Muscle satellite cells: one of the important factors in the occurrence and development of sarcopenia

Peng Zhang1*, Wen-Hui Jiang1*, Juan-Juan Gao1, Wen-Xia Yu1, Shu-Quan Lv1*

1Department of Endocrinology, Cangzhou Hospital of Integrated Traditional Chinese Medicine and Western Medicine, Cangzhou 061013, China.

*These authors contributed equally to this work and are co-first authors for this paper.

Abstract
Sarcopenia, or muscle loss, has been one of the hot topics in the medical field in recent years. Due to limited attention and effective treatments for sarcopenia in the past, many patients, especially the elderly, suffered irreversible damage to their motor function caused by sarcopenia. However, recent scientific studies have found that the occurrence and development of sarcopenia are closely related to the function and quantity of muscle satellite cells. This article briefly discusses the relationship between muscle satellite cells and sarcopenia.

Keywords: sarcopenia; muscle satellite cells; skeletal muscle cells
Introduction
Sarcopenia, an age-related degenerative disease. The older people are, the higher the incidence of sarcopenia becomes. It is a clinical syndrome characterized by decreased skeletal muscle mass and function, leading to reduced motor ability. The physiological functions of skeletal muscle include: 1. Assisting in movement, 2. Maintaining the posture and balance of the human body, and 3. Generating heat. With the increasing aging of the global population, aging has become a global challenge, and in the coming decades, every country in the world will face the significant impact of a large number of elderly people on society and the healthcare system. Sarcopenia is one of the challenges brought by aging. As aging increases, sarcopenia has gradually become one of the hot topics in modern medicine. Like osteoporosis, sarcopenia is insidious, with low awareness and even lower treatment rates. Even some healthcare workers often overlook the severe consequences of sarcopenia. Sarcopenia has a significant impact on the motor ability of middle-aged and elderly people, seriously affecting their daily lives. Some severely affected middle-aged and elderly people with sarcopenia may lose their ability to live independently. Sarcopenia increases the number of disabled elderly in society, bringing economic burdens and tremendous pressure to society. Therefore, preventing and treating sarcopenia is one of the key development directions of modern medicine in the future, and sarcopenia is also one of the challenges facing the global society in the future [1].

Skeletal muscle is the largest tissue in the human body, playing a crucial role in regulating glucose metabolism, overall body metabolism, and maintaining daily activities. The function of skeletal muscle depends on its mass, and sarcopenia refers to the reduction in skeletal muscle mass and decline in motor function. In recent years, the harm of sarcopenia has gradually attracted the attention of health departments in various countries, and it is currently one of the hot issues in global health challenges [2].

The occurrence and development of sarcopenia are caused by various pathological factors, and current studies have shown that the etiology of sarcopenia is often unclear. Some scholars believe that sarcopenia is related to the excessive activation of mitochondrial autophagy in skeletal muscle cells. Other scholars have found that sarcopenia is closely related to inflammatory factors. In addition, some scholars speculate that sarcopenia is associated with metabolic disorders of adipose tissue. However, after years of research and experimental exploration, numerous global studies have shown that the number and function of muscle satellite cells play an extremely important role in the occurrence and development of sarcopenia. The decrease in the number and abnormal function of muscle satellite cells can severely affect the number and function of skeletal muscle cells. Abnormalities in the number and function of muscle satellite cells can lead to muscle cell fibrosis, resulting in decreased muscle mass and atrophy, and premature decline in motor function [3].

Muscle satellite cells, first discovered in the mid-20th century, are located between the basal lamina of muscle fibers and the membrane of skeletal muscle cells. They play a crucial role in muscle regeneration and development. Scientist Mauro was the first to discover muscle satellite cells in frog muscle [4]. Currently, there are two hypotheses regarding the origin of muscle satellite cells: one is from somites, and the other is from endothelial cells [5, 6]. Muscle satellite cells have the ability to transform into skeletal muscle cells in specific environments. Additionally, muscle satellite cells (also known as muscle stem cells) possess powerful self-proliferation, self-renewal, and self-repair capabilities for damaged skeletal muscle cells [7, 8]. Muscle satellite cells can also differentiate into vascular endothelial cells, secrete vascular formation factors, and experiments have shown that when muscle satellite cells are transplanted onto mice, the vascular density of the experimental group significantly increases after 3 months [9]. They can also be transformed into osteoblasts and adipocytes under different stimuli [10]. The activation process and molecular regulation mechanism of muscle satellite cells have not been thoroughly studied, and their activation process and regulatory mechanism remain unclear. However, in many studies, scientists have identified multiple targets and signal transduction pathways to explain the function and mode of action of muscle satellite cells.

The molecular mechanisms of muscle satellite cells in sarcopenia
Pax7 expression gene
Multiple scientists have discovered that pax7 is one of the expression genes of muscle satellite cells [11]. In the bodies of ordinary people, muscle satellite cells are often in a dormant, inactive state, known as mitotic quiescence. When muscle satellite cells are activated and regulated, the expression of genes represented by pax7 gradually decreases. However, when skeletal muscle is injured or stimulated by external factors, the pax7 expression gene can be activated, prompting muscle satellite cells to awaken and exit their dormant state. These cells then utilize their abilities of self-renewal, self-proliferation, and self-transformation to convert and differentiate into skeletal muscle cells [12, 13]. Studies on the pax7 expression gene have shown that when pax7 is eliminated, the number of muscle satellite cells in adults significantly decreases [14]. When muscle satellite cells are in a quiescent state, pax7 is in an activated state, while Myod is in a suppressed state. In contrast, when muscle satellite cells are in a state of self-renewal and self-proliferation, pax7 is suppressed, while Myod is activated [15].

Met receptor
Met is a type of tyrosine kinase receptor that promotes the increase of cell growth factor activity. It is widely distributed in muscle satellite cells. Multiple studies have shown that if the Met receptor is deficient, muscle satellite cells will be unable to transform into muscle cells [16].

Ezh2 Protein
Multiple studies have demonstrated that the Ezh2 protein can assist in the transformation of muscle satellite cells into skeletal muscle cells, promoting their self-renewal and self-proliferation capabilities [17]. A study found that in experimental mice lacking Ezh2 protein, the number of muscle satellite cells and skeletal muscle cells decreased significantly [18].

Notch Signaling Pathway
Research has also shown that the Notch signaling pathway is a crucial component regulating the function of muscle satellite cells. As people age, the Notch signaling transduction weakens, leading to a decrease in muscle satellite cell activity. The Notch signaling pathway can disrupt muscle fibrill proteins and muscle protein [19]. The most difficult process in skeletal muscle injury is often the impairment of fibrosis development. Skeletal muscle fibers are divided into fast muscle fibers and slow muscle fibers. However, the number of muscle satellite cells in slow muscle fibers is much higher than in fast muscle fibers, and the mechanism behind this is currently unclear [20].

Wnt Signaling Pathway
The Wnt signaling pathway is involved in the transmission of information between cells and is closely related to cell growth, development, and apoptosis. It plays a crucial role in promoting cell proliferation, differentiation, transformation, and renewal, especially in the induction of muscle satellite cells to differentiate into skeletal muscle cells. Common Wnt proteins in skeletal muscle include Wnt4, Wnt5a, Wnt5b, and Wnt7a. Among them, Wnt7a in the Wnt signaling pathway can activate the Wnt7a-Frizzel-7-FCP signaling pathway during muscle satellite cell renewal, promoting the transformation of muscle satellite cells into skeletal muscle cells [21]. Scientists have found that physical exercise can accelerate the transmission efficiency of the Wnt signaling pathway and activate muscle satellite cells, increasing their number. In particular, appropriate resistance training can increase the number of muscle satellite cells, improve their function, and enhance muscle endurance [21]. The Wnt signaling pathway is regulated by p38α, an activated protein kinase that can
transmit many important mediators (such as certain inflammatory factors) in specific environments. Among them, the p38 MARK signaling pathway is crucial in muscle formation. The p38 MARK signaling pathway can inhibit the expression of the pax7 gene through phosphorylation, keeping muscle satellite cells active and promoting their differentiation into skeletal muscle cells. Additionally, the p38 MARK signaling pathway can bind to transcription factors in the nucleus of skeletal muscle cells, facilitating the conversion of DNA to RNA and then protein, thus promoting the formation of muscle protein [21].

There are still many mechanisms and pathways that are being continuously explored and discovered, and among them, the role of exercise in sarcopenia, muscle satellite cells, and skeletal muscle mass and quantity cannot be overlooked. Appropriate exercise can activate the renewal and transformation of muscle satellite cells, maintaining a relatively constant state of skeletal muscle mass and quantity. Muscle satellite cells can self-renew in a quiescent state, maintaining the number of skeletal muscle cells. When skeletal muscle is damaged or stimulated by exercise, drugs, or other conditions, muscle satellite cells become activated, transitioning from a quiescent state to a proliferative state. During this activation process, various signaling pathway protein factors within the body become active, with significant upregulation of Myod and Myf5 protein expression and Pax7 expression genes beginning to enter a quiescent state [22]. As muscle satellite cells proliferate, they gradually transform into skeletal muscle cells. The transformation process of muscle satellite cells is regulated by a series of transcription factors, with Myod protein factors playing a decisive role in the formation of skeletal muscle cells. The increase in skeletal muscle mass and the occurrence of skeletal muscle atrophy are not only dual regulatory processes but are also regulated by different transduction pathways and regulatory factors. Not all types of exercise can promote the proliferation of muscle satellite cells. Aerobic exercise and some resistance exercises can activate muscle satellite cells and promote the repair of skeletal muscle [23].

The dual impact of aerobic exercise on muscle satellite cells and skeletal muscle

Research has found that aerobic exercise is more effective in promoting the proliferation and differentiation of muscle satellite cells. Among them, moderate-intensity aerobic training can activate satellite cells. Taking cycling as an example, among the many subjects who received aerobic exercise training on bicycles, when their tissues were collected, it was found that the number of muscle satellite cells was significantly increased compared to the control group. It was also found that the volume of skeletal muscle in these subjects increased relatively, and a large number of muscle fibers were regenerated, and the cross-sectional area of muscle fibers also increased relatively [24]. In many mouse experiments, it was also found that after performing regular moderate-intensity physical exercise on the experimental mice, the number of muscle satellite cells in the experimental group increased several times compared to the control group [25]. However, short-term endurance activities can also promote the proliferation of muscle satellite cells, but they do not promote the transformation of muscle satellite cells into skeletal muscle cells. Exercise also has a double-edged sword effect on muscle satellite cells. Excessive and ultra-intensive exercise can also damage muscle satellite cells and skeletal muscle cells. Studies have shown that after several months of excessive exercise on rats, the skeletal muscle mass of the excessive exercise group was significantly lower than that of the non-exercise group, and the content of creatine kinase in the serum was also much higher than that of the non-exercise group. This indicates that excessive exercise can lead to the production of a large number of abnormal factors in the body, resulting in protein degradation in skeletal muscle and leading to a decrease in muscle mass [26]. Exercise has a two-way regulatory effect on skeletal muscle mass, so a moderate exercise program is beneficial for maintaining the quality and function of skeletal muscle. The above discussion indicates that moderate-intensity endurance physical exercise has the best effect on activating muscle satellite cells and plays an important role in the prevention and treatment of sarcopenia.

The dual impact of resistance training on muscle satellite cells and skeletal muscle

Resistance exercises include pull-ups, sit-ups, machine training, and functional training. Most scientists believe that resistance exercise is effective in preventing and treating sarcopenia and is one of the most effective methods for increasing muscle mass and improving muscle function. Numerous studies have focused on investigating the preventive and therapeutic effects of resistance exercise on sarcopenia among older adults. All of these studies have found that after a period of resistance exercise training, muscle satellite cells in the skeletal muscle of the subjects were significantly activated, renewed, and differentiated, resulting in a noticeable increase in muscle fiber volume and effectively delaying muscle fiber atrophy [27]. Similar conclusions have been drawn from experiments conducted on aged rats. Rats that underwent resistance exercise training showed activated mitochondrial function, indicating that resistance exercise can promote the self-renewal of muscle satellite cells. Observation of skeletal muscle tissue sections from these rats revealed a significant increase in the volume of type II muscle fibers, which formed in a regular and orderly manner. Compared to conventional aerobic exercise, resistance exercise is more effective in activating the renewal and transformation functions of muscle satellite cells [28]. Exercise training can improve the function of muscle satellite cells, activate their proliferation and transformation, and delay the onset and progression of skeletal muscle atrophy. Resistance exercise has been found to be more effective than aerobic exercise in activating muscle satellite cell renewal. However, further research is needed to determine the most appropriate type, duration, and frequency of exercise for different age groups.

Prospects

There is a close relationship between sarcopenia and muscle satellite cells. However, so far, modern medicine has discovered several signal transduction pathways. Various methods have been explored to restore the ability of muscle satellite cells by inhibiting or activating these signal transduction pathways, thereby treating sarcopenia. Through mechanisms involving the pax7 gene, Met receptor, Ezh2 protein, notch signaling pathway, Wnt signaling pathway, and more, researchers are exploring how to better promote the activation and proliferation of muscle satellite cells. The signal pathways for muscle satellite cell activation are numerous and complex, requiring further investigation and validation. Multiple studies have found that exercise is an important way to improve muscle satellite cell function. Both aerobic and resistance exercises can prevent and treat sarcopenia. The effective utilization of these mechanisms in treating sarcopenia still needs time to be verified.

References


Submit a manuscript: https://www.tmrjournals.com/lr


Submit a manuscript: https://www.tmrjournals.com/lr