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Review

Inflammatory, mitochondrial, and senescence-related markers: Underlying biological pathways of muscle aging and new therapeutic targets

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ABSTRACT

The maintenance of functional health is pivotal for achieving independent life in older age. The aged muscle is characterized by ultrastructural changes, including loss of type I and type II myofibers and a greater proportion of cytochrome *c* oxidase deficient and succinate dehydrogenase positive fibers. Both intrinsic (e.g., altered proteostasis, DNA damage, and mitochondrial dysfunction) and extrinsic factors (e.g., denervation, altered metabolic regulation, declines in satellite cells, and inflammation) contribute to muscle aging. Being a hub for several cellular activities, mitochondria are key to myocyte viability and mitochondrial dysfunction has been implicated in age-associated physical decline. The maintenance of functional organelles via mitochondrial quality control (MQC) processes is, therefore, crucial to skeletal myofiber viability and organismal health. The autophagy-lysosome pathway has emerged as a critical step of MQC in muscle by disposing organelles and proteins via their tagging for autophagosome incorporation and delivery to the lysosome for clearance. This pathway was found to be altered in muscle of physically inactive older adults. A relationship between this pathway and muscle tissue composition of the lower extremities as well as physical performance was also identified. Therefore, integrating muscle structure and myocyte quality control measures in the evaluation of muscle health may be a promising strategy for devising interventions fostering muscle health.

1. Introduction

Functional health is pivotal for achieving independent life in older age. Physical performance measures serve as metrics of aging and predict incident disability and other relevant health outcomes in older adults (Bernabei et al., 2022; Fanning et al., 2020; Groessl et al., 2019; Guralnik et al., 1995; Pahor et al., 2020; Pavasini et al., 2016). The complementation of physical performance indices with measures of underlying muscle biology offers a more comprehensive landscape for investigating age-related muscle decline (Calvani et al., 2020; Marzetti et al., 2020; Picca et al., 2019b).

Ultrastructural changes, including loss of type I and type II myofibers and a greater proportion of cytochrome *c* oxidase deficient (COX^{-}) and succinate dehydrogenase positive (SDH^{++}) fibers, have been described in the aged muscle (Wilkinson et al., 2018). This disruption of muscle architecture is a major contributor to muscle fatigability and reduced force production during aging (Shur et al., 2021) and originates from extrinsic (systemic) and intrinsic factors. Denervation, altered metabolic

Abbreviations: AMPK, AMP activated protein kinase; BNIP3, Bcl-2 interacting protein 3; COX, cytochrome c oxidase; ECM, extracellular matrix; FUNDC1, FUN14 Domain Containing 1; GDF8, growth differentiation factor 8; ICAM-1, intercellular adhesion molecule 1; IL, interleukin; LC3, microtubule-associated protein 1 light chain 3B; MDVs, mitochondrial-derived vesicles; MMPs, metalloproteinases; MQC, mitochondrial quality control; Mrf4, myogenic regulating factor 4; NAD, nicotinamide adenine dinucleotide; PF&S, physical frailty and sarcopenia; PGAM5, phosphatase phosphoglycerate mutase 5; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PINK1, PTEN-induced kinase 1; SASP, senescence-associated secretory phenotype; SCs, satellite cells; SDH, succinate dehydrogenase; TFEB, transcription factor EB; TIMPs, tissue inhibitors of metalloproteinases; TNFα, tumor necrosis factor-α; ULK1, unc-51 like autophagy activating kinase 1.

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regulation, declines in satellite cells (SCs), and inflammation are relevant extrinsic factors that contribute to muscle aging. Altered proteostasis, DNA damage, and mitochondrial dysfunction are major intrinsic factors. Extensive extracellular muscle matrix remodeling involving protein aggregates deposition and changes in extracellular matrix niche has also been reported (Schüler et al., 2021). In addition, differences in genetic background have been suggested to explain, at least partly, inter-individual heterogeneity in muscle responses to stressors during aging (Sirago et al., 2022).

Mitochondrial dysfunction, a hallmark of aging, contributes substantially to physical decline in older people. Its role should be framed in the context of the many biological pathways in which mitochondria are implicated (Coen et al., 2013; Gouspillou et al., 2014; Joseph et al., 2012; Picca et al., 2020, 2019a; Sandri et al., 2013; Short et al., 2005). Due to their relevance to energy metabolism, mitochondria are critical to myofiber viability (Picca et al., 2023a) but can also signal at the systemic level (Picca et al., 2017). As part of mitochondrial quality control (MQC) processes, a central role in muscle aging has recently been attributed to the autophagy-lysosome pathway (Tan et al., 2023). This degradative route disposes organelles and proteins by their tagging for autophagosome incorporation and delivery to the lysosome for clearance (Pohl and Dikic, 2019). The inhibition of the autophagy-lysosome system has been shown to induce muscle weakness, atrophy, and dysfunction of neuromuscular junctions in preclinical models (Carnio et al., 2014; Masiero et al., 2009; Nemazanyy et al., 2013; Paré et al., 2017; Raben et al., 2008). In addition, an accrual of lipofuscin, a non-degradable lysosomal component, has been identified in aged muscles of mice and humans (Carter et al., 2018; Hütter et al., 2007), which is due to impairment of cellular quality control systems. Altered autophagy, mitophagy, and lysosomal signaling have also been reported in the muscle of physically inactive older adults (Carnio et al., 2014; Drummond et al., 2014; Picca et al., 2023b) and related to tissue composition of the lower extremities and physical performance (Picca et al., 2023b). In this context, the evaluation of muscle quality, by integrating muscle structure and myocyte quality control pathways, should be implemented for devising interventions that may exploit the differentiation ability of SCs for achieving muscle health.

Herein, we provide an overview of the structural and functional changes observed in muscle aging, the molecular pathways underlying such alterations, and the interventions that may be developed to counteract muscle and functional decline with aging.

2. Targeting mitochondrial quality control processes for preserving muscle homeostasis

Mitophagy, a specialized form of autophagy that sequesters damaged or depolarized mitochondria into double-membrane autophagosomes for lysosomal degradation, is a major factor in the maintenance of muscle homeostasis (Chatzinikita et al., 2023). Mitophagy operates in a tight coordination with mitochondrial biogenesis and dynamics, and this set of processes is collectively referred to as mitochondrial quality control (MQC). MQC maintains mitochondrial fitness and protects myocytes from accumulating mitochondrial damage during muscle aging (Pickles et al., 2018; Romanello and Sandri, 2016). Several pathways and mediators have been described and integrated in the process of mitophagy-driven muscle quality. Canonical and uncanonical routes and related factors have been described (Ashrafi and Schwarz, 2013; Sugiura et al., 2014; Tan et al., 2023). Briefly, the canonical pathway of mitophagy involves fissioned and depolarized mitochondria that are targeted for degradation within lysosomes via ubiquitination and Parkin-mediated tagging (Fig. 1).

The B-cell lymphoma 2 (BCL2) family proteins are central to the regulation of mitochondrial homeostasis as they "decide" mitochondrial and cell fate by alternatively triggering mitophagy, mitochondrial fission, or apoptosis (Ma et al., 2020). Within this signaling pathway, the phosphatase phosphoglycerate mutase 5 (PGAM5), a mitochondrial serine/threonine phosphatase located at the inner mitochondrial membrane, serves as a molecular switch to select cell's responses to specific stresses (i.e., mitophagy vs. apoptosis) (Ma et al., 2020). This function of PGAM5 is achieved via dephosphorylation of the apoptosis inhibitor

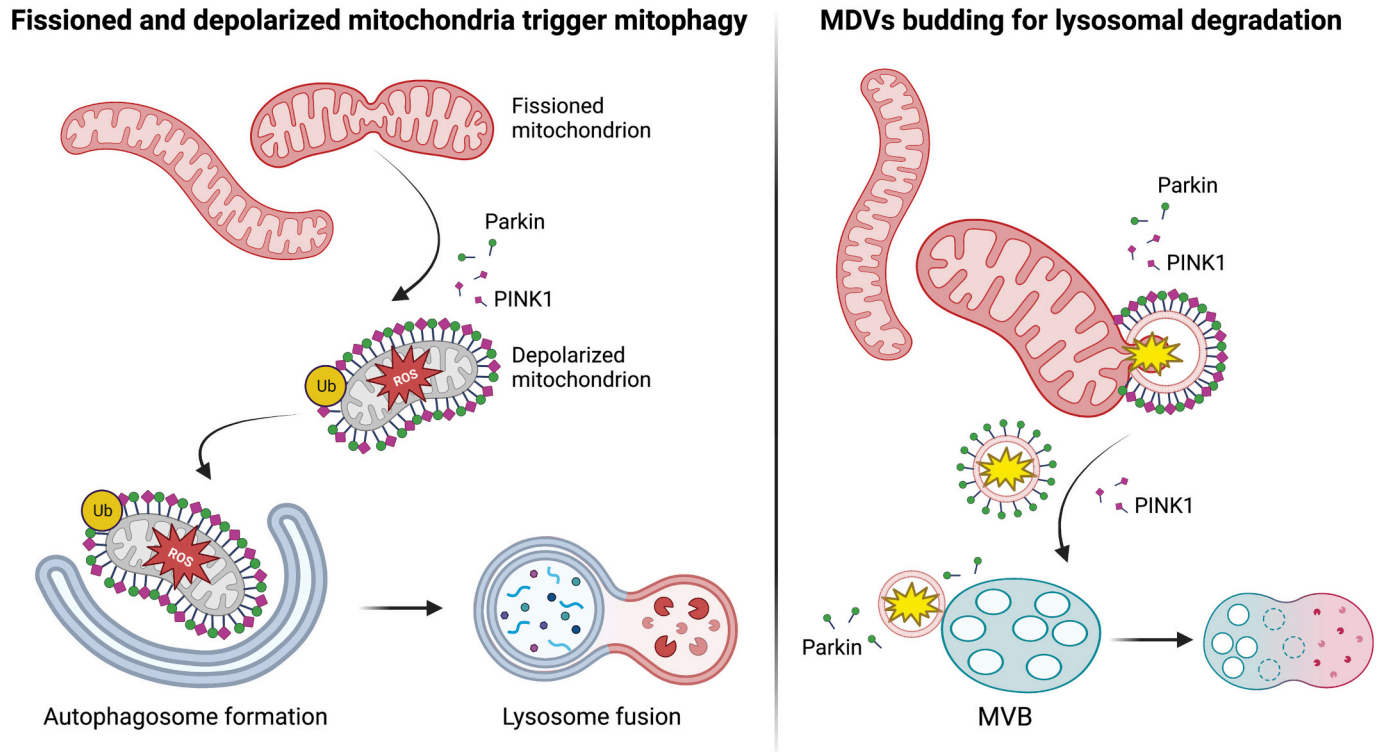

Fig. 1. Schematic representation canonical and uncanonical mitophagy pathways.
Abbreviations: PINK1, PTEN-induced kinase 1; MDV, mitochondrial-derived vesicle; MVB, multivesicular body; ROS, reactive oxygen species; Ub, ubiquitin.

BCL-xL and the mitophagy receptor FUN14 Domain Containing 1 (FUNDC1) (Ma et al., 2020).

As part of the uncanonical signaling routes, mitochondrial-derived vesicles (MDVs) have been proposed as an alternative MQC process that disposes portions of damaged mitochondria when mitophagic degradation cannot be pursued (Sugiura et al., 2014). The MDV-mediated pathway involves the segregation of damaged proteins at the mitochondrial membranes, cardiolipin oxidation and herniation to form membrane curvatures (Sugiura et al., 2014). These structures recruit PTEN-induced kinase 1 (PINK1) at the outer mitochondrial membrane, followed, by Parkin-mediated vesicle budding and tagging to multivesicular bodies (Sugiura et al., 2014).

Dysregulation of MQC processes and/or decline in any of its molecular pathways may lead to inefficient removal of dysfunctional mitochondria resulting in muscle bioenergetic failure and triggering of inflammation (Marchi et al., 2023; Picca et al., 2017). In this setting, mitochondrial dysfunction is further amplified. Only a few studies have analyzed the possible involvement of the autophagy–lysosomal system in human muscle aging and across muscle pathological conditions (Calvani et al., 2013; Hyatt and Powers, 2021; Marzetti et al., 2013; Romanello and Sandri, 2016).

Preliminary evidence exists on MQC alterations in physically inactive older adults with muscle atrophy and/or reduced physical performance (Joseph et al., 2012; Picca et al., 2023b). These studies showed that protein levels of the biogenesis regulator peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), the mitochondrial dynamics fusion protein optic atrophy 1, and the mitochondrial sirtuin 3 were reduced in older adults relative to younger controls (Joseph et al., 2012). Moreover, the protein expression of the autophagy mediator microtubule-associated protein 1 light chain 3B (LC3) was found to be reduced in the muscle of sarcopenic older people (Marzetti et al., 2016). In a subsequent study, protein levels of the autophagy receptor p62 and of the mitophagy regulator Bcl-2 interacting protein 3 (BNIP3) were found to be higher in older adults compared with young controls (Picca et al., 2023b). A higher basal mitophagy flux has also been reported in the skeletal muscle of old rodents (Carter et al., 2018; Triolo et al., 2022a). This suggests that upregulation of mitophagy in the aged muscle may be promoted to compensate for mitochondrial dysfunction in the setting of age-related low muscle quality. Correlation analysis in physically inactive older people revealed a negative association between protein expression of the two mitophagy mediators p62 and BNIP3 and tissue composition of the lower extremity (Picca et al., 2023b). The inverse association observed between p62 and BNIP3 and the performance on the 5-time sit-to-stand test further supports the relevance of MQC impairment as a contributor to age-related decline in physical performance (Picca et al., 2023b). The final step of MQC involves the activity of the mitophagy–lysosome system that works in coordination with mitochondrial biogenesis and bioenergetics (Baixauli et al., 2015; Carter et al., 2018; Triolo et al., 2022b, 2022a). A reduced mitochondrial oxidative capacity triggers upregulation of the lysosomal transcription factor EB (TFEB) to enhance lysosomal protein synthesis and induce autophagy (Baixauli et al., 2015; Carter et al., 2018; Triolo et al., 2022b, 2022a). Unlike preclinical models, no increase in lysosomal markers and/or activity has been found in the human muscle. However, lipofuscin granules in myocytes of old rodents and humans (Hütter et al., 2007; O'Leary et al., 2013) co-localizing with depolarized mitochondria have been described (König et al., 2017; Terman, 2001), which supports the view of mitophagy–lysosome system as a key regulator of MQC and muscle homeostasis.

3. Inflammatory and senescence-related markers in muscle aging

Metabolic perturbations, including a dysregulation of the cytokine network, have been described in older adults with physical frailty and sarcopenia (PF&S) (Bano et al., 2017; Cesari et al., 2004; Furman et al., 2019; Wilson et al., 2017). Inflamm-aging, the chronic low-grade inflammatory state observed in older adults (Franceschi et al., 2000), has also been shown to have pro-sarcopenic and pro-disability effects in older people (Bano et al., 2017; Furman et al., 2019; Wilson et al., 2017). Inflamm-aging is an underlying factor of several age-associated conditions and may represent a converging point for the mechanistic hallmarks of aging (Calvani et al., 2020; Marzetti et al., 2020). A chronic low-grade inflammatory milieu is installed upon bulk neutrophil- and macrophage-mediated release of inflammatory molecules in response to different stressors, including endogenous debris referred to as damage-associated molecular patterns and gut microbial products (Franceschi et al., 2018). Although manifesting later in life, this form of sterile inflammation is also the result of an immune system programming occurring very early in life (Furman et al., 2019). Maternal exposure to social, environmental and lifestyle factors, the so-called exposome, confers epigenetic inheritance and contributes, at least partly, to the development of diseases across lifespan (Furman et al., 2019). A tight link exists between chronic sterile inflammation, the development of chronic conditions and the acquisition of cell's hypersecretory phenotype during aging (Olivieri et al., 2018). Cellular senescence is characterized by cell's growth arrest and the release of a set of molecules referred to as circulating senescence-associated secretory phenotype (SASP) factors, including interleukins (ILs), chemokines, growth factors, proteases, and components of the extracellular matrix (Coppé et al., 2010). Findings of longitudinal studies have shown that plasma levels of SASPs can predict biological and chronological age, morbidity, mortality, and other negative health outcomes (Basisty et al., 2020; Schafer et al., 2020; Tanaka et al., 2020).

Of the inflammatory factors associated with PF&S, the tumor necrosis factor-α (TNF-α)/IL6 dyad has been proposed as an endophenotypic expression of inflamm-aging in older adults (Picca et al., 2022b). Studies in humans and rodents showed an association between low muscle mass and strength and high levels of TNF-α and IL6 (Rieu et al., 2009; Visser et al., 2002). Moreover, results of a systematic review and meta-analysis included these two mediators among the few biomarkers shared between frailty and sarcopenia in older adults (Picca et al., 2022b). More specifically, while IL6 is associated with frailty and sarcopenia only in those younger than 75, high levels of TNF-α characterize community-dwelling older adults with frailty and sarcopenia regardless of age (Picca et al., 2022b).

Markers of extracellular matrix (ECM) remodeling have also been identified among the circulating mediators characterizing older adults with PF&S. ECM remodeling is a major regulator of tissue homeostasis (Freitas-Rodríguez et al., 2017). The coordinated activity of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) regulates ECM composition and mechanical properties (Freitas-Rodríguez et al., 2017). In the setting of MMP and TIMP imbalance, the low abundance of ECM-bound growth factors impinges on cellular stemness, and a senescent phenotype can ensue (Blokland et al., 2020; Freitas-Rodríguez et al., 2017). The high serum levels of ECM remodeling factor TIMP-1 and the cellular surface receptor intercellular adhesion molecule 1 (ICAM-1) in older adults with PF&S suggests that SASP-related factors may also be involved in muscle aging and loss of physical function (Picca et al., 2022a). Positive associations among serum concentrations of TNF-α, TIMP-1, and Serpin E1, also known as PAI-1 because of its role as repressor of the plasminogen system, have also been observed (Picca et al., 2022a). These associations may represent a senescence-guided response to the pro-atrophy ECM changes occurring in PF&S. Serpin E1 has also been involved in the modulation of MMPs activity by blunting the activation of pro-MMPs (Leivonen et al., 2013). Conversely, plasmin triggers MMP secretion (Pins et al., 2000). Therefore, high levels of PAI-1 may enact a negative feedback for limiting ECM degradation (Rahman and Krause, 2020). For instance, an increase in the levels of PAI-1 and TIMPs has been found in the setting of fibrosis (Alameddine and Morgan, 2016; Rahman and Krause, 2020). Associations between SASP factors and measures of physical

performance have also been reported in the Lifestyle Intervention For Elders (LIFE) study (Fielding et al., 2022).

Additional investigation is needed to untangle the molecular determinants linking inflamm-aging, cellular senescence, and muscle decline to devise therapeutic strategies targeting these pathways.

4. Satellite cells and muscle remodeling

SCs are the major muscle stem cells contributing to muscle mass maintenance during steady state and regeneration following injury (Chang and Rudnicki, 2014; Mauro, 1961). Strategically positioned between the basal lamina and the plasma membrane of muscle fibers, SCs respond to signals released by injured fibers by undergoing several rounds of proliferation and ultimately differentiating to form new myofibers (Relaix and Zammit, 2012; Sambasivan et al., 2011; Tedesco et al., 2010). A proportion of the activated SCs self-renew and return to a quiescent state, thereby maintaining the stem cell pool (Evano and Tajbakhsh, 2018). Whether SCs play a direct role in the development of sarcopenia remains unclear. However, a change in their number and function with advancing age compromises muscle homeostasis and regenerative potential, which in turn contributes to and accelerates the progression of sarcopenia (Hong et al., 2022; Sousa-Victor and Muñoz-Cánoves, 2016; Wang et al., 2019).

SC's function is critically influenced by the surrounding microenvironment composed of ECM proteins as well as various cell types and their secreted factors, collectively known as "the SC niche" (Yin et al., 2013). Among the cell populations belonging to the SC niche are capillary endothelial cells typically found in close association with SCs, fibrocyte/adipocyte progenitors (FAPs), and immune cells in the nearby interstitial space (Christov et al., 2007; Joe et al., 2010; Rizzo et al., 2020; Ziemkiewicz et al., 2021). This complex niche regulates both the SC's quiescent state during homeostasis and their activation in response to injury, supporting the various stages of muscle regeneration. When regeneration is complete, the SC niche provides the signals necessary for the return to quiescence and the preservation of the SC pool (Verma et al., 2018; Zhang et al., 2019). Numerous studies have demonstrated that aging is associated with changes in the SC niche such that it fails to maintain SC quiescence and, instead, promotes SC activation, differentiation, and senescence (Ryan et al., 2006; Wang et al., 2019). Normally, SCs are protected from becoming senescent during prolonged periods of quiescence by employing the mitophagy and autophagy pathways necessary for the maintenance of cell viability (Chang, 2020; Fiacco et al., 2016; Lin et al., 2021). However, with advancing age, these pathways become ineffective and, hence, senescence of quiescent SCs seems inevitable (García-Prat et al., 2016; Sousa-Victor et al., 2014). The changes associated with aging encompass both local and systemic factors, such as circulating inflammatory cytokines, that drive SC activation and differentiation leading to the exhaustion of the SC pool, and phenotypic and functional changes to the cell components of the niche (Wang et al., 2019). Thus, the aged niche favors the replacement of normal muscle tissue with fibrous and adipose tissue (Wang et al., 2015). Nevertheless, it is worth noting that exposure of old SCs to a young niche fails to prevent senescence, suggesting that both cell intrinsic and extrinsic defects are responsible for muscle aging (Sousa-Victor et al., 2014). Mitochondrial dysfunction is one of the key cell intrinsic factors contributing to impaired muscle regeneration during aging (Herbst et al., 2007). The induction of systemic mitochondrial dysfunction in a transgenic mouse model of mtDNA double-strand breaks promotes premature aging and muscle wasting by causing a significant reduction in the number of SCs (Wang et al., 2013). Recently, Kimoloi et al. (2022) also demonstrated that mtDNA changes in myofibers during aging triggered muscle regeneration and led to sarcopenia only if accompanied by mtDNA alterations in SCs. However, further work is needed to unravel the precise contribution of SCs mitochondrial alterations to sarcopenia. Of note, mitochondrial dysfunction, which is associated with a reduction in cellular levels of nicotinamide adenine dinucleotide (NAD) (Gomes et al., 2013), was reversed in SCs following treatment with NAD precursors such as nicotinamide riboside, thereby preventing SC senescence and ameliorating their function in old mice (Zhang et al., 2016).

At present, there are no validated SC biomarkers that can be used to monitor the development and progression of sarcopenia. However, some potential biomarkers of impaired SC function have recently been proposed, including growth differentiation factor 8 (GDF8) or myostatin, myogenic regulating factor 4 (Mrf4), and activation of the Wnt pathway. These markers could in principle be detected in liquid biopsies and warrant future investigation (Fernández-Lázaro et al., 2022).

5. Interventions for muscle "rejuvenation"

Exercise and nutrition are to date the two best characterized and successful strategies for preventing muscle loss and functional decline in old age (Bernabei et al., 2022). At the myocyte level, downregulation of the ubiquitin-proteasome system and upregulation of autophagy-related genes have been reported among the beneficial effects of exercise training in patients with inflammatory myopathies (Borges et al., 2021). Moreover, AMP activated protein kinase (AMPK)-mediated phosphorylation of unc-51 like autophagy activating kinase 1 (ULK1) has been described as a pivotal step for targeting and delivering mitochondrial to the lysosomes in exercise-induced mitophagy in mice (Laker et al., 2017).

Specific contributions to myocyte and mitochondrial fitness have been described depending on exercise modality (Harper et al., 2021). Furthermore, time-dependent patterns of molecular adaptations and MQC mediators have been observed under chronic exercise (Arribat et al., 2019). Young adults practicing moderate cycling alone or coupled with exercise sprints showed an increase in protein levels of BNIP3, LC3 I, and Parkin, and the mitochondrial electron transport chain complex I, while those of LC3 II and p62 were found unvaried (Brandt et al., 2018). These exercise-induced changes occurred within the time frame of 2 h of recovery and eight weeks of exercise (Brandt et al., 2018).

As per the exercise modality, aerobic exercise in sarcopenic mice was able to blunt inflammation, increase muscle mass, strength, and fiber cross-sectional area, and rescue mitochondrial function via the AMPK-Sestrin 2 pathway (Liu et al., 2021). A selective increase in the abundance of p53 in the nucleus, instead, was observed in individuals undergoing acute endurance exercise training compared with a non-exercised control group (Tachtsis et al., 2016). Conversely, the autophagy protein 5 was decreased in the mitochondrial protein fraction of participants in the exercised group, while cytoplasmic levels of PINK1 were be increased only in the control group after 3 h of rest (Tachtsis et al., 2016). Finally, no changes were observed in the levels of PGC-1α following acute endurance (Tachtsis et al., 2016). Taken as a whole, these findings suggest that the events underlying muscle remodeling induced by exercise may follow a time-dependent transition. At first, a pro-autophagic muscle response is mounted to clear damaged proteins and organelles, followed by mitochondrial biogenesis and muscle remodeling (Tachtsis et al., 2016). However, conflicting results have been reported. A lack of mitophagy activation in individuals practicing endurance exercise (Schwalm et al., 2017) or mitochondrial biogenesis has been described (Balan et al., 2019). Furthermore, no changes in markers of mitophagy and mitochondrial remodeling (i.e., PINK1 and Parkin) or those of mitochondrial biogenesis (i.e., nuclear respiratory factor 1, PGC-1α, and mitochondrial transcription factor A) were observed in older adults engaged in resistance exercise training (Mesquita et al., 2020).

The impact of lifelong high-volume endurance training on mitochondrial function and network in older adults was also evaluated (Ringholm et al., 2022). Higher mitochondrial mass and connectivity were found in older adults under intense training compared with moderately trained and untrained controls (Ringholm et al., 2022). However, highly trained older adults showed a decrease in protein levels

of the mitophagy mediator Parkin and no variations in markers of oxidative stress despite but higher protein levels of the mitochondrial antioxidant superoxide dismutase 2 (Ringholm et al., 2022). These results indicate that lifelong high-volume endurance training increases mitochondrial volume and network connectivity and confers greater oxidative capacity to the skeletal muscle of older adults (Ringholm et al., 2022). In line with these findings, another investigation evaluating the effect of lifelong exercise training in humans and mice reported reduced mRNA levels of the biogenesis master regulator reduced PGC-1α and lower protein levels of p62 and p21 in the muscle of older people (Dethlefsen et al., 2018). High protein levels of the autophagy mediator BNIP3 and low mRNA levels of p53 were identified in individuals on lifelong exercise training (Dethlefsen et al., 2018). Altogether these data indicate an association between healthy aging and regulation of skeletal muscle apoptosis, autophagy, and mitophagy (Dethlefsen et al., 2018).

The combined effects of exercise and nutrition on MQC have also been investigated in muscle of older adults. High protein levels of markers of mitophagy and mitochondrial dynamics were identified in runners following endurance training and a high-fat meal (HFM) diet compared with sedentary controls, while HFM diet alone did not alter autophagy or mitophagy in either groups (Tarpey et al., 2017). Twelve-week supplementation with leucine combined with resistance training has also been reported to induce an increase in mitochondrial content in pre-frail older women (Jacob et al., 2021).

Exercise has also been indicated as a strategy for circumventing the inexorable decline of SC function, which along with its direct effect on muscle fibers, leads to activation of SCs and muscle hypertrophy (Cartee et al., 2016; Chen et al., 2020; McCormick and Thomas, 1992; Petrella et al., 2008). Depletion of SCs abrogates exercise-associated muscle hypertrophy (Rosenblatt and Parry, 1992). Moreover, exercise is known to have beneficial effect on the SC niche and the inflammatory status (Docherty et al., 2022; Garg and Boppart, 2016; Gleeson et al., 2011). Even if exercise does not fully prevent the development of sarcopenia, its ability to reduce the adverse effects associated with sarcopenia makes it a valuable approach for the management of this condition. A variety of pharmacological interventions against sarcopenia are under investigation (i.e., myostatin/Activin receptor type 2B signaling inhibitors, anabolic hormones) (Kwak and Kwon, 2019). Compounds acting on receptors/pathways related to the aging process and referred to as geroTherapeutics mimic some of the actions of nutritional and exercise interventions (Couteur and Barzilai, 2022; Kulkarni et al., 2022). GeroTherapeutics, such as metformin, rapamycin, and NAD precursors, are actively investigated as possible strategies to obtain therapeutic gain against muscle aging and, more in general, chronic degenerative diseases.

6. Conclusion

In addition to defining the repertoire of mediators of muscle aging, establishing the metrics of healthy aging, and setting efficacy endpoints for intervention studies, the quantification of inflammatory, mitochondrial, and senescence-related markers is key to disentangle the events underlying age-related muscle wasting and functional decline. For instance, circulating markers, either in the form of free molecules or carried within extracellular vesicles, have been proposed as proxies of mitophagy-related changes and MQC measures. Upon validation, the implementation of these measures in research and clinical settings may enable accessing muscle-specific changes without invasive analytical approaches. Circulating mediators that could be exploited for biomarker discovery and therapeutic purpose are highly sought after.

Declaration of competing interest

The authors declare no competing interests.

Data availability

No data were used for the research described in the article.

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