Review

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Update on mitochondria and muscle aging: all wrong roads lead to sarcopenia

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Abstract: Sarcopenia is a well-known geriatric syndrome that has been endorsed over the years as a biomarker allowing for the discrimination, at a clinical level, of biological from chronological age. Multiple candidate mechanisms have been linked to muscle degeneration during sarcopenia. Among them, there is wide consensus on the central role played by the loss of mitochondrial integrity in myocytes, secondary to dysfunctional quality control mechanisms. Indeed, mitochondria establish direct or indirect contacts with other cellular components (e.g. endoplasmic reticulum, peroxisomes, lysosomes/vacuoles) as well as the extracellular environment through the release of several biomolecules. The functional implications of these interactions in the context of muscle physiology and sarcopenia are not yet fully appreciated and represent a promising area of investigation. Here, we present an overview of recent findings concerning the interrelation between mitochondrial quality control processes, inflammation and the metabolic regulation of muscle mass in the pathogenesis of sarcopenia highlighting those pathways that may be exploited for developing preventive and therapeutic interventions against muscle aging.

Keywords: inflammation; mitochondrial biogenesis; mitochondrial proteostasis; mitochondrial quality control; mitophagy; muscle wasting.

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Introduction

Sarcopenia, the progressive loss of muscle mass and strength/function during aging, is increasingly recognized as a major factor responsible for the occurrence of negative health outcomes (Landi et al., 2017). As such, sarcopenia has been endorsed as a relevant biomarker allowing for the discrimination, at a clinical level, of biological from chronological age (Marzetti et al., 2017a). Although several biochemical pathways have been associated with the onset and progression of sarcopenia (Ziaaldini et al., 2017), its pathophysiology has not yet been completely deciphered, making it difficult to identify biological targets that could be exploited for developing effective interventions.

From a histological point of view, sarcopenia is characterized by atrophy and loss of muscle fibers (Lexell et al., 1986), which in turn are ascribed to multiple factors (reviewed by Marzetti et al., 2009). Among others, reduced satellite cell number/function, decreased motor unit number, changes in hormonal levels, altered proteostasis, increased levels of inflammatory cytokines and mitochondrial dysfunction are the most accredited mechanisms underlying muscle degeneration (Figure 1).

Being the hub for many cellular activities (e.g. fuel supply, regulation of intracellular calcium homeostasis, modulation of cell proliferation, integration of apoptotic signaling), the maintenance of a pool of well-functioning mitochondria is instrumental in preserving cellular homeostasis. The loss of mitochondrial integrity in myocytes, secondary to dysfunctional quality control mechanisms, is indeed indicated as a main factor in muscle degeneration (Calvani et al., 2013). Not surprisingly, the

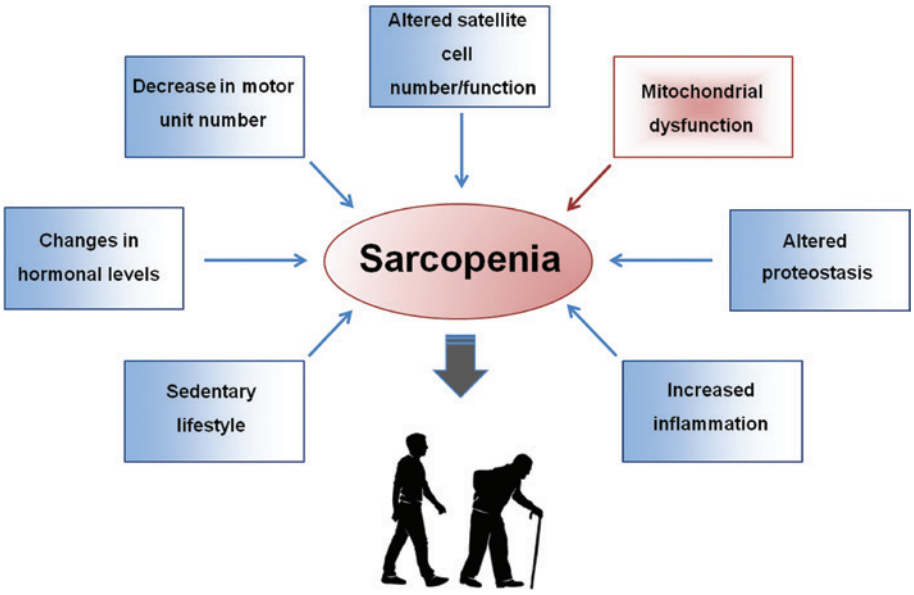

Figure 1: Age-related fiber atrophy and loss characterizing sarcopenia have been attributed to a wide range of factors, including sedentary lifestyle, declines in anabolic hormone levels, decreased motor unit number, reduced satellite cell number/function, mitochondrial dysfunction, altered proteostasis and chronic inflammation.
Mitochondrial dysfunction (highlighted in red) is especially relevant to fiber atrophy due to reduced oxidative capacity and increased levels of oxidative stress and damage.

last few years have witnessed a tremendous increase in the amount of data enlightening the intricate and tightly regulated nature of mitochondrial plasticity and quality control. Together with mitochondrial dysfunction, chronic inflammation is acknowledged as a distinctive trait of aging and as factor involved in the pathogenesis of sarcopenia (Picca et al., 2017a). Notably, alterations of mitochondrial quality control (MQC) and systemic inflammation appear to be linked to one another, through reciprocal reinforcing mechanisms (Picca et al., 2017a). Here, we overview recent findings concerning the involvement of dysfunctional MQC and inflammation in the pathogenesis of sarcopenia, highlighting the pathways that may be exploited for devising preventive and therapeutic interventions.

Mitochondria, aging, and sarcopenia: when old friends turn into enemies

Although it is still controversial whether mitochondrial dysfunction is a cause or a consequence of aging and its associated conditions, mitochondrial DNA (mtDNA) mutations induce phenotypes that resemble premature aging (Wallace and Fan, 2009). Evidence supporting a causal role for mtDNA mutations in aging has been obtained from the mtDNA-mutator mouse. This model harbors a proofreading-deficient version (D257A) of mtDNA polymerase γ (PolG) and undergoes premature aging characterized by alopecia, kyphosis, hearing loss, osteoporosis, sarcopenia and reduced lifespan (Trifunovic et al., 2004; Kujoth et al., 2006). PolG mice accumulate somatic mtDNA mutations and show systemic mitochondrial dysfunction, including reduced respiratory chain function, accelerated apoptosis in post-mitotic tissues and impaired MQC (Trifunovic et al., 2004; Kujoth et al., 2006; Hiona et al., 2010; Joseph et al., 2013). In this model, mitochondrial dysfunction precedes the development of the aging phenotype. Remarkably, PolG mice do not exhibit increased levels of oxidative stress (Hiona et al., 2010). Similarly, macromolecular oxidative damage does seem to accrue in aged human muscle (Hutter et al., 2007). These observations have ignited controversies around the long-standing notion of reactive oxygen species (ROS) contributing to aging via mtDNA mutations (Lewis et al., 2013). Indeed, long-lived naked mole-rats reach very old age in the face of oxidative stress through unknown cytoprotective mechanisms (Lewis et al., 2013). Collectively, these findings indicate that accumulation of mtDNA mutations during aging may compromise cell signaling pathways and promote apoptosis independent of oxidative stress.

Regardless of the actual role of mitochondrion-generated ROS, mitochondrial dysfunction has been listed among the hallmarks of aging (Lopez-Otin et al., 2013) and is indicated as a major causative factor in sarcopenia (Calvani et al., 2013).

Gene expression profiling studies have shown that the mitochondrial involvement in aging is tissue-specific and is particularly relevant in brain, heart and skeletal muscle that are heavily dependent on oxidative metabolism (Anderson and Weindruch, 2010). Due to their post-mitotic nature, neurons and myocytes cannot clear damaged organelles through cell division, but rely on MQC efficiency to preserve mitochondrial homeostasis. MQC is accomplished through the coordination of mitochondrial proteostasis, biogenesis, dynamics and autophagy (Twig et al., 2008). Derangements at any level of the MQC axis can easily result in mitochondrial dysfunction, energy shortage and ultimately loss of cell viability.

A role for mitochondrial dysfunction and deranged MQC in fiber loss during sarcopenia is supported by substantial experimental evidence. Damaged mitochondria accumulate in myocytes of transgenic mice with abrogation of autophagy, and induce oxidative stress, apoptosis and eventually muscle atrophy and weakness (Masiero et al., 2009). Skeletal muscles from aged rats (Wanagat et al., 2001), monkeys (Lee et al., 1993) and humans (Bua et al., 2006) show an increased number of fibers with electron transport chain (ETC) deficiencies as evidenced by the loss of cytochrome C oxidase activity (COX^{-}) and succinate dehydrogenase hyperactivity (SDH^{++}). ETC abnormalities can be distributed focally, thus involving single cells within the muscle, or occur within discrete regions of an individual cell (Wanagat et al., 2001). These regions vary in length with longer abnormal segments being prone to atrophy and breakage (Bua et al., 2004). Noticeably, mtDNA deletion mutations co-localize with ETC abnormalities (Lee et al., 1993; Wanagat et al., 2001) and, above a certain threshold, lead to disruption of ETC activity (Bua et al., 2006; Herbst et al., 2007). As a whole, these data support the hypothesis that mtDNA deletion mutations accumulate in muscle fibers, compromise mitochondrial bioenergetics and contribute to fiber atrophy and loss.

Contrasting findings indicating no changes in mitochondrial function and enzyme activities have been reported in aged human muscle (Rasmussen et al., 2003). Such discrepancies may be attributable to different experimental conditions (e.g. mitochondrial purity, type of assays) as well as age ranges and physical activity levels of participants.

Mitochondria, oxidative stress and sarcopenia: a rusty relationship

The "mitochondrial theory of aging" postulates that mitochondria contribute to the aging process primarily through respiratory dysfunction and oxidant generation (Harman, 1983).

Mitochondria are autonomous and highly dynamic double-membrane organelles of eukaryotic cells containing multiple copies of their own DNA (mtDNA). The mammalian mitochondrial genome is composed of ~16.5 kb of circular, double-stranded DNA coding for two ribosomal RNAs, 22 transfer RNAs and 13 protein subunits of the ETC, all of which are essential for proper mitochondrial function (reviewed by Picca and Lezza, 2015). The majority of mitochondrial proteins are encoded by the nuclear genome and imported into mitochondria.

MtDNA is organized into protein-DNA complexes, called nucleoids, within the mitochondrial matrix (Gilkerson, 2009). Although mtDNA is packaged into nucleoids, which provide more protection to the genome than was originally thought, it still remains in close proximity to the ETC. This is the main cellular source of ROS that are generated as a byproduct of substrate oxidation and oxidative phosphorylation.

In moderate amounts, ROS function as intracellular signaling molecules that improve defense mechanisms by inducing an adaptive response, a phenomenon referred to as mitohormesis (Ristow and Schmeisser, 2014). In the case of skeletal muscle, moderate amounts of oxidants are necessary for optimal excitation-contraction coupling and force generation, stimulate mitochondrial biogenesis, and improve cellular antioxidant and repair capacity (Reid et al., 1985). This hormetic response is preserved in older individuals (Safdar et al., 2010). A hydrogen peroxide cell-warning system for oxidative stress operates through the mitochondrial leakage of this compound and acts as a retrograde signal to nuclear-targeted cytosolic pathways (Mishra and Chan, 2016). When intracellular ROS concentrations overwhelm antioxidant defenses, the resulting oxidative stress can result in loss of ROS signal localization and disruption of cell homeostasis (Wu et al., 2016).

The finding of decreased antioxidant activity with advancing age has placed oxidative stress among the contributors to the aging process (Lopez-Otin et al., 2013). However, if and how oxidative stress plays a role in the pathogenesis of sarcopenia remains to be established. Several studies aimed at exploring this possibility. Ablation of the anti-oxidant genes coding for the two antioxidant enzymes superoxide dismutase (SOD) and

glutathione peroxidase 1 (GPX1) results in altered mitochondrial function, increased sensitivity to apoptosis, cancerogenesis, acceleration of age-associated muscle atrophy and neuromuscular junction degeneration (Williams et al., 1998; Esposito et al., 2000; Lee et al., 2006; Zhang et al., 2009; Jang et al., 2010).

In the context of oxidative stress, mitochondrial constituents are primary targets of oxidative damage. In particular, mtDNA can undergo qualitative and/or quantitative alterations (e.g. bases modifications, abasic sites, single- and double-strand breaks, point mutations, large-sized deletions) that affect its structure and function. Age-related changes in mtDNA content have been found in various mammalian tissues (Barazzoni et al., 2000; Short et al., 2005; McInerny et al., 2009; Picca et al., 2013a,b, 2014), especially those of post-mitotic nature, such as the muscle (Cortopassi et al., 1992; Pesce et al., 2001, 2005).

Among qualitative mtDNA alterations, large-size deletions have been actively investigated. These deletions can result in the removal of more than one half of the mitochondrial genome and have been causally related to aging and age-related disorders (Cheema et al., 2015). Studies combining microdissection of individual fiber sections with quantitative polymerase chain reactions showed that ETC abnormalities always co-localize with accumulation of deletion mutations (Wanagat et al., 2001; Gokey et al., 2004).

ROS-induced mtDNA modifications also include base modifications [i.e. 8-oxoguanine (8-oxoG), abasic sites, 2,6-diamino-4-hydroxy-5-formamidopyrimidine (FapyG), 4,6-diamino-5-formamidopyrimidine (FapyA) and thymine glycol]. The most frequent oxidative lesion within the cell is 8-oxoG (Bohr et al., 2002) that can be removed from mtDNA through base excision repair (BER) by the mitochondrial targeted splice variant of oxoguanine DNA glycosylase (OGG1) (de Souza-Pinto et al., 2001). If 8-oxoG is not removed, an A can be inserted opposite to 8-oxoG during replication. This can result in a G:C→T:A transversion at the site of the adduct (Wallace, 2002). 8-oxoG accumulates with age to a greater extent in mtDNA than in nuclear DNA (nDNA) (Mecocci et al., 1993). An age-related increase in oxidative damage to nDNA and mtDNA has been found in the vastus lateralis muscle of older persons (Short et al., 2005). Conversely, attenuation of the aging phenotype in a progeroid mouse model following endurance training was accompanied by reduced mtDNA depletion/mutations and apoptosis, as well as amelioration of MQC activities (Safdar et al., 2011).

The potential implication of mtDNA oxidative lesions in aging, either through mutagenicity or disruption of normal replication and transcription of mtDNA, emphasizes the importance of mtDNA repair systems (Hebert et al., 2010). Among them, BER is acknowledged as the most relevant to mtDNA maintenance (Croteau et al., 1997). As opposed to other tissues, both single-nucleotide (SN)- and long-patch (LP)-BER activities decrease in murine muscle (Szczesny et al., 2010). The resulting greater susceptibility to oxidative damage of skeletal myocytes may in turn play a role in sarcopenia (Szczesny et al., 2010). However, several aspects need to be considered. For instance, larger fast-twitch glycolytic fibers (type II) with lower mitochondrial content are more susceptible to atrophy during aging than small slow-twitch oxidative fibers (type I) which are enriched with mitochondria (Lexell et al., 1986). Whether mtDNA BER operates with different efficiency depending on fiber type is presently unknown. The existence of two distinct mitochondrial subpopulations in skeletal muscle displaying differential responses to aging further complicates the matter. Indeed, subsarcolemmal (SS) mitochondria show greater reduction in membrane potential, higher proton leak, enhanced ROS production and increased lipid peroxidation compared with intermyofibrillar mitochondria. Therefore, SS may be particularly relevant to sarcopenia (Crane et al., 2010). The possibility that a variable efficiency of mtDNA BER may contribute to explaining the differential involvement of the two mitochondrial subsets in muscle aging warrants further research.

Derangements in MQC systems: losing muscle resilience

To ensure the maintenance of well-functioning mitochondria, a complex and tightly coordinated quality control axis is in place and involves a protein quality control system, mitochondrial biogenesis, dynamics and selective degradation (mitophagy). The following subsections summarize recent evidence in support of MQC derangements as a factor in sarcopenia.

Mitochondrial proteostasis system

Mitochondrial proteostasis ensures protein turnover and degradation of misfolded or oxidized proteins. These tasks are achieved through the coordination of organelle-specific proteases (mitoproteases) and the ubiquitin-proteasome system (UPS) (Baker and Haynes, 2011). Mitoproteases act as the first line of defense against mild mitochondrial damage (Quirós et al., 2015).

Within the mitochondrial matrix, protein turnover is controlled by 3 AAA proteases: the soluble Lon and ClpP and the membrane-bound m-AAA (Voos, 2013). In the inter-membrane space, mitochondrial protein quality is ensured by the membrane-bound i-AAA Yme1L1, the soluble HtrA2/Omi, the metallopeptidases OMA1 and the presenilins-associated rhomboid-like protein (PARL) (Quirós et al., 2015).

The level and activity of these mitoproteases change with aging. Indeed, the expression and function of LonP decrease with age (Ngo and Davies, 2007). In contrast, LonP upregulation is protective against several stressors (Ngo et al., 2013). Loss of Htra2 in non-neuronal tissues induces premature aging in mice as a consequence of mtDNA deletion accrual (Kang et al., 2013). In addition to this, deletions of genes encoding mitoproteases, such as Afg3l2, Clpp and Parl, cause severe defects in mice (e.g. axonal degeneration, multisystem disorder, cachexia) which ultimately shorten their lifespan through mitochondrial dysfunction (Cipolat et al., 2006; Maltecca et al., 2008; Gispert et al., 2013).

Mitochondrial protein turnover is also ensured by the cytosolic UPS (Jeon et al., 2007). However, the mechanism whereby cytosolic UPS degrades integral mitochondrial membrane proteins needs to be clarified.

Similar to the endoplasmic reticulum (ER), mitochondria possess a stress responsive system for protein degradation named mitochondrial unfolded protein response (UPRmt) (Zhao et al., 2002). UPRmt shares with its ER analog some key components, including the AAA ATPase p97 and the cofactor Npl4 (Heo et al., 2010). In the presence of stressors, the expression of nuclear genes encoding mitochondrial stress proteins (e.g. chaperonin 10 and 60, mtDnaJ, ClpP, Yme1) is induced (Zhao et al., 2002). Through these mediators, the UPRmt promotes mitochondrial proteostasis by improving protein folding and degrading irreversibly damaged proteins.

Mitochondrial biogenesis

Mitochondrial biogenesis is a multistage process that involves changes in the expression of more than 1000 genes, the cooperation of two genomes, and the activation of several transcriptional coactivators. The output of this cascade is the generation of newly synthetized organelles. Several (patho)physiological conditions, such as exercise, fasting, oxidative stress and inflammation, promote mitochondrial biogenesis that, depending on the stimulus, is achieved through the activation of specific signaling pathways (reviewed by Hood et al., 2016).

At the nuclear level, the concerted regulation of a large number of genes is ensured by the interaction of the RNApol II complex with various target promoters. In addition to nuclear genes (which encode for more than 95% of mitochondrial proteins), mitochondriogenesis requires the participation of mtDNA, which codes for most hydrophobic proteins of the ETC as well as for mitochondrial tRNAs and rRNAs. A set of transcription factors and cofactors orchestrates the activation and regulation of mitochondrial biogenesis. Relevant transcriptional coactivators are those belonging to the peroxisome proliferator activated receptor gamma coactivator-1 (PGC-1) family (PGC-1α and PGC-1β), the nuclear respiratory factor 1 and 2 (NRF-1 and NRF-2), and the estrogen-related receptor alpha (ERRα), which regulate the expression of mitochondrial proteins encoded by nDNA (reviewed by Picca and Lezza, 2015). As a result, an increase in the expression of many mitochondrial proteins, including those binding the mtDNA occurs [e.g. mitochondrial transcription factor A (TFAM) and mitochondrial transcription factors B1 and B2 (TFB1M and TFB2M)] (Rebelo et al., 2011). These mediators are transported into mitochondria via the protein import machinery and subsequently activate mtDNA transcription and replication through their binding to mtDNA (Rebelo et al., 2011).

Mammalian mtDNA contains two noncoding regions (NCRs): (1) the major NCR, namely the D-loop, which encompasses the transcription promoter of both heavy and light strands (HSP1 and HSP2, LSP) and the origin of replication of the heavy strand (OriH), and (2) the minor NCR which includes the origin of replication of the L strand (OriL). The D-loop region is the major site of transcriptional regulation, as reflected by its interaction with multiple regulatory proteins.

TFAM is one of the prominent components of mitochondrial nucleoids which associates with the inner mitochondrial membrane (Bogenhagen, 2011). This transcription factor is a member of the high-mobility-group (HMG) proteins, able to bind, unwind and bend mtDNA without sequence specificity, but with preferential interaction with some regions (Ohgaki et al., 2007). Recent studies employing *in vivo* binding analysis of TFAM to specific mtDNA regions have suggested the modulation of TFAM-mtDNA interaction as one of the mechanisms regulating mitochondrial biogenesis (Picca et al., 2013a; Picca and Lezza, 2015). Recent evidence shows that a differential binding of TFAM due to dysregulation of this interaction, secondary to TFAM and/or mtDNA alterations, could contribute to impairing mitochondrial function during aging in several tissues, including skeletal muscle (Picca et al., 2014). However, the relevance of this mechanism to sarcopenia has not yet been established.

There is compelling evidence, instead, linking PGC-1α with muscle maintenance. Although lacking mtDNA binding activity, PGC-1α translocates from the cytosol to both the nucleus (Wright et al., 2007) and mitochondria (Safdar et al., 2011). This relocalization may facilitate nuclear-mitochondrial crosstalk in the setting of mitochondrial biogenesis and mtDNA repair (Safdar et al., 2011).

Reduced levels of PGC-1α and its downstream targets in skeletal muscle have been reported in old people (Conley et al., 2000; Short et al., 2005; Safdar et al., 2010; Joseph et al., 2012). Moreover, a positive correlation among PGC-1α content, oxidative capacity and functional status has been found in young adults, patients with congestive heart failure (Garnier et al., 2005), and elderly persons (Joseph et al., 2012). PGC-1α mRNA levels drop in different atrophying conditions such as denervation (Sandri et al., 2006), unloading (Cannavino et al., 2015), type II diabetes (Patti et al., 2003) and aging (Chabi et al., 2008). Conversely, the maintenance of PGC-1α expression preserves muscle mass during sarcopenia, hind limb suspension, cachexia, denervation and fasting, by promoting mitochondrial turnover and quality control (Sandri et al., 2006; Cannavino et al., 2015).

Similar beneficial effects have recently been obtained by overexpressing PGC-1β, a homolog of PGC-1α (Brault et al., 2010). PGC-1β is necessary for the maintenance of mitochondrial function (Zechner et al., 2010). Indeed, deletion of PGC-1α and PGC-1β induces severe mitochondrial dysfunction, rapid depletion of glycogen stores, and early fatigue (Zechner et al., 2010). Interestingly, these factors share a subset of target genes and display partly overlapping functions.

Recently, a new splicing variant of the *PGC-1α* gene, PGC-1α4, has been identified and shown to be involved in the regulation of muscle mass (Ruas et al., 2012). PGC-1α4 expression is induced during resistance exercise and its transgenic overexpression in murine muscles promotes hypertrophy (Ruas et al., 2012). Moreover, PGC-1α4 overexpression counteracts muscle loss induced by hind limb suspension and cancer cachexia (Ruas et al., 2012). However, the relevance of PGC-1α4 to human muscle physiology is presently unclear. Indeed, PGC-1α4 seems to be regulated transiently during exercise in young persons (Ydfors et al., 2013; Lundberg et al., 2014). Furthermore, increases in muscle mass and strength do not correlate with changes in the expression of PGC-1α4 during either resistance exercise or a combination of aerobic and resistance training (Lundberg et al., 2014).

The effects of transcriptional coactivators on muscle physiology are accomplished via multiple pathways. First of all, diet and exercise modulate PGC-1α levels through the activity of the 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 is induced by oxidative stress following endurance training in young and older adults (Lanza et al., 2008). Data obtained in animal models indicate that SIRT3 is a downstream target of PGC-1α able to modulate the effects of this transcriptional coactivator on mitochondrial metabolism and ROS production (Kong et al., 2010). Strategies that increase NAD^+ levels (i.e. nicotinamide riboside administration or calorie restriction) improve muscle health in old mice by reducing hypoxia-inducible factor 1α (HIF-1α) levels (Gomes et al., 2013). Moreover, boosting NAD^+ levels with poly (ADP-ribose) polymerase (PARP) inhibitors is protective against muscle dysfunction induced by mitochondrial dysfunction (Pirinen et al., 2014).

Another pathway regulating mitochondrial metabolism during aging involves insulin-like growth factor 1 (IGF-1). This signaling pathway has been proposed to operate through phosphorylation of ATP citrate lyase (ACL), an enzyme that catalyzes mitochondrion-derived citrate into oxaloacetate and acetyl CoA. ACL activity is reduced in skeletal muscle of old mice. Higher ACL levels stimulate ETC activity and improve oxygen consumption, which suggests that age-induced reductions in IGF-1 concentrations may impair mitochondrial ETC activity via ACL (Harris et al., 1997). This implies that the stimulation of the IGF-1/ACL pathway may serve as a possible intervention to attenuate mitochondrial dysfunction and sarcopenia (Das et al., 2015).

The inhibition of the autophagic-lysosomal and the ubiquitin proteasome pathways is another relevant signaling route involving PGC-1 transcriptional coactivators. PGC-1α and β reduce protein breakdown by inhibiting the transcriptional activity of forkhead box O3 (FoxO3) and nuclear factor κB (NF-κB) (Brault et al., 2010). These cofactors can therefore prevent overactivation of proteolytic systems by reducing the activity of pro-atrophy transcription factors without affecting protein synthesis (Romanello and Sandri, 2016).

Mitochondrial dynamics

Mitochondrial fusion and fission processes are crucial for genetic complementation, organelle function, and proper distribution of newly synthesized mitochondria in dividing cells. Mitochondrial fusion allows for the generation of interconnected organelles, thereby ensuring mtDNA

mixing within the network, preventing focal accumulation of mutant mtDNA and preserving mtDNA integrity (Twig et al., 2008). Mitochondrial fission, instead, segregates unnecessary or defective organelles for their subsequent removal through mitochondrial autophagy (mitophagy) (Twig et al., 2008). The integration of mitochondrial dynamics and mitophagy ensures an efficient MQC and preserves metabolic cellular 'fitness'.

Aberrant mitochondria are often found in aged tissues, including the muscle (Sebastián et al., 2016), indicating that mitochondrial dynamics are altered in advanced age. Morphological abnormalities are accompanied and, perhaps underlain, by changes in the expression of fusion and fission proteins, including mitofusin (Mfn) 1 and 2, optic atrophy protein 1 (Opa1), dynamin-related protein 1 (Drp1), and fission protein 1 (Fis1) (Crane et al., 2010; Joseph et al., 2012; Marzetti et al., 2016; Picca et al., 2016, 2017a,b). Yet, the mechanisms whereby altered mitochondrial dynamics intervene in the aging process are largely unexplored. The neurodegenerative disorders dominant optic atrophy (DOA) (Amati-Bonneau et al., 2008) and Charcot-Marie-Tooth type 2A (CMT2A) (Zuchner et al., 2004) occur as consequence of mutations of Opa1 and Mfn2 genes, respectively. Patients with DOA and CMT2A develop myopathies. Mice with Opa1 mutations show neuromuscular defects related to axonal and myelin degeneration resembling those found in DOA patients (Alavi et al., 2009). These mice also present aberrant and fragmented mitochondria in muscle characterized by disorganized cristae and lipid droplet accumulation. Recent results from a mouse model overexpressing Opa1 support a role for this fusion mediator in the maintenance of muscle homeostasis (Varanita et al., 2015). Indeed, Opa1 transgenic mice seem to be protected from acute muscle loss induced by denervation (Varanita et al., 2015). Finally, muscle-specific ablation of Opa1 in adult mice has been shown to affect whole-body metabolism (Tezze et al., 2017). Indeed, ER stress resulting from Opa1 ablation induces an UPR, stimulates FoxO signaling, and induces a catabolic muscle program. Inhibition of ER stress, either pharmacologically or via muscle-specific deletion of fibroblast growth factor 21 (FGF21), compensates for the loss of Opa1, restoring a normal metabolic state and preventing muscle atrophy and premature death (Tezze et al., 2017).

A role for Mfn signaling in muscle homeostasis has also been suggested. Mfn2 expression is reduced in muscle in several catabolic conditions (Bach et al., 2005; Hernandez-Alvarez et al., 2010; Marzetti et al., 2017b). In addition, decreased protein levels of Mfn2 have been found in muscles from old hip-fractured patients with sarcopenia (Marzetti et al., 2016). Notably, muscle-specific ablation of Mfn1 and Mfn2 in mice induces muscle atrophy, associated with mitochondrial dysfunction, compensatory mitochondrial proliferation, reduction of mtDNA abundance, and accumulation of mtDNA point mutations and deletions (Chen et al., 2010).

Interestingly, muscle ablation of PGC-1α and 1β leads to substantial down-regulation of the gene expression of Mfn1, Mfn2, and Drp1 (Zechner et al., 2010). This finding suggests that mitochondrial dynamics are controlled, at least in part, by these transcriptional coactivators (Soriano et al., 2006). From a mechanistic standpoint, Mfn deficiency may favor muscle atrophy by interfering with mitochondrial networking leading to organelle dysfunction, ROS production, and ultimately UPR (Sebastian et al., 2012).

Similar to mitochondrial fusion, alterations in fission signaling have been shown to induce muscle atrophy. Indeed, overexpression of the fission machinery disintegrates the mitochondrial network causing mitochondrial dysfunction, energy shortage and AMP-activated protein kinase (AMPK) activation (Romanello et al., 2010). In turn, AMPK stimulates FoxO3 activity which induces muscle atrophy via the UPS and autophagy (Romanello et al., 2010). Indeed, FoxO3 induces the expression of several autophagy mediators in muscle, including microtubule-associated protein 1 light chain 3 (LC3) and BCL2 Interacting Protein 3 (Bnip3), as well as the ubiquitin ligases atrogin-1 and muscle RING finger-1 (MuRF-1) (Zhao et al., 2007). Conversely, fission inhibition or AMPK downregulation protects against muscle loss under atrophying conditions (Romanello et al., 2010). Noticeably, fission gene expression was found to be up-regulated in muscles of gastric cancer patients with cachexia (Marzetti et al., 2017b).

Taken as a whole, these findings suggest a causal link between changes in mitochondria morphology and muscle atrophy, which may be harnessed as a therapeutic target for sarcopenia. Given the intricacy of the signaling pathways involved, further research is necessary on the subject, especially in humans.

Autophagy

Autophagy is a recycling process by which intracellular components are degraded within lysosomes as an adaptive response to various stresses (reviewed by Xie and Klionsky, 2007). Mitophagy, instead, involves the selective autophagic removal of mitochondria, a constitutive mechanism governing mitochondrial turnover. Mitophagy is triggered by the loss of mitochondrial membrane potential

(reviewed by Twig et al., 2008) and is aimed at limiting ROS generation and preserving cell homeostasis through the clearance of dysfunctional organelles. However, mitophagy is an extreme attempt of maintaining cellular fitness as mitochondria can also dispose damaged components through an alternative route before organelle degradation is triggered. Indeed, matrix components can be cleared within vesicles budding from dysfunctional but not yet depolarized mitochondria (Soubannier et al., 2012). The signaling pathways activated by the release of mitochondria-derived vescicles (MDV) are illustrated later in the review.

The accumulation of damaged macromolecules and dysfunctional organelles in post-mitotic cells during aging is a major consequence of defective quality control mechanisms, including autophagy.

An age-related decline in the expression of several autophagy and mitophagy regulators and sustained activation of the target of mammalian rapamycin complex 1 (mTORC1) (White et al., 2016) have been found in laboratory rodents and humans (Russ et al., 2012; Joseph et al., 2013; Sandri et al., 2013; Marzetti et al., 2016a; Sebastián et al., 2016). However, increased or unvaried levels of autophagic factors have also been reported (Fry et al., 2013; O'Leary et al., 2013; Picca et al., 2017b).

Either activation or inhibition of autophagy through genetic manipulation is detrimental for myofiber homeostasis and leads to muscle atrophy (Mammucari et al., 2007; Masiero et al., 2009; Romanello et al., 2010). While deficiency of basal autophagy results in the accumulation of dysfunctional cellular components, its overactivation causes cellular stress and protein catabolism. For instance, suppression of autophagy via muscle-specific ablation of autophagy regulatory protein (Atg) 5 and 7 in mice exacerbates the age-related deterioration of neuromuscular junctions (Carnio et al., 2014) and aggravates denervation-induced muscle wasting (Masiero et al., 2009). Similarly, ablation of PTEN-induced putative kinase 1 (PINK1) and Parkin, which are required for mitochondrial priming to mitophagy, induces mitochondrial dysfunction and muscle degeneration (Clark et al., 2006).

Sustained activation of mTORC1 signaling in murine muscles leads to inhibition of autophagy and severe myopathy characterized by the accumulation of p62-containing protein aggregates and dysfunctional mitochondria (Castets et al., 2013). Furthermore, muscle-specific depletion of the autophagy inducer AMPK results in mitochondrial dysfunction and muscle weakness (Bujak et al., 2015). A similar phenotype has been reported in mice with muscle ablation of Mfn2, which leads to inhibition of mitophagy and accumulation of dysfunctional mitochondria (Sebastián et al., 2016).

Dysregulated autophagic flux and alterations of lysosomal enzymes have been found in patients with Pompe disease, Vici syndrome (Sandri et al., 2013; Nascimbeni et al., 2017), and congenital muscular dystrophies (Grumati et al., 2010; De Palma et al., 2012; Ramos et al., 2012). Muscles from these patients show aberrant mitochondria and fiber degeneration. Conversely, increased autophagic flux in muscles has been documented during exercise (LoVerso et al., 2014) and catabolic conditions (Sandri et al., 2013). On the other hand, balanced autophagy maintains quiescence and avoids the senescence of satellite cells in mice, thereby preserving their regenerative capacity (García-Prat et al., 2016).

Well-functioning autophagy in myocytes has relevant implications also for whole-body metabolism. Mice with muscle-specific autophagy inhibition, besides developing muscle atrophy, show browning of white adipose tissue and lipodystrophy (Kim et al., 2013; Guridi et al., 2015). These systemic effects are mediated by the chronic release of fibroblast growth factor 21 (FGF-21) from myocytes secondary to mitochondrial dysfunction (Kim et al., 2013; Guridi et al., 2015). Elevations of circulating FGF-21 levels have also been documented following exercise. Under this circumstance FGF-21 is thought to regulate energy metabolism by stimulating glucose and lipid oxidation (Cuevas-Ramos et al., 2012). In addition to FGF-21, other molecules, collectively termed 'exerkines', are released from exercising muscles and mediate some of the beneficial effects of physical activity (Safdar et al., 2016). Secretory autophagy, a recently described variant of macroautophagy through which the content of autophagosomes is extruded in the extracellular space (Ponpuak et al., 2015), may be a mechanism whereby exerkines and myokines are released. Notably, the muscle secretory factor cathepsin B has recently been indicated as a possible mediator of the beneficial effects of exercise on cognition (Moon et al., 2016).

Given the wide spectrum of processes directly or indirectly influenced by autophagy, its fine tuning is instrumental for maintaining muscle and organismal health into old age. However, several important aspects need to be further investigated in order to develop therapeutic strategies that exploit the homeostatic function of autophagy without incurring the detrimental consequence of its defective or excessive activation. Furthermore, the signaling pathways orchestrating muscle autophagy-induced systemic adaptations need to be dissected to unveil new potential targets for interventions against sarcopenia and organismal aging as a whole.

Feeding inflamm-aging through mitochondrial dysfunction: the circulating mtDNA legacy

Together with mitochondrial dysfunction, chronic inflammation is another hallmark of aging. The term 'inflamm-aging' has been coined to specifically refer to the chronic systemic inflammatory state occurring at a subclinical level during aging (Pinti et al., 2014).

As discussed earlier, while mitochondria that are severely damaged are fissioned and targeted for mitophagy (Youle and Narendra, 2011), dysfunctional but not yet depolarized mitochondria are delivered within MDVs to lysosomes as an early response to oxidative stress (Soubannier et al., 2012). The MDV pathway is also used to release exerkines following exercise through a system of vesicles called exosomes (Safdar et al., 2016).

The accumulation of severely damaged mitochondria in the context of defective mitophagy has been shown to induce the extrusion of several components able to stimulate inflammation (Caielli et al., 2016). This pathway operates through the accumulation and release of damage-associated molecular patterns (DAMPs) (i.e. cell-free mtDNA, *N*-formyl peptides and cardiolipin) by injured cells (Krysko et al., 2011) that activate caspase-1 and induce the release of pro-inflammatory cytokines.

Circulating cell-free mtDNA has been indicated as one of the DAMPs that may establish a functional relationship between mitochondrial damage and systemic inflammation (reviewed by Picca et al., 2017a). MtDNA contains hypomethylated CpG motifs resembling those of bacterial DNA and therefore able to induce an inflammatory response (Davies et al., 2013). These regions bind and activate membrane or cytoplasmic pattern recognition receptors (PRRs), such as the Toll-like receptor (TLR), the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR) (Collins et al., 2004), and the cytosolic cyclic GMP-AMP synthase (cGAS)-stimulator of interferon genes (STING) DNA sensing system-mediated pathways (Cai et al., 2014). Notably, circulating levels of mtDNA molecules increase progressively with age and correlate with those of systemic pro-inflammatory cytokines, including interleukin (IL) 6, tumor necrosis factor alpha (TNF-α), regulated on activation normal T cell expressed and secreted (RANTES), and IL1 receptor antagonist (Pinti et al., 2014). Some of these cytokines can also modulate the gene expression program of

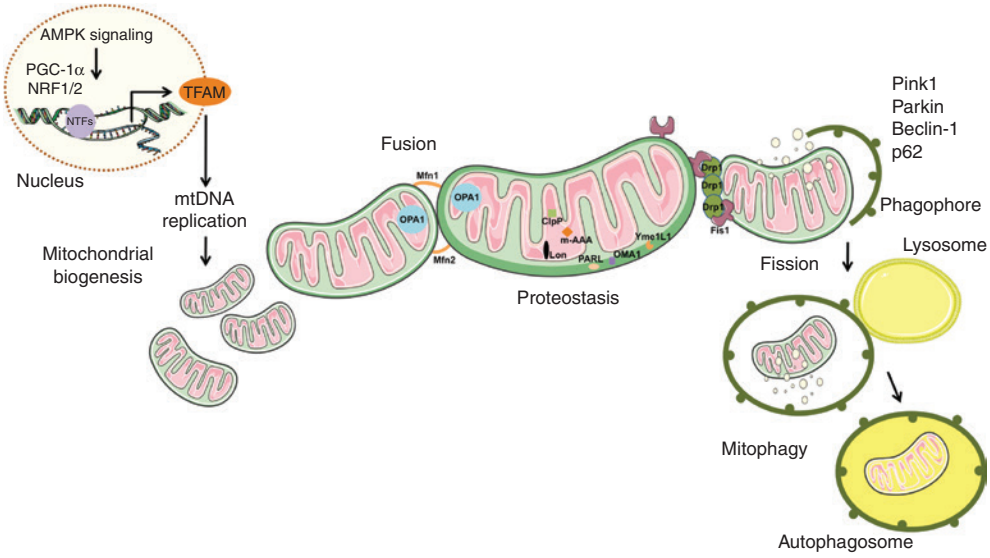

Figure 2: Mitochondrial quality control relies on the coordinated activity of mitochondrial biogenesis, dynamics, proteostasis and mitophagy.
Mitochondrial biogenesis is triggered by several stimuli [e.g. AMP-activated protein kinase (AMPK) signaling] and converges on the expression of specific transcription factors (TFs) [e.g. peroxisome proliferator-activated receptor gamma coactivator-1 (PGC-1), nuclear respiratory factor 1 and 2 (NRF-1/2), mitochondrial transcription factor A (TFAM)]. TFAM is subsequently transported into mitochondria and, through its binding to mitochondrial DNA (mtDNA), modulates the replication of the mitochondrial genome which is crucial to mitochondriogenesis. Mitochondrial dynamics involves fusion and fission events through the recruitment of mitofusin (Mfn) 1 and 2, optic atrophy protein 1 (OPA1), dynamin-related protein 1 (Drp1) and fission protein 1 (Fis1). Mitochondrial proteostasis regulates mitochondrial function through the activity of specific mitoproteases (e.g. Lon, ClpP, Oma1, Yme1L1, PARL). Finally, mitophagy ensures the selective degradation of dysfunctional organelles through several mediators, including PTEN-induced putative kinase 1 (PINK1), Parkin, Beclin 1 and p62.

satellite cells, thereby influencing muscle regeneration (Thorley et al., 2015).

Systemic inflammation is also a feature of several musculoskeletal disorders. Recently, a fracture-initiated systemic inflammatory response syndrome (SIRS), characterized by increased circulating levels of cell-free mtDNA, has been documented in patients with hip fracture (Li et al., 2016). In this context, circulating mtDNA seems to promote the development of inflammation by recruiting leucocytes (Li et al., 2016). We recently described two candidate mechanisms (i.e. dysregulation of TFAM binding to mtDNA, and impairment of mitophagy) generating inflammatory mediators in sarcopenia and cachexia, two major muscles wasting disorders (Picca et al., 2018). However, additional research is needed in order to provide better understanding of these conditions.

Taken together, these findings suggest the existence of a functional link between mitochondrial dysfunction in myocytes and systemic inflammation, possibly mediated by the release of mtDNA into the circulation. Conversely, anti-inflammatory interventions such as moderate aerobic exercise, decrease systemic cell-free mtDNA levels in healthy adults (Shockett et al., 2016).

Conclusions and future perspectives

Although we are still far from understanding the events that occur first and trigger muscle atrophy during aging, there is wide consensus on the central role played by mitochondrial dysfunction in this process. MQC mechanisms, although orchestrated as a single operating unit within the cell, result from the convergence of multiple signaling routes (Figure 2). These pathways, either *per se* or in crosstalk with other cellular processes, contribute to the maintenance of muscle homeostasis (Figure 3).

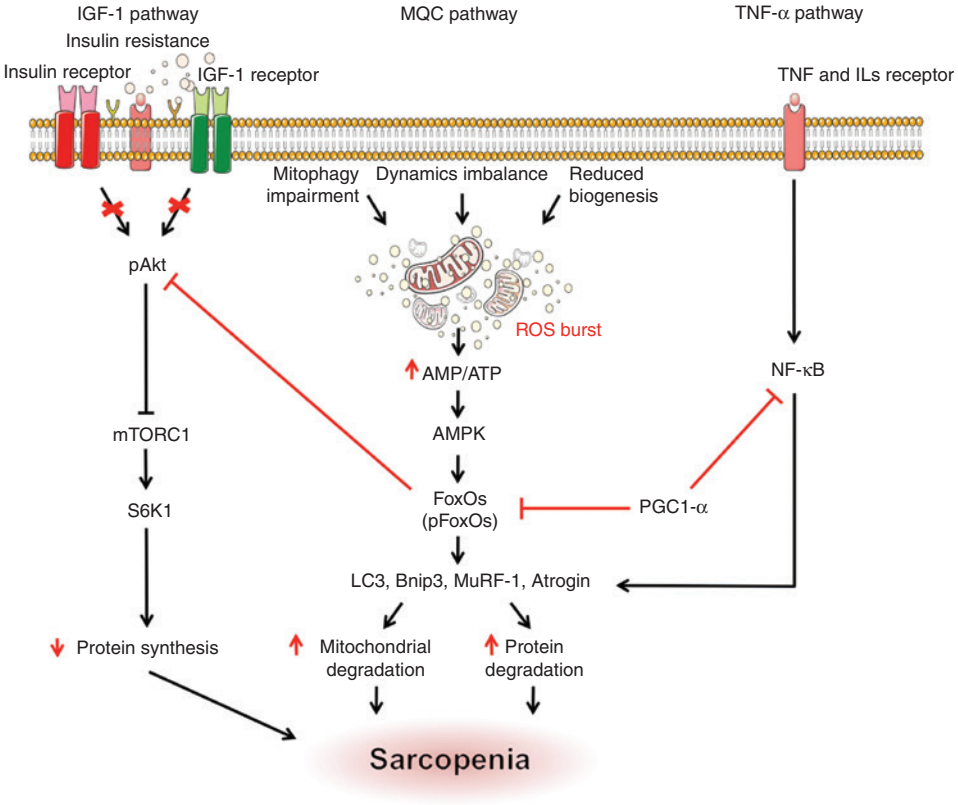

Figure 3: Insulin-like growing factor-1 (IGF-1) signaling, mitochondrial quality control (MQC) mechanisms and inflammatory pathway are among the most relevant routes generating mediators controlling muscle mass.
In particular, alterations at any level of the MQC axis perpetuate along the mitochondrial network and accumulate damaged organelles. As a consequence, the increase in the AMP/ATP ratio and the ROS burst arising from defective organelles activate a catabolic pathway that leads to muscle atrophy through the activation of forkhead box O (FoxO) family members via AMPK signaling. This route involves both autophagy-related mediators [e.g. microtubule-associated protein 1 light chain 3 (LC3), BCL2 Interacting Protein 3 (Bnip3)] and muscle catabolism inducers [e.g. muscle RING finger-1 (MuRF-1), atrogin] leading to mitochondrial degradation and protein breakdown to provide alternative energy sources.

Derangements at any level of the MQC machinery can impinge the whole system. Suffice is to say that the transcriptional coactivators PGC-1α and PGC-1β control the protein expression of mitochondrial Mfn1 and Mfn2 (Soriano et al., 2006) and fine tune autophagy during some forms of disuse atrophy (Vainshtein et al., 2015).

Over the last years, mitochondria have been recognized to establish direct or indirect contacts with other cellular components (e.g. ER, peroxisomes and lysosomes/vacuoles) as well as the extracellular environment through MDV release. However, the functional consequences of these interactions to muscle physiology are not yet fully appreciated and represent a new frontier in the research field. Indeed, mitochondria-derived metabolites can shuttle within cells and the whole organism. Exploring the interrelation between MQC pathways and the metabolic regulation of muscle mass as well as the muscle-interorgans crosstalk may provide additional insights to unveil new pathways that may be exploited for devising preventive and therapeutic interventions against muscle aging.

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