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Skeletal Muscle Memory and Its Implications

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Abstract. Skeletal muscle memory can be defined as the ability of skeletal muscle to respond differently to stimuli encountered before. However, the forming mechanism of skeletal muscle memory is not concrete. It has been proposed that myonuclear increase and epigenetic modification are the leading causes of skeletal muscle memory. This article will briefly review the literature on the development and supporting evidence of the two theories. Meanwhile, the implications of skeletal muscle memory in sarcopenia and anti-aging treatment will be discussed. The review concludes that existing studies have shown many unknown issues and inconsistencies, which may indicate future research directions.

Keywords: Skeletal muscle, muscle memory, myonuclei, epigenetics, aging

1. Introduction

“Muscle memory” is commonly used in daily life to refer to the ability to remember specific movements and exercise them unconsciously. For example, people say riding bicycles is a type of muscle memory. Studies have found another type of muscle memory, which is related to the ability of skeletal muscle to respond differently to the stimuli if it is encountered before [1,2]. For example, fitness enthusiasts may find out that their strength can be quickly restored even after a period of training suspension because their previous training is memorized by their muscles. Though the two types of muscle memory share some similarities by both emphasizing the ability to exist for a long time and can be reawakened easily, it has to be clear that the two phenomena are regulated by distinct biological systems. Riding a bicycle is more like neurological motor learning, while muscle strength restoration is related to complicated changes to muscle cells. To be more precise, some researchers suggest using the term "skeletal muscle memory" to describe the muscle's restoration ability [2,3].

The forming mechanism of skeletal muscle memory, however, is not intuitive, and there are still arguments for the exact reasons. Inspection of similar activities in the human body may provide inspiration for understanding skeletal muscle memory. For example, it is already known that the memory in the immune system, where the second encounter with the same pathogen triggers a more rapid and intense immune response, is caused by irreversible changes in the genes of lymphocytes and inheritable methylation of DNA [4]. Therefore, it is reasonable to hypothesize that permeabilized epigenetic and cellular changes may also cause skeletal muscle memory.

This article will summarize the hypotheses of the forming mechanisms of skeletal muscle memory by reviewing the studies on muscle memory and its related applications. The implications

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of the research on forming mechanisms will also be discussed at the end of the review. It is expected that the understanding of skeletal muscle memory may inspire new ideas in anti-aging therapies and many other fields. In addition, the limitations of current studies and future perspectives will be discussed in the article. This review may help researchers to have a clear big picture and find promising research directions.

2. Myonuclear theory

Human skeletal muscle cells have multiple nuclei, each nuclear controlling a cytoplasm domain, known as the myonuclear domain [5,6]. In a skeletal muscle memory process, skeletal muscles grow in mass and strength after resistance training, which is called hypertrophy and has been discovered and proven by experiments [6,7]. During the second training, muscle size is expected to be restored more rapidly. Therefore, understanding the reason for muscle growth in response to the environment is the key to understanding skeletal muscle memory. Nevertheless, the reason for hypertrophy was not clearly illustrated. If the muscle strength and size were to change in response to training, the myonuclear domain, or the number of myonuclei, would have to increase. It was once believed that the size of the myonuclear domain is constant due to the limited DNA content of nuclear and other reasons [8,9]. This idea could lead to speculation that the change in muscle size is caused by the increase in nuclei.

2.1 Experimental evidence of myonuclear increase

Past studies started with researching the adaptive growth of muscle. In Rutherford and Jones' study, the human participants were asked to do weight-lift training, and the weight-lifting during the test was recorded to increase as the experiment continued. The researchers attributed this to a better coordination of all muscles involved in the weight-lifting movement [10]. Since the research was not conducted on the level of a single muscle group, the study proved muscle growth but was not that helpful in understanding the mechanism of muscle growth. Recent studies have shown additional evidence by examining a single muscle group after the removal of its synergist muscles. In addition to recording the changes in muscle size, Bruusgaard et al. observed the increase of muscle nuclei in the extensor digitorum longus of mice happening before the hypertrophy. After 14 days of overloading, the number of myonuclei increased by 37%, which is 3 days earlier than the increase in cross-sectional area. Importantly, the number of myonuclei did not significantly decrease during the following 14 days of denervation, which suggests that the myonucleus may be the main carrying entity of skeletal muscle memory [11]. The results were also supported by similar studies, where muscle overloading is caused by steroids instead of resistance training [12]. Not only is the myonucleus increase related to hypertrophy, but the cause-and-effect relation between myonucleus increase and hypertrophy was also proved in other studies by inhibiting myonuclear accumulation and the following decreased hypertrophy [13-15]. These studies suggest that the increase in myonuclei during the loading process and the maintenance of nuclei can partly explain skeletal muscle memory. Meanwhile, they also prove that the nuclear domain is not a constant in cells. During the denervation period in the experiment of Bruusgaard et al., the myonuclei acquired before did not degenerate, while the muscle size decreased. This proved the idea of a consistent myonuclear domain wrong. Instead, the myonuclear domain is variable within a specific limit, where a nuclear has control over the cytoplasm.

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2.2 The role of satellite cells and the Notch pathway

Satellite cells, which are skeletal muscle stem cells resting between the basal lamina and the plasma membrane, are believed to be responsible for the increase in myonuclei [16,17]. Under specific conditions, such as muscle injury, the satellite cells will be activated and self-renew, and the new cells then fuse with injured muscle fibers to repair them. The repairing process may be under the regulation of the Notch pathway, which was first discussed as a mutation-related gene in Drosophila melanogaster [18]. Previously, the Notch pathway has been found to be responsible for many developmental events, such as the development of hematopoietic and lymphoid systems [19,20]. It has been found that the Notch pathway also plays an important role in satellite cell quiescence and proliferation. Note that the fusion of satellite cells and muscle cells is a key process in myonuclear increase. Experiments have shown that the blocked Notch pathway leads to defective muscle regeneration ability and dystrophy [21-23]. By the same principle, the reactivation of the Notch pathway in the Duchenne muscular dystrophy model mouse and aged mouse restores the ability of satellite cells to self-renew [22,24]. Therefore, it is hoped that activating the Notch pathway may be a new approach to treating muscle aging and sarcopenia because of its ability to rehabilitate myonuclei and strengthen muscle mass.

2.3 Controversy and research limitations

However, there are still arguments around the myonuclear theory. Murach et al. doubted the maintenance of myonuclei during detraining [25]. They analyzed the experimental results from the study of Psilander et al., where the increase in myonuclei was not observed during the second training, and muscle strength was also not restored [26]. As the article indicates, the discrepancy with myonuclear theory cannot fundamentally challenge the myonuclear hypothesis because the myonuclear number did not increase significantly at the first training. The result may be affected by heterogeneity between individuals, and it leads to another point worth noticing: The study of Psilander et al. was done on human participants, while the myonuclear theory, though first observed in humans, is explored and studied in animals to a great extent. The discrepancy in this study alerts us that the difference between animal models and humans is undeniable. Anyhow, more studies on humans are expected to get consistent results. How long the increased myonuclei can be kept in the muscle remains undetermined. Theoretically, the myonuclei gained from resistance training will be kept for quite a long time. Some studies, however, showed that the number of myonuclei is less in old people (70-86 years old) than in the young (under 69 years old), mainly for type II muscle fiber [27]. In addition, it is found in the elderly that training-induced hypertrophy is weakened, and the deficit in the proliferation function of muscular satellite cells is suspected to be the reason [15,28,29]. These indicate that myonuclei may decrease after a period, though it is unclear how long exactly it will take.

3. Epigenetic theory

Despite the efforts in physiological explanations, researchers have noticed the evidence at the genetic level. Epigenetics was originally proposed and discussed in embryology, where it describes the changes in the phenotype by modifying gene expression rather than altering the genetic code in response to external stimuli [30]. The causes of epigenetic changes are often external factors, such as environment and diet. DNA methylation is one of the main ways epigenetics influences phenotypes. It is commonly believed that CpG sites, which are DNA sequences rich in cytosine and

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guanine nucleotides, are often locations where methylation happens [31,32]. The idea of epigenetics makes it easy to think of how muscle hypertrophy is induced by training. It can be proposed that training, as an environmental factor, may change muscle size through epigenetic mechanisms.

3.1 Evidence and the PI3K/Akt pathway

Seaborne et al. first reported the epigenetic change in humans during the training, detraining, and retraining process [33]. In their experiment, eight male participants finished one acute resistance training session, then loading, unloading, and reloading, each lasting for 7 weeks. The muscle size and overall hypomethylation level are in line with the skeletal muscle memory hypothesis. During loading and unloading, the number of hypomethylated CpG sites is greater than that of hypermethylated sites. The muscle size and strength increased during loading and then decreased somewhat during unloading. During the reloading process, however, the genes undergo a significant hypomethylation event. The muscle size and strength also increased rapidly and reached a higher level than during the loading process. Interestingly, the major pathway under influence is the PI3K/Akt pathway. It has been reported to be related to cell growth and reproduction. For example, the PI3K/Akt pathway is involved in the positive regulation of cell proliferation through growth-factor-receptor tyrosine kinases, which are also expected to be the target of novel cancer therapy [34]. This suggests that epigenetics may take effect by stimulating muscle cell growth and that the epigenetic hypothesis is not opposite to the myonuclear hypothesis. However, whether myonuclear or cytoplasm is increased remains unknown. Indeed, the increase in muscle size is mainly contributed to by the fusion of satellite cell nuclei. Nevertheless, as mentioned before, the myonuclear domain is variable within a limit. Whether the myonuclear domain is also enlarged along with the increase in nuclei needs further study.

3.2 The genetic basis of skeletal muscle memory

Moreover, Seaborne et al. classified the whole DNA genome based on methylation events in different experimental stages. Two clusters of genes were of particular interest: One of them, including RPL35a, C12orf50, BICC1, ZFP2, UBR5, HEG1, PLA2G16, SETD3, and ODF2 genes, remained hypomethylated throughout the loading, unloading, and reloading process. As a consequence, its expression level kept increasing. The other cluster, including AXIN1, GRIK2, CAMK4, TRAF1, NR2F6 and RSU1, was consistent with the muscle mass change. It was hypomethylated while the muscle mass increased and hypermethylated while the muscle mass decreased. Seaborne et al. deduce that the cluster that remained hypomethylated is responsible for memorizing the previous resistance training by epigenetic downregulation, while the other cluster regulates load-induced skeletal muscle growth. The two clusters work together to realize skeletal muscle memory. In another work, researchers also proved that epigenetic changes can be memorized [35]. The male human participants took short-term high-fat and normal diets. Biopsies of their muscle indicated that 6508 genes had been influenced, and the methylation of these genes was not restored to the original level after 6-8 weeks. These studies show that epigenetic change could be the carrier of skeletal muscle memory and can be kept for the long term.

3.3 Limitations of current studies

There are many unanswered questions in epigenetic memory. For example, there is an inconsistency between the methylation patterns of genes. In the study of Seaborne et al., the two clusters of genes

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were observed and behaved distinctly [33]. One of the clusters was found to be only hypermethylated during the loading process and maintained hypomethylated during other processes. The other cluster was only hypermethylated during the unloading and reloading process. The behaviors of these clusters are not consistent with muscle size and strength. More importantly, they show that the methylation pattern during loading was not reproduced during reloading, which is contrary to the epigenetic skeletal muscle memory hypothesis. Though the two clusters may be responsible for other metabolic activities contributing to skeletal muscle memory, their distinct behavior needs to be further clarified.

In addition, the cluster that kept hypomethylated throughout the loading, unloading, and reloading process is expected to memorize the previous training. Its expression level kept increasing during the whole experiment. Such behavior may cause a heavy burden on the cell, investing too much energy and materials into skeletal muscle memory. The issue of expression burden is a common problem in synthetic biology, which means exogenous genes share limited resources with endogenous genes. Therefore, the expression and translation function of endogenous genes are influenced, leading to abnormal cell behavior [36]. In terms of skeletal muscle memory, the cluster of genes that are kept expressing could cause similar problems, especially in skeletal muscle cells, where energy is expensive [37]. The discovery of the over-expression gene reminds us that skeletal muscle memory is a balanced result between energy and function. It may also have significant values in evolution.

It is suggested that histone modification, another major epigenetic modification, also plays a part in skeletal muscle memory. McGee et al. reported that the acetylation level of histone 3 lysine 36 (H3K36) in human participants was significantly increased after 60 minutes of cycling [38]. The acetylation of H3 is a typical modification in epigenetics, and a study like this proves that epigenetics forms skeletal muscle memory with both DNA methylation and histone acetylation.

4. Discussion

In addition to the theories mentioned above, the possible role of irreversible feedback regulation in the formation of skeletal muscle memory may be worth attention. An irreversible feedback regulation is common in biological development and can be established by positive feedback. For example, if a substrate can promote its own modification after being modified, then the substrate and its modifying enzyme can form positive feedback [39,40]. It has been proved that positive feedback is irreversible once activated, as if the activation of the circle had been memorized [39]. The idea is consistent with skeletal muscle memory, and positive feedback pathways may be involved during its formation. Though it is also suggested that muscle growth in size and strength is induced by refined innervation of cells, the theory is not well explained in the article. Moreover, the detailed function of specific genes and pathways has also not been thoroughly explained in the article for illustration purposes.

Exploring the enigma of skeletal muscle memory could be beneficial in the medical treatment of aging. Statistics have estimated that over 22% of the global population will be over 60 years old by 2050, making aging a serious issue in the near future [41]. Sarcopenia refers to a disease common in older people, which is marked by the loss of muscle mass and function. It is also associated with other health problems, such as fractures, falls, and functional decline [42]. Currently, there are no effective drugs and therapies for sarcopenia, and skeletal muscle memory could be a promising aspect. Clinical practice often suggests exercising as a non-drug therapy. However, old and disabled patients usually have difficulties in doing physical activities [43]. Understanding the formation of skeletal muscle memory might help us directly rejuvenate the muscle cells by activating specific

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pathways or genes. It is also hoped that revoking the skeletal muscle memory the patients gained in previous training will help muscle restoration.

5. Conclusion

In summary, this article aims to review the main hypotheses of the formation of skeletal muscle memory. The myonuclear hypothesis proposes that physiological change, namely, myonuclear increase, is the reason for muscle strength and size growth. Epigenetic theory provides additional views on the mechanisms of skeletal muscle memory. Moreover, it has been found that the methylation of certain genes and the acetylation of histone H3 may contribute to skeletal muscle memory. The discrepancy among studies has been mentioned in the article, which leads to future research directions and reminds us of those missing points.

This review can be refined by statistical analysis of current studies, which gives a more comprehensive view of the big picture. Further work can also be done by exploring the related pathways and pointing out possible therapeutic target sites. It is expected that a deeper understanding of skeletal muscle memory will pave the way to the novel treatment of aging.

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