

REVIEW

Mitochondrial Adaptations in Aged Skeletal Muscle: Effect of Exercise Training

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Summary

The aging process is associated with a decline in mitochondrial functions. Mitochondria dysfunction is involved in initiation and progression of many health problems including neuromuscular, metabolic and cardiovascular diseases. It is well known that endurance exercise improves mitochondrial function, especially in the elderly. However, recent studies have demonstrated that resistance training lead also to substantial increases in mitochondrial function in skeletal muscle. A comprehensive understanding of the cellular mechanisms involved in the skeletal muscle mitochondrial adaptations to exercise training in healthy elderly subjects, can help practitioners to design and prescribe more effective exercise trainings.

Key words

Mitochondrial dysfunction • Aging • Exercise training

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Introduction

Aging is an intricate phenomenon characterized by progressive decline in physiological functions and increase in mortality that is often accompanied by many pathological diseases (Cui *et al.* 2012). Mitochondrial dysfunction is heavily implicated in the ageing process (Trifunovic and Larsson 2008). Many studies have demonstrated that a disruption of mitochondrial integrity leads to the initiation and progression of many

health problems including neuromuscular (Jones *et al.* 2003, Wallace 1989), metabolic (Lowell and Shulman 2005, Saxena *et al.* 2006) and cardiovascular diseases (Hall *et al.* 2014, Mercer 2014). Mitochondria are intracellular organelles whose main duty is to provide cellular energy requirements (Verdin *et al.* 2010). Mitochondrion contain a double membrane layer and hundreds of protein and 2-10 copies of mitochondrial DNA (mtDNA) are surrounded in matrix by the mitochondrial inner layer (Lee and Wei 2005). Although the mitochondrion has its own genome, it codes just 13 mitochondrial proteins, hence mitochondrial biogenesis arises from a coordinated regulation of nuclear and mitochondrial genes (Goffart and Wiesner 2003). In addition to ATP synthesis, mitochondria are involved in pyrimidines and hemes biosynthesis (Atamna 2004, Sherman 2008), apoptosis (Estaquier *et al.* 2012, Wang and Youle 2009) as well as transcription, translation and replication of mtDNA (Clayton 2000). Mitochondrial network is also a major source of reactive oxygen species (ROS) (Murphy 2009). Reduced mitochondrial function as a result of aging in skeletal muscle (Hebert *et al.* 2010, Picard *et al.* 2011, Sahin and Depinho 2010) could support the claim that mitochondria play a critical role in the survival of the cells.

It is well recognized that acute and chronic of endurance training (ET) (Holloszy and Coyle 1984, Holloszy *et al.* 1970, Willis and Jackman 1994, Wright *et al.* 2007b) and resistance training (RT) (Shepherd *et al.* 2014, Wang *et al.* 2011) have effects on mitochondrial function in young and adults subjects.

Despite a large body of literature on many aspects of the role of exercise training and mitochondria on different tissues such as heart, kidney and liver and also age related pathologic condition and diseases such as neuromuscular (Abresch *et al.* 2012, Nardin and Johns 2001), metabolic (Newman *et al.* 2012, Tjonna *et al.* 2008) and cardiovascular (Jenkins *et al.* 2012, Lesnefsky *et al.* 2001) disease, little is known about the impact of exercise training on skeletal muscle mitochondrial (SM-mito) adaptations in healthy aged mammalian cells.

In this article, first we will have a short overview on mitochondrial function. Then mitochondrial changes in healthy aged subjects will be discussed and finally we will review studies in relation with the effect of exercise training on SM-mito in the elderly. This review solely concerns studies that have investigated the influence of exercise training on SM-mito responses in healthy elderly subjects including humans and animals.

A brief overview of mitochondria function

Mechanism controlling mitochondria dynamic

Mitochondrial function is dependent on a number of factors including mitochondrial biogenesis and mitochondrial dynamics (Shabrokh *et al.* 2014). Mitochondria are highly dynamic organelles (Westermann 2012) and are recognized as important constituents of cellular quality control (Westermann 2010). This dynamic behavior of mitochondria includes mitochondrial fission and fusion: the two events controlling mitochondrial shape, size, and number (Scott and Logan 2011). Fusion involves the mixing of mitochondrial material, whereas fission divides the organelle into smaller components (Iqbal and Hood 2014). In mammalian cells, three large GTPases are important for mitochondrial fusion, which requires the coordinated fusion of the outer and inner membranes. The mitofusins, Mfn1 and Mfn2, are located on the mitochondrial outer membrane and are involved in early steps in membrane fusion. The dynamin-related protein OPA1 is associated with the inner membrane and is essential for inner membrane fusion (Chen *et al.* 2010). The opposing process of mitochondrial fission depends on the dynamin-related protein Drp1 (Chan 2006). The fusion process requires three steps: docking, mitochondria outer membrane (MOM) fusion and mitochondria inner membrane (MIM) fusion. Mfn1 and Mfn2 are thought to play an important role in docking

and MOM fusion. Optic atrophy 1 (Opa1) seems to be involved in the formation of cristae junctions as well as in MIM fusion, which occurs in a GTP-dependent manner. Mitochondrial fission 1 (Fis1) is a MOM protein and is thought to recruit Drp1 to the MOM by means of adaptor proteins (Seo *et al.* 2010). Upon stimulation, Drp1 is activated and translocates to the scission sites of OMM through interaction with Fis1, where they oligomerize and form spirals to constrict OMM through GTP hydrolysis, resulting in mitochondrial fission (Zhan *et al.* 2013) (Fig. 1A).

Mechanism controlling mitochondria biogenesis

Mitochondrial biogenesis is a key physiological process that is required for normal growth and development and for maintenance of ongoing cellular energy requirements during aging (Stefano *et al.* 2012). Mitochondrial biogenesis is now recognized as a vital and exciting area of cell biology and can be defined as the growth and division of pre-existing mitochondria (Jornayvaz and Shulman 2010, Joseph *et al.* 2006). Mitochondrial biogenesis is a highly regulated process that requires a close coordination between both nuclear and mitochondrial gene expression and recruitment or import of new mitochondrial proteins into preexisting mitochondrial compartments (Sharma *et al.* 2014, Wright *et al.* 2008). Controlling the biogenesis of mitochondria and the maintenance of mtDNA is a complex biological process (Lee and Wei 2005). It involves changes in the expression of more than 1,000 genes, the cooperation of two genomes, and alters the level of approximately 20 % of cellular proteins (Lopez-Lluch *et al.* 2008). At the molecular level, several transcription factors and cofactors are involved in the activation and regulation of mitochondrial biogenesis (Lopez-Lluch *et al.* 2008). Expression of genes promoting mitochondrial biogenesis is predominantly controlled by the global principles of gene regulation, that is, transcription initiation and interaction at the gene promoter. Therefore, transcription factors and transcriptional coactivators represent critical regulators of mitochondrial biogenesis (Hawley 2009). Transcription factors involved in this process are mitochondrial transcription factor A (TFAM), nuclear respiratory factors (Nrf1, Nrf2), cyclic AMP-activated protein kinase (AMPK), peroxisome proliferator-activated receptors (PPARs) and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1 α) (Bori *et al.* 2012) (Fig. 1B).

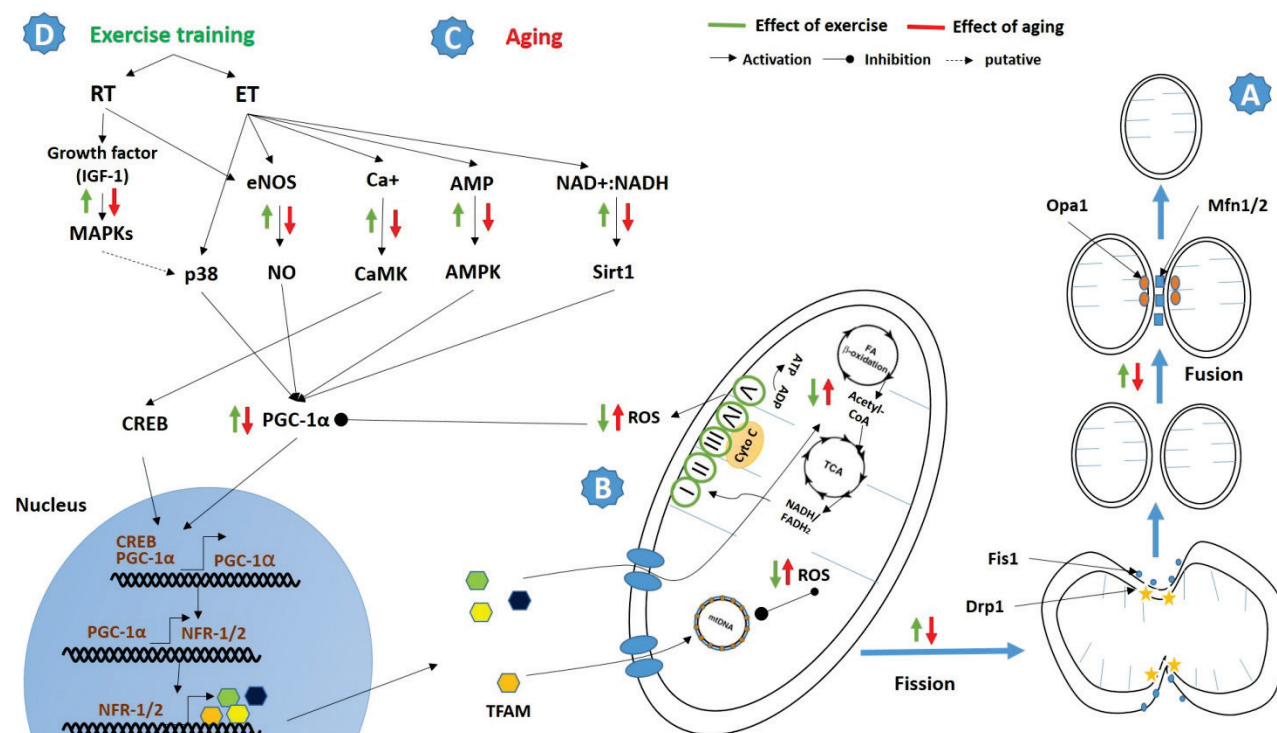


Fig. 1. Diagrammatic summary of the interaction between aging and exercise training and its effect on mitochondria function in healthy mammalian skeletal muscle cell. **(A)** Fission and fusion. Fis1 is localized uniformly to the mitochondrial outer membrane, whereas Drp1 is localized to the cytosol and associates with Fis1, forming an oligomeric ring-like structure leading to separation of the mitochondria. Fusion is regulated by Mfn1 and Mfn2 isoforms in the outer mitochondrial membrane and by OPA1 protein in the inner mitochondrial membrane. **(B)** Mitochondria biogenesis. PGC-1 α is known as a master regulator of mitochondria biogenesis which its gene expression is mediated by other factors such as AMPK, Sirt1, CaMK, NO and p38. PGC-1 α gene expression along with the expression of NRF-1 and NRF-2 induce the expression of TFAM, which is imported into mitochondria. TFAM regulates the expression of the mtDNA gene products, including proteins such as cytochrome c oxidase subunit I (COX I) and also is involved in ATP synthesis. **(C)** Aging reduced mitochondria function by several ways. Increasing ROS accumulation in cytosol due to an increased O₂ leaking from ETC decreases PGC-1 α activity. Also, increased ROS level inside mitochondria leads to mtDNA mutation and consequently negative effects on mitochondria dynamic and efficiency. Aging is also along with a decrease in PGC-1 α upstream signaling pathways such as the levels of eNOS, Ca²⁺, AMP:ATP and NAD⁺:NADH as well as decreased growth factor levels like IGF-1. **(D)** Both types of ET and RT exercise-induced initiation and propagation of mitochondrial biogenesis in muscle. Intracellular levels of Ca²⁺, cAMP, NO, and the ATP/AMP ratio are modulated by exercise and induced up-regulation of PGC-1 expression. PGC-1 also seems to regulate its own transcription. Increased expression and activity of PGC-1 α stimulate mitochondrial biogenesis by activating relevant transcription factors (e.g. NRF-1, NRF-2, and TFAM) resulting in an increase in mitochondrial volume and biogenesis. RT can also positively regulate mitochondria biogenesis. One potential mechanism can be due to the activation of IGF-1/MAPK pathway following RT.

Signals controlling mitochondrial biogenesis: central role of PGC-1 α

Despite the complexity of the various signaling pathways that converge to regulate mitochondrial biogenesis, they all seem to share the common key component of the PGC-1 family of co-transcription factors (Lopez-Lluch *et al.* 2008). PGC-1 α is preferentially expressed in muscles enriched in slow-twitch type I fibers and drives the formation of slow-twitch fibers (Li *et al.* 2011). Overexpression of PGC-1 α in the mouse skeletal muscle and heart has been shown to increase mitochondrial biogenesis and function (Dillon *et al.* 2012). There is growing evidence to suggest that PGC-1 α is a major regulator of mitochondrial biogenesis (Davinelli *et al.* 2013, Dillon *et al.* 2012, Lee and Wei

2005) (Fig. 1B).

PGC-1 α downstream signaling pathways

Most relevant to the onset of mitochondrial biogenesis is the interaction of PGC-1 α with the nuclear respiratory factors NRF-1 and NRF-2 (Hood 2009). Furthermore, NRF-1 is implicated in the interaction with several mitochondrial genes including the TFAM, one of the most important mammalian transcription factors for mtDNA (Davinelli *et al.* 2013) that directly stimulates mtDNA replication and transcription (Kang *et al.* 2013). TFAM binds to mtDNA at both the heavy- and light-strand promoters to initiate the transcription of genes. It also leads to an increase in mtDNA copy number (Huang and Hood 2009) (Fig. 1B).

PGC-1 up-stream signaling pathways

Multiple endogenous and exogenous factors regulate mitochondrial biogenesis through the PGC-1 α (Lopez-Lluch *et al.* 2008). PGC-1 α expression and activity are largely regulated by upstream signaling pathways of protein kinases (Yan *et al.* 2012) such as p38 mitogen-activated protein kinase (p38 MAPK) (Hood 2009, Joseph *et al.* 2006, Kang *et al.* 2013, Li *et al.* 2011), AMPK (Jager *et al.* 2007, Reznick *et al.* 2007, Zong *et al.* 2002). Moreover, it was demonstrated that changes in intracellular Ca²⁺ concentrations stimulate calcium/calmodulin-dependent protein kinase IV (CaMK). Thus, CaMK overexpression appeared to induce a coordination of the nuclear and the mitochondrial genomes through PGC-1 α (Joseph *et al.* 2006, Lee and Wei 2005, Lopez-Lluch *et al.* 2008).

PGC-1 α is also regulated by post-translational modification, such as phosphorylation and deacetylation. The NAD-dependent deacetylase silent mating type information regulation 2 homolog-1 (Sirt1) is also purported to have a key role in mitochondrial biogenesis *via* functional regulation of PGC-1 α (Palmer 2010, Yan *et al.* 2012). Recently, nitric oxide (NO) was shown to regulate mitochondrial biogenesis through the transcriptional activation of PGC-1 α (Lopez-Lluch *et al.* 2008). In addition, targeted disruption of the endothelial nitric oxide synthase (eNOS) gene *in vivo* resulted in significant reduction in the level of mitochondrial mass (Lee and Wei 2005, Nisoli *et al.* 2003) (Fig. 1B).

Ageing-induced SM-mito dysfunction

Mitochondrial net has an essential role in energy production (Bori *et al.* 2012) and an impaired in mitochondrial health, including reducing the size and content associated with decreased muscle mass and mtDNA mutation (Konopka *et al.* 2014, Menshikova *et al.* 2006). Studies on humans and animals have shown that aging leads to a decrease in the several complexes of electron transport chain I, II, III and IV 28 % – 42 % (Hood 2009, Kumaran *et al.* 2004), a decrease in oxidative phosphorylation capacity in muscle (Coggan *et al.* 1992a, Cooper *et al.* 1992), low mitochondria enzyme activity such as citrate synthase (CS), succinate dehydrogenase (SDH) and Beta-hydroxyacylCoA dehydrogenase (B-HAD) (Melov *et al.* 2007), decreased mtDNA content (Short *et al.* 2005) and increased oxidative stress (Huang and Hood 2009, Parise *et al.* 2005). Electron microscopy analysis showed a reduction

in the volume and density (66 % and 25 % respectively) of mitochondria in skeletal muscle in older adults compared to young (Huang and Hood 2009). Also significant decrease observed in muscle protein content of Cytochrome C and Cox4 of old rats compared to young ones which was an indicating of decreased mitochondria content (Ziaaldini *et al.* 2015). It has also shown that the mitochondria in aging muscles are abnormally rounded (Terman *et al.* 2010). Specific mechanisms leading to the changes of aging are unclear now (Menshikova *et al.* 2006). Studies on human and animal models have shown that mitochondrial dysfunction is associated with excessive production of ROS and metabolic changes (Bori *et al.* 2012, Ziaaldini *et al.* 2015). Mitochondrial theory of aging, which was first introduced in 1979 by Herman Denham suggest that leakage of free radicals and attack neighboring mtDNA leading to mitochondrial mutations that undermine mitochondrial function (Cobley *et al.* 2013, Nisoli and Carruba 2006). In fact, mtDNA has no protective histones and has substantially less repair mechanisms than nuclear DNA. Thus, ROS-induced accumulations in faulty proteins, oxidized fatty acids, and mtDNA mutations would result in a progressive, feed-forward, and irreversible cycle of cellular dysfunction that leads to the onset of phenotypes associated with aging (Huang and Hood 2009). Functional and dynamic changes of mitochondria associated with aging may contribute to mitochondrial dysfunction. Mitofusion (MFN1, MFN2) and mitofission (Fis1, Drp1) proteins act as morphological mechanisms and remove the mutant and damaged proteins out of mitochondria for disintegration and contribute to new organelles synthesis (Lee and Wei 2005). However, the impact of aging on these genes is still poorly understood. Konopka *et al.* reported that there was no difference in levels of MFN1, MFN2 and Fis1 between old (74 \pm 3 years) and young men (20 \pm 1 years) (Konopka *et al.* 2014). Joseph *et al.* (2012) achieved similar results where there was no significant difference in levels of MFN2, Drp1 and Fis1 but an increase in OPA1 among older (81 \pm 1 years) rather than young (23 \pm 1 years) men and women. In line with the previous research, Bori *et al.* (2012) reported which significant differences were not observed in the mRNA levels of young and old sedentary individuals for Fis1, Mfn1. However, animal model studies have shown an age-related increase in protein levels of Drp1 and Fis1 (Bo *et al.* 2013, Lanza and Nair 2009) and a decrease in levels of MFN1 (Estaquier *et al.* 2012). Among the many factors that affect the aging

process, malnutrition and decreased mitochondrial biogenesis appear to be of potential contribution to aging. The exact cause of decreased mitochondrial biogenesis during aging is currently unknown, but it seems the internal and external regulatory factors are involved (Lopez-Lluch *et al.* 2008). In accordance, it has been reported that there is no difference between AMPK and p38MAPK, two key signaling molecules, but levels of PGC-1 α were reduced by ~50 % in skeletal muscle of elderly participants compared to young ones (Joseph *et al.* 2012). Nonetheless, Lanza *et al.* (2008) couldn't find any significant difference in levels of PGC-1 α in older men compared with young men. However, both of these studies have reported which levels of the PGC-1 α targeted proteins, nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (TFAM) did not differ across groups (Joseph *et al.* 2012, Lanza *et al.* 2008). Interestingly, data from recent studies suggest a significant decrease in PGC-1 α levels in skeletal muscle of aged animal models (Dillon *et al.* 2012, Ljubicic *et al.* 2009). For more details about age-related SM-mito, there are quality review papers which are recommended for consultation (Chistiakov *et al.* 2014, Gaziev *et al.* 2014, Johnson *et al.* 2013) (Fig. 1C).

Age-related SM-mito responses to exercise training

SM-mito dynamic responses to ET

Mitochondrial dynamic plays a critical role in vertebrate cells during cell division, differentiation, and development and could also be involved in the mitochondrial response to skeletal muscle challenge (Garnier *et al.* 2005, Liu *et al.* 2014). The machinery involved in mitochondrial dynamics requires the participation of several proteins (Yan *et al.* 2012). In both human and animal model studies, it has been shown that acute and chronic exercise affect markers of mitochondrial content and dynamics in young and adult subjects (Cartoni *et al.* 2005, Ding *et al.* 2010, Koltai *et al.* 2012, Perry *et al.* 2010, Slivka *et al.* 2012a, Slivka *et al.* 2012b). Nevertheless, limited data exist about the impact of the exercise training on SM-mito in healthy age groups. Bori *et al.* (2012) studied mitochondria response to acute effect of exhausted aerobic exercise on active and sedentary old healthy men. They found that in the old sedentary group mRNA levels of both Mfn1 and Fis1 significantly decreased ($p < 0.05$) after exercise. In old active group, mRNA levels of Fis1 also decreased

($p < 0.01$) but there was no change for Mfn1. In contrast to acute aerobic exercise, Konopka *et al.* (Konopka *et al.* 2014) reported that twelve weeks aerobic training on a cycle ergometer significantly increased ($p < 0.05$) mitochondrial protein contents of Mfn1, Mfn2 and Fis1 in the in healthy old subjects (93 % \pm 44 %, 36 % \pm 8 % and 201 % \pm 98 % respectively). However, there was no change in mRNA levels of Opa1 (Konopka *et al.* 2014). At variance with humans' studies, endurance training led to a significant decrease in protein levels of Mfn1 in SM-mito of old rats (Bo *et al.* 2013, Koltai *et al.* 2012). Nevertheless, twelve weeks treadmill training increased ($p < 0.05$) Drp1 expression in old rats (Bo *et al.* 2013). Ziaaldini *et al.* (2015) also reported that six weeks of treadmill running at the intensity of 60 % of VO₂max eliminated the age-associated loss of muscle cytochrome C and COX4 protein content in old rats (Fig. 1D).

SM-mito biogenesis responses to ET

It is well established that endurance exercise training not only increases physical performance (Yan *et al.* 2012) but also induces a numbers of adaptations in aged SM-mito including increased aerobic capacity (Holloszy 1967, Holloszy and Coyle 1984), number and size (Palmer 2010, Yan *et al.* 2012) and consequently mitochondria biogenesis (Joseph *et al.* 2006, Little *et al.* 2010) in young and adult of both humans and animals. However, several studies have investigated acute and chronic effects of ET on SM-mito adaptations on old subjects (Huang and Hood 2009, Kang *et al.* 2013, Li *et al.* 2011, Menshikova *et al.* 2006, Palmer 2010, Russell *et al.* 2014, Toledo and Goodpaster 2013, Yan *et al.* 2012) and have reported a wide range of structural and functional adaptations in SM-mito such as an increased protein content and volume (Coggan *et al.* 1992b, Jubrias *et al.* 2001, Sharman *et al.* 2001), oxidative, Krebs cycle and electron transport chain enzymes activity (Kang *et al.* 2013, Li *et al.* 2011, McArdle *et al.* 2001, Menshikova *et al.* 2006). Despite the fact that mitochondria biogenesis requires a coordinated regulation between nuclear and mitochondria encoded gens, the main mechanism involved in SM-mito adaptation in older humans is not well understood yet.

In recent years, PGC-1 α has widely been investigated in cell metabolism (Hood 2009). As mentioned before, PGC-1 α is one of the main regulators of mitochondria adaptations and involves in regulation and expression of gens which are involved in

mitochondria biogenesis including NRF-1 and NRF-2 and consequently TFAM and mtDNA replication (Broskey *et al.* 2014). However, data from studies in connection with expression and content levels of PGC-1 α in SM-mito in response to ET, is inconsistent as they show increase (Hood 2009, Kang *et al.* 2013, Konopka *et al.* 2014, Yan *et al.* 2012), decrease (Bori *et al.* 2012, Koltai *et al.* 2012, Lanza *et al.* 2008) and no change (Konopka *et al.* 2010). For example, Kang *et al.* (2013), have demonstrated 12 weeks of ET (five days/week, 45 min/day, 10 % slope and 17.5 m/min) resulted in increase to 2.3 folds of PGC-1 α protein content in aged rat soleus muscle compared with the control group. Whereas, the study by Konopka *et al.* (2010), revealed that 12 weeks ET on bicycle ergometer led to a reduction of approximately 20 % ($p < 0.05$) in protein content of PGC-1 α SM-mito in old women (Konopka *et al.* 2010). Finally, Bori *et al.* (2012), studied mitochondria protein expression in response to acute exhaustive ET health active and sedentary aged men. Results from vastus lateralis before and after exercise intervention showed there was not difference in mRNA levels of PGC-1 α neither of the two groups (Bori *et al.* 2012). However, large numbers of studies have reported that PGC-1 α downstream transcription factors, NRF-1 and TFAM, increased following the ET (Broskey *et al.* 2014, Hood 2009, Kang *et al.* 2013, Lanza *et al.* 2008, Russell *et al.* 2014). Interestingly, some studies which reported significant decreased (Konopka *et al.* 2010) or unchanged (Bori *et al.* 2012) level of protein content and mRNA expression of PGC-1- α showed unaltered levels in mRNA of TFAM and decreased level of NRF-1 respectively.

Under normal conditions, control and regulation of PGC-1 α in skeletal muscle in response to ET mainly occurs by activation of CaMK, p38MAPK, AMPK and NAD⁺ (Gerhart-Hines *et al.* 2007, Irrcher *et al.* 2009, Wright *et al.* 2007a, Zhang *et al.* 2014). ET induces p38 MAPK phosphorylating and activating transcription factor-2 (ATF-2), allowing the latter to bind to the cAMP-response element-binding protein (CREB) site on the PGC-1 α promoter and induce PGC-1 α gene expression (Russell *et al.* 2014). In this regard, Kang *et al.* (2013), have demonstrated 12 weeks ET significantly increased p-p38mapk expression in old rats which was along with elevated levels of CREB phosphorylation and DNA binding. However, among p38 isoforms (i.e. α , β and γ), it seems p38 γ MAPK plays an important role for normal metabolic adaptation to ET inside skeletal muscle

(Yan *et al.* 2012). Kang *et al.* (2013), also reported p-AMPK, containing another upstream enzyme which regulates CREB activity, significantly increased in response to ET (Kang *et al.* 2013). In another study, it was demonstrated that age related reduction in total p-AMPK reversed following 6 week ET and significantly increased in old rats (Koltai *et al.* 2012).

It has been shown that Sirtuin family, especially Sirt1, can be involved in SM-mito adaptations to ET (Radak *et al.* 2013). Mechanical stretch promote Sirt1 transcription by Early growth response protein 1 (Egr1) recruitment to the Sirt1 promoter (Pardo and Boriek 2011). Exercise diminish the ATP/AMP ratio, activate AMPK which leads to an increase in NAD availability by inducing Nicotinamide phosphoribosyltransferase (Nmpt) expression (Pardo and Boriek 2011). The consequent increase in Sirt1 content and/or activity modulates the transcriptional activity of PGC-1 (Pardo and Boriek 2011). It has been well established that Chronic and acute ET increased mRNA expression and protein content of Sirt1 in SM-mito in both old human and animals (Bori *et al.* 2012, Kang *et al.* 2013, Koltai *et al.* 2012, Lanza *et al.* 2008). Koltai *et al.* reported Sirt1 activity significantly increased following 6 weeks ET in the cytoplasmic and nuclear extracts of quadriceps muscle in 28 old rats. They also found exercise increased NAMPT level and prevented the age-dependent decrease in NAD⁺ level in muscles of aged animals suggesting that the age-associated decreases in NAD⁺ and NAMPT levels were reversed with regular exercise, leading to increased specific activity of SIRT1 (Koltai *et al.* 2010) (Fig. 1D).

Resistance training adaptation

Resistance training is well known for increasing muscle mass and protein synthesis in difference ages (Tarnopolsky 2009), although a number of studies have documented some SM-mito adaptations to RT such as improved endurance capacity (Ades *et al.* 1996), increased mitochondria capacity and abundance of translation (Tarnopolsky 2009). Also an increase in mitochondrial volume has been reported following the 12 months RT in old women (% of mitochondria = 0.86 % at baseline, 1.19 % at six months and 1.04 % at 12 months, $p < 0.05$) (Manfredi *et al.* 2013). These findings along with other studies that demonstrated RT leads to an increase in mitochondrial ATP production and mitochondrial protein gene expression in healthy old subjects (Melov *et al.* 2007, Williams *et al.* 2007), support the hypothesis that RT results in structural and

functional adaptation in SM-mito network (Hiona *et al.* 2010, Marzetti *et al.* 2013, Wu *et al.* 2009).

It has been proposed that the loss of autophagy with age leads to accumulation of damaged mitochondria, which promote cell death and inflammation, both of which are otherwise limited by autophagy (Green *et al.* 2011). Recently it has been shown by Luo *et al.* (2013), that following the 9 weeks RT in old rats, levels of autophagy regulatory proteins, including Beclin 1, Atg5/12, Atg7, and the lysosomal enzyme cathepsin L increased. They also have shown RT reduced cytochrome c level in the cytosol but increased its level in mitochondrial fraction, and inhibited cleaved caspase 3 production and apoptosis. Furthermore, RT upregulated the expression of IGF-1 and its receptors, the expression of total AMPK, phosphorylated AMPK, and FOXO3a (Luo *et al.* 2013). The exact molecular mechanisms of these adaptations are not well understood yet. However, one possibility mechanism for SM-mito adaption to RT can be by activation of IGF-1/MAPK pathway. It is well established that RT increases levels of IGF-1 in the elderly (Caetano *et al.* 2008, Cassilhas *et al.* 2010, Hameed *et al.* 2004). MAPK pathways regulate diverse processes ranging from proliferation and differentiation to apoptosis (Qi and Elion 2005). The MAPKs consist of growth factor-regulated extracellular signal related kinases 1 and 2 (ERK1/2), and the stress-activated MAPKs, c-jun NH2-terminal kinase (JNK) and p38 MAPK and increased MAPK activity after exercise has been shown to be important for exercise-mediated gene expression, which may contribute to the role of exercise ameliorating the effects of aging in skeletal muscle (Flach and Bennett 2010).

Another possibility, as recent studies have reported, could be the expression of new transcription form of PGC-1 α (PGC-1 α 4), which abundantly expressed in skeletal muscle, increased after RT in human and animals (Millay and Olson 2013, Ruas *et al.* 2012, Ydfors *et al.* 2013). However, it is questionable whether biological effects of PGC-1 α 4 is limited to skeletal muscle hypertrophy (Ruas *et al.* 2012) or it is also involved in SM-mito adaptation to RT (Ydfors *et al.* 2013) (Fig. 1D).

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Conclusion

A decline in mitochondrial function including impaired biogenesis and dynamics of mitochondria not only endangers the performance of the cell but also along with other factors such as increased systemic inflammation and reduced growth factors (such as IGF-1) associated with aging (Marzetti and Leeuwenburgh 2006, Roubenoff 2000), leads to the development of programmed cell death and ultimately cell senescence (Chabi *et al.* 2008, Hiona *et al.* 2010). Investigations done on healthy elderly, suggest the decrease in gene expression and the content of PGC-1 α is associated with mitochondrial dysfunction in skeletal muscle of elderly subjects (Lopez-Lluch *et al.* 2008, Wenz *et al.* 2009). This decline in activity and content of PGC-1 α can be, at least in part, due to age-related disruption in the upstream pathways of AMPK (Salminen and Kaarniranta 2012) and NAD⁺/NADH (Braidly *et al.* 2011). Exercise has been shown to effectively improve mitochondrial function in the healthy elderly. Although the exact mechanism of this adaptation is not well understood, however, it can be, at least in part, due to an increased activity of AMPK (Bori *et al.* 2012, Hardman *et al.* 2012, Li *et al.* 2012) and NAD⁺/NADH ratio due to the increasing energy requirements (Hipkiss 2010, Koltai *et al.* 2010), as well as increased levels of growth factors (Craig *et al.* 1989, Vale *et al.* 2009, Yarasheski *et al.* 1995, Ziaaldini *et al.* 2015) followed both endurance and resistance exercise. Finally, despite the beneficial health effects of exercise in the elderly, in order to prescribe the optimal physical activity, future research should answer the following questions:

Which type of training can lead to more favorable effects? How about concurrent training?

In order to achieve the greatest impact, how it should be designed the intensity, duration and frequency of exercise?

Can nutritional and pharmaceutical interventions enhance the effects of physical activity?

Conflict of Interest

There is no conflict of interest.

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