated kinase 1 and 2 (ERK1/2) refer to its role in maintaining neuromuscular synapse and maintaining the type of muscle fiber. But the aging process may in fact inhibit the contractile function of skeletal muscle to stimulate ERK1/2 phosphorylation (Parkington et al., 2004; Rimer, 2020; Seaberg et al., 2015). According to investigations, MAPK regulates cellular stress. But in between the MAPK signaling pathway is activated by exercise activities. Moreover, the previous research has referred to the role of the intensity and duration of the exercise activities (Kramer & Goodyear, 2007). In this regard, Takegaki et al. conducted a study on male rats and obtained evidence indicating that despite no change in the volume and intensity of training, consecutive sessions of resistance training will attenuate phosphorylation of p38 MAPK, ERK1 / 2, p90RSK. Perhaps the attenuation of mTORC1 activity will ensue following this effect of training (Takegaki et al., 2019). Investigation of MAPK signaling pathways in skeletal muscle of active young and old men at rest and exercise conditions shows differences between these two age groups. The results indicated that the old people at rest showed a higher increase in phosphorylation of pathway proteins (ERK 1/2, p90RSK, Mnk 1,

p38 MAPK and JNK/SAPK) as compared with the young men. However, this trend was reversed with a period of resistance training, and a higher level of phosphorylation of MAP protein was observed in the youth compared to the old men. The remarkable point is that in comparison to the young men, the protein phosphorylation levels showed no significant difference in the elderly after training except for ERK 1/2 protein. These conditions indicate that older men's muscles may be under stress due to higher levels of phosphorylation at rest (Williamson et al., 2003).

As aforementioned in this review study, regular physical activity can effectively prevent sarcopenia through metabolic and transcriptional pathways. In this section, we briefly investigate the role and importance of resistance, aerobics, and combined exercise activities in sarcopenia.

Resistance exercise activities and sarcopenia

Various hormonal, neurological, muscular, immune, nutritional factors or sedentary lifestyle-related conditions can play a role in the pathology of sarcopenia. However, these factors will finally result in pathophysiological changes at the neuromuscular and tendon levels. Additionally, the evidence indicates that muscle mass gradually reduces 3–8% in people per decade after the age of 30 onward and this rate of muscle mass decline is even increased more after the age of 60. This will gradually result in the loss of muscle strength, which will significantly attenuate performance and lead to the independence of the elderly. Therefore, lifestyle changes will be one of the effective and beneficial strategies to prevent and attenuate the adverse effects of sarcopenia (Mielgo-Ayuso & Fernández-Lázaro, 2021). For this purpose, performing resistance exercises is one of the effective solutions to enhance the muscle strength based on the obtained evidence and results for people aged 50 and older whose physical performance, strength, and physical status have been impaired and reduced (Iolascon et al., 2014). As sarcopenia causes all of these skeletal muscles to be affected by this pathology, it is thus recommended based on studies that the exercises performed focus more on major muscle groups for the purpose of the whole body. Therefore, the evidence puts emphasis more on the useful effects of high-intensity resistance exercises (%80 1RM) and resistance training with blood flow restriction on muscle mass improvement, growth, strength, and function (Beckwée et al., 2019). Additionally, eight to 10 resistance exercises are recommended be performed for various muscle groups. For this purpose, the exercises had better be performed with eight to 12 repetitions twice a week on non-consecutive days (Phu et al., 2015). The recent systematically reviewed evidence shows that performing resistance and strength exercises or combining this type of exercises with aerobic exercise activities will result in the improvement of anthropometric indices and muscle function. However, it is of par--amount importance that these exercises are prescribed tailored to the characteristics of each person and take the place of the ordinary aerobic exercises, such as walking (Barajas-Galindo et al., 2021). The obtained results show that performing resistance exercises will increase the skeletal muscle fibers size and cross-sectional area over time. This amount of change occurs, especially in fast-twitch muscle fibers (type IIa and IIx), but slow-twitch fibers (type I) showed no change (Yoo et al., 2018). However, regular resistance training programs may effectively improve muscle strength and physical function in the elderly who have previously been diagnosed with sarcopenia, but the extent of the effect and the obtained clinical results can hardly be attributed to them and further research is required to confirm these findings (Cardoso et al., 2018; Melouane et al., 2020).

Aerobic exercise activities and sarcopenia

The effect of the aging period on the cardiovascular system is accompanied by a decline in cardiorespiratory capacity. Based on the obtained evidence, this decline is in fact associated with the maximum cardiac output, maximum stroke volume, heart rate, and changes in venous arterial oxygen difference. On the other hand, performing regular aerobic exercise can affect the central and environmental adaptations, resulting in improvement of maximal oxygen consumption (VO2max), as well as the increased skeletal muscle ability to produce energy via oxidative metabolism, which finally attenuates the adverse effects of age-related phenomena. According to the conducted studies, programming aerobic exercises for the elderly had better be initiated for 5-10 minutes in the first weeks. The training program duration can be increased to 15-30 minutes a day, 3-7 days per week. In this training program, exercise activities sessions can be split into small few minute-segments during the day without any decline in the efficiency and effectiveness of the exercise. But the important point mentioned in research studies is that the most effective result to achieve fitness and improve some health factors is obtained by doing moderate to severe-intensity aerobic exercise. Moreover, the positive effects of high-intensity intermittent exercise (HIIT) were observed within 1- 4 minutes' intervals of training performed with 85-95 % of maximum heart rate (Izquierdo et al., 2021).

The useful effectiveness of exercise activities can be of great help to the aged people with sarcopenia. In this regard, Galindo et al. stated in their systematic review that performing regular aerobic activities, such as walking does not have many positive effects for patients with sarcopenia. The positive effects of aerobic exercise on anthropometric factors and muscle function will be greater when this type of exercise is performed in combination with strength and balance exercises. Additionally, the characteristics and conditions of each person should be fully taken into account in planning training for these patients (Barajas-

Galindo et al., 2021). On the other hand, in their research on the elderly, Brightwell et al. stated that performing aerobic exercises, especially moderate-intensity walking (at 70% of heart rate reserve (HRR) three days a week) is a way to prevent the decline in muscles functional strength and even the danger of falling in these individuals. Moreover, the evidence obtained from this study showed that the synthesis of basal myofibrillar protein, as well as the rate of angiogenesis in these individuals have increased, but lean body mass has not improved in them. These individuals have also been recommended participate in strength training programs to promote muscle hypertrophy (Brightwell et al., 2019). One of the significant things mentioned based on the obtained evidence regarding the importance of aerobic exercise activities is to prevent and delay the aging process in the elderly in non-pathological conditions. This effectiveness of aerobic exercise is in fact due to the easy implementation and diversity of training methods. In other words, this type of exercise has become a key and vital solution to prevent and reduce sarcopenia-induced skeletal muscle atrophy throughout life (J. Liang et al., 2021a). In this vein, Short et al. in their research on the elderly showed that the regeneration rate of total tissue protein is attenuated with an increase in age, and this disorder will finally lead to a decline in many organs' function and repair. However, a 4-month aerobic training program including foot muscles in the elderly caused no change in the rate of total body protein turnover. But in contrast, the rate of muscle protein synthesis increased. This study shows that the aging-induced-muscle protein synthesis during the aging process can be reversed using interventions, such as exercise (Short et al., 2004). The obtained results also show that the intensity of performing aerobic training (60 – 80% VO2max) should be considered because this rate of intensity can reduce the aerobic capacity and muscle mass induced by the aging phenomenon (Harber et al., 2012). In addition, the findings and evidence obtained with regard to performing advanced aerobic exercises by the old women show that this type of training improves muscle size and function. The important thing about doing this type of training is the qualitative changes made in muscle composition, which are not usually caused by resistance training. In other words, an increase in water content and a reduction in concentration of muscle myofibrillar protein are observed following aerobic training. Furthermore, performing regular aerobic training seems to increase contractile properties of skeletal muscle at the cell surface, such as contractile rate and power generation capacity in slow-twitch myofibers, in the elderly, and overall contribute to skeletal muscle plasticity (Harber et al., 2009). Though the results from conducted studies reveal the vital importance of resistance training for muscle mass maintenance, there is evidence indicating that the skeletal muscle function and mass are also maintained even during the aging period by performing regular aerobic exercises throughout the life. However, further broad research is required to investigate the way in which aerobic exercise, which is usually associated with lean muscle phenotype, can maintain muscle mass and function during old age (Laurin et al., 2019).

Concurrent exercise activities and sarcopenia

Special studies have been conducted on the role of aerobic and resistance training on sarcopenia (Mielgo-Ayuso & Fernández-Lázaro, 2021). However, the obtained evidence and results show that the elderly are usually interested in resistance training activities probably due to more injuries caused by aerobic exercise (Lavin et al., 2019). In contrast, based on the obtained findings, performing concurrent exercises by the elderly is the best key and important way to enhance cardiorespiratory readiness and muscle strength (Eduardo Lusa Cadore et al., 2010). A study by Lustosa et al. on the aged women found that performing concurrent exercises is more effective and efficient to increase the functional capacity and muscular strength of the lower extremity in women at risk of sarcopenia (Lustosa & Gomes Pereira, 2014). In this vein, Ferrari et al. compared the effect of a concurrent training program performed twice a week with the same training program performed three times a week on the trained elderly men above the age of 65 years. The obtained results revealed similar responses with regard to muscular power in both training programs. Accordingly, it is important to note that prescribing concurrent training programs even with a shorter time interval in this high-risk population may provide better adaptation and adherence to the training conditions and lead to better results (Ferrari et al., 2016). In order to properly schedule concurrent training for the elderly, the minimum weekly repetitions in cycle (1 session per week of strength training and 1 session per week of endurance training) for performing this type of exercises can be an efficient method for the elderly. On the other hand, performing strength training (high-speed muscle contractions) prior to endurance training can improve the endurance capacity in the elderly due to making incremental changes in the neuromuscular system (Eduardo L. Cadore & Izquierdo, 2013). It has even been stated that the elderly can simultaneously perform moderate to high-intensity strength training combined with moderate-intensity endurance training during weekly training sessions without experiencing any impairment in aerobic function (Eduardo L Cadore et al., 2011). But the results from a recent meta-analysis showed that performing concurrent training, especially when aerobic and strength exercises are simultaneously performed in one session will attenuate the explosive strength gain, while achieving the optimal adaptation together with separation of aerobic and strength exercises will improve the explosive strength function of the individuals participating in this type of training (Schumann et al., 2021). Another important point is to consider the greater volume of strength training that seems to be necessary to optimize muscular hypertrophy in the elderly. The

Table 1. Effects of various training methods on age-related sarcopenia.

	Subject	Sex	Age	Exercise protocol	Results	References
1	Human	Female	≥ 65 years	Tele- exercise program (resistance training/12weeks)	lower limb muscle mass, appendicular lean soft tissue, total muscle mass, chair sit-and-reach length ↑	(Hong et al., 2017)
2	Human	Male/ female	≥ 20 years	in-hospital exercise (median 2.5 metabolic equivalents (METs)/20–40 minutes/day)	skeletal muscle index (ΔSMI), muscle mass ↑	(Koya et al., 2019)
3	Mice	Male	3 months	Lifelong Aerobic Exercise (treadmill running)	Improve mass of skeletal muscle and ultrastructure of aged myofibrils through mitochondrial biogenesis and dynamics↑ improve autophagy/mitophagy via the AMPK/PGC-1α aging-induced atrophy of skeletal muscle↓	(J. Liang et al., 2021b)
4	Human	Male/ female	≥ 65 years	Information collected included exercise habit in middle age	muscle strength and physical performance↑ prevalence of sarcopenia in older age↓	(Akune et al., 2014)
5	Human	Male/ female	≥ 60 years	resistance exercise program 3 times a week for 12 weeks	muscle strength and physical performance↑ severe sarcopenia↓	(del Campo Cervantes et al., 2019)
6	Mice	Male/ female	14.5 months	34 weeks voluntary resistance wheel exercise (RWE)	intramuscular mitochondrial density and oxidative capacity, LC3II/I ratios (a marker of autophagy) ↑ mRNA expression of Gadd45α (males only) and Runx1(females only) ↓ age-related muscle wasting↓	(White et al., 2016)
7	Human	Female	≥ 60 years	progressive elastic band resistance training for 12 weeks (3 times per week)	the fat proportion of body composition↓ bone mineral density↑	(Huang et al., 2017)
8	Human	Female	65-80 years	10-week resistance exercise program	no significant between-group differences for any of the outcomes	(Vasconcelos et al., 2016)
9	Human	Male/ female	18-80 years	resistance exercise with high or moderate intensity for 12 weeks at three times per week	↑ interleukin (IL)-6, IL-10 ↓ tumor necrosis factor (TNF)-α	(Dong et al., 2019)
10	Human	Men	91 years	strength training program low intensity in isolation (LI) or with blood flow restriction (LI-BFR) / 3 month	LI-BFR training improved strength, muscle mass, IGF-1, endothelial function	(Grutter Lopes et al., 2019)
11	Mice	Male	24 weeks & 44 weeks	16 weeks/ 5 days in week/ treadmill/ 15 m/min for 30 min	preserved muscle mass and muscle strength muscle protein synthesis and mitochondrial function↑	(Aoki et al., 2020)
12	Rat	Male	20 months	ladder climbing, progressive load, 3 times a week for 12 weeks	GLUT-4, G6PDH, Hk-2 and Gly-Syn-1↑ TNF-α, TWEAK/Fn14 axis; FOXO-1, Atrogin-1 and MuRF1; Myostatin↓ IGF-1-mTOR-p70S6sk-1 axis; MyoD↑	(Ribeiro et al., 2017)
13	Mice	Male	12 months	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)	aerobic exercise alleviates the negative effects resulting from sarcopenia via the Sesn2/AMPKα2 pathway	(S. Liu et al., 2021)

Table 1. Effects of various training methods on age-related sarcopenia (Continue)

	Subject	Sex	Age	Exercise protocol	Results	References
14	Human	Male/ female	≥ 65 years	12 weeks conventional high-load resistance training (CRT) and low-load resistance training combined with blood flow restriction (LRT-BFR)	alternative training method to CRT, LRT-BFR may be a potential training method to prevent the progression of sarcopenia	(Chen et al., 2021)
15	Human	Men	60-70 years	Concurrent Training: ET (endurance training) followed by RT (resistance training) & RT followed by ET/ 3 exercise sessions per week for 8 weeks	body composition and power and VO2max↑ performing ET before RT may be more effective at enhancing skeletal muscle mass, Myf5 and Pax7 and lower and upper body power	(Moghadam et al., 2020)
16	Rat	Female	12 months	high-intensity resistance training/ 12 weeks	↑muscle volume ↑ concentrations of IGF-1, IL-1, IL-6 and TNF-α	(Corazza et al., 2013)
17	Mice	Male/ female	15 months	resistance wheel exercise (RWE)/ 8 month	prevented the sarcopenia. had no cellular impact on the aging nerves, apart from an increased number of old nerves containing aggregates.	(Krishnan et al., 2017)
18	Human	Male/ female	87.3 ± 5.4 years	12 weeks mixed exercise program including balance and resistance exercise and 12 weeks resistance exercise program	mixed exercise program (balance exercise plus resistance exercise) have improved the activities of daily living, strength, and physical performance among older sarcopenic patients	(Y. Liang et al., 2020)
19	Human	Men	64.3 ± 3.5 years	concurrent training (CT) / 8 weeks/ 3 times per week	follistatin / myostatin ratio↑ improved weight, body composition, muscle mass, function, and aerobic fitness myostatin (MSTN) and growth differentiation factor 11 (GDF11) ↓	(Bagheri et al., 2020)
20	Human	Men	55-70 years	progressive resistance training program for 8 weeks	strength in the sarcopenic group↑ Quadriceps cross-sectional area more in the healthy group↑ Myostatin concentration in both groups after training↓ testosterone increased in both group↑	(Negaresh et al., 2019)

other important point mentioned in the results of the research studies conducted with regard to the concurrent exercises in the elderly is that performing high repetitions of concentric exercises to the point of fatigue will not improve the neuromuscular function, muscular hypertrophy, and explosive strength as compared with the low repetitions in these individuals. Additionally, as the muscular strength is associated with functional capacity, the concurrent exercises had better include high-speed strength training to increase the optimal function capacity in the elderly, leading to the improvement of muscular strength (Eduardo Lusa Cadore & Izquierdo, 2019; Neves et al., 2018). For better and more accurate evaluation of the effects of various training methods on age-related sarcopenia, they are summarized in Table 1:

Conclusion

Considering the multifaceted etiology of sarcopenia, the review of the signaling pathways, transcription factors, gene expression, and protein in this study show that the association of various molecular pathways can play a key role in this age-related pathology. Therefore, further broad research is required to be conducted on humans for better and more complete perception of these pathways to prevent the age-related sarcopenia phenomenon. Additionally, the obtained evidence shows that performing aerobic and resistance exercises is probably beneficial in prevention of sarcopenia in the elderly. However, the effectiveness and efficiency of concurrent exercises seems to be better for the elderly at risk for sarcopenia. Nevertheless, further research is required to be conducted in the future to achieve more accurate and complete results to choose more efficient training methods for the elderly with sarcopenia.

What is already known on this subject?

Research studies indicate that a wide range of factors can play a key role in the onset of muscle atrophy and its progression, especially during old age.

What this study adds?

The obtained evidence shows that performing aerobic and resistance exercises is probably beneficial in prevention of sarcopenia in the elderly. However, the effectiveness and efficiency of concurrent exercises seems to be better for the elderly at risk for sarcopenia.

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