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REVIEW

Targeting mitochondrial quality control for treating sarcopenia: lessons from physical exercise

Anna Picca[a,b], Riccardo Calvani[a,b], Christiaan Leeuwenburgh[c], Hélio José Coelho-Junior[a,d], Roberto Bernabei[a,b], Francesco Landi[a,b] and Emanuele Marzetti[b]

[a]Università Cattolica del Sacro Cuore, Institute of Internal Medicine and Geriatrics, Rome, Italy; [b]Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS, Rome, Italy; [c]Department of Aging and Geriatric Research, Institute on Aging, University of Florida, Gainesville, FL, USA; [d]Applied Kinesiology Laboratory–LCA, School of Physical Education, University of Campinas, Campinas, Brazil

ABSTRACT

Introduction: Mitochondrial dysfunction is a hallmark of aging and hence is a candidate target for intervention. Sarcopenia of aging is a prevalent condition and is associated with numerous negative health outcomes. Alterations in mitochondrial homeostasis have been reported in sarcopenic muscle.

Area covered: We discuss the evidence that points to mitochondrial dysfunction having a causative role in sarcopenia and the mechanisms involved in the accumulation of damaged mitochondria in the aged muscle. We also discuss the effects of physical exercise on mitochondrial quality control and muscle health in advanced age.

Expert opinion: In the aged muscle, the mitochondrial quality control axis is altered at several levels, including proteostasis, biogenesis, dynamics, and autophagy. Mitochondrial dysfunction arising from impaired quality control is thought to play a major role in the pathogenesis of sarcopenia. Physical exercise is the most effective strategy for the management of sarcopenia. Improvements in mitochondrial health and plasticity may mediate several beneficial effects of exercise in muscle. A greater understanding of the molecular changes that occur in the aged muscle following exercise and how they impact mitochondrial homeostasis is necessary for the exploration of potential targets that are amenable for interventions.

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1. Introduction

The natural course of aging is marked, among other phenomena, by the progressive loss of muscle mass and strength/function, referred to as sarcopenia. This condition is a causative factor for an array of negative health-related events (e.g., falls, morbidity, disability, loss of independence, and mortality) [1]. At the tissue level, sarcopenia is characterized by increased levels of myonuclear apoptosis, reduced muscle bioenergetic capacity, and increased reactive oxygen species (ROS) production [2]. Given the central role played by mitochondria in these processes, mitochondrial dysfunction has become an actively investigated pathogenic mechanism of sarcopenia [3]. Such a view is also rooted in the observation that preservation of well-performing mitochondria ensures the maintenance of muscle homeostasis during aging [4].

Mitochondria serve several functions within the cell, including energy provision, calcium and iron buffering, iron-sulfur cluster and heme biosynthesis, and regulation of programmed cell death [5]. Due to these vital responsibilities, an integrated system of quality control processes is in place to ensure the maintenance of a functional mitochondrial pool [6]. Studies have shown that, in the aged muscle, the mitochondrial quality control (MQC) axis is altered at several levels, including proteostasis, biogenesis, dynamics, and autophagy [3,7]. Mitochondrial dysfunction arising from impaired quality control, in turn, is supposed to be critically involved in the pathogenesis of sarcopenia [6,8].

Yet, it is presently unclear whether these changes are attributable to aging *per se* or occur as a consequence of other phenomena, such as reduction in physical fitness and activity levels or comorbidities [8–12]. Noticeably, engagement in regular exercise preserves muscle mass and strength [13], physical performance [14], and myocyte mitochondrial function in older adults [15]. These adaptations may be accomplished through improvement of MQC [16].

This review summarizes the current understanding of the mechanisms underlying mitochondrial dyshomeostasis in the context of sarcopenia. A special focus is placed on the pathways modulated by physical exercise and that may be exploitable for developing/optimizing therapeutic interventions to preserve muscle health in advanced age.

2. Mitochondrial quality control

MQC ensures the maintenance of a healthy mitochondrial pool within the cell [17]. This task is accomplished through a complex nucleus-mitochondrion crosstalk that orchestrates several interrelated processes (i.e., protein folding and degradation, mitochondrial biogenesis, mitochondrial fission and fusion, and mitochondrial autophagy) (Figure 1).

CONTACT Riccardo Calvani riccardo.calvani@gmail.com Università Cattolica del Sacro Cuore, Institute of Internal Medicine and Geriatrics, L.go F. Vito 1, Rome 00168, Italy

Article Highlights

- Sarcopenia is the age-related loss of muscle mass and strength/function and is associated with several negative health-related events.
- A set of interrelated processes referred to as mitochondrial quality control (MQC) (proteostasis, biogenesis, dynamics, and mitophagy) is in place to ensure muscle cell homeostasis.
- Mitochondrial dysfunction amplified by failing quality control mechanisms, is considered to be a relevant player in the pathophysiology of sarcopenia.
- Preclinical and clinical evidence suggests that physical exercise modulates MQC in muscle.
- Current unknowns include the optimal window of exercise training interventions (timing and intensity) able to improve MQC function to prevent/combat sarcopenia.

This box summarizes key points contained in the article.

While mitochondrial biogenesis is necessary to generate an adequate number of organelles, the removal of damaged/dysfunctional mitochondria is vital to prevent their accumulation. The selective removal of mitochondria, referred to as mitophagy, is part of the larger, evolutionarily conserved autophagy pathway.

2.1. Mitochondrial biogenesis

The generation of new mitochondria is attained through the coordinated expression of nuclear and mitochondrial DNA encoded genes (Figure 1). The process is orchestrated by members of the peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 (PGC-1) family of transcriptional co-activators, namely PGC-1α and PGC-1β (reviewed in [18]). Their interaction with several transcription factors [i.e., nuclear respiratory factors 1 and 2 (NRF1 and NRF2), estrogen-related receptor alpha (ERRα), and the PPAR family of transcription factors] regulates the expression of mitochondrial proteins, including mitochondrial transcription factor A (TFAM) and B2 (TFB2M) (reviewed in [18]). Once synthesized, TFAM and TFB2M are imported into the mitochondrion where they serve important housekeeping activities [18]. Specifically, TFAM binds to mitochondrial DNA (mtDNA) either as a histone-like protein that unwinds and bends mtDNA or to specific non-coding regions (NCRs) [19]. Dysregulation of TFAM binding to NCRs has been indicated as a potential mechanism underlying the impairment of mitochondrial biogenesis in aged rat tissues, including the skeletal muscle [20]. Recent evidence also indicates that TFAM binds more avidly to oxidized D-loop regions, the major site of transcriptional

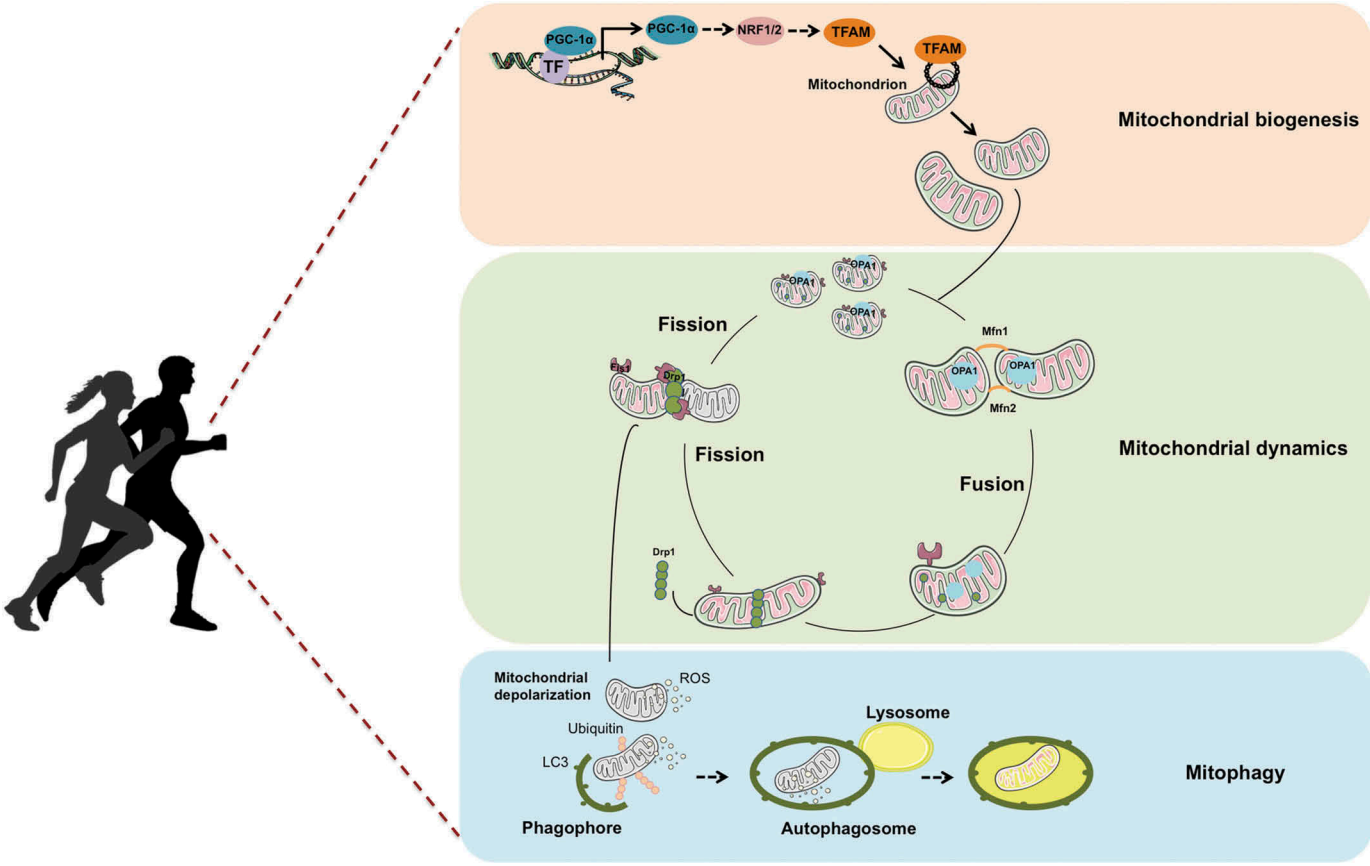

Figure 1. Mitochondrial quality control pathways elicited by physical exercise.

Mitochondrial biogenesis, dynamics, and autophagy cooperate to ensure mitochondrial homeostasis. Following exercise, the upregulation of peroxisome proliferator-activated receptor (PPAR) gamma coactivator-1 alpha (PGC1α) controls the expression of several transcription factors (TFs) which activates the transcription of nuclear genes encoding mitochondrial proteins, including mitochondrial transcription factor A (TFAM). TFAM is thereafter imported into mitochondria and binds to mitochondrial DNA (mtDNA). TFAM binding to mtDNA modulates its replication and transcription and ultimately mitochondriogenesis. Mitochondrial morphology and turnover rely on dynamic processes mediated by fusion [mitofusin 1 (MFN1), MFN2, and mitochondrial dynamin-like 120 kDa protein (OPA1)] and fission [dynamin 1-like protein (DNM1L) and mitochondrial fission 1 protein (FIS1)] proteins. Fusion facilitates the dilution of damaged mitochondrial components while fission targets mitochondria to their subsequent clearance. Finally, a specialized autophagic pathway, referred to as mitophagy, is in place to recycle organelle components. LC3, microtubule-associated proteins 1A/1B light chain 3; NRF1, nuclear respiratory factor 1; NRF2, nuclear respiratory factor 2; ROS, reactive oxygen species.

regulation, and contributes to impairing mitochondrial function in the aged heart [21]. Whether such a mechanism plays a role in the setting of muscle aging is yet to be established.

Substantial evidence exists linking PGC-1α signaling to muscle mass maintenance via its translocation from the cytosol to the nucleus [22] and mitochondria [23]. The nuclear control over mitochondrial protein synthesis is blunted in aged muscles, suggesting reduced mitochondriogenesis [24]. Indeed, lower levels of PGC-1α and its downstream targets have been reported in muscle of older persons [10]. Furthermore, the expression of PGC-1α in skeletal myocytes has been positively correlated with oxidative capacity and functional status in young and older adults [10]. Under muscle atrophying conditions such as denervation, unloading, type II diabetes, and aging, decreased abundance of PGC-1α mRNA has been detected (reviewed in [3]). Conversely, maintenance of PGC-1α expression preserves muscle mass during aging, hind limb suspension, cachexia, denervation, and fasting, through stimulating mitochondrial turnover [25]. PGC-1α also acts by inhibiting the signaling cascade triggered by Forkhead box O3a (FoxO3a), a potent transcriptional inducer of muscle atrophy [26], and nuclear factor κB (NF-κB), a major regulator of inflammation [27]. Blockade of these transcription factors, in turn, prevents the activation of proteolytic systems without affecting protein synthesis [28].

The muscle-protecting effects of PGC-1α have recently been confirmed in old mice genetically engineered to overexpress this transcriptional cofactor in skeletal muscle [29]. In this model, an increased expression of genes associated with energy metabolism and muscle integrity and regeneration was determined. These effects occurred without changes in mtDNA deletion levels [29].

Splice variants of PGC-1α have been identified in skeletal muscle. Truncated variants, NT-PGC-1α, are produced by alternative 3´ splicing of PGC-1α mRNA at exon 1a. Full-length and truncated PGC-1α variants are expressed in the same proportion in muscle [30]. In particular, the full-length isoforms (PGC-1α1, PGC-1α2, and PGC-1α3) promote mitochondrial biogenesis and oxidative phosphorylation [31], whereas NT-PGC-1α-b (also termed PGC-1α4) is involved in the regulation of muscle mass [32,33]. PGC-1α4 expression is upregulated following resistance exercise and its overexpression induces hypertrophy in murine muscles [32,33]. Moreover, PGC-1α4 overexpression counteracts muscle loss induced by hind limb suspension and during cachexia [33]. However, the relevance of PGC-1α4 to human muscle physiology is presently unclear.

Diet and exercise modulate PGC-1α activity through NAD^+-dependent deacetylases sirtuins (SIRTs). SIRT1 (cytosolic) and SIRT3 (mitochondrial) are the two isoforms mainly involved in muscle maintenance. The expression of SIRT3 is reduced in aged muscle, whilst it is induced by oxidative stress following endurance training in young and older adults [34]. Data from preclinical models indicate that SIRT3 is a downstream target of PGC-1α and is involved in modulating energy metabolism and ROS production [35]. Strategies targeting NAD^+ levels (i.e., nicotinamide riboside administration and calorie restriction) improve muscle health in old mice by reducing hypoxia-inducible factor 1α (HIF-1α) levels [36]. Moreover, boosting NAD^+ levels by poly (ADP-ribose) polymerase (PARP) inhibitors is protective against muscle dysfunction related to mitochondrial dyshomeostasis [37].

The aforementioned findings may explain the contribution of age-related PGC-1α deficits to muscle loss and, at the same time, suggest that this mediator represents a promising molecular target for the management of sarcopenia.

2.2. Mitochondrial dynamics

Mitochondrial fusion and fission in conjunction with mitophagy (mitochondrial autophagy) are essential for controlling organellar plasticity and disposal (Figure 1). Under oxidative stress, damaged mitochondria show reduced membrane potential and are selectively targeted for mitophagic removal by fission. Meanwhile, functional organelles continue to fuse and divide and allow for mixing mtDNA and metabolites along the network.

Electron microscopy analyses have shown aberrant mitochondria in several human and rodent tissues, including muscle [38], indicating that mitochondrial dynamics are altered during aging. Notably, morphological abnormalities of mitochondria are associated with changes in the expression of several mediators of mitochondrial dynamics, including mitofusin (Mfn) 1 and 2, optic atrophy protein 1 (Opa1), dynamin-related protein 1 (Drp1), and fission protein 1 (Fis1) [39–42]. Recently, a shift of dynamics signaling toward fission has been shown in old hip-fractured patients with sarcopenia [43]. It should be noted that fissioned mitochondria are less bioenergetically efficient, produce greater amounts of ROS, and are more prone to trigger myonuclear apoptosis [44,45]. In further support of the involvement of mitochondrial fragmentation in muscle atrophy, overexpression of Drp1 and Fis1 causes muscle wasting in mice [45]. Along similar lines, downregulation of fusion in myocytes has shown to induce muscle loss in murine models [46,47]. In contrast with the proposition that excessive mitochondrial fission is maladaptive, Rana et al. [48] found that promoting mitochondrial fission in middle-aged flies is beneficial to organismal health. Although a species-specific regulation of mitochondrial dynamics may not be ruled out, the existence of a life window in which upregulation of fission prevents the accumulation of dysfunctional organelles deserves further investigation.

Interestingly, downregulation of mitochondrial fusion in motor neurons has been found to be an early event during the development of amyotrophic lateral sclerosis in mice [49]. Furthermore, Mfn2 deficiency induces mitochondrial dysfunction and increases motor neuron vulnerability to glutamate excitotoxicity [50].

Though these findings point to the involvement of unbalanced mitochondrial dynamics in muscle aging, the extent to which these alterations contribute to sarcopenia is presently unclear. Further research is warranted to clarify the role of aberrant mitochondrial dynamics in muscle wasting and identify relevant target for interventions.

2.3. Ubiquitin-proteasome system and mitochondrial proteostasis

Mitoproteases are the first line of defense in response to mild mitochondrial damage [51]. The system is composed of

several proteases located in different organelle domains: mitochondrial matrix (i.e., soluble Lon and ClpP and the membrane-bound m-AAA) [52] and inter-membrane space [i.e., membrane-bound i-AAA Yme1L1, soluble HtrA2/Omi, the metallopeptidases OMA1, and the presenilins-associated rhomboid-like protein (PARL)] [51]. The level and activity of mitoproteases decline with aging [53,54], but the relevance of this phenomenon to myocyte mitochondrial dysfunction in the setting of sarcopenia is currently unknown.

The UPS is a catabolic pathway that, in conjunction with the autophagy-lysosome system, controls intracellular protein recycling under the modulation of 5′ AMP-activated protein kinase (AMPK) and the FoXO transcription factor family [45]. The expression of constitutively active FoXO3 has shown to induce atrophy of cultured myotubes and muscle wasting in mice by stimulating the transcription of the ubiquitin ligase atrogin-1 (MAFbx) [55,56,57]. In addition, FoXOs inhibit the muscle anabolic signaling of mammalian target of rapamycin complex 1 (MTORC1) [58]. Notably, inhibition of MTORC1 in muscles of tuberous sclerosis complex (TSC) knockout mice is associated with loss of muscle mass and strength and downregulation of mitophagy [59].

The control of UPS activity through FOXO seems to be especially relevant during the final steps of protein degradation. Indeed, FoXOs activate lysosomal cathepsins and cytosolic calpains leading to ATP-dependent UPS activation and Muscle RING-finger protein-1 (MuRF-1) and MAFbx upregulation [60]. However, whether alterations in FoXO-mediated control of MTORC1 signaling or a failure in the regulation of anabolic pathways trigger muscle protein breakdown during aging remains to be established. Conflicting results have been reported on the topic. Indeed, UPS mediators [61], 26S proteasome, polyubiquitinated proteins [62], MuRF-1, and MAFbx expression are all increased in hind limb muscles of sarcopenic rats as compared with younger counterparts [62,63]. Similarly, a higher expression of UPS components was found in the quadriceps muscles of old persons relative to younger adults [61]. However, other studies reported lower MuRF-1 and MAFbx expression in muscles of old rats [64] and no changes in the vastus lateralis of old humans [65]. Such discrepancies might be explained by differences in age, sex and lifestyle habits of the subjects under study as well as in the experimental settings and methods used to measure the expression and activity of MuRF-1 and MAFbx.

Mitochondrial protein turnover is also ensured by the cytosolic UPS under the control of several PGC-1α splice variants [66]. Stimulation of protein synthesis and downregulation of UPS activity via PGC-1α2, PGC-1α3, and PGC-1α4 have been shown in cultured myotubes and mouse skeletal muscle [33,67]. Furthermore, PGC-1α attenuates UPS-mediated muscle protein degradation by blocking NF-κB and FoXO3 activity [26,27]. An organelle stress-responsive system for protein degradation, the mitochondrial unfolded protein response (UPRmt), is also in place [68] and is composed mainly of AAA ATPase p97 and the cofactor Npl4 [69]. The expression of mitochondrial stress proteins (e.g., chaperonin 10 and 60, mtDnaJ, ClpP, Yme1) is induced under stress conditions to promote mitochondrial proteostasis [68]. However, if and to what extent UPRmt intervenes in muscle aging warrants further investigation.

2.4. Mitophagy

The term mitophagy refers to the selective removal of dysfunctional or unnecessary mitochondria through autophagy [5]. This organellar recycling process is especially relevant to muscle homeostasis given the high metabolic demand and limited regenerative capacity of skeletal myocytes [70]. As such, dysregulation of mitochondrial autophagy has been indicated as a major pathogenic mechanism of muscle wasting [2]. According to the garbage catastrophe theory of aging, the loss of efficiency of autophagy would result in the progressive accumulation of cellular ‘waste’, including protein aggregates, damaged mitochondria and lipofuscin, which further depresses autophagy [71]. This vicious circle eventually culminates in cell and tissue degeneration. As a proof of concept, genetic ablation of critical autophagy genes (i.e., Atg7) in mice has been shown to induce inflammation, decrease myofiber size and number (preferentially in fast-twitch fibers), impair muscle function, and shorten survival [72,73]. Conversely, Atg5 overexpression stimulates autophagy and attenuates several aging phenotypes, including myocyte mitochondrial dysfunction and muscle weakness, while extending lifespan in mice [74].

During aging, the autophagic flux is reduced in murine muscles [75]. Decreased protein levels of Atg7 and lipidated microtubule-associated protein 1 light chain 3 (LC3 II) were also found in muscle biopsies of sedentary older people [75], which was markedly attenuated in senior sportsmen [75]. In addition, lower LC3 expression has been detected in muscle samples from old hip-fractured patients with sarcopenia [43]. Yet, increased or unvaried expression of key autophagy markers has been reported in muscles of aged rodents and humans [42,44,45,76,77]. When interpreting these findings, it should be considered that measurements of protein expression of autophagy mediators only provides a snapshot of a highly dynamic process [78,79]. Therefore, the implementation of new methodologies allowing for accurate analysis of autophagic flux are highly sought after to obtain more conclusive information on the actual involvement of dysfunctional autophagy in sarcopenia [78,79].

3. Conclusion

Accumulating evidence indicates that an efficient MQC is crucial for maintaining myocyte homeostasis. Indeed, derangements at various critical MQC checkpoints underpin mitochondrial dysfunction and muscle wasting during aging. Noticeably, engagement in regular exercise, either aerobic or resistance, prevents or even reverses the age-associated impairment of MQC. This, in turn, contributes to fostering mitochondrial function and muscle health in old age.

However, interpreting the outcome of changes in protein expression of MQC mediators during aging and in response to exercise is challenging. Important limitations exist in the tools available for monitoring these processes in vivo, especially in humans. Therefore, the development of new strategies and experimental settings allowing for visualization of mitochondria in living cells, together with novel biochemical

approaches, is necessary to achieve a more comprehensive understanding of MQC functioning.

4. Expert opinion

Growing evidence indicates that derangements in MQC are involved in age- and disease-associated muscle wasting. Hence, MQC has been proposed as a promising target for developing novel therapeutic interventions against sarcopenia. As of now, physical exercise is the only strategy that has consistently shown to promote muscle health, even in very old, frail people [80]. Interestingly, this intervention acts as a powerful modulator of MQC. Both aerobic and resistance training ameliorates mitochondrial function and stimulates mitochondriogenesis in muscle [81]. It should however be considered that enhanced mitochondriogenesis does not necessarily translate into a gain of function, unless the number of damaged organelles is proportionally reduced. Indeed, mitochondria carrying deleted mtDNA can proliferate by virtue of a replicative advantage over those harboring wild-type molecules [82]. This may be avoided if a fully working MQC axis is in place. Although the whole spectrum of mitochondrial adaptations elicited by chronic exercise has not yet been disentangled, evidence has accumulated indicating that this intervention acts at several MQC checkpoints beyond mitochondrial biogenesis [83,84]. Recently, a PGC-1α-p53 axis has been shown to regulate apoptosis, autophagy, and mitophagy in murine and human muscles [85]. It is hypothesized that dysfunctional PGC-1α-p53 signaling may be involved in the pathogenesis of sarcopenia. Interestingly, age-related derangements of the PGC-1α-p53 axis are prevented by life-long exercise training [85]. Another recent study showed that, in muscles of old mice, while basal mitophagy was enhanced, it did not increase following acute exercise compared with younger controls [86]. These findings suggest that upregulation of mitophagy may be an additional means through which exercise promotes muscle health and that this adaption might be blunted during aging.

The mammalian target of rapamycin (mTOR) is another major signaling pathway modulated by exercise, though the outcome is different depending on the training modality [87]. The activity of mTOR is finely tuned by two energy sensors, the insulin-RACα serine/threonine protein kinase (Akt) and AMPK [88]. Following a single bout of resistance exercise, Akt is transiently activated, resulting in Rheb-mediated activation of mTOR [89]. The latter, in turn, promotes muscle growth by suppressing autophagy and stimulating protein synthesis [87]. The signaling cascade initiated by Akt does not seem to be active during endurance training [90]. Under this training modality, mTOR activity is suppressed by AMPK which also phosphorylates FoXO3, thereby upregulating autophagy and the UPS [91–93]. These adaptations may serve to mobilize muscle protein as a source of energy. At same time, stimulation of mitochondrial autophagy is necessary to clear exercise-induced organellar damage [94]. Replenishment of the mitochondrial pool is ensured by the concomitant AMPK-mediated upregulation of PGC-1α [93].

Stimulation of mitophagy by exercise may be particularly beneficial in the aged muscle, as it may counteract the accrual of mitochondrial damage. Notably, the mRNA abundance of LC3-II, Atg7 and lysosome-associated membrane protein 2 (LAMP-2) was increased in the vastus lateralis muscle of old overweight women following a 6-month weight-loss plus moderate intensity exercise program [77]. Moreover, life-long exercise (regular exercise in the past 30 years) was found to maintain the expression of LC3-II and Atg7 in muscle of older adults to levels similar as those of young controls [75]. Similar adaptations have been observed in the plantaris muscle of old rats on life-long exercise and mild calorie restriction [94]. It is noteworthy that stimulation of autophagy was accompanied by reduced levels of myonuclear apoptosis.

Taken as a whole, these findings suggest that the fine tuning of MQC is a major mechanism whereby physical exercise conveys its beneficial effects on skeletal muscle [81]. A deeper understanding of the molecular changes occurring in the aged muscle following exercise and how they impact mitochondrial homeostasis is necessary to identify relevant target for drug development.

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Declaration of interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Landi F, Calvani R, Cesari M, et al. Sarcopenia: an overview on current definitions, diagnosis and treatment. Curr Protein Pept Sci. 2018 May;19:633–638. PubMed: 28595526.
2. Marzetti E, Calvani R, Cesari M, et al. Mitochondrial dysfunction and sarcopenia of aging: from signaling pathways to clinical trials. Int J Biochem Cell Biol. 2013 Oct;45:2288–2291. PubMed: 23845738.
   • **Comprehensive review on mitochondrial alterations in muscle wasting with insightful considerations for developing clinical trials targeting mitochondrial dysfunction to treat sarcopenia.**
3. Picca A, Calvani R, Bossola M, et al. Update on mitochondria and muscle aging: all wrong roads lead to sarcopenia. Biol Chem. 2018 Apr;399:421–426. PubMed: 29384724.
4. Romanello V, Sandri M. Mitochondrial quality control and muscle mass maintenance. Front Physiol. 2016 Jan 12;6:422. PubMed: 26793123.
5. Nunnari J, Suomalainen A. Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148:1145–1149. PubMed: 22424226.

6. Calvani R, Joseph AM, Adhihetty PJ, et al. Mitochondrial pathways in sarcopenia of aging and disuse muscle atrophy. Biol Chem. 2013 Mar;394:393–414. PubMed: 23154422.
7. Pesce V, Cormio A, Fracasso F, et al. Age-related changes of mitochondrial DNA content and mitochondrial genotypic and phenotypic alterations in rat hind-limb skeletal muscles. J Gerontol A Biol Sci Med Sci. 2005 Jun;60:715–723. PubMed: 15983173.
8. Alway SE, Mohamed JS, Myers MJ. Mitochondria initiate and regulate sarcopenia. PubMed: 28098577. Exerc Sport Sci Rev. 2017 Apr;45:58–69
9. Picard M, Ritchie D, Thomas MM, et al. Alterations in intrinsic mitochondrial function with aging are fiber type-specific and do not explain differential atrophy between muscles. Aging Cell. 2011 Dec;10:1047–1055. PubMed: 21933339.
10. Joseph AM, Adhihetty PJ, Buford TW, et al. The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals. Aging Cell. 2012 Oct;11:801–809. PubMed: 22681576.
11. St-Jean-Pelletier F, Pion CH, Leduc-Gaudet JP, et al. The impact of ageing, physical activity, and pre-frailty on skeletal muscle phenotype, mitochondrial content, and intramyocellular lipids in men. J Cachexia Sarcopenia Muscle. 2017 Apr;8:213–228. PubMed: 27897402.
12. Willingham TB, McCully KK. *In vivo* assessment of mitochondrial dysfunction in clinical populations using near-infrared spectroscopy. PubMed: 28959210. Front Physiol. 2017 Sep;8:689
13. Landi F, Calvani R, Tosato M, et al. Animal-derived protein consumption is associated with muscle mass and strength in community-dwellers: results from the Milan EXPO survey. J Nutr Health Aging. 2017;21(Sep):1050–1056. PubMed: 29083447.
14. Landi F, Calvani R, Picca A, et al. Impact of habitual physical activity and type of exercise on physical performance across ages in community-living people. PLoS One. 2018;13(Jan):e0191820. PubMed: 29370306.
15. Dodds RM, Davies K, Granic A, et al. Mitochondrial respiratory chain function and content are preserved in the skeletal muscle of active very old men and women. Exp Gerontol. 2018 Nov;113:80–85. PubMed: 30266472.
16. Konopka AR, Suer MK, Wolff CA, et al. Markers of human skeletal muscle mitochondrial biogenesis and quality control: effects of age and aerobic exercise training. PubMed: 23873965. J Gerontol A Biol Sci Med Sci. 2014 Apr;69:371–378
17. Twig G, Hyde B, Shirihai OS, Mitochondrial fusion, fission and autophagy as a quality control axis: the bioenergetic view. PubMed: 18519024. Biochim Biophys Acta 2008 Sep;1777:1092–1097.

•• **Excellent review on the integration of mitochondrial dynamics and autophagy in organelle quality control.**

18. Picca A, Lezza A. Regulation of mitochondrial biogenesis through TFAM-mitochondrial DNA interactions: useful insights from aging and calorie restriction studies. PubMed: 26437364. Mitochondrion. 2015 Nov;25:67–75
19. Ohgaki K, Kanki T, Fukuoh A, et al. The C-terminal tail of mitochondrial transcription factor a markedly strengthens its general binding to DNA. J Biochem. 2007 Feb;141:201–211. PubMed: 17167045.
20. Picca A, Pesce V, Fracasso F, et al. A comparison among the tissue-specific effects of aging and calorie restriction on TFAM amount and TFAM-binding activity to mtDNA in rat. Biochim Biophys Acta. 2014 Jul;1840:2184–2191. PubMed: 24631828.
21. Chimienti G, Picca A, Sirago G, et al. Increased TFAM binding to mtDNA damage hot spots is associated with mtDNA loss in aged rat heart. Free Radic Biol Med. 2018 Aug;124:447–453. PubMed: 29969715.

•• **The study describes the relationship between mtDNA damage and TFAM binding to specific regions of the mitochodrial genome in the heart of old rats.**

22. Wright DC, Han D-H, Garcia-Roves PM, et al. Exercise-induced mitochondrial biogenesis begins before the increase in muscle PGC-1alpha expression. J Biol Chem. 2007 Jan 5;282:194–199. PubMed: 17099248.
23. Safdar A, Saleem A, Tarnopolsky M. The potential of endurance exercise-derived exosomes to treat metabolic diseases. Nat Rev Endocrinol. 2016;12(Sep):504–517. PubMed: 27230949.

•• **Excellent perspective discussing how the release of extracellular vesicles following endurance exercise may be exploited to treat metabolic diseases.**

24. Ljubicic V, Joseph A-M, Adhihetty PJ, et al. Molecular basis for an attenuated mitochondrial adaptive plasticity in aged skeletal muscle. Aging (Albany NY). 2009 Sep;1:818–830. PubMed: 20157569.
25. Cannavino J, Brocca L, Sandri M, et al. The role of alterations in mitochondrial dynamics and PGC-1α over-expression in fast muscle atrophy following hindlimb unloading. J Physiol. 2015 Apr;593:1981–1995. PubMed: 25565653.
26. Sandri M, Lin J, Handschin C, et al. PGC-1alpha protects skeletal muscle from atrophy by suppressing FoxO3 action and atrophy-specific gene transcription. Proc Natl Acad Sci U S A. 2006 Oct;103:16260–16265. PubMed: 17053067.
27. Brault JJ, Jespersen JG, Goldberg AL. Peroxisome proliferator-activated receptor gamma coactivator 1alpha or 1beta overexpression inhibits muscle protein degradation, induction of ubiquitin ligases, and disuse atrophy. PubMed: 20404331. J Biol Chem. 2010 Jun;285:19460–19471
28. Romanello V, Sandri M. Mitochondrial quality control and muscle mass maintenance. PubMed: 26793123. Front Physiol. 2015 Jan;6:422
29. Garcia S, Nissanka N, Mareco EA, et al. Overexpression of PGC-1α in aging muscle enhances a subset of young-like molecular patterns. Aging Cell. 2018 Apr;17:E12707. PubMed: 29427317.
30. Zhang Y, Huypens P, Adamson AW, et al. Alternative mRNA splicing produces a novel biologically active short isoform of PGC-1alpha. J Biol Chem. 2009 Nov;284:32813–32826. PubMed: 19773550.
31. Millay DP, Olson EN. Making muscle or mitochondria by selective splicing of PGC-1α. PubMed: 23312277. Cell Metab. 2013 Jan;17:3–4
32. Silvennoinen M, Ahtiainen JP, Hulmi JJ, et al. PGC-1 isoforms and their target genes are expressed differently in human skeletal muscle following resistance and endurance exercise. Physiol Rep. 2015 Oct;3:E12563. PubMed: 26438733.
33. Ruas JL, White JP, Rao RR, et al. A PGC-1α isoform induced by resistance training regulates skeletal muscle hypertrophy. Cell. 2012 Dec;151:1319–1331. PubMed: 23217713.

• **First study showing that the expression of PGC-1α4 induced by resistance training coordinates factors involved in skeletal muscle hypertrophy.**

34. Lanza IR, Short DK, Short KR, et al. Endurance exercise as a countermeasure for aging. Diabetes. 2008 Nov;57:2933–2942. PubMed: 18716044.
35. Kong X, Wang R, Xue Y, et al. Sirtuin 3, a new target of PGC-1alpha, plays an important role in the suppression of ROS and mitochondrial biogenesis. PLoS One. 2010 Jul;5:e11707. PubMed: 20661474.
36. Gomes AP, Price NL, Ling A, et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. 2013 Dec;155:1624–1638. PubMed: 24360282.
37. Pirinen E, Cantó C, Jo YS, et al. Pharmacological inhibition of poly (ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. Cell Metab. 2014 Jun;19:1034–1041. PubMed: 24814482.
38. Sebastián D, Sorianello E, Segalés J, et al. Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. Embo J. 2016 Aug;35:1677–1693. PubMed: 27334614.
39. Picca A, Lezza A, Leeuwenburgh C, et al. Fueling inflamm-aging through mitochondrial dysfunction: mechanisms and molecular targets. Int J Mol Sci. 2017 Apr;18:933. PubMed: 28452964.
40. Picca A, Calvani R, Lorenzi M, et al. Mitochondrial dynamics signaling is shifted toward fusion in muscles of very old hip-fractured patients: results from the Sarcopenia in HIp FracTure (SHIFT) exploratory study. Exp Gerontol. 2017 Oct;96:63–67. PubMed: 28602957.
41. Gomes LC, Scorrano L. High levels of Fis1, a pro-fission mitochondrial protein, trigger autophagy. PubMed: 18515060. Biochim Biophys Acta. 2008 Jul;1777:860–866

42. Joseph A-M, Adhihetty PJ, Wawrzyniak NR, et al. Dysregulation of mitochondrial quality control processes contribute to sarcopenia in a mouse model of premature aging. PLoS One. 2013;8(Jul):e69327. PubMed: 23935986.
43. Marzetti E, Calvani R, Lorenzi M, et al. Association between myocyte quality control signaling and sarcopenia in old hip-fractured patients: results from the sarcopenia in HIp FracTure (SHIFT) exploratory study. Exp Gerontol. 2016 Jul;80:1–5. PubMed: 27064052.
44. Iqbal S, Ostojic O, Singh K, et al. Expression of mitochondrial fission and fusion regulatory proteins in skeletal muscle during chronic use and disuse. Muscle Nerve. 2013 Dec;48:963–970. PubMed: 23494933.
45. Romanello V, Guadagnin E, Gomes L, et al. Mitochondrial fission and remodelling contributes to muscle atrophy. Embo J. 2010 May;29:1774–1785. PubMed: 20400940.
•• **The study describes the mechanisms whereby mitochondrial hyperfission induces muscle atrophy in rodents.**
46. Tezze C, Romanello V, Desbats MA, et al. Age-associated loss of OPA1 in muscle impacts muscle mass, metabolic homeostasis, systemic inflammation, and epithelial senescence. Cell Metab. 2017 Jun;25:1374–1389. PubMed: 28552492.
• **The study reports the deleterious effects of defective mitochondrial fusion on muscle mass, systemic inflammation, and cell senescence.**
47. Chen H, Vermulst M, Wang YE, et al. Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. Cell. 2010 Apr;141:280–289. PubMed: 20403324.
48. Rana A, Oliveira MP, Khamoui AV, et al. Promoting Drp1-mediated mitochondrial fission in midlife prolongs healthy lifespan of Drosophila melanogaster. Nat Commun. 2017 Sep;8:448. PubMed: 28878259.
49. Liu W, Yamashita T, Tian F, et al. Mitochondrial fusion and fission proteins expression dynamically change in a murine model of amyotrophic lateral sclerosis. Curr Neurovasc Res. 2013 Aug;10:222–230. PubMed: 23713734.
50. Wang W, Zhang F, Li L, et al. MFN2 couples glutamate excitotoxicity and mitochondrial dysfunction in motor neurons. J Biol Chem. 2015 Jan;290:168–182. PubMed: 25416777.
51. Quirós PM, Langer T, López-Otín C. New roles for mitochondrial proteases in health, ageing and disease. PubMed: 25970558. Nat Rev Mol Cell Biol. 2015 Jun;16:345–359
52. Voos W. Chaperone-protease networks in mitochondrial protein homeostasis. PubMed: 22705353. Biochim Biophys Acta. 2013 Feb;1833:388–399
53. Ngo JK, Davies K. Importance of the lon protease in mitochondrial maintenance and the significance of declining lon in aging. PubMed: 18056957. Ann N Y Acad Sci. 2007 Nov;1119:78–87
54. Ngo JK, Pomatto L, Davies K. Upregulation of the mitochondrial lon protease allows adaptation to acute oxidative stress but dysregulation is associated with chronic stress, disease, and aging. PubMed: 24024159. Redox Biol. 2013 Feb;1:258–264
55. Sandri M, Sandri C, Gilbert A, et al. Foxo transcription factors induce the atrophy-related ubiquitin ligase atrogin-1 and cause skeletal muscle atrophy. PubMed: 15109499. Cell. 2004 Apr;117:399-412.
56. Tang H, Inoki K, Lee M, et al. mTORC1 promotes denervation-induced muscle atrophy through a mechanism involving the activation of FoxO and E3 ubiquitin ligases. PubMed: 24570486. Sci Signal. 2014 Feb;7:ra18.
57. Castets P, Rüegg MA. MTORC1 determines autophagy through ULK1 regulation in skeletal muscle. PubMed: 23896646. Autophagy. 2013 Sep;9:1435–1437
58. Rom O, Reznick AZ. The role of E3 ubiquitin-ligases MuRF-1 and MAFbx in loss of skeletal muscle mass. PubMed: 26738803. Free Radic Biol Med. 2016 Sep;98:218–230
59. Cai D, Kkh L, Li M, et al. Ubiquitin expression is up-regulated in human and rat skeletal muscles during aging. Arch Biochem Biophys. 2004 May;425:42–50. PubMed: 15081892.
60. Altun M, Besche HC, Overkleeft HS, et al. Muscle wasting in aged, sarcopenic rats is associated with enhanced activity of the ubiquitin proteasome pathway. J Biol Chem. 2010 Dec;285:39597–39608. PubMed: 20940294.
61. Clavel S, Coldefy A-S, Kurkdjian E, et al. Atrophy-related ubiquitin ligases, atrogin-1 and MuRF1 are up-regulated in aged rat tibialis anterior muscle. Mech Ageing Dev. 2006 Oct;127:794–801. PubMed: 16949134.
62. Edström E, Altun M, Hägglund M, et al. Atrogin-1/MAFbx and MuRF1 are downregulated in aging-related loss of skeletal muscle. J Gerontol A Biol Sci Med Sci. 2006 Jul;61:663–674. PubMed: 16870627.
63. Whitman SA, Wacker MJ, Richmond SR, et al. Contributions of the ubiquitin-proteasome pathway and apoptosis to human skeletal muscle wasting with age. Pflugers Arch. 2005 Sep;450:437–446. PubMed: 15952031.
64. Jeon HB, Choi ES, Yoon JH, et al. A proteomics approach to identify the ubiquitinated proteins in mouse heart. Biochem Biophys Res Commun. 2007 Jun;357:731–736. PubMed: 17451654.
65. Martínez-Redondo V, Jannig PR, Correia JC, et al. Peroxisome proliferator-activated receptor γ coactivator-1 α isoforms selectively regulate multiple splicing events on target genes. J Biol Chem. 2016 Jul;291:15169–15184. PubMed: 27231350.
66. Zhao Q, Wang J, Levichkin IV, et al. A mitochondrial specific stress response in mammalian cells. Embo J. 2002 Sep;21:4411–4419. PubMed: 12198143.
67. Heo J-M, Livnat-Levanon N, Taylor EB, et al. A stress-responsive system for mitochondrial protein degradation. Mol Cell. 2010 Nov;40:465–480. PubMed: 21070972.
68. Drake JC, Yan Z. Mitophagy in maintaining skeletal muscle mitochondrial proteostasis and metabolic health with ageing. PubMed: 28795394. J Physiol. 2017 Oct;595:6391–6399
69. Terman A, Kurz T, Navratil M, et al. Mitochondrial turnover and aging of long-lived postmitotic cells: the mitochondrial-lysosomal axis theory of aging. PubMed: 19650712. Antioxid Redox Signal. 2010 Apr;12:503–535
70. Masiero E, Agatea L, Mammucari C, et al. Autophagy is required to maintain muscle mass. Cell Metab. 2009 Dec;10:507–515. PubMed: 19945408.
71. Masiero E, Sandri M. Autophagy inhibition induces atrophy and myopathy in adult skeletal muscles. PubMed: 20104028. Autophagy. 2010 Feb;6:307–309
72. Pyo JO, Yoo SM, Ahn HH, et al. Overexpression of Atg5 in mice activates autophagy and extends lifespan. Nat Commun. 2013;4:2300, PubMed: 23939249
73. Carnio S, LoVerso F, Baraibar MA, et al. Autophagy impairment in muscle induces neuromuscular junction degeneration and precocious aging. Cell Rep. 2014 Sep;8:1509–1521. PubMed: 25176656.
74. O'Leary M, Vainshtein A, Iqbal S, et al. Adaptive plasticity of autophagic proteins to denervation in aging skeletal muscle. Am J Physiol Cell Physiol. 2013 Mar;304:C422–30. PubMed: 23220115.
75. Wohlgemuth SE, Lees HA, Marzetti E, et al. An exploratory analysis of the effects of a weight loss plus exercise program on cellular quality control mechanisms in older overweight women. Rejuvenation Res. 2011;14:315–324, PubMed: 21631380
76. Klionsky DJ, Abdelmohsen K, Abe A, et al. Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). Autophagy. 2016 Jan;12:1–222. PubMed: 26799652.
77. Yoshii SR, Mizushima N. Monitoring and measuring autophagy. Int J Mol Sci. 2017 Aug 28;18:1865. PubMed: 28846632.
78. Fiatarone MA, Marks EC, Ryan ND, et al. High-intensity strength training in nonagenarians. effects on skeletal muscle. JAMA. 1990 Jun;263:3029–3034. PubMed: 2342214.
79. Groennebaek T, Vissing K. Impact of resistance training on skeletal muscle mitochondrial biogenesis, content, and function. PubMed: 28966596. Front Physiol. 2017 Sep;8:713
80. Russell OM, Fruh I, Rai PK, et al. Preferential amplification of a human mitochondrial DNA deletion in vitro and in vivo. Sci Rep. 2018;8(Jan):1799. PubMed: 29379065.
81. Kim Y, Triolo M, Hood DA. Impact of aging and exercise on mitochondrial quality control in skeletal muscle. Oxid Med Cell Longev. 2017;2017: 3165396. PubMed: 28656072.

82. Carter HN, Kim Y, Erlich AT, et al. and mitophagy flux in young and aged skeletal muscle following chronic contractile activity. J Physiol. 2018 Aug;596:3567–3584. PubMed: 29781176.
83. Dethlefsen MM, Halling JF, Møller HD, et al. Regulation of apoptosis and autophagy in mouse and human skeletal muscle with aging and lifelong exercise training. Exp Gerontol. 2018 Oct;111:141–153. PubMed: 30030137.
84. Chen CCW, Erlich AT, Crilly MJ, et al. Parkin is required for exercise-induced mitophagy in muscle: impact of aging. Am J Physiol Endocrinol Metab. 2018 Sep;315:E404–15. PubMed: 29812989.
85. Sanchez AM, Bernardi H, Py G, et al. Autophagy is essential to support skeletal muscle plasticity in response to endurance exercise. Am J Physiol Regul Integr Comp Physiol. 2014 Oct;307:R956–69. PubMed: 25121614.
•• **Comprehensive review illustrating the differential modulation of cellular quality control pathways in muscle by specific exercise modalities.**
86. Jung CH, Ro SH, Cao J, et al. mTOR regulation of autophagy. FEBS Lett. 2010 Apr;584:1287–1295. PubMed: 20083114.
87. Song Z, Moore DR, Hodson N, et al. Resistance exercise initiates mechanistic target of rapamycin (mTOR) translocation and protein complex co-localisation in human skeletal muscle. Sci Rep. 2017 Jul;7:5028. PubMed: 28694500.
88. Atherton PJ, Babraj J, Smith K, et al. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. FASEB J. 2005 May;19:786–788. PubMed: 15716393.
89. Sanchez A, Csibi A, Raibon A, et al. AMPK promotes skeletal muscle autophagy through activation of forkhead FoxO3a and interaction with Ulk1. J Cell Biochem. 2012 Feb;113:695–710. PubMed: 22006269.
90. Zhao J, Brault JJ, Schild A, et al. Coordinate activation of autophagy and the proteasome pathway by FoxO transcription factor. Autophagy. 2008 Apr;4:378–380. PubMed: 18227643.
91. Jamart C, Francaux M, Gy M, et al. Modulation of autophagy and ubiquitin-proteasome pathways during ultra-endurance running. J Appl Physiol (1985). 2012 May;112:1529–1537. PubMed: 22345427.
92. Laker RC, Drake JC, Wilson RJ, et al. Ampk phosphorylation of Ulk1 is required for targeting of mitochondria to lysosomes in exercise-induced mitophagy. Nat Commun. 2017 Sep;8:548. PubMed: 28916822.
93. Jäger S, Handschin C, St-Pierre J, et al. AMP-activated protein kinase (AMPK) action in skeletal muscle via direct phosphorylation of PGC-1alpha. Proc Natl Acad Sci U S A. 2007 Jul;104:12017–12022. PubMed: 17609368.
94. Wohlgemuth SE, Seo AY, Marzetti E, et al. Skeletal muscle autophagy and apoptosis during aging: effects of calorie restriction and life-long exercise. Exp Gerontol. 2010 Feb;45:138–148. PubMed: 19903516.