Emerging Molecular Mediators and Targets for Age-related Skeletal Muscle Atrophy

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Abstract

The age-associated decline in muscle mass has become synonymous with physical frailty among the elderly due to its major contribution in reduced muscle function. Alterations in protein and redox homeostasis along with chronic inflammation, denervation and hormonal dysregulation are all hallmarks of muscle wasting and lead to clinical sarcopenia in older adults. Reduction in skeletal muscle mass has been observed and reported in the scientific literature for nearly two centuries; however, identification and careful examination of molecular mediators of age-related muscle atrophy have only been possible for roughly three decades. Here we review molecular targets of recent interest in age-related muscle atrophy and briefly discuss emerging small molecule therapeutic treatments for muscle wasting in sarcopenic susceptible populations.

Keywords

inflammation; neuromuscular junction; proteostasis; sarcopenia; redox homeostasis

Introduction

One of the first interpretations in recorded history of frailty in older adults was made around ~400 B.C. by Hippocrates whose notions on aging reflect the current accepted concept of aging as increased frailty [1, 2]. Hippocrates viewed aging as a late stage of life in which there is an increased susceptibility to disease [1]. Around the fifth decade, humans will begin to lose on average ~1% of lean mass per year resulting in a 30-50% reduction in muscle mass by 80 years of age [3–7]. This age-related decline in muscle mass and associated muscle weakness, referred to as sarcopenia [8–10], has been clinically classified by several geriatrics organizations as two standard deviations below the mean for healthy young adults 20-30 years of age [11–14]. Based on the clinical definition, roughly 11-50% of adults 80 years of age and older are considered sarcopenic, although adults that are at least 50 years old typically exhibit age-related muscle atrophy of some degree [6, 14].

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Promoting the maintenance of skeletal muscle in the elderly is vital to delay physical frailty as well as to preserve amino acid reservoirs in the body to reduce morbidity and mortality [15–19]. In the early twentieth century there was a gap in knowledge between the identification of muscle wasting in aging and the mechanisms involved. An early theory disproven by the Harvard Fatigue Laboratory in 1946 was that a loss of water content was the major contributor to the shrinking of muscle tissue [20]. More recent advances in cell physiology and molecular biology allowed the identification of numerous cellular signaling pathways and biological functions that are altered in association with age-associated muscle deterioration and influenced by a myriad of molecular mediators (Table 1) [21–27]. The mediators that have been most widely investigated in regards to muscle wasting during aging over the past few decades can be categorized in a few key areas: proteostasis, inflammation, denervation, redox homeostasis, and hormonal regulation. This review will focus on novel molecular mediators of age-related muscle atrophy within these areas that have been reported in the past decade and emerging drug treatments for sarcopenia.

Proteostasis and Age-related Muscle Atrophy

The maintenance of protein turnover through mediators of protein synthesis and degradation has been well documented for healthy aging and preservation of skeletal muscle tissue during aging in *C. elegans*, drosophila, and mammals [28–31]. Skeletal muscle comprises ~60% of proteins in the body [32]. Thus, the regulation of the Akt/mTOR pathway has been a major focus for maintaining skeletal muscle health [33, 34]. In the past few decades, exercise and calorie restriction interventions targeting protein homeostasis have produced improved lifespan and healthspan through maintaining muscle mass [35–38] demonstrating the importance of protein synthetic signaling in skeletal muscle during aging [33, 34]. Examples confirming the importance of mTOR in muscle maintenance have used a transgenic mouse model where the TOR agonist complex protein, TSC, is knocked out in the muscle leading to constitutive activation of mTORC1 [39, 40]. These mice display accelerated neuromuscular aging and autophagy dysfunction as early as 9 months of age and will typically perish within 12 months [39, 40].

Previous research investigating protein signaling upstream of Akt (e.g. IGF-1) has indicated that maintaining insulin signaling is necessary to preserve skeletal muscle mass in older individuals [41, 42]. As a specific illustration, induction of the upstream target of Akt, PI3k subunit p110α, has been reported to lead to increased muscle atrophy during aging [43]. M-p110αKO mice displayed decreased PI3k activity and Akt phosphorylation which led to muscle atrophy in most hind limb muscles by 24 months of age [43]. The intracellular enzyme, PI3k, is critical in the insulin signaling pathway and its relevance to the dietary restriction pathway may suggest its role to maintain proteostasis in older adults [44, 45].

The latest reports of molecular mediators of proteostasis as potential contributors to age-associated skeletal muscle atrophy show less reliance on regulating mTORC1 and more dependence on other mechanisms. For example, Activating Transcription Factor 4 (ATF4) has recently been identified as a molecular target for muscle wasting in aging [46], although its regulation within protein synthetic signaling has not been fully elucidated [46–48]. Support for the importance of ATF4 in regulating muscle mass during aging is provided by

the observations of Ebert and colleagues that treatment with either ursolic acid or tomatidine, small molecules known to reduce age-related deficits in skeletal muscle mass. After 2 months of treatment with ursolic acid or tomatidine, a strong inverse relationship was found between ATF4-dependent mRNAs and either ursolic acid- or tomatidine-sensitive mRNAs, demonstrating a potential link between ATF4 and age-associated muscle atrophy. Moreover, 22-month-old muscle-specific *Atf4* knockout mice had 8% larger skeletal muscle mass than wild-type controls, suggesting that ATF4 has a direct role in muscle wasting during aging [46].

Regulators of wingless type (WNT) signaling appear to play a role in maintaining muscle mass in aging muscle as well. Dkk3 is a secreted glycoprotein in skeletal muscle and non-canonical WNT signaling antagonist that induces muscle atrophy when upregulated [49–54]. Furthermore, Dkk3 level is increased in blood of older adults and is upregulated in senescent prostate epithelial cells [55, 56]. Conversely, Yin and colleagues found that Dkk3 is a key activator of Fbxo32 and Trim63 through recruitment of β-catenin, and Dkk3 is upregulated in muscles of 20-month old mice [56]. Moreover, reduction of Dkk3 through intramuscular injection of shRNA against Dkk3 restored skeletal muscle mass in aged mice [56].

The fibroblast growth factor FGF21 is a hormone secreted by fibroblasts and others cell types within skeletal muscle and is an important regulator of whole body metabolism [57–59]. FGF21 increases systemically with age in humans, and Tezze and colleagues found that muscle specific knockout of the autophagy gene, Opa1, increased levels of FGF21 and reduced muscle mass in slow, fast and mixed fiber type hind limb muscles of mice [57]. While Opa1 deficiency in muscle reduced muscle mass and increased FGF21, deletion of both Opa1 and FGF21 in mice partially restored skeletal muscle mass suggesting that FGF21 compensates for Opa1 and may be a key regulator of age-associated muscle wasting [57]. There are numerous other regulators of FGF21 involved with metabolism and energy homeostasis suggesting that FGF21 may play a central role in muscle maintenance in aging [57–59]. Altogether, evidence support that components of proteostasis including key signaling molecules in protein synthesis and autophagy are essential for the regulation of skeletal muscle maintenance in older adults.

Inflammation Induced Muscle Atrophy in Older Adults

The immune system plays a vital role in the protection against pathogens, in tissue and organ repair and remodeling, and in the maintenance of skeletal muscle tissue [60–63]. It has been reported that senescence of the immune system can be detected in middle aged mice (10-15 months old), earlier than many other organ systems [64, 65]. Specifically, substantial senescent changes in immune function precede skeletal muscle atrophy, which is not observed in C57BL/6 mice until they reach at least 18 months of age [22, 40, 41, 66–70]. These observations hint that proper regulation of the immune system may be necessary to maintain skeletal muscle mass. Due to physiological senescence within the immune system, older adults exhibit chronic low-grade systemic inflammation (Inflammaging) [26, 71–73]. Increased levels of pro-inflammatory cytokines (e.g. TNF, IL-6, CRP, etc.) are associated with declines in muscle mass and numerous studies have implied that excess pro-

inflammatory cytokines systemically negatively impact skeletal muscle [60, 71, 73]. Hence, the systemic environment can contribute to age-related atrophy.

Several novel immune mediators are currently being investigated for their role in age-associated skeletal muscle atrophy. TWEAK or TNF-related weak inducer of apoptosis was first characterized in 1997 and has been reported to be secreted by immune cells and lowly expressed in skeletal muscle [74–76]. TWEAK can signal through TNF receptor 1 (TNFR1) but has higher affinity to interact with fibroblast growth factor inducible molecule 14 (Fn14) [77, 78]. The Fn14 receptor has been reported to be upregulated in aged mice, which also exhibit a ~20% reduction in muscle fiber CSAs in comparison to young mice [76, 79]. Consistent with the association between Fn14 and muscle fiber atrophy, genetic knockout of Fn14 rescued TA muscle fiber CSA and enhanced levels of contractile proteins compared to wild-type littermates [79]. Kumar's laboratory also found the downstream target of Fn14, NF-κB, had reduced activity in aged skeletal muscle tissue of Fn14-KO mice and suggested that the TWEAK-Fn14 pathway regulates multiple muscle atrophy pathways within aging skeletal muscle [79].

The anabolic muscle cytokine (myokine), IL-15, has been examined due to its direct association with declining mass with aging [80]. Calorie restricted diets that increase lifespan and preserve lean mass in elderly populations maintain IL-15 signaling in aged rats and subsequently reduce TNF-α secretion and NF-κB activity [81]. Thus, IL-15, an anti-apoptotic cytokine, has been proposed to act through the downregulation of TNF-α and induction of phosphorylation of the IκB to inhibit apoptosis [81]. Overall, various soluble mediators of the immune system have the capability to trigger skeletal muscle atrophy in aging.

Denervation-Induced Atrophy in Aging

The neuromuscular junction (NMJ) is an excitatory cholinergic synapse that constitutes the primary site of signaling between the nervous system and skeletal muscle. The primary cellular components of the NMJ are the presynaptic motor neuron, the postsynaptic muscle fiber and Schwann cells that cap the NMJ. Since the NMJ is critical for muscle contraction, any degenerative changes at the NMJ have the potential to impair muscle function contributing to physical frailty. With aging, NMJ fragmentation occurs as indicated by thinly dispersed acetylcholine receptor (AChR) clusters at the synapse [82] and is thought to be a result of continuous remodeling of NMJs throughout the lifespan that is reduced in effectiveness with aging. In parallel, extensive branching of motor nerve terminals at the NMJ is seen with aging [83–85]. Whether spinal motor neurons themselves are lost with age or remain intact is a controversial topic in the field. Nevertheless, progressive denervation is seen in late life in both humans [86] and rodents [87–89] and is likely contributing to muscle weakness and muscle fiber loss. Schwann cells, which maintain NMJs via trophic and antioxidant support, have recently been reported to reduce in number at the NMJ with age [90], however, their impact on NMJs with age is the least studied of the three NMJ cell types.

The most well studied and understood NMJ maintenance pathway is the Agrin-Lrp4-MuSK signaling pathway. Agrin, a proteoglycan that is secreted by motor neurons, acts by binding to its receptor low-density lipoprotein receptor-related protein (LRP4) located on muscle fibers, which then activates muscle specific kinase (MuSK). MuSK activation triggers a critical signal transduction cascade that leads to agrin-induced AChR clustering at the NMJ. Mice deficient for key proteins in this pathway (i.e. Agrin, Lrp4, and MuSK) are unable to assemble proper NMJs [91–93]. Recent studies in the literature have demonstrated the importance of the Agrin-Lrp4-MuSK signaling pathway in maintaining skeletal muscle mass. When conditionally knocking out agrin or LRP4, NMJ fragmentation similar to that seen in aging is observed [93, 94]. Furthermore, mice overexpressing neurotrypsin, which cleaves agrin, results in significant denervation and subsequent sarcopenic-like phenotype [95]. All components of the Agrin-LRP4-MuSK signaling pathway are critical for NMJ viability, however, only LRP4 protein levels are reduced in aged mice [96], suggesting that a deficiency in agrin signaling is not due to the nerve's ability to synthesize agrin. In addition, reduced phosphorylation of LRP4 and MuSK was reported. Sarcoglycan α (SGα), a key component of the dystroglycoprotein complex and stabilizer of LRP4, was overexpressed in aged muscles and was found to be effective at preventing denervation, AChR fragmentation, and improve neuromuscular transmission in aged mice [96]. Hence, alterations to the Agrin-LRP4-MuSK signaling pathway, which are observed in the later stages of life, appear to contribute to muscle wasting in older adults.

Redox Homeostasis and Muscle Wasting

Progressive declines with aging in muscle mass and strength along with mitochondrial dysfunction [97–99] are accompanied by significant alterations in redox status in skeletal muscle resulting in part from increased reactive oxygen species (ROS) generation [100]. Both muscle and nerve contain regulatory systems to maintain intracellular ROS levels below a physiological threshold that would lead to cellular oxidative stress or aberrant ROS induced signaling. Clearance of ROS is performed in part by regulatory enzymes such as catalase, glutathione peroxidases, and superoxide dismutases (SOD). Although disagreement remains regarding whether the activity of these enzymes increases or decreases with aging, there is strong evidence supporting increases in biomarkers for DNA and mitochondrial DNA damage, protein oxidation, and lipid oxidation in skeletal muscle with aging [101–103]. Despite clear changes with aging in ROS generating and buffering systems, cause-effect relationships between alterations in redox regulation and sarcopenia have not been established.

Administration of exogenous antioxidants has yielded contradictory results in the field of exercise physiology and sarcopenia. Natural antioxidants function by inhibiting the oxidation of biomolecules. Vitamin C (ascorbic acid), for example, functions as an electron donor to lipid radicals to terminate lipid peroxidation [104]. In addition, vitamin C can interact with superoxide and hydroxyl-free radical and singlet oxygen. Vitamin C also has a role in regenerating vitamin E on cell membranes by reducing vitamin E radicals. Vitamin E is a fat-soluble antioxidant that is important for scavenging peroxide radicals [105] and vitamin E supplementation has been reported to be effective in lowering basal and post-exercise levels of lipid peroxides in older men [106]. A more recent study using combined

supplementation of vitamin E and C showed reduced levels of oxidative stress (H2O2, total GSH, GSH/GSSG ratio, malondialdehyde and 8-OHdG) and increases in SOD1/2 and catalase activities in old rats, but no differences in muscle mass and maximal force production was seen [107].

Another non-specific antioxidant that has received much attention is N-Acetylcysteine (NAC), which functions by directly scavenging ROS and supplies cysteine for synthesis of glutathione. Glutathione is a substrate for glutathione peroxidase, an important enzyme required for removal of hydrogen peroxide [108]. Benefits of NAC have been reported in skeletal muscle [109, 110], however, it seems that these benefits are primarily observed in athletes that are capable of producing large amounts of ROS or in muscles that are in a pre-fatigued state [111]. However, a meta-analysis on NAC supplementation for sport performance and risk of adverse effects found no significant benefit or risk of side effects with NAC use [112]. Recent reports have found a phenotype improvement in mdx mice with treatment with Tempol, a superoxide dismutase mimetic [113, 114]. The investigators found improvements in force generating capacity and metabolic enzyme activity (citrate synthase and lactate dehydrogenase) in diaphragm muscles from mdx mice [114]. Hermes et al. also found improvements in grip strength as well as reduced markers of inflammation in dystrophic diaphragm and bicep brachii muscles in mdx mice treated with Tempol. Although promising, the safety and efficacy of Tempol needs further investigation in other conditions of frailty such as sarcopenia. In addition, other investigators have found no significant benefits with antioxidant vitamin supplementation on muscle function during aging [115–117]. The discrepancies between findings across studies could be owed to differences in dosage, administration timing, outcome measures, and muscles studied. Targeting specific antioxidant pathways may also provide greater therapeutic benefits than the administration of general antioxidants and may also explain the great variability of study results on antioxidant supplementation.

Despite contradictory data surrounding the utility of antioxidant supplementation, numerous studies using transgenic manipulations have shown that accumulation of ROS (and other free radicals) produce a pronounced neuromuscular degenerative phenotype in rodent models. Our group and collaborators have shown that mice deficient for CuZnSOD (SOD1) have high levels of oxidative damage, generate less muscle force, experience mitochondrial function deficits and show neuromuscular junction abnormalities and muscle fiber loss [98, 99]. Interestingly, the neurodegenerative phenotype is fully rescued in mice that express Sod1 solely in neurons, suggesting an important interaction between motor neurons and muscle fibers [22, 118, 119].

A recent report from Hsieh and colleagues (2019), found that non-selenocysteine-containing phospholipid hydroperoxide glutathione peroxidase (GPx7), an oxidative stress sensor, inhibits O-GlcNAcylation to protect motor neurons from ROS accumulation with aging. The study found that an increase in ROS in motor neurons with aging leads to increased activity of GPx7 and subsequent inhibition of O-GlcNAcase (OGA), an enzyme responsible for the removal O-GlcNAc. O-GlycNAcylation is a posttranslational modification important in the stress response that confers cellular stress protection against ROS accumulation. O-GlcNAc levels are reduced in spinal cords of ALS mouse models [120, 121]. Mice deficient for GPx7

contain reduced O-GlcNAcylation and higher levels of ROS compared to wild type mice, and show spinal motor neuron death, paralysis, and muscle denervation [122]; however, pharmacological inhibition of OGA with Thiamet-G (TMG) increased O-GlycNAcylation and survival of spinal motor neurons during aging. Although this study offers an intriguing new pathway that has potential for pharmacological intervention, further studies are needed to understand the role of GPx7 in a more geriatric cohort of mice and to determine the efficacy of TMG in later timepoints of age. In summary, proper function of antioxidant enzymes SOD1, SOD2, and GPx7 are crucial to prevent oxidative stress-induced age-related skeletal muscle atrophy.

Pharmacological Sarcopenia Therapeutics

Over the past 20 years, much more attention has been focused on the treatment and even the prevention or delay of sarcopenia in older adults. In 2000, there were only two interventional studies for sarcopenia aimed at the amelioration of both muscle wasting and muscle weakness and now over 300 interventions have been completed or are ongoing through clinical trials for the treatment of sarcopenia (Figure 1). These interventional studies have utilized various approaches to combat age-related muscle wasting including nutraceuticals, meal modification, exercise intervention, and mechanical devices. In addition, roughly 30 small molecules or drugs have gone through clinical trials in past 20 years (Figure 2). Although pharmaceutical companies have investigated sarcopenia in clinical trials for 15 years, there have been substantial delays between the current research on novel targets of age-related atrophy and clinical trials for FDA approval, partially due to the fairly recent recognition of sarcopenia as an independent disease state in 2016 [123–125]. An example of this gap between basic research and translation to treatments for sarcopenia is the investigation of anabolic hormones and age associated muscle wasting. Growth hormone and testosterone were among the first researched targets in sarcopenia in the 1990's and were the dominant drug intervention for clinical trials in the early 2000's [126–130]. However, the majority of clinical trials investigating testosterone/androgen treatment failed to demonstrate clinically significant improvements in muscle mass or strengh, which shifted the focus to other targets to treat muscle wasting in aging.

In the late 2000's more promising drugs with fewer known side-effects targeting modulation of proteostasis and glucose metabolism (metformin, empagliflozin, pioglitazone), redox homeostasis (allopurinol), inflammation (ibuprofen) and other biological functions (BIO 101, potassium citrate) were introduced into clinical trials for sarcopenia[131–141]. Not to mention, multiple major pharmaceutical companies raced to bring the first small molecules to market that modify myostatin signaling and selective androgen receptor modulators to preserve muscle mass in sarcopenic patients (see review [125]).

Metabolic Therapeutics

Ghrelin is one satiety hormone that was selected by an investigator as a potential therapeutic for frailty due to its ability to stimulate growth hormone and improve appetite in older adults [142]. In phase 2 trials 16 subjects 70 years and older were given 7.5 mcg/kg of Ghrelin once a day subcutaneously for 12 weeks in addition to participation in resistance training

(NCT01898611). The results obtained by Dual Energy X-ray Absorptiometry (DEXA) showed no differences in the changes in lean body mass between the placebo and Ghrelin treatment groups that participated in strength training.

Multiple drugs that have been used to treat type 2 diabetes have also been examined as potential treatments for sarcopenia. Metformin (Glucophage) is one promising drug with an expired patent that has been used extensively to lower blood sugar in type 2 diabetes mellitus [143, 144]. More recently, metformin has been examined for its role in longevity and muscle maintenance in *C. elegans*, fruit flies, and mice [145–147]. Metformin is an activator of AMPK and indirect mTOR antagonist that could be beneficial for both healthspan and lifespan in humans [147, 148]. Metformin went through phase 1/phase 2 clinical trials in 2014 to assess skeletal muscle mass, muscle function, and muscle characteristics over a 3-year period in adults 65 years of age and older (NCT01804049). Although there are no results reported, it has been suggested in the literature that metformin can delay muscle atrophy and improve muscle maintenance in aging mammals [149].

One ambitious phase 4 clinical trial performed by researchers at the Sticht Center on Aging attempted to improve body composition of older adults through the combination of Pioglitazone with hypocaloric diet and/or resistance exercise training. The major objective of these studies were to reduce fat free mass in older adults while preserving lean body mass (NCT00315146). Pioglitazone is a type 2 diabetes drug known to lower blood glucose levels that was selected based on its function as a PPAR-γ agonist that improves glucose and lipid metabolism in muscle. In these studies, 40 women and 48 men between 65-79 years of age with a BMI of at least 25 kg/m^2 were randomly selected for a placebo or Pioglitazone with all groups being placed on a hypocaloric diet (calorie deficit of 500 kcal/day) and some groups participating in resistance exercise [138, 139]. The trials were partially successful because even though older adults on Pioglitazone and hypocaloric diet had reductions in fat and lean body mass, when resistance training was added to the intervention there was a reduction in the loss of skeletal muscle mass [138, 139].

An anti-hyperglycemic medication used for type 2 diabetes patients, Empagliflozin, is currently in phase 4 trials to determine whether this small molecule can delay the progression of age-related skeletal muscle atrophy [137]. Over 120 participants will be randomly selected to participate in 10 weeks of circuit resistance training (CRT), a Vegetarian-Mediterranean diet, or given a daily treatment of 10 mg Empagliflozin (NCT03560375). All three groups will follow-up with an additional 10 weeks of CRT along with their previous diet intervention. Changes in lean body mass will be measured using a body composition analyzer and completed results should be reported after November 2020.

Other Therapeutics

Therapeutics in several other categories have gone through clinical trials in the past decade and some of these drugs may contribute to treating sarcopenia in the near future. For example, the non-steroidal anti-inflammatory drug (NSAID) Ibuprofen was examined because chronic low grade inflammation and muscle atrophy are associated with aging [26, 72, 73, 150]. In this 9-month study, post-menopausal women were either given a placebo or 400 mg of Ibuprofen after resistance exercise 3 days a week (NCT01886196). The clinical

trial was unsuccessful in showing that either ibuprofen or ibuprofen with the addition of resistance exercise training could improve lean body mass in aging [141]. Resistance training alone however, maintained skeletal muscle mass in older women thus suggesting that NSAIDs may not be beneficial in sarcopenic adults.

Allopurinol is another drug that has gone through clinical trials and may partially remedy age-related skeletal muscle atrophy in humans [151]. Allopurinol has been used in the past to treat gout and kidney stones and has completed phase 4 trials for sarcopenia [152, 153]. Allopurinol activates the antioxidant enzyme xanthine oxidase to salvage redox homeostasis in older adults and thus is proposed to have potential to rescue lean body mass in the elderly [151]. Limited reports by investigators from the University of Dundee have shown that 5 months of treatment with allopurinol improves muscle energetics (NCT01550107). Whether oral ingestion of allopurinol can aid in muscle maintenance longitudinally, has yet to be examined.

Potassium citrate is a urinary alkalinizing medication that has been explored in clinical trials to determine if the substance can be repurposed to treat sarcopenia. The premise for the usage of this substance is that potassium citrate will neutralize the excess acid production that is observed in individuals that consume a Western diet, thus improving skeletal muscle mass in older adults (NCT00509405). Phase 3 trials were completed in over 200 participants in ages 65-80 years old with 2 years of treatment; however, results were never reported for this clinical trial.

Sarconeos (BIOL101) is a novel small molecule that is currently going through phase 2 trials. It is suggested that BIOL activates the MAS receptor (angiotensin agonist G protein-coupled transmembrane receptor) in muscle cells potentially through the drug's active ingredient, 20-hydroxyecdysone [130]. Over 200 subjects 65 years of age and older are being administered either a placebo or BIOL orally to determine the efficacy of the 6-month treatment (NCT03452488). Clinical trials for this study should wrap up by the end of 2020. Overall, small molecules display promise to offset, delay, or at the very least reduce the decline of muscle mass that is attributed with aging. Moreover, there are new delivery systems for sarcopenic drugs (e.g. chewing gum [US20140294915A1]. whey protein micelles [EP2768322A1]) and numerous novels targets yet to be explored by pharmaceutical companies (Table 3), which leaves the area of sarcopenic treatment full of opportunity to improve the quality of life in the elderly community.

Perspectives & Conclusion

Herein we have discussed the primary pathways and biological functions implicated in age-related skeletal muscle atrophy stemming from both longevity and muscle biology research. Moreover, these pathways likely interplay with multiple processes to delay or offset skeletal muscle atrophy in aging as well as intersect with each other. Novel mediators that influence proteostasis, including pi 10α PI3K, UCP1, and heat shock proteins (HSPs) have demonstrated dual benefits in several organisms for enhancement of lifespan and healthspan [28, 30, 31, 154, 155] and should be further investigated for their role in age-associated muscle atrophy and treatment of sarcopenia in humans.

The role of inflammation in relation to muscle wasting and aging is being re-evaluated highlighting the source and location of immune cells in response to the microenvironment. Historically, gerontology studies were focused predominately on low-grade, chronic, systemic inflammation in aging, in the absence of overt infection (termed inflammaging) [26, 71, 156]. More recent investigations of the contribution of inflammation to aging skeletal muscle have shifted focus towards inflammatory mediators released by the myofibers themselves with alterations in so called "myokines" tending to favor muscle deterioration with aging [59, 157– 159]. Nonetheless, general inflammaging and studies of myokines do not consider cytokines secreted by other cell types localized in skeletal muscle tissue. These additional sources of soluble immune mediators should not be overlooked because altered secretion of cytokines from macrophages, fibroblasts, and fibro/adipogenic progenitors within skeletal muscle have potential to negatively impact skeletal muscle maintenance during aging [160, 161].

Prevention of NMJ decline and preservation of synaptic transmission with age may provide therapeutic benefits. Although no current drug exists that specifically targets neuromuscular degeneration, life-long high intensity exercise has been shown to be an effective at preventing motor unit loss in humans [162]. In addition, caloric restriction, considered the most effective non-genetic intervention of aging and life-span extension, is effective at preserving NMJs and reducing muscle fiber turnover in the tibialis anterior muscle in aged mice [163]. These studies suggest that critical preservation pathways exist that facilitate NMJ maintenance in aged animals and could potentially be enhanced for therapeutic utility.

Furthermore, determining the important ROS mediated pathways that lead to muscle denervation and fiber loss will likely produce novel therapeutics. While the field has mainly focused on oxidative damage (i.e. DNA, lipid, protein oxidation) future studies are needed to understand the dual roles of ROS; cell signaling and redox homeostasis. Since sarcopenia is accompanied by multifactorial changes in both muscle and nerve it is likely that both tissue-specific ROS mediated signaling and redox homeostatic changes are involved and therefore simultaneously targeting specific mediators in the antioxidant network will provide the most effective therapeutic potential.

Although rodent and cell culture models have been predominately used to identify novel molecules as targets for age-related skeletal muscle atrophy, the contributions of human studies to the identification of key mediators of muscle wasting should not be overlooked. Molecular analysis of tissues from older adults are indeed necessary to confirm whether certain proteins are involved in muscle wasting in humans and to what degree specific mediators and signaling pathways influence skeletal muscle maintenance. Research studies using human tissues from older adults also give insight for future directions that need to be further explored and characterized in rodent models (e.g. myokines, metabolome) [164, 165]. As an example, in the early 2000's Welle and colleagues revealed that over 1100 genes in older women and over 700 genes in older men have differential gene expression in comparison to their younger counterparts, and a gene involved with DNA repair, Gadd45a may be involved in muscle wasting in humans [166, 167]. Since then more compelling evidence has shown a direct link of Gadd45a and muscle atrophy [47, 168], but whether there is direct contribution to sarcopenic muscle atrophy remains unknown.

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Finally, because the Food & Drug Administration only oversees the approval of drugs that treat a disease state, clinical trials of pharmaceutical approaches for the prevention of sarcopenia are hampered somewhat. Continued expansion of the list of potential targets emerging from basic research along with recent consensus on the classification and diagnosis of sarcopenia will enhance the development of pharmaceuticals approaches to treat age-related skeletal muscle atrophy and physical frailty in elderly populations [123, 124].

Acknowledgements

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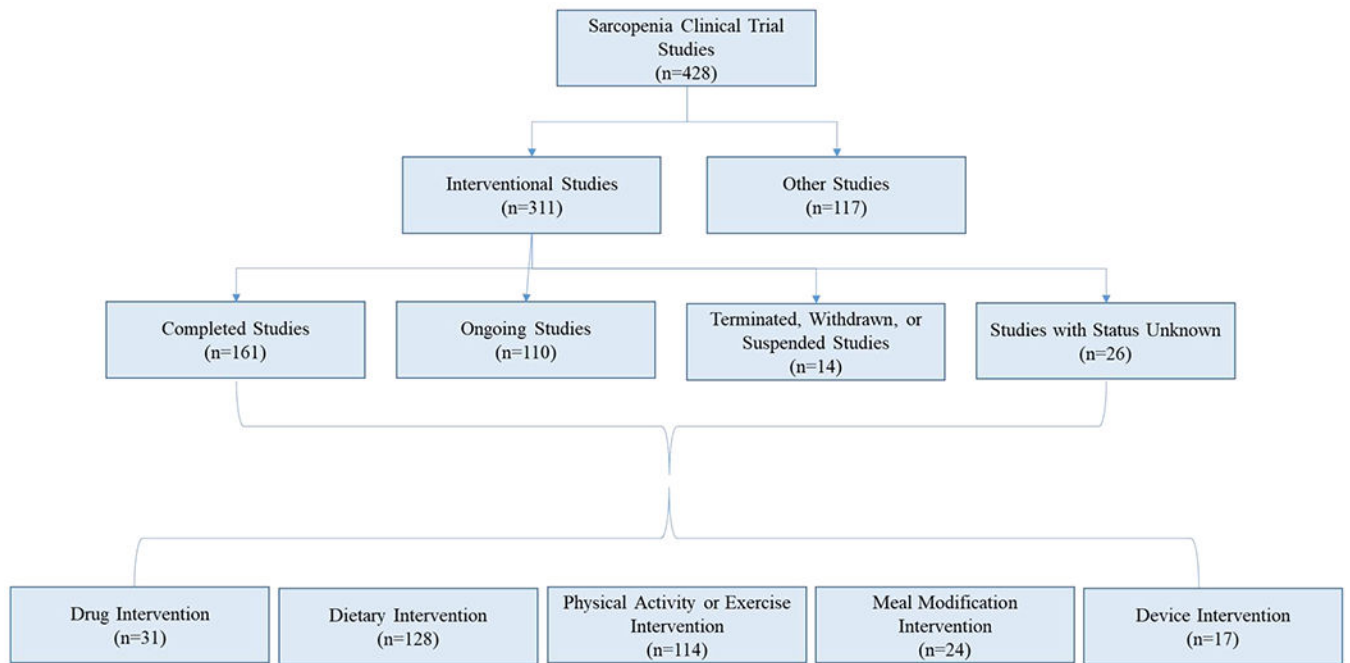
Figure 1.
Flow chart of sarcopenia clinical trial studies since October 2019. Data received from clinicaltrials.gov. Roughly three quarters of clinical trials have an interventional approach to investigate treatments for sarcopenia. The interventional approaches to retain lean body mass in older adults have been focused more on lifestyle changes (dietary, exercise) and less on patented technologies (drugs, devices).

Sarcopenia Clinical Trials (1998-2019)
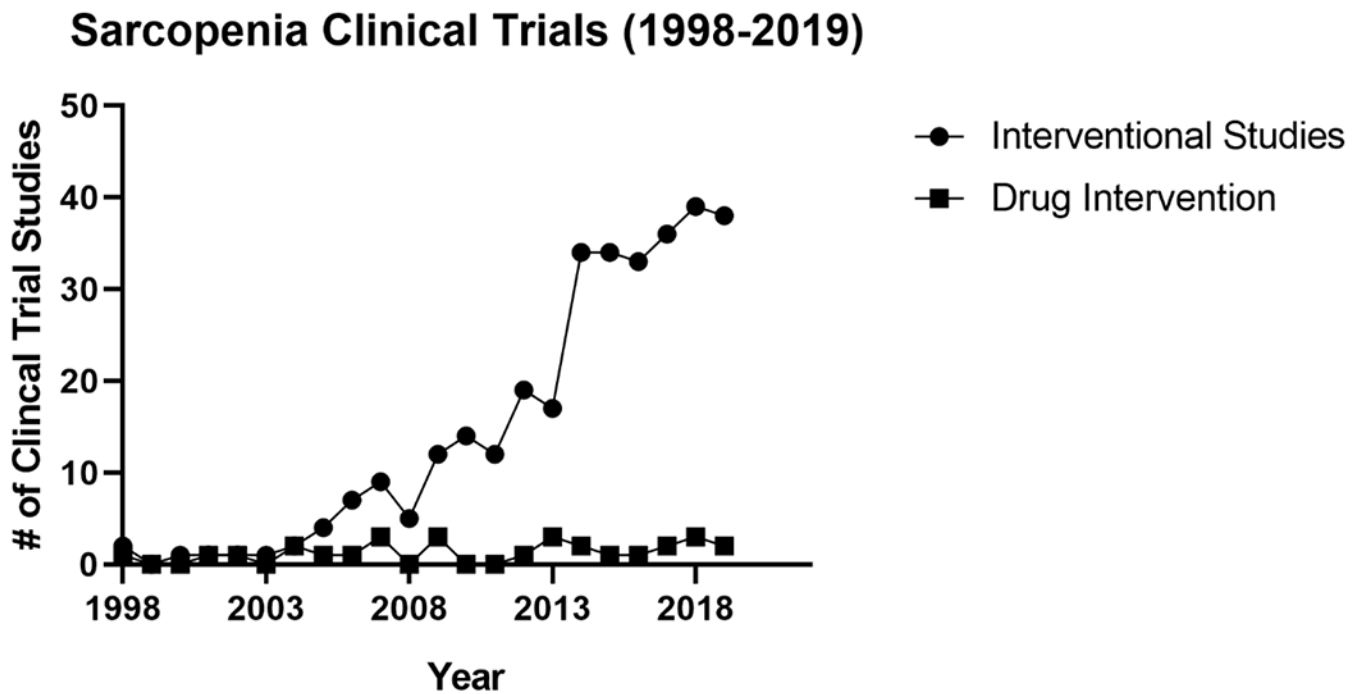
Figure 2.

Timeline of interventional clinical trial sarcopenia studies. Sarcopenia studies have gradually increased within the first decade of interventional trials and have abruptly grown within the last decade. Although, production of interventional studies from both the industry and institutions have progressively increased in the past couple decades, drug interventions have remained stable even after the classification of sarcopenia as a disease state in 2016.

Table 1.

Previous identified molecular targets of muscle wasting in aged mammals

Classification	Molecular Targets	Age-related Atrophy Year Identification	Reference(s)
Anabolic Hormones	Testosterone	1992	[128]
	DHEA	1995	[169]
	Growth Hormone	1998	[170, 171]
	IGF-1	1998	[172]
Proteostasis	mTOR signaling	2004	[173]
	Caspases	2004	[174]
	FoxO [*]	2004 [*]	[175]
Immune System	TNF-α	2005	[176, 177]
	IL-6 [*]	1997 [*]	[178, 179]
Denervation-Induced Atrophy	AchR	1984	[85]
Redox Homeostasis	SOD1	2006	[180]

[*] denotes targets or dates of only age-associated data in regards to muscle atrophy.

Abbreviations: AchR, acetylcholine receptor; DHEA, dehydroepiandrosterone; FoxO, forkhead family of transcription factors; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; mTOR, mammalian target of rapamycin; MuSK, muscle-specific kinase; SOD1, superoxide dismutase 1; TNF-α, tumor necrosis factor alpha.

Table 2.

Summary of novel targets of age-related skeletal muscle atrophy (2009-2019)

Classification	Molecular Targets	Atrophy-related Mediated Targets	Age-related Atrophy Year Identification	Reference(s)
Proteostasis	TSC	Fox03, mTORC1	2014	[39]
	dkk3	Fox03-p-catenin, WNT signaling	2018	[56]
	ATF4	*4E-BP1?*	2015	[46]
	FGF21	FoxOs	2017	[57]
	p110α PI3K	mTORCl	2019	[43]
Immune System	TWEAK-Fn14	NF-κB	2014	[79]
	IL-15	NF-κB, IL-15Ra, TNF-R1	2009	[81]
	IL-10 [*]	Unknown	2016	[181]
Denervation-Induced Atrophy	Sarcoglycan α	LRP4, MuSK	2018	[96]
	LRP4	MuSK	2014	[93]
	Agrin	LRP4	2012	[94]
Redox Homeostasis	GPx7	OGA	2019	[122]

[*] denotes target with no evidence from muscle weight data.

Abbreviations: ATF4, activating transcription factor 4; dkk3, dickkopf 3; FoxO, forkhead family of transcription factors; FGF21, fibroblast growth factor 21; GPx7, non-selenocysteine-containing phospholipid hydroperoxide glutathione peroxidase; IL, interleukin; mTORC1, mammalian target of rapamycin complex 1; LRP4, low-density lipoprotein receptor-related protein 4; MuSK, muscle-specific kinase; NF-κB, necrosis factor kappa-light-chain-enhancer of activated B cells; OGA, *o*-GlcNAcylation; TNF-R1, tumor necrosis factor receptor 1; TWEAK, TNF-related weak inducer of apoptosis; WNT, wingless-INT.

Table 3.

Selected sarcopenia drugs in clinical trials

Drug Name	Drug Target	Phase	Status	Date	Result	Sponsor Company/ Institution	NCT ID
Anabolic Hormone							
Testosterone Undecanoate	AR	N/A	Ongoing	Jul-19		Institute of Liver and Biliary Sciences	NCT03995251
Topical Testosterone	AR	Phase 2	Completed	Sep-02	↑ LBM	National Institute on Aging (NIA)	NCT00183040
Testosterone Gel	AR	Phase 4	Completed	Oct-04		Manchester University NHS Foundation	NCT00190060
Testosterone Gel 1%	AR	Phase 3	Ongoing	Sep-17		Washington University School of Medicine	NCT02938923
MK-0773	AR	Phase 2	Completed	Oct-07	↑ LBM	Merck Sharp & Dohme Corp.	NCT00529659
Enobosarm	AR	Phase 2	Completed	Sep-18		GTx (Merged with Oncternal Therapeutics)	NCT03241342
Recombinant HGH	GHR	Phase 2	Completed	Sep-02	*↑ LBM	National Institute on Aging (NIA)	NCT00183040
Anamorelin HCL	GHS-R	Phase 1	Ongoing	Aug-19		Tufts University	NCT04021706
MK-677	GHS-R	Phase 1,2	Completed	Jul-98	↑ LBM	University of Virginia	NCT00474279
DHEA	NMDA, GABA, σ_1-R	Phase 3	Completed	Apr-01		Washington University School of Medicine	NCT00205686
Oxytocin nasal spray	Oxytocin-R	Phase 1,2	Ongoing	Sep-17		University of Texas Health Science Center	NCT03119610
Metabolic							
Ghrelin	GHS-R	Phase 2	Completed	Jul-13		University of Pennsylvania	NCT01898611
Metformin	PKB	Phase 1,2	Completed	Apr-14		VA Office of Research and Development	NCT01804049
Empagliflozin	SGLT2	Phase 4	Ongoing	May-18		Tel-Aviv Sourasky Medical Center	NCT03560375
Pioglitazone	PPAR-y	Phase 4	Completed	Apr-06	↓ LBM	Wake Forest University Health Sciences	NCT00315146
Anti-inflammatory							
Ibuprofen (NSAIDs)	Prostaglandins	N/A	Completed	Apr-13	No diff	University of Saskatchewan	NCT01886196
Redox Homeostasis							
Allopurinol	Xanthine Oxidase	Phase 4	Completed	Feb-15		University of Dundee	NCT01550107
Other							
BIO101	MAS-R	Phase 2	Onqoinq	May-18		Biophytis	NCT03452488
Bimaqrumab	ActRII	Phase 2	Completed	Jul-15	= LBM	Novartis	NCT02468674
Landoqrozumab	Myo statin	Phase 2	Completed	May-12	↑ LBM	Eli Lilly	NCT01604408
Trevoqrumab	Myo statin	Phase 2	Completed	Nov-13	↑ LBM	Reqeneron	NCT01963598
Garetosmab	ActivinRIlA	Phase 1	Completed	Apr-13		Reqeneron	NCT02943239
Potassium citrate	Acidic Compounds	Phase 3	Completed	Jul-07		Kantonsspital Baseband Bruderholz	NCT00509405

Sarcopenia clinical trial studies that have at least one lean body mass outcome measure in older adults were included.

*
Increase in lean body mass was observed in combination to topical testosterone.

Date (Study start date). *Abbreviations:* AR, androgen receptor; DHEA, dehydroepiandrosterone; GABA, gamma aminobutyric acid; GHR growth hormone receptor; GHS, growth hormone secretagogue; LBM, lean body mass; N/A, not available; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; PKB, protein kinase B; PPAR-γ, peroxisome proliferator-activated receptor gamma; -R, receptor; SGLT2 sodium glucose co-transporter 2.