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The Clinical Impact and Biological Mechanisms of Skeletal Muscle Aging

Zaira Aversa[1,2,*], **Xu Zhang**[1,2,*], **Roger A. Fielding**[3], **Ian Lanza**[4], **Nathan K. LeBrasseur**[1,2]

[1]Department of Physical Medicine and Rehabilitation, Mayo Clinic, Rochester, Minnesota

[2]Robert and Arlene Kogod Center on Aging, Mayo Clinic, Rochester, Minnesota

[3]Nutrition, Exercise Physiology, and Sarcopenia Laboratory, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts

[4]Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Mayo Clinic, Rochester, Minnesota

Abstract

Skeletal muscle is a highly plastic tissue that remarkably adapts to diverse stimuli including exercise, injury, disuse, and, as discussed here, aging. Humans achieve peak skeletal muscle mass and strength in mid-life and then experience a progressive decline of up to 50% by the ninth decade. The loss of muscle mass and function with aging is a phenomenon termed *sarcopenia.* It is evidenced by the loss and atrophy of muscle fibers and the concomitant accretion of fat and fibrous tissue. Sarcopenia has been recognized as a key driver of limitations in physical function and mobility, but is perhaps less appreciated for its role in age-related metabolic dysfunction and loss of organismal resilience. Similar to other tissues, muscle is prone to multiple forms of age-related molecular and cellular damage, including disrupted protein turnover, impaired regenerative capacity, cellular senescence, and mitochondrial dysfunction. The objective of this review is to highlight the clinical consequences of skeletal muscle aging, and provide insights into potential biological mechanisms. In light of population aging, strategies to improve muscle health in older adults promise to have a profound public health impact.

Correspondence: Nathan K. LeBrasseur, PT, PhD, Mayo Clinic, 200 First Street, SW, Rochester, MN 55905, P/ 507-293-0813, F/ 507-293-3853, lebrasseur.nathan@mayo.edu.

*These authors contributed equally to this manuscript

Declaration of interest

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Author Statement

Zaira Aversa: Data curation; Roles/Writing – original draft

Xu Zhang: Data curation; Roles/Writing – original draft

Roger Fielding: Conceptualization; Roles/Writing- original draft

Ian Lanza: Data curation; Roles/Writing – original draft

Nathan LeBrasseur: Conceptualization; Roles/Writing- original draft; Writing –- review & editing

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Introduction

In nearly all species from c. elegans to humans, skeletal muscle exhibits marked changes in its form and function with advancing age that profoundly impact health. As a primary driver of movement, age-related changes in muscle compromise the ability of an organism to move efficiently within its environment. Mobility is required for survival and represents one of the most essential and necessary forms of physical function across all species. Skeletal muscle is also a robust metabolic organ, which can store, utilize, and provide vast amounts of energy. These physiological processes commonly falter with age, however, and contribute to the pathogenesis of metabolic disease. Skeletal muscle also appears to bestow resilience to physical challenges, and the loss of muscle with advancing age increases vulnerability to adverse outcomes following medical and surgical interventions. Collectively, these consequences of skeletal muscle aging pose substantial socioeconomic burden. In light of population aging, new strategies to optimize muscle health in older adults are desperately needed.

The phenomenon of skeletal muscle aging has been termed sarcopenia, from the Greek words sarx (flesh) and penia (poverty) [1]. The most widely appreciated feature of sarcopenia is the attrition of muscle mass. This has been largely attributed to both the loss and atrophy of postmitotic, multinucleated muscle cells, termed *fibers.* Lexell and colleagues, for example, observed a 40% reduction in the cross-sectional area of whole *vastus lateralis muscle* from 20 to 80 years of age, and noted that the number of both type 1 (slow-twitch and more oxidative) and type 2 (fast-twitch and more glycolytic) fibers were reduced, and the size of type 2 fibers was particularly diminished at advanced ages [2] (Figure 1). Their analysis further revealed that fat and fibrous tissue replaced lost and shrunken muscle fibers. Though arguably less studied, such alterations in the cellular composition of muscle may equally contribute to the clinical impact of muscle aging as the reduction in muscle mass.

The recognition of sarcopenia as an important clinical syndrome has led to multidisciplinary efforts to identify, understand, prevent, and treat this condition [3-5]. One evidence-based [6] and several consensus-based [7-10] definitions of sarcopenia have been proposed. Despite progress, there is not yet a universally accepted clinical definition; however, a unique International Classification of Diseases, 10th Revision (ICD10), code for sarcopenia was assigned in 2016 [11, 12], The heterogeneity in sarcopenia definitions has made estimates of its prevalence in older adults vary widely, ranging from 0.5 to 13% [13].

Remarkable progress has been made in elucidating the causal molecular pathways of aging. The diverse forms of age-related molecular and cellular damage, commonly referred to as hallmarks [14] or pillars [15] of aging, which include loss of proteostasis, deregulated nutrient sensing, stem cell exhaustion/dysfunction, cellular senescence, genomic instability, mitochondrial dysfunction, and epigenetic alterations, are plausible contributors to

sarcopenia. To date, however, there are currently no approved pharmacologic therapies. The burden of sarcopenia on older adults combined with population aging highlight the need to better understand and address age-related muscle loss and dysfunction. To this end, the objective of this review is to discuss the clinical consequences of skeletal muscle aging and highlight recent discoveries relevant to fundamental biological mechanisms.

Clinical consequences of skeletal muscle aging

Physical Function.

Skeletal muscle's unique capacity to generate force and power is perhaps one of its most important functions. Maximum skeletal muscle force generating capacity, strength, is a product of the cross-sectional area of the muscle and the capacity of the nervous system to fully activate the corresponding motor neurons. Cross sectional analyses reveal a close association between muscle size and maximum strength among older adults. However, longitudinal studies examining changes in muscle mass/size and strength have revealed a more complex relationship. Data from both the Baltimore Longitudinal Study of Aging and the Health Aging and Body Composition (HABC) Study have confirmed age-related changes in muscle size or appendicular lean mass to occur at a rate of approximately 0.5 to 1.0% per year; whereas changes in lower extremity muscle strength occurs at rates between 1.0 to 2.0% per years [16, 17]. The longitudinal divergence observed between muscle mass/size and strength suggest that other biological factors independent of changes in muscle size/mass may play a fundamental role in the well characterized changes in motor performance throughout the lifespan.

The age-related declines in muscle mass and strength occur in conjunction with reductions in mobility and physical functioning [17-23]. Sarcopenia leads to age-related functional limitations, including difficulties in walking, climbing stairs and carrying objects [24, 25]. In turn, the penalties of functional decline include falls [26], disability [27-30], institutionalization [31], and even death [32-35]. Methods to indirectly quantify skeletal muscle mass in humans have relied on imaging techniques such as dual-energy X-ray absorptiometry (DXA), computed-tomography (CT), and magnetic resonance imaging [5]. Somewhat surprisingly, the reported associations between muscle/lean mass estimated from DXA and measures of physical function and other distal outcomes, including falls, fractures, and mortality, have been inconsistent [36-41]. Studies using CT to assess muscle size and quality may be more reliable and assess a direct physical property of muscle composition in comparison to measures of lean mass assessed by DXA. Specifically, muscle attenuation as assessed using CT, a relative measure intramyocellular fat infiltration, independently predicts incident mobility disability (self-reported difficulty walking ¼ mile) in community dwelling older adults [42]. Moreover, changes in muscle cross sectional area over 5 years as measured by CT in HABC Study participants were related to an increased risk of mortality (relative risk 1.21 C.I.: 1.08-1.35) [41]. More recent approaches to measure direct properties of muscle quantity by using the isotopic dilution of deuterium-labelled creatine have revealed stronger associations between skeletal muscle mass (estimated by creatine dilution) and measures of physical functioning (Short Physical Performance Battery (a composite measure of gait speed, repeated chair stand time, and standing balance) and usual walking

speed), incident mobility limitation (self-reported difficulty walking 2-3 blocks), and serious fall injury [43]. These findings suggest that tools that more directly assess skeletal muscle mass, size, and/or quality may be more sensitive and thus be more predictive of poor physical function, mobility limitations and more distal clinically relevant outcomes. Future studies need to more extensively interrogate the performance characteristics of new methodologies such as the creatine-dilution technique and other imaging tools in more diverse populations of older adults.

Metabolic Homeostasis.

Aging is strongly associated with T2D, a condition characterized by a resistance to insulin action that accounts for > 90% of cases of diabetes (DC ADA position statement [44]. The incidence of T2D notably increases from 3.1 diagnoses per 1000 persons age 18-44 years to 10.9 diagnoses per 1000 persons age 45 to 65 years [45]. This dramatic mid-life shift in T2D onset, commonly attributed to obesity and physical inactivity, also corresponds to the onset and progression of skeletal muscle aging.

Skeletal muscle is a robust metabolic organ. It is the primary site of insulin-mediated glucose disposal. With the advent of the glycemic clamp technique, the laboratories of DeFronzo and Olefsky demonstrated that insulin sensitivity and, more specifically, post-receptor insulin action, are significantly reduced in healthy, non-obese older women and men [46, 47]. Despite effective binding to its cognate receptor, insulin-mediated activation of Akt2 and the subsequent phosphorylation and inactivation of RabGTPases, which enable glucose transporter type 4-containing vesicles to translocate to the cell membrane to import glucose, are decreased in aged skeletal muscle [48]. Exercise-stimulated muscle glucose transport also diminishes with advancing age. This has been attributed to blunted activation of AMP-activated protein kinase (AMPK), a master regulator of glucose and lipid homeostasis, insulin sensitivity, and mitochondrial biogenesis [49]. Alterations in muscle glucose uptake partly contribute to a marked ~38% reduction in muscle glycogen content in older compared to younger adults [50]. This has notable consequences since skeletal muscle is the largest reservoir of glycogen in the human body and reduced glycogen stores impact endurance, performance, and onset of fatigue [51].

Skeletal muscle further impacts whole-body metabolism as a chief determinant of both resting energy expenditure ((REE), often referred to as basal metabolic rate) and activity-associated energy expenditure (AEE) [52]. REE routinely accounts for 50-70% of total energy expenditure among adults and has been show to decline by 1-2% each decade [53]. This is predominantly a consequence of the loss of lean mass, and skeletal muscle in particular, as nicely summarized by Roberts and Rosenberg [54]. Finally, age-associated changes in AEE are perhaps even more striking and reflect the progressive decrease in both habitual physical activity and purposeful exercise with advancing age. The use of an objective measure of physical activity (accelerometry) in the National Health and Nutrition Examination Survey revealed a 55% decrease in moderate to vigorous activity counts from age 39 to 70+ years, and a 75% decrease in time spent performing moderate to vigorous activity [55]. Indeed, physical activity and exercise have profound effects on skeletal muscle energy demand, including increasing skeletal muscle glucose uptake and fatty acid

oxidation, and, in turn, systemic metabolic homeostasis. Determinants of physical activity and participation in structured exercise are undoubtedly multifactorial (e.g., physical, social, environmental, sex, race), and innovative strategies to counteract the age-associated decline in these behaviors are desperately needed as they promise to profoundly impact human health.

Physical Resilience.

The loss of resilience, defined as the ability to resist and/or recover from a stress or challenge, is a critical phenotype of aging that has recently gained increased attention [56-59]. Challenges to physical resilience, such as infections, surgery, medication exposures, and falls, intensify with advancing age. Considerable evidence suggests sarcopenia is a contributor to the age-related loss of resilience. For example, older persons with low muscle mass experience delayed recovery [60] and higher rates of complications and infections following surgery [61], greater drug toxicity [62], and higher disease-specific and all-cause mortality [63-65]. Moreover, performance-based measures of grip strength and gait speed and self-reported measures of endurance and physical activity, are core components of the frailty phenotype and, arguably, indicative of skeletal muscle health [66]. The associations between frailty and adverse outcomes are robust and have been extensively studied and reviewed elsewhere (e.g., [67-69]). Support for a causal relationship between low muscle mass and the loss of resilience stems from preclinical studies in which blockade of factors responsible for muscle wasting, such as activin A, at least in the context of cancer, enhance survival without altering tumor growth or the systemic inflammation [70]. The potential of muscle-based interventions to improve the resilience of older adults to adverse health outcomes following medical and surgical challenges and/or enhancing their subsequent functional recovery offers a unique clinical trial paradigm.

Collectively, the clinical consequences of skeletal muscle aging profoundly impact the health, independence, and quality of life of older adults and pose a significant burden on healthcare resources and health expenditures. Through a better understanding of the biological mechanisms that cause muscle aging, new interventions can be pursued.

Biological mechanisms of skeletal muscle aging

Proteostasis.

Under physiological conditions, a dynamic interplay between protein degradation and synthesis ensures the maintenance of protein homeostasis within skeletal muscle and allows an adequate adaptation to changes in physical activity, nutritional input and metabolic needs [71, 72]. A progressive loss in protein homeostasis is believed to contribute to the pathogenesis of muscle loss and dysfunction during aging, although the precise mechanisms are still far from being fully elucidated.

Among the proteolytic systems, the ubiquitin-proteasome and the autophagy-lysosome pathways play a prominent role in skeletal muscle protein degradation [73]. In the ubiquitin-proteasome system proteins destined for degradation are first covalently attached to a chain of ubiquitin molecules through an enzymatic cascade (involving the ATP-dependent E1

ubiquitin activating enzymes, the E2 ubiquitin conjugating enzymes and the E3 ubiquitin ligases) and are then processed by the 26S proteasome [74]. Hyperactivation of the ubiquitin-proteasome system has been implicated in several muscle wasting conditions [75], but its role in skeletal muscle aging is more controversial. Indeed, studies on aged skeletal muscle have reported both increased and decreased proteasome activity [76, 77]. Moreover, several studies on skeletal muscle aging have reported unchanged and even reduced mRNA levels for atrogin-1/MAFbx and MuRF1 [76-82], which are two important muscle-specific E3 ubiquitin ligases transcriptionally upregulated in many conditions associated to muscle atrophy [73, 83]. Interestingly, experimental studies have shown that MuRF1-null mice display preserved muscle mass at old age, but a decline in muscle force [77, 80], while mice lacking atrogin-1/MAFbx, which did not reach old age because of precocious death, displayed a reduction of muscle mass and force at 15 months of age [80].

Macroautophagy (hereafter referred as autophagy) is an evolutionary conserved homeostatic mechanism that allows the degradation and recycling of cellular components (bulk cytoplasm, long-lived or misfolded proteins, damaged organelles) by their sequestration in a double membrane vesicle called an autophagosome that next fuses with the lysosome for enzymatic digestion of its content [84]. Although long-considered a non-specific degradative pathway, it is becoming increasingly evident that autophagy can also selectively remove protein aggregates or damaged organelles (such as mitochondria via mitophagy) [85]. Autophagy plays an essential role in the maintenance of skeletal muscle mass and its alteration has been linked to the pathogenesis of muscle atrophy during different pathological conditions [80, 86]. Recently, several studies on aging have evaluated the muscular expression of proteins commonly used to monitor autophagy such as beclin-1, microtubule-associated protein 1 light chain 3 isoform I (LC3I) and the lipidated isoform LC3II, and SQSTM1/p62 [87, 88] . Although the patterns of autophagy markers assessed and reported in these studies were slightly different, overall, they suggested impaired autophagic degradation in aged skeletal muscle [89-93]. However, since autophagy is a highly dynamic process and measurement of these markers in static conditions has some limitations [87, 94], recent experiments have been also performed using the autophagy inhibitor colchicine, which blocks the autophagosome-lysosome fusion [95]. Results obtained in whole muscle extracts as well as in mitochondria isolated from the muscle of aged rodents would suggest an increase in basal autophagy and mitophagy flux, although further studies are needed to evaluate whether autophagosome formation is followed by an efficient lysosomal degradation of the cargo during the final step of autophagy [82, 96, 97]. Indeed, an accumulation of lipofuscin has been previously reported in aged skeletal muscle, which would suggest some impairment in lysosomal function [96, 98].

Interestingly, experiments conducted using mice with a muscle-specific deletion of Atg7 (a crucial autophagy gene) suggested that impaired autophagy may contribute to sarcopenia. Indeed, genetic inhibition of autophagy in murine muscle reduced survival and induced muscular alterations resembling those observed during aging such as atrophy and weakness, neuromuscular junction degeneration, mitochondrial dysfunction and enhanced oxidative stress [86, 91]. In addition, in a recent study genetic impairment of autophagy by Atg7 deletion in the satellite cells of young mice induced entry into senescence and regenerative failure [99]. Of note, a decline in basal autophagy was also observed in physiologically aged

satellite cells and its reactivation by pharmacological treatment or Atg7 overexpression prevented senescence and restored their regenerative capacity.

In coordination with degradative processes, an important contribution to the maintenance of skeletal muscle mass is made by protein synthesis. The insulin-like growth factor 1 (IGF-1)/Akt/mechanistic/mammalian target of rapamycin (mTOR) signaling is a well characterized anabolic pathway, which also plays an important role in regulating protein degradation [100]. Indeed, Akt activation, besides stimulating mTOR and thereby protein synthesis, can also inhibit the Forkhead Box O (FoxO) transcription factors, which control the expression of genes involved in the autophagy as well as in the ubiquitin proteasome-pathway [101, 102]. mTOR functions through formation of two different complexes: mTORC1, which stimulates protein synthesis by phosphorylating p70S6 kinase (S6K) and the eukaryotic translation initiation factor 4E-binding protein 1 (4E-BP1), and mTORC2, which phosphorylates Akt in a feedback loop [71]. Besides regulating protein synthesis, mTORC1 can also suppress autophagy by inhibiting ULK1 (a kinase involved in autophagy induction) and the transcription factor EB (TFEB), which regulates the expression of genes involved in lysosomal biogenesis and autophagy [103]. Importantly, several lines of evidence suggest that mTORC1 activity can be further regulated by diverese inputs such as amino acids and mechanical stimuli, although the molecular mechanisms involved still need to be fully elucidated [103, 104]. The role of the IGF-1/Akt/mTOR pathway in the pathogenesis of skeletal muscle aging is still controversial, but a few studies have suggested that mTORC1 signaling is hyperactivated in the skeletal muscle of aged rodents [80, 93, 105]. Interestingly, different patterns of modulation of the Akt/mTOR pathway have also been shown in the skeletal muscle of female and male aged rodents as well as in different muscles suggesting that the regulation of this pathway may vary with aging by sex and muscle type, at least under the experimental conditions analyzed [106-108]. In humans, reduced, unchanged and increased mTORC1 signaling has been reported [80, 109, 110], underscoring the need for additional research to better understand how modulation of this pathway may contribute to skeletal muscle aging.

Skeletal muscle aging is not associated with a reduction in basal muscle protein synthesis, but rather an impaired protein synthetic response to anabolic stimuli, a phenomenon called *anabolic resistance* [72]. Data obtained in the skeletal muscle of aged rodents have shown, in spite of high basal mTORC1 signaling, a blunted activation in response to a single bout of muscle contraction compared to younger animals [106]. An impaired activation of mTORC1 signaling has also been shown in the skeletal muscle of elderly subjects in response to acute bout of resistance exercise or essential amino acids ingestion [111, 112]. Despite evidence for aging-associated anabolic resistance, a recent systematic review was less conclusive. Several differences, however, were noted among the included studies in terms of anabolic stimuli utilized as well as experimental methodology and design adopted, which may have contributed to the resultant inconsistencies [113]. Additional research is needed to advance our understanding of anabolic resistance and identify strategies to counteract this consequence of aging.

Stem Cell Exhaustion and Function.

Satellite cells are the essential skeletal muscle stem cell. As their name implies [114], these cells reside juxtaposed to the mature muscle fiber; external to its plasma membrane yet enveloped by the surrounding basal laminae. In addition to their location, satellite cells can be identified by their expression of several molecular markers, including the paired homeodomain transcript factor, Pax7, which is essential for satellite cell specification, expansion and function [115, 116]. Considerable research has been conducted to understand the impact of aging on satellite cells and their role in skeletal muscle health.

Satellite cells are absolutely essential for skeletal muscle regeneration following injury. Indeed, targeted depletion of satellite cells in adult mice harboring a human diphtheria toxin receptor under the control of the *Pax7* promoter completely disrupted muscle regeneration following both extreme (intramuscular injection of cardiotoxin (see also [117]) and physiological (downhill running on a treadmill) muscle injury [118]. In the absence of satellite cells, skeletal muscle atrophy, fiber loss, fibrosis, fat accumulation, immune cell infiltration, and inflammation are evident and severe following injury. The extent to which sarcopenia per se is influenced by the health and function of satellite cells is less clear. Targeted elimination of most (~83%) *Pax7*-expressing cells in mice failed to hasten or exacerbate the age-related loss in muscle fiber cross-sectional area or muscle mass, despite clear defects in muscle regenerative capacity [119]. It is possible that the satellite cells that remained were sufficient to maintain muscle fiber size and mass, as reported in a separate study [120], particularly given the limited demands placed on skeletal muscle by captive laboratory mice. Interestingly, mice deficient in satellite cells did exhibit significant increases in fibrosis, a phenotype of aging muscle that further highlights the dynamic interplay between the diverse cell types residing in skeletal muscle [119], In sum, the findings by Fry and colleagues are provocative, and have stimulated further investigations into the contributions of satellite cells to muscle adaptations to aging and other physiological stimuli.

Muscle regenerative capacity is markedly impaired by aging. The number of muscle stem cells and their capacity to self-renew have been shown to decline with age in both mice [121, 122] and humans [123], particularly in fast-twitch glycolytic muscle fibers. In addition to number, satellite cells exhibit age-associated changes in their molecular phenotype. Purified muscle progenitor cells (highly enriched for *Pax7*) obtained from aged 24-month-old mice demonstrated markedly impaired (two-thirds reduction) engraftment compared to young 2-month-old donor cells when transplanted into muscle of young immunodeficient recipient mice [120], Further analyses revealed increased activation of p38α/β stress signaling and increased expression of senescence-associated cyclin dependent kinase inhibitors $p16^{Ink4a}$ and $p21^{Cip1}$ in the aged muscle stem cells, consistent with their diminished proliferative potential [120], Pharmacological inhibition of p38α/β restored aged muscle stem cell proliferative capacity *in vitro*, and markedly improved engraftment *in vivo.* A recent analysis of satellite cells derived from geriatric mice (28 to 32 months of age) also revealed elevated expression of $p16^{Ink4a}$, a cyclin-dependent kinase inhibitor involved in the cell fate of senescence (see below) [124], Following cardiotoxin injury to the muscle of young mice, transplanted satellite cells from geriatric mice were unable to activate and expand. Targeted

repression of *p16*^{Ink4a} by short hairpin RNA, however, restored satellite cell activation in culture, and augmented engraftment and self-renewal. Collectively, these studies provide compelling evidence for intrinsic changes in satellite cells as a consequence of aging that, at a minimum, severely compromise skeletal muscle's capacity for regeneration.

During muscle regeneration, the transition of satellite cells from quiescence and their subsequent proliferation and differentiation are also regulated by extrinsic factors in the local environment, or niche [125], These cues include cytokines, growth factors, and extracellular matrix proteins and remodelers, which are produced by the mature myofibers and diverse myogenic (i.e., satellite cells) and non-myogenic (e.g., endothelial cells, fibroadipogenic progenitors, immune cells, and invading monocytes, etc.) cell types [126, 127], potentially in the context of senescence as discussed below. Dysregulation of the niche during muscle regeneration results in aging-like phenotypes, including impaired satellite cell proliferation and differentiation and increased fibrosis and fat accumulation.

The experimental model of parabiosis, in which two organisms are joined in a manner so that they share a common circulatory network, has led to the study of *progeronic* factors from an older organism that adversely affect the health and function of cells in a younger organism, and *antigeronic* factors from a younger organism that positively affect the health and function of cells in an older organism. Indeed, injury to the skeletal muscle of a younger mouse that shares the circulation of an older mouse leads to compromised tissue regeneration. In contrast, an injured older mouse coupled to a younger mouse experiences restored satellite cell function and ameliorated age-related tissue fibrosis [128], Progeronic factors include Wnt proteins, a large family of secreted glycoproteins, that promote the transition of myogenic satellite cells to a fibrogenic lineage [129], Transforming growth factor-β, which is particularly liberated from aged muscle, also exhibits progeronic activity that involves the phosphorylation of Smad3 and the disruption of Notch signaling in satellite cells [130], Notch signaling is a critical determinant of the satellite cell pool and satellite cell fate [131-133], In older mice, failed activation of Notch in satellite cells leads to "mitotic catastrophe [134]." Antigeronic factors have remained more elusive; however, one example is oxytocin, a hormone produced by the hypothalamus whose abundance declines with age. Systemic administration of oxytocin to aged mice rescued satellite cell proliferation and skeletal muscle regeneration to levels observed in young mice following injury [135], Collectively, these data demonstrate that age-associated alterations in the niche can markedly effect satellite cell function and muscle regeneration. The biological mechanisms that drive alterations in the niche warrant further study.

Cellular Senescence.

Senescent cells and their dynamic secretome—the senescence-associated secretory phenotype (SASP)—have been strongly implicated as drivers of aging [136-139] and aging-related diseases, including vascular dysfunction [140], atherosclerosis [141], lung disease [142], diabetes [143, 144], osteoarthritis [145], osteoporosis [146], and neuropathology [147, 148]. Senescence, a state of stable growth arrest, is principally a fate of proliferating cells. In response to genomic, proteomic, metabolic, or replicative stress, the senescence program is initiated by cell cycle inhibitor proteins, including p16^{Ink4a} and p21^{Cip1}, that

antagonize the actions of cyclin dependent kinases to ultimately halt cell proliferation [149, 150]. Senescence is therefore an inherently protective, tumor-suppressive program [151], With advancing age, however, senescent cells accumulate [152, 153], presumably due to their resistance to apoptosis and inefficient removal by the immune system [139, 154]. By depleting the mitotically active progenitor pool and abundantly secreting a mix of cytokines, chemokines, matrix remodeling proteins, and growth factors, senescent cells compromise regeneration and mediate inflammation, deterioration, and fibrosis in tissues of older organisms [154, 155]. Intuitively, senescent cells and the SASP could underlie skeletal muscle aging and sarcopenia, yet this concept has not been methodically tested.

Support for senescent cells and the SASP as drivers of skeletal muscle dysfunction comes from a number of observations. First, transplantation of senescent cells (either syngeneic preadipocytes or autologous ear fibroblasts) into young adult mice compromised measures of grip strength and physical function, including walking speed and hanging endurance [137]. In turn, systemic elimination of *p16*^{Ink4a}-expressing cells through either activation of a suicide transgene, or the pharmacological targeting of senescent cells (based on their significant upregulation of pro-survival factors (see [139])), modestly improved measures of physical function in older (24-month-old) mice. Whether the detrimental effects of senescent cells on physical function, or the beneficial effects of their removal, resulted from a direct influence on parameters of muscle aging (e.g., atrophy, fibrosis, denervation, or cellular composition) was not studied. Instead, the effects on adipose tissue senescent cell burden and SASP and, correspondingly, systemic inflammation, was demonstrated. This potential mechanism is in line with a prior report showing pharmacological inhibition of the Jak pathway, which was shown to regulate the SASP in senescent preadipocytes and endothelial cells *in vitro,* suppressed markers of both adipose tissue and systemic inflammation and improved parameters of physical function in aged mice [156]. It is also worth noting that associations between the number of *p16*^{Ink4a}-expressing cells in thigh adipose tissue and measures of muscle performance and physical function have been observed in older humans [157].

It is unclear whether senescent cell populations within muscle mechanistically contribute to age-related changes in its mass, composition or function. As discussed above, Sousa-Victor and colleagues have demonstrated the significant impact of *p16*^{Ink4a}-expressing satellite cells on muscle regeneration [124]. However, the longer-term effects of senescent cells or their removal on sarcopenia, fibrosis, fat infiltration and measures of muscle performance have not been carefully investigated. In part, this is a practical challenge as sarcopenia is relatively late phenomenon in mice, compared to its progressive nature in humans. As emphasized, aged muscle is compositionally heterogenous, and senescence of resident cell populations beyond satellite cells, including fibroadipogenic progenitor, endothelial, and immune cells, may also contribute to muscle aging. Consequently, there is a need to identify and comprehensively phenotype the cell populations within aged muscle that are prone to senesce and determine the extent to which they mechanistically contribute to muscle loss and dysfunction.

Mitochondrial function.

Mitochondria play a pivotal role in skeletal muscle function. These organelles are recognized for their role in generating chemical energy in the form of ATP to fuel the metabolic demands within muscle fibers, including contractile function, maintenance of membrane potential, calcium handling, and overall cellular maintenance and homeostasis. In addition to their role as energetic powerhouses, mitochondria are also a primary source of reactive oxygen species (ROS). As reviewed authoritatively elsewhere [158], ROS function as important signaling molecules but can simultaneously initiate cell death through damage to cellular components such as DNA, proteins, and lipids. Given their critical role for cellular homeostasis, mitochondria have been implicated in the etiology of sarcopenia and multiple age-related diseases (e.g., diabetes, cancer, cardiovascular disease) [159-161] and pursued as therapeutic targets [162, 163].

More than 20 years ago, Rooyackers and colleagues first demonstrated that the activities of two key mitochondrial enzymes, citrate synthase and cytochrome c oxidase, decrease with age in skeletal muscle biopsies from men and women across a wide age range [164]. Additional studies supported the premise that aging adversely affects skeletal muscle mitochondria, including decreased mitochondrial ATP production rates [165-167], decreased mitochondrial gene expression [168], decreased mitochondrial DNA copy number [169, 170], reduced mitochondrial volume density [171], and increased oxidative damage [172]. These findings were not universal; however, as a number of carefully conducted studies failed to observe age-related impairments in skeletal muscle mitochondrial function [173-177]. Indeed, several important factors may confound the effects of aging on muscle mitochondrial physiology:

1. *Aging vs. disuse.* Plasticity of mitochondria makes them exquisitely responsive to use and disuse (i.e., exercise and sedentariness). To what extent do observed changes in skeletal muscle mitochondria simply reflect changes in muscle use across the lifespan? Multiple studies have shown that age-related changes in muscle oxidative capacity and mitochondrial function are not evident when studies carefully control for habitual physical activity [174, 178, 179]. However, some age-related mitochondrial changes occur independent of physical activity levels. For example, mitochondrial DNA copy number decreases with age in young and older adults who are matched for physical activity levels [180]. Furthermore, the age-associated reduction in mtDNA abundance is also evident even in highly-trained masters level endurance athletes [180].

2. *Age-related mitochondrial changes may be muscle-specific.* Fast-glycolytic muscle fibers undergo a more profound age-related atrophy than slow-oxidative muscle fibers [181]. The *vastus lateralis* muscle, characterized by a mixed fiber type composition, is often studied in humans because its large size, accessibility, and location relative to major blood vessels makes it convenient for repeated sampling by percutaneous biopsy with minimal complications. Samples from *vastus lateralis* typically reveal age-related declines in mitochondrial function [166, 167, 182, 183], whereas studies in other muscle groups such as tibialis anterior [174], forearm muscles [184], and plantarflexors [185] report similar

mitochondrial function in young and old. Indeed, muscle oxidative capacity, measured *in vivo* by ^{31}P magnetic resonance spectroscopy, was found to be reduced with age in *vastus lateralis,* but not in *tibialis anterior* [186, 187]. A recent systematic review on this topic clearly shows that muscle group is a significant moderator of age-related changes in skeletal muscle oxidative capacity [188].

3. *Reductionistic vs. Integrative Studies of Mitochondrial Physiology.* Studies commonly draw conclusions based on the expression of a gene or the activity of a single cytochrome chain or TCA cycle enzyme. Even gold-standard measurements of oxygen consumption and ATP production in intact mitochondria isolated from skeletal muscle have been criticized because the organelles are studied *ex vivo* under non-physiological conditions where cellular circulatory and regulatory systems have been stripped away. Picard and colleagues nicely demonstrated how measurements in isolated mitochondria may overstate the degree to which aging influences muscle mitochondrial biology [176]. In this study they show that salient indices defining mitochondrial function, including respiration, ROS production, and calcium sensitivity, are significantly impaired with aging when examined in isolated muscle mitochondria. However, the effects of age were less apparent when measurements were made in permeabilized yet intact muscle fibers. Phosphorous magnetic resonance spectroscopy (^{31}P-MRS) enables the study of human skeletal muscle bioenergetics *in vivo* [189], and was first applied to study aging skeletal muscle in the 1980s [177]. Kent and Fitzgerald have authored an authoritative review of studies that have used ^{31}P-MRS to investigate the effects of aging on mitochondrial oxidative capacity [190]. They concluded that much of the ambiguity regarding the effects of aging can be ascribed to differences in muscle group investigated or subject characteristics (e.g., physical activity, age, sex, and presence of age-related comorbidities). An important message from this body of literature is that not all of the mitochondrial changes observed in muscles of older adults are consequences of aging *per se,* but may be largely driven by environmental and lifestyle factors.

Regardless whether age-related functional changes in muscle mitochondria are consequent to biological aging or simply paraphenomena, the changes experienced by older adults are real. The extent to which age-related changes in muscle mitochondria drive aging phenotypes (e.g., sarcopenia, insulin resistance) is a topic that remains at the leading edge of aging research [191, 192].

Interventions for skeletal muscle aging

Despite the prevalence and impact, there are no currently approved pharmacological interventions for sarcopenia. A number of *anabolic* interventions to augment protein synthesis have been trialed, such as testosterone and growth hormone, and shown to have minor to modest effects on muscle mass, strength, and/or physical function (e.g., [193-196]), but have also generated significant concerns about safety [197, 198]. There has been great

interest in approaches to disrupt myostatin signaling, a *catabolic* transforming growth factor β (TGFP) superfamily member that is predominantly synthesized and secreted by skeletal muscle that triggers protein degradation and disrupts protein synthesis pathways, as we have recently reviewed [199, 200]. A number of early phase clinical trials in older adults have been completed [201-204], and shown favorable effects on muscle mass or volume, muscle strength, and/or some functional outcomes, including stair climb time, chair rise time, maximal gait speed, and six-minute walk distance. These studies and their outcomes have been nicely summarized in a recent issue of *Bone* [205]. It is worth noting that other TGFβ family members, including GDF11 and activin A, also compromise skeletal muscle health and function and serve as potential therapeutic targets for sarcopenia [206-211]. Of note, neither myostatin nor GDF11 increase with chronological age in humans [212, 213], and an important study by Latres and colleagues demonstrated critically important species differences in the abundance of myostatin, GDF11, and Activin A [214]. Specifically, circulating concentrations of myostatin are markedly higher in mice than humans, whereas activin A is much higher in humans than in mice, and GDF11 is extremely low in both species. These data potentially help explain why the profound effects of myostatin inhibition on muscle mass in mice do not necessarily translate to humans and may help inform future therapeutic approaches.

Finally, the search for small molecules and biologics to enhance skeletal muscle health and function should not overshadow nor trivialize the remarkably protective effects of exercise against the biology of aging. Indeed, exercise is safe and scalable, and effectively improves measures of muscle mass, strength, power, and physical function, even in those with overt age-associated deficits. The salutary effects of exercise on aging-associated changes in skeletal muscle have recently and very thoughtfully been reviewed [215]. The power of exercise, and the challenge to harness or *mimic* it in a pill, stems from the array of mechanical, metabolic, hormonal, and neural signals it elicits. Impressively, exercise has been show to counter a range of age-induced forms of damage, including those discussed here; *i.e.,proteotoxic stress* by inducing autophagy [216], *stem cell dysfunction by* stimulating muscle satellite cell activation [217], *cellular senescence* by mitigating senescence-inducing stressors (e.g., DNA damage [218]), and *mitochondrial dysfunction* by restoring the hermetic response to oxidative stress [219]. As new interventions targeting the biology of aging emerge, there will be value in studying how their effects are augmented by exercise.

Conclusions

Population aging coupled with the clinical consequences of sarcopenia have generated considerable interest to understand and identify strategies to counter the biological mechanisms of skeletal muscle aging. The underlying causes of this process are multifactorial, and in no way is this review all inclusive. We apologize to the authors of the important studies we have not included. An outstanding, incredibly comprehensive review on sarcopenia, led by Dr. Marco Sandri, was very recently published [220].

In sum, strategies to promote muscle health in late life promise to have beneficial effects on physical function, metabolism, and resilience, and subsequently, the independence and

quality of life of older adults. While new interventions are on the horizon, physical activity and structured exercise can have an immediate and far-reaching impact. Given physical activity and exercise delay the onset and progression of the majority of age-related diseases and geriatric syndromes, broad reaching public health strategies are warranted to promote adoption and compliance.

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Highlights

- Muscle mass and cellular composition are altered with advancing age
- Muscle aging negatively affects physical function, metabolism, and resilience
- Diverse forms of age-related molecular and cellular damage drive muscle aging
- New interventions targeting hallmarks of aging may benefit late-life muscle health
- Notably, exercise effectively counters muscle aging and its consequences

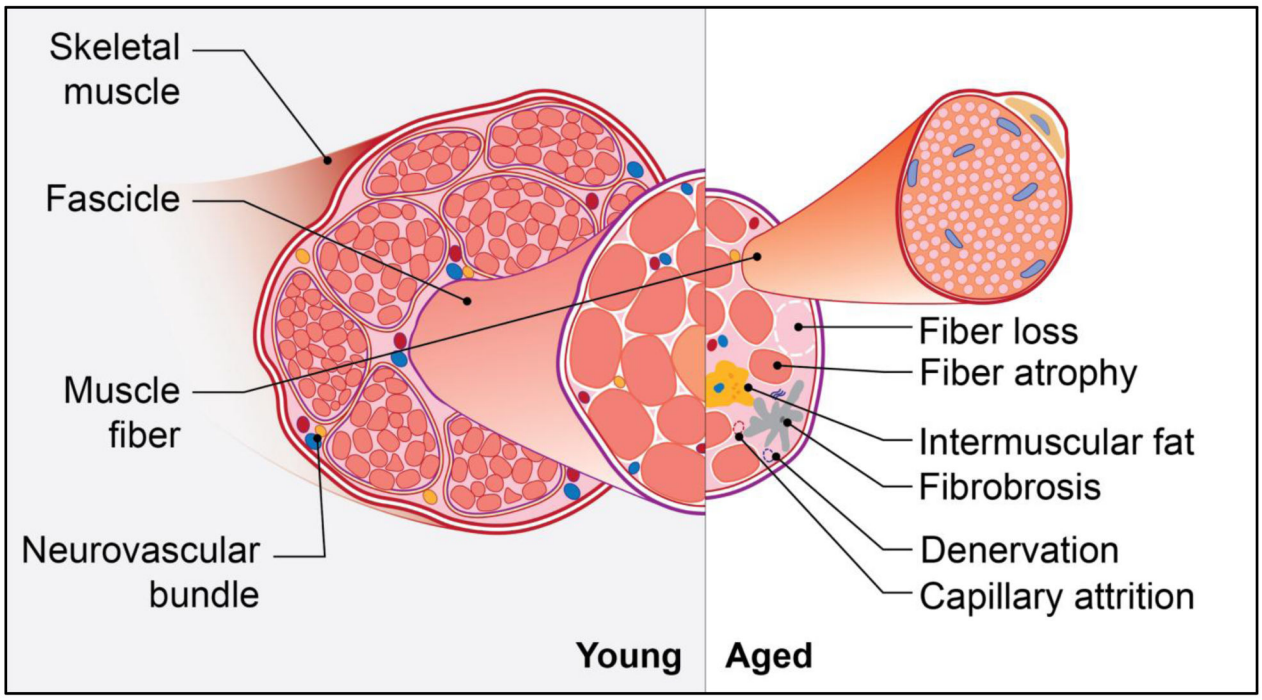

Figure 1. Age-related changes in skeletal muscle.

The considerable loss of muscle mass and volume with advancing age is attributed to both the loss and atrophy of muscle fibers. The progressive decrease in functional contractile tissue is matched with the accretion of fat and fibrotic tissue. These alterations, along with progressive loss of innervating motor neurons and capillaries, contribute to the age-related loss of muscle strength, power, and endurance.

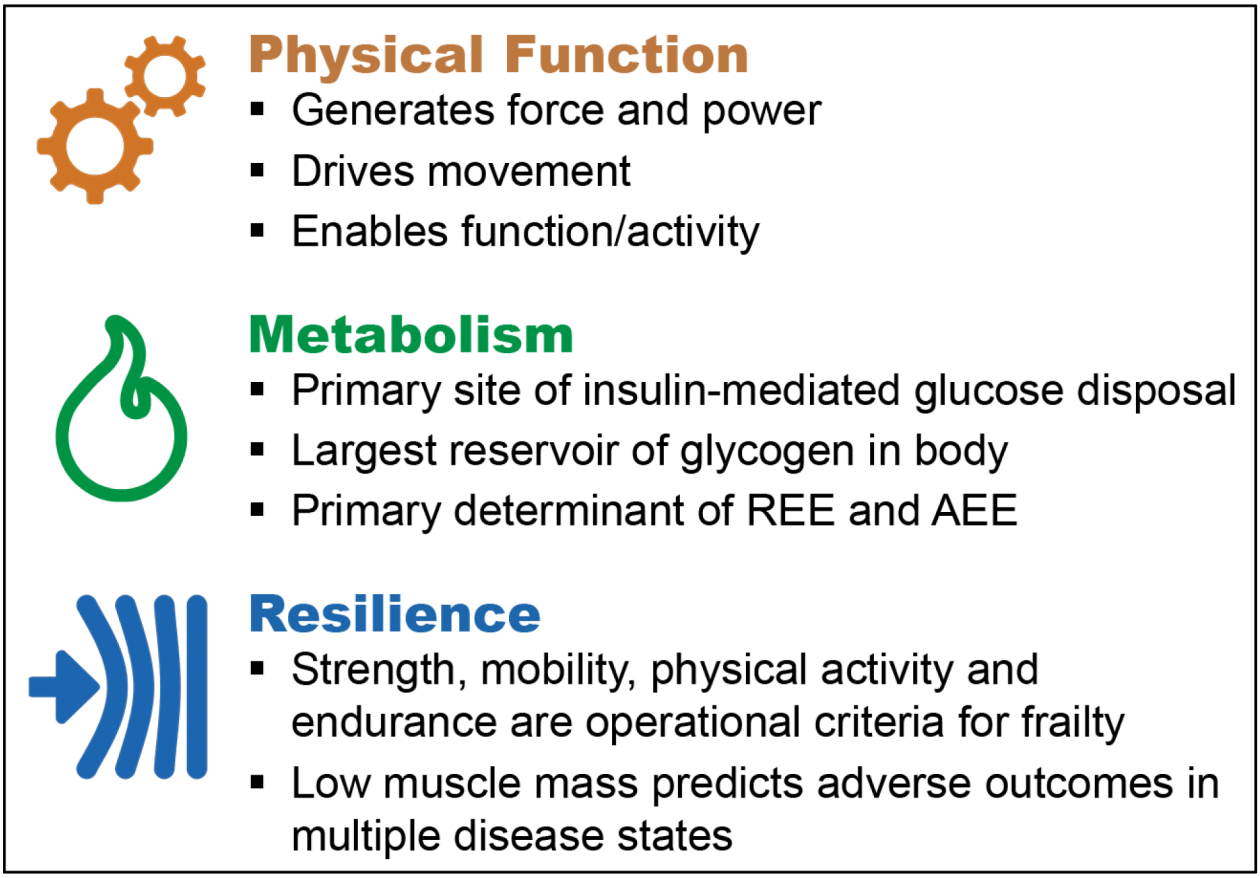

Figure 2. Skeletal muscle in health, aging and disease.

Skeletal muscle uniquely generates force and power for diverse forms of physical function, including mobility. It is also a critical metabolic organ that is responsible for the storage of glucose, the oxidation of fatty acids, and is a rich source of amino acids. Based on its size and metabolic activity during both rest and movement, muscle strongly influences both resting energy expenditure (REE) and activity associated energy expenditure (REE). Measures of muscle performance, physical function, and mass are also determinants of physical resilience, the capacity to resist and recover from diverse challenges.