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Review

Molecular mechanical regulation of skeletal muscle extracellular matrix under exercise-induced conditions: From mechanical signals to dynamic mechanisms of muscle regeneration

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Abstract: The maintenance of skeletal muscle function depends on the structure and mechanical properties of the extracellular matrix (ECM), which not only offers mechanical support but also regulates muscle cell behavior. Exercise, as a non-pharmacological intervention, can modulate ECM remodeling through various mechanical signals, hence facilitating muscle adaptation, regeneration, and repair. However, the molecular mechanical mechanisms underlying ECM remodeling during exercise remain systematically unexplored. Our review seeks to explore how exercise regulates skeletal muscle ECM remodeling through mechanical signals, elucidates the role of ECM in muscle regeneration and repair, and summarizes the molecular mechanisms by which various types of exercise modulate ECM. Besides, we assess the potential applications of exercise in muscle injury repair and fibrosis inhibition. Research reveals that exercise regulates ECM stiffness and elasticity through mechanical signals such as stretching, compression, and shear stress. These signals are transmitted via integrin receptors, which activate intracellular signaling pathways such as YAP/TAZ and PI3K/Akt, facilitating muscle cell proliferation, migration, and differentiation. Exercise plays a significant role in muscle injury repair by strengthening ECM synthesis and degradation, slowing down, or preventing excessive fibrosis. Especially in aging and muscle-related diseases, exercise intervention displays potential for promoting muscle function and slowing aging.

Keywords: exercise; skeletal muscle; extracellular matrix; molecular mechanical regulation; mechanical signals; muscle regeneration

1. Introduction

Skeletal muscle is a critical tissue for maintaining movement and daily functions, and its functionality depends not only on the activity of muscle cells but also on the ECM, a complex network of structural and bioactive molecules that provides mechanical support and regulates cell behavior [1]. As a complex three-dimensional structure, the ECM of skeletal muscle is composed of various molecular components, comprising collagen, elastin, and glycosaminoglycans, and performs multiple functions, such as offering mechanical support, regulating cell behavior, and maintaining tissue integrity [1]. These ECM components directly influence skeletal muscle cells by their mechanical properties—including stiffness, elasticity, and shear force—thereby regulating cell morphology, proliferation, migration, and differentiation. Thus, ECM is essential in both physiological and pathological muscle processes [2].

Lately, the impact of exercise on skeletal muscle ECM has gained widespread attention. Exercise not only acts as a direct driving force for muscle growth and repair but also regulates ECM remodeling through various mechanical signals, hence facilitating muscle adaptation and damage repair [3]. Resistance training, notably, enhances ECM rigidity through stretching and compressive stress, enabling it to withstand greater loads and boost muscle hypertrophy [4]. On the other hand, aerobic exercise modulates the ECM structure by enhancing shear stress and cell hydration, strengthening the environment for muscle repair [5]. These mechanical signals are transmitted to the cells through receptors, such as integrins, a family of transmembrane receptors that mediate ECM-cell interactions and convert mechanical cues into biochemical signals, activating a series of signaling pathways (e.g., YAP/TAZ, PI3K/Akt), which further regulate the cells' response to the ECM and the muscle regeneration process [6].

In the context of skeletal muscle injury and repair, the ECM not only provides cellular support but also regulates extracellular signaling and the interaction with the cytoskeleton, ensuring the proper functioning of muscle cells in both physiological and pathological states [1]. Exercise, notably, boosts muscle adaptation and remodeling by regulating the synthesis and degradation of ECM. Existing research reveals that the ECM remodeling mechanism induced by exercise is closely linked to the mechanical sensitivity of the cells. The transmission of mechanical signals not only regulates the composition of the ECM but also promotes muscle repair after injury through cell-matrix interactions [7]. Despite our initial understanding of how exercise affects skeletal muscle ECM remodeling, numerous questions remain unanswered. The specific impact of various types of exercise on ECM and their molecular mechanisms has yet to be fully elucidated.

In light of this background, this study follows a narrative review approach, synthesizing current research on exercise-induced skeletal muscle ECM remodeling, with a focus on molecular mechanical regulation. Our review aims to explore the molecular mechanical regulation mechanisms of skeletal muscle ECM induced by exercise and investigate its underlying utilization in muscle regeneration and repair. By integrating current research findings, we hope to supply new theoretical foundations and practical guidance for sports medicine, skeletal muscle pathology, and clinical treatments.

2. Molecular mechanical properties of skeletal muscle extracellular matrix

Beyond its structural role, ECM actively regulates cell behavior through its mechanical properties and biochemical composition, influencing muscle adaptation to external stimuli. The primary components of ECM include collagen, elastin, glycosaminoglycans, fibronectin, and others [1]. Type I collagen is a key structural component of the ECM. It provides strong tensile strength and structural stability to the muscle, helping to maintain the integrity and morphology of muscle tissue [8]. Elastin imparts elasticity and flexibility to the muscle, allowing it to maintain adaptability during contraction and stretching, hence preventing excessive hardening [9]. Glycosaminoglycans (e.g., hyaluronic acid, chondroitin sulfate) are closely linked

to hydration, resulting in a suitable environment for cells. They are also involved in processes like signal transduction and cell migration [10]. Fibronectin is an adhesion molecule in the ECM that not only connects cells to the matrix but also boosts cell adhesion, migration, and signal transduction through interaction with integrin receptors [11]. Integrins play a significant role in the interaction between cells and ECM, serving as receptors for external mechanical signals at the cell surface [11].

The mechanical properties of the ECM are crucial for skeletal muscle cell function, in particular, in terms of stiffness, elasticity, and shear force [2]. Given the dynamic nature of the ECM, it is essential to understand how these properties respond to external stimuli, such as mechanical forces generated during exercise. Studies have demonstrated that ECM stiffness affects the morphological stability of muscle cells. High-stiffness ECM provides necessary mechanical support during intense exercise, maintaining the integrity of cell structures [12]. Besides, the elasticity of the ECM determines its recovery ability after being subjected to stress. An ECM with good elasticity aids in muscle extension and contraction and prevents excessive deformation due to exercise [13]. Shear stress affects the arrangement, migration, and morphological changes of muscle cells, hence regulating muscle tissue adaptability and remodeling [13]. However, the specific mechanisms of shear force require further research.

In skeletal muscle, the ECM not only provides mechanical support but also plays a key role in regulating cell behavior. It supplies the necessary structural support to muscle cells, enabling them to maintain stable morphology in the context of exercise and growth [14]. Moreover, the stiffness and nanoscale topology of the ECM affect organism progression and physiological as well as pathological processes. Through integrins and other adhesion molecules, the ECM boosts cell-matrix adhesion and signal transduction, hence regulating biological processes, such as muscle cell proliferation, migration, and differentiation [15]. In addition, the ECM interacts with the cytoskeleton, regulating the mechanical force-sensing function of cells, and plays a core role in cellular movement and adaptive remodeling of muscle tissue [14]. The synergistic effects of these mechanical properties ensure the proper function of skeletal muscle cells under various physiological and pathological conditions [15]. Understanding these properties sets the foundation for exploring how mechanical forces, particularly those induced by exercise, influence ECM remodeling. This leads us to the next section, where we examine how different types of exercise contribute to the dynamic adaptation of the skeletal muscle ECM.

3. Exercise and the dynamic remodeling of skeletal muscle extracellular matrix

Exercise modulates ECM structure and function through mechanical signals, influencing muscle adaptation and repair. ECM remodeling is largely dictated by mechanical forces, including tensile, compressive, and shear stresses, which different types of exercise impose on muscle tissue. Resistance and aerobic exercises exert distinct effects on ECM remodeling. While ECM properties provide the structural foundation for skeletal muscle function, their adaptability is largely governed by the mechanical environment imposed by exercise. **Figure 1** displays exercise and dynamic

remodeling of the extracellular matrix in skeletal muscle.

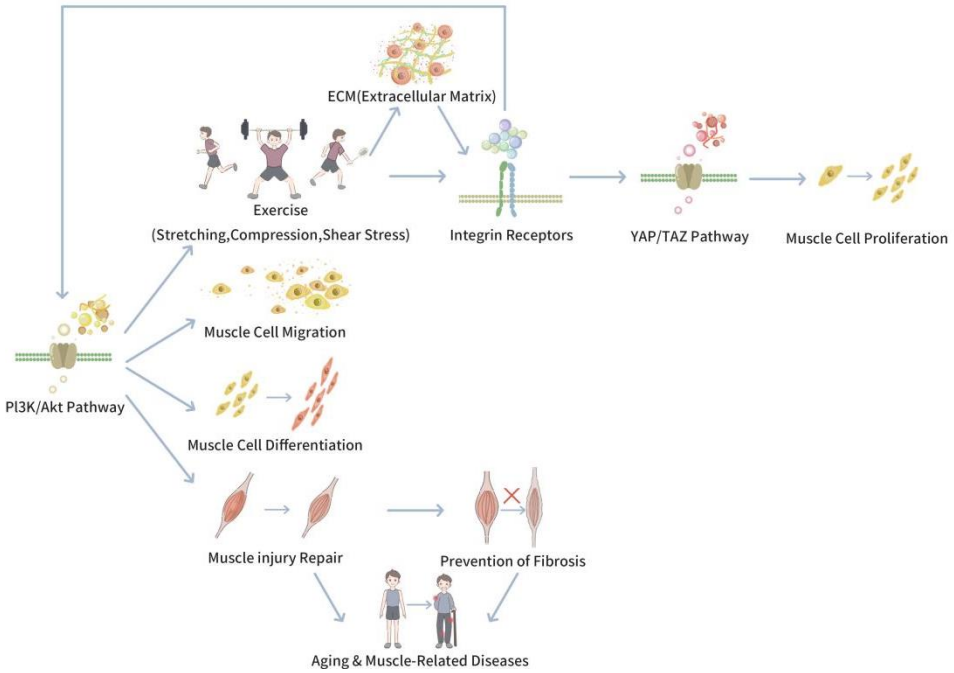

Figure 1. Exercise and dynamic remodeling of the extracellular matrix in skeletal muscle.

Figure 1 illustrates the mechanisms by which exercise affects muscle. Exercise generates tensile, compressive, and shear stresses, which act on the ECM and promote muscle cell proliferation through the activation of the YAP/TAZ pathway by integrin receptors; at the same time, exercise also affects the migration and differentiation of muscle cells through the PI3K/Akt pathway, which helps to repair muscle damage and prevent fibrosis and also has a positive significance for the prevention and treatment of aging and muscle-related diseases.

3.1. Mechanical signals generated by exercise

Mechanical signals from exercise drive ECM remodeling, with distinct effects depending on exercise type. Resistance training enhances ECM remodeling by increasing collagen crosslinking and improving rigidity and tensile strength [4,5]. These changes help muscles bear greater loads during prolonged, high-intensity exercise, promoting the muscle's resistance to stretch. In contrast, aerobic exercise induces a distinct remodeling pattern, primarily characterized by increased hydration and elasticity rather than stiffness. Aerobic exercise primarily influences ECM by increasing shear forces and hydration [5]. While aerobic exercise does not vitally alter ECM stiffness, it supports maintaining an optimal ECM environment, offering better conditions for cell repair and regeneration [4].

3.2. Exercise-induced ECM remodeling mechanisms

ECM remodeling is driven by stretching, compression, and shear forces [16]. In the context of resistance training, muscle cells experience intense stretching and compressive stresses, triggering collagen and other matrix components in the ECM to

rearrange and crosslink, making the ECM more robust and stretch-resistant, hence enabling it to withstand prolonged mechanical loads [17]. Exercise training promotes ECM adaptation in muscle cells, supporting muscle maintenance [3]. Shear stress during eccentric movements promotes ECM remodeling, leading to collagen proliferation in the endomysium and perimysium. This process is closely linked to delayed onset muscle soreness (DOMS) following exercise [7].

As mechanical forces reshape ECM structure, cells must continuously detect and respond to these changes. The next section explores how skeletal muscle cells perceive and integrate mechanical cues through specialized receptors and signaling pathways.

3.3. ECM and cellular response

Cells sense mechanical signals via integrins and mechanosensitive cytoskeletal proteins, activating pathways that regulate ECM composition and cellular behavior [18]. Integrins are core receptors between cells and the ECM, capable of sensing and transducing mechanical signals into biochemical cascades that regulate cellular responses [18]. In addition to integrins, ion channels, and focal adhesion complexes also contribute to ECM-mediated signaling, depending on mechanical loading conditions [19]. This raises an important question: To what extent do integrins dominate ECM sensing, and could their role be context-dependent?

In the context of exercise, integrins transmit external stretching, compressive, or shear forces to the cell interior by binding to the ECM, activating a series of signaling pathways, such as YAP/TAZ and PI3K/Akt, which further regulate the cell's response to the ECM [6]. Recent studies highlight that YAP/TAZ activation is particularly sensitive to substrate stiffness, with rigid ECM environments favoring YAP nuclear translocation and promoting cell proliferation. However, conflicting reports indicate that excessive YAP activation under chronic mechanical stress may contribute to fibrosis rather than regenerative repair, suggesting a finely tuned regulatory mechanism that remains poorly understood [20].

Mechanosensitive proteins (such as actin and talin) interact with the cytoskeleton, supporting cells as they dynamically respond to mechanical changes [19]. These cell-ECM interactions not only affect cell morphology and adhesiveness but also regulate cell migration and proliferation, offering necessary support for muscle repair and regeneration [18]. Interestingly, while integrin-mediated signaling is widely regarded as essential for ECM remodeling, emerging evidence suggests that the cytoskeletal tension generated through actomyosin interactions may independently regulate cellular responses to mechanical stress. This has led some researchers to propose a dual-regulation model, where both integrins and cytoskeletal tension act synergistically or independently depending on the mechanical environment [21].

The activation of these signaling pathways is crucial not only for ECM adaptation but also for broader muscle regenerative processes. However, it remains unclear whether exercise-induced mechanotransduction primarily enhances regeneration or if, under certain conditions, it could contribute to pathological remodeling. Some studies suggest that prolonged mechanical overload can shift ECM remodeling toward a fibrotic response rather than a regenerative one, highlighting the need for further investigation into the threshold between beneficial and maladaptive ECM changes

[22].

Future research should identify thresholds that differentiate regenerative from fibrotic ECM responses. In the next section, we explore how these molecular responses translate into functional outcomes, particularly in muscle repair and fibrosis prevention.

4. Effects of exercise on skeletal muscle regeneration and repair

Exercise promotes muscle regeneration by activating satellite cells and enhancing repair. As previously discussed, exercise-induced ECM remodeling plays a critical role in muscle adaptation. Beyond adaptation, ECM regulates muscle regeneration, ensuring effective tissue recovery. **Figure 2** illustrates the role of exercise in skeletal muscle regeneration and repair.

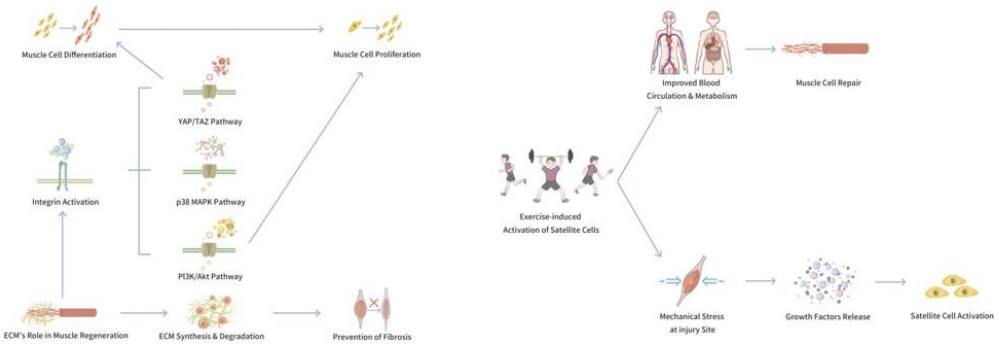

Figure 2. The role of exercise in skeletal muscle regeneration and repair.

Figure 2 shows the mechanism related to muscle regeneration. ECM plays a role in muscle regeneration, which can trigger YAP/TAZ, p38 MAPK, PI3K/Akt, and other signaling pathways through integrin activation to promote muscle cell differentiation and proliferation, and at the same time, carry out the synthesis and degradation of ECM to prevent fibrosis; in addition, exercise can activate the satellite cells, and the mechanical stress at the site of injury can lead to the release of growth factors, which can further activate satellite cells, combined with the improvement of blood circulation and metabolism, and help the repair of muscle cells. In addition, exercise can activate satellite cells, and the mechanical stress at the injury site leads to the release of growth factors, which further activate satellite cells, and in combination with improved blood circulation and metabolism, help muscle cell repair.

4.1. Exercise and muscle regeneration

Exercise plays a critical role in skeletal muscle recovery. Exercise promotes satellite cell activation and proliferation, accelerating tissue repair [20]. By increasing mechanical stress, exercise stimulates growth factor release and activates key regenerative pathways [20]. Moreover, exercise not only directly influences satellite cell function but also modifies the ECM environment, creating a supportive niche for muscle repair. Besides, exercise increases blood circulation and metabolism, further facilitating recovery at the injury site and helping skeletal muscle return to normal function more quickly [21].

4.2. The role of ECM in muscle regeneration

ECM supports muscle fiber survival and functional recovery during repair. Exercise training enhances muscle adaptation by regulating ECM synthesis and degradation [3]. Specifically, exercise not only stimulates collagen synthesis in the ECM but also regulates the degradation process, preventing excessive fibrosis and maintaining the ECM's optimal properties, hence strengthening muscle repair and regeneration [3]. While ECM remodeling ensures structural integrity during muscle repair, it is also tightly regulated by intracellular signaling pathways that coordinate collagen synthesis, degradation, and deposition. Exercise-induced ECM remodeling regulates collagen-related gene expression, promoting muscle repair [7].

4.3. The application of exercise in diseases

Exercise interventions have demonstrated significant potential in the treatment of muscle diseases by facilitating muscle adaptation and remodeling, thereby mitigating muscle degeneration. Studies highlight that exercise regulates ECM remodeling, optimizing conditions for muscle maintenance and repair [3]. These effects are crucial in conditions like muscular dystrophy or age-related muscle loss, where ECM remodeling is impaired. Besides, exercise interventions, notably, have been observed to vitally improve gait endurance in patients, although the improvement in muscle strength is more limited in patients with diseases like muscular atrophy [22]. Moderate exercise slows muscle function loss while supporting cell repair, offering a potential treatment strategy.

To fully understand how exercise influences ECM remodeling at a molecular level, the next section explores the key mechanisms of mechanical signal transduction in muscle adaptation and repair.

5. Mechanisms of mechanical signal transduction

In exploring the mechanisms of mechanical signaling, the first thing that needs to be clarified is the key role of cell surface receptors in this process. In particular, integrins, which are the main connecting bridges between cells and the ECM, are responsible for sensing mechanical signals from the ECM and transmitting them into the cell. This section now focuses on the molecular pathways that translate these mechanical cues into biological signals. **Figure 3** illustrates mechanical signal transduction mechanisms.

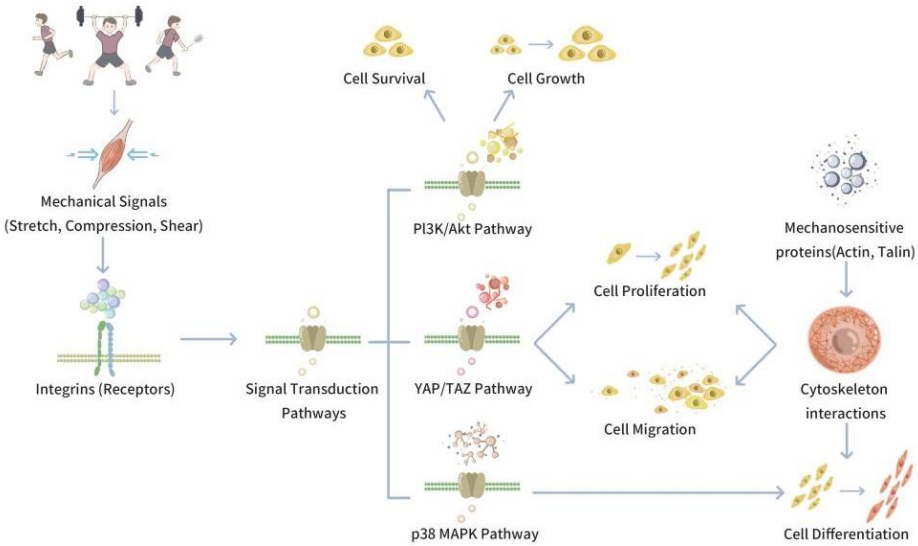

Figure 3. Mechanisms of mechanical signal transduction.

Figure 3 shows the transmission of mechanical signals (stretch, compression, shear) from external motion to the cell. These signals first act on integrin receptors and subsequently affect a variety of physiological processes such as cell survival, growth, proliferation, migration, differentiation, etc., through signaling pathways such as PI3K/Akt, YAP/TAZ, p38 MAPK, etc., and involve the interaction of mechanosensitive proteins with the cytoskeleton. The interaction of mechanosensitive proteins with the cytoskeleton is also involved.

5.1. Integrins and the transmission of mechanical signals

Integrins are the main mechanosensitive receptors on the cell surface that can sense mechanical signals transmitted from the ECM and exert their effects by binding with ECM components [23]. Upon activation, integrins cluster and recruit cytoskeletal adaptor proteins, transmitting mechanical cues that regulate ECM-related gene expression [18]. Given their pivotal role in mechanical sensing, integrins not only mediate cell-matrix adhesion but also orchestrate various downstream signaling events essential for tissue homeostasis. Integrin-mediated mechanical signal transduction regulates cellular physiological processes, comprising proliferation, survival, migration, and tissue differentiation, playing a crucial role in maintaining tissue homeostasis. When extreme or prolonged mechanical stress is applied, abnormalities in this process can result in pathological conditions, such as fibrosis and tumors [18].

In muscle cells, integrins are especially significant as they not only serve as bridges between cells and the ECM but also promote the cells' mechanosensation through interactions with the cytoskeleton [18]. An article indicates that integrins play a key role in mechanical signal transmission, as they can sense mechanical changes in the ECM and regulate cellular activities, such as migration, proliferation, and tissue repair via signaling pathways [18]. For instance, integrins interact with the cytoskeleton to regulate ECM remodeling, hence facilitating muscle repair and regeneration [18].

5.2. Activation of signaling pathways

Multiple intracellular signaling pathways mediate ECM-induced cellular responses. Among them, the YAP/TAZ pathway governs mechanosensitive gene expression, the MAPK pathway regulates satellite cell activation, and the PI3K/Akt pathway controls cell growth and metabolism. The following sections discuss their distinct roles in ECM remodeling [18].

5.2.1. The YAP/TAZ pathway: A mechanotransduction hub

YAP/TAZ signaling regulates muscle cell responses to mechanical stimuli by modulating gene expression and cellular adaptation. Under conditions of increased ECM stiffness, YAP/TAZ becomes activated, translocates to the nucleus, and promotes gene transcription that supports cell proliferation and migration. Conversely, when ECM stiffness is low, YAP/TAZ activity is suppressed, favoring differentiation and tissue maturation [24].

This phenomenon is mediated through cytoskeletal tension, where rigid ECM substrates enhance cellular shape changes and cytoskeletal aggregation, promoting YAP/TAZ nuclear localization and the upregulation of key regenerative genes [25]. However, excessive YAP/TAZ activation in a persistently stiff ECM environment has also been implicated in fibrosis, suggesting that fine-tuned regulation is required for optimal muscle repair. Future studies should address the threshold at which YAP/TAZ signaling shifts from regenerative to fibrotic pathways, which remains an unresolved question in the field.

5.2.2. The MAPK pathway: Regulating satellite cell activation

The mitogen-activated protein kinase (MAPK) pathway, particularly p38 MAPK, plays a pivotal role in the activation and differentiation of satellite cells, which are essential for muscle regeneration [26]. Mechanical stress, including shear and stretch forces, activates p38 MAPK via integrin signaling, leading to enhanced satellite cell proliferation and differentiation [27,28].

Importantly, while p38 MAPK is recognized as a pro-regenerative signaling pathway, recent evidence suggests that its activation dynamics are critical: prolonged or excessive activation may induce stress responses rather than promote effective muscle regeneration [29]. This highlights the need for a precise balance in MAPK signaling to prevent maladaptive responses during exercise-induced muscle remodeling.

5.2.3. The PI3K/Akt pathway: A nexus of growth and survival

The PI3K/Akt pathway is a major intracellular regulator of cell growth, metabolism, and survival, and its activation is strongly linked to exercise-induced mechanical stimulation. Integrin-mediated mechanotransduction during exercise leads to PI3K/Akt pathway activation, supporting cell growth and survival [30].

For example, exercise training has been shown to robustly enhance PI3K/Akt signaling in skeletal muscle, increasing protein synthesis and promoting muscle repair [31]. Beyond cell proliferation, this pathway is also involved in autophagy regulation, mitochondrial function, and metabolic adaptations, making it a key determinant of muscle endurance and resilience. A recent study demonstrated that aerobic exercise modulates the PI3K/Akt-mTOR signaling axis, reducing neuronal apoptosis and

facilitating neuroprotection [32]. These findings suggest that PI3K/Akt signaling not only promotes muscle adaptation but may also have broader implications for systemic tissue homeostasis.

However, the long-term effects of PI3K/Akt hyperactivation remain controversial, as persistent stimulation could lead to metabolic dysregulation or uncontrolled hypertrophic responses. Future research should investigate the threshold at which PI3K/Akt signaling shifts from beneficial to potentially deleterious outcomes.

5.2.4. Integration of multiple pathways in ECM-mediated repair

While each of these pathways—YAP/TAZ, MAPK, and PI3K/Akt—plays distinct roles in skeletal muscle adaptation, they do not operate in isolation. Instead, their interactions converge to create a complex signaling network that integrates mechanical inputs with biochemical responses.

For instance, YAP/TAZ activation is often coordinated with PI3K/Akt signaling to regulate cell proliferation and survival, while p38 MAPK may act in parallel to fine-tune cellular responses based on stress levels. Understanding how these pathways crosstalk and establish hierarchical control over ECM remodeling remains a major research challenge in mechanobiology.

The next section will explore how these molecular signals translate into functional outcomes, particularly in muscle cell migration, repair, and fibrosis prevention.

5.3. Muscle cell response

During exercise, muscle cells (such as satellite cells) need to proliferate at the injury site and differentiate into mature muscle fibers [33]. This process is regulated by both signaling pathways and ECM mechanical properties. The YAP/TAZ pathway plays a critical role in this process, where high YAP activity boosts satellite cell proliferation, and YAP deactivation boosts differentiation [34]. Besides, the PI3K/Akt signaling pathway also plays a vital role in satellite cell proliferation and differentiation, supporting cell growth and progression through activation of IGF2BP3 [35]. These signaling pathways work together to ensure that muscle cells successfully enter the repair and regeneration stages.

ECM-integrin interactions guide muscle cell migration to injury sites, facilitating repair [18]. For instance, ECM stiffness and elasticity play a significant role in cell migration, as cells sense these mechanical signals to regulate their migration speed and direction. An article has demonstrated that ECM transient transition matrices, containing glycoproteins such as fibronectin, laminin, and hyaluronic acid, serve as key initiators for muscle repair, offering signals that boost muscle stem cell regeneration [17]. Besides, ECM properties vitally affect muscle mechanical behavior. As ECM stiffness increases, the stress-strain relationship of muscle becomes more linear, and the stretch range turns into smaller [36]. These changes in mechanical signals and properties help muscle cells maintain adaptability during the repair process, ensuring effective repair of the injured area.

6. The effect of exercise on ECM fibrosis

Before delving into an analysis of the regulatory role of exercise, an

understanding of the underlying process of ECM fibrosis is essential to elucidate how exercise affects fibrosis. By understanding the mechanisms of fibrosis, we can better understand the potential role of exercise in regulating this process and how it modulates the synthesis and degradation of the ECM through different biological pathways, which in turn attenuates the extent of fibrosis.

6.1. The fibrosis process

After skeletal muscle injury, the ECM experiences a series of remodeling processes, which mainly include the synthesis, accumulation, and degradation of ECM components [1]. When muscle tissue is injured, ECM components, such as collagen and glycosaminoglycans, are synthesized in large quantities at the injury site to provide structural support and repair. However, excessive ECM accumulation, interestingly, may result in fibrosis, which further impairs muscle function. Articles confirm that ECM remodeling after muscle injury includes the synthesis of Type I and Type III collagen, which provide essential structural support during repair, but an overaccumulation of ECM can cause fibrosis, affecting the muscle's regenerative capacity [1–17].

Fibrosis is triggered by the abnormal activation of fibroblasts and myofibroblasts, causing the excessive deposition of ECM [37]. Transforming growth factor-beta (TGF-β) plays a key role in this process, as it induces the differentiation of fibroblasts into myofibroblasts, hence enhancing ECM synthesis [37]. Under chronic injury or continuous mechanical stress, persistent activation of TGF-β signaling results in excessive accumulation of ECM components, such as collagen, while inhibiting the activity of matrix metalloproteinases (MMPs), hence resulting in fibrosis [38,39].

In the context of fibrosis, the structure of ECM changes, causing tissue hardening and further impairing cellular function [40]. This is especially evident in certain pathological conditions, such as idiopathic pulmonary fibrosis (IPF), where excessive activation of fibroblasts and sustained ECM accumulation create a persistent fibrotic feedback loop, exacerbating tissue stiffness and functional loss [41]. Specifically, during pulmonary fibrosis, the mechanical properties of ECM, such as elasticity and viscoelasticity, change as fibrosis progresses, affecting the response of lung cells and inducing disease further [42].

6.2. How exercise regulates fibrosis

Moderate exercise has a positive effect on muscle repair and regeneration, in detail, in regulating ECM remodeling. Research has demonstrated that exercise can promote muscle tissue regeneration by balancing ECM component synthesis and degradation, hence inhibiting fibrosis [3–43]. For instance, exercise has been uncovered to increase the synthesis of ECM components, such as collagen and glycoproteins, which support the survival and repair of muscle fibers [3–43].

Exercise, apparently, by enhancing mechanical tensile and shear forces, activates integrins and other mechanical receptors in muscle cells, hence regulating ECM remodeling [42]. Studies indicate that mechanical stretching can activate integrins and trigger a series of biochemical signaling processes, which regulate the expression of ECM-related genes, comprising collagen and MMPs [44]. Moreover, exercise can

regulate TGF-β signaling pathways, facilitating collagen synthesis and enhancing MMP activity, hence facilitating the degradation of excessive collagen and preventing detrimental fibrosis formation. Research has stressed the significant impact of substrate stiffness on TGF-β activation, and TGF-β activation further regulates collagen synthesis and MMP activity, playing a critical role in ECM remodeling [45]. The anti-fibrotic effect of exercise is closely linked to its regulation of fibroblast activity. An article has demonstrated that exercise training, interestingly, can increase the expression of fibroblast growth factor 21 (FGF21), inhibit the activation of the TGF-β1-Smad2/3-MMP2/9 signaling pathway, and lower cardiac fibrosis, oxidative stress, and apoptosis, hence promoting cardiac function [46]. Besides, physical stimuli in the environment can strongly affect the phenotype of resident fibroblasts, hence regulating ECM remodeling and the fibroblast-to-myofibroblast transition (FMT), which plays a significant role in the fibrosis process [47]. Moreover, exercise counteracts fibrosis through mechanisms involving the regulation of oxidative stress. Studies show that regular exercise enhances the body's antioxidant capacity, improves redox balance, and thus alleviates oxidative stress and inflammation, reducing the accumulation of reactive oxygen species (ROS) and positively impacting ECM remodeling [48,49]. Moderate exercise, apparently, by enhancing antioxidant defenses, lowers the negative effects of excessive free radicals, hence facilitating muscle recovery and slowing down the excessive accumulation of ECM [48,49].

Overall, moderate exercise effectively regulates ECM synthesis and degradation through various mechanisms, facilitating healthy muscle repair. Exercise not only lowers fibrosis formation but also strengthens muscle tissue repair by promoting the cellular microenvironment, regulating fibroblast activity, and inhibiting adverse inflammatory responses. As a non-pharmacological intervention, exercise holds great promise in treating functional impairments caused by muscle fibrosis, in detail, in interventions for exercise injuries, muscle aging, and chronic muscle diseases. Exercise is considered a significant therapeutic approach in these contexts.

7. Conclusion and outlook

7.1. Conclusion

Our review summarized the mechanisms by which exercise regulates the molecular mechanics of the ECM in skeletal muscle, with a focus on how various types of exercise induce ECM remodeling through mechanical signals and modulate muscle regeneration and repair processes. Articles reveal that exercise not only affects the rigidity and elasticity of the ECM in the context of mechanical signals, such as stretching, compression, and shear, but also regulates a series of intracellular signaling pathways, comprising YAP/TAZ, PI3K/Akt, via receptors like integrins, facilitating adaptive changes in muscle and injury repair. In the muscle repair process after exercise-induced injury, in particular, mechanical signals play a crucial role in regulating cellular behavior, facilitating muscle fiber regeneration, and inhibiting fibrosis. By balancing ECM synthesis and degradation, exercise prevents excessive fibrosis formation, hence offering strong support for the healthy recovery of skeletal muscle tissue. Consequently, exercise, as a non-pharmacological intervention, holds significant potential in facilitating muscle repair, slowing aging, and treating muscle-

related diseases.

7.2. Outlook

Existing research provides a rich theoretical foundation for exercise-induced ECM remodeling in skeletal muscle, but numerous unresolved questions remain. A key challenge is to precisely determine the specific mechanisms through which different types of exercise influence ECM properties, particularly in terms of their impact on ECM composition, mechanical properties, and cell-matrix interactions. The effects of exercise intensity, frequency, and duration on ECM remodeling require more refined experimental approaches and systematic analysis. Furthermore, the intricate signaling pathways mediating mechanical signal transduction in ECM remodeling, especially their synergistic effects in complex biological environments, remain a central focus of research. Future studies should explore these directions by integrating advanced methodologies: (1) Employing cutting-edge single-cell transcriptomics and spatial multi-omics techniques to decipher the fine regulatory networks governing ECM remodeling at the molecular and cellular levels, while leveraging 3D bioengineering platforms to simulate exercise-induced ECM microenvironments and dynamically track cell-matrix interactions; (2) Investigating the role of ECM in muscle aging and chronic muscle diseases by utilizing organoid models, CRISPR-based genetic editing, and biomechanical assays in both in vitro and in vivo systems to elucidate how ECM alterations affect muscle regeneration under pathological conditions; (3) Translating ECM-related findings into clinical applications through personalized exercise intervention strategies, integrating computational biomechanics, machine learning-driven predictive models, and biomarker discovery to optimize individualized rehabilitation protocols. Future interdisciplinary collaborations among molecular biology, biomechanics, and clinical practice will further drive the development of precision exercise medicine, providing novel therapeutic insights into ECM-targeted interventions for muscle injury repair, aging-related muscle decline, and chronic muscular disorders.

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