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Review

Murine models of atrophy, cachexia, and sarcopenia in skeletal muscle ☆

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ABSTRACT

With the extension of life span over the past several decades, the age-related loss of muscle mass and strength that characterizes sarcopenia is becoming more evident and thus, has a more significant impact on society. To determine ways to intervene and delay, or even arrest the physical frailty and dependence that accompany sarcopenia, it is necessary to identify those biochemical pathways that define this process. Animal models that mimic one or more of the physiological pathways involved with this phenomenon are very beneficial in providing an understanding of the cellular processes at work in sarcopenia. The ability to influence pathways through genetic manipulation gives insight into cellular responses and their impact on the physical expression of sarcopenia. This review evaluates several murine models that have the potential to elucidate biochemical processes integral to sarcopenia. Identifying animal models that reflect sarcopenia or its component pathways will enable researchers to better understand those pathways that contribute to age-related skeletal muscle mass loss, and in turn, develop interventions that will prevent, retard, arrest, or reverse this phenomenon. This article is part of a Special Issue entitled: Animal Models of Disease.

1. Introduction

During development skeletal muscle fibers grow in size and number, manifesting increased overall size and strength in the organism. Muscle fibers decrease in size and/or number with age, disuse, and disease. As muscle fiber number and size decrease there is a corresponding decrease in the ability of the muscle to generate force. Muscle force demonstrated is commonly termed strength. In the case of muscle atrophy as a result of disuse, muscle fiber size can be restored over time with active exercise. Strength loss in those experiencing cachexia (wasting accompanying disease) or sarcopenia (muscle mass loss accompanying aging) is especially problematic, as fiber size and strength are not so easily recovered, producing frailty which tends to spiral into greater dependence and increased falls in the aged and chronically ill. The ever-increasing life span without an accompanying increase in health span in humans leads to larger populations experiencing sarcopenia and cachexia. With all these considerations, sarcopenic and cachectic frailty imposes a considerable financial burden on the healthcare system as well as greater stress on individual families, and a decreased quality of life of the individuals affected. Although sarcopenia is considered a natural consequence of aging, studies have demonstrated that the process can be slowed, and there is research that suggests that the process can be stopped and even reversed [1].

Although atrophy, cachexia, and sarcopenia share a common trait in loss of muscle mass, there are distinct differences in their wasting outcomes as well as in the biochemical processes that promote them. Sarcopenia (a term reserved for the atrophy that accompanies the physiological process of aging) [2], is characterized by a loss in both fiber size and number [3] with fiber type II transitioning to type I [4,5]. In contrast, in disuse atrophy, fiber size is decreased yet fiber number is maintained [6] with a tendency of type I fibers transitioning to type II [7,8]. Wasting in cachexia involves both adipose tissue and skeletal muscle tissue [9], with cachexia targeting fiber types depending on the pathology. Muscle wasting from cancer is primarily directed toward type II fibers [10], while congestive heart failure tends to degrade type I or type IIA contractile proteins [11,12]. Atrophy and weakness are generated in each of these conditions (aging, disuse and cachexia), yet each is difficult to separate mechanistically because of overlapping signaling systems. Mechanisms of sarcopenia will be addressed in this paper with allusions made to cachexia and disuse atrophy when appropriate.

The identification of appropriate animal models and the pathways to arrest or even reverse the process of fiber loss and atrophy, will provide a better understanding of the sarcopenia pathways. This greater understanding is critical to increase health span by delaying the onset of frailty in the presence of aging.

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2. Mechanisms of muscle loss

Skeletal muscle is a postmitotic tissue, arriving at its final number of cells (the muscle fibers), early in life, after which changes in muscle size are dependent on the change in individual fiber size. Satellite cells, most likely, account for the increased DNA content observed in muscle tissues during development [13–15]. Cells can elongate and increase girth through the addition of sarcomeres [14] and myofibrils [13], respectively; however, muscle fiber number stays constant into adulthood, At this point, fiber number and size decline from the early 3rd decade [3,16] through senescence, such that muscle mass declines from 50% of total body weight to 25% [17,18]. Muscle cells can repair or replace damaged muscle fibers when stress (e.g., exercise or trauma) activates the neighboring quiescent satellite cells, causing them to proliferate, migrate, and replace/repair the injured myofibers [19].

There are several pathways involved in the process of muscle loss (Fig. 1). Its course involves an imbalance between anabolism and catabolism, with protein loss ultimately the stronger influence [20]. Endocrine and inflammatory factors are the general mediators of this balance [21]. Negative regulators of skeletal muscle mass that could play a role in sarcopenia include the endosome–lysosome, Ca^{2+}-dependent, caspase-dependent, and ubiquitin/proteasome-dependent pathways [22]. Protein synthesis in skeletal muscle is driven by growth hormone, IGF-1 [23], insulin, and testosterone [20] being undergirded by adequate nutrition and exercise [24].

2.1. PI3K/Akt pathway

One of the central pathways to muscle size control is the PI3K/Akt pathway, a pathway modulated by IGF-1 and insulin [25]. Stimulation of protein synthesis and hypertrophy involves these hormones interacting with their respective tyrosine kinase receptors to phosphorylate IRS (insulin receptor substrate)-1 and activate PI3K/Akt (phosphatidylinositol-3-kinase/protein kinase B) signaling [26], that activates mTOR (mammalian target of rapamycin) [27], and in turn, phosphorylates the targets $p70^{S6K}$ (ribosomal p70 S6 kinase) and 4E-BP1 (4E-binding protein) [28,29]. The activation of Akt simultaneously resists atrophy by phosphorylating FoxO transcription factors, preventing translocation to the nucleus where they would otherwise promote transcription of atrophy-related genes MuRF1 (muscle ring finger 1) and MAFbx (muscle atrophy F-box [also known as atrogin-1]) [30], both of which are ubiquitin ligases that degrade proteins [31]. Inhibition of Akt phosphorylation promotes muscle atrophy, preventing the phosphorylation of FoxO transcription factors, and drives the transcription of MuRF1 and MAFbx atrophy genes [30,32]. These genes can also be activated through a pathway independent from Akt signaling, the NF-κB pathway mentioned below.

2.2. NF-κB pathway

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is a transcription factor that is elevated in disuse atrophy [33] and cachectic conditions [34,35] but not typically in sarcopenia [22,36,37]. Cytokines activate NF-κB, its translocation to the nucleus where it can then bind to the MuRF1 promoter, and initiate proteasome-induced muscle degradation [38]. In muscle wasting of cachexia, TNF-α often activates NF-κB by activating IKK (IκB kinase), which then phosphorylates and degrades the NF-κB inhibitor protein, Iκ-Bα [39]. However, in disuse atrophy the NF-κB pathway still involves IKK activation, yet it is triggered by an alternative pathway without elevation of inflammatory cytokines [33]. At the nuclear level, the atrophy of cachexia proceeds with the nuclear entry of p50 and p65 heterodimers from IκB degradation, while disuse atrophy is characterized by binding of a p50 homodimer to Bcl-3 (B cell lymphoma 3) in the nucleus [40,41].

2.3. Myostatin pathway

Myostatin is a negative regulator of muscle growth [42], activating and phosphorylating Smad2/3 transcription factors [43,44] by way of the Activin IIB membrane receptor [45], and modulating the transcription of genes, e.g., MyoD [44]. Although the IGF-I/PI3K/Akt pathway inhibits myostatin-dependent signaling, it has been suggested that the myostatin–Smad pathway inhibits Akt in its promotion of protein synthesis [46]. Myostatin levels increase alongside muscle atrophy in disuse and cachexia situations. In older animals myostatin levels are relatively unchanged, although inhibiting myostatin has produced fiber size and muscle mass gains [47,48].

2.4. Apoptosis

Apoptosis, the process of programmed cell death, in contrast to necrosis [49], contributes to both sarcopenia and cachexia [50]. Apoptosis is unique in muscle fibers in that muscle fibers are multi-nucleated, and therefore loss of some nuclei does not necessarily result in the destruction of the muscle fiber [51]. Apoptosis appears to play a role in disuse atrophy; however, the typical apoptotic events (such as involvement of various proteolytic caspases) vary depending on the experimental models used [52,53]. The extent to which apoptosis is involved with disuse atrophy is unknown beyond the relatively short term (14 days) of the disuse in the above studies. There is some evidence in the 14-day unloading model that the apoptotic process changes to a more anti-apoptotic process as time progresses to limit the mass loss [54]. Reactive oxygen species are associated with immobilization [55] and unloading [56] atrophy and can directly activate NF-κB without the influence of TNF-α [57]. In the case of cachexia, skeletal muscle has demonstrated activation of DNA fragmentation and resultant apoptosis [58]. Certain signaling molecules in apoptotic pathways can either promote or inhibit NF-κB activation [59,60]. A solid connection between muscle apoptosis and sarcopenia has not yet been established, even though some studies suggest a link in part because fibers are multinucleated [61–63].

2.5. Autophagy/lysosomal pathway

Autophagy is a process in which a cell's contents are degraded by its own enzymes [64]. It occurs constitutively to maintain a dynamic anabolic/catabolic balance within the cell. Even so, oxidative stress [65,66] or extreme catabolic conditions [67,68] can upregulate autophagy. mTOR is integrally involved in autophagy pathways [69], yet in skeletal muscles, FoxO3 is the main inducer of autophagy genes such as LC3 and Bnip3 [70]. Well-controlled FoxO3-induced gene expression is a key to balanced autophagy.

2.6. Satellite cells

Satellite cells provide myoblasts for postnatal growth [71,72] and are critical for skeletal muscle repair [73]. These cells are quiescent until a stress (trauma, exercise) is imposed. There is controversy as to whether satellite cells actually decrease in number with aging [74–78]; however, their proliferative response and regenerative capacity to perturbation are reduced [79,80]. Evidence indicates that reduced regenerative function is more likely a result of a less optimal cellular environment than the cells being deficient due to age [81,82]. The reduced function in the satellite cell with aging is at least coincidental with sarcopenia, and could possibly be a contributing factor of that process such that satellite cells in aged are less responsive to muscle damage.

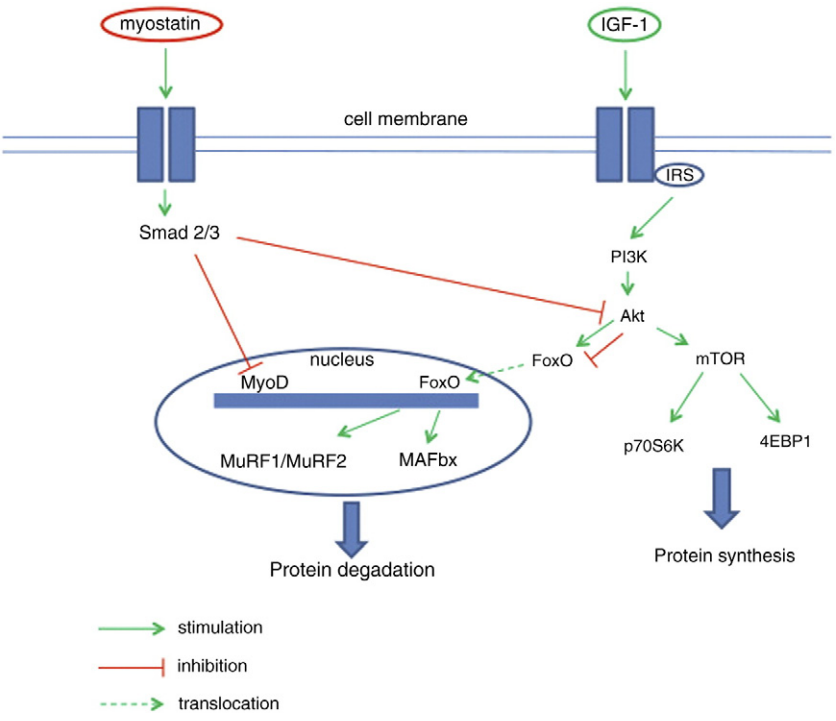

Fig. 1. Protein synthesis and degradation pathways. Akt when activated will promote protein synthesis and inhibit protein degradation; inhibiting Akt will promote translocation of FoxO to the nucleus to drive protein degradation. Degradation components: FoxO—forkhead box transcription factor, MAFbx—muscle atrophy F-box, MuRF—muscle ring finger protein, and Smad 2/3—receptor-regulated transcription factors. Synthesis components: IGF-1—insulin-like growth factor-1, IRS—insulin receptor substrate, PI3K—phosphatidylinositol-3-kinase, Akt—protein kinase B, mTOR—mammalian target of rapamycin, S6K— ribosomal p70 S6 kinase, 4EBP1 — 4E-binding protein, and MyoD—muscle differentiation protein.

3. Murine models of sarcopenia

Numerous genetic mutant mouse models have been developed to determine the biochemical and physiological pathways that influence the processes of sarcopenia. We will examine some of the animals that have assisted in our understanding of the roles of the various molecules and their contribution to the process of sarcopenia. The animal models and affected pathways are summarized in Fig. 2.

3.1. IGF-1/PI3K/Akt pathway

Several laboratories have focused on the growth factors and their downstream effectors in their evaluation of muscle function as it relates to muscle loss.

3.1.1. IGF-1

Transgenic mice (MKR) [83] expressing mutated IGF-1 receptors in skeletal muscle were exposed to functional overload [84] to observe whether loading could promote muscle growth in the absence of a functional IGF-1 receptor. Hypertrophy occurred with functional overload in the presence and absence of normal IGF-1 receptors. IGF-1 typically activates the PI3K/Akt pathway to induce protein synthesis and muscle development. Significant increases of Akt and p70S6K were demonstrated in both wild type and MKR mice. MKR and wild type mice demonstrated equivalent gains in plantaris muscle weight following a 35-day loading regimen. These results indicate that muscle overload can induce muscle growth through PI3K/Akt activation independent of an operational IGF-1 receptor. We know that plasma IGF1 levels decrease with aging (in rodents and humans), thus skeletal muscle growth in older animals may occur via both IGF-1-dependent and -independent mechanisms [85].

Mavalli [86] and coworkers developed mice deficient in GH receptors or IGF-1 receptors in skeletal muscle. Both mutants displayed reduced muscle fiber number and cross-sectional area. The GH receptor knockout mice had a lower proportion of type I gastrocnemius fibers and a higher proportion of type II than wild type mice at 6 weeks of age, yet fiber sizes were equivalent. Type II:type I fiber ratios were approximately 90:10 and 80:20 in GH receptor null and wild type, respectively. At 16 weeks of age, fiber cross-sectional area was approximately 75% for both fiber types comparing GH receptor knockout to wild type, with the difference continuing through 26 weeks of age. Fiber type ratios were nearly the same between strains, 90:10, type II:type I. For the IGF-1 receptor null mouse, a similar fiber type proportion was present between the mutant and wild type at 6 weeks as was seen with the GH receptor knockout but this difference remained at 16 weeks. Myofibril cross-sectional areas were smaller in the IGF-1 receptor knockout than wild type at both 6 weeks and 16 weeks of age. These models speak to the integral role of both GH and IGF-1 and their associated receptors in the normal development of skeletal muscle.

Several mouse models with disrupted GH/IGF-1 pathways are known for their extended life spans [87]. The mechanism remains to be determined as to how this hormone deficiency promotes increased longevity. Ames dwarf, Snell dwarf, Laron dwarf, and "little" mice are either deficient in GH/IGF-1 or signaling is blocked at the cell membrane receptor and thus lack the protein synthesis promotion possessed by animals with intact GH/IGF-1 pathways. These animals pose a conundrum in that although lacking a significant component of the protein synthesis and muscle growth pathway, a condition which should promote increased frailty and therefore early death, these animals instead have extended life spans. Further work is needed to determine how the GH/IGF-1 axis plays an apparently vital part in muscle growth, while its absence confers another advantage to animal models, that of increased longevity.

3.1.2. IRS

Immediately downstream of insulin and IGF-1 is the effector IRS-1. An IRS-1 knockout mouse exhibited continued PI3K/Akt signaling, leading to the discovery of IRS-2, an alternate substrate for PI3K. This insulin-resistant mouse demonstrated general reduced growth by 30% to 60% compared to wild type [88,89]. Unfortunately, no specific information on muscle physiology has been reported at this time.

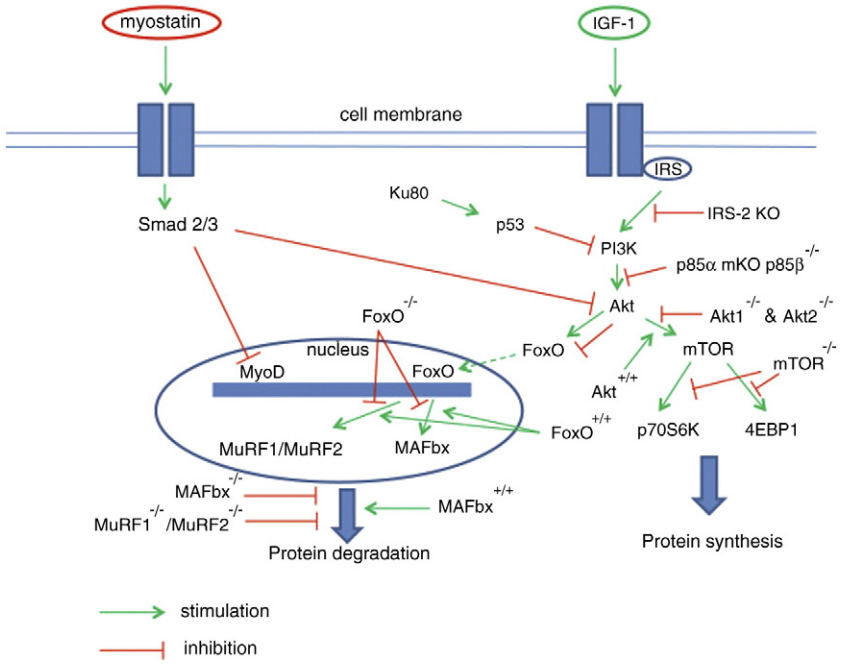

Fig. 2. Murine models and their respective pathway influences. MKR/GHRKO — IGF receptor mutant/growth hormone receptor knockout mice, IRS-2 KO — IRS-2 knockout mouse, P85α mKO p85$\beta^{-/-}$ — PI3K knockout mouse, Akt1$^{-/-}$ & Akt2$^{-/-}$ — Akt knockout mice, Akt$^{+/+}$ — Akt overexpression mouse, mTOR$^{-/-}$ — mTOR knockout mouse, Ku80 — Ku80 mutant mouse, p53 — tumor suppressor protein 53, FoxO$^{-/-}$ — FoxO knockout mouse, FoxO$^{+/+}$ — FoxO overexpression mouse, MAFbx$^{-/-}$ — MAFbx knockout mouse, MAFbx$^{+/+}$ — MAFbx overexpression mouse, MuRF1$^{-/-}$/MuRF2$^{+/+}$ — MuRF1 and MuRF2 double knockout mouse, and Mstn$^{-/-}$ — myostatin knockout mouse.

IRS-2 null mice have been generated also but no reports regarding skeletal muscle components have been published. However, these mice weighed 90% of wild type mice at birth but displayed greater than 50% reduction in PI3K activity upon insulin stimulation compared to the PI3K activity in IRS-1 mice under comparable conditions [90]. Thus, both the IRS-1 and IRS-2 null mice contribute information regarding the impact of growth factors such as insulin, GH and IGF-1 on muscle development but provide less information on muscle loss.

3.1.3. PI3K

Several PI3K knockout mouse models have been developed. Most of these mice exhibit normal growth; however, a null model was established for the p85α/p55α/p50α and p85β regulatory subunits of PI3K in heart and muscle, producing a mouse with reduced heart size but essentially unchanged skeletal muscle size and morphology [91]. Exercise-induced cardiac hypertrophy was attenuated in the p85α mKO p85$\beta^{-/-}$ mouse when exposed to 4 weeks of swim training; however, the lack of PI3K in skeletal muscle did not adversely impact this tissue's exercise capability in these animals. This particular knockout model focuses on the deletion of regulatory subunits of class I_A PI3K which impacted growth of cardiac muscle without influencing its contractility. Skeletal muscle growth and performance were unaffected by this regulatory subunit deletion. Based on this evidence, it appears that other regulatory subunits of the PI3K pathway may have a greater impact on sarcopenia, namely atrophy and strength decrement. Thus, similar to the IRS-1 and IRS-2 knockout mice, some of these PI3K mutants may not be as useful for studying sarcopenia.

3.1.4. Akt

The Akt1$^{-/-}$ (Akt 1null) mouse is a viable strain, yet it has a shorter life span when exposed to gamma irradiation. This mouse is smaller than wild type littermates; however, overall physiology is minimally altered, including a nondiabetic phenotype [92]. The Akt2 null mouse is indistinguishable in appearance at birth from wild type mice but develops insulin resistance [93]. With regard to skeletal muscle physiology, Goncalves and coworkers [94] found decreased mass of extensor digitorum longus (EDL), gastrocnemius, and quadriceps in Akt1$^{-/-}$ compared to wild type. The Akt2$^{-/-}$ also demonstrated a mass decrease in EDL and gastrocnemius but a mass increase in soleus when compared to the wild type. Mean cross-sectional area of glycolytic EDL was reduced in both Akt1 null and Akt2 null mice compared to wild type. The more oxidative soleus muscle cross-sectional area was not different between genotypes. The proportion of type II soleus fibers in the Akt1 null mouse was reduced but not in Akt2 null animals. Soleus type II fiber cross-sectional areas in Akt1 null mice were smaller and that same fiber type number was reduced when compared to wild type. Both of these Akt null mice show promise as models to study sarcopenia with their tendency to demonstrate muscle fiber size decrease. The Akt1 null mouse also exhibits a decrease in type II fiber proportion that is consistent with sarcopenia.

Akt1/Akt2 double-knockout mice exhibit a severe growth deficiency and skeletal muscle atrophy, resembling the IGF-1 receptor null mouse [95]. Although phenotypically similar to IGF-1 receptor deficient mice, atrophy in the Akt double knockout is mainly due to reduced muscle cell size while the IGF-1 deficient mouse exhibits decreased muscle cell number. In addition, the activity of mTOR, appears to be downregulated in the Akt double knock out [96]. However, since this mutant dies soon after birth, it is not useful in the study of sarcopenia.

3.1.5. Akt overexpression

In contrast to the KO mutants, the overexpression of constitutively active Akt in vitro leads to phosphorylation of p70S6K, PHAS-1/4E-BP1 and to marked hypertrophy of myotubes [25]. Denervated muscle fibers in Akt transgenic mice were significantly larger than denervated fibers of wild type mice and were of a fiber size distribution representative of mice without nerve injury after 7 days. This experiment demonstrates that Akt overexpression increases muscle atrophy resistance and maintenance of fiber size distribution following denervation [29]. This particular model may be useful in researching sarcopenia by aiding in the study of downstream events of Akt overexpression.

3.2. mTOR

A viable mTOR null mouse has been developed that exhibits reduced fast twitch muscle growth resulting in stunted postnatal growth [97]. At 6 weeks of age, type II muscles such as gastrocnemius, tibialis anterior, and plantaris experienced reduced weights compared to wild type mice. The cross-sectional area of tibialis anterior was also reduced compared to wild type mice while both cross-sectional area and weight of soleus were increased (when normalized to body weight). mTOR null mice showed dystrophic features that were especially prominent in oxidative fibers, possibly explaining the soleus size increases. Fiber number differences between strains were not evident at 6 weeks. Since the skeletal muscle morphological changes in the mTOR null mouse resemble more the changes seen in the myopathy of muscular dystrophy, this mutant may not serve well as a sarcopenia model. In addition, these animals exhibit shortened life spans [97].

3.3. FoxO

Transgenic mice overexpressing FoxO1 weighed less than wild type mice and have reduced comparative muscle mass [98]. Microarray analysis discovered decreased gene expression of structural proteins of slow twitch muscle. At 3 months of age there was a marked decrease in the size of type I and II fibers and a significant decrease in the number of type I fibers when compared to wild type mice. Gene expression of cathepsin L, a lysosomal proteinase that is typically upregulated with muscle atrophy, was elevated. The FoxO1 transgenic also displayed reduced spontaneous locomotor activity at 9 to 10 weeks of age. The described characteristics in this murine model are indicative of sarcopenia. However, the propensity for selectively-reduced type I muscle fiber gene expression is counter to that seen in sarcopenia, in which type I fiber function is maintained better than type II [21].

FoxO1 null mice exhibit a reduction in slow twitch fiber formation in soleus muscle while the predominantly type II fiber plantaris muscle composition was unchanged [99]. Both male and female FoxO1 mice demonstrated reduced endurance compared to wild type, a finding consistent with the reduction in type I fiber content. This model, similar to the FoxO1 transgenic mouse, displays a reduction in slow fiber content while not affecting type II fiber composition. This characteristic does not parallel the fast-to-slow fiber transition observed in sarcopenia. Unfortunately, this study did not address muscle size, so the contribution of this mutant to our understanding of sarcopenia is unclear.

3.4. MuRF1 and MAFbx

Two factors shown to be specifically involved in muscle atrophy are MuRF1 and MAFbx. Mice null for either MuRF1 or MAFbx resisted muscle atrophy following sciatic denervation, showing 36% and 56% gastrocnemius muscle weight sparing at 14 days following injury, respectively, with most of the loss occurring by the 7-day mark [100]. $MAFbx^{+/+}$ mice continued to lose muscle mass between 7 and 14 days. MAFbx null mice exhibited larger muscle fibers than the wild type in the affected muscles. Interestingly, these atrogene knockout mice had normal muscle size and morphology as well as normal viability, fertility and longevity before sciatic nerve denervation.

Double MuRF1 and MuRF2 knockouts individually are healthy, normal-appearing animals [101]. Double knockout (dKO) MuRF1/MuRF2 (all four MuRF1 and MuRF2 alleles inactivated) mice develop skeletal muscle hypertrophy stemming from individual fiber growth, resulting in a 38% increase in quadriceps to body weight ratios compared to wild type. By contrast, either allele knockout produced 11% to 17% increase in the quadriceps to body weight ratios. The double allele inactivation did not influence degradative entities, such as MAFbx/atrogin1 expression. Mutant mice that underexpress the E3 ubiquitin ligases are good models for atrophy following denervation and possibly for disuse atrophy; however, their utility may be limited as sarcopenic models, because muscle loss from sarcopenia is limited [102].

3.5. Myostatin

Some rodent models of neuromuscular disease have benefitted from the application of myostatin neutralizing antibodies with increased muscle fiber size (however not enhanced muscle function) [103,104]. Myostatin gene knockout in mice ($Mstn^{-/-}$) increased muscle mass by way of both hypertrophy and hyperplasia [43]. Antiapoptotic factor expression increased in these $Mstn^{-/-}$ mice as well [105]. The reduction in myostatin expression in $Mstn^{-/-}$ mice increased both satellite cell number and type IIB/X fiber cross-sectional area in tibialis anterior muscles with improved regenerative potential [47]. Satellite cell activation, also an indicator of regenerative capability, was reduced in both old $Mstn^{-/-}$ and wild type mice. Young $Mstn^{-/-}$ mice had higher satellite cell number and activation than young wild type mice. Young $Mstn^{-/-}$ mice also had a higher percentage of glycolytic muscle fibers while the older $Mstn^{-/-}$ mice had more oxidative fibers. However, McMahon and coworkers [106] found $Mstn^{-/-}$ mice to be more susceptible to atrophy from unloading. Although myostatin's role in sarcopenia is debated, with myostatin mRNA expression ranging from decreased [107] to unchanged [108] to increased [109] in aging rodent studies, the retention of muscle mass in the aged myostatin knockout mouse supports the consideration of myostatin as an influence on muscle mass and the $Mstn^{-/-}$ mouse as a model for study of age-related muscle loss [110].

Elevated myostatin levels in mice by injection induced significant muscle mass loss [111], yet myostatin overexpression in adult mice inhibited Akt/mTOR signaling without the promotion of atrogene expression [112,113], therefore this pathway appears to be more involved in limiting hypertrophy than promoting atrophy [63]. Myostatin's role, however, in the atrophy of unloading is conflicted, with studies reporting both increased and unaltered [114,115] myostatin expression. Those studies whose results yielded increased myostatin expression found myostatin changes primarily within fast muscle types [116,117].

In a cachexia model, increased myostatin expression did result in protein degradation via FoxO1 expression [118]. These unloading and cachexia models suggest that myostatin does play a role in atrophy under certain conditions [63].

3.6. Apoptosis

The expression of muscle apoptosis genes (caspase-3, caspase-9, bax, and Smac/DIABLO) are decreased in the female GHRKO (growth hormone receptor/binding protein knockout) mouse skeletal muscle when compared to wild type mice. This mouse is known for its longevity due to its disrupted growth hormone signaling pathway. Other advantages these mice exhibit include enhanced oxidative stress handling [119–121] and reduced incidence of neoplasms [122]. Reduced apoptosis gene and protein expression may also contribute to the extension of life span in this animal. Caloric restriction is also known for increasing life span [123]; however, the addition of caloric restriction in this study did not alter the expression of apoptotic genes [124]. Although reduced apoptosis typically increases incidence of neoplasms [125], mice with decreased circulating IGF-1 demonstrate reduced incidence and/or delayed development of tumors [122,126]. Since research suggests that apoptosis in skeletal muscle is linked to sarcopenia [61,127] and since lack of caspase-3 has shown a protective effect against skeletal muscle atrophy from denervation [128], this model could serve as a good candidate for sarcopenia studies. However, as mentioned earlier, atrophy from denervation follows a different biochemical pathway than sarcopenia. Also, skeletal muscle growth via the IGF-1/PI3K/Akt pathway is likely impacted in this knockout, therefore, it would be important to distinguish whether any resemblance to

inhibiting sarcopenia is due to the decrease in apoptosis expression or the decrease in growth hormone signaling.

The Mstn$^{-/-}$ (myostatin null) mice described earlier exhibit increased expression of antiapoptotic genes [105]. However, the significance of a relationship between apoptotic proteins and muscle growth remains to be understood. Skeletal muscle appears able to defend against apoptosis with its high level of endogenous inhibitors [129], with apoptotic events promoted with the stress of exercise and muscle pathology [130–132].

Pathways that are key to the protein synthesis critical for muscle growth are well established. Some of the models discussed demonstrate a perturbation of those pathways; yet they do not always have a strong connection to an aging influence on muscle mass loss or fiber composition change. As these pathways do have an influence on muscle growth, their continued inclusion in research in aging will likely give additional insights into the process behind muscle loss with age.

3.7. Accelerated aging models

Investigations focused on aging have generated specific information on muscle function over the life span and have contributed to our understanding of muscle loss. Several mouse models with an accelerated aging phenotype have been developed, enabling a "fast-forward" observation of aging's influence on muscle physiology and form. Animals identified as accelerated models of aging afford us the convenience of examining the effects of aging earlier in the life of the animal, shortening the requisite wait for senescence. However, accelerated aging models do not always demonstrate characteristics typical of aging for the animal studied. The genetic manipulation performed in developing these animals often affects the physiology of other body systems, influencing results in the tissues studied. Several of these examples are summarized in Fig. 3. The *Zmpste24*$^{-/-}$ mouse, mimicking Hutchinson–Gilford progeria syndrome, stops growing at 5 weeks of age and has a median survival age of 123 days [133,134]. Greising and coworkers [133] compared muscle characteristics between these mice with a mutation in the gene encoding metalloproteinase for lamin A maturation against littermates without the mutation. Very late in life for the *Zmpste24*$^{-/-}$ mouse (20 weeks), the homozygous knockout exhibited less physical activity and had less than half the body mass of the wild type mouse. The *Zmpste24*$^{-/-}$ mice displayed reduced grip strength and whole body tension when controlled for body size. The knockout demonstrated progressive ankle range of motion losses after 5 weeks of age while the wild type retained its ankle mobility. Passive ankle torques in the *Zmpste24*$^{-/-}$ mice were high, indicating increased joint stiffness. The collagen content of leg muscles was 45%–72% higher in the *Zmpste24*$^{-/-}$ mouse, possibly explaining the increased joint and muscle stiffness in that strain. Anterior leg muscles (extensor hallucis longus, tibialis anterior, extensor digitorum longus) were weaker in the knockout mouse, while posterior hindlimb muscles exhibited equivalent strength between strains. Ex vivo strength testing (maximal isometric tetanic force) of these same muscle groups showed the same results. Actual muscle mass of hind limbs across strains was comparable after adjusting for body mass. Serum creatine kinase levels were similar between strains; higher levels would have indicated muscle injury. Although the mean cross-sectional area of soleus fibers was not different between strains, there was a different distribution of soleus fiber sizes, with *Zmpste24*$^{-/-}$ having more small and large fiber sizes. A similar percentage of soleus fiber types were observed in both strains. *Zmpste24*$^{-/-}$ mice had more nuclei, yet no difference was seen in the percentage of fibers with centrally- (indicative of dysfunction) versus extracellularly-positioned nuclei. Extensor digitorum longus fibers were smaller in the *Zmpste24*$^{-/-}$ mice and had more type IIa and fewer type IIb fibers. Histologically, in general, the *Zmpste24*$^{-/-}$ had normal, healthy appearing muscles, with no signs of dystrophy or degeneration. The general phenotype is one of impaired neuromuscular performance and selective muscle weakness when compared to the *Zmpste24*$^{+/+}$ littermates, which are characteristics matching those of aged mice. How well this model represents accelerated aging is controversial, as humans with progeria exhibit some aspects of rapid aging but not others [135].

Another model of aging is the senescence-accelerated mouse (SAM) [136]. Lineages of this mouse include 14 senescence-prone inbred strains and 4 senescence-resistant inbred strains, with mean life spans of 9.7 and 13.3 months, respectively [137]. Characteristic aging features in the senescence-prone mice initially include abnormal behavior, skin lesions, cataracts, elevated amyloidosis, and increased spinal lordokyphosis [137]. Other pathologies simulating aging, such as learning and memory deficits, degenerative joint disease, osteoporosis, tumors, and kidney dysfunction, have also been discovered [138]. Research suggesting that SAMP6 [139] and SAMP8 [140] strains are appropriate as aging muscle models investigated fiber size and quadriceps tubular aggregate accumulation, respectively. Derave and coworkers [136] examined several properties of muscle physiology, including muscle metabolites, muscle mass, contractile properties, force generation, fatigability, and fiber size and distribution among 2 strains of senescent-accelerated (SAMP6, SAMP8) and 1 strain of senescent-resistant (SAMR1) mice. All mice were studied at 10, 25, and 60 weeks of age. Both accelerated aging models displayed reduced muscle contractility, decreased fiber size and muscle phosphocreatine levels with aging. However, SAMP8 exhibited the features most demonstrative of accelerated muscle aging with greater reduction in muscle phosphocreatine levels, muscle mass and contractility, and type-II fiber size atrophy, with aging features developing earlier and at a faster rate than SAMP6 or SAMR1. Muscle fiber composition in soleus showed a shift toward more type I fibers over time in both SAMP6 and SAMP8; however the difference wasn't significant. No fiber size or type distribution change was significant in the extensor digitorum longus of either SAMP6 or SAMP8. These findings suggest that the SAMP8 mouse soleus is a reasonable model for muscular aging studies.

The Ku80$^{+/-}$ mouse is an animal that displays accelerated muscle aging in the presence of normal postnatal growth. The Ku80 knockout mouse exhibits both reduced postnatal growth and severe progeria. The Ku80 heterodimer assists in the repair of DNA double strand breaks and helps with telomere stability [141]. Didier and colleagues [142] found that the Ku80$^{-/-}$ mice displayed an increased proportion of slow fibers with a decreased proportion of fast fibers in soleus muscle compared to young Ku80$^{+/+}$ mice. Ku80$^{+/-}$ animals also demonstrated a size reduction in all soleus fiber types as compared to Ku80$^{+/+}$. The Ku80$^{-/-}$ mouse is smaller than the Ku80$^{+/+}$ mouse [143] and smaller type I and II fibers were found in the knockout mouse [142]. The Ku80$^{+/-}$ mouse is the same size as the Ku80$^{+/+}$ mouse; however, both type I and II soleus fibers are also smaller than those of the Ku80$^{+/+}$ mice, so in this model it appears that the fiber size is not associated with body size. Following serial injuries, both Ku80$^{+/-}$ and Ku80$^{-/-}$ mice exhibited reduced tibialis anterior muscle regeneration potential and also reduced stem-cell self-renewal compared to the homozygous wild type. At birth, Ku80 wild type and Ku80 null mice had equal numbers of satellite cells while at 15 days the Ku80$^{-/-}$ mouse had significantly fewer. Satellite cell numbers for heterozygous and wild type were not different at those two life points. Ku80$^{-/-}$ mice exhibited muscle stem cell DNA damage while no DNA damage was detected in Ku80$^{+/-}$ or in wild type young and old mice. Crossing Ku80$^{+/-}$ mice on a p53 null background recovered the wild type mixed fiber (I/IIa) proportion that is reduced in Ku80 heterozygous animals, a picture of accelerated aging. Although this cross restored a more "youthful" fiber composition mix, the regenerative capacity typical of wild type muscle was still absent in the Ku80$^{+/-}$.

Another model of accelerated aging which mimics sarcopenia is the POLG mouse, a homozygous knock-in mouse with impaired

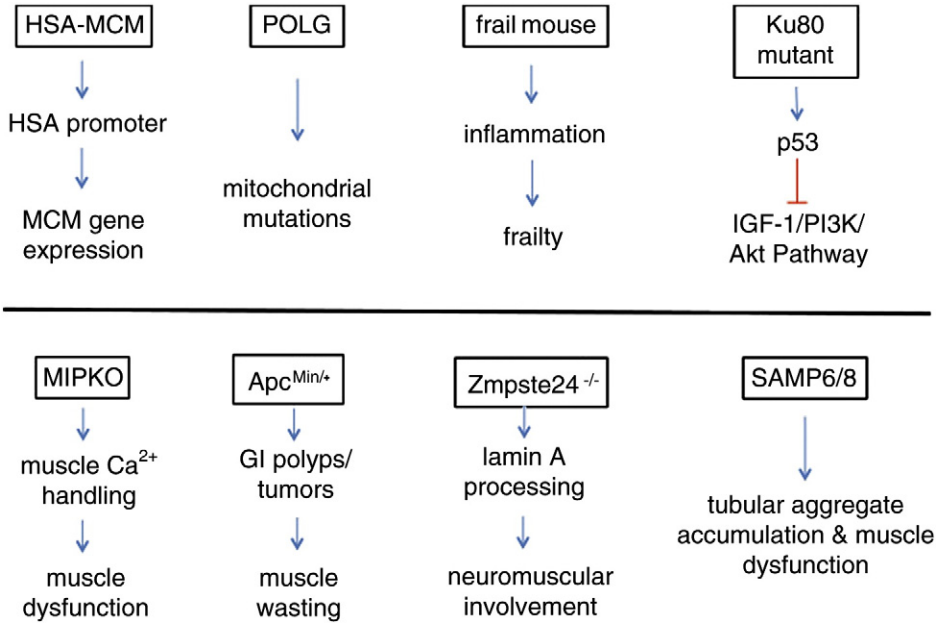

Fig. 3. Accelerated aging mouse models and their respective phenotypes.

proofreading capability of its mitochondrial DNA polymerase [144]. This mouse exhibits increased mtDNA point mutations and deleted mtDNA. Its reduced life span (median survival less than 50% of wild type) and physical traits such as spinal kyphosis, osteoporosis, and alopecia suggest a causal relationship between the mtDNA mutations and premature aging. Although finding no evidence of elevated oxidative stress in the presence of these mutations, Kujoth and colleagues [145] discovered increased induction of apoptosis by examining caspase-3 activation in several tissues at earlier ages. Notably, brain and skeletal muscle (both postmitotic tissues) apoptosis induction was not elevated to the same extent at earlier ages as in tissues with rapid cellular turnover, suggesting a resistance to induction of apoptosis. POLG mice exhibited a 10% decrease in weight in both gastrocnemius and quadriceps muscles at 9 months of age, while at 3 months of age respective muscle weights were comparable. The evidence for muscle loss in this prematurely aging animal over a 6-month period indicates that it may show promise as a useful model of sarcopenia in the presence of increased mtDNA mutation load.

A mouse model has been developed that exhibits the frailty seen in the elderly [146]. The "frail" mouse is characterized by a homozygous deletion of the IL-10 gene, an anti-inflammatory cytokine. The absence of this interleukin promotes the expression of NF-κB inflammatory mediators. To mimic human frailty, typical characteristics of muscle weakness, inflammation, decreased physical function, and overall reduced activity should appear later in life. Signs of frailty in the IL-$10^{tm/tm}$ mouse such as decreased strength and slowed weight gain appeared after 10 months. Old IL-$10^{tm/tm}$ mice (50 weeks) had higher levels of serum IL-6 than age-matched wild type mice. Levels of IL-6, known to promote frailty and disease in older humans, were different between young and old frail mice but not between young and old wild type mice. Upregulated genes in the IL-$10^{tm/tm}$ mice included those known for apoptosis and mitochondrial function. Downregulated genes in the frail mouse were those involved in protein transport and regulation of cell growth and maintenance. This particular model of aging appears to reflect well those features of frailty; however, there is less support for the involvement of inflammation in sarcopenia. Therefore, the frail mouse is useful for the study of muscle wasting in the presence of inflammation but would be limited as a model of sarcopenia, which involves the loss of muscle mass without the influence of disease or inflammation.

Fewer models of cachexia have been created solely for the study of muscle atrophy but each may be important in determining the roles of other factors involved. The $Apc^{Min/+}$ mouse is a genetic model of colon cancer, triggered by a mutation of the polyposis coli (*Apc*) gene [147], leading to intestinal polyps and eventually tumor formation [148]. This mouse has also become a model of cachexia, with a significant loss of muscle and fat tissue by 6 months of age [148,149]. At 3 months of age $Apc^{Min/+}$ and C57BL/6 mice have similar body weights and gastrocnemius and soleus sizes; however by 6 months, gastrocnemius and soleus muscle weights fall by 45% and 25%, respectively, with soleus muscle mean fiber cross-sectional area decreasing by 24%. Nuclei number and location (myofiber, extracellular matrix, or centralized) in the soleus indicate that there is considerable degeneration and regeneration in the more highly oxidative muscle. IL-6 is a cytokine known for its cachectic impact, and the $Apc^{Min/+}$ mouse exhibits elevated levels of circulating IL-6 when compared to age-matched wild type mice. An $Apc^{Min/+}/IL\text{-}6^{-/-}$ was created and showed that at 26 weeks of age, muscle mass was similar to wild type (C57BL/6), as opposed to the observation in the $Apc^{Min/+}$ strain where a significant loss of gastrocnemius weight was detected. Gastrocnemius mass was reduced by 23% with IL-6 overexpression and 32% in $Apc^{Min/+}$ and $Apc^{Min/+}/IL\text{-}6^{-/-}$ mice, respectively. Wild type mice and $Apc^{Min/+}$ mice without polyp burden did not experience cachexia or muscle mass loss in the presence of IL-6 overexpression. IL-6 levels may increase tumor burden and the tumor burden appears to promote the cachexia. However, Baltgavis and coworkers [150] demonstrated that muscle mass decreased even with low levels of IL-6 while others associate high IL-6 levels with muscle wasting [151,152]. Although MuRF-1 expression did not change with age in $Apc^{Min/+}$ mice, MAFbx expression was increased 10-fold as circulating IL-6 increased. MAFbx protein levels increased as well [153]. With IL-6 overexpression, MAFbx expression and protein levels also increased, while MuRF-1 expression remained unchanged [153]. These investigators suggested that an interaction between tumors and IL-6 levels promotes an environment favorable to the degradation of skeletal muscle [150]. Exercise which is often used to counteract muscle atrophy of various origins was found to reduce the muscle wasting effects accompanying IL-6 presence, even IL-6 overexpression, in conditions that promote cachexia [154,155].

The MIPKO (muscle-specific inositide phosphatase knock out) mouse is an animal lacking muscle-specific inositide phosphatase,

an enzyme important for entry, storage, and release of Ca^{2+} for excitation–contraction coupling in skeletal muscle [156]. This animal demonstrates several characteristics consistent with premature aging relative to muscle structure and function [157]. The MIPKO is spontaneously less active and reaches exhaustion earlier than similarly aged wild type littermates. Body weight and muscle mass loss, including reduced extensor digitorum longus fiber cross-sectional area, is apparent by 18 months of age compared to the wild type [156,157]. Contractile force generation was reduced in both old wild type and mature and old MIPKO mice compared to mature wild type mice. Ca^{2+} homeostasis in muscle was altered, both the old wild type and mature MIPKO displayed dysfunctional Ca^{2+} resting levels, Ca^{2+} release, and Ca^{2+} transient recovery. In general, similarities between muscle morphology and function were found between mature (12–14 month) MIPKO and old wild type (22–24 month) mice, demonstrating an accelerated aging muscle phenotype in the MIPKO mouse. This model focuses on the physical dysfunction elements of sarcopenia. Thus, we await further studies in this animal to examine the muscle morphology changes and atrophy pathways more closely.

The models listed above are all examples of constitutive influences of genetic expression on pathways and resultant phenotypes. As these animals assume their knockout or transgenic genotype, they will experience that influence from the time of conception through development to the end of life. Sarcopenia is a postmaturational phenomenon whose process could be altered and therefore be inaccurately represented when influenced by these constitutive models. An inducible model exists in which muscle gene expression can be initiated after attaining maturity [158]. The HSA-MCM mouse allows for limb and craniofacial skeletal muscle-specific expression of a protein to occur only upon the administration of a tamoxifen trigger. This type of model enables the researcher to assess protein expression at any point along the life span, minimizing confounding influences that genetic manipulation might elicit when spanning great time periods or crossing developmental transition points.

4. Conclusion

Sarcopenia, as described by the European Working Group on Sarcopenia in 2010, is a progressive and generalized loss of both skeletal muscle mass and function [159]. Evans [160] adds that sarcopenia is age-related and is a different condition than cachexia. Although atrophy is considered the source of the resultant functional loss, some believe that the loss of muscle function cannot be fully explained by muscle atrophy alone [161–163]. In any case, the phenomenon of sarcopenia has devastating ramifications for senior citizens as they experience the loss of muscle mass and strength to the point at which they can no longer be independent.

The murine models of muscle loss described above provide some insight into their utility to better understand this process. We reviewed models that exert an influence along the IGF-1/PI3K/Akt pathway, a biochemical pathway known to play a large role in the regulation of skeletal muscle growth [164]. We have also examined models whose overall phenotype is that of an accelerated aging animal, observing whether the aging phenotype has manifested itself in the skeletal muscle system as decreased mass, decreased strength, and fiber type composition transfer, typical of sarcopenia. The described models have provided useful, yet incomplete, insight into the sarcopenia process. Some of the mutants have very short lives and, therefore, do not provide an animal that can develop and advance through life to old age. Some of the animals impact muscle growth; however, the muscle characteristics such as fiber type composition or type I or type II size may not resemble that of sarcopenic muscle. Several of the models listed have collected limited data relative to physical muscle characteristics that define sarcopenia. Important information relating to sarcopenia pathways has been extracted, however, similar measures have not been performed across these model systems, creating difficulty in evaluating their appropriateness for studying various causes of skeletal muscle atrophy, whether it is disuse, cachexia, or sarcopenia. Sarcopenia continues to interfere with health and is becoming a larger and larger socioeconomic burden to society. Identifying or creating valid models of sarcopenia will be an important endeavor in reducing its negative impact.

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