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Influence of anaerobic and aerobic exercise on age-related pathways in skeletal muscle

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Introduction

The aging process is characterized by the progressive loss of physiological stability, lower physical and cognitive reserve, and increased vulnerability to death. This progressive deterioration in organismal homeostasis is considered the underlying trigger of most chronic diseases like diabetes, neurodegenerative diseases and cancer. Experimental challenges that increase the rate of biological and cognitive decline are linked to accelerated aging while interventions that slow the aging process are accompanied by an extension in healthy lifespan (Lopez-Otin et al., 2013; Kennedy et al., 2014).

Skeletal muscles perform several functions essential for locomotion and posture, and the loss of adequate mobility that occurs with aging causes the muscle to decrease its oxidative capacity and function. Gait speed represents an important integrative measure of muscle function and efficiency in the elderly (Peel et al., 2013) and its decline can be considered the best predictor of survival and health outcomes in humans (Perera et al., 2016). The age-associated decline in energy supply caused by mitochondrial dysfunction and/or reduction in the numbers of mitochondria adversely affects skeletal muscle function and homeostasis. One significant way to increase or preserve skeletal muscle quality and strength needed for healthy aging is through regular physical activity (Cartee et al., 2016). The present review addresses key facets of human aging and presents a summary of relevant metabolic sensors in skeletal muscle that coordinate the organismal response to exercise. We will explore various aspects of exercise that contribute to the regulation of metabolic pathways implicated in muscle strength and regeneration, as well as in mitochondria recycling and

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IN-E wrote the main text and both IN-E and MB designed the figures. MB, GB-C and RdC provided critical feedback on content, design and revision of the manuscript. All authors have edited and approved the final version of the manuscript.

efficiency. The benefits of exercise as a universal therapeutic “pill” for healthy aging will also be discussed.

Overview of the major hallmarks of aging

Aging is a complex multifactorial process. In order to provide better understanding of its natural progression, a formal classification has been put forward using a variety of criteria, including frailty, wasting of muscle mass, metabolic disorders, and incidence of cancer. Nine predominant hallmarks of aging have been proposed by Lopez-Otín and colleagues, and we will briefly review each of them for their most salient features. **First**, the accumulation of genetic damage throughout life triggers genomic instability, a condition often observed in some premature aging diseases (Burtner and Kennedy, 2010; Moskalev et al., 2013).

Second, impaired stability of mitochondrial genome (mtDNA) against environmental damage (Park and Larsson, 2011) affects the aging phenotype and lifespan (Kujoth et al., 2005). In addition, the influence of mtDNA haplotype on mitochondrial function and energy metabolism has profound effects on longevity and healthy living (Latorre-Pellicer et al., 2016). **Third**, telomeres are dynamic nucleoprotein-DNA structures that cap and protect linear chromosome ends: Telomere attrition or shortening is another hallmark of normal aging that is observed in human, mice, and zebrafish, and genetic defects affecting telomere stability contribute to age-related phenotypes and associated diseases (Blasco, 2007; Carneiro et al., 2016; Opresko and Shay, 2017). **Fourth**, epigenetics is determined by the cellular environment and produces specific and potent changes in gene transcription through reversible modifications of histone and nonhistone proteins, as well as DNA and noncoding RNA that affect DNA transcriptional activity without altering the DNA primary sequence (Dwivedi et al., 2011). Lifespan is epigenetically determined and links have been established between normal aging and chromatin signatures across species and from tissues to cellular models (Pal and Tyler, 2016; Sen et al., 2016). **Fifth**, healthy aging relies on proper unfolded protein responses to avoid accumulation of misfolded proteins and associated intracellular damage. The capacity of a system to recognize and handle misfolded proteins requires coordination of a multidimensional proteostasis network (Kaushik and Cuervo, 2015). The longest living species have more stable proteomes (Treaster et al., 2014), as exemplified by the naked mole rat known for its extended lifespan that correlates with enhanced activity of the proteostasis system (Perez et al., 2009). Interventions that modulate the action of the proteostasis network extend lifespan in invertebrates and mammals (Labbadia and Morimoto, 2015). **Sixth**, stem cell exhaustion is also considered one of the hallmarks of aging, as the decline in the capacity of tissues and organs to regenerate leads to an accumulation of senescent cells (Campisi and Robert, 2014; van Deursen, 2014).

Epigenetics and endogenous oxidative stress are among the factors that contribute to stem cell exhaustion (Davalli et al., 2016; Tome et al., 2014). Because metabolic defects are also responsible for stem cell exhaustion (Ito and Ito, 2016), a balance between self-renewal and differentiation of stem cells must occur through coordination of metabolic pathways and distribution of mitochondria in order to provide lifelong tissue homeostasis. The quiescence and proliferation/commitment of neural stem cells require adequate nutritional and metabolic conditions to guarantee lifelong neurogenesis while avoiding premature exhaustion (Cavallucci et al., 2016). Accumulation of genomic damage has a negative

impact on stem cell functionality through diverse mechanisms and activation of downstream signals (Behrens et al., 2014). **Seventh**, insulin and insulin-like growth factor 1 (IGF-1) activate important metabolic pathways that are key in maintaining cellular/tissue homeostasis (Barzilai et al., 2012). Restricted diets and calorie restriction (CR) mimetics extend lifespan in several animal models by impeding the activity of protein scaffolds, enzymes, and/or transcription factors implicated in insulin/IGF-1 signaling (de Cabo et al., 2014). **Eighth**, telomere shortening and nontelomeric DNA damage leads to growth arrest and induction of senescence-like phenotype (Bodnar et al., 1998; Collado et al., 2007). Old tissues and organs show significantly more senescence via higher production of senescent cells and/or decrease in their clearance rate (Lopez-Otin et al., 2013). **Ninth**, stimuli that induce senescence prevent the release of hormones and neuroendocrine factors that are required for maintaining resilient neuronal network (Zhang et al., 2013). Conversely, restoration of the age-associated loss in intercellular communication improves cellular functions and survival (Rando and Chang, 2012).

The recent review by Garatachea et al. summarizes the impact of regular exercise on various phenotypic changes associated with aging (Garatachea et al., 2015). Here, we have tried to capture the essence of this outstanding review (Figure 1).

Metabolic sensors in aging

The cellular and molecular hallmarks of aging described so far have direct and indirect repercussions on metabolism (Lopez-Otin et al., 2016). Genetic syndromes that cause premature aging in humans are often linked to metabolic defects (Vermeij et al., 2016), and robust gene variants mapping to nutrient-sensitive signaling pathways are found in centenarians (Broer and van Duijn, 2015). In aging and human metabolic diseases, some of these nutrient-sensing pathways are deregulated (Efeyan et al., 2015) due to the breakdown of the integration between intracellular sensors, downstream signaling pathways, and cellular response needed to maintain metabolic homeostasis and energy balance (Mitchell et al., 2016). Genomic background and sex contribute significantly to these integrated molecular and cellular processes (Mitchell et al., 2016).

1. AMPK, NAD⁺, and SIRT6

AMP-activated protein kinase (AMPK) and NAD⁺-dependent sirtuin deacetylases (SIRT6) are two energy sensors that contribute to lifespan extension in response to low cellular metabolic energy levels, as evidenced by the rise in AMP/ATP ratio, and high catabolic activity (Houtkooper et al., 2012). The ability of the antidiabetic drug metformin to confer antioxidant protection as well as healthspan and lifespan extension in mice stems from the activation of AMPK due to the partial inhibition of mitochondrial respiration and oxygen consumption, which are responsible for oxidative damage accumulation and chronic inflammation (Anisimov et al., 2011; Martin-Montalvo et al., 2013). Both AMPK and SIRT6 have been reported to directly affect the activity of the transcriptional co-activator proliferator-activated receptor gamma coactivator-1-alpha (PGC1α) through phosphorylation and deacetylation, respectively. Activation of PGC-1α increases mitochondrial biogenesis and fatty acid oxidation (Feige et al., 2008) and mediates the

health span-promoting effects of resveratrol in obese mice (Baur et al., 2006; Lagouge et al., 2006). Transcription factor EB (TFEB) induces also the expression of genes involved in mitochondrial biogenesis and fatty acid oxidation, independently of changes in PGC-1 α protein, as well as those that have been implicated in glucose homeostasis [e.g., glucose uptake and glycogen content] during exercise (Mansueto et al., 2017).

NAD⁺ is a key energy-sensing intermediate that contributes to the maintenance of metabolic homeostasis and has the ability to promote lifespan and health span extension (Canto et al., 2015; Verdin, 2015). The age-dependent decline in cellular NAD⁺ levels is partly due to the NADase activity of CD38, an enzyme that promotes mitochondrial dysfunction in mice (Camacho-Pereira et al., 2016). Other NAD⁺-consuming enzymes that regulate NAD⁺ homeostasis during aging include SIRT6, poly-ADP-ribose polymerases (PARPs), and C-terminal binding proteins (CtBPs). Diet supplementation with NAD⁺ precursors or pharmacological inhibition of PARP activity reverses age-induced mitochondrial dysfunction and increases health in mice. Age-associated arterial dysfunction can be rescued and returned to young mice levels after supplementation with nicotinamide mononucleotide (NMN), a key NAD⁺ intermediate capable to increase SIRT1 activity (de Picciotto et al., 2016). Intraperitoneal administration of NMN significantly increases NAD⁺ levels both in liver and muscle of diet-induced obese mice, but leads to improvement in glucose tolerance and the recovery in citrate synthase activity only in the liver (Uddin et al., 2016). Interestingly, exercise allows the restoration of citrate synthase activity in muscle of obese mice on a high-fat diet indicating that NMN exerts tissue-specific effect *in vivo* (Uddin et al., 2016).

Sirtuins (SIRT) connect energy metabolism, oxidative stress, and aging through deacetylation of key proteins implicated in transcriptional control, epigenetics and other cellular functions (Canto et al., 2015; Guarente, 2007, 2013). The SIRT family contains seven homologs of yeast Sir2 in mammals (Frye, 2000), distributed in mitochondria (SIRT3, SIRT4 and SIRT5), nucleus (SIRT1, SIRT6 and SIRT7), or present in both the nucleus and cytoplasm (SIRT2) (Nakagawa and Guarente, 2014; Verdin et al., 2010). In addition to the regulation of fatty acid oxidation (Hirschey et al., 2010; Liu et al., 2012), sirtuins play an important role in cellular homeostasis, inflammation and senescence, and by acting as energy sensors (Du et al., 2011; Ghosh and Zhou, 2015; Haigis and Sinclair, 2010; Jiang et al., 2013; Kida and Goligorsky, 2016; Santos et al., 2016).

The loss in cellular antioxidant capacity that occurs with aging translates into a progressive change in the redox status due to the accumulation of ROS (Ying, 2008). Indeed, a whole process of general oxidation occurs within aging cells, as evidenced by the alteration in the NAD⁺/NADH ratio, which, in turn, negatively impacts on the global activity of sirtuins (Radak et al., 2013). Of note, interventions that enhances the level/activity of nicotinamide phosphoribosyltransferase (NAMPT), a key NAD⁺ biosynthetic enzyme, can extend vascular smooth muscle cell viability in a SIRT1-dependent manner (Koltai et al., 2010; van der Veer et al., 2007).

Physical exercise has been recently proposed as an effective intervention to improve mitochondrial function in the healthy elderly (Cobley et al., 2015; Park et al., 2016). Several

mechanisms have been put forward to explain such benefit of exercise, which include strengthened AMPK activity (Bori et al., 2012; Li et al., 2012; Wolfe, 2006), changes in NAD^+/NADH ratio due to differential energetic requirements (Hipkiss, 2010), and increase in circulating growth factor levels (Vale et al., 2009; Ziaaldini et al., 2016; Ziaaldini et al., 2015). By improving mitochondrial function through changes in NAD^+/NADH ratio, physical exercise may possibly promote the activation of some members of the NAD^+ -dependent sirtuins.

Table 1 summarizes the recent information on the impact of acute and chronic exercise on SIRT expression and activity in skeletal muscle. With acute, endurance training in human, Guerra and colleagues reported a significant increase in SIRT1 protein levels two hours after a single bout of sprint exercise (Guerra et al., 2010), whereas the content and activity of SIRT3 protein was not impacted after 6 weeks of sprint interval training at 4 times/week in human vastus lateralis muscle (Edgett et al., 2016). PubMed search did not return any relevant information on the effect of resistance training on SIRT2 or SIRT4-7 expression.

The practice of chronic, endurance training resulted in significant increase in SIRT1 protein level and activity in rat skeletal muscle (Gerhart-Hines et al., 2007; Suwa et al., 2008), and daily swimming for 12 weeks produced an accumulation of SIRT1 protein in both gastrocnemius and soleus muscles of 3- and 12-month-old, but not 18-month-old rats (Huang et al., 2016). The level of SIRT2, SIRT4, SIRT5 and SIRT7 proteins was unchanged, while that of SIRT3 significantly increased, in rat skeletal muscle after a 1-year voluntary aerobic wheel running (Karvinen et al., 2016). A significant decrease in SIRT6 protein expression was observed in sedentary young and old humans and in active individuals after a single bout of aerobic exercise (Radak et al., 2011).

Based on the information currently available, we hypothesize that physical exercise has a beneficial impact not only on SIRT1 and SIRT3 function, but also as a modulator of SIRT2 activity by virtue of its ability to increase the NAD^+/NADH ratio (Hipkiss, 2010). Tubulin has two isoforms, α -tubulin and β -tubulin, that form microtubules which are considered the main component of cytoskeleton in eukaryotic cells. Tubulin is subject to posttranslational modifications, among which include deetyrosination/tyrosination, glutamylation, glycylation, and acetylation, the latter occurring on lysine-40 of α -tubulin (Hammond et al., 2008). These post-translational modifications alter the stability and structure of microtubules and microtubule-regulated functions such as ciliary beating, cell division, and trafficking (Suzuki and Koike, 2007; Westermann and Weber, 2003). Because SIRT2 protein can selectively deacetylate tubulin (North et al., 2003; Skoge et al., 2014), we surmise that physical exercise may modify the integrity and cellular functions of microtubules through the deacetylation of α -tubulin by SIRT2 (Figure 2).

2. Cyb5r3

The control of energy homeostasis via NAD^+ metabolism is conserved from yeast to man. The membrane-bound form of cytochrome b_5 reductase (Cyb5R) utilizes a one-electron reduction mechanism to convert coenzyme Q and cytochrome b_5 in the presence of NADH. The generation of NAD^+ that ensues contribute to cellular NAD^+ homeostasis and activation of a number of NAD^+ -consuming enzymes (de Cabo et al., 2009), many of which implicated

in nuclear-mitochondrial communication (Gomes et al., 2013). Cyb5R confers protection against metabolic disorders through regulation of lipid metabolism, improvement in mitochondrial function, and increased health span (Martin-Montalvo et al., 2016). A decrease in polyunsaturated fatty acids after knockdown of the *CYB5R3* homologous gene (HPO-19) in *C. elegans* is accompanied by delayed growth and shorter lifespan (Zhang et al., 2016). Overexpression of *CYB5R3* in human neuroblastoma cells confers resistance to oxidative insults *in vitro* by attenuating lipid and protein damages and partially preventing apoptosis (Hyun and Lee, 2015), while knockdown of *CYB5R3* increases sensitivity of mammalian cells to oxidative stress via growth inhibition and development of a senescent-like phenotype (Siendones et al., 2014). Lipid-anchored Cyb5R is located in the plasma membrane and microsomes as well as in the outer mitochondrial membrane, where it participates in the activation of mitochondrial oxidative phosphorylation (Hyun and Lee, 2015; Siendones et al., 2014). The ability of CR to increase the formation of NAD⁺ by Cyb5R (De Cabo et al., 2004; Hyun et al., 2006; Lopez-Lluch et al., 2005) may account for the lifespan- and health span-extending properties of Cyb5R overexpression (Jimenez-Hidalgo et al., 2009; Martin-Montalvo et al., 2016).

3. Klotho and FGF signaling

Klotho is another factor that contributes to age regulation. Mutation in mouse klotho gene causes premature aging-like phenotypes and shortens lifespan about 6% of that of WT mice (Kuro-o, 2012), and overexpression extends lifespan in mice (Kurosu et al., 2005). The Klotho gene encodes for a transmembrane protein that is produced in few organs, mainly in kidney, and is released in the bloodstream either by alternative splicing (Matsumura et al., 1998), proteolytic cleavage of the extracellular domain of the transmembrane protein (Chen et al., 2007), or cleaved from the Na⁺/K⁺-ATPase-Klotho complex at the cell surface in response to the fluctuation of extracellular calcium (Imura et al., 2007). Circulating klotho acts as a hormone affecting most cells and tissues (Hum et al., 2016) by inhibiting, for instance, the insulin/IGF1 signaling pathway, which, in turn, contributes to lifespan extension by increasing FOXO-mediated transcriptional activation of antioxidant enzymes that confer resistance to oxidative stress (Yamamoto et al., 2005). Klotho also displays many functions associated to growth, stem cells functionality, endothelial protection by nitric oxide, calcium homeostasis, and regulation of intracellular signaling pathways (see for reviews (Wang and Sun, 2009; Buendia et al., 2016)).

Klotho is an anti-aging protein whose circulating form decreases with age (Xiao et al., 2004) with resultant manifestation of several age-associated diseases (Kim et al., 2015). Klotho interacts directly with the transmembrane form of the fibroblast growth factor receptor (FGFR) family and increases the binding affinity of FGF19 family members to FGFRs (Kuro-o, 2010; Kurosu and Kuro, 2009). These functional interactions are considered vital in the protection from chronic diseases via regulation of phosphorus (Pi) and vitamin D metabolism, oxidative stress, growth factor signaling, ion homeostasis, and suppression of inflammation-mediated cellular senescence (Hum et al., 2016; Kim et al., 2015). Notably, the discovery of klotho-deficient mice and *Fgf23* knockout mice displaying similar physical and biochemical phenotypes (Razzaque and Lanske, 2006) is of significance because not only is FGF23 produced in bones to regulate serum concentrations of calcitriol and

phosphate and kidney functions (Andrukhova et al., 2014; Hu et al., 2013), but the detection of FGF23 mRNA in mouse skeletal muscle would indicate a role in muscle function (Liu et al., 2003). Indeed, FGF23 mRNA levels are induced in skeletal muscle of chronically and acutely exercised mice, and chronic exercise upregulates the cytosolic pool of FGF23 protein (Li et al., 2016). Administration of exogenous FGF23 extends time to exhaustion during chronic exercise, which is linked to a decrease in ROS production and improvement in citrate synthase activity, consistent with increased mitochondrial bioenergetics pathway (Li et al., 2016).

FGF21 is another member of the FGF19 family that stimulates glucose and lipid metabolism, thereby contributing to energy balance. It is secreted into the circulation mainly from the liver, and also from pancreas and adipose tissue (Kharitonov et al., 2005; Otero et al., 2014; Potthoff et al., 2009). Additionally, cardiomyocytes secrete FGF21 in basal conditions (Planavila et al., 2013) and in response to cardiomyopathy and heart failure and upon cardiac stress (Dogan et al., 2014; Planavila et al., 2015). FGF21-mediated cardiac protection during exercise is related to stress resistance (Guo et al., 2016) through replenishment of skeletal muscle with glucose and fatty acids, although other mechanisms may come into play.

The increase in circulating FGF21 levels in sedentary young female and male volunteers after two weeks of acute exercise has been linked to higher lipolysis in adipose tissue (Cuevas-Ramos et al., 2012; Kim et al., 2013). This type of exercise in mice also produced significant increase in hepatic FGF21 mRNA levels (Kim et al., 2013). Similarly, healthy sedentary men and young male mice showed higher circulating levels of FGF21 stemming from increased FGF21 mRNA and protein levels in liver and skeletal muscle and higher levels of lipolytic products (Tanimura et al., 2016). In another study performed by Taniguchi et al. (2016a), a significant reduction in FGF21 levels was detected in both young and old men at 24 hours after acute exercise ended (Taniguchi et al., 2016a). On the other hand, endurance exercise induced a decrease of FGF21 serum levels in elderly men combined with a decrease of hepatic fat content (Taniguchi et al., 2016b). Part of the discrepancies between these results and the earlier studies could be explained by differences in the experimental approach, e.g., duration and intensity of exercise, timing of sample collection, and/or the specific muscle used. To reconcile these differences, further studies will be needed to reinforce the involvement of FGF21 in some of the benefits of exercise.

There is evidence to suggest that the modulation of FGF21 levels by regular exercise confers anti-obesogenic benefits. The increase in circulating FGF21 levels in obese individuals (Zhang et al., 2008) is reduced after a 3-month bout of exercise, thus providing evidence that exercise may lower cardiovascular risk, in part, through the modulation of FGF21 (Reinehr et al., 2015; Scalzo et al., 2014; Slusher et al., 2015). In that regard, *Fgf21*^{-/-} mice on a high-fat diet are refractory to exercise-mediated activation of AMPK in skeletal muscle, which lead to excess hepatic triglyceride content and impaired glucose tolerance, but without impact on physical performance compared to WT littermates (Lloyd et al., 2016). Taken together, these studies would indicate the role of FGF21 in conveying the pleiotropic benefits of exercise in combatting metabolic syndrome.

4. mTOR and sestrins

The insulin/IGF-1 signaling pathway is evolutionary conserved and involves downstream effectors, including mechanistic target of rapamycin (mTOR) complexes and transcription factors such as FOXO family members. mTOR and FOXO are implicated in cell growth regulation, proliferation, survival, autophagy, protein synthesis, and transcription. Mutations that affect the activity of these nutrient sensors have potent effects on longevity in mammals due to alterations in bioenergetics (Barzilai et al., 2012). Mechanistic TOR complex 1 (mTORC1) is a multiprotein complex that functions, in part, as an energy sensor through the increase in oxidative metabolism, mitochondrial biogenesis, and mitochondrial DNA content (Cunningham et al., 2007; Laplante and Sabatini, 2012). Studies have shown that mTORC1 downmodulation extends lifespan and improves healthspan in response to dietary restriction (Mattison et al., 2012; Mitchell et al., 2015) and insulin/IGF-1 pathway attenuation through improvement in mitochondrial efficiency (Foukas et al., 2013; Lopez-Lluch et al., 2006; Ortega-Molina et al., 2012) and subsequent lowering in oxidative mitochondrial metabolism that causes cellular damage. As with the control of protein synthesis, mTORC1 drives also hypoxia-inducible factor 1 α (HIF1 α) synthesis and signaling under hypoxic conditions. HIF1 α participates in the upregulation of genes encoding glycolytic enzymes implicated in the anaerobic ATP production in muscle (Hudson et al., 2002). Along with other anti-aging transcription factors, HIF1 α participates in the control of oxygen homeostasis, glucose metabolism, and muscle cell survival in response to CR (Fontana et al., 2010). Reduction in nutrient availability has been found to contribute to the regulation of TOR signaling pathways through inhibition of mTORC1 by the AMPK-mediated activation of the tuberous sclerosis complex (Lee et al., 2016). In addition to this dietary approach, pharmacological inhibition of mTOR with rapamycin mimics the beneficial effects of CR (Johnson et al., 2013) and extends lifespan in male mice (Harrison et al., 2009).

Sensing the changes in nutrient availability is monitored by a family of highly conserved stress-inducible proteins known as sestrins (Parmigiani and Budanov, 2016). Sestrins participate in the control of metabolism by acting as leucine sensor in the mTORC1 signaling pathway (Wolfson et al., 2016). The function of sestrins as negative regulators of mTORC1 and ROS signaling contributes to the attenuation of cell damage by oxidative stress and the prevention of age-associated diseases (Ho et al., 2016). Sestrin2 regulates thermogenesis in brown adipose tissue by reducing mitochondrial respiration through regulation of uncoupling protein 1 (UCP1) expression (Ro et al., 2014; Ro et al., 2015), while sestrin3 improves metabolic homeostasis by protecting mice against high-fat diet-mediated insulin resistance (Tao et al., 2015). Induction of sestrin2 in response to endoplasmic reticulum stress results in the activation of unfolded protein response proteins with subsequent reduction in cellular damage and increase in cell survival (Saveljeva et al., 2016). An interesting aspect of the anti-aging properties of sestrins relates to their activation of autophagy, a process that is intimately linked to skeletal muscle atrophy and the preservation of muscle mass (Masiero et al., 2009). Taken together, the function of mTORC1 on protein synthesis in human skeletal muscle represents, therefore, an important putative therapeutic target for the prevention and treatment of muscle wasting disorders (Dickinson et al., 2011; Ham et al., 2016).

As mentioned earlier, overnutrition and excessive intake of calorie-rich food have severe impact on health and can shorten lifespan through aberrant mTOR signaling by the insulin/IGF-1 pathway. In contrast, fasting and low carb diet result in activation of nutrient sensors, including AMPK, PGC-1 α , sirtuins, and FOXO3a, which are key for healthy lifestyle and extended lifespan. In the next sections, we will discuss current research in the biology of human aging that involves gaining a greater understanding of molecular changes and metabolic dysfunctions in skeletal muscle and testing of interventions that can improve quality of life, decrease morbidity, and extend lifespan (Kennedy et al., 2014; Lopez-Otin et al., 2016).

Muscle metabolism in aging

Sarcopenia is a severe condition that causes a decrease in skeletal muscle strength and mass (Cruz-Jentoft et al., 2010a; Hughes et al., 2001). It is the most common disorder in the elderly in terms of frailty, disability, and morbidity in non-active seniors and drastically limits the autonomy of a person (Cruz-Jentoft et al., 2010b). The incidence and economic burden of sarcopenia is substantial and will increase with the explosion of the world's elderly population.

Skeletal muscle capacity is highly dependent on mitochondrial bioenergetics in terms of ATP production, NAD⁺ homeostasis, and pyrimidine nucleotide biosynthesis. Although the production of mitochondrial reactive oxygen species (ROS) extends longevity in flies (Scialo et al., 2013; Scialo et al., 2016), dysfunction of the cell's powerhouse is considered a hallmark of aging (Gonzalez-Freire et al., 2015; Lopez-Otin et al., 2013). The role of mitochondrial ROS in aging is still controversial, but the newly available techniques to measure ROS *in vivo*, combined with state-of-the-art technology to edit the genome, indicate that ROS has lifespan-extending properties in lower organisms such as worms and flies (Sanz, 2016). The dismutation of ROS by superoxide dismutase and related cellular antioxidant systems can be defective in several conditions, such as sedentariness, thereby causing oxidative stress-associated damage to DNA and proteins to trigger a number of chronic diseases. With aging, there is impairment in redox homeostasis due to increased formation of ROS mainly in mitochondria (Dai et al., 2014). Acute exercise improves the body's ability to maintain proper physiological responses and these benefits can be maintained with long-term training (Cobley et al., 2014; Cobley et al., 2015). Low levels of ROS are indispensable for proper activation of cellular antioxidant systems needed to neutralize the excess ROS generated by oxidative metabolism and the modulation/regulation of cellular redox homeostasis (Kerksick and Zuhl, 2015). Muscle contraction and exercise training generate ROS mainly from complexes I and III of the mitochondrial respiratory chain (St-Pierre et al., 2002), although other cellular processes are also involved in exercise-mediated ROS formation (Gomez-Cabrera et al., 2016). Excessive exercise can cause cellular damage (Davies et al., 1982); however, monitored exercise allows improvement and positive adaptation of the skeletal muscle's contractile capacity through activation of antioxidant enzymes and redox-regulated enzyme reactions (Jackson, 2008, 2009). It is worth to mention that diet supplementation with specific concentrations of antioxidants before exercise can prevent ROS signaling and, therefore, decrease or abolish exercise-mediated benefits in muscle performance (Mason et al., 2016).

Exercise-mediated increase in ROS signaling is caused by activation of various signaling pathways, including nuclear factor erythroid 2-related factor 2 (Nrf2), which is encoded by the *NFE2L2* gene in humans. Under basal conditions, the transcription factor Nrf2 is held inactive in the cytosol by binding to KEAP1; however, in response to oxidative stress, the Nrf2-KEAP1 complex dissociates with subsequent nuclear translocation of Nrf2 leading to the transactivation of a number of antioxidant and cellular protective genes (Kaspar et al., 2009). Recent reports have shown that intensity and duration of exercise contribute to different degrees of Nrf2 activation in mouse skeletal muscle (Li et al., 2015). For example, six hours after a bout of acute exercise, redox effector factor-1 (Ref1) and Nrf2 are activated, which led to increased expression of mitochondrial manganese superoxide dismutase (MnSOD) and higher cellular glutathione content (Wang et al., 2016). Repeated regular bouts of exercise appear to confer the greatest degree of Nrf2-mediated expression of genes containing antioxidant response element (ARE) in their promoters, thereby providing skeletal muscle with a greater ability to counteract the damaging effects of oxidants on nucleic acids, proteins, and lipids (Done and Traustadottir, 2016).

Besides oxidative stress, inflammation is also induced by exercise and both components appear to contribute to muscle damage (Sanchis-Gomar et al., 2015). NFκB transcription factor belongs to the Ref1 family and it is activated by redox mechanisms (Meyer et al., 1994). Some of the antioxidant and inflammatory genes transcriptionally activated by NFκB include MnSOD, iNOS, COX-2, and cytokines (Ghosh and Karin, 2002). Also, acute exercise has been reported to activate this pathway by increasing NFκB binding after few hours of muscle contraction (Ji et al., 2004). This explains an earlier report showing increased NFκB binding in nuclear extracts of rat skeletal muscle following a single bout of exhaustive exercise, which led to inducible expression of the *MnSOD* gene (Hollander et al., 2001). Thus, exercise of different intensities and durations could confer protection against future waves of oxidative stress through coordination of the Nrf2 (oxidative stress) and NFκB (inflammation) signaling pathways and subsequent expression of relevant target genes (Sallam and Laher, 2016).

Acute exercise is associated with activation of hepatic gluconeogenesis and breakdown of liver glycogen stores in order to increase the release of glucose into the bloodstream and meet the bioenergetics demand of the skeletal muscle. Moreover, exercised muscle releases lactate, which is converted to pyruvate and then glucose by the liver (Hoene and Weigert, 2010; Shephard and Johnson, 2015). Therefore, similar to skeletal muscle, the liver adapts to exercise through regulation of oxidative stress and inflammatory pathways that are needed for energy requirements and redox homeostasis (Pillon Barcelos et al., 2017).

Further mechanistic studies are required to extend these conclusions to humans. Patients with mitochondrial disorders age rapidly with evidence of severe skeletal muscle disability, sarcopenia, and eventually rhabdomyolysis (Pillard et al., 2011) without loss of mitochondrial activity in highly aerobic skeletal muscles of elderly patients (Amara et al., 2007). Muscle efficiency depends on the provision of a carbon source, such as glucose and fatty acids (Kennedy et al., 2014), and interventions that affect carbon source (e.g., CR) accelerate the removal process of damaged proteins and organelles (Lopez-Lluch and Navas, 2016; Yang et al., 2016). CR diet containing either fish oil or lard as the main fat elicits

differential pattern of mitochondrial vs. peroxisomal fatty acid oxidation in mice, with greater mitochondrial activity with fish oil diet and higher peroxisomal activity with lard (Lopez-Dominguez et al., 2016). Unexpectedly, CR-fed mice supplemented with lard lived significantly longer than mice on CR that were maintained on fish oil (Lopez-Dominguez et al., 2015).

The mitochondrial respiratory chain encompasses four multiprotein complexes (complexes I to IV) that are connected by two mobile electron transporters: coenzyme Q and cytochrome c. Respiratory chain complexes are synthesized and assembled by the coordination of mtDNA and nuclear genomes, except complex II and the electron transporters that depend only on the nuclear genome. This assembly of respiratory chain complexes is highly regulated by energy requirements as well as by cellular and mitochondrial homeostasis. High-energy electrons move from either NADH or FADH₂ to oxygen through 'complex I-complex III-complex IV' or 'complex II-complex III-complex IV', respectively, to generate the mitochondrial membrane potential that drives ATP synthesis. The complexes are not randomly distributed in the inner mitochondrial membrane but, instead, are assembled in dynamic supercomplexes (Lapiente-Brun et al., 2013), which provide mitochondrial efficiency especially in high-energy dependent tissues like skeletal muscle (Genova and Lenaz, 2014). Interestingly, moderate aerobic exercise in humans remodels the assembly profile of supercomplexes in skeletal muscle to provide higher respiratory efficiency (Greggio et al., 2016).

Complex I in mitochondria encompasses the NADH dehydrogenase (ubiquinone), which accepts electrons from the Krebs cycle electron carrier NADH during aerobic cellular respiration. The breakdown of glucose and its conversion to pyruvate constitutes the major pathway of glucose metabolism known as glycolysis. The entry of pyruvate into the Krebs cycle requires conversion to acetyl-CoA. Insulin increases entry of glucose into muscle and adipose tissue by inducing the translocation of GLUT4, a high-affinity glucose transporter, from the endosomal compartment to the plasma membrane. The trafficking of GLUT4 in insulin-responsive cells involves activation of the PI3-kinase/AKT module (Lizcano and Alessi, 2002); however, a PI3-kinase-independent pathway provides a second route for GLUT4 recruitment to the plasma membrane in which the insulin receptor catalyzes the Casitas B-lineage Lymphoma (Cbl) phosphorylation and association with the adaptor protein CAP to facilitate the translocation of GLUT4-containing vesicles into lipid rafts at the plasma membrane (Richter and Hargreaves, 2013). These alternative mechanisms that guarantee glucose supply to skeletal muscle are further supported by recent evidence showing the differential contribution of Rab guanosine triphosphatase-activating proteins in the translocation of GLUT4, with AS160 being selective for insulin stimulation and TBC1D1 for exercise (Stockli et al., 2015).

The pathways described above are regulated by nutrient availability and environmental stress, both of which producing a unique survival response. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) transcription factor coordinates the response to oxidative stress by regulating the expression of antioxidant enzymes (Zhang, 2006), and formation of a complex between Nrf2 and FOXO3a improves stress response gene regulation (Siendones et al., 2014). Although the Nrf2-dependent antioxidant response in skeletal muscle decreases with age

(Done et al., 2016; Sachdeva et al., 2014), exercise training induces expression of two Nrf2 target genes, namely mitochondrial transcription factor (TFAM) and nuclear respiratory factor 1 (NRF-1) in mouse skeletal muscle (Merry and Ristow, 2016). Pulmonary rehabilitation exercises improve the adaptation of oxidative phosphorylation in skeletal muscles in patients with chronic obstructive pulmonary disease via induction of TFAM and PGC1 α (Jarosch et al., 2016). The report of Jarosch et al. (2016) and many others highlight the fact that mitochondrial signaling plays a functional role in promoting exercise efficiency. Both NRF-1 and PGC1 α stimulate human telomere transcription in response to exercise via AMPK activation, connecting telomere protection in aging with metabolism (Diman et al., 2016). Increase in the ADP/ATP ratio that follows physical activity induces AMPK activity in muscle, and, in so doing, regulates the β -oxidation capacity of muscle and mitochondrial biogenesis (Winder et al., 1997; Zong et al., 2002). The decrease in AMPK activity that occurs with age (Reznick et al., 2007) could explain the mitochondrial dysfunction and energy imbalance observed in old skeletal muscles (Kennedy et al., 2014; López-Otín et al., 2013; López-Otín et al., 2016).

Exercise promotes muscle homeostasis in aging

The beneficial effects of physical activity on skeletal muscle and mitochondrial function have been confirmed by both proteomics and metabolomics analyzes. When comparing frail elderly with healthy older subjects, there are significant differences in their adaptive mechanisms to prolonged resistance exercise training (Fazelzadeh et al., 2016). Because each type of skeletal muscle fibers shows a differential response to the types of exercises (Capitanio et al., 2015), it raises the question of the importance of establishing a personalized exercise program for the elderly. Physical activity programs are one of the most plastic interventions available that can be tailored for the specific needs of each individual.

Both strength and flexibility exercises build muscles and keep the body nimble, thus facilitating everyday activities even in old age. Studies have shown that exercise and CR prevent or delay the onset of sarcopenia in animal models (mice to monkeys) and humans (de Cabo et al., 2014) by inducing changes in muscle bioenergetics through improved coordination in the utilization of lipid and glucose as sources of energy. The systemic response to exercise brings clear changes in several metabolic markers such as insulin, irisin, glucose, and triglycerides (Clark-Matott et al., 2015). Human longitudinal studies like the Baltimore Longitudinal Study of Aging (BLSA) at the National Institute on Aging have investigated muscle fitness and disability of healthy individuals and people suffering from different disorders (www.blsa.nih.gov). In addition, transgenic mouse strains with specific manipulation of genes required for the mitochondrial respiratory chain have been created and tested for alterations in their rates of aging (Garcia-Corzo et al., 2013; Ross et al., 2013). Moreover, nutritional interventions such as CR and the use of CR-mimetics, including resveratrol, rapamycin, and metformin have shown improvement in muscle strength and functional capabilities in mice (de Cabo et al., 2014).

Frequent and regular physical exercise has clear anti-aging effects through the reduction in morbidity and mortality risks (Neufer et al., 2015). Exercise mainly affects skeletal muscle by modulating key metabolic pathways (Bowen et al., 2015; Cartee et al., 2016) and it is

also the only intervention to successfully prevent sarcopenia (Glass and Roubenoff, 2010). Most tissues and organs are affected by the pleiotropic effects of exercise both at the metabolomic and transcriptomic levels (Fontana et al., 2010). Studies in mice have reported exercise-mediated improvement in mitochondrial function through mitophagy and mitochondrial biogenesis (Hood et al., 2015; Overmyer et al., 2015), and moderate-intensity aerobic exercise in old humans increases mainly complex I and the reorganization of supercomplexes in the form of I+III(2)+IV, as an adaptation to energy demand (Greggio et al., 2016). Exercise also enhances memory *via* cathepsin B release (Moon et al., 2016). Depending on its intensity, exercise can mimic the beneficial effects of CR and fasting by regulating similar signaling pathways and processes (de Cabo et al., 2014; Hord et al., 2016; López-Otín et al., 2016; Sharples et al., 2015).

Muscle dysfunction and sarcopenia are associated with a decline in the efficiency of muscle regeneration driven by muscle stem cells (satellite cells) (Alway et al., 2014; Schiaffino et al., 2013). The negative impact of aging on the regulation of satellite cells causes a significant reduction in human skeletal muscle plasticity (Snijders et al., 2015). However, exercise increases the number and activation of satellite cells and their capacity to partially differentiate into myotubes with proper structure and function (Cisterna et al., 2016). Some of the mechanisms involved in sarcopenia are dependent on the negative regulation of satellite cells by the TGF β pathway (Dumont et al., 2015). Growth differentiation factor-11 (GDF11) and myostatin (GDF8) are members of the TGF β superfamily that bind the activin type II receptor to mediate downstream activation of Smad2/Smad3 complex (McPherron et al., 2009). Defective regeneration of damaged muscle during aging correlates with increased GDF11 expression (Egerman et al., 2015; Zhou et al., 2016).

Neuromuscular junction (NMJ) is a synapse site between the terminal branch of motoneurons and skeletal muscle fiber. It is a complex and highly adaptive structure that loses some of its properties with age (Deschenes et al., 2013; Gault and Willems, 2013) (Figure 3). The mechanisms involved in age-mediated NMJ degeneration are poorly understood; however, muscular dystrophies and sarcopenia share defects in NMJ through structural and molecular alterations that involve numerous factors (Gonzalez-Freire et al., 2014). Controversies abound on the effects of exercise in NMJ structure and function due mainly to the variety of experimental protocols used in the published studies (Krause Neto et al., 2015). However, there is agreement about the specificity of exercise in NMJ's pre- and post-synaptic endplate remodeling, which affects specific muscles such as plantaris, but not extensor digitorum longus, through the increase in age-associated slow-twitch myofibers and decrease in the percentage of fast-twitch myofibers (Deschenes et al., 2016; Deschenes et al., 2015). As a consequence of exercise training in rats, there is increased formation of acetylcholinesterase tetramers in NMJ, which represents a mechanism for optimal synaptic transmission (Blotnick and Anglister, 2016). More research and use of additional animal models are key for better understanding of the role of exercise in the prevention and treatment of NMJ defects that contribute to age-associated muscle wasting and dysfunction.

Perspectives

Exercise includes different levels of intensity, duration, and frequency. Resistance exercise is basically anaerobic by nature with short duration and high intensity that is aimed at increasing muscle mass and strength. Conversely, an aerobic or endurance exercise takes place for a long period, with variable intensities and low resistance (Cartee et al., 2016). There are evidence that both types of exercise have positive benefits in the elderly, but no information is available yet on the impact of age (old vs. young) with regard to the pleiotropic effects of exercise on glucose and/or lipid metabolism, insulin resistance, and signaling pathways. The genetic and epigenetic basis of each individual opens the possibility of a personalized exercise prescription for health improvement, as some seniors show blunted adaptation to a particular mode of exercise that is likely due to differences in physiological reserve over time (Cartee et al., 2016) or expression of specific genetic variants with strong influence in exceptional longevity (Sebastiani et al., 2013; Sebastiani and Perls, 2012).

Exercise training improves physical fitness and activity levels and other important clinical outcomes, such as health-related quality of life and post-operative morbidity, in hospitalized rectal cancer patients (EMPOWER trial) (Loughney et al., 2016). Moreover, aerobic training prevents muscle atrophy in patients who were immobilized post-surgery or after suffering different diseases (Souza et al., 2014). Although there is clear evidence on the health benefits of exercise, the accumulated information is not consistent in terms of frequency, willfulness, and intensity to provide a definitive translational protocol to the bedside, in metabolic disorders, and aging (Zierath and Wallberg-Henriksson, 2015).

Both aerobic and anaerobic exercises can induce permanent or transitory adjustments in the organism, but there is a differential response of individuals (Osler et al., 2015). Additionally, most of the training programs include both aerobic and anaerobic sets of exercises, giving intermediate benefits (Fyfe et al., 2014). The differential response must be exhaustively studied in a simple isogenic model of young and old animals, by determining the molecular and biochemical markers affected by each type of exercise. A personalized physical exercise approach during or after treatment of patients has provided a more sustainable impact on the physical activity level in breast cancer patients than the usual care, suggesting that the rehabilitation program should be personalized (Baumann et al., 2016). Personalized self-management program including exercise has been also used to increase active prevention in musculoskeletal disorders (Lanhers et al., 2016), and exercise interventions in clinical trials have raised positive results by 67% on quality of life outcomes of prostate cancer patients (Menichetti et al., 2016). Various 'omics' approaches should be also included to identify similarities and differences of the crosstalk among tissues and organs and elucidate the molecular mechanisms implicated in the beneficial outcomes of exercise (Tanaka et al., 2016). Circulating microRNAs associated to different types of exercise have been proposed as useful biomarkers of physical performance capacity and training adaptation (Polakovicova et al., 2016).

Concluding Remarks

The specificity of various types of exercise is potentially translatable not only for the elderly, but also for people suffering of metabolic diseases, obesity, and mitochondrial disorders. The establishment of an individualized exercise program could be a valid therapeutic option in the prevention or delay of muscle dysfunction and wasting in aging and immobilized patients.

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Highlight

- Different types of exercise are potentially beneficial and translatable not only for the elderly, but also for people suffering chronic diseases associated with aging. Establishing a combination of personalized treatments and exercise programs could lead to effectively prevent or delay the onset of muscle dysfunction and wasting that occur with aging and subjects on bed rest.

STEM CELL EXHAUSTION	Increased proliferation and migration of some types of stem cells.
LOSS OF PROTEOSTASIS	Induces autophagy in skeletal muscle through several mechanisms (IGF-1, AKT/mTOR) and modulates ubiquitin-proteasome system
GENOMIC STABILITY	Reduced DNA and mtDNA damage: - Increases antioxidant defense and DNA repair - Reduces genomic instability - Reduces premature mortality
CELLULAR SENESENCE	Regulates cellular senescence through: - Increases NK-cell activity, senescence markers, telomere and activity. - Decreases inflammation senescent cells, and apoptosis.
MITOCHONDRIAL DYSFUNCTION	Improvement in mitochondrial function and biogenesis: - Increases PGC-1 α , SIRT, mtDNA shifting, antioxidant defense, respiratory chain assembly.
TELOMERE ATTRITION	Prevents telomere shortening: - Increases telomerase activity - Increases TERT activity & expression - Increases shelterin complex
ALTERED INTERCELLULAR COMMUNICATION	"Inflammaging" counter effects: - Increases IL-4, IL-6, IL-10, IL-13, AUF1 - Decreases NLRP3
EPIGENETIC ALTERATION	Regulation through: - Increases DNA methylation - Increases miRNA regulation - Increases histone PTM's
DEREGULATED NUTRIENT-SENSING	Activates nutrient-sensing pathways: - Increases mTOR, AMPK, SIRT, Glut4, testosterone, GH and IGF-1

Figure 1.
Impact of regular exercise on the hallmarks of aging. Modified from (Garatachea et al., 2015).

Figure 2. Effects of regular exercise on Sirt 1, Sirt 3 and proposed model of Sirt 2

We surmise that physical exercise may modify the integrity and cellular functions of microtubules through the deacetylation of α -tubulin by SIRT2.

Figure 3. Schema depicting the impact of exercise on the functional and structural adaptations of skeletal muscle

With age, there are defects in neuromuscular junctions and the number of satellite cells. A narrowing of muscle fibers and deposition of extracellular matrix (ECM) contribute also to poor neuromuscular activity, which is controlled by neuronal, mechanical, metabolic, and hormonal inputs.

Table 1

Summary of the recent information on the impact of acute and chronic exercises on SIRT expression and activity in skeletal muscle.

	SIRT1	SIRT3	SIRT 2,4,5,7	SIRT6
Acute, resistance training	Two hours after a single bout of sprint exercise (Wingate test), SIRT1 protein level was increased in human skeletal muscle (Guerra et al., 2010).	SIRT3 protein content and activity was not impacted after a 6-week sprint interval training, 4 times/week (Edgett et al., 2016).	No relevant data published	No relevant data published
Chronic, endurance training	<ul style="list-style-type: none"> SIRT1 protein level and activity were increased in rat skeletal muscle after endurance exercise (Gerhart-Hines et al., 2007; Suwa et al., 2008). SIRT1 protein content in both gastrocnemius and soleus muscles was increased after 12 weeks of daily swimming in 3 and 12-month-old, but not in 18 month-old rats (Huang et al., 2016). 	1 year of voluntary aerobic wheel running increased SIRT3 protein level in rats (Karvinen et al., 2016).	1 year of voluntary aerobic wheel running had no effect on SIRT2,4,5,7 protein levels in rats (Karvinen et al., 2016).	Significant decrease in SIRT6 in young and old sedentary humans and in active individuals following a single bout of aerobic exercise (Radak et al., 2011).