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From mitochondria to sarcopenia: role of inflammaging and RAGE-ligand axis implication

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Abstract

Sarcopenia is characterized by a loss of muscle mass and function that reduces mobility, diminishes quality of life, and can lead to fall-related injuries. At the intracellular level, mitochondrial population alterations are considered as key contributors to the complex etiology of sarcopenia. Mitochondrial dysfunctions lead to reactive oxygen species production, altered cellular proteostasis, and promotes inflammation. Interestingly, the receptor for advanced glycation end-products (RAGE) is a pro-inflammatory receptor involved in inflammaging.

In this review, after a brief description of sarcopenia, we will describe how mitochondria and the pathways controlling mitochondrial population quality could participate to age-induced muscle mass and force loss. Finally, we will discuss the RAGE-ligand axis during aging and its possible connection with mitochondria to control inflammaging and sarcopenia.

Key-words: mitochondria; sarcopenia; inflammation; aging; inflammaging; RAGE

Introduction

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability, and mortality (Cruz-Jentoft *et al.*, 2019*a*). Concomitantly to physical alteration, the sarcopenia process is accompanied by a time-dependent progressive deterioration of cellular function (Son & Lee, 2019). Metabolism and inflammation have emerged as key regulators. Indeed, mitochondrial alterations correlate with the decrease of muscle strength, cardiorespiratory function, and muscle function (Brookes *et al.*, 2004), whereas inflammation increases during sarcopenia development (Dalle *et al.*, 2017). In this context, mitochondria are considered to play a key role due to their production of reactive oxygen species (ROS) and their ability to release pro-inflammatory components. However, important aspects of mitochondrial biology remain to be investigated in the sarcopenia process (Gouspillou & Hepple, 2016). The objective of the review is to describe the mitochondrial pathways linked to sarcopenia with a specific focus on inflammation and the hypothesis of the involvement of the receptor for advanced glycation end-products (RAGE).

First, we provide a brief overview of the loss of muscle mass and function in sarcopenia. We then describe the mitochondrial involvement in sarcopenia with specific emphasis on mitochondrial function, mitochondrial biogenesis, and mitochondrial proteostasis. We discuss the potential link between mitochondrial dysfunction and inflammaging. Finally, we consider the possible interplay between RAGE and mitochondria in the inflammaging and sarcopenia.

Sarcopenia: Loss of muscle mass and function

Loss of muscle mass and strength is a fundamental feature of sarcopenia. In the recent diagnostic guidelines, muscle strength comes at the forefront, as it is recognized that strength is better than mass in predicting adverse outcomes (Cruz-Jentoft *et al.*, 2019*b*). Muscle strength declines between 3 and 8% per decade after midlife and, after 60 years, the rate of decline accelerates (Goodpaster *et al.*, 2006). The loss of strength appeared to be much more rapid than the concomitant loss of muscle mass, suggesting that muscle quality is also impaired in sarcopenia. Indeed, changes in the motor unit occur with aging. One of the primary causes of sarcopenia is the loss of muscle fiber innervation by α-motoneurons triggered by spinal motor neuron apoptosis and distal axon retraction (Hunter *et al.*, 2016). This process begins gradually with aging, accelerates after 60 years and beyond (Tomlinson & Irving, 1977), and is in part due to oxidative stress and inflammation (Opalach *et al.*, 2010). Moreover, an age-related decrease in muscle contractility along with alterations in excitation-contraction coupling and contractile parameters (maximal force and unloaded shortening velocity) have been reported (Payne *et al.*, 2010; Hunter *et al.*, 2016). A decrease up to 28% in maximal force and in maximal unloaded shortening velocity in single permeabilized fibers from human *vastus lateralis* has been observed (D'Antona *et al.*, 2003). The reduced contraction velocity is associated with slower cross-bridge kinetics, which are probably due to slower cross-bridge mechanics and slower rates of Ca^{2+} uptake into the sarcoplasmic reticulum (Hunter *et al.*, 2016). In addition, morphological changes in the fiber type composition occur with smaller fibers in old and very old adults compared with young adults (Lexell *et al.*, 1988). While some evidence supports that the age-related reduction in fiber cross-sectional area occurs to a greater extent in fast-twitch muscle fibers, atrophy is marked in all fiber types in very old adults (Lexell *et al.*, 1988; Purves-Smith *et al.*, 2014).

The age-related changes in muscle morphology and properties alter performance assessed by muscle isometric or dynamic strength and fatigability tests. The maximal isometric strength reduction observed during aging parallels the loss of muscle mass (Metter *et al.*, 1999). Based on cross-sectional studies, muscle isometric strength is usually reduced by ~10% per decade which begins at approximately 40-50 years of age and accelerates in very old age, so that the average strength of an 80 year-old person can be ~40% that of a 30 year-old man (Hunter *et al.*, 2016). The strength decrease is explained in part by greater infiltration of fat and connective tissue (Goodpaster *et al.*, 2008). Concomitantly, the maximal torque during isokinetic dynamic contraction is also reduced with aging, both at slow and fast angular velocities (Frontera *et al.*, 2000). However, the reduction in maximal torque is larger at fast angular velocity than at low velocity (Lanza *et al.*, 2003). A sex-related difference has been reported with greater preservation of maximal torque in women in eccentric contraction (Lindle *et al.*, 1997). The underlying mechanisms for the age and sex-related differences may involve elastic, structural, and cross-bridge properties of the skeletal muscle (Hunter *et al.*, 2016).

Similarly, sarcopenia-related reductions in maximal power have been observed and are greater in magnitude than for maximal strength (Fried *et al.*, 2001; Bischoff *et al.*, 2003; Johnson Stoklossa *et al.*, 2017). The assessment of the maximal power is of interest as it is predictive of functional tasks and disability (Bischoff *et al.*, 2003). The ability to reach fast velocities (>270 deg/s) decreases in older adults and may be the result of concomitant reductions in maximal shortening velocities of single fibers, especially fast-twitch fibers and the role of inadequate activation of the motor units (Fried *et al.*, 2001; Bischoff *et al.*, 2003; Hunter *et al.*, 2016).

The ability to maintain a determined level of force or power decreases with aging (Ishii *et al.*, 2014). Isometric fatigue during maximal and submaximal exercise increases with aging even when matched for strength for both men and women (Bahat *et al.*, 2018*b*, 2018*a*). Moreover, the increased fatigability impairs performance of daily activities and may further exacerbate the age-related loss of strength and power (Hunter *et al.*, 2016; Johnson Stoklossa *et al.*, 2017).

Mitochondrial involvement in sarcopenia

Mitochondria are organelles involved in the regulation of many critical cellular processes in skeletal muscle. Indeed, they play a central role in energy supply, cellular proteostasis, ROS production, calcium homeostasis, and regulation of apoptosis (Brookes *et al.*, 2004). Mitochondrial bioenergetic alterations with aging correlate with muscle strength, cardiorespiratory measurements, and muscle function, supporting the involvement of mitochondria in the sarcopenia process (Gouspillou *et al.*, 2014; Gonzalez-Freire *et al.*, 2018) (Figure 1A). Indeed, evidence from the Baltimore Longitudinal Study of Aging indicates that mitochondrial respiration in skeletal muscle parallels the decline of maximal aerobic capacity, time in 400m test, grip strength, and leg muscle strength (Gonzalez-Freire *et al.*, 2018).

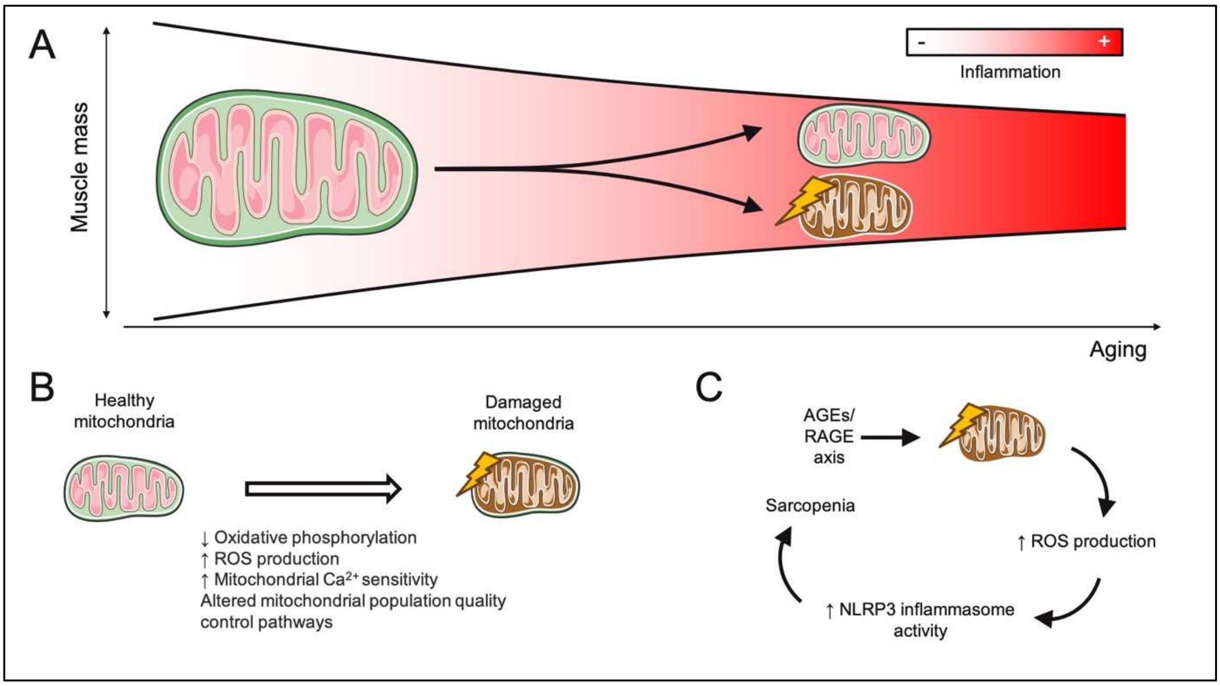

Figure 1: Mitochondrial involvement in sarcopenia and inflammaging processes. A. Skeletal muscle mass decreases with aging, inflammation and mitochondrial dysfunctions, which lead to decreased oxidative phosphorylation, enhanced ROS production and mitochondrial calcium sensitivity, and altered mitochondrial population quality control pathways (biogenesis, dynamics, mitophagy, proteostasis). B. Characteristics of healthy *vs.* damaged mitochondria. C. Mitochondria may promote inflammation through the increase of the Nod-like receptor family, pyrin domain containing 3 (NLRP3) activity that will participate to sarcopenia. Advanced glycation end-products (AGEs)/Receptor for advanced glycation end-products axis may promote mitochondrial dysfunctions leading to the vicious circle of inflammaging.

In vitro experiments on mitochondrial function have provided conflicting results. While some studies observed an aging-related decrease in maximal oxidation rate (Tonkonogi *et al.*, 2003; Gouspillou *et al.*, 2014), others failed to observed any modification of mitochondrial oxidative phosphorylation (Rasmussen *et al.*, 2003; Picard *et al.*, 2010). This lack of consensus may be explained by: i) the differences in experimental procedures as mitochondrial respiration is affected by the isolation process independently of aging (Picard *et al.*, 2010), ii) many studies have not controlled important covariates such as physical activity (Boffoli *et al.*, 1994), and iii) all the studies assessed mitochondrial oxidative phosphorylation only under extreme conditions of mitochondrial activity (*i.e.*, maximal respiratory activity and basal respiration in the absence of ATP synthesis). However, a recent study comparing the molecular signatures of sarcopenic *vs.* healthy older people observed that low mitochondrial bioenergetic capacity is the dominant signal in the transition from physiological to pathological muscle aging across ethnic groups (Migliavacca *et al.*, 2019*a*). Collectively, these findings support altered mitochondrial oxidative capacity as a major determinant in sarcopenia.

Cellular proteostasis is a key process to maintain all cellular functions. When there is a mismatch between the rate of ATP production and the demand for ATP, expendable cellular processes are sacrificed (Hou, 2013). When ATP production is constrained, cells make trade-offs between growth and somatic maintenance (Hou, 2013). Therefore, mitochondrial alterations to produce ATP can in turn compromise cellular proteostasis.

Mitochondria are considered as the main source of ROS production. While transient higher ROS production supports signaling mechanisms, chronic elevation of oxidative stress is often pathogenic and may trigger muscle atrophy (Powers *et al.*, 2011). Indeed, mild oxidative stress production increases skeletal muscle force, while further increases reduce force and promote muscle fatigue (Kramer *et al.*, 2015). Aging-related increase in mitochondrial ROS production has been extensively described (Capel *et al.*, 2005; Picard *et al.*, 2010; Dai *et al.*, 2014). Moreover, mitochondria from aged muscle generate more ROS compared to young counterparts for a given concentration of ADP, suggesting that qualitative adaptations occur (Holloway *et al.*, 2018). Considering the age-related decrease of cellular antioxidant activities, higher ROS production leads to an increase in the concentration of unscavenged ROS (Dai *et al.*, 2014). Collectively, the enhanced mitochondrial ROS production with aging supports the free radical theory of aging proposed by Harman in 1956, which suggests that free radical-induced accumulation of damage to cellular macromolecules is a primary driving force of aging (Harman, 1956).

Calcium is a key regulator of mitochondrial function and acts at several levels within the organelle. For instance, mitochondrial calcium overload increases ROS production and stimulates mitochondrial permeability transition pore opening, inducing the release of pro-apoptotic factors such as cytochrome c or endonuclease G (Brookes *et al.*, 2004). Animal studies showed an increased sensitivity of mitochondrial permeability transition pore with aging (Chabi *et al.*, 2008*a*; Picard *et al.*, 2010). This is consistent with studies indicating an increased incidence of apoptosis in aged skeletal muscle (Siu *et al.*, 2005; Chabi *et al.*, 2008*a*).

Collectively, these data support that mitochondrial alterations are important contributors to the complex etiology of sarcopenia (Figure 1B, C). Thus, therapeutic strategies that improve mitochondrial function may mitigate, delay or treat sarcopenia (Coen *et al.*, 2018). While the importance of normal mitochondrial function is well recognized for muscle physiology, there are important aspects of mitochondrial biology that require to be investigated in the sarcopenia process (Gouspillou & Hepple, 2016). These include mitochondrial dynamics, biogenesis, proteostasis, and mitophagy.

Mitochondrial dynamics in sarcopenia

Mitochondria are not independent organelles but rather constitute a network in constant remodeling, animated by fusion and fission processes that are crucial to keep a healthy mitochondrial population (Yu *et al.*, 2020). Fusion is mainly controlled by mitofusins 1 and 2 (MFN1/MFN2), GTPases inserted in the outer membrane, as well as the optic atrophy 1 (OPA1) protein, which mediates the inner membrane fusion. In turn, it allows mtDNA exchange ensuring mtDNA integrity and complementation as well as the maintenance of the OXPHOS capacity (Chen *et al.*, 2010). On the other hand, recruitment of the cytosolic GTPase dynamin-related protein 1 (DRP1) through interaction with outer membrane proteins such as the mitochondrial fission factor (MFF) or the mitochondrial fission 1 (FIS1) favors mitochondrial fission upon GTP hydrolysis.

Alterations in mitochondrial morphology and function have been associated with changes in mitochondrial dynamics in aged skeletal muscle in humans and experimental animal models. For instance, elderly subjects elicit lower amount of muscular OPA1 (Joseph *et al.*, 2012; Tezze *et al.*, 2017*a*; Liu *et al.*, 2020) and MFN2 proteins (Marzetti *et al.*, 2016; Liu *et al.*, 2020). Similar results are found in mouse models of aging (Sebastián *et al.*, 2016; Liu *et al.*, 2020). The causative link between changes in mitochondrial dynamics and sarcopenia is suggested by the results obtained from mice invalidated for mitochondrial dynamics genes. Indeed, Mfn2 deficiency leads to mitochondrial dysfunction, reduces autophagy, impairs muscle force, and promotes sarcopenia (Sebastián *et al.*, 2016). Opa1 ablation also alters mitochondrial morphology and function, inducing a catabolic program of muscle loss (Tezze *et al.*, 2017*a*; Romanello *et al.*, 2019). Unbalance of the mitochondrial dynamics through alteration of the fission machinery, by invalidating Drp1, also alters morphology, function and calcium homeostasis in mitochondria (Favaro *et al.*, 2019), causing muscle wasting and weakness. Interestingly, rather than alterations in whether fusion or fission, a proper balance between these two processes is suggested to be the most important (Romanello *et al.*, 2019).

Mitochondrial biogenesis in sarcopenia

Beside mitochondrial morphology alterations, fewer mitochondria have been observed in skeletal muscle from aged adults (Crane *et al.*, 2010). This points to the mitochondrial biogenesis program, which involves a cooperation between nuclear and mitochondrial genomes, through successive expression of transcription factors (Popov, 2020). The most important is the peroxisome proliferator-activated receptor-γ coactivator (PGC)-1α, whose activity is enhanced by phosphorylation and sirtuin 1-dependent deacetylation. This master regulator allows the expression of nuclear respiratory factors 1 & 2 (NRF 1 & 2), nuclear hormone receptors, such as peroxisome proliferator-activated receptor PPARα, PPARδ, the estrogen-related receptor-α (ERR-α), and the mitochondrial transcription factor A (TFAM) (Vega *et al.*, 2000; Scarpulla, 2006; Wang *et al.*, 2013). TFAM is a key protein for the replication, transcription, and protection of mitochondrial DNA (mtDNA), while PGC-1α activation enhances expression and import of mitochondrial proteins involved in the fatty acid oxidation, tricarboxylic acid cycle, and OXPHOS.

In skeletal muscle of elderly people, lower amount of PGC-1α along with reduced amount in mitochondrial proteins have been reported (Short *et al.*, 2005; Safdar *et al.*, 2010; Joseph *et al.*, 2012; Migliavacca *et al.*, 2019*b*). Reduction in biogenesis-related gene expression is also found in experimental aging (Chabi *et al.*, 2008*b*; Liu *et al.*, 2020). Involvement of mitochondrial biogenesis in the aging process has been confirmed by Nrf2 invalidation, which leads to muscle atrophy and declined physical function in old mice. As expected, it was associated with a reduction in mitochondrial content, mtDNA copy number and mitochondrial protein expression, and with higher oxidative stress (Huang *et al.*, 2019; Kitaoka *et al.*, 2019). In line, overexpression of PGC-1α in muscle (Dillon *et al.*, 2012; Garcia *et al.*, 2018) minimized the effects of aging on muscle oxidative capacity, mitochondrial protein content, and changes gene expression towards a younger transcriptome profile. This suggests that the mitochondrial biogenesis program could participate to sarcopenia.

Towards a role of mitochondrial proteostasis in sarcopenia

Mitochondrial proteins can undergo oxidative posttranslational modifications and be misfolded. Elimination of these abnormal proteins requires specific proteases and sorting pathways towards the proteasome. Altered mitochondrial protein defenses regroup a large number of proteases, called mitoproteases, that can, among other functions, degrade misfolded and damaged proteins and may be involved in the mitochondrial stress response. Among these mitoproteases are found Lon protease homologue 1 (LONP1), the ATP-dependent Clp protease proteolytic subunit (CLPP), the mitochondrial inner membrane protease ATP23, and the intermembrane high-temperature requirement Serine Peptidase 2 (HTRA2/OMI) (Quirós *et al.*, 2015). While expression of the Lon protease has been found to be reduced in muscle from old rats, exercise training blunted this decrease and could help mitochondria to cope with altered mitochondrial proteins that increase with age (Koltai *et al.*, 2012). Interestingly, invalidation of HTRA2/OMI in mice led to a sarcopenic phenotype associated with impaired mitochondrial function, reduced mitochondrial biogenesis signaling, and altered mitochondrial Unfolded Protein Response (mtUPR) activation (Zhou *et al.*, 2020). The mtUPR is a signaling pathway aiming at improving folding capacity in response to OXPHOS alterations, ROS production, stoichiometric imbalance between nuclear and mitochondrial-encoded proteins, and accumulation of misfolded proteins. This pathway leads to phosphorylation of the eukaryotic translation initiation factor 2 subunit 1 (eIF2α). Although better understood in *C. elegans (Shpilka & Haynes, 2018)*, in mammals, activated eIF2α will preferentially translate C/EBP homologous *protein* (CHOP), activating transcription factors 4 & 5 (ATF4 & ATF5). Among their target genes belong the mitochondrial chaperone mtHSP70, LONP1, and CLPP. Moreover, growth/differentiation factor 15 (GDF15) and fibroblast growth factor 21 (FGF21), hormones released upon mitochondrial stress and considered as myomitokines, are the respective target genes of CHOP and ATF4 (Kim *et al.*, 2013; Chung *et al.*, 2017). Their circulating levels are increased with age and may contribute to muscle wasting and sarcopenia (Ito *et al.*, 2018; Oost *et al.*, 2019; Nakajima *et al.*, 2019; Semba *et al.*, 2020). However, whether the implication of the mtUPR is the underlying mechanism requires specific studies in the context of sarcopenia.

Removal of damaged mitochondrial components in sarcopenia

Autophagy of mitochondria (mitophagy) is an additional system ensuring the quality of the mitochondrial population through the recycling of damaged mitochondrial components (Pickles *et al.*, 2018). It shares common features with autophagy (Dikic, 2017), including the formation of a double-membrane vesicle which engulfs cytosolic material and closes to form the autophagosome. The latter will fuse with lysosomes to allow the acidic lysosomal proteases degrading its content. Among mitophagy proteins, PTEN-induced putative kinase 1 (PINK1) and cytosolic E3 ubiquitin ligase Parkin seem to be involved in response to mitochondrial damage (Chen *et al.*, 2020). Under basal conditions, PINK1, which is imported into mitochondria through translocase complexes, undergoes proteolytic cleavage and is sent to the proteasome for degradation. In case of damaged mitochondria, PINK1 can no longer be imported to mitochondria and remains uncleaved, leading to its stabilization. In turn, PINK1 phosphorylates Parkin, favoring ubiquitination of various mitochondrial substrates. Ubiquitin moieties are then recognized by autophagy protein receptors that will be connected to autophagosomes (Pickles *et al.*, 2018).

Studies indicate that aging modifies mitophagy-related proteins (O'Leary *et al.*, 2013; Drummond *et al.*, 2014; Marzetti *et al.*, 2016; Sebastián *et al.*, 2016; Sebastián & Zorzano, 2016; Sakellariou *et al.*, 2016; Yeo *et al.*, 2019; Liu *et al.*, 2020) although flux studies have not always been performed to conclude on its activation or inhibition (Klionsky *et al.*, 2016). Nevertheless, insight is brought by mitophagy-related gene modulation. Overexpression of Parkin led to increased muscle mass and strength, along with improved mitochondrial biogenesis and activity (Leduc-Gaudet *et al.*, 2019). It also weakened the oxidative stress observed in aged animals. Thus, activation of mitophagy by Parkin could prevent or delay muscle mass loss (Leduc-Gaudet *et al.*, 2019). Nevertheless, other studies point to the complexity and the interrelationships between the different pathways controlling mitochondria fitness. For instance, Mfn2 ablation, which favored muscle aging, also reduced the autophagy and could contribute to the accumulation of defective mitochondria (Sebastián *et al.*, 2016; Sebastián & Zorzano, 2016). Alternatively, PGC-1α overexpression reduced the expression of mitophagy proteins that were increased by aging (Yeo *et al.*, 2019). Surprisingly, ROS inhibition increased PINK1 recruitment in isolated muscle mitochondria, suggesting higher mitophagy (Sakellariou *et al.*, 2016). However, these changes were not associated with a reduction of age-induced muscle atrophy (Sakellariou *et al.*, 2016). Control of mitophagy may even be more complex since miRNA could also be involved. Indeed, miR181a, which is downregulated with age, was associated with accumulation of abnormal mitochondria, probably due to impaired mitophagy flux (Goljanek-Whysall *et al.*, 2020).

Mitochondria-derived vesicles (MDV) have also been identified as alternative pathways to eliminate damaged mitochondria (Neuspiel *et al.*, 2008; Roberts *et al.*, 2016). Recently, small extracellular vesicles have been found to be increased in serum from physical frailty and sarcopenic subjects compared to controls but these vesicles did not seem to be MDV since they did not content ATP5A (complex V), NDUFS3 (complex I), and SDHB (complex II), although other mitochondrial components such as mtDNA have not been evaluated (Picca *et al.*, 2020). This could highlight that, as mitophagy, the mitochondrial-lysosomal axis is inefficient to eliminate damaged mitochondria. Nevertheless, MDV could serve as a biomarker for physical frailty and sarcopenia (Picca *et al.*, 2020).

Disturbances in mitochondrial population quality: a link towards inflammaging and sarcopenia?

Chronic low grade and sterile inflammation is a key feature observed during aging and is now referred to as inflammaging. Although the pro-inflammatory state is far from acute inflammation caused by bacteria, viruses or parasites, 3 to 5-fold increases in IL-1β and TNFα are observed in 70-year-old patients compared to 20-year-old subjects (Zembron-Lacny *et al.*, 2019).

Increases in IL-6 and C reactive protein (CRP) are also reported (Schaap *et al.*, 2006; Meng *et al.*, 2015). More importantly, these inflammatory variables are inversely associated with the poor physical performance (Wannamethee *et al.*, 2002; Schaap *et al.*, 2006; Meng *et al.*, 2015; Dalle *et al.*, 2017; Zembron-Lacny *et al.*, 2019)(Figure 1A). Indeed, inflammation could lead to imbalance between protein synthesis and degradation, reduction in satellite cell activation or increased cell apoptosis (Dalle *et al.*, 2017). An upstream trigger of inflammaging could be mitochondria since mitochondrial components can be released to promote inflammation. Indeed, human neutrophils have a constitutive defect in mitophagy but developed alternative pathways to eliminate damaged mitochondrial components: inner mitochondrial components extrusion or exportation to lysosomes (Caielli *et al.*, 2016). In case of oxidative stress, a hallmark of aging, oxidized mtDNA can eventually be extruded and stimulate inflammation. Other altered mitochondrial components such as N-formyl peptides, cardiolipin or TFAM can also be released and constitute mitochondrial Damage-Associated Molecular Patterns (DAMPs) (Nakahira *et al.*, 2015; Tezze *et al.*, 2017*b*). Interestingly, mtDNA plasma levels increase after 60 years of age. Elderly people with the highest amount of circulating mtDNA also had the highest amount of pro-inflammatory cytokines such as TNFα or IL-6 (Pinti *et al.*, 2014). Downstream pathways could involve the activation of Toll-like receptors, the STING-TBK1 pathway and also the Nod-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome, which is a multi-protein signaling complex that triggers the activation of inflammatory caspases and the maturation of interleukin-1ß (Jo *et al.*, 2016; Sun *et al.*, 2016). Thus, mitochondria can be considered as the principal drivers of NLRP3-mediated inflammation as they can modulate innate immunity *via* redox-sensitive inflammatory pathways or directly activate the inflammasome complex. This is of particular interest since NLRP3 activation may contribute to sarcopenia (McBride *et al.*, 2017; Sayed *et al.*, 2019). Therefore, upstream strategies aiming at improving mitochondrial population quality, including stimulation of mitophagy (Chen *et al.*, 2020), could represent innovative ways to fight age-related disorders, including sarcopenia.

Alternatively, another interesting target could be the advanced glycation end-products (AGEs), compounds resulting from the Maillard reaction between sugars and proteins. Indeed, increases in AGEs may trigger mitochondrial dysfunction (Neviere *et al.*, 2016) and more importantly several studies indicate that AGEs are also capable of NLRP3 activation in different settings (Kong *et al.*, 2017; Son *et al.*, 2017; Song *et al.*, 2017) (Figure 1C). While it remains unknown whether these AGEs could link inflammation and age-related muscle mass loss, their action could be counterbalanced since they bind to specific receptors.

RAGE: a bridge between mitochondrial dysfunction and inflammaging?

RAGE, the Receptor for Advanced Glycation End-products, is a transmembrane receptor expressed by most of the cells in human tissues and organs (Schmidt *et al.*, 1992; Boulanger *et al.*, 2007). RAGE expression and activation have been initially studied during diabetes mellitus because of high AGEs levels especially N_{ε}carboxymethyllysine (CML), the AGE presenting the highest affinity for RAGE (Schmidt *et al.*, 1992; Tessier *et al.*, 2016). AGEs form a heterogeneous group of molecules resulting from sugar binding to amino-compounds like lysine and arginine, specifically (Boulanger *et al.*, 2004). Their production is increased during hyperglycemia (diabetes), renal failure, inflammation (oxidative stress), and aging (time)(Frimat *et al.*, 2017).

RAGE activation is followed by a pro-inflammatory, pro-oxidative, pro-adhesion, pro-apoptotic, pro-angiogenic, and pro-fibrotic cell response. Its activation by AGEs has been identified in the skeletal muscle of diabetic patients and elevated circulating AGEs in elderly and/or diabetic patients correlate with muscle mass reduction, lower grip strength, and walking speed (Chiu *et al.*, 2016). AGE production and accumulation in myofibrils are linked with RAGE overexpression, muscular atrophy, and intolerance of exercise in murine models (Egawa *et al.*, 2017). In RAGE null mice, AGE accumulation in skeletal muscle of diabetic mice prevents AGE deleterious effects on organ function (Chiu *et al.*, 2016). RAGE activation is followed by ROS generation through cytosolic NADPH oxidase and mitochondrial electron transport chain. Activation of RAGE-ligand axis decreases cellular stress defenses, such as sirtuins (SIRT). Since AGE exposure is associated to suppression of SIRT1 and SIRT3 expression, inhibition of RAGE-ligand axis could reduce deleterious oxidative stress, especially here, on muscular mitochondria (Cai *et al.*, 2012; Yu *et al.*, 2017).

More than 28 RAGE ligands have been reported today, most of them being DAMPs or pathogen-associated molecular patterns (PAMPs). Some of these ligands also belong to the group of molecules produced during physiological aging. Such molecules are associated to the SASP, Senescence-Associated Secretory Phenotype. It is very interesting to hypothesize that during physiological aging, the production of "SASP molecules" like S100 and high–mobility group box-1 (HMGB-1), which are RAGE ligands for example, can therefore activate RAGE. Apart from physiological aging, S100 and HMGB-1 are also produced in response to RAGE activation during pathological conditions: diabetes, renal failure, inflammation. It is then easy to conceptualized the vicious circle of RAGE implication during inflammaging, that we call "RAGEING", illustrated in Figure.2 (Wautier, 2019).

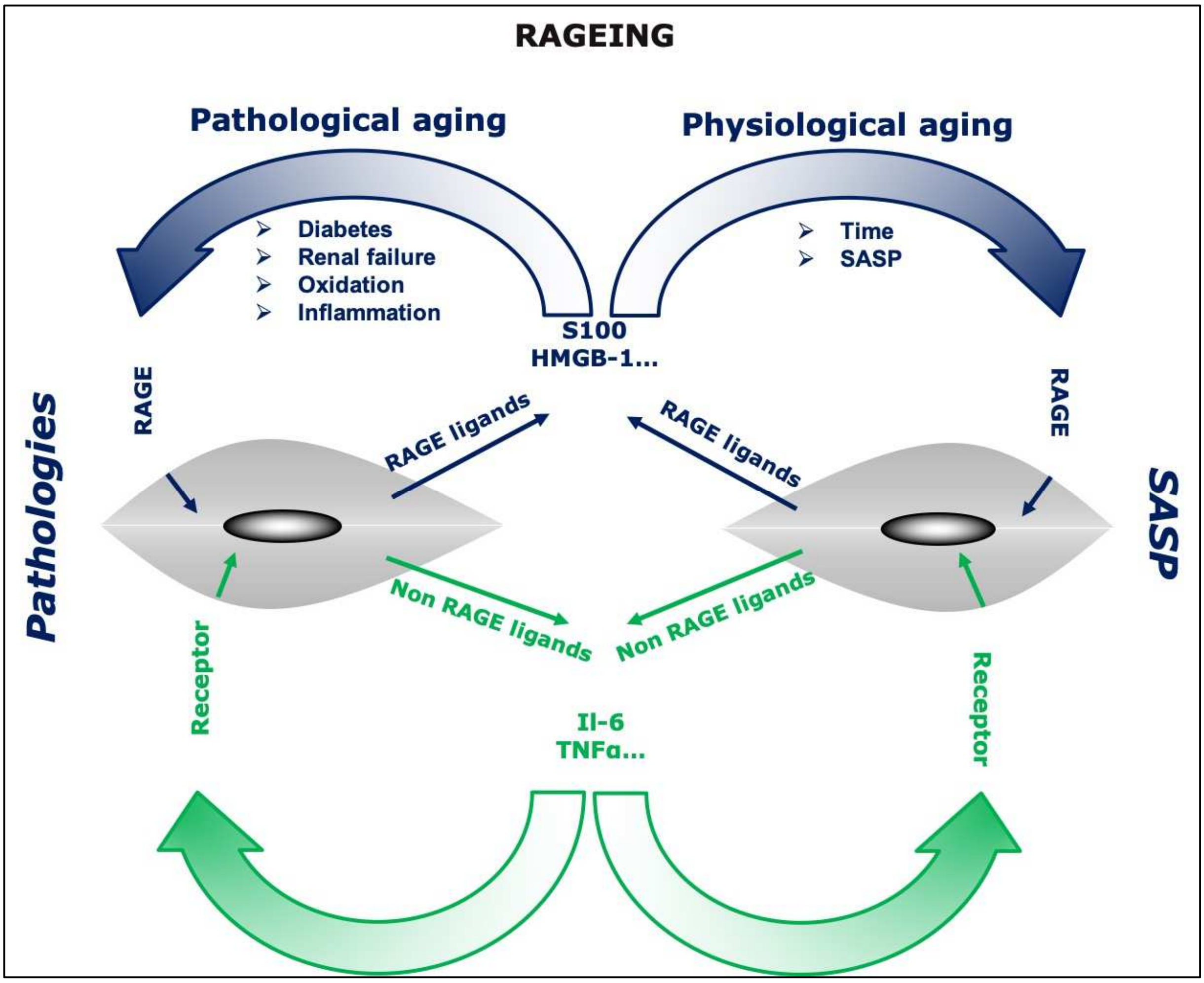

Figure 2: RAGEING, the vicious circle of inflammaging. RAGE implication during pathological and physiological aging. RAGE, Receptor for advanced glycation end-products; SASP, senescence-associated secretory phenotype. HMGB-1, high–mobility group box 1; Il-6, interleukine-6: TNFα, tumor necrosis factor α. Adapted from T Teissier, The Receptor RAGE in Vascular and Cerebral Dysfunction (JL Wautier, Cambridge Scholars Publishing, ISBN 1-5275-2692-5).

Our team demonstrated that modulation of the RAGE pathway can improve mitochondrial damage and myocardial dysfunction in high-fat diet mice (Yu *et al.*, 2017). We also recently described a significant prevention of inflammation, oxidation and aged-related nephrosclerosis lesions in RAGE null mice, suggesting that RAGE plays a central role in renal aging (Teissier *et al.*, 2019). While RAGE is, by itself, important for skeletal muscle physiology (Riuzzi *et al.*, 2018), it could also directly modulate mitochondrial function. Indeed, RAGE activation may favor mitochondrial fission (Lo *et al.*, 2015; Mao *et al.*, 2018, 2018) or modulate mitophagy (Kang *et al.*, 2011; Lo *et al.*, 2015; Yu *et al.*, 2017). Interestingly, RAGE may also translocate to mitochondria to promote ATP production (Kang *et al.*, 2014). Nevertheless, connections between RAGE activation, mitochondria, and inflammation/inflammaging and their involvement in the sarcopenia process are poorly described but seem very likely. Through controlling inflammaging and mitochondria, we suggest that RAGE may represent a major receptor playing a key role during in physiological aging and aged-related sarcopenia (Figure 1C).

References

Bahat G, Oren MM, Yilmaz O, Kılıç C, Aydin K & Karan MA (2018*a*). Comparing SARC-F with SARC-CalF to Screen Sarcopenia in Community Living Older Adults. *J Nutr Health Aging* **22,** 1034–1038.

Bahat G, Yilmaz O, Kılıç C, Oren MM & Karan MA (2018*b*). Performance of SARC-F in Regard to Sarcopenia Definitions, Muscle Mass and Functional Measures. *J Nutr Health Aging* **22,** 898–903.

Bischoff HA, Stähelin HB, Monsch AU, Iversen MD, Weyh A, von Dechend M, Akos R, Conzelmann M, Dick W & Theiler R (2003). Identifying a cut-off point for normal mobility: a comparison of the timed "up and go" test in community-dwelling and institutionalised elderly women. *Age Ageing* **32,** 315–320.

Boffoli D, Scacco SC, Vergari R, Solarino G, Santacroce G & Papa S (1994). Decline with age of the respiratory chain activity in human skeletal muscle. *Biochim Biophys Acta* **1226,** 73–82.

Boulanger E, Grossin N, Wautier M-P, Taamma R & Wautier J-L (2007). Mesothelial RAGE activation by AGEs enhances VEGF release and potentiates capillary tube formation. *Kidney Int* **71,** 126–133.

Boulanger E, Wautier M-P, Gane P, Mariette C, Devuyst O & Wautier J-L (2004). The triggering of human peritoneal mesothelial cell apoptosis and oncosis by glucose and glycoxydation products. *Nephrol Dial Transplant* **19,** 2208–2216.

Brookes PS, Yoon Y, Robotham JL, Anders MW & Sheu S-S (2004). Calcium, ATP, and ROS: a mitochondrial love-hate triangle. *Am J Physiol, Cell Physiol* **287,** C817-833.

Cai W, Ramdas M, Zhu L, Chen X, Striker GE & Vlassara H (2012). Oral advanced glycation endproducts (AGEs) promote insulin resistance and diabetes by depleting the antioxidant defenses AGE receptor-1 and sirtuin 1. *Proc Natl Acad*

Sci USA **109,** 15888–15893.

Caielli S, Athale S, Domic B, Murat E, Chandra M, Banchereau R, Baisch J, Phelps K, Clayton S, Gong M, Wright T, Punaro M, Palucka K, Guiducci C, Banchereau J & Pascual V (2016). Oxidized mitochondrial nucleoids released by neutrophils drive type I interferon production in human lupus. *J Exp Med* **213,** 697–713.

Capel F, Rimbert V, Lioger D, Diot A, Rousset P, Mirand PP, Boirie Y, Morio B & Mosoni L (2005). Due to reverse electron transfer, mitochondrial H2O2 release increases with age in human vastus lateralis muscle although oxidative capacity is preserved. *Mech Ageing Dev* **126,** 505–511.

Chabi B, Ljubicic V, Menzies KJ, Huang JH, Saleem A & Hood DA (2008*a*). Mitochondrial function and apoptotic susceptibility in aging skeletal muscle. *Aging Cell* **7,** 2–12.

Chabi B, Ljubicic V, Menzies KJ, Huang JH, Saleem A & Hood DA (2008*b*). Mitochondrial function and apoptotic susceptibility in aging skeletal muscle. *Aging Cell* **7,** 2–12.

Chen G, Kroemer G & Kepp O (2020). Mitophagy: An Emerging Role in Aging and Age-Associated Diseases. *Front Cell Dev Biol* **8,** 200.

Chen H, Vermulst M, Wang YE, Chomyn A, Prolla TA, McCaffery JM & Chan DC (2010). Mitochondrial fusion is required for mtDNA stability in skeletal muscle and tolerance of mtDNA mutations. *Cell* **141,** 280–289.

Chiu C-Y, Yang R-S, Sheu M-L, Chan D-C, Yang T-H, Tsai K-S, Chiang C-K & Liu S-H (2016). Advanced glycation end-products induce skeletal muscle atrophy and dysfunction in diabetic mice via a RAGE-mediated, AMPK-down-regulated, Akt pathway. *J Pathol* **238,** 470–482.

Chung HK et al. (2017). Growth differentiation factor 15 is a myomitokine governing systemic energy homeostasis. *J Cell Biol* **216,** 149–165.

Coen PM, Musci RV, Hinkley JM & Miller BF (2018). Mitochondria as a Target for Mitigating Sarcopenia. *Front Physiol* **9,** 1883.

Crane JD, Devries MC, Safdar A, Hamadeh MJ & Tarnopolsky MA (2010). The effect of aging on human skeletal muscle mitochondrial and intramyocellular lipid ultrastructure. *J Gerontol A Biol Sci Med Sci* **65,** 119–128.

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M & Zamboni M (2019*a*). Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48,** 16–31.

Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, Cooper C, Landi F, Rolland Y, Sayer AA, Schneider SM, Sieber CC, Topinkova E, Vandewoude M, Visser M & Zamboni M (2019*b*). Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* **48,** 16–31.

Dai D-F, Chiao YA, Marcinek DJ, Szeto HH & Rabinovitch PS (2014). Mitochondrial oxidative stress in aging and healthspan. *Longev Healthspan* **3,** 6.

Dalle S, Rossmeislova L & Koppo K (2017). The Role of Inflammation in Age-Related Sarcopenia. *Front Physiol* **8,** 1045.

D'Antona G, Pellegrino MA, Adami R, Rossi R, Carlizzi CN, Canepari M, Saltin B & Bottinelli R (2003). The effect of ageing and immobilization on structure and function of human skeletal muscle fibres. *J Physiol (Lond)* **552,** 499–511.

Dikic I (2017). Proteasomal and Autophagic Degradation Systems. *Annu Rev Biochem* **86,** 193–224.

Dillon LM, Williams SL, Hida A, Peacock JD, Prolla TA, Lincoln J & Moraes CT (2012). Increased mitochondrial biogenesis in muscle improves aging phenotypes in the mtDNA mutator mouse. *Hum Mol Genet* **21,** 2288–2297.

Drummond MJ, Addison O, Brunker L, Hopkins PN, McClain DA, LaStayo PC &

Marcus RL (2014). Downregulation of E3 ubiquitin ligases and mitophagy-related genes in skeletal muscle of physically inactive, frail older women: a cross-sectional comparison. *J Gerontol A Biol Sci Med Sci* **69,** 1040–1048.

Egawa T, Tsuda S, Goto A, Ohno Y, Yokoyama S, Goto K & Hayashi T (2017). Potential involvement of dietary advanced glycation end products in impairment of skeletal muscle growth and muscle contractile function in mice. *Br J Nutr* **117,** 21–29.

Favaro G, Romanello V, Varanita T, Andrea Desbats M, Morbidoni V, Tezze C, Albiero M, Canato M, Gherardi G, De Stefani D, Mammucari C, Blaauw B, Boncompagni S, Protasi F, Reggiani C, Scorrano L, Salviati L & Sandri M (2019). DRP1-mediated mitochondrial shape controls calcium homeostasis and muscle mass. *Nat Commun* **10,** 2576.

Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA & Cardiovascular Health Study Collaborative Research Group (2001). Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* **56,** M146-156.

Frimat M, Daroux M, Litke R, Nevière R, Tessier FJ & Boulanger E (2017). Kidney, heart and brain: three organs targeted by ageing and glycation. *Clin Sci* **131,** 1069–1092.

Frontera WR, Hughes VA, Fielding RA, Fiatarone MA, Evans WJ & Roubenoff R (2000). Aging of skeletal muscle: a 12-yr longitudinal study. *J Appl Physiol* **88,** 1321–1326.

Garcia S, Nissanka N, Mareco EA, Rossi S, Peralta S, Diaz F, Rotundo RL, Carvalho RF & Moraes CT (2018). Overexpression of PGC-1α in aging muscle enhances a subset of young-like molecular patterns. *Aging Cell*; DOI: 10.1111/acel.12707.

Goljanek-Whysall K, Soriano-Arroquia A, McCormick R, Chinda C & McDonagh B (2020). miR-181a regulates p62/SQSTM1, parkin, and protein DJ-1 promoting mitochondrial dynamics in skeletal muscle aging. *Aging Cell* **19,** e13140.

Gonzalez-Freire M, Scalzo P, D'Agostino J, Moore ZA, Diaz-Ruiz A, Fabbri E, Zane A, Chen B, Becker KG, Lehrmann E, Zukley L, Chia CW, Tanaka T, Coen PM, Bernier M, de Cabo R & Ferrucci L (2018). Skeletal muscle ex vivo mitochondrial respiration parallels decline in vivo oxidative capacity, cardiorespiratory fitness, and muscle strength: The Baltimore Longitudinal Study of Aging. *Aging Cell*; DOI: 10.1111/acel.12725.

Goodpaster BH, Chomentowski P, Ward BK, Rossi A, Glynn NW, Delmonico MJ, Kritchevsky SB, Pahor M & Newman AB (2008). Effects of physical activity on strength and skeletal muscle fat infiltration in older adults: a randomized controlled trial. *J Appl Physiol* **105,** 1498–1503.

Goodpaster BH, Park SW, Harris TB, Kritchevsky SB, Nevitt M, Schwartz AV, Simonsick EM, Tylavsky FA, Visser M & Newman AB (2006). The Loss of Skeletal Muscle Strength, Mass, and Quality in Older Adults: The Health, Aging and Body Composition Study. *J Gerontol A Biol Sci Med Sci* **61,** 1059–1064.

Gouspillou G, Bourdel-Marchasson I, Rouland R, Calmettes G, Biran M, Deschodt-Arsac V, Miraux S, Thiaudiere E, Pasdois P, Detaille D, Franconi J-M, Babot M, Trézéguet V, Arsac L & Diolez P (2014). Mitochondrial energetics is impaired in vivo in aged skeletal muscle. *Aging Cell* **13,** 39–48.

Gouspillou G & Hepple RT (2016). Editorial: Mitochondria in Skeletal Muscle Health, Aging and Diseases. *Front Physiol*; DOI: 10.3389/fphys.2016.00446.

Harman D (1956). Aging: a theory based on free radical and radiation chemistry. *J Gerontol* **11,** 298–300.

Holloway GP, Holwerda AM, Miotto PM, Dirks ML, Verdijk LB & van Loon LJC

(2018). Age-Associated Impairments in Mitochondrial ADP Sensitivity Contribute to Redox Stress in Senescent Human Skeletal Muscle. *Cell Rep* **22,** 2837–2848.

Hou C (2013). The energy trade-off between growth and longevity. *Mech Ageing Dev* **134,** 373–380.

Huang D-D, Fan S-D, Chen X-Y, Yan X-L, Zhang X-Z, Ma B-W, Yu D-Y, Xiao W-Y, Zhuang C-L & Yu Z (2019). Nrf2 deficiency exacerbates frailty and sarcopenia by impairing skeletal muscle mitochondrial biogenesis and dynamics in an age-dependent manner. *Exp Gerontol* **119,** 61–73.

Hunter SK, Pereira HM & Keenan KG (2016). The aging neuromuscular system and motor performance. *J Appl Physiol* **121,** 982–995.

Ishii S, Tanaka T, Shibasaki K, Ouchi Y, Kikutani T, Higashiguchi T, Obuchi SP, Ishikawa-Takata K, Hirano H, Kawai H, Tsuji T & Iijima K (2014). Development of a simple screening test for sarcopenia in older adults. *Geriatr Gerontol Int* **14 Suppl 1,** 93–101.

Ito T, Nakanishi Y, Yamaji N, Murakami S & Schaffer SW (2018). Induction of Growth Differentiation Factor 15 in Skeletal Muscle of Old Taurine Transporter Knockout Mouse. *Biol Pharm Bull* **41,** 435–439.

Jo E-K, Kim JK, Shin D-M & Sasakawa C (2016). Molecular mechanisms regulating NLRP3 inflammasome activation. *Cell Mol Immunol* **13,** 148–159.

Johnson Stoklossa CA, Sharma AM, Forhan M, Siervo M, Padwal RS & Prado CM (2017). Prevalence of Sarcopenic Obesity in Adults with Class II/III Obesity Using Different Diagnostic Criteria. *J Nutr Metab* **2017,** 7307618.

Joseph A-M, Adhihetty PJ, Buford TW, Wohlgemuth SE, Lees HA, Nguyen LM-D, Aranda JM, Sandesara BD, Pahor M, Manini TM, Marzetti E & Leeuwenburgh C (2012). The impact of aging on mitochondrial function and biogenesis pathways in skeletal muscle of sedentary high- and low-functioning elderly individuals.

Aging Cell **11,** 801–809.

Kang R, Livesey KM, Zeh HJ, Lotze MT & Tang D (2011). Metabolic regulation by HMGB1-mediated autophagy and mitophagy. *Autophagy* **7,** 1256–1258.

Kang R, Tang D, Schapiro NE, Loux T, Livesey KM, Billiar TR, Wang H, Van Houten B, Lotze MT & Zeh HJ (2014). The HMGB1/RAGE inflammatory pathway promotes pancreatic tumor growth by regulating mitochondrial bioenergetics. *Oncogene* **33,** 567–577.

Kim KH, Jeong YT, Kim SH, Jung HS, Park KS, Lee H-Y & Lee M-S (2013). Metformin-induced inhibition of the mitochondrial respiratory chain increases FGF21 expression via ATF4 activation. *Biochem Biophys Res Commun* **440,** 76–81.

Kitaoka Y, Tamura Y, Takahashi K, Takeda K, Takemasa T & Hatta H (2019). Effects of Nrf2 deficiency on mitochondrial oxidative stress in aged skeletal muscle. *Physiol Rep* **7,** e13998.

Klionsky DJ et al. (2016). Guidelines for the use and interpretation of assays for monitoring autophagy (3rd edition). *Autophagy* **12,** 1–222.

Koltai E, Hart N, Taylor AW, Goto S, Ngo JK, Davies KJA & Radak Z (2012). Age-associated declines in mitochondrial biogenesis and protein quality control factors are minimized by exercise training. *Am J Physiol Regul Integr Comp Physiol* **303,** R127-134.

Kong X, Lu A-L, Yao X-M, Hua Q, Li X-Y, Qin L, Zhang H-M, Meng G-X & Su Q (2017). Activation of NLRP3 Inflammasome by Advanced Glycation End Products Promotes Pancreatic Islet Damage. *Oxid Med Cell Longev* **2017,** 9692546.

Kramer PA, Duan J, Qian W-J & Marcinek DJ (2015). The Measurement of Reversible Redox Dependent Post-translational Modifications and Their Regulation of Mitochondrial and Skeletal Muscle Function. *Front Physiol*; DOI:

10.3389/fphys.2015.00347.

Lanza IR, Towse TF, Caldwell GE, Wigmore DM & Kent-Braun JA (2003). Effects of age on human muscle torque, velocity, and power in two muscle groups. *J Appl Physiol* **95,** 2361–2369.

Leduc-Gaudet J-P, Reynaud O, Hussain SN & Gouspillou G (2019). Parkin overexpression protects from ageing-related loss of muscle mass and strength. *J Physiol (Lond)* **597,** 1975–1991.

Lexell J, Taylor CC & Sjöström M (1988). What is the cause of the ageing atrophy? Total number, size and proportion of different fiber types studied in whole vastus lateralis muscle from 15- to 83-year-old men. *J Neurol Sci* **84,** 275–294.

Lindle RS, Metter EJ, Lynch NA, Fleg JL, Fozard JL, Tobin J, Roy TA & Hurley BF (1997). Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. *J Appl Physiol* **83,** 1581–1587.

Liu H-W, Chang Y-C, Chan Y-C, Hu S-H, Liu M-Y & Chang S-J (2020). Dysregulations of mitochondrial quality control and autophagic flux at an early age lead to progression of sarcopenia in SAMP8 mice. *Biogerontology* **21,** 367–380.

Lo M-C, Chen M-H, Lee W-S, Lu C-I, Chang C-R, Kao S-H & Lee H-M (2015). Nε-(carboxymethyl) lysine-induced mitochondrial fission and mitophagy cause decreased insulin secretion from β-cells. *Am J Physiol Endocrinol Metab* **309,** E829-839.

Mao YX, Cai WJ, Sun XY, Dai PP, Li XM, Wang Q, Huang XL, He B, Wang PP, Wu G, Ma JF & Huang SB (2018). RAGE-dependent mitochondria pathway: a novel target of silibinin against apoptosis of osteoblastic cells induced by advanced glycation end products. *Cell Death Dis* **9,** 674.

Marzetti E, Calvani R, Lorenzi M, Tanganelli F, Picca A, Bossola M, Menghi A, Bernabei R & Landi F (2016). Association between myocyte quality control signaling and sarcopenia in old hip-fractured patients: Results from the Sarcopenia in HIp FracTure (SHIFT) exploratory study. *Exp Gerontol* **80,** 1–5.

McBride MJ, Foley KP, D'Souza DM, Li YE, Lau TC, Hawke TJ & Schertzer JD (2017). The NLRP3 inflammasome contributes to sarcopenia and lower muscle glycolytic potential in old mice. *Am J Physiol Endocrinol Metab* **313,** E222–E232.

Meng Y, Wu H, Yang Y, Du H, Xia Y, Guo X, Liu X, Li C & Niu K (2015). Relationship of anabolic and catabolic biomarkers with muscle strength and physical performance in older adults: a population-based cross-sectional study. *BMC Musculoskelet Disord* **16,** 202.

Metter EJ, Lynch N, Conwit R, Lindle R, Tobin J & Hurley B (1999). Muscle quality and age: cross-sectional and longitudinal comparisons. *J Gerontol A Biol Sci Med Sci* **54,** B207-218.

Migliavacca E et al. (2019*a*). Mitochondrial oxidative capacity and NAD+ biosynthesis are reduced in human sarcopenia across ethnicities. *Nat Commun* **10,** 5808.

Migliavacca E et al. (2019*b*). Mitochondrial oxidative capacity and NAD+ biosynthesis are reduced in human sarcopenia across ethnicities. *Nat Commun* **10,** 5808.

Nakahira K, Hisata S & Choi AMK (2015). The Roles of Mitochondrial Damage-Associated Molecular Patterns in Diseases. *Antioxid Redox Signal* **23,** 1329–1350.

Nakajima T, Shibasaki I, Sawaguchi T, Haruyama A, Kaneda H, Nakajima T, Hasegawa T, Arikawa T, Obi S, Sakuma M, Ogawa H, Toyoda S, Nakamura F, Abe S, Fukuda H & Inoue T (2019). Growth Differentiation Factor-15 (GDF-15) is a Biomarker of Muscle Wasting and Renal Dysfunction in Preoperative Cardiovascular Surgery Patients. *J Clin Med*; DOI: 10.3390/jcm8101576.

Neuspiel M, Schauss AC, Braschi E, Zunino R, Rippstein P, Rachubinski RA, Andrade-Navarro MA & McBride HM (2008). Cargo-selected transport from the mitochondria to peroxisomes is mediated by vesicular carriers. *Curr Biol* **18,** 102–108.

Neviere R, Yu Y, Wang L, Tessier F & Boulanger E (2016). Implication of advanced glycation end products (Ages) and their receptor (Rage) on myocardial contractile and mitochondrial functions. *Glycoconj J* **33,** 607–617.

O'Leary MF, Vainshtein A, Iqbal S, Ostojic O & Hood DA (2013). Adaptive plasticity of autophagic proteins to denervation in aging skeletal muscle. *Am J Physiol, Cell Physiol* **304,** C422-430.

Oost LJ, Kustermann M, Armani A, Blaauw B & Romanello V (2019). Fibroblast growth factor 21 controls mitophagy and muscle mass. *J Cachexia Sarcopenia Muscle* **10,** 630–642.

Opalach K, Rangaraju S, Madorsky I, Leeuwenburgh C & Notterpek L (2010). Lifelong calorie restriction alleviates age-related oxidative damage in peripheral nerves. *Rejuvenation Res* **13,** 65–74.

Payne MJ, Hurst WJ, Miller KB, Rank C & Stuart DA (2010). Impact of fermentation, drying, roasting, and Dutch processing on epicatechin and catechin content of cacao beans and cocoa ingredients. *J Agric Food Chem* **58,** 10518–10527.

Picard M, Ritchie D, Wright KJ, Romestaing C, Thomas MM, Rowan SL, Taivassalo T & Hepple RT (2010). Mitochondrial functional impairment with aging is exaggerated in isolated mitochondria compared to permeabilized myofibers. *Aging Cell* **9,** 1032–1046.

Picca A, Beli R, Calvani R, Coelho-Júnior HJ, Landi F, Bernabei R, Bucci C, Guerra F & Marzetti E (2020). Older Adults with Physical Frailty and Sarcopenia Show Increased Levels of Circulating Small Extracellular Vesicles with a Specific Mitochondrial Signature. *Cells*; DOI: 10.3390/cells9040973.

Pickles S, Vigié P & Youle RJ (2018). Mitophagy and Quality Control Mechanisms in Mitochondrial Maintenance. *Curr Biol* **28,** R170–R185.

Pinti M, Cevenini E, Nasi M, De Biasi S, Salvioli S, Monti D, Benatti S, Gibellini L, Cotichini R, Stazi MA, Trenti T, Franceschi C & Cossarizza A (2014). Circulating mitochondrial DNA increases with age and is a familiar trait: Implications for "inflamm-aging." *Eur J Immunol* **44,** 1552–1562.

Popov L-D (2020). Mitochondrial biogenesis: An update. *J Cell Mol Med* **24,** 4892–4899.

Powers SK, Talbert EE & Adhihetty PJ (2011). Reactive oxygen and nitrogen species as intracellular signals in skeletal muscle. *J Physiol (Lond)* **589,** 2129–2138.

Purves-Smith FM, Sgarioto N & Hepple RT (2014). Fiber typing in aging muscle. *Exerc Sport Sci Rev* **42,** 45–52.

Quirós PM, Langer T & López-Otín C (2015). New roles for mitochondrial proteases in health, ageing and disease. *Nat Rev Mol Cell Biol* **16,** 345–359.

Rasmussen UF, Krustrup P, Kjær M & Rasmussen HN (2003). Experimental evidence against the mitochondrial theory of aging A study of isolated human skeletal muscle mitochondria. *Experimental Gerontology* **38,** 877–886.

Riuzzi F, Sorci G, Sagheddu R, Chiappalupi S, Salvadori L & Donato R (2018). RAGE in the pathophysiology of skeletal muscle. *J Cachexia Sarcopenia Muscle* **9,** 1213–1234.

Roberts RF, Tang MY, Fon EA & Durcan TM (2016). Defending the mitochondria:

The pathways of mitophagy and mitochondrial-derived vesicles. *Int J Biochem Cell Biol* **79,** 427–436.

Romanello V, Scalabrin M, Albiero M, Blaauw B, Scorrano L & Sandri M (2019). Inhibition of the Fission Machinery Mitigates OPA1 Impairment in Adult Skeletal Muscles. *Cells*; DOI: 10.3390/cells8060597.

Safdar A, Hamadeh MJ, Kaczor JJ, Raha S, Debeer J & Tarnopolsky MA (2010). Aberrant mitochondrial homeostasis in the skeletal muscle of sedentary older adults. *PLoS ONE* **5,** e10778.

Sakellariou GK, Pearson T, Lightfoot AP, Nye GA, Wells N, Giakoumaki II, Vasilaki A, Griffiths RD, Jackson MJ & McArdle A (2016). Mitochondrial ROS regulate oxidative damage and mitophagy but not age-related muscle fiber atrophy. *Sci Rep* **6,** 33944.

Sayed RKA, Fernández-Ortiz M, Diaz-Casado ME, Aranda-Martínez P, Fernández-Martínez J, Guerra-Librero A, Escames G, López LC, Alsaadawy RM & Acuña-Castroviejo D (2019). Lack of NLRP3 Inflammasome Activation Reduces Age-Dependent Sarcopenia and Mitochondrial Dysfunction, Favoring the Prophylactic Effect of Melatonin. *J Gerontol A Biol Sci Med Sci* **74,** 1699–1708.

Scarpulla RC (2006). Nuclear control of respiratory gene expression in mammalian cells. *J Cell Biochem* **97,** 673–683.

Schaap LA, Pluijm SMF, Deeg DJH & Visser M (2006). Inflammatory markers and loss of muscle mass (sarcopenia) and strength. *Am J Med* **119,** 526.e9-17.

Schmidt AM, Vianna M, Gerlach M, Brett J, Ryan J, Kao J, Esposito C, Hegarty H, Hurley W & Clauss M (1992). Isolation and characterization of two binding proteins for advanced glycosylation end products from bovine lung which are present on the endothelial cell surface. *J Biol Chem* **267,** 14987–14997.

Sebastián D, Sorianello E, Segalés J, Irazoki A, Ruiz-Bonilla V, Sala D, Planet E, Berenguer-Llergo A, Muñoz JP, Sánchez-Feutrie M, Plana N, Hernández-Álvarez MI, Serrano AL, Palacín M & Zorzano A (2016). Mfn2 deficiency links age-related sarcopenia and impaired autophagy to activation of an adaptive mitophagy pathway. *EMBO J* **35,** 1677–1693.

Sebastián D & Zorzano A (2016). When MFN2 (mitofusin 2) met autophagy: A new age for old muscles. *Autophagy* **12,** 2250–2251.

Semba RD, Gonzalez-Freire M, Tanaka T, Biancotto A, Zhang P, Shardell M, Moaddel R, CHI Consortium & Ferrucci L (2020). Elevated Plasma Growth and Differentiation Factor 15 Is Associated With Slower Gait Speed and Lower Physical Performance in Healthy Community-Dwelling Adults. *J Gerontol A Biol Sci Med Sci* **75,** 175–180.

Short KR, Bigelow ML, Kahl J, Singh R, Coenen-Schimke J, Raghavakaimal S & Nair KS (2005). Decline in skeletal muscle mitochondrial function with aging in humans. *Proc Natl Acad Sci USA* **102,** 5618–5623.

Shpilka T & Haynes CM (2018). The mitochondrial UPR: mechanisms, physiological functions and implications in ageing. *Nat Rev Mol Cell Biol* **19,** 109–120.

Siu PM, Pistilli EE & Alway SE (2005). Apoptotic responses to hindlimb suspension in gastrocnemius muscles from young adult and aged rats. *Am J Physiol Regul Integr Comp Physiol* **289,** R1015-1026.

Son JM & Lee C (2019). Mitochondria: multifaceted regulators of aging. *BMB Rep* **52,** 13–23.

Son S, Hwang I, Han SH, Shin J-S, Shin OS & Yu J-W (2017). Advanced glycation end products impair NLRP3 inflammasome-mediated innate immune responses in macrophages. *J Biol Chem* **292,** 20437–20448.

Song Y, Wang Y, Zhang Y, Geng W, Liu W, Gao Y, Li S, Wang K, Wu X, Kang L &

Yang C (2017). Advanced glycation end products regulate anabolic and catabolic activities via NLRP3-inflammasome activation in human nucleus pulposus cells. *J Cell Mol Med* **21,** 1373–1387.

Sun N, Youle RJ & Finkel T (2016). The Mitochondrial Basis of Aging. *Mol Cell* **61,** 654–666.

Teissier T, Quersin V, Gnemmi V, Daroux M, Howsam M, Delguste F, Lemoine C, Fradin C, Schmidt A-M, Cauffiez C, Brousseau T, Glowacki F, Tessier FJ, Boulanger E & Frimat M (2019). Knockout of receptor for advanced glycation end-products attenuates age-related renal lesions. *Aging Cell* **18,** e12850.

Tessier FJ, Niquet-Léridon C, Jacolot P, Jouquand C, Genin M, Schmidt A-M, Grossin N & Boulanger E (2016). Quantitative assessment of organ distribution of dietary protein-bound 13 C-labeled Nε -carboxymethyllysine after a chronic oral exposure in mice. *Mol Nutr Food Res* **60,** 2446–2456.

Tezze C et al. (2017*a*). Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. *Cell Metab* **25,** 1374-1389.e6.

Tezze C et al. (2017*b*). Age-Associated Loss of OPA1 in Muscle Impacts Muscle Mass, Metabolic Homeostasis, Systemic Inflammation, and Epithelial Senescence. *Cell Metab* **25,** 1374-1389.e6.

Tomlinson BE & Irving D (1977). The numbers of limb motor neurons in the human lumbosacral cord throughout life. *J Neurol Sci* **34,** 213–219.

Tonkonogi M, Fernström M, Walsh B, Ji LL, Rooyackers O, Hammarqvist F, Wernerman J & Sahlin K (2003). Reduced oxidative power but unchanged antioxidative capacity in skeletal muscle from aged humans. *Pflugers Arch* **446,** 261–269.

Vega RB, Huss JM & Kelly DP (2000). The coactivator PGC-1 cooperates with peroxisome proliferator-activated receptor alpha in transcriptional control of nuclear genes encoding mitochondrial fatty acid oxidation enzymes. *Mol Cell Biol* **20,** 1868–1876.

Wang R, Li JJ, Diao S, Kwak Y-D, Liu L, Zhi L, Büeler H, Bhat NR, Williams RW, Park EA & Liao F-F (2013). Metabolic stress modulates Alzheimer's β-secretase gene transcription via SIRT1-PPARγ-PGC-1 in neurons. *Cell Metab* **17,** 685–694.

Wannamethee SG, Lowe GDO, Whincup PH, Rumley A, Walker M & Lennon L (2002). Physical activity and hemostatic and inflammatory variables in elderly men. *Circulation* **105,** 1785–1790.

Wautier J-L (2019). *The Receptor RAGE in Vascular and Cerebral Dysfunctions*, Cambridge Scholars Publishing. Cambridge Scholars Publishing. Available at: https://www.cambridgescholars.com/the-receptor-rage-in-vascular-and-cerebral-dysfunctions [Accessed August 25, 2020].

Yeo D, Kang C, Gomez-Cabrera MC, Vina J & Ji LL (2019). Intensified mitophagy in skeletal muscle with aging is downregulated by PGC-1alpha overexpression in vivo. *Free Radic Biol Med* **130,** 361–368.

Yu R, Lendahl U, Nistér M & Zhao J (2020). Regulation of Mammalian Mitochondrial Dynamics: Opportunities and Challenges. *Front Endocrinol (Lausanne)* **11,** 374.

Yu Y, Wang L, Delguste F, Durand A, Guilbaud A, Rousselin C, Schmidt AM, Tessier F, Boulanger E & Neviere R (2017). Advanced glycation end products receptor RAGE controls myocardial dysfunction and oxidative stress in high-fat fed mice by sustaining mitochondrial dynamics and autophagy-lysosome pathway. *Free Radic Biol Med* **112,** 397–410.

Zembron-Lacny A, Dziubek W, Wolny-Rokicka E, Dabrowska G & Wozniewski M (2019). The Relation of Inflammaging With Skeletal Muscle Properties in Elderly

Men. *Am J Mens Health* **13,** 1557988319841934.

Zhou H, Yuan D, Gao W, Tian J, Sun H, Yu S, Wang J & Sun L (2020). Loss of high-temperature requirement protein A2 protease activity induces mitonuclear imbalance via differential regulation of mitochondrial biogenesis in sarcopenia. *IUBMB Life* **72,** 1659–1679.