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Advances in Sarcopenia mouse models: establishment strategies and mechanisms

Abstract

Sarcopenia is a common geriatric disease characterized by the decline of muscle strength, mass, and function. Its pathogenesis is complex and there is no unified conclusion. Establishing appropriate mouse models is fundamental to studying this disease. Currently, methods for constructing sarcopenia mouse models include induced injection, aging models, muscle atrophy models, and transgenic models. Each model has its applicable conditions and limitations. Therefore, through a literature review of sarcopenia, this paper summarizes the modeling methods and mechanisms of sarcopenia in mice and provides an overview, aiming to provide references for related research.

Keywords: sarcopenia, animal model, skeletal muscle aging, modeling method

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Introduction

Sarcopenia, also referred to as muscle wasting syndrome, was originally defined by muscle mass loss alone. In 2018, the European Working Group on Sarcopenia in Older People (EWGSOP) revised its definition to characterize sarcopenia as a prevalent geriatric muscle disorder, clinically manifested by reduced muscle strength, decreased muscle mass, and impaired physical function.[1] Studies have shown that the prevalence rate of sarcopenia is 8%–36% among individuals under 60 years old and 10%–27% among those over 60. This condition tends to make older adults more prone to a decline in their ability to take care of themselves, falls, fractures, disability, and even death.[2] It is more prevalent among the elderly, but the decline in muscle mass begins at the age of 40. Scholars both domestically and internationally have conducted a series of studies on the pathogenesis of sarcopenia and believe that age,[3] oxidative stress,[4] the ubiquitin-proteasome system,[5] the *mammalian target of rapamycin* (*mTOR*) signaling pathway,[6] and myostatin levels[7] are all related to the occurrence of sarcopenia. Currently, there is no unified conclusion on the mechanism of sarcopenia, which may be a combination of multiple factors, and there is no definitive treatment.[8] As mouse models serve as the cornerstone for sarcopenia research, a comprehensive understanding of modeling methodologies is critical. This review systematically summarizes the latest advances in sarcopenia mouse model establishment strategies and their underlying mechanisms, evaluates their respective advantages and limitations, and provides insights for optimizing model selection in future studies.

Sarcopenia animal models

Commonly employed animal species for sarcopenia modeling include rats,[9] mice, nematodes,[10] rhesus monkeys,[11] zebrafish.[12]

However, each has its limitations. Mouse models are the most widely used due to their similarity in the aging process to humans, as well as lower research costs and shorter timeframes.[13] Based on different experimental approaches, sarcopenia modeling methods can be classified into the following four categories.

Drug injection: Drug injection refers to the injection of substances that induce muscle aging into animals to induce sarcopenia. Currently, dexamethasone and D-galactose are commonly used as inducers in research.

Dexamethasone is a synthetically produced glucocorticoid with anti-inflammatory and immunosuppressive effects.[14] Long-term and high-dose injection of dexamethasone can lead to skeletal muscle degradation and inhibit skeletal muscle protein synthesis, resulting in sarcopenia[15] Lee et al.[16] demonstrated that intraperitoneal injection of dexamethasone in mice results in a decrease in the proportion of lean tissue and atrophy of the gastrocnemius muscle, indicating the feasibility of the model. This modeling method often uses young mice, and the changes in muscle strength and function it induces are similar to those in humans. However, the manifestation of weight loss differs somewhat from that in human age-related sarcopenia.[17] There are differences in molecular mechanisms compared to natural aging.[18] While this approach is widely accepted globally, further optimization of dosage and treatment duration is required to enhance translational relevance.

D-galactose, a reducing sugar, has been widely used in establishing murine aging models.[19] Wang Jing[20] reported that D-galactose intervention induces significant declines in muscle strength and exercise capacity in mice. Additionally, treated mice exhibit multiple aging-related phenotypes,[21] attributed to D-galactose-induced perturbations in functional metabolism that mimic physiological aging processes.[22] This method can gradually increase the degree of aging but has little impact on the recovery ability of the mice. Attention should be paid to this point if developing drugs for the treatment of sarcopenia.

Aging: Aging is a major influencing factor of sarcopenia,[23] so aging models are widely used in the establishment of sarcopenia models. Currently, the more commonly used methods for establishing aging models include natural aging mice, rapidly aging mice, and high-fat feeding.

The natural aging model is often used in sarcopenia research because the muscle atrophy pattern in this model is closest to that of the elderly, and it is easy to operate. The expected lifespan of mice is 24 months, and a 15-month-old mouse is equivalent to a 50-year-old human. Oh et al.[24] found that the muscle strength, mass, and fiber size of aged mice were significantly lower than those of young mice, which can be diagnosed as sarcopenia. In addition, regarding gender selection, most researchers tend to choose male mice. This is because male mice have a longer lifespan than female mice, and using male mice can avoid high hormonal variability. Compared with

male mice, female mice secrete more estrogen. Estrogen can reduce fat content, possess antioxidant activity, and decrease the occurrence of inflammation,[25] all of which are pathogenic factors of sarcopenia.

Senescence-accelerated mice exhibit a short lifespan and display age-related characteristics similar to elderly humans during their geriatric phase, with modeling requiring 6-8 months. Noguchi et al.[26] fed senescence-accelerated mice to 35 weeks of age and confirmed sarcopenia by measuring muscle mass, muscle fiber cross-sectional area, and protein levels controlling skeletal muscle breakdown. This model is widely used in studies evaluating exercise interventions for sarcopenia[27] and novel drug therapies for sarcopenia.[28]

The high-fat diet (HFD) model has a relatively short modeling duration compared to other aging model establishment methods. Dowling et al.[29] fed mice a high-fat diet for 8 weeks and observed increased body weight, reduced endurance, and decreased muscle mass ratio. Perry et al.[30] similarly reported muscle mass loss and increased heart weight following HFD. However, long-term HFD feeding causes damage to organs such as the liver,[31] and kidneys,[32] limiting its widespread use.

Muscle atrophy models: Muscle atrophy models refer to neurogenic or disuse sarcopenia induced by denervation or joint immobilization. This method has a short modeling duration and low infrastructure requirements but demands high-level technical proficiency from experimenters.

Surgical resection refers to the establishment of a mouse sarcopenia model by resecting mouse nerves. Motor nerves are crucial for controlling the growth and development of skeletal muscles. Denervation leads to abnormalities in the morphology and structure of muscle cells, resulting in muscle weakness and inducing sarcopenia. Jeong et al.[33] found that transection of the right hindlimb sciatic nerve in mice resulted in atrophy of muscle fibers, as well as disorder in their morphology and structure. Resection of the sciatic nerve leads to an increase in serum angiopoietin-like protein levels and a decrease in reactive oxygen species content.[34] The levels of these two substances are related to skeletal muscle atrophy. Due to the higher surgical skill requirements for establishing denervated mouse models, researchers often choose to use rats for modeling.

The hindlimb unloading model is an animal model developed by the aerospace industry to simulate weightlessness. This method involves fixing the mouse tail to a metal disk, lifting the mouse's hindlimbs, and causing skeletal muscle atrophy after 15 days.[35] However, this model results in type I muscle atrophy. This type of muscle fiber mainly undergoes oxidative metabolism and is responsible for maintaining posture and endurance exercise. It is prone to damage when there is a long-term lack of mechanical load, which highly coincides with the characteristics of muscle loss in conditions such as weightlessness and long-term bed rest. This is inconsistent with the type II muscle atrophy caused by aging. This type of muscle fiber relies on glycolysis for energy supply and is related to explosive power and rapid contraction functions. Its atrophy is directly associated with the decline in strength in the elderly and has no impact on the recovery ability of mice.[36] Therefore, it is highly effective for studying sarcopenia induced by bed rest, microgravity, or immobilization.

Joint immobilization is a method used to simulate disuse sarcopenia caused by plaster cast fixation following fractures. Immobilizing murine legs with plaster casts restricts limb movement and induces sarcopenia. Burks et al.[37] used surgical screws to fix the leg joints of mice for 21 days and found that the muscle loss after fixation was due to the loss of muscle fibers in the skeletal muscle rather than atrophy of the muscle fibers. Joint fixation can effectively mimic the sarcopenia model of being bedridden due to illness, but its disease characteristics differ from those of age-related sarcopenia. Therefore, this model is not suitable for studying sarcopenia in the elderly.

Transgenic models: The development of sarcopenia is closely associated with oxidative stress, inflammation, and mitochondrial dysfunction. Transgenic models manipulate gene expression to affect muscle mass in mice, offering the advantage of shorter modeling duration compared to senescence-accelerated mice. This approach includes gene knockout models and gene overexpression models.

Gene knockout models involve disrupting or replacing a target gene to create a mouse model. For example, knocking out *interleukin-10* in mice leads to a shortened lifespan and accelerated aging, but this is accompanied by an inflammatory response in the small intestine.[38] Ahn et al.[39] found that the absence of superoxide dismutase 1 results in the loss of muscle mass in mice, due to metabolic imbalance caused by oxidative stress, which reduces skeletal muscle protein synthesis. In mice with double knockout of the *Optic Atrophy 1 (OPA1)* and *Dynamin-related protein 1 (DRP1)* genes, both the gastrocnemius and soleus muscles exhibit decreased mass.[40] This also leads to systemic inflammation, accelerated aging, and a shortened lifespan in these mice.[41]

Gene overexpression models involve artificially increasing the expression of a target gene in mice to induce sarcopenia. Some studies have found that excessive accumulation of inflammatory factors in the body can lead to the occurrence of sarcopenia, such as tumor necrosis *factor-α*, *interleukin-6*,[42] *C-reactive protein*, *interleukin-1β*, and others. Li et al.[43] demonstrated that TNF gene replacement in mice leads to elevated *TNF-α* levels in gastrocnemius muscles, accompanied by reduced muscle strength. Additionally, the mass of the tibialis anterior, soleus, and gastrocnemius muscles in aged mice was lower compared to young mice. Yoshida et al. Yoshida et al.[44] found that activation of the *Wnt/β-catenin* signaling pathway induces muscle atrophy, and expression of the *(pro)renin receptor [(P)RR]* can activate this pathway, thereby promoting sarcopenia in mice. Inhibition of *(P)RR* expression ameliorates age-related muscle atrophy. Researchers can select different transgenic mouse models based on their research objectives.

The four modeling methods discussed above each have their own advantages and disadvantages. Researchers should select appropriate modeling approaches based on research objectives (pathophysiology and its progression or evaluation of therapeutic effects), budget, equipment, and time requirements.

Mechanisms of sarcopenia development

Aging

Aging is a fundamental characteristic of individual life, defined as the progressive decline in biological structure and function over time, ultimately leading to organismal death.[45] With the global aging population, health issues associated with aging have become increasingly prominent. Key manifestations of aging include gradual physiological decline, such as mitochondrial dysfunction,[46] DNA damage,[47] elomere attrition,[48] lipid peroxidation,[49] and protein oxidation modification.[50] These changes not only accelerate the aging process but also serve as significant risk factors for various aging-related diseases. Aging is accompanied by various diseases, such as cancer, metabolic disorders, skeletal muscle atrophy, and cardiovascular diseases.[51] These conditions may further lead to embolism, infarction, and life-threatening complications in severe cases.[52]

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Sarcopenia, as a neurodegenerative disease, is closely related to aging.[53] With the onset of aging, muscle function and muscle mass gradually decline,[54] Studies have shown that from the age of 50, skeletal muscle mass decreases at a rate of 0.8% to 2.0% per year, and muscle strength decreases at a rate of 1.5% to 5.0% per year. The rate of decline in skeletal muscle mass and strength accelerates with increasing age.[55] Kim et al.[56] demonstrated that aging inhibits muscle protein synthesis while promoting muscle protein breakdown, disrupting the balance between the two processes and leading to skeletal muscle mass loss. Cruz-Jentoft et al.[57] reported that aging induces morphological changes in skeletal muscle fibers, characterized by a reduction in fiber number and thinning of muscle fibers. Annamaria Zaia et al.[58] proposed that aging results in intramuscular and intermuscular fat infiltration, which plays a critical role in the development and progression of sarcopenia by causing both muscle dysfunction and mass reduction.

Oxidative stress

Oxidative stress plays a critical role in the pathophysiology of sarcopenia. Under normal conditions, endogenous antioxidant activity in skeletal muscle is activated to maintain reactive oxygen species (ROS) at physiological levels. As cellular metabolites, ROS production is accelerated when pathological changes occur in the body, leading to ROS accumulation, disrupting the balance between antioxidant capacity and oxidative reactions, and ultimately causing oxidative stress. The increase in ROS in the body can damage cellular structure and function, leading to various diseases. Oxidative stress has been identified as a core mechanism in skeletal muscle aging and sarcopenia.[59] The accumulation of ROS generated by metabolic products has a significant impact on muscle.[60] In sarcopenic muscle, ROS are inefficiently cleared and accumulate within cells.[61] This has also been identified in cells exhibiting aging phenotypes.[62] The occurrence of oxidative stress in the body leads to skeletal muscle atrophy. This is because oxidative stress promotes the expression of genes related to cellular autophagy, raises the level of free calcium between cells, which activates calpain, and oxidatively modifies myofibrillar proteins, making them more sensitive to proteases. As a result, protein breakdown in skeletal muscle is accelerated, giving rise to sarcopenia.

Inflammation

Inflammation is a significant factor in the development and progression of sarcopenia,[63] promoting skeletal muscle atrophy and serving as an important characteristic of age-related sarcopenia. It can induce the onset of sarcopenia through various pathways. The excessive accumulation of inflammatory cytokines leads to skeletal muscle atrophy,[64] including tumor necrosis *factor-α, interleukin-6*,[65] *C-reactive protein, interleukin-1β*, and others.[66] Studies have shown that tumor necrosis *factor-α* inhibits the regenerative capacity of skeletal muscle by suppressing the production of *myogenin (MyoG)*.[67] The *nuclear factor kappa B (NF-κB)* pathway is also a classic inflammatory signaling pathway.[68] Research by Mukund et al.[69] has demonstrated that the target genes of *NF-κB* act on the ubiquitin ligase E3 system, thereby promoting skeletal muscle protein atrophy.

Ubiquitin-proteasome system

The ubiquitin-proteasome pathway represents the primary intracellular protein degradation machinery, exerting significant effects on muscle atrophy.[70] It is responsible for the specific degradation of most intracellular proteins and is an efficient protein degradation pathway. It plays a crucial role in skeletal muscle atrophy. The ubiquitin-proteasome pathway consists of ubiquitin and a series of enzymes involved in degrading intracellular proteins. It is mainly composed of three parts: ubiquitin, ubiquitin-related enzymes, and the proteasome.[71] Ubiquitin's role is to tag proteins for degradation by the proteasome.[72] Ubiquitin-related enzymes include E1 ubiquitin-activating enzyme, E2 ubiquitin-conjugating enzyme, E3 ubiquitin ligase, E4 ubiquitin chain extension enzyme, and deubiquitinating enzymes.[73] The ubiquitination of natively folded proteins is achieved through the first three enzymes. E3 ubiquitin ligase is a specific substrate-binding component that plays a key role in the ubiquitin-mediated protein degradation cascade. E3 ligases undergo auto-ubiquitination, making them susceptible to proteasomal degradation. In the ubiquitin-proteasome system, E3 ligases are key enzymes, including *muscle ring finger 1 (MuRF-1)* and *atrophy gene-1 (Atrogin-1)*, which have been shown to be closely related to skeletal muscle atrophy.[74]

Hormones

The anabolic level of hormones significantly declines with aging.[75] Growth hormone (GH) exerts an influence on bodily growth and metabolism.[76] As a potent anabolic agent, it promotes protein synthesis within muscle cells, thereby increasing muscle mass.[77] Studies have found that serum GH levels in women significantly decline starting from the age of 50.[78] GH and *insulin-like growth factor 1 (IGF-1)* are important growth hormones that regulate cellular homeostasis, playing crucial roles in cell differentiation, function, and survival. *IGF-1* levels change over time, reaching a peak during puberty and gradually decreasing with age.[79] *IGF-1* promotes protein synthesis by activating the *PI3K/Akt* pathway and regulates growth hormone secretion through a negative feedback mechanism.[80]

Summary and prospects

Methods for constructing mouse models of sarcopenia include drug induction, aging simulation, muscle atrophy induction, and transgenic technologies. Each model has its own advantages and disadvantages in simulating pathological features, cost, and timeliness. The occurrence of sarcopenia is driven by the interaction of multiple factors such as aging, oxidative stress, inflammation, and others. Current research needs to further optimize model standardization and deeply explore the laws of multi-mechanism synergies. In the future, more precise models can be constructed using gene editing technologies to discover novel molecular targets. Additionally, efforts should be strengthened to translate model findings into clinical treatments, providing a more solid theoretical foundation for intervention strategies for sarcopenia.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

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