

Research Progress on Epigenetic Mechanism of Sarcopenia

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Abstract

In recent years, sarcopenia, as a progressive muscular atrophy and weakness, has become one of the common diseases in the elderly. Although its cause is not fully understood, a growing body of research suggests that epigenetic mechanisms play an important role in the pathogenesis of sarcopenia. The purpose of this review is to summarize the current research progress in the epigenetics of sarcopenia, focusing on the role of DNA methylation, RNA methylation and non-coding RNA in the pathogenesis of sarcopenia. While exploring the epigenetic mechanism of sarcopenia, this study will also look into the application prospect of epigenetics in the treatment strategy of sarcopenia, which will provide new ideas and directions for the treatment of sarcopenia.

Keywords

Sarcopenia, Epigenetics, DNA Methylation, RNA Methylation, Noncoding RNA

1. Introduction

Sarcopenia is a progressive geriatric syndrome [1]. In addition to age-related sarcopenia, a large number of studies have been conducted on the etiology and pathogenesis of sarcopenia. Smith *et al.* showed [2] The occurrence of sarcopenia is related to factors such as age, nutritional status, physical activity, polypharmacy, chronic inflammation, hormone levels, acute and chronic diseases (such as diabetes, chronic obstructive pulmonary disease, liver cirrhosis, tumor) and geriatric syndromes (such as depression, frailty, cognitive impairment) [3]. Sarcopenia is usually characterized by muscle atrophy, but there are some differences in clinical manifestations, mainly related to the patient's age, gender, muscle type, etiology and other factors. In addition to muscle atrophy, other

signs and symptoms include loss of activity, flexibility and strength of skeletal muscles, mainly manifested as loss of muscle mass, muscle strength and muscle dysfunction. Sarcopenia is a complex multifactorial phenomenon, including both intrinsic factors (endocrine factors, motor neuron loss, mitochondrial dysfunction) and extrinsic factors (nutrition, exercise). However, the precise underlying molecular mechanisms of sarcopenia have not been fully verified. According to data, the current number of sarcopenia patients in the world is about 50 million. This number is expected to grow to 500 million by 2050. In China, the prevalence of sarcopenia in the elderly aged 80 years and above is about 67.1% [4]. This data shows that sarcopenia has become a global health problem that needs our sufficient attention. In recent years, more and more studies on the epigenetic mechanism of sarcopenia have been conducted, which indicates that epigenetics plays an important role in the pathogenesis of sarcopenia.

2. Overview of Sarcopenia

2.1. The Health Effects of Sarcopenia

The health effects of sarcopenia are mainly reflected in decreased quality of life, physical frailty, and increased risk of falls, fractures, hospitalizations, and death. For many elderly patients with sarcopenia, the loss of skeletal muscle and muscle mass, muscle strength, and muscle function can severely affect their exercise capacity and self-care ability, which puts them at higher risk [5]. Patients with sarcopenia often experience difficulty in movement and decreased strength in daily life, especially during muscle activities and sports, muscle weakness and fatigue are more obvious. These symptoms not only affect the physical function and physical activity ability of patients, but also may lead to mobility difficulties, falls and other accidents, which bring certain threats to the physical and mental health of patients. Benjumea *et al.* [6] conducted a cross-sectional study of 534 participants (mean age, 74; 75% women) in a fall and fracture rehabilitation clinic. A comprehensive assessment of bone mass, muscle strength, and gait speed index was performed using the European Working Group on Sarcopenia in Older Adults. The results showed that 71.2 percent of the subjects were diagnosed with sarcopenia. The study further confirmed a significant association between sarcopenia and the risk of disability in motor ability, activities of daily living (ADL), and instrumental activities of daily living (IADL) after strictly controlling for all other potentially contributing factors. The health effects of sarcopenia are also reflected in the respiratory system, with patients often experiencing difficulty breathing and shortness of breath. Shortness of breath and shortness of breath are more obvious in patients with sarcopenia, especially during strenuous exercise or prolonged activities. In addition, sarcopenia can also affect the functions of the digestive and metabolic systems, and patients are prone to symptoms such as loss of appetite, weight loss, and dyspepsia. Weakened muscle strength not only affects the ability to ingest food on a daily basis but also leads to digestive system dysfunction, affecting the digestion and ab-

sorption of food. At the same time, the physical energy consumption of patients with sarcopenia increases accordingly, which makes them prone to weight loss and metabolic disorders due to low metabolic levels.

2.2. Genetic and Environmental Factors of Sarcopenia

There is evidence that sarcopenia may be influenced by genetic factors. Researchers have found a link between changes in the level of genetic molecules, such as growth differentiation factors, angiotensin-converting enzymes, apolipoproteins and aquaporins, and muscle aging. A study of aging-related actin expression in mouse skeletal muscle points out that growth differentiation factor 15 may be an actin produced by aging stress, and this protein has the ability to regulate the aging phenotype [7]. In addition, the expression of ACE2 in skeletal muscle was found to be decreased in exercise-induced tissues in exercise-trained wild-type mice, which may indicate a relationship between ACE2 and muscle exercise [8]. These findings provide a new perspective and potential therapeutic targets for further study of the pathogenesis of sarcopenia. In the study of genes involved in the neuromuscular junction, the researchers found that the expression levels of molecules such as apolipoprotein E, synthetic protein a1 and aquaporin 4 were significantly reduced in the muscles of the elderly [9]. This finding suggests that there may be a link between changes in the expression of these genes and sarcopenia. These gene abnormalities can lead to muscle cell damage and atrophy, which can cause sarcopenia. Therefore, genetics plays an important role in the pathogenesis of sarcopenia. In addition to genetic factors, environmental factors also play an important role in the pathogenesis of sarcopenia. Studies have found that environmental factors such as malnutrition, chronic inflammation, and lack of exercise are closely related to the occurrence and development of sarcopenia. For a long time, the research on sarcopenia has mainly focused on genetic factors, while the research on environmental factors is relatively rare. However, recent studies have shown that environmental factors play a non-negligible role in the pathogenesis of sarcopenia, which also provides new ideas and directions for the prevention and treatment of sarcopenia.

3. Overview of Epigenetics

3.1. Definition of Epigenetics

Epigenetics refers to changes in the expression level and function of genes that maintain the same DNA sequence, resulting in the emergence of heritable phenotypic characteristics. This change is not achieved by modifying the DNA sequence itself but through mechanisms such as DNA methylation, histone modification and chromatin remodeling. Together, these mechanisms can have profound effects on gene expression and function, which in turn affect the phenotype and identity [10]. It plays an important role in cell function and development by maintaining the stability of the genome and regulating the transcription and translation process of genes. At present, the research in the field of epigenetics

mainly focuses on DNA methylation, histone modification and non-coding RNA, which regulate gene expression and function through different ways. DNA methylation and histone modification are important mechanisms for regulating gene transcription, which affects gene expression by changing the structure of chromatin. At the same time, changes in the expression of non-coding RNA also affect the ability of mRNA to be translated into protein, which further affects DNA methylation, histone modification and non-coding RNA formation. These processes are interrelated and interact with each other to form a complex regulatory network, which eventually leads to the change of the phenotype of the organism [11]. Any abnormality in this network can have profound effects on gene expression and organism traits. Understanding the interrelationships among these mechanisms and their effects on the whole biological system is of great significance for further studying the development of organisms and the pathogenesis of diseases.

3.2. DNA Methylation

DNA methylation is an epigenetic regulatory mechanism that does not involve DNA sequence changes. It causes heritable changes in gene expression and function by affecting chromatin structure, DNA conformation, and the interaction between DNA and proteins, which further affects the related genetic performance. DNA methylation, as one of the most intensively studied epigenetic regulatory mechanisms, involves the process of covalent bonding of the cytosine fifth carbon site of CpG dinucleotides in the genome to obtain methyl groups through the catalysis of specific DNA methyltransferases [12] [13]. This methylation modification process plays a crucial role in regulating gene expression, maintaining the stability of chromosome structure, and participating in X chromosome inactivation and other biological processes. This modification is relatively stable and can be passed on to future generations with DNA replication [14]. The stimulation of the external environment can trigger DNA methylation modification, which in turn regulates gene expression. In human genes, the promoter regions mostly exist in the peripheral regions rich in dinucleotide “CG”, which are called “CPG islands”. CPG islands play a key role in the composition of chromatin structure and the regulation of gene expression. DNA methylation mainly occurs in the promoter region of CPG islands [15] [16]. Basic research and experiments have shown that abnormal DNA methylation is closely related to the occurrence of a variety of diseases, especially the DNA methylation of CPG island promoter region [17]. This methylation regulates gene expression by affecting DNA stability and different chromatin configurations. At present, the study of the impact of DNA methylation on different diseases has become a research hotspot in the field of global life science, and it is considered to be an important direction of research in the post-gene era.

3.3. RNA Methylation

RNA methylation is a process in which methyl groups replace nitrogen and

oxygen atoms in RNA molecules at the post-transcriptional stage by methyl groups using S-adenosylmethionine as a methyl donor catalyzed by methyltransferase [18]. N6-methyladenosine (m6A) modification is an important and conserved post-transcriptional modification that widely exists in bacterial and eukaryotic mrnas. Specifically, this modification occurs at the sixth nitrogen atom of the adenylate in the RNA molecule and is modified by methylation. As a key regulatory mechanism, m6A modification plays an indispensable role in a variety of biological processes. The enzymes involved in m6A methylation modification mainly include methyltransferases, demethylases, and methylation-recognition enzymes. These enzymes directly participate in the modification process of m6A and regulate the epigenetic transcriptome of m6A, thereby affecting the stability and translation efficiency of mRNA in cells. Moreover, they themselves have unique biological activities and can directly or indirectly participate in the regulation of a variety of biological processes. For example, m6A-related enzymes play important roles in immune response, ribosome function, osteogenic and adipogenic differentiation of bone marrow mesenchymal stem cells, and play specific functions in tumorigenesis, hematopoiesis, virus replication, immune response, adipogenesis, and bone metabolism [19]. In recent years, researchers have discovered an m6A demethylase, fat mass and obesity-associated (FTO) protein, which is closely related to human obesity. This discovery brings a new perspective and definition to our understanding of m6A modification, and confirms that m6A modification is a dynamic and reversible process, which is of great significance for regulating the occurrence and development of diseases. Therefore, in-depth study of the mechanism of m6A modification and its related enzymes is expected to provide new ideas and strategies for the prevention and treatment of diseases [20].

3.4. Non-Coding RNA

3.4.1. Track lncRNA

lncRNA, also known as long non-coding RNA, is more than 200 nucleotides in length and does not participate in protein synthesis. In the early stage of genetic research, lncrnas did not become a major research focus due to their lack of ability to directly encode proteins. However, with the deepening of biological research, the regulatory role of lncRNA at the gene level has gradually emerged and occupied a central position in cell biology. Although lncrnas may far outnumber protein-coding transcripts, only a few of them have been confirmed to be involved in the regulation of gene expression. These regulatory effects involve multiple levels, including epigenetic, transcriptional, post-transcriptional and translational regulation. At the epigenetic level, lncrnas can mediate chromatin remodeling and modification, thereby affecting gene expression. In addition, lncrnas can also interact with transcription factors to affect the regulation of transcription. In addition, lncrnas can bind to mRNAs to form double strands, and then specifically regulate various post-transcriptional processes of mRNAs, including splicing, transport, translation, and lncRNA plays an important role in

the regulation of gene expression, involving multiple levels and complex mechanisms [21]. With further research, we are expected to have a more comprehensive understanding of the biological functions and potential applications of lncRNAs.

3.4.2. miRNA

MicroRNAs (miRNAs) are a class of short non-coding RNA molecules, usually composed of 20 - 30 nucleotides. They regulate gene expression at the post-transcriptional level by binding to specific target sites within messenger RNA (mRNA). This binding can lead to the degradation or translational repression of mRNA, thereby achieving the fine regulation of gene expression. The miRNA regulatory system is unique in its complexity and flexibility. A single miRNA may simultaneously regulate hundreds of different target genes, while the same mRNA may also be coregulated by multiple miRNAs [22]. This intricate regulatory network makes miRNAs play crucial roles in biological processes, especially in skeletal muscle homeostasis, development, regeneration and atrophy, where miRNAs play an indispensable role. Studies have shown that the miRNA expression profile is significantly changed in patients with muscle atrophy, and a variety of specific miRNAs have been identified that are closely related to muscle atrophy. In summary, miRNAs are not only expected to be novel diagnostic markers for muscular dystrophy and other diseases, but also provide potential targets for the development of new therapeutic strategies. Through in-depth study of the regulatory mechanism and function of miRNA, we are expected to provide new ideas and methods for the treatment and prevention of muscular dystrophy and other diseases.

4. Epigenetic Mechanisms of Sarcopenia

4.1. DNA Methylation and Sarcopenia

DNA methylation, often described as a “silent” epigenetic mark [23], plays a key role in multiple biological processes, including gene silencing, chromatin modification, and embryonic development [24]. This process is catalyzed by DNA methyltransferases (DNMT), which bind cytosine nucleotides to S-adenosylmethionine (SAM) to modify cytosine residues on CpG islands. The research of DNMT has been one of the hot spots in the field of gene methylation. DNMT3A regulates the differentiation of osteoclasts by interacting with SAM-mediated metabolic pathways. This finding provides new ideas for the prevention and treatment of various bone diseases. Li *et al.* [25] found that the hypermethylation status of miRNA-149 could activate the SDF-1/CXCR4 signaling pathway, which in turn promoted osteogenic differentiation of MSCs. DNMT inhibitor 5-aza-CdR reversed this process and promoted the binding of miR-149 to SDF-1, thereby inhibiting osteogenesis. These findings further reveal the important role of DNA methylation in bone development and differentiation. Ebrahimi *et al.* [26] found 28,549 CpG sites that were similar to methylation in bone and blood when studying the cross-tissue association between bone and blood on the epigenome.

Among them, 33% - 49% of the sites were associated with bone phenotypes from GWAS. This finding not only enriches the main pathways related to bone regulation, but also suggests that blood may be an effective tool to capture methylation sites related to bone regulation. In the future study of DNA methylation, the detection of related biomarkers in peripheral blood may be used as a supplementary or preliminary determination method.

4.2. RNA Methylation and Sarcopenia

Regarding the relationship between m6A modification and sarcopenia, current studies mainly focus on muscle stem cell differentiation. Kudou *et al.* [27] found that muscle stem cells require MyoD regulators to maintain differentiation potential and that m6A modifications encoding MyoD are enriched in the 5'utr. The m6A methylase METTL3 can stabilize MyoD regulators by promoting myogenic differentiation mRNA processing in proliferating cells. Knockdown of METTL3 significantly down-regulated the expression of MyoD mRNA in adult myoblasts. Knockdown of METTL3 in mouse C2C12 cells and muscle stem cells reduces the level of m6A modification and leads to premature differentiation of adult myoblasts, suggesting that METTL3 plays an important role in m6A regulation [28]. METTL3 can enhance protein expression by increasing m6A modification through the Notch signaling pathway, and improve the translation efficiency of mRNA through YTHDF1 reading protein. This suggests that METTL3 is essential for regulating muscle stem cells and promoting muscle recovery after injury [29]. Similarly, FTO demethylase was also found to be involved in the regulation of muscle stem cells. Increased expression of FTO has been observed during muscle cell differentiation and regulates mTOR-PGC-1 α -mediated intra-mitochondrial synthesis (affecting muscle cell differentiation) through its own demethylase activity [30]. In addition, AMPK (AMP-activated protein kinase) expression is a key regulator of lipid metabolism and m6A modification in skeletal muscle. These proteins are negatively correlated with lipid accumulation in skeletal muscle. Lipid accumulation can be reduced by inhibiting the demethylase activity of FTO and increasing the level of m6A modification [31]. In summary, although the current evidence does not directly verify the relationship between m6A modification and sarcopenia, the ability of m6A to regulate muscle stem cell differentiation will provide us with a future direction.

4.3. Non-Coding RNAs and Sarcopenia

4.3.1. Lncrnas and Sarcopenia

Long non-coding RNAs (lncrnas) play an important regulatory role in the process of muscle differentiation. They are not only involved in muscle formation and differentiation, but also closely related to the occurrence and development of muscular atrophy [32]. Jin *et al.* [33] found a conserved lncRNA named lncRNA-SYISL, which plays a key role in the regulation of sarcopenia. By binding to miRNA, lncRNA-SYISL can enhance the expression of muscle atrophy related genes MuRF1, Atrogin-1 and FoxO3a, thereby accelerating the process of muscle

atrophy. However, when lncRNA-SYISL was knocked down or knocked out, the sarcopenia symptoms were observed to be alleviated in aging mice. This suggests that lncRNA-SYISL may be a potential target for the treatment of sarcopenia. In addition, Cai *et al.* [34] These findings further reveal the regulatory mechanism of lncRNA in the process of muscular atrophy. However, not all lncRNAs promote muscle atrophy. Li *et al.* [35] found that lncRNA-MAAT can act as a regulator of muscle atrophy by regulating the expression of downstream and neighboring genes through cis- and trans-acting, thereby alleviating aging-induced muscle atrophy. This suggests that lncRNA-MAAT may have a role in inhibiting muscle atrophy. In addition, it was also found that lncRNA-IRS1 could down-regulate the expression of key Atrogin-1 and MuRF3 by activating the IGF1-PI3K/AKT pathway. This suggests that lncRNA-IRS1 may also serve as a therapeutic target for muscle atrophy [36]. As more and more lncRNAs are identified to be closely related to muscle atrophy, our understanding of skeletal muscle biology and the pathogenesis of sarcopenia will continue to deepen. These findings will provide new ideas and potential targets for future therapeutic strategies against sarcopenia.

4.3.2. Mirnas and Sarcopenia

Studies have shown that the expression pattern of miRNAs in skeletal muscle changes with age. The proteins regulated by these miRNAs are involved in several key biological processes, including muscle protein synthesis and breakdown, mitochondrial biosynthesis, and satellite cell differentiation. With aging, the ability of old muscle to synthesize new proteins in response to anabolic stimuli decreases. Analysis of miRNA expression in skeletal muscle after acute resistance exercise revealed that the Akt-mTOR signaling pathway, which is closely related to protein synthesis, is targeted by specific miRNAs. Changes in mitochondrial dynamics play a key role in the deterioration of skeletal muscle function. Quantitative proteomics data show that mitochondrial protein content gradually decreases with aging, while the expression of mitophagy-related proteins is up-regulated. In-depth study of the upstream regulators of mitochondrial dynamics revealed that miR-181a can precisely regulate the key genes related to autophagy and mitochondrial dynamics. Animal experiments further confirmed that restoring miR-181a in aged mice can effectively prevent the accumulation of p62, PARK2 and DJ-1 proteins, maintain mitochondrial content, and thereby increase muscle fiber size and muscle strength [37]. In addition, the reduction of satellite cell number is also one of the important causes of sarcopenia. Studies have found that the expression of miR-24 in muscle is closely related to age, and it maintains the activity and function of satellite cells by regulating reactive oxygen species (ROS) -related pathways, thereby promoting the regeneration of skeletal muscle [38]. In summary, mirnas play a pivotal role in the regulation of skeletal muscle function and the development of sarcopenia by precisely regulating proteins involved in protein synthesis and breakdown, mitochondrial biosynthesis, and satellite cell differentiation. This provides an important scien-

tific basis for further understanding the biological characteristics of skeletal muscle and the development of effective therapeutic strategies for sarcopenia.

5. Summary and Prospect

In summary, the epigenetic mechanisms of sarcopenia represent a challenging but also promising area of research. We look forward to more research results that will provide deeper insights into the understanding of this disease, as well as theoretical basis and practical guidance for the development of new therapeutic strategies. In the future, we look forward to a deeper understanding of the epigenetic mechanisms of sarcopenia. Firstly, comprehensive methylation, RNA methylation and non-coding RNA profiling of more genes is needed to discover more epigenetic marks associated with sarcopenia. Second, we need to investigate how these epigenetic marks affect muscle growth and repair processes, and the way they interact with other biomolecules such as proteins, mRNAs, etc. Finally, we expect to be able to use these findings to develop new therapeutic strategies by regulating how these epigenetic marks affect muscle growth and repair processes and how they interact with other biomolecules (e.g., proteins, mRNAs, etc.). Finally, we hope to use these findings to develop novel therapeutic strategies to modulate these epigenetic marks to improve muscle function and alleviate the symptoms of muscle atrophy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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