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The aging muscle: sarcopenia, mitochondrial function, and redox biology

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Sarcopenia, age-related skeletal muscle loss and weakened strength, hinders functional independence, elevates mortality risk, and strains healthcare systems. Diagnosis varies among working groups, leading to diverse prevalence estimates. Recent meta-analyses suggest a 10% overall prevalence, increasing with age and peaking at 50% for those aged 80 or older. Standardized diagnostic criteria are essential for addressing this significant health concern. Sarcopenia is associated with structural and functional muscle changes, including mitochondrial alterations and disruptions in redox balance. Given the pivotal role of mitochondria in the pathogenesis of sarcopenia, further preclinical and clinical studies are needed to gain a deeper comprehension of redox signaling pathways and to identify targeted therapeutic strategies.

Key words: sarcopenia, elderly, muscle mass, redox

INTRODUCTION

Sarcopenia is characterized by low muscle strength as the primary parameter, with a diagnosis confirmed by the presence of low muscle quantity or quality, and considered severe when low muscle strength, low muscle quantity/quality, and low physical performance are all detected [1]. This condition exerting a negative effect on functional autonomy due to muscle weakness and disability, and increasing the risk of mortality [2-4]. Furthermore, sarcopenic subjects show a higher mortality rate as well as a considerable economic burden for healthcare systems [5,6]. Even though a decrease in skeletal muscle mass is frequently indicated as the "primum movens" of sarcopenia, strength reduction can occur even several years before muscle mass loss [7]. Age-related loss of muscle strength without involvement of muscle mass is named dynapenia [7]. From a clinical perspective, sarcopenia can be diagnosed by applying different criteria related to skeletal muscle mass, strength and performance. Procedures of working groups on sarcopenia are constantly updated, resulting in a loss of uniformity in diagnostic criteria without universal consensus. Indeed, diagnosis of sarcopenia according to the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), the Asian Working Group for Sarcopenia (AWGS), the Sarcopenia Definition and Outcomes Consortium (SDOC), and the Foundation for the National Institute of Health (FNIH) relies on different diagnostic criteria [1,8-10]. Use of different criteria and diagnostic methods leads to different prevalence values in the same population [11,12].

Indeed, according to a recent meta-analysis, the overall prevalence among individuals aged ≥ 60 may range from 10 to 27% [13]. Of note, the

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prevalence of sarcopenia increases with age, peaking to 50% in people aged 80 years or older [14].

SKELETAL MUSCLE CHANGES DURING AGING

Aging is associated to changes in body composition, represented by an increase in fat mass and a decrease in lean mass and bone mineral density [15]. From 20 to 80 years of age, bout 30% of skeletal muscle mass and 20% of cross-sectional area (CSA) are lost [16]. In community-dwelling individuals aged 75 years or older, longitudinal studies report the rate of skeletal muscle mass loss at 0.64-0.70% per year in women and 0.80-0.98% per year in men, this rate is worsened by muscle unloading in inactive old people [3,17]. Several underlying mechanisms drive this change, with a network of interacting dysfunctional systems involving protein turnover, reactive species, reduced number of satellite cells, neuromuscular and mitochondrial changes, and inflammation [3] (Fig. 1). These processes may promote a decrease in the number of skeletal muscle fibers and CSA, and impaired regeneration, as described in older humans [3]. In old age, both size and contractile function of fibres expressing slow myosin heavy chain (MHC) I are preserved, whereas there is a marked decrease of these features in fibres expressing the MHC II isoforms [18].

Progression of aging is associated with a significant reduction in the regenerative capacity of the muscle. Importantly, capillarization is crucial in this scenario. Trained aged animals showed a greater capillarization as compared to aged sedentary counterparts, suggesting that early revascularization may facilitate improved recovery in regenerative response. In fact, muscle capillarization not only facilitates a direct interaction between endothelial cells and satellite cells, but also allows for the distribution of growth factors from other cell types. Exercise can improve muscle capillarization in animal models [19].

Aging and skeletal muscle metabolism

Skeletal muscle mass depends on proteostasis, defined as the dynamic balance between muscle protein synthesis (MPS) and breakdown (MPB), folding and trafficking, in turn influenced by two main factors: food intake and physical activity [20]. One of the most important pathways involved in the muscle protein synthesis is modulated by the PI3K/Atk (PKB)/mechanistic target

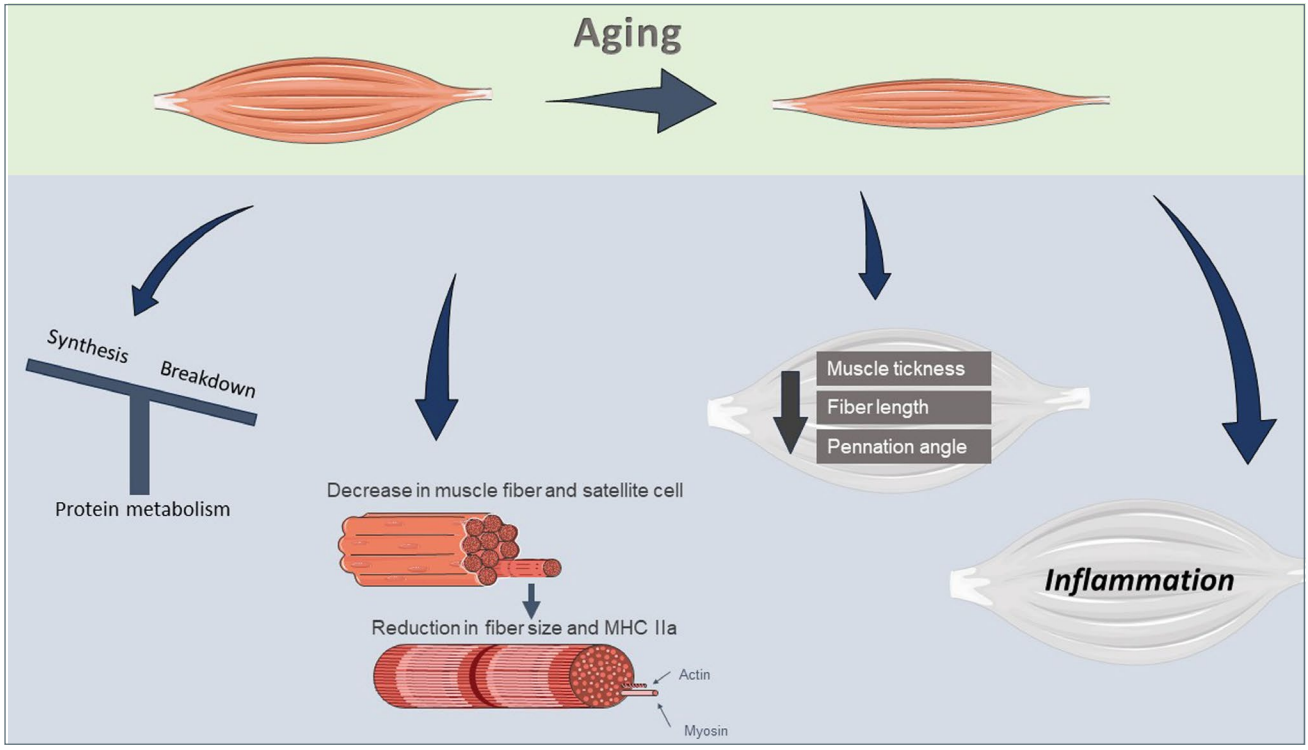

Figure 1. Mechanisms underlying the changes associated with muscle aging.
Several interconnected mechanisms underlie muscle aging, such as impaired protein turnover, increased production of reactive species, reduced numbers of satellite cells, dysfunctional neuromuscular and mitochondrial changes, and an elevation in circulating pro-inflammatory mediators. The Figure was partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license (https://creativecommons.org/licenses/by/3.0/).

of rapamycin (mTOR) signalling [21]. The mammalian target of rapamycin complex 1 (mTORC1) is an essential site of integration for anabolic signals, such as amino acids, insulin, and resistance exercise, to stimulate protein synthesis in human skeletal muscle via ribosomal protein S6 kinase 1 (S6K1) and eukaryotic initiation factor 4E-binding protein 1 (4E-BP1) [22]. Skeletal muscle protein degradation depends by four major proteolytic pathways: the ubiquitin-proteasome system (UPS), calpains, caspases, and the autophagy-lysosomal pathway [21]. In particular, the UPS plays a pivotal role in degradation of misfolded and aggregated proteins that accumulate during aging in skeletal muscle [23].

Loss of skeletal muscle mass during aging is associated to unbalance between proteostasis. Increased catabolism may be attributed to differences in health status, insulin sensitivity, physical activity, and/or dietary habits in elderly subjects as compared to young [24-26]. In old people, basal total protein levels of mTOR, S6K1, and 4E-BP1 are downregulated as compared to young individuals [27]. Also, changes in mitochondrial DNA and ATP production affect muscle energy metabolism in older people. Aging is associated to reduction in mitochondrial mass, activity of tricarboxylic acid cycle enzymes, O2 consumption, and ATP synthesis [28,29]. Furthermore, age-related changes in tissue metabolism lead to impaired glucose, fat, protein uptake and utilization, and finally energy production. A natural decline in sex hormones, including androgens and estrogens, is a common aspect of aging. In men, bioavailable testosterone tends to decrease by approximately 2 to 3% annually after the age of 30. Women experience a reduction in estrogen levels during menopause. The observed variations in skeletal muscle metabolism and distinctions between males and females may be influenced, in part, by the age-related changes in sex hormones [30]. The disparities between males and females stem from the impact of sex hormones, contributing to greater skeletal muscle loss and increased visceral fat in males. This is accompanied by a prevalent reduction in capillarization of type II glycolytic myofibers [31]. Estrogen, particularly estradiol, plays a crucial role in modulating skeletal muscle strength through various pathways involving immune cells and satellite cells [32]. During menopause, the decline in estrogen levels is associated with a reduction in lean body mass and a decline in the regenerative capacity of muscles. Similarly, testosterone has a significant impact on muscle mass growth, and diminishing testosterone levels during aging are linked to a decrease in both muscle mass and strength. Studies have shown that testosterone supplementation in hypogonadal men can increase muscle mass and reduce fat content, possibly by elevating the number of satellite cells and promoting subsequent hypertrophy [33]. Low skeletal muscle capillarization may contribute to sarcopenia and reduced exercise capacity in older adults by limiting diffusion of substrates, oxygen, hormones, and nutrients [34]. Transcapillary transport of insulin is a major determinant of glucose uptake in metabolically active tissues, so that the age-related alterations of skeletal muscle capillarization contribute to insulin-resistance. In fact, impaired glucose tolerance or type 2 diabetes increase with advancing age [35]. Transporters involved in glycolysis and glycogen metabolism, as well as glucose transporter-4 (GLUT4), are downregulated [31]. Several other age-related alterations in insulin signalling were reported in skeletal muscle, contributing to systemic insulin resistance and impaired glucose metabolism [31]. As regards the proteolytic pathways in aged skeletal muscle, recent evidence attributes to E3 ubiquitin ligases (e.g., Parkin, UBR4, and Mib1) a key role in the development of proteostasis alterations. The reduction of E3 ubiquitin ligases may have detrimental effects on muscle homeostasis and function, although an accumulation in other E3 ubiquitin ligases can be just as deleterious [23].

Aging, muscle fibers, and neuromuscular changes

During aging, several changes occur in the structure of skeletal muscle characterized by decreased satellite cell and fiber number, reduced fiber size, and decline in the expression of myosin heavy chain (MHC) isoform IIa (MHC IIa) [36]. Satellite cells (SCs) play a key role in repair and regeneration of skeletal muscle. However, aging affects the ability of SCs to regenerate muscle and replace lost myofibers. This impaired function appears to be mediated by changes in growth factors and cytokines present in the surrounding connective tissue microenvironment [37,38]. Impaired SCs function contributes to the development of sarcopenia [39]. Aging is associated with muscle fiber size reduction [36]. This reduction mostly involves type II fibers, with a 10-40% reported increase in the ratio of type I to type II fibres in humans [3,40]. Changes in fiber size seem to be related to fewer SCs in type II fibers and lower protein synthesis, which reduce the speed of skeletal muscle growth and repair [36]. SCs alteration in fast type II fibers suggests that stem cell depletion is prevalent in sarcopenia and may facilitate age-associated fast-to-slow transition [41].

Also, a key role for the development of sarcopenia is played by age-induced loss of motor units (MU). In fact, loss of MU may lead to fiber denervation and consecutively increased risk of muscle atrophy. Denervated fibers may be reinnervated by nearby axons in a process named MU remodelling [20]. In turn, aged MU remodelling is linked to the preferential denervation of fast-twitching type II fibers, characterizing faulty patterns of reinnervation by smaller motor neurons that establish

slower-contracting type I MU [41]. A failure to reinnervate fibers characterizes sarcopenic from no-sarcopenic aged subjects [20].

However, conflicting data exist demonstrating no changes in the percentage of type I and type II fibres with age in humans [3,42]. These contradictory findings are most probably dependent on a slight number of younger participants in studies [3].

Aging and muscle architecture

Muscle architecture is one of the most important determinants of muscle strength and power performance [43]. Muscle architecture relies on muscle thickness, fiber fascicle length, and pennation angl [44,45]. Larger pennation angle is associated with higher skeletal muscle strength as well as higher CSA, leading to an improved ability of the muscle to develop strength [46]. Elderly people show decreased muscle thickness, fascicle length (FL), and pennation angle (PA) as compared to young adults [47,48]. Data show a reduction of 19.1% for cross-sectional area (CSA), 10.2% for FL, and 13.2% for PA in the gastrocnemius medialis muscle in old subjects as compared to young controls [48]. Magnitude of age-related decline expressed as percentage of muscle thickness appears to change across the different lower-limb and trunk muscles as compared to young [49]. Changes in muscle performance may precede alteration in muscle mass. Strength is lost more rapidly with a rate of 3-4% per year in men and 2.5-3% per year in women; indeed, the latest guidelines from EWGSOP2 have centered the diagnostic pathway for sarcopenia primarily on muscle loss [17,49]. Muscle composition has been correlated to maximal strength, independently of muscle size [50]. However, muscle power, defined as the product of the force and speed of muscle contraction, declines earlier and more markedly with aging as compared to muscle strength [51,52]. Indeed, patients affected by sarcopenia with reduced muscle CSA and volume exhibit changes in the spatial arrangement of muscle fibres, including alterations in fibre fascicle length, pennation angle, and muscle thickness. A decrease in fascicle length predicts a loss of sarcomere in series and a decrease in pennation angle, as well as a loss of sarcomeres arranged in parallel [44].

Aging, skeletal muscle and inflammation

As individuals age, the immune system experiences significant changes, often referred to as immune senescence [53]. Inflammation represents a key factor in the development of sarcopenia and, interestingly, skeletal muscle has emerged as a regulator of immune function [53,54]. Aging is associated with higher levels of circulating cytokines and acute-phase proteins, characterizing a condition of chronic low-grade inflammation defined as “inflamm-aging” [54,55]. Circulatory cytokines contribute in activating or blocking signalling pathways involved in protein synthesis and proteolysis [56]. In fact, inflammatory mediators affect muscle protein metabolism, and elevated level of interleukin (IL)-6, tumor necrosis factor (TNF) and C-reactive protein (CRP) are associated with sarcopenia [53,57]. Data in elderly people show a significant association between high level of circulant IL-6 and sarcopenia, as well as high level of Il-6 and muscle strength reduction [56]. IL-6 exerts a complex biological profile with both pro- and anti-inflammatory effects, and further promotes skeletal muscle anabolism or catabolism, depending on the target structure. IL-6 facilitates skeletal muscle atrophy by blunting muscle anabolism and energy homeostasis, and it may also directly mediate muscle catabolism [53]. However, IL-6 knockout mice showed no significant difference in muscle catabolism as compared to wild type mice in an experimental model, so it can be assumed that the sole action of IL-6 is not sufficient to induce muscle wasting; indeed, the catabolic effect of IL-6 is dependent on the synergistic interaction with other factors that mediate the inflammatory response such as TNF-α [53,58]. TNF plays a crucial role in the loss of skeletal muscle mass by promoting protein degradation and decreasing protein synthesis [56]. Recently, Wu et al. demonstrated how TNF contributes to sarcopenia by triggering gasdermin E (GSDME)-mediated pyroptosis in myotubes. This occurs through the activation of caspase-8 and caspase-3, and they utilized caspase-8 and caspase-3 inhibitors for their study. Specifically, TNF-α activates caspase-8 and caspase-3 via TNF Complex IIb, leading to pyroptosis in myotubes. Consequently, pyroptotic myotubes show reduced expression of MHC1 and subsequent muscle fiber loss, which culminates in sarcopenia [59]. These pieces of evidence suggest that chronic low-grade inflammation can induce muscle wasting, while the homeostasis of skeletal muscle plays a role in maintaining healthy immune function. This interplay suggests that age-related disturbances in the balance between muscle and the immune system could be central to conditions like sarcopenia, where both systems potentially amplify each other’s dysfunctions [53].

Epigenetics and muscle aging

The regulation of gene expression significantly influences the phenotype of every tissue, and play a role in the aging process [60]. One hallmark of aging is the alteration in the epigenetic landscape, with DNA methylation being the most extensively studied epigenetic modification. DNA methylation can lead to heritable changes in gene expression without modifying the nucleotide sequence. Both genetic and environmental factors contribute to individual DNA methylation patterns, leading to variability of muscle aging [61,62]. Specifically, DNA methylation in aged skeletal muscle affect tissue-specific genes and, compared to young skeletal muscle, shows genome-wide

hypermethylation. Early exposure to inflammatory stress during proliferative phases can lead to sustained hypermethylation of certain muscle regulatory factors [62]. Past research, has highlighted both an age-related rise in DNA methylation and a decline in gene expression, underscoring the influence of DNA methylation on crucial metabolic genes in muscle and its potential involvement in age-associated metabolic diseases [63,64]. Notably, recent studies by Antoun et al., revealed extensive changes in muscle methylation associated with sarcopenia and related factors such as grip strength, lean mass, and gait speed. Their findings demonstrated that inhibiting Enhancer of Zeste Homologue 2 in human primary myoblast altered key cellular processes and methylation patterns. These insights emphasize the central role of epigenetics in muscle functionality and propose potential strategies for enhancing ATP production in sarcopenic muscle cells through targeted interventions [61]. Additionally, consistent physical activity, encompassing endurance and resistance training, is associated with a reduction in genome methylation in young muscle, contrasting the hypermethylation observed with age, suggesting that increased activity levels might mitigate some age-related DNA methylation changes [62].

MITOCHONDRIAL FUNCTION IN SKELETAL MUSCLE

Mitochondria are organelles serve as the primary source of energy for cells. Mitochondrial respiration and ATP synthesis primarily rely on ADP sourced from ATP-consuming reactions occurring in the cytosol [65].
Skeletal muscle mitochondria form an interconnected three-dimensional reticulum within and between skeletal muscle fibers, able to distribute energy and metabolites throughout the cell [66]. Almost two types of mitochondria subpopulation can be recognized, with differing morphology and biochemical properties: subsarcolemmal (SS) and intermyofibrillar (IMF) mitochondria [67]. A third mitochondrial subpopulation, called perinuclear, is located around the nucleus as a continuation of SS, even though it is less characterized than SS and IMF [31]. SS mitochondria provide ATP for membrane active transport, while IMF mitochondria provide ATP to the contractile filaments within muscle to facilitate contraction. Also, the location of IMF mitochondria between the myofibrils adjacent to Z-line of sarcomere and in direct contact with transverse tubules, accounts for their key role in Ca2+ signalling within the cell [67]. Through regulation of Ca2+ levels, mitochondria in skeletal muscle modulate not only contraction, but also metabolism and intracellular signalling [31,67]. The different fiber types that compose human skeletal muscle (type I, IIa, and IId/x fibers) present with a different metabolic profile. Type I slow-twitch and IIa fast-twitch fibers are characterized by an oxidative profile with higher expression of oxidative enzymes, mitochondria, and capillary supply; on the contrary, type IId/x fibers exhibit a glycolytic metabolic profile, with prevalent expression of glycolytic enzymes, less mitochondria and capillary supply [68].
Whole-body aerobic capacity depends mostly on skeletal muscle mitochondrial respiration [69]. However, the aerobic capacity, defined as the maximal ability to use oxygen to meet the energy demand of physical activity, tends to decline with age, especially after 50 years [28].

Mitochondria during skeletal muscle aging

Mitochondrial dysfunction is a hallmark of aging and is associated with changes in skeletal muscle energy metabolism [31,70]. In addition, mitochondrial dysfunction is associated with skeletal muscle apoptosis [71]. In aged skeletal muscle, mitochondria appear enlarged and more rounded in shape, with matrix vacuolization and smaller cristae when compared with skeletal muscle mitochondria from young subjects [29]. With advancing age, there is a decrease in mitochondrial content in skeletal muscle. This reduction is associated with a decrease in mitochondrial number and density, as well as a decreased mitochondrial deoxyribonucleic acid (DNA) copy number and protein expression [70]. Such decline in mitochondrial content may contribute to the loss of skeletal muscle mass, resulting from reduced mitochondrial biogenesis, an imbalance of mitochondrial dynamics, and impaired mitophagy [70,72]. Peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α), an important gene regulating mitochondrial biogenesis and skeletal muscle insulin sensitivity, is decreased in skeletal muscle of aged rodent models 70. Also, PGC-1α modulates the crosstalk of signalling pathways related to mitochondrial quality in old age, such as expression of mitofusin 2 (Mfn2) that plays a significant role in fusion dynamics and mitophagy, and expression of sirtuin (SIRT) 3 involved in deacetylation of key mitochondrial metabolic and antioxidant enzymes [21]. Mitochondrial dynamics is related to the ability of these organelles to quickly modulate their size, shape, and distribution by fission and fusion events [31]. Alterations in mitochondria dynamics were observed in skeletal muscle aging. Dynamin-related protein 1 (DRP1) content tends to significantly increase with age, together with mitochondrial network reorganization and reduced mitochondrial DNA copy number. Also, activation of the dsRNA-dependent protein kinase/eukaryotic initiation factor 2/fibroblast growth factor 21 pathway by Drp1 overexpression leads to decreased skeletal muscle protein synthesis and downregulation of the growth hormone pathway. In a mouse model, Mfn2 expression decreases with skeletal muscle aging. Selective Mfn2

knockout in mouse skeletal muscle reduces mitophagy and decreases mitochondrial function. The reduction in Mfn2 expression associated to aging can lead to skeletal muscle metabolic disorders and sarcopenia [70]. AMP-activated protein kinase (AMPK) disrupts defective and fragmented mitochondria through FoxO3-dependent mitophagy. Dysfunctional mitochondria with exaggerated sensitivity to mitochondrial permeability transition pore (MPTP) opening tends to accumulate in aged skeletal muscle due to impaired mitophagy, resulting in a progressive accumulation of a non-degradable and polymeric material called lipofuscin in lysosomes. Lipofuscin has been suggested to contribute to the functional impairment in skeletal muscle with advanced age [71].

MITOCHONDRIAL PRODUCTION OF REACTIVE SPECIES DURING SKELETAL MUSCLE AGING

Generation of reactive oxygen and nitrogen species (ROS and RNS), with associated oxidative damage and/or defective redox signalling, is one of the major mechanisms involved in the development of sarcopenia [21]. Metabolic reactions produce both reactive oxygen and nitrogen species (ROS and RNS, respectively), globally termed as reactive species or oxidants [73]. Redox signalling changes are observed during aging process, with increased exposure or modulation of mitochondrial reactive species. Furthermore, aged skeletal muscle is vulnerable to oxidative damage to DNA, lipids, and proteins [29]. Excessive production of mitochondrial ROS/RNS is associated with altered mitochondrial energy metabolism and sarcopenia [74]. With age, skeletal muscles show a decline in mtDNA and mRNA abundance, mitochondrial ATP production and oxygen consumption [71]. Complexes I and IV activities are decreased in aged muscles, probably due to their content in subunits encoded by the mtDNA, which is more vulnerable to ROS/RNS derived from the respiratory chain. Also, increase in ROS/RNS production affects mitochondrial content and protein expression of PGC-1α with a rise of mitochondrial apoptotic susceptibility. These alterations are potentially involved in the development of age-related sarcopenia [71]. Furthermore, AMPK and SIRT1 can directly affect PGC-1α activity through phosphorylation and deacetylation, respectively. Data from in vivo transgenic models show that AMPK, SIRT1, and PGC-1α might act as a network to control cellular energy expenditure and to improve metabolic fitness [75]. Elevated levels of ROS such as H2O2 can inhibit phosphorylation of Akt, mTOR, and the downstream mTOR targets 4E-BP1 and p70S6K [13,21]. Excess ROS/RNS produced in aged muscles may inhibit key components of the Akt/mTOR pathway, thereby limiting their capacity to respond to exercise stimul [21].

The insulin-like growth factor-1/phosphatidylinositol 3-kinase/protein kinase B (IGF-1/PI3K/PKB) is one of the main pathways that promote protein synthesis 76. ROS/RNS activate the IGF-1/Akt/mTOR pathway in myocytes, stimulating protein synthesis and cellular hypertrophy. However, increased resistance to IGF-1-mediated signalling occurs during muscle aging [77]. Conversely, Akt phosphorylates FoxOs, affecting their nuclear translocation and transcription, and counteracting the FoxO1-mediated protein catabolism in skeletal muscle [78].

During muscle aging, a close connection is also present between ROS/RNS and inflammation. In fact, ROS/RNS induce the release of TNF that in turn activates the NF-κB-mediated signalling which induces an increase in muscle protein degradation [79]. TNF-α signaling pathways are involved in the healing process consequent to muscle injury and are predominantly associated with tissue degradation [80]. TNF-α plays an important role in sarcopenia through its complex signalling pathways, mostly interconnecting different types of programmed cell death. TNF-α is released by inflammatory cells as well as skeletal muscle cells, activating complex cell death signalling by binding to TNF receptor 1. In a murine model of sarcopenia, a pro-inflammatory state and higher levels of TNF-α were associated with loss of skeletal muscle mass and grip strength [59].

During aging, both mitochondrial dysfunction and oxidative stress enhance myonuclear apoptosis [75]. In rodent models, skeletal muscle aging is associated with increased apoptosis as well as mono- and oligonucleosome fragmentation. Both mitochondria-independent and mitochondria dependent pathways may be involved in the apoptotic process [31]. Changes in mitochondrial structure decrease aerobic energy efficiency and may result into apoptosis [81].

MITOCHONDRIA-TARGETED THERAPY FOR THE PREVENTION AND TREATMENT OF SARCOPENIA

Therapeutic strategies targeting both the quality and function of mitochondria can be categorized based on either molecular size and type, or by taking into account the molecular mechanism. Considering the structural features, the most effective approach for targeting mitochondria to treat sarcopenia includes particles ranging from 1 to 1000 nm in size, which can directly activate myotubes or inflammatory cells. According to the mechanism of action, both passive and active mechanisms are outlined. Passive targeting depends on the physical and chemical properties of carrier systems,

whereas active targeting relies on specific interactions (such as ligand-receptor or antigen-antibody) at mitochondrial sites. However, to date, exercise is the only proven therapy for sarcopenia, as it can limit changes induced by muscle aging [82]. Whole-body resistance exercises are suggested for targeting the major muscle groups in older adults. Exercises focusing on the lower body muscles should be the main part of the program because they help with everyday tasks like walking, standing up, and climbing stairs. It's also important to work on muscles such as the quadriceps, hamstrings, glutes, calves, and the muscles of the foot and ankle. Strengthening upper-body muscles is key for tasks like dressing, cooking, and taking care of oneself [83].

Studies are underway to assess treatments aimed at reducing the loss of muscle mass, targeting various factors. Anti-myostatin antibodies have been developed and tested in humans, showing positive effects on lean mass and, in some cases, evidence of improved physical performance. Recently, the inhibition of activin A in primates has shown improved muscle growth. Testosterone also exerts important effects on muscle trophism through Akt/mTOR activation, reduction in adipose stem cells, and activation of satellite cell recruitment. In accordance with this, evidence shows an increase in skeletal muscle mass after treatment with testosterone, although there is some conflicting data regarding the effect on physical function and muscle strength. The growth hormone/insulin-like growth factor-1 (GH/IGF-1) axis tends to decline with age, and it has been demonstrated that administering human GH to older, healthy individuals can increase muscle mass [84]. Recently, growing evidence has highlighted the role of ECM remodeling in muscle health, as well as in the development and progression of sarcopenia, and the potential association between ECM remodeling and mitochondrial function in muscle tissue. In this context, the ECM/mitochondrial pathway could be a potential target to counteract the onset and progression of sarcopenia [85].

CONCLUSIONS

Mitochondria play a key role during skeletal muscle aging. In recent years, significant progress has been made in understanding the different pathways involved in muscle changes with age. Age-associated dysregulation of redox signaling appears to be one of the major mechanisms involved in the mitochondrial alterations observed in aged muscle. However, while further preclinical, and clinical studies are essential to discern the exact role of different pathways in the age-related sarcopenia, it's pivotal to differentiate between immediate clinical implications and the typical geriatric multidimensional ones. Addressing this differentiation becomes even more critical when considering the development of molecules tailored for skeletal muscle mitochondria. In addition to this, we must also acknowledge the complexities introduced by the challenges of routine health assessments in non-gerontologic settings. These settings may not always be equipped or trained to recognize subtle geriatric nuances or the intricate interactions between muscle aging and overall health. As a result, there's a risk of oversight or misinterpretation of early signs of age-related conditions. Such targeted interventions hold promise not only in enhancing efficacy but also in minimizing the associated toxicity, thereby presenting potential solutions to challenges observed in current therapies.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

ALB, FB: writing – original draft preparation; GV: writing – review and editing. All authors have read and agreed to the published version of the manuscript.

Ethical consideration

Not applicable.

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