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The Role of Epigenetic Mechanisms in Skeletal Muscle Aging

Abstract

The article examines the role of epigenetic mechanisms – specifically DNA methylation, histone modifications and miRNAs – in the aging process of skeletal muscle and analyzes the potential of physical activity to interfere with these mechanisms. Studies conducted in different age groups show that regular physical exercise enhances muscle regeneration by regulating gene expression through epigenetic pathways and prevents degenerative changes associated with aging. Analyses conducted at the molecular level have proven that physical activity restores muscle proteosynthesis and structural stability by stimulating demethylation at CpG sites. At the same time, the changes observed in the expression of miRNAs are of great importance for muscle regeneration and metabolic stability. It has been studied that physical activity can regulate a large part of these changes. In conclusion, the article highlights the proposal of targeting epigenetic modifications through physical activity as an effective and non-pharmacological strategy against the biological processes of aging.

Keywords: *skeletal muscle aging, epigenetic mechanisms, DNA methylation, miRNA, muscle regeneration*

Introduction

Skeletal muscle aging, a reality of the modern era, is being studied as one of the main aspects of biological aging and not only genetic factors, but also epigenetic regulatory mechanisms play an important role in this process. As the aging process causes functional impairment of a number of systems in human physiology, skeletal muscle mass and strength decrease, which is known as sarcopenia. Sarcopenia is the age-related loss of muscle mass that can seriously reduce the mobility, quality of life and independence of individuals. Recent studies have shown that these changes can be explained not only by genetic factors, but also by epigenetic mechanisms – that is, the influence of the environment and lifestyle on gene expression. Epigenetic modifications – methylation, histone modifications and the activity of microRNAs – are among the main mechanisms that regulate cell function. These changes play an important role in the aging process by affecting the regenerative capacity of muscle cells, energy metabolism and stress response mechanisms. Interestingly, these mechanisms are dynamic and certain lifestyle changes, especially physical activity can improve the functional state of skeletal muscle by affecting the epigenetic state. Regular exercise, especially strength training can change gene expression in muscle cells and prevent age-related atrophy. In addition, physical activity can also lead to a decrease in inflammatory processes in muscles, improved mitochondrial function and increased cell proliferation. Recent studies suggest that epigenetic modifications are one of the main reasons behind these changes (Zykovich et al., 2014).

Research

DNA methylation is a key epigenetic mechanism involved in the regulation of gene expression. As a result of genome-wide analyses by Zykovich et al. (2014), it was determined that age-related changes in methylation levels occur in skeletal muscle and these changes negatively affect the energy balance and regeneration capacity of the cell. **Histone modifications and miRNAs** also

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play an important role in muscle aging. Sharples (2016) showed that muscle-specific microRNAs such as miR-1 and miR-206 regulate muscle differentiation and their expression changes with age. At the same time, histone acetylation and deacetylation can affect gene transcription, reducing or increasing the proliferative capacity of muscle cells. **Studies on the epigenetic effects** of physical activity have shown that strength and endurance training have the ability to alter the "epigenetic memory" of muscles. A study by Seaborne (2018) noted that muscles can be epigenetically programmed in response to past exercise and this memory is involved in future adaptations. Other studies have shown that exercise activates intracellular signaling pathways – s pecifically PGC-1α, AMPK, and mTOR signaling – which increases gene expression and supports muscle homeostasis (McGee & Hargreaves, 2020). These changes are observed in the maintenance of mitochondrial biogenesis, anti-inflammatory status, and protein balance in muscle. Most researchers also note that the effects of physical activity may vary depending on individual factors such as gender, age, and genetic background.

Table 1.
Results from the conducted studies.

Epigenetic Factors	Effect of Physical Activity Related	Genes and Signaling	Pathways Source
DNA methylation	Decreases or normalizes	PGC-1α, MyoD	Zykovich et al., 2014
Histone acetylation	Increases (activates gene expression)	SIRT1, HDAC, MEF2C	McGee & Hargreaves, 2020
miRNAs (miR-1, miR-206)	Expression level is regulated	Myf5, Pax7	Sharples et al., 2016

Essentially, epigenetic mechanisms are the fundamental molecular processes that regulate gene expression without altering the genetic code. The most important epigenetic mechanisms in skeletal muscle aging can be divided into three groups: DNA methylation, histone modifications and expression of microRNAs (miRNAs). DNA methylation is a mechanism that regulates gene transcription by adding methyl groups (CH_3) to cytosine nucleotides. Skeletal muscle is characterized by increased methylation levels associated with aging, which impairs the cells' ability to produce energy, synthesize proteins, and regenerate (Zykovich et al., 2014). These changes, which reduce the transcriptional potential of muscle cells, play an important role in the development of sarcopenia. Histones are proteins involved in the structuring of genetic material (DNA). As a result of their chemical modifications, such as acetylation, methylation, and phosphorylation, the chromatin structure changes, which in turn affects gene expression. During aging, muscle cells experience a decrease in histone acetylation, which leads to the silencing of genes involved in muscle regeneration (Sharples et al., 2016). And, due to the increased activity of histone deacetylase enzymes, a weakening of the ability to proliferate is observed. miRNAs are small non-coding molecules that regulate the stability or degradation of mRNAs. The expression of muscle-specific miRNAs, in particular miR-1, miR-133 and miR-206, decreases with age (Sharples et al., 2016). These miRNAs regulate the activity of genes involved in muscle regeneration, differentiation and cell cycle. Changes in their expression levels can lead to a decrease in muscle mass and impaired regeneration capacity. Interplay of epigenetic mechanisms. These mechanisms interact with each other. For example, miRNAs can target both DNA methyltransferase (DNMT) enzymes and histone modification enzymes. At the same time, histone modifications can also regulate the methylation process at specific gene regions. This interaction creates a complex epigenetic regulatory network, which explains the multifactorial nature of aging-related muscle changes (Seaborne et al., 2018). Skeletal muscles play a key role in maintaining the movement and metabolic homeostasis of the human body. However, with aging, these muscles experience loss of strength, atrophy and reduced regeneration capacity.

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Table 2.
Effects of Physical Activity on Muscle Function through Epigenetic Pathways.

Graph/Scheme	Descriptive	Benefit
"Effect of Physical Activity on Muscle Function via Epigenetic Pathways"	Physical activity → DNA demethylation → miRNA expression changes → Muscle regeneration	Visual explanation of the process
"Age-related CpG site changes"	Changes in CpG count in young and old (bar graph)	Comparison based on statistical analysis
"Epigenetic Memory" model	Effect of prior exercise on gene expression	Explanation of the concept of epigenetic memory

Although these changes have traditionally been explained by hormones, oxidative stress, and disruptions in protein synthesis, in recent years the role of epigenetic mechanisms in these processes has come into greater focus. Thus, epigenetic modifications – particularly DNA methylation, histone modifications and miRNAs – influence the functional state of muscle tissues by altering gene expression.

Conclusion

A number of real-world studies have been conducted to show how epigenetic changes in skeletal muscle change in response to physical activity. In an analysis of individuals aged 54–77 years by Zykovich (2014), it was shown that 5962 CpG sites were differentially methylated in muscle tissue of older individuals compared to young individuals. Most of these changes were located in regions that regulate transcription, indicating the epigenetic influence of aging on gene expression. Another study by Seaborne et al. (2018) involved 8 young men undergoing a 7-week strength training program, followed by a 7-week rest period and a retraining phase.

Table 3.
Epigenetic changes in response to activity (Seaborne et al., 2018).

Research phase	CpG demethylation count	Key observation
Exercise 1 (7 weeks)	17,365	Increase in gene expression
Passivity (7 weeks)	Decrease in demethylation	Decrease in gene expression
Exercise 2 (7 weeks)	27,155	Strong response with epigenetic memory

As a result, demethylation of 17,365 CpG sites was observed in muscle cells after exercise and it was shown that these epigenetic changes were partially restored during the period of inactivity, but that the subsequent exercise resulted in stronger gene expression than the previous exercise. These observations suggest that muscles have an “epigenetic memory” and that previous exercise experiences have a long-term effect on gene expression. Sharples et al. (2016) compared miRNA expression in muscle biopsies from elderly (60–75 years) and young (20–30 years) individuals and confirmed that muscle-specific miRNAs such as miR-1, miR-133a, and miR-206 decreased with age. These differences were partially reversed by a vigorous exercise program. These results suggest that physical activity does not only induce short-term physiological changes, but also optimizes muscle function through long-term epigenetic programming. Thus, epigenetic changes associated with skeletal muscle aging can be regulated to some extent and physical activity is one of the key factors that positively influences this process.

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