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Article

The integrative role of physical exercise and muscle satellite cells in remodeling muscle structure and function

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Abstract: With the aging of the population and changes in lifestyle, sustaining muscular function has become essential for enhancing quality of life. Muscle satellite cells, as the principal source of regeneration for skeletal muscles, are essential for muscle growth, maintenance, and repair. Our review explores how physical exercise (PE) impacts the remodeling of muscle structure and function by modulating the activity of Muscle satellite cells (MuSCs), and further identifies the underlying implications of this process for the prevention and treatment of degenerative muscle diseases. By exploring current evidences on the interaction between MuSCs and PE, our review investigating the effect of PE on the activity, proliferation, and differentiation capabilities of MuSCs, and how these changes improve the enhancement of muscle mass and function. Evidences confirmed that PE can enhance the contribution of MuSCs to muscle fibers, particularly by boosting muscle adaptability through changes in muscle fiber type and size. PE-induced activation of MuSCs is linked not only to an increase in the number of muscle fibers but also with promoted endurance and strength performance of muscles. Besides, the positive effects of PE on MuSCs may vary with the form, intensity, and duration of PE. Additionally, PE plays a crucial role in the remodeling of muscle structure and function through the activation and proliferation of MuSCs, stressing the potential value of developing appropriate PE interventions in the prevention and treatment of muscle-related diseases, particularly among the elderly. Future research should further explore the specific effects of various types and intensities of PE on MuSCs activities to maximize exercise prescriptions for strengthening muscle health and function.

Keywords: muscle satellite cells; physical exercise; muscle structure; muscle function; age-related muscle diseases; muscle enhancement; muscle endurance

1. Introduction

Muscle constitutes one of the largest tissues in the human body, playing vital roles in supporting the skeleton, generating movement, and sustaining vital life processes. With the modifying lifestyle patterns and the trend towards an aging population, sustaining muscular function has become increasingly vital. Current scientific inquiries have centered on how physical exercise (PE) reshapes muscle structure and function by affecting muscle satellite cells. Evidence has uncovered that PE enhances the contribution of Muscle satellite cells (MuSCs) to myofibers, a process correlated with the load imposed [1]. In addition, the availability of proteins impacts role of MuSCs in skeletal muscle adaptation, highlighting their significance in myofiber remodeling post-resistance and endurance training [1]. These insights

are essential for recognizing the adaptive changes in muscle and treating related disorders.

MuSCs, located beneath the basal lamina of muscle fibers, are myogenic cells playing a pivotal role in muscle growth, maintenance, and repair [2]. In a quiescent state under rest, these muscle MuSCs activate, proliferate, and eventually differentiate into mature muscle cells upon muscle damage or stimulation, such as through PE, thereby engaging in muscle remodeling. Article confirmed that the activation, proliferation, and differentiation of MuSCs are key components of the muscle's adaptive response [3]. Additionally, evidence suggested that muscle loading or injury triggers the proliferation and differentiation of MuSCs, with observations in animal models displaying a clear behavior during muscle hypertrophy and regeneration compared to the muscle regeneration process [4].

PE, as an effective non-pharmacological intervention, has been extensively validated to trigger muscle mass and function. Evidences stressed that various forms and intensities of PE can induce adaptive changes in muscle, comprising fiber type transformation, strength and endurance increase, and promoted repair capability. In details in the elderly, PE has been observed to enhance muscle strength, physical performance, and body composition [5,6]. These changes largely count on the activity of MuSCs, essential for sustaining overall muscle health and function. MuSCs that have underwent injury retain a strong regenerative capacity over the long term, showing a lasting positive role in muscle regeneration, which may profoundly affect enhancing muscle repair capacity and functional recovery [7].

As a consequence, recognizing the interplay between PE and MuSCs, and how they collaboratively affect the remodeling of muscle structure and function, is essential for strengthening exercise regimes, preventing, and treating degenerative muscle diseases. We delve into the intricate interaction mechanisms and investigate how PE effectively activates MuSCs to trigger muscle health and functionality.

2. The fundamental biology of MuSCs

MuSCs are integral for muscle repair and regeneration. In their quiescent state under normal conditions, they exist as non-dividing cells but can swiftly activate in response to muscle injury. Activation is a significant step, marking the onset of a sequence involving proliferation and differentiation to replace damaged muscle fibers, thereby stressing their indispensable role in muscle health and functionality [7,8].

MuSCs exhibit a highly modulated quiescent state, sustained through the expression of specific genes that inhibit premature activation. This regulation is essential for preserving the cell's potential to support muscle regeneration when necessary. Notably, the Notch signaling pathway plays a vital role in sustaining MuSCs in their quiescent state by modulating the expression of genes that inhibit cell cycle advance [8].

Upon muscle injury, MuSCs are activated, beginning a process that includes proliferation, differentiation, and eventually, the formation of new muscle fibers. This process is affected by various intrinsic cellular mechanisms and extrinsic

signals from the muscle microenvironment, which together guide the regenerative and repair functions of these cells [7,9].

Identifying the fundamental biology of MuSCs, comprising their activation dynamics and pluripotency, is essential for leveraging their potential in therapeutic contexts, in detail, in diseases and conditions refined by impaired muscle regeneration, such as certain muscular dystrophies and age-related muscle loss [8,10,11]. The biological characteristics of MuSCs are described in detail in **Figure 1**.

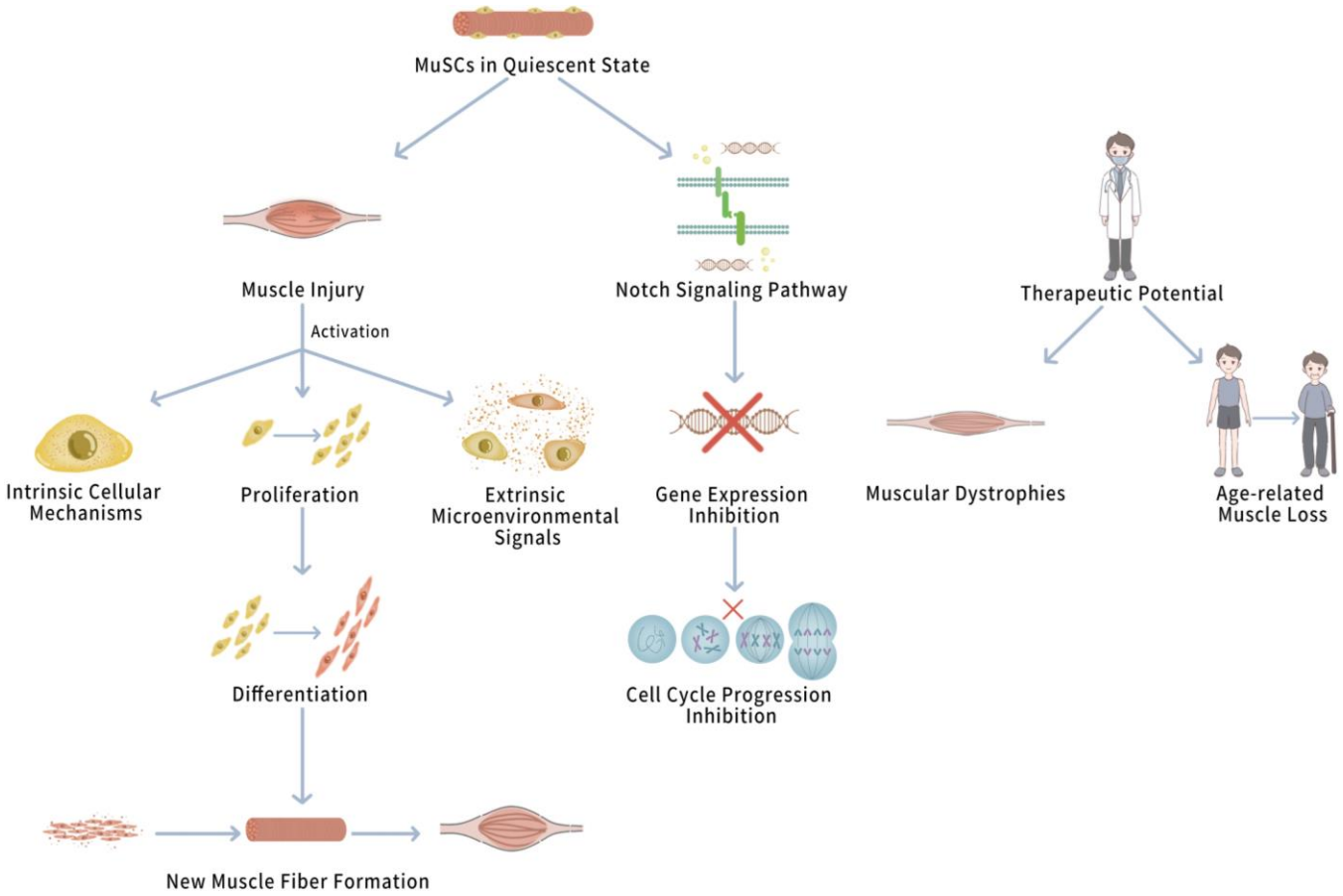

Figure 1. Biological characteristics of MuSCs.

This figure illustrates how MuSCs, when activated from their quiescent state, undergo proliferation and differentiation through intrinsic cellular mechanisms and extrinsic microenvironmental signals, ultimately forming new muscle fibers to repair muscle injury. Meanwhile, abnormalities in the Notch signaling pathway inhibit gene expression and cell cycle progression, leading to muscular dystrophies. Understanding these mechanisms offers significant therapeutic potential for treating muscular dystrophies and age-related muscle loss.

2.1. Definition and biological characteristics of MuSCs

MuSCs, the main regenerative source for adult skeletal muscle, are small, mononuclear, undifferentiated cells located beneath the basal lamina of muscle fibers. These cells were first recognized by Alexander Mauro in 1961. Owing to their unique position adjacent to muscle fibers yet outside their basal lamina, they were

called “MuSCs” [12]. In a quiescent state, MuSCs are characterized by a small volume, a large nucleus, and minimal cytoplasm, sustaining a near-quiescent state compared to mature muscle fibers [13,14].

2.1.1. Pluripotency

MuSCs, mononuclear cells located beneath the basal lamina of skeletal muscle fibers, play a pivotal role in the repair and regeneration of skeletal muscle following injury. Upon muscle damage, MuSCs become activated, enter the cell cycle, and commence proliferation, subsequently differentiating into muscle fibers to improve muscle repair and regeneration [9,15,16].

The activation and proliferation of MuSCs are affected not only by signals from the injured muscle itself but also by additional cell types, particularly immune cells such as macrophages. For instance, macrophages support the proliferation and differentiation of MuSCs by discharging inflammatory cytokines (such as TNF-α (tumor necrosis factor α) and IL-6(interleukin-6)) and factors essential for MuSCs proliferation (such as IGF-1) [15]. In addition, other types of immune cells, resembling eosinophils, also participate in modulating MuSCs function, for instance, by secreting IL-4 to improve MuSCs proliferation and differentiation, thus enhancing muscle regeneration [15]. With aging, both the number and regenerative capacity of MuSCs decrease, a phenomenon particularly evident in athletes and the elderly. PE can affect MuSCs activities and muscle regenerative capacity, with appropriate PE considered to boost MuSCs function, thereby aiding in sustaining muscle health and regenerative ability [16].

2.1.2. Activation and Differentiation

Activated MuSCs experience proliferation, differentiation, and fusion processes, ultimately forming new muscle fibers or merging with existing fibers to repair damage. During the proliferation stage, they express specific markers such as Myf5 and MyoD. Myf5 and MyoD are muscle-specific transcription factors essential for MuSCs differentiation [17,18]. These findings confirm that during the activation phase, MuSCs express MyoD and Myf5, marking their transition from a dormant to an activated state. The expression of MyoD and Myf5 is a key step in the cell differentiation process during muscle regeneration, with their activity directly affecting muscle repair and regeneration [19]. Therefore, Myf5 and MyoD play a core role in the activation, proliferation, and differentiation processes of MuSCs, becoming muscle-specific transcription factors essential for the repair process following muscle injury.

2.1.3. Self-renewal

The self-renewal capacity of MuSCs is achieved through asymmetric cell division, where a subset of cells remains undifferentiated while an additional subset embarks on a differentiation pathway, a fact indicated by numerous studies. Previous review stressed that with aging, the ability of MuSCs to undergo symmetric and asymmetric division is affected, a process modulated by both intrinsic and extrinsic complex mechanisms. This stresses several perspectives of MuSCs fate renewal under normal and aging conditions, comprising the balance between self-renewal and committed division, causing muscle regeneration, homeostasis, aging, and

disease [20]. Additionally, the heterogeneity of MuSCs and the molecular mechanisms during the self-renewal process are vital. MuSCs constitute a heterogeneous population, displaying this heterogeneity not only in gene expression and cell surface marker analysis but also in their functional capacity for self-renewal and differentiation. A study elaborated on two clear modes of cell division for MuSCs self-renewal: one through asymmetric division discharging progeny committed to myogenic differentiation and self-renewing progeny; the additional through symmetric division generating two functionally identical 'stem' progeny. This process is modulated by various gene expressions, cellular microenvironments, and niche signaling [13].

2.1.4. Environmental dependence

The activity of MuSCs is profoundly affected by their surrounding microenvironment, which includes the extracellular matrix (ECM), neighboring cells, and discharged signaling molecules. These factors collectively regulate the activation, proliferation, and differentiation processes of MuSCs.

Precise regulation of the cell cycle is essential for ensuring the appropriate advance of MuSCs through these overlapping states. In adult resting muscle, MuSCs are in a dormant state known as quiescence or reversible G0 phase. Besides, a studyhave uncovered the Notch signaling pathway as a primary regulator of the quiescent state in MuSCs, particularly, Notch signaling activity is higher in quiescent MuSCs (QSCs) than in activated myogenic cells, likely mediated by the interaction between the Notch ligand Delta1 expressed on muscle fibers and the Notch receptor and its co-receptors, syndecan 3, on MuSCs [8]. In addition, the activation and differentiation of MuSCs are also affected by intercellular interactions within the macroenvironment. For instance, various types of macrophages improve MuSCs proliferation and additional macrophage recruitment by discharging pro-inflammatory cytokines (such as TNF-α and IL-6), thereby supporting MuSCs proliferation and differentiation [15]. Angiogenesis is also essential for successful muscle regeneration by restoring blood supply in injured skeletal muscle. A study indicated that Vascular Endothelial Growth Factor (VEGF) increases skeletal muscle repair by facilitating angiogenesis [11].

Additionally, the behavior of MuSCs during muscle repair is also affected by the dynamic remodeling of the muscle microenvironment. MuSCs are inherently in a hypoxic state within their niche, with QSCs expressing HIF2A but not HIF1A, showing role of HIF-mediated hypoxic signaling in sustaining the quiescent state of MuSCs under hypoxic conditions [21]. Conversely, specific proteins discharged from damaged muscle fibers, such as tenascin-C and GAPDH, have been displayed to induce the activation and proliferation of MuSCs. Besides, various factors derived from macrophages (such as TWEAK, GFD3, GDF15, and IGF1) have been recognized as regulators of MuSCs proliferation and differentiation [4].

These findings emphasize the complex interactions between MuSCs and their microenvironment during skeletal muscle regeneration, comprising intercellular interactions, the impact of signaling molecules, and regulation under hypoxic conditions. These interactions ensure that MuSCs can properly activate, proliferate, and differentiate after injury, thereby facilitating muscle recovery and regeneration.

2.1.5. Response to mechanical stress

MuSCs are highly sensitive to mechanical stress, and PE, among additional forms of mechanical stress, can improve the activation and proliferation of MuSCs, thus supporting muscle growth and repair after PE. A study illustrated that PE boosts the accumulation of MuSCs and the enhancement of myofiber nuclei in a load-dependent manner. The experimental setup included various degrees of mechanical load to study its effect on muscle hypertrophy. Findings stressed that with enhanced PE load, the contribution of MuSCs to myofibers also increased, determining that PE can activate MuSCs to improve muscle growth and repair [1].

2.2. Role of MuSCs in muscle development, maintenance, and repair

2.2.1. Muscle development

During embryonic development, MuSCs originate from the mesoderm and serve as the pivotal stem cells for skeletal muscle regeneration. These MuSCs remain quiescent within the adult skeletal muscle, located between the basal lamina and the sarcolemma of the muscle fiber. Upon physiological stimuli or injury, they are activated and partake in muscle regeneration through symmetric or asymmetric division. Symmetric division yields two identical daughter cells (Pax7+), maintaining the SC pool in adult skeletal muscle. Conversely, asymmetric division generates both committed (Pax7+/Myf5+/Myod1+) and stem cell (Pax7+) progeny. Committed SCs (Pax7−/Myf5+/Myod1+) can also proliferate through symmetric division to augment the number of myogenic precursors, thereby playing a vital role in muscle regeneration [22]. Evidence confirms the heterogeneity of SCs, proving that despite the majority of MuSCs expressing Pax7, which once caused the belief that they were a homogeneous group of myogenic precursors, gene expression and cell surface marker analyses have revealed MuSCs as a heterogeneous population. Beyond Pax7, numerous MuSCs also express Myf5, M-cadherin, α7-integrin, CD34, Syndecan-3/4, or calcitonin receptor, among others. This heterogeneity is signified in their varied capabilities for activation, proliferation, and differentiation following muscle damage [13].

As development progresses, MuSCs position beneath the basal lamina of mature muscle fibers, poised to cause growth and regeneration. In mature muscle, these cells remain quiescent but play a decisive role in enhancing muscle fiber number and volume through proliferation and differentiation during growth periods. In details, upon stimulation, such as post-injury or following PE, MuSCs activate from quiescence, undergo proliferation, and eventually differentiate into muscle fibers, thus facilitating muscle growth and repair [23]. **Figure 2** illustrates Cellular interactions and signaling pathways of MuSCs in skeletal muscle maintenance and repair.

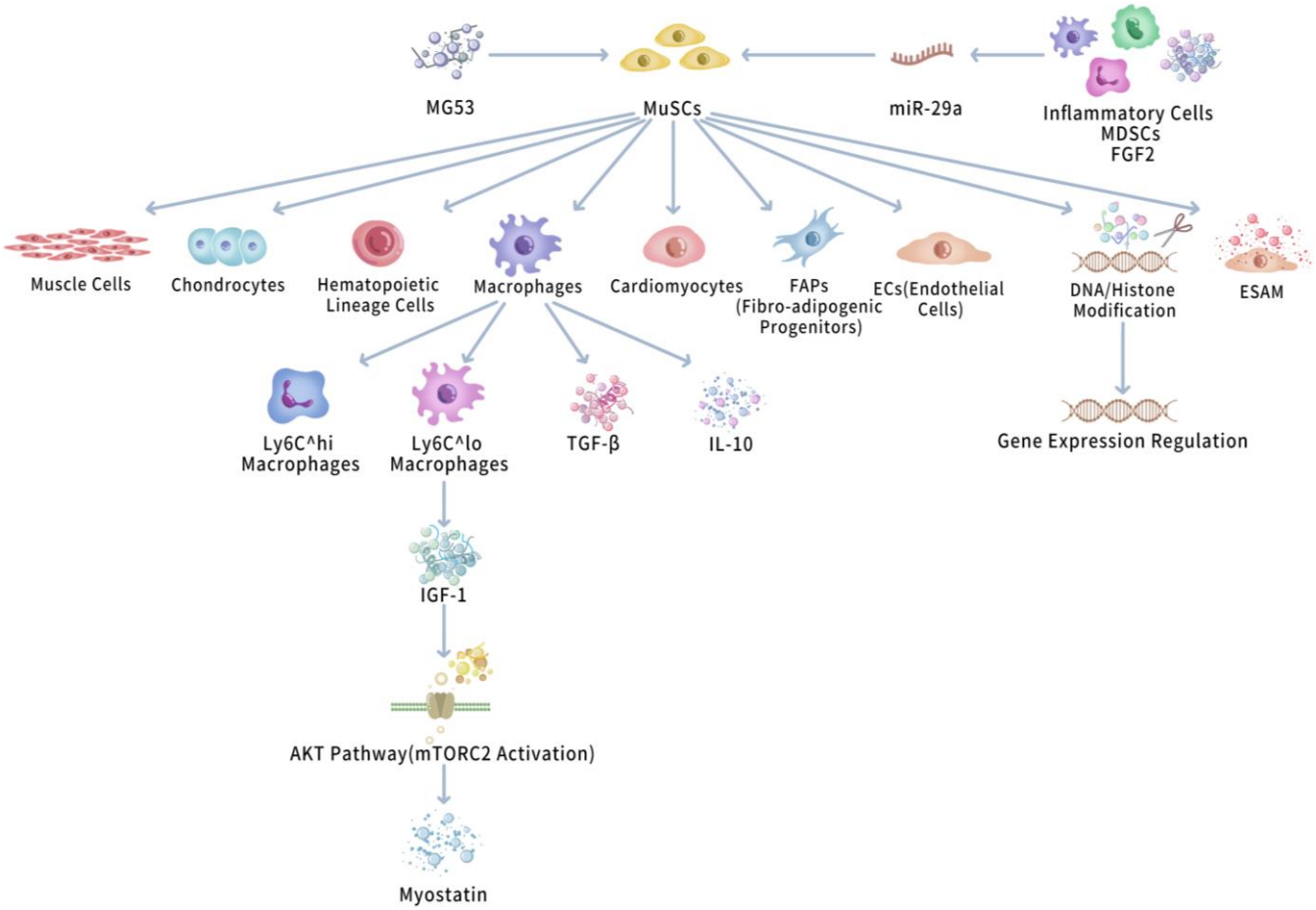

Figure 2. Cellular interactions and signaling pathways of MuSCs in skeletal muscle maintenance and repair.

This figure illustrates the regulatory mechanisms of skeletal MuSCs and their roles in muscle tissue regeneration and repair. It shows that MuSCs influence various cell types within the tissue, including muscle cells, chondrocytes, hematopoietic lineage cells, macrophages, cardiomyocytes, FAPs, and ECs. MuSCs regulate gene expression and histone modifications through specific factors, such as miR-29a and MG53, while also inhibiting the negative effects of inflammatory cells (MDSCs) and FGF2. In the regulation of macrophages, MuSCs activate different macrophage subtypes (Ly6C^hi and Ly6C^lo), which subsequently release IGF-1 to activate the AKT pathway (specifically mTORC2), ultimately regulating the expression of myostatin. Additionally, factors such as TGF-β and IL-10 play critical roles in immune modulation and tissue repair. Overall, these mechanisms work in concert to facilitate muscle regeneration, repair, and gene expression regulation.

2.2.2. Muscle maintenance

In adult muscle, MuSCs, though constituting a minor fraction of the total muscle fiber count, are essential for sustaining muscle integrity and function. As adult MuSCs, they are responsible for tissue homeostasis and post-injury repair, ensuring skeletal muscle integrity. Research illustrates that MuSCs, alongside multipotent myogenic stem cells (MDCSs), exhibit diverse differentiation capacities, capable of differentiating not only into muscle cells but also into chondrocytes, cardiomyocytes, and hematopoietic lineage cells, highlighting their core role in

muscle injury repair [24]. In addition, MuSCs plays a core role in skeletal muscle regeneration. Skeletal muscle fibers often incur damage during strenuous activities, and the quantity of MuSCs along with the pace of the regeneration process directly impacts the training schedule of athletes. This process depends on the involvement of inflammatory cells. Under the control of various factors discharged by MuSCs upon muscle fiber damage and at different regeneration stages, MuSCs participate in multiple responses and pathways, although not all these factors are fully identified [16]. Therefore, MuSCs are indispensable in the maintenance, repair, and regeneration of adult muscle. QSCs can swiftly respond to injury signals, entering an active state, pivotal in muscle regeneration. Following injury, MuSCs interact with immune cells (such as macrophages), fibro-adipogenic progenitors (FAPs), and endothelial cells (ECs), engaging in activation, proliferation, and differentiation to replenish new muscle fibers or repair damaged ones [15]. Notably, macrophages play an indispensable role in muscle regeneration, facilitating MuSCs proliferation and differentiation through the secretion of inflammatory factors and engaging in various stages of muscle regeneration [15]. Additionally, the metabolic state profoundly impacts MuSCs function. The metabolic regulation of MuSCs is tightly realeted to their epigenetic status, with various metabolites directly engaging in the modification of DNA or histones, thereby modulating gene expression, affecting cell fate, and functionality [25]. Besides, the functions of macrophages in muscle regeneration change continuously with the regeneration steps, with Ly6C^hi macrophages dominating the early post-injury phase, transitioning to repair-facilitating Ly6C^lo macrophages, discharging factors like Insulin-like Growth Factor-1 (IGF-1) to improve MuSCs activation and differentiation [15]. IGF-1 positively modulates muscle regeneration, affecting muscle fiber growth through the activation of the AKT pathway, where mTORC2 plays a core role in Akt activation, along with roles of IGFBPs, mechanical signals, and myostatin in modulating the IGF1-Akt signaling pathway [26]. In addition, macrophages can also produce IL-10 and TGF-β, factors whose levels enhance during the post-injury regeneration process, engaging in modulating muscle regeneration and repair processes [15]. This mechanism ensures muscle can repair minor daily wear and tear, sustaining its structural and functional integrity, even without significant damage.

Ultimately, MuSCs are crucial for adult muscle maintenance and repair, responding to injury by activating, proliferating, and interacting with immune and additional cells. Macrophages support MuSCs activities, while metabolic regulation and IGF-1/Akt signaling play core roles in muscle regeneration. The specific mechanisms involved are represented in **Figure 2**.

2.2.3. Muscle repair

MuSCs play a vital role in the repair process following muscle injury. Overuse, trauma, or disease-induced muscle damage activates MuSCs. These cells proliferate and differentiate into muscle cells, replacing damaged muscle fibers or fusing with existing fibers to restore muscle structure and function. One study stressed the crucial expansion of myogenic progenitors within the skeletal muscle niche for muscle regeneration. The activation of these progenitors' counters on the disassembly of the basal lamina and the increase of growth factors such as Fibroblast

Growth Factor-2 (FGF2). The microRNA profile uncovered FGF2-induced miR-29a-mediated myogenic cell proliferation, showing the involvement of microRNA-based regulatory mechanisms in muscle regeneration [27]. Besides, the role of MG53 (a key protein in muscle membrane repair) has been highlighted in the context of muscle dystrophy and heart failure. In animal models, systemic delivery of MG53 via gene therapy has displayed promising cause boosting muscle membrane integrity and alleviating symptoms of muscle dystrophy and heart failure, stressing the potential of targeting muscle membrane repair mechanisms as a therapeutic strategy for muscle-related diseases [28].

MuSCs are not only capable of repairing damage but also retain a portion of cells to revert to a quiescent state through self-renewal mechanisms, preparing for future repair needs. Sudo T, et al.'s research uncovered that the expression of endothelial cell-selective adhesion molecule (ESAM) effectively confirms the activation status of hematopoietic stem cells (HSCs). ESAM levels clearly signify the quiescence and activation transition among HSCs, where HSCs with high ESAM expression, despite being in an active division state, still maintain high long-term reconstitution capability [29]. This shows the significance of ESAM in HSCs reverting to a quiescent state and their involvement in future injury repair, essential for long-term muscle health, particularly after repeated injuries or as age advances.

Ultimately, MuSCs are crucial for muscle repair after injury, activated to regenerate muscle fibers. Growth factors like FGF2 and microRNAs (e.g., miR-29a) modulate this process. MG53 supports repair muscle membranes and indicates promise in gene therapy for muscle disorders. ESAM marks hematopoietic stem cell activation, significantessential for sustaining long-term muscle health. These mechanisms are depicted in **Figure 2**.

2.3. Regulatory signaling pathways of MuSCs activities

When investigating the regulatory signaling pathways of MuSCs, it's crucial to identify how these pathways interact to sustain and activate MuSCs. This section explores the fundamental concepts and functions of these regulatory pathways in detail. The chapter centers on the Notch, Wnt, TGF-β, PI3K/Akt, and MAPK/ERK signaling pathways. Through the coherent explanation in these sections, we obtain a comprehensive understanding of how various pathways collectively affect MuSCs behavior and their vital role in muscle health and repair. Each pathway provides unique insights and underlying therapeutic targets. Roles of these pathways in MuSCs are presented in **Table 1**.

Table 1. Regulatory signaling pathways linked to MuSCs, key interactions, and their context of expression and activation.

Signaling Pathway	Role in MuSCs	Key Interactions and Effects	Expression and Activation Contexts	References
Notch Signaling Pathway	Maintains and activates MuSCs.	Directly induces genes like Hey1, HeyL, and Hes1 to maintain undifferentiated state. Essential interactions with immune cells and ECs for proper muscle regeneration.	Activated during muscle maintenance and regeneration; inhibited can cause premature differentiation.	[15,30,31]

Table 1. (*Continued*).

Signaling Pathway	Role in MuSCs	Key Interactions and Effects	Expression and Activation Contexts	References
Wnt Signaling Pathway	modulates proliferation and differentiation of MuSCs.	Upregulation of MyoD-dependent myogenin expression. β-catenin's role in differentiation and control of cell-cell interactions at the membrane.	Activated during muscle differentiation; essential for the transition from proliferation to differentiation.	[32–34]
TGF-β Signaling Pathway	Balances activation and inhibition of MuSCs.	Interacts with IL-33 in renal fibrosis, showing cross-talk with additional pathways.	Activated to maintain quiescence or during differentiation in specific environments like inflammation.	[36–39]
PI3K/Akt Signaling Pathway	Maintains cellular survival, proliferation, differentiation. Involved in various cellular functions comprising metabolism and apoptosis.	Involved in cellular response to IGF1 and mechanical signals, modulating growth and differentiation.	Frequently activated in cancer; essential for muscle satellite cell proliferation and response to stress.	[40–44]
MAPK/ERK Signaling Pathway	Activates and differentiates MuSCs.	Activates transcription factors in the nucleus, modulating gene expression for cell cycle and differentiation.	Activated in response to muscle injury, stress, and growth factors; essential for muscle repair and hypertrophy.	[4,45,47–48]

2.3.1. Notch signaling pathway

The Notch signaling pathway plays a pivotal role in the maintenance and activation of MuSCs. In a quiescent state, Notch signaling supports maintain the MuSCs pool by hindering cell division and facilitating the maintenance of an undifferentiated state. The pathway is crucial in balancing the MuSCs pool by directly inducing target genes such as Hey1, HeyL, and Hes1 through Rbp-J-NICD (Notch Intracellular Domain) to sustain MuSCs in an undifferentiated state [30]. Inhibition of Notch signaling lowers MuSCs proliferation capacity, causing premature differentiation. Intriguingly, the absence of Notch activity results in enhanced proliferation of MuSCs in uninjured animals at muscle interstitium, showing that Notch is essential for sustaining MuSCs' homeostasis at the muscle interstice, akin to its role in sustaining quiescence in MuSCs in mammals [31]. In addition, interactions between MuSCs and immune cells (e.g., macrophages), FAPs, and ECs are essential for muscle regeneration. These interactions are crucial for proper muscle regeneration. Early post-muscle injury, inflammatory monocytes characterized as Ly6C^hiCCR2^+ are recruited and mainly differentiate into Ly6C^hi macrophages. Ly6C^hi and Ly6C^lo macrophages improve muscle regeneration by supporting MuSCs proliferation and differentiation in various manners [15]. Hence, the Notch signaling pathway plays a significant role in sustaining the MuSCs pool by limiting cell division and facilitating an undifferentiated state, essential for muscle regeneration and sustaining tissue homeostasis.

Notably, the activation of the Notch signaling pathway is critical to the behavior of MuSCs during muscle injury or when regeneration is required. A study confirms that Notch signal activation improves MuSCs activation and entry into the cell cycle while simultaneously restricting premature differentiation, ensuring sufficient cell numbers for the repair process [31]. The dual role of the Notch signaling pathway ensures that MuSCs can respond swiftly when needed, by proliferating to enhance

cell numbers while slowing differentiation to sustain the stem cell pool until a sufficient number of cells accumulate to complete muscle repair and regeneration [15]. Additionally, in interactions with MuSCs, immune cells such as macrophages play an essential role by discharging factors like IGF-1 and TGF-*β*, further facilitating MuSCs activation and differentiation, essential for correct muscle regeneration [15].

2.3.2. Wnt signaling pathway

The Wnt signaling pathway plays a considerable role in the proliferation and differentiation of MuSCs. Activated Wnt signaling, by upregulating the expression of muscle-specific transcription factors like MyoD and Myogenin, boosts the transition of MuSCs from a proliferative state to a differentiated state. In detailsParticularly, the Wnt3a/*β*-catenin signal governs multiple steps in adult myogenesis, comprising facilitating early muscle differentiation, through the induction of MyoD-dependent myogenin expression [32]. Besides, *β*-catenin is essential for the differentiation of primary myoblasts, through cooperation with MyoD and *α*-catenin. *β*-catenin's nuclear function, in cooperation with MyoD, coordinates the expression of a plethora of muscle-specific genes, while its interaction with *α*-catenin at the membrane assists in governing cell-cell interactions [33]. Research also indicates that canonical Wnt signaling is involved in the transition from cell proliferation to muscle differentiation, with overexpression of Wnt4 profoundly enhancing muscle differentiation of C2C12 cells, showing that Wnt4 can improve muscle differentiation and induce C2C12 cell fusion [34]. These findings highlight the essential role of Wnt signaling in modulating the transition of MuSCs from proliferation to differentiation, particularly through the regulatory expression of MyoD and Myogenin, offering an understanding of the molecular mechanisms for muscle repair and regeneration.

In addition, Wnt signaling is critical to the self-renewal capabilities of MuSCs, profoundly affecting the long-term ability for muscle regeneration. A study highlights the role of LSD1 in modulating Wnt/*β*-catenin signaling, which is essential for the fate of MuSCs during the skeletal muscle regeneration process. LSD1 assists in balancing nuclear *β*-catenin through demethylation of lysine 180, which is crucial for the recruitment of *β*-catenin to the MyoD1 core enhancer region, thereby initiating the differentiation commitment of MuSCs. This process also involves role of LSD1 in facilitating Wnt3A-mediated mitotic spindle orientation, stressing the complexity and significance of Wnt signaling in muscle regeneration [35]. Additionally, the diversity and self-renewal of muscle MuSCs, including MuSCs, stress the complex mechanisms modulating muscle regeneration. MuSCs expressing Pax7 are essential for the regeneration of adult skeletal muscle, signifying the necessity of these cells in sustaining muscle health and functionality [13].

2.3.3. Transforming growth factor-*β* (TGF-*β*) signaling pathway

The TGF-*β* signaling pathway has a dual effect on the activity of MuSCs. Precise regulation of the TGF-*β* signaling pathway is essential for balancing the activation and inhibition of MuSCs, as well as for facilitating effective muscle repair.

It can inhibit the proliferation and differentiation of MuSCs through Smad protein-mediated signal transduction, sustaining their quiescent state. This pathway

operates through a series of molecular interactions involving TGF-*β* ligands, type I and II serine/threonine kinase receptors, and the Smad protein family, mediating signal transduction to the nucleus to control gene expression. In details, TGF-*β* ligands are synthesized as precursors, activated in the ECM, where they can bind to cell surface receptors. When TGF-*β* ligands bind to type II receptors, which then phosphorylate and activate type I receptors, the signal transduction process begins. This activation boosts the phosphorylation of receptor-modulated Smads (R-Smads), particularly, Smad2 and Smad3 of the TGF-*β* signal. Once phosphorylated, R-Smad forms a complex with Smad4 (a common Smad (Co-Smad)) and translocates to the nucleus, where they modulate the transcription of target genes [36]. Additionally, signal transduction is finely tuned by I-Smads, such as Smad6 and Smad7, establishing a negative feedback loop to regulate the pathway's activity. I-Smads can inhibit the phosphorylation of R-Smads and their complex formation with Smad4, thus modulating the signal transduction of TGF-*β* family cytokines [36]. In the context of HSCs, which share regulatory mechanisms with MuSCs, TGF-*β* signaling has been displayed to affect cell proliferation and maintenance. TGF-*β* can strengthen or lower the growth of specific cell types or lineages in the hematopoietic system, stressing its role in sustaining cellular quiescence and preventing over-proliferation [37].

Conversely, in several cases, TGF-*β* signaling can also improve cell differentiation, particularly in an inflammatory environment. Evidencesy have observed that TGF-*β* signaling modulates muscle satellite cell differentiation through the phosphorylation of Smad3. For instance, one study displayed that in the case of CSRP3 gene silencing, differentiation of chicken muscle MuSCs was profoundly lowered by facilitating the activation of TGF-*β*/Smad3 signaling [38]. Additionally, the interaction between TGF-*β* signaling and additional signaling pathways is one of the significant mechanisms modulating cell differentiation. For instance, IL-33 improves the phosphorylation of Smad2 and Smad3 through interaction with TGF-*β*R, enhancing the production of the ECM in the context of renal fibrosis, playing a core role in facilitating renal fibrosis [39].

2.3.4. PI3K/Akt signaling pathway

PI3K/Akt signaling pathway plays a pivotal role in sustaining cellular survival, proliferation, differentiation, among additional functions, being indispensable particularly during embryonic development and in the self-renewal and fate determination of pluripotent stem cells. This pathway plays its effects by facilitating various cellular functions such as phagocytosis, metabolic reactions, cell growth, and survival. The activation of its key components (PI3K, AKT, and mTOR) is frequently uncovered in a multitude of cancers, highlighting its significance in cell biology [40].

The activation of Akt plays a crucial role in processes such as cell survival, proliferation, metabolism, motility, and apoptosis. Akt acts as the core of a signaling network, becoming a focal point of research owing to its vital role in cellular life activities. It improves survival by restricting apoptotic pathways and activating pro-survival pathways [41]. During Akt activation, Akt phosphorylates and hinders several pro-apoptotic members of the Bcl-2 family, comprising Bad, Bax, and Bim,

and also inhibits the expression of pro-apoptotic factors Bim and Noxa by directly restricting and excluding the pro-apoptotic transcription factor Forkhead Box O(FOXO3a) [41]. Besides, AKT positively modulates the anti-apoptotic pathway through phosphorylation and activation of the NF-κB transcription factor, thereby facilitating the transcription of anti-apoptotic genes BCL-2 and BCL-XL [42]. AKT also phosphorylates and activates the pro-survival protein XIAP, which increases its binding to caspases 3, 7, and 9, vital enzymes for the induction of apoptosis [41,42]. AKT also plays a critical pro-survival role in the mTOR signaling pathway by phosphorylating and activating the mTOR kinase, thus causing the phosphorylation and activation of the anti-apoptotic protein Mcl-1 [41,42]. In details, Akt improves the proliferation of muscle MuSCs by activating the mTOR Complex 1 (mTORC1). This shows in the positive regulation of cellular survival by the AKT signaling pathway, comprising the activation of the anti-apoptotic protein Mcl-1 through phosphorylation and activation of the mTOR kinase (Spandidos Publications) [42].

In addition, Akt is involved in modulating cell differentiation, impacting the expression of muscle-specific genes through various mechanisms. This process is tightly linked tolinked to multiple signaling pathways and cellular mechanisms. For instance, studies on PIP5K1α emphasize its upregulation during myoblast differentiation, mediated by Akt activation and calcium release, essential for muscle differentiation. Knockout of PIP5K1α hinders C2C12 differentiation, stressing its vital role in this process [43]. Besides, the IGF1-Akt pathway is a component of the regulation of skeletal muscle growth, with Akt serving as a core mediator. This pathway is regulated by various factors, comprising mechanical signals and myostatin, displaying its regulatory complexity. The activation of Akt is essential for the phosphorylation of downstream targets involved in cell growth and differentiation, such as FoxO and mTORC2 [26]. Mechanical stress also plays a significant role in modulating cellular functions, comprising facilitating the biological functions of C2C12 myoblasts through the activation of the PI3K/AKT/mTOR signaling pathway. This stresses the significance of environmental cues in muscle cell differentiation and growth, further highlighting the multifaceted role of Akt in these processes [44]. These studies collectively emphasize the significance of Akt in modulating cell differentiation through its interactions with various signaling molecules and response to mechanical stress, particularly within muscle cells.

2.3.5. MAPK/ERK signaling pathway

The MAPK/ERK signaling pathway plays a pivotal role in the activation and differentiation of muscle MuSCs. Activation of ERK is critical in modulating downstream transcription factors and target gene expression, profoundly affecting the proliferation and early differentiation stages of MuSCs. This process is mediated through the ERK/MAPK signaling pathway, which is essential for governing cell growth, development, division, and apoptosis. The ERK/MAPK pathway involves a series of phosphorylation events, commencing with the activation of upstream Ras proteins, causing the activation of Raf (MAP3K), then activating MEK (MAP2K), and culminating in the activation of ERK (MAPK). Once activated, ERK translocates to the nucleus where it affects the activity of transcription factors and the

expression of target genes essential for cellular processes [45]. In the context of muscle regeneration and hypertrophy, MuSCs activate and proliferate in response to various signals, playing a core role in muscle repair and growth by entering the cell cycle and differentiating into myocytes, which then fuse to form new muscle fibers or repair damaged ones. The activation and proliferation of MuSCs can be affected by mechanical stress, cytokines, growth factors, and the ECM. The ERK pathway supports the early response post-activation of MuSCs by modulating the expression of immediate early genes such as Jun, Egr1, and Fosb. In addition, environmental and specific signals, like those from damaged muscle fibers or macrophage-derived factors, play a crucial role in identifyingidentifying the behavior of MuSCs in the muscle regeneration process [4].

Besides, ERK plays a vital role in responding to environmental stresses, comprising inflammation and mechanical stress, thereby affecting the functionality of MuSCs. A review on role of ERK1/2 signaling pathway in ischemia-reperfusion injury stressed that ERK1/2, a crucial component of the MAPK family, is involved in various physiological processes through signal transduction from surface receptors to the nucleus, engaging in gene expression regulation, governing numerous physiological processes, and can cause reparative or cell death outcomes depending on the context [46]. Anadditional comprehensive review on ERK as a regulator of cell growth, inflammation, and gene expression elucidated that once activated, ERK1/2 moves to the nucleus to activate transcription factors, thus modulating genes responsible for cell cycle advance, differentiation, and response to environmental stimuli. This mechanism stresses the pathway's significance under various pathological conditions, such as cancer, chronic inflammation, and osteoporosis, stressing its potential as a therapeutic intervention target [47]. In addition, research on the dynamics and control of the ERK signaling pathway stresses its complexity, comprising feedback loops that modulate the amplitude, duration, and frequency of ERK signaling. These feedback mechanisms are essential for identifying cellular responses to external stimuli, illustrating the pathway's adaptability and precision in governing cellular outcomes [48].

These insights collectively show the multifaceted role of the ERK signaling pathway in mediating cellular responses to environmental stresses, comprising its involvement in inflammation and mechanical stress, which are essential for the normal function and regulation of MuSCs.

3. The impact of PE on muscle structure and function

3.1. How PE impacts the types and sizes of muscle fibers

PE impacts the type and size of muscle fibers through the activation of MuSCs, a crucial perspective of muscular adaptative changes. MuSCs, pivotal in muscle regeneration, are activated under muscle damage or pathological conditions to proliferate and differentiate, with the Notch signaling pathway playing a core role in sustaining MuSCs quiescence. This pathway assists in sustaining MuSCs dormancy by various means, comprising maintaining Pax7 expression, suppressing MyoD expression, and enhancing MuSCs positioning [49]. Muscle fibers can be categorized into type I (slow-twitch), IIa (fast-twitch, fatigue-resistant), and IIx (fast-twitch,

fatigable) types [25]. These fiber types possess clear physiological characteristics and functional roles. For instance, slow-twitch fibers (type I) mainly apply fats for energy production, showcasing higher endurance and oxidative capacity, whereas fast-twitch fibers (type II) count on carbohydrates for energy, displaying lower oxidative capacity and greater fatigability [25]. A shift between muscle fiber types can occur over prolonged PE or under disease conditions, with endurance or resistance training individuals displaying a greater proportion of slow-twitch fibers [25]. **Figure 3** illustrates Mechanisms of PE effects on muscle fiber type and size map.

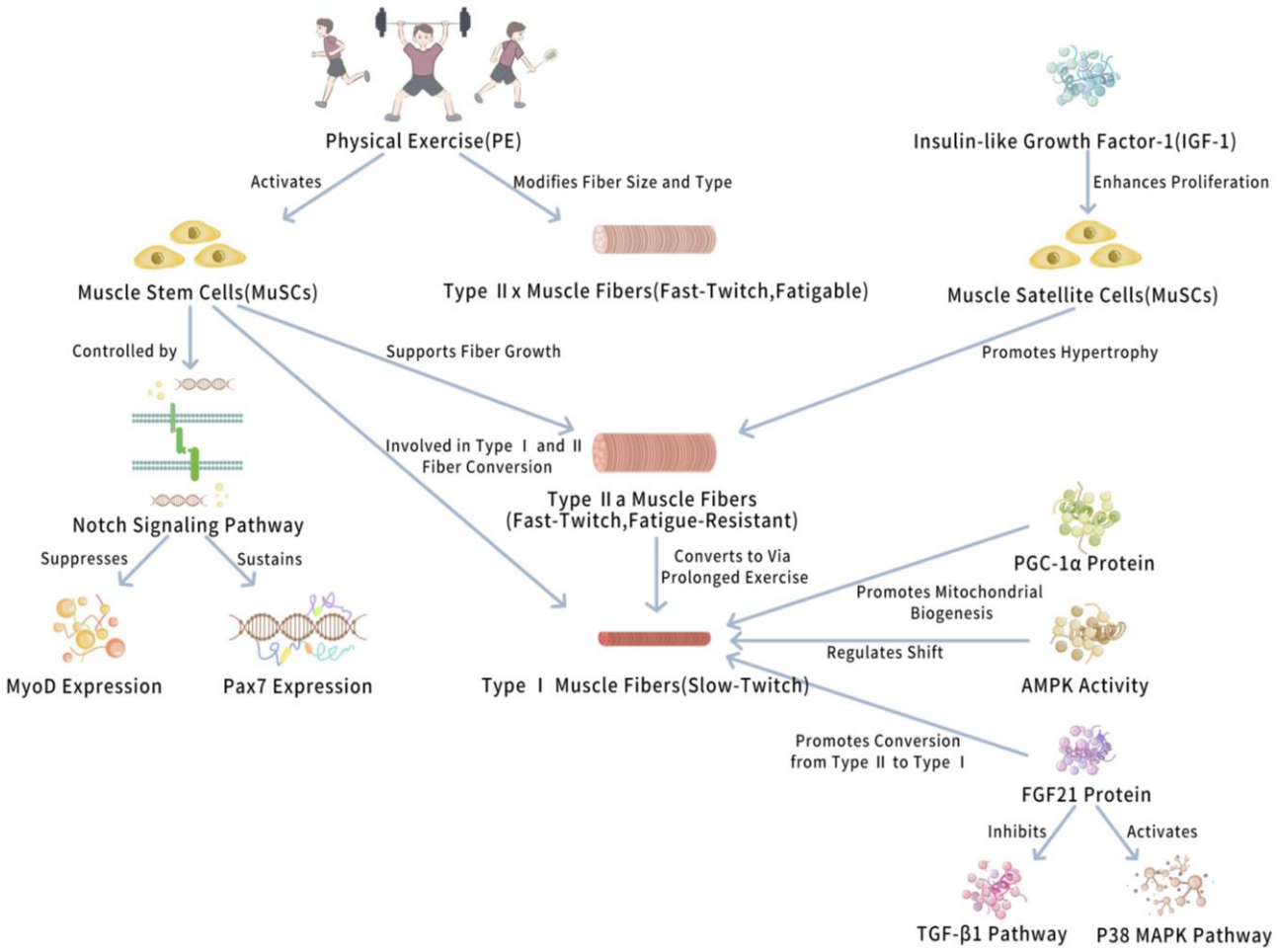

Figure 3. Mechanisms of PE effects on muscle fiber type and size map.

This figure illustrates the mechanisms by which PE regulates muscle fibers and stem cells to promote muscle growth and adaptation. PE activates MuSCs, leading to muscle growth and fiber type modifications. IGF-1 enhances the proliferation of MnSCs, which promotes muscle hypertrophy. MuSCs are regulated by the Notch signaling pathway, which suppresses MyoD expression and sustains Pax7 expression to maintain the functionality of muscle stem cells. PE also impacts muscle fiber size and type. Fast-twitch, fatigue-prone Type IIx muscle fibers can be converted to fatigue-resistant Type IIa muscle fibers through prolonged PE, which can further transition into slow-twitch Type I muscle fibers. This fiber type conversion is facilitated by AMPK activity and PGC-1α protein, which promote mitochondrial

biogenesis and regulate the shift in fiber types. Additionally, FGF21 protein plays a role in promoting the conversion of Type II to Type I fibers by inhibiting the TGF-β1 pathway and activating the P38 MAPK pathway, ensuring a dynamic balance in muscle fiber types during and after PE adaptation.

3.1.1. Conversion of fiber types

Prolonged aerobic exercise, such as running and swimming, has been illustrated to promote the transformation of muscle fibers from fast-twitch (Type II) to slow-twitch (Type I). In this conversion process, the Fgf21 protein plays a pivotal role in modulating muscle growth and function, mainly by restricting the TGF-β1 signaling pathway and activating the p38 MAPK signaling pathway to improve the shift in muscle fiber type. Aerobic exercise increases the levels of Fgf21 in the liver and muscles, triggering the transition from fast-twitch to slow-twitch fibers. This transformation augments muscular endurance, as Type I fibers contain more mitochondria, myoglobin, and oxidative enzymes, making them more suitable for sustained low-intensity activities [50].

Besides, long-term PE induces a shift in muscle fibers from Type II (fast-twitch) to Type I (slow-twitch), especially during endurance training such as long-distance running or cycling. This shift results from a confluence of mechanisms, comprising alterations in intramuscular enzyme activity, adjustments in energy metabolism, and changes in the protein composition of muscle fibers. The expression of peroxisome proliferator-activated receptor gamma coactivator-1 alpha (PGC-1α) protein is tightly linked to the shift in muscle fiber type and mitochondrial biogenesis, while Adenosine monophosphate-activated protein kinase (AMPK) activity plays a crucial role in modulating the transition of muscle fiber type [51]. Owing to their higher mitochondrial content and fatigue resistance, Type I fibers are advantageous in prolonged low-intensity activities, efficiently applying oxygen to generate energy and meeting the demands of endurance activities. Research shows that after extensive endurance training, fast-twitch Type II fibers can convert to slow-twitch Type I fibers, enhancing muscular endurance and oxidative capacity [52]. During weight training or speed training, a conversion from Type I to Type II fibers is uncovered, which is beneficial for rapid force production and speed, essential for explosive or high-intensity activities. A study displayed the fiber type-specific impact of acute PE on the redox state of skeletal muscle in healthy adults, displaying a higher redox ratio in MHC I fibers compared to MHC IIa fibers at baseline, with an enhancement in oxidative protein intensity across all fiber types post-exercise [53]. MuSCs play a vital role in these PE-induced muscle fiber type transitions, contributing additional nuclei and supporting muscle fiber protein synthesis, thereby facilitating the adaptive remodeling of muscles [1].

3.1.2. Increase in fiber size

Resistance training mainly increases muscle strength by facilitating the proliferation and differentiation of MuSCs and augmenting the volume of muscle fibers. Notably, the hypertrophic effect on type II muscle fibers is particularly significant, unveiling the pivotal role of resistance training in muscle augmentation, particularly through modulating the quantity and functionality of MuSCs. These cells play a vital role in the enlargement of type II muscle fibers, which are crucial in the

hypertrophic process following training [16,54]. In addition, the involvement of MuSCs in muscle repair and the expansion of muscle fiber volume under non-damaging conditions stresses their significance. This is particularly evident when muscles experience mechanical stimuli such as weight training, prompting MuSCs to activate from a quiescent state and commence proliferation. Subsequently, these proliferating MuSCs differentiate and integrate into existing muscle fibers, enhancing the number of nuclei and total protein content within the fibers, causing an enhancement in fiber size [3]. This reflects that the magnitude of mechanical load directly impacts the activation and proliferation of MuSCs, thereby impacting muscle fiber growth. Further exploration shows that PE-induced muscle hypertrophy not only illustrates load dependency but also varying degrees of MnSC accumulation and muscle fiber growth in both animal and human studies, where higher loads are linked to larger muscle fiber volumes and greater strength generation capabilities [1,3]. These findings stress the significance of appropriate training intensity for strengthening muscle enlargement and highlight the need for adequate protein intake to maintain this process.

In addition to mechanical load, endocrine factors like growth hormone, testosterone, and Insulin-like IGF-1 also play a crucial role in muscle enlargement. In details, role of IGF-1 in skeletal muscle hypertrophy has been extensively confirmed, displaying its significance in enhancing the proliferative capacity of muscle MuSCs and its close association with the development of muscle mass and strength [55,56]. Additionally, the synthesis of IGF-1 in MuSCs of injured muscle is enhanced, further facilitating the proliferation and myogenic differentiation of MuSCs, showing that moderate PE, like blood flow restriction training, might be tightly linked to the mechanisms facilitating MnSC proliferation [55,56].

3.2. PE-induced muscular adaptations

When exploring the effects of PE on muscular adaptations, we can look at the three main areas of enhanced muscular strength, endurance, and recovery. **Figure 4** depicts PE-Induced muscular Adaptations.

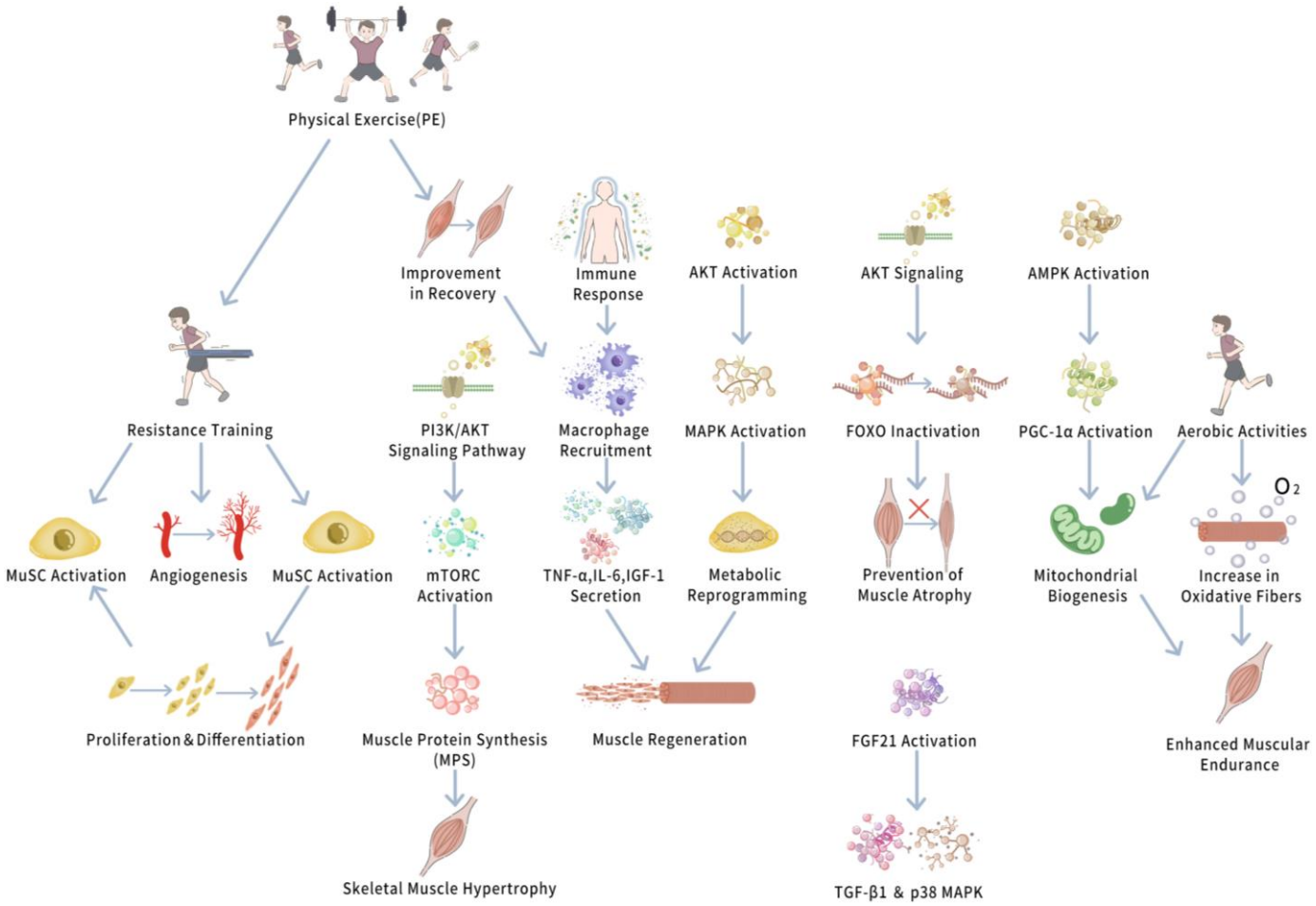

Figure 4. PE-induced muscular adaptations.

This figure illustrates how PE, including resistance training and aerobic activities, enhances muscle function and overall health through multiple signaling pathways. Resistance training activates satellite cells, the PI3K/AKT-mTORC pathway, and angiogenesis, promoting muscle protein synthesis, hypertrophy, and regeneration. Aerobic activities activate AMPK and PGC-1α pathways, enhancing mitochondrial biogenesis, oxidative metabolism, and muscle endurance. Additionally, PE modulates immune responses by recruiting macrophages and driving metabolic reprogramming, while preventing muscle atrophy via FOXO inactivation and supporting regeneration through FGF21 activation. Together, these processes optimize recovery, muscle health, and overall physical performance.

3.2.1. Enhancement of muscle Strength

PE, notably resistance training, has a significant impact on augmenting muscle strength. This process is mainly promoted through the activation of MuSCs, facilitating their proliferation and differentiation, thereby replenishing or enlarging muscle fibers. Notably, research has uncovered that both single sessions and prolonged sixteen-week regimens of resistance training effectively activate MuSCs, a report corroborated through the observation of cells co-labeled with Pax7 and 4’,6-diamidino-2-phenylindole (DAPI), coupled with cells marked with Pax7, MyoD, and DAPI. This stresses the vital role of resistance training in muscular adaptative changes, particularly its positive effects on angiogenesis, which boosts the

availability of components necessary for muscle regeneration [16]. In addition, the research stresses the impact of PE modality on muscle growth and its potential in preventing sarcopenia in the elderly, with moderate-intensity endurance training observed to be essential for enhancing MuSCs numbers. However, it is noteworthy that resistance training activates MuSCs populations in untrained muscles to a greater extent than in muscles accustomed to endurance training cycles, displaying the significant impact of the cellular environment on MuSCs proliferative activity [16].

Besides, PE increases muscle contractility through the enhanced incorporation of myosin within muscle fibers. The PI3K/Akt signaling pathway plays a pivotal role in this process, activating the mTORC complex and thereby augmenting muscle protein synthesis (MPS). Long-term resistance training also causes skeletal muscle hypertrophy, further validating the efficacy of resistance training in facilitating muscle strength and mass [57]. Additionally, Akt improves muscle growth by phosphorylating and thereby inactivating the FOXO transcription factors, which in turn hinders the transcription of muscle atrophy-related genes, further highlighting the crucial role of PE in sustaining and enhancing muscle functionality [58].

Ultimately, PE, particularly resistance training, profoundly boosts muscle strength and adaptability through the activation and augmentation of MuSCs functionality. This process involves multiple signaling pathways and molecular mechanisms, stressing the significance of well-designed training programs in facilitating health and preventing muscle-related diseases.

3.2.2. Enhancement of endurance

It is worth noting that PE, particularly aerobic activities, lays a vital biological foundation for enhancing muscular endurance by strengthening energy utilization in muscles and boosting the oxidative capacity of muscle fibers. This process encompasses not only the promotion of mitochondrial biogenesis but also a significant enhancement in the proportion of oxidative fibers in muscles, thereby effectively augmenting muscular endurance performance. Notably, evident research by Venturaclapier et al [59]. Has elucidated how endurance training profoundly increases the oxidative capacity of skeletal muscle, confirmed by a reduced depletion of phosphocreatine and an increase in ADP during PE, causing an accelerated resynthesis of phosphocreatine, reflecting a substantial enhancement in the oxidative capacity of skeletal muscle [59]. In addition, the work of Luo et al. Extends the knowledge in this domain by exploring how endurance PE-induced Fgf21 triggers the conversion of skeletal muscle fibers via the TGF-β1 and p38 MAPK signaling pathways, displaying that the transformation and functional adaptation of skeletal muscle fiber types in response to endurance training could be mediated by Fgf21 and its downstream signaling pathways [50].

Additionally, aerobic PE plays a crucial role in enhancing the density of blood vessels in muscles and boosting the supply of oxygen and nutrients. AMPK and PGC-1α are key players in this process. According to Liang et al., lifelong aerobic PE mitigates the onset and advance of sarcopenia by activating autophagy and restricting protein degradation, thus enhancing mitochondrial quality control through the AMPK/PGC-1α signaling pathway [60]. In addition, aerobic exercise triggers

mitochondrial biogenesis in skeletal muscle by enhancing both the gene and protein levels of PGC-1α, as corroborated in both murine and human models [61].

Ultimately, these finding stress the pivotal role of aerobic exercise in triggering adaptive changes in muscle, enhancing endurance, and boosting muscular function, particularly through the regulation of various biochemical pathways and molecular mechanisms.

3.2.3. Enhancement in recovery capability

PE plays a dual role in triggering muscle recovery. It is tightly apparent that it improves the functionality of muscles, and additional conversely, it accelerates the recuperation process following muscle injury [15]. This bifunctional effect is attributable to the pivotal roles of immune cells and MuSCs in the PE-induced inflammatory response [15]. In addition, it is noteworthy that macrophages are recruited to the damaged site post-injury, offering support for the proliferation and differentiation of MuSCs. By discharging pro-inflammatory and regenerative factors such as TNF-α, IL-6, and Type I IGF-1, macrophages improve the activity of MuSCs, thereby facilitating muscle regeneration [15].

Further research stresses how PE improves muscle regeneration through clear molecular mechanisms, particularly by affecting the proliferation and renewal of MuSCs. These mechanisms include the activation of AKT and MAPK signaling pathways and metabolic reprogramming, which collectively target the functionality of MuSCs, thus triggering muscle repair and growth [62]. Besides, PE not only fosters the muscle's adaptive capacity and defense against atrophy but also boosts muscle repair through stem cell proliferation. In details in aged mice, PE triggers the regenerative capacity of MuSCs by activating specific molecular regulators, such as the AKT signaling pathway. This process is accompanied by the restoration of cyclin D1 expression, subsequently activating MuSCs, which is essential for health maintenance in an aging society [62].

Ultimately, PE plays a positive impact on muscle recovery and adaptive changes through various mechanisms. These mechanisms involve the interaction between immune cells and MuSCs, activation of signaling pathways, and regulation of metabolic processes. These findings not only increase our understanding of the biological effects of PE but also supply underlying directions for future therapeutic methods.

3.3. Relationship between PE and muscle plasticity

3.3.1. Molecular mechanisms of PE

PE is not only an effective means to trigger our quality of life but also a crucial strategy to improve muscle plasticity. Through precise molecular mechanisms, PE activates signaling pathways essential for muscle growth and prevention of atrophy, thereby unveiling the scientific principles behind it. It is noteworthy that role of the PI3K/Akt signaling pathway is significant as it is key in facilitating muscle growth and preventing muscle atrophy [63,64]. Besides, roles of AMP-activated AMPK and PGC-1α are critically significant in modulating mitochondrial biogenesis and transcriptional activation [65]. Additionally, research confirmed that PE can effectively modulate the PI3K/Akt signaling pathway, AMPK, and PGC-1α in

skeletal muscle, affecting mitochondrial function [66]. This finding stresses the significance of PE in activating these pathways, thus facilitating muscle health. Further studies have displayed those various forms of PE, resembling resistance training [67], aerobic exercise [68], and even blood flow restriction training [56,69], profoundly facilitate muscle quality and strength. This enhancement is achieved through the activation of the IGF-1/PI3K/Akt signaling pathway, which triggers protein synthesis and hinders protein degradation pathways [70].

According to aging and muscle degeneration, role of the IGF-1/PI3K/Akt pathway becomes particularly prominent. In details, IGF-1 increases skeletal MPS through the activation of PI3K/Akt/mTOR and PI3K/Akt/GSK3β pathways, and hinders the ubiquitin-proteasome system (UPS) mediated protein degradation via the PI3K/Akt pathway [63]. Besides, AMPK can activate FoxO factors by phosphorylating various regulatory sites, and the activation of FoxO improves the expression of atrogin-1 and muscle atrophy. However, these effects can be impaired by various mechanisms, such as through PGC1α, which protects mature muscle from FoxO-dependent atrophy [26]. Furthermore, AMPK plays a dual role in the energy state of muscles depending on its activation status. While AMPK activation can inhibit the mTORC1 pathway, lowering protein synthesis under certain conditions, it can also activate the FoxO-dependent protein degradation pathway. Nevertheless, role of PGC-1α is particularly noteworthy as it counters muscle atrophy by restricting FoxO-dependent activation of atrophy-related genes, stressing the complex interplay of these pathways in muscle physiology [26,64]. Through the activation of these mechanisms, PE profoundly modulates the balance between protein synthesis and degradation, identifying overall muscle mass and health status.

3.3.2. Enhancement of mitochondrial function

PE has been displayed by numerous evidences to impact muscle plasticity through the augmentation of mitochondrial quantity and enhancement of their function. Mitochondria are seen as the “powerhouses” of the cells, modulating energy metabolism and engaging in critical cellular processes such as calcium homeostasis and cell survival [71]. In this backdrop, PE is considered a non-pharmacological strategy to safeguard mitochondrial health, triggering the repair/removal of damaged mitochondria and the synthesis of new ones through the regulation of Mitochondrial Quality Control (MQC), thereby restoring metabolic status [71].

In the regulation of muscle plasticity, PGC-1α plays a pivotal role as a key regulatory factor of mitochondrial biogenesis. It activates the transcription of target genes by binding to histone acetyltransferases such as CBP/p300 and SRC-1, and through interaction with the NAD-dependent deacetylase SIRT1 [72]. Although PGC-1α is a vital participant in mitochondrial biogenesis, current evidences confirms that PGC-1α is not an absolute requirement for the induction of mitochondrial biogenesis, thus necessitating further investigation into the necessity of PGC-1α and the potential compensatory roles of additional transcriptional co-activators, particularly in the context of PE [73]. PE induces expression changes in multiple transcription factors, comprising PGC-1α, that are involved in mitochondrial biogenesis. Over time, engaging in PE causes the accumulative increase of PGC-1α

protein and additional significant co-activating transcription factors, such as NRF-1 and their downstream target Tfam, thereby modulating mitochondrial adaptations to PE [72].

These evidences display that PE improves muscle plasticity by enhancing the number and functionality of mitochondria, tightly linked to the activation of molecules like AMPK and PGC-1α. Through the modulation of these molecules, PE not only increases mitochondrial efficiency and quantity but also sustains mitochondrial health, thus boosting muscular endurance.

4. Role of MuSCs in PE

Review have found that MuSCs play a central role in PE, and PE induces the activation and proliferation of MuSCs through mechanical stress and metabolic changes. This process promotes MuSCs repair, remodeling, and long-term adaptation by participating in different biological signaling cascades, including AMPK and mTOR, in combination with a range of growth factors and cytokines (e.g., IGF-1, fibroblast growth factor (FGF), and hepatocyte growth factor (HGF)). In addition, the study found the specific effects of PE type, intensity and duration on the function of MuSCs, and how these cells enhance PE performance and muscle health by promoting muscle fiber type transformation and enhancing muscle regeneration. **Figure 5** illustrates these specific roles of MuSCs in PE in detail.

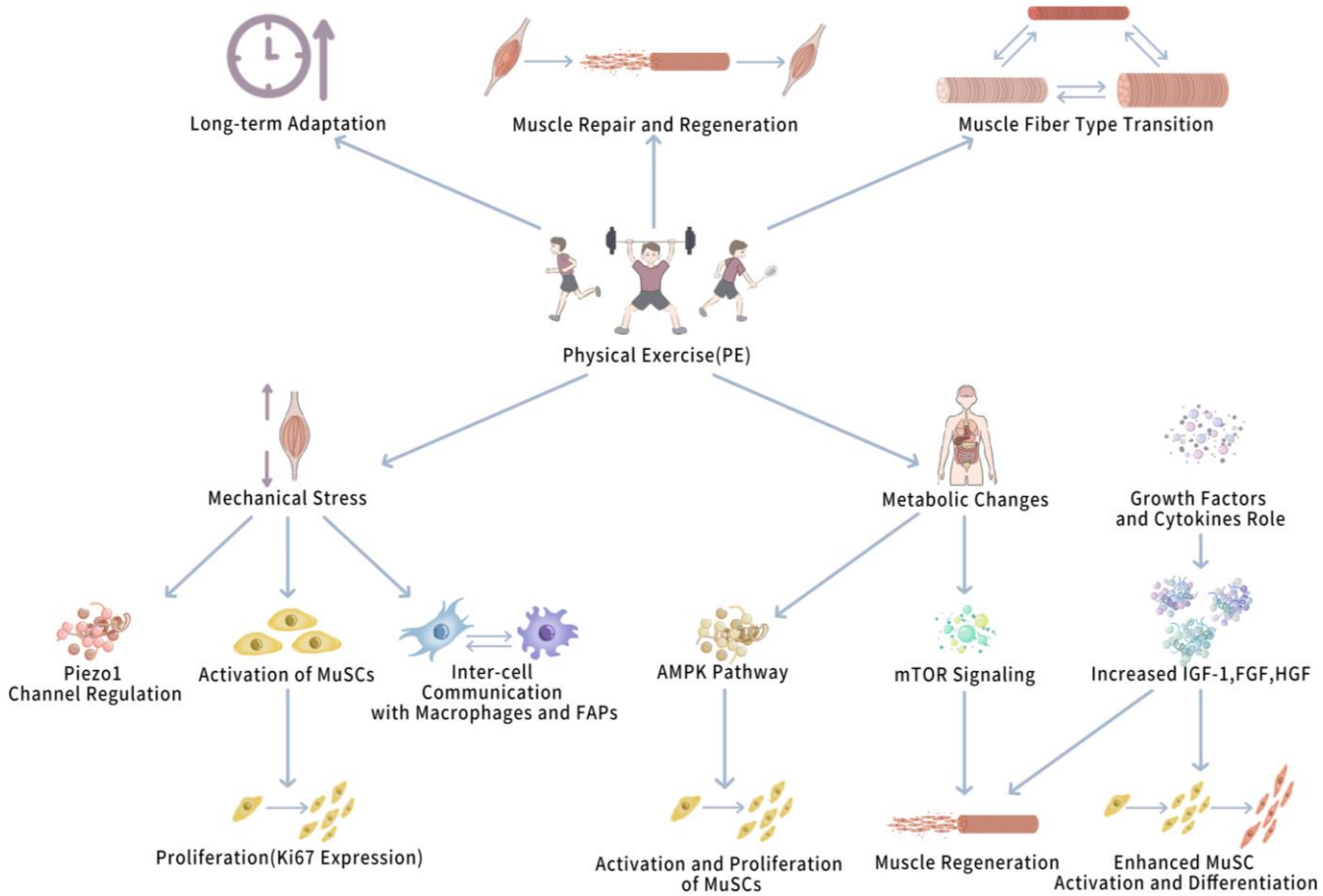

Figure 5. Molecular Mechanisms and Long-term Adaptation Processes of PE facilitating Activation, Proliferation and muscle Regeneration of MuSCs.

This figure illustrates how PE promotes skeletal muscle repair and adaptation through two main pathways: mechanical stress and metabolic changes. Mechanical stress activates Piezo1 channels, enhances the proliferation of MuSCs, and facilitates intercellular communication with macrophages and FAPs, thereby contributing to muscle regeneration. Metabolic changes regulate the AMPK and mTOR signaling pathways, promoting the secretion of growth factors such as IGF-1, FGF, and HGF, which further enhance the activation and differentiation of MuSCs. Additionally, PE induces muscle fiber type transitions and long-term adaptations, improving overall muscle function and repair capacity.

4.1. Activation of MuSCs by PE

4.1.1. Mechanical stress-induced activation

PE plays a significant impact on the muscle microenvironment by generating mechanical stress, particularly in activating muscle MuSCs. Research has determined mechanical stress as a crucial factor in the activation of MuSCs. Fukada et al (2022). in a muscle overload model, displayed that MuSCs subjected to mechanical stress begin to express Ki67, a clear marker of their proliferation. This proliferative response appears around four days post-surgery and continues to increase thereafter [4]. This reflects that mechanical loading, such as that from PE, can directly facilitate the activation and proliferation of MuSCs. Besides, intercellular communication within the muscle plays a vital role. Interactions between MuSCs and immune cells (such as macrophages) and FAPs are essential for the adaptive changes and regeneration of muscle, boosting the activation, proliferation, and eventual differentiation of MuSCs into mature muscle fibers [15].

Under the impact of mechanical stress, the forces transmitted by muscle fibers and the basement membrane act on MuSCs, causing their activation. The Piezo1 channel plays a significant role in skeletal muscle physiology, modulating the activity of myogenic progenitors, skeletal muscle regeneration, and angiogenesis. Its functional expression in MuSCs is tightly linked to skeletal muscle regeneration, and its deletion can even slow the regeneration of muscle fibers post-injury [73]. Additionally, it is evidently clear that changes in the ECM profoundly impact the activation of MuSCs and subsequent skeletal muscle regeneration. Variations in ECM components, resembling laminins and collagens, are linked to the activation process of MuSCs, and the upregulation of laminins is linked to this activation, further highlighting the direct impact of PE on MuSCs activation, with mechanical stress playing a key driving role [74].

Mechanical stress-activated signaling pathways, like PI3K/Akt, MAPK, and Wnt, play a significant role in the transition of MuSCs from a quiescent state to an activated state. These signaling pathways not only impact the activity status of MuSCs but also play an essential role in the transition from the G1 to S phase of the cell cycle. The PI3K/AKT/mTOR and Wnt signaling pathways are in detail significant for the G1-S phase transition, reflecting a process that is notably evident in cancer cells [75]. The MAPK signaling pathway also plays a significant role in modulating erythropoiesis and cell proliferation and survival, stressing its vital role

in cellular processes [76]. These findings stress the complex and precise mechanisms through which PE activates MuSCs via mechanical stress.

4.1.2. Effects of metabolic changes

In the context of the microenvironment of muscle, PE-induced metabolic alterations play a pivotal role in activating MuSCs. These changes, comprising enhanced energy demands and accumulation of metabolic byproducts, promote their activation and proliferation by modulating the metabolic sensing pathways of MuSCs. Apparently, AMP-activated AMPK and the mTOR signaling pathways play core during PE [77]. AMPK, acting as an energy sensor, responds to fluctuations in cellular energy levels by monitoring the ratio of AMP to ATP. This monitoring triggers adaptive responses, such as increased glucose uptake and lipid oxidation, aiding in the maintenance of energy equilibrium. The preservation of this energy balance is essential for muscle health and function [77]. In addition, PE affects the mTOR signaling pathway through AMPK activation, thereby modulating protein synthesis and muscle growth [78]. Additionally, PE-induced metabolic stress may also affect MuSCs, facilitating their responsiveness to energy state fluctuations, thus indicating cellular proliferation and subsequent differentiation [79]. This mechanism signifies how PE optimizes muscle regeneration and repair through metabolic regulation.

In the repair process of damaged muscle, macrophages, by discharging inflammatory factors such as TNF-α and IL-6, improve the proliferation of MuSCs. These cells also support the activation and differentiation of MuSCs by discharging insulin-like IGF-1, thus enhancing the positive effect of PE on muscle regeneration [15]. Research also shows that various disease states, such as Duchenne muscular Dystrophy and age-related metabolic changes, may impact the functionality of MuSCs and muscle regenerative capacity, highlighting the significance of recognizing how PE impacts MuSCs activities and metabolic alterations, and how this knowledge can be utilized to increase muscle regeneration under specific health conditions [80].

4.1.3. Role of growth factors and cytokines

PE profoundly impacts the activation of MuSCs, mainly through the modulation of growth factors and cytokine levels. An evidence published by Koike H, y uncovered that PE can enhance the local and systemic levels of growth factors and cytokines, comprising insulin-like IGF-1, FGF, and HGF, thereby affecting MuSCs activities. In details, role of IGF-1 is stressed as it is discharged by macrophages following muscle injury, thus facilitating the activation and differentiation of MuSCs [15].

Further exploration shows the significance of IGF-1 in muscle regeneration post-exercise, where it activates the Akt signaling pathway, enhancing MuSCs proliferation and survival. This process involves complex control mechanisms, comprising positive and negative feedback loops within the IGF1-Akt pathway. For instance, mTORC2 triggers Akt activity through phosphorylation, while myostatin serves as a negative regulator by restricting Akt, hence governing muscle growth [26]. Within the context of muscle regeneration, macrophages again play a crucial

role by discharging IGF-1 to stimulate MuSCs activation and differentiation, thereby facilitating the muscle regeneration process [15].

Besides, evidence demonstrates that activation of the IGF-1 signaling pathway can improve the differentiation and enlargement of muscle cells, with Akt being a core component in the signaling cascade triggered by the IGF-1 receptor [81]. These findings collectively highlight the vital role of PE in activating MuSCs through the modulation of growth factor and cytokine levels, reflecting underlying mechanisms in facilitating muscle regeneration and repair.

4.1.4. Immunomodulatory role of PE-induced inflammatory response

The local inflammatory response induced by PE, through specific immunomodulatory actions, activates MuSCs, thus triggering muscle repair and regeneration. During this process, immune cells, such as macrophages and T cells, play a vital role at the site of muscle injury. The cytokines they release, such as TNF-α, IL-1β, IL-6, and TGFβ, are essential for MuSCs proliferation, forming an essential component of muscle repair [82].

Of particular interest is role of macrophages, which, by discharging inflammatory cytokines like IL-6 and TNF-α, not only improve MuSCs proliferation but also recruit additional macrophages to participate in the muscle repair process [15]. These immune cells are recruited to the injury site through CCR2 and CX3CR1 signaling pathways, engaging in the early wound response and facilitating muscle regeneration. In the early wound response, specific inflammatory monocytes become macrophages, discharging IGF-1 to further activate MuSCs, thereby supporting muscle regeneration [15].

As the muscle repair process progresses, macrophages with low Ly6C expression release IL-10 and TGF-β, aiding in lowering inflammation and facilitating muscle cell differentiation and regeneration, essential for the ultimate recovery of muscle [15]. Additionally, research on MuSCs themselves shows their core role in muscle repair and regeneration. Even a small number of transplanted MuSCs can fully regenerate muscle, displaying their potent potential in muscle recovery [83]. In addition, the diversity and plasticity of MuSCs in vitro, capable of differentiating into non-muscle cell lineages, may provide new perspectives for future therapeutic strategies [83].

Ultimately, the complex network of interactions between the PE-induced inflammatory response and immune cells in muscle repair and regeneration not only involves the participation of macrophages and T cells but also stresses the core role of MuSCs in responding to injury and inflammation.

4.2. The specific role of MuSCs in muscle remodeling after PE

4.2.1. Proliferation and differentiation

In the backdrop of PE, activated MuSCs proliferate and generate multiple progenies, which is the initial stage of muscle remodeling. These progeny cells then experience differentiation to become myocytes, a vital step in muscle remodeling. Myocytes not only form new muscle fibers, but also fuse with existing muscle fibers, thereby repairing damage [4].

The regulation of this process involves various signaling pathways, including Notch, Wnt, and TGF-β, which play vital roles in identifying the fate of MuSCs. For the Notch signaling pathway, its primary role lies in the activation and proliferation of MuSCs, allowing MuSCs to self-regulate or modulate signals linked to each cell division mode and external communication between sister cells, with NUMB and DNA chains discharging differentiated and self-renewing progeny [20]. Conversely, the TGF-β signaling pathway exhibits significant expression during muscle development and affects the activity of MuSCs. The expression of TGF-β1 is tightly linked to the fiber type composition around the muscle fibers and has a dual role, restricting the proliferation of MuSCs and fusion of muscle fibers, inhibiting the differentiation of fetal myocytes, thus impacting muscle regeneration. It also helps to convert muscle-derived cells into fibrotic cells, facilitating muscle repair processes after injury by modulating inflammation and MuSCs activation [84].

The Wnt signaling pathway also plays a crucial role in muscle dynamics, not only modulating embryonic development and stem cell fate, but also being linked to diseases such as cancer and metabolic disorders. Wnt signaling can be activated in various ways, such as through Wnt mimetics or synthetic peptides like UM206 to initiate the canonical Wnt/β-catenin signaling pathway, which improves tissue regeneration and plays a significant role in neurodegenerative diseases [85]. In addition, notably, recombinant Norrin, a protein that activates the Wnt/β-catenin signaling pathway, observes potential in treating diseases with vascular components because of its promotion of angiogenesis and neuroprotection [85]. The interaction of these cells and signaling pathways shows the complex and finely tuned regulatory mechanisms of MuSCs in the process of muscle remodeling after PE.

4.2.2. Muscle fiber type transition

Evidences have illustrated that PE not only profoundly affects the quantity and activity of MuSCs but also improves the transition of muscle fiber types, a cornerstone of muscular adaptation and performance enhancement. In details, the transition in muscle fiber type is affected not only by the type of training—such as the clear effects of endurance versus strength training—but is also tightly linked to the function and quantity of MuSCs. The alteration in the number of slow-twitch and fast-twitch fibers shows the significance of the distribution and activity of MuSCs [52]. Apparently, the abundance of MuSCs in slow-twitch fibers compared to fast-twitch fibers stresses their core role in sustaining and modifying muscle tissue type [25].

In addition, the metabolic state of MuSCs is intimately linked to the transition of muscle fiber types. This connection is confirmedindicated by an evidence displaying that the function and quantity of MuSCs are compromised in certain disease states (such as obesity and diabetes), and how this impacts muscle regenerative capacity and fiber type transition [25]. This signifies that the health status of MuSCs has profound implications for muscle adaptability and function. Obviously, obesity induced by a high-fat diet and the consequent decrease in MuSCs function impair muscle regeneration, while a calorie-restricted dietary application can enhance the number of MuSCs and increase their oxidative capacity, further

revealing the potential to promote muscle metabolic characteristics and contractile function by modulating the function and quantity of MuSCs [25].

Ultimately, these findings not only stress the significant role of PE on MuSCs and muscle fiber type transition but also show the possibility of facilitating muscle remodeling by strengthening the quantity and function of MuSCs.

4.2.3. Muscle repair and regeneration

MuSCs play a pivotal role in the repair and regeneration of muscle tissue post-exercise, by replacing damaged muscle cells, aiding in the resolution of inflammation, and reconstructing the ECM. This process is essential for sustaining the structural integrity and functional restoration of muscles [49,86]. Evidence confirms that the quiescent state of MuSCs is actively sustained through various signaling cascades, in which they remain inactive until needed for repair. In details, Notch signaling pathway plays a core role in this maintenance, coordinating with additional mechanisms to prevent spontaneous MuSCs activation, thus assuring a reserve of stem cells ready for activation upon muscle injury [49]. In addition, MuSCs can experience symmetric and asymmetric division to expand their population or to generate stem and progenitor cells, respectively. The mode of division and fate are affected by the distribution of template DNA and various proteins during cell division, ensuring the preservation of stem cell traits or facilitating differentiation [49].

The ECM and mechanical forces, also profoundly affect MuSCs behavior, impacting their ability to proliferate, differentiate, and maintain stemness. For instance, substrate stiffness mimicking the natural rigidity of skeletal muscle has been displayed to trigger MuSCs differentiation and maintain their stemness, which is vital for effective muscle regeneration [86]. Hence, recognizing the mechanisms underlying MuSCs maintenance in quiescence, their activation, and the effect of mechanical stimuli on their behavior provides valuable insights into the processes of muscle repair and regeneration.

4.2.4. Long-term adaptation and enhancement

Current evidences have illustrated that regular PE has a long-term positive effect on the quantity and function of MuSCs coupled with on the structural and functional adaptation of muscles. These changes are mediated through a complex array of molecular mechanisms and signaling pathways. Particularly, the regulation of mitochondrial biogenesis, autophagy, and selective mitochondrial removal (mitophagy) plays a crucial role in facilitating beneficial adaptations in muscle and additional metabolically active tissues [87]. As stressed by Roberts and Markby (2021), these processes are essential for sustaining and enhancing muscle function [87].

Further, regular PE increases the efficiency of skeletal muscle fibers in applying substrates for ATP production, causing enhanced fatigue resistance. These adaptive changes, comprising the modified expression of specific contractile proteins (such as actin heavy chain) and enhanced mitochondrial activity and content, collectively result in the so-called enhancement of “oxidative capacity” [51]. Apparently, these adaptations can occur independently, proving the existence of multiple signaling pathways each responsible for various types of adaptive responses.

In terms of intracellular signaling pathways, the study of AMPK and PGC-1α has uncovered their core roles in modulating muscle adaptation processes. AMPK, serving as a "fuel gauge," plays a vital metabolic role during PE, enhancing muscle glucose uptake and engaging in the metabolism of fatty acids and carbohydrates to restore ATP levels [51]. Simultaneously, PGC-1α, a primary regulator of mitochondrial biogenesis, boosts the shift of muscle fiber type from II to I upon overexpression. These insights not only deepen our understanding of the mechanisms underlying skeletal muscle adaptation to PE but also open avenues for developing new therapeutic strategies for metabolic and cardiovascular diseases [51].

4.2.5. Aging and regenerative capacity

With advancing age, the capacity for remodeling in elderly skeletal muscle is profoundly compromised, a phenomenon partly attributable to the decrease in number and function of muscle MuSCs [16]. These cells are crucial in the regeneration process following muscle injury, particularly in their integration with damaged muscle fibers or in the formation of new muscle fibers. This finding is confirmed by research from Kaczmarek et al., which illustrates that MuSCs can regenerate their population through symmetrical division, asymmetrical division, and direct differentiation, thus sustaining the muscle's regenerative capacity [16].

Nonetheless, aging impacts not only overall health but also induces complex changes at the cellular level, particularly in the functionality of MuSCs [9,88]. The self-renewal capacity of MuSCs is compromised with age, as evidenced by studies displaying that aging muscle fibers expressing FGF2 lead to some MuSCs to exit quiescence and lose their self-renewal ability [9,88]. This lowered function limits the remodeling capacity of elderly muscle, posing a threat to individual mobility and quality of life.

Despite aging being an irreversible natural process, scientific research has displayed that appropriate interventions, in detail, regular PE, can mitigate this process to some extent. Such interventions not only trigger the regenerative capacity of elderly MuSCs but also lower the advance of muscle aging, sustaining muscle function and quality of life [23].

4.3. Changes in MuSCs activities under PE conditions

4.3.1. Impact of PE type

Endurance and strength training exhibit clearly various effects on the activation and function of muscle MuSCs. Strength training, by generating high-intensity mechanical loads, prompts rapid activation and differentiation of MuSCs, essential for repairing damaged muscle fibers and enhancing their size. Evidences have stressed that in humans, the adaptive response of muscles following a single session of strength training can examine the regulation of MuSCs function, with a significant increase in MuSCs on the first day post-exercise, peaking over the subsequent 72 h, particularly after high-force eccentric exercises, closely linked to selective recruitment and/or damage of type II muscle fibers [3]. Conversely, endurance training, such as running or cycling, affects MuSCs through clear biological mechanisms, displaying that endurance PE can boost heart rate variability, metabolic adaptation, and the microstructural properties of muscle fibers [89].

4.3.2. PE intensity and frequency

High-intensity training may rapidly activate MuSCs, facilitating their proliferation and differentiation. Research has displayed that MuSCs are activated during muscle regeneration, linked to factors discharged by dying muscle fibers, such as tenascin-C and GAPDH, which induce the activation and proliferation of MuSCs [4]. Additionally, various metabolic states and nutrient-modulated metabolites can regulate the gene expression of MuSCs through epigenetic modifications, impacting their function and fate [25]. Conversely, low to moderate intensity sustained training may result in a gradual increase in MuSCs activities, linked to ongoing muscle adaptation and endurance increase, affected by factors comprising the ECM, intercellular communication, and metabolic pathway alterations [49].

4.3.3. Effects of PE duration

Long-term PE programs cause sustained changes in MuSCs quantity and function. Research has displayed that prolonged resistance training increases the content of MuSCs and muscle cell nuclei, uncovered in both healthy young and elderly individuals, showing the crucial role of MuSCs in long-term muscle fiber hypertrophy, significant for counteracting muscle loss linked to sarcopenia [90]. Regarding short-term high-intensity PE, it has been shown that MuSCs behavior during load-induced muscle hypertrophy is modulated by various pathways without necessitating muscle fiber loss, with muscle hypertrophy observable in overloaded muscles in the short term, similar to control mice in models of surgical overload without interstitial precursor cells [4].

4.3.4. Impact of age-related changes

The non-modifiable factors of age and gender profoundly affect the response of MuSCs under PE conditions. Research has uncovered how aging impacts the proliferative potential and quantity of MuSCs, particularly the notable decrease observed in the elderly, linked to the reduced content, proportion, and cross-sectional area of type II fibers, proving that MuSCs dysfunction may be a key factor in muscle aging [91]. In addition, age-related mitochondrial functional changes and oxidative stress increase due to overactive mTOR pathway further exacerbate muscle function decrease [91]. Conversely, PE as a means of facilitating tissue regeneration activates MuSCs and additional progenitor cells, engaging in the repair of skeletal muscle, nervous, and vascular systems. PE-induced activation of bone marrow mesenchymal stem cells involves multiple signaling pathways, stressing role of PE in enhancing tissue regenerative capacity [62].

4.3.5. Role of gender differences

Gender differences play a crucial role in the PE response of MuSCs. Evidences have uncovered significant differences in the skeletal muscle microRNA profiles between males and females at baseline and in response to PE, linked to the enrichment of specific transcription factors for gender-biased miRNA genes, beyond just the influence of sex chromosomes or cyclic hormones [92].

4.3.6. Significance of nutrition and diet

Appropriate nutrition and recovery are vital for sustaining PE-induced MuSCs activities. Nutrient intake, particularly adequate protein consumption, plays a core role in post-exercise muscle recovery, acute repair, growth, and overall adaptation, while metabolic recovery relies on the availability of energy substrates [93]. Additionally, royal jelly, propolis, and bee pollen have varying positive effects on skeletal muscle quality, strength, and function, likely through enhanced MuSCs responsiveness and promoted blood supply to skeletal muscle [94,95]. Hence, nutrition and diet may have underlying strengths for the post-exercise recovery of MuSCs and skeletal muscles.

5. Molecular mechanisms of interaction between PE and MuSCs

5.1. Regulation of MuSCs activities through PE-induced molecular signaling

To comprehensively understand how PE influences MuSCs, it is essential to examine the specific molecular mediators involved in this regulatory process. Among these mediators, growth factors play a pivotal role in orchestrating the cellular responses necessary for muscle adaptation and regeneration. The subsequent section delves into the critical functions of growth factors, elucidating their mechanisms of action and their impact on MuSCs activities in the context of PE-induced signaling. **Table 2** demonstrates Regulation of MuSCs activities by PE-induced molecular signaling and its role.

Table 2. Regulation of MuSCs activities by PE-induced molecular signaling and its role.

Section	Key Molecules/Pathways	Effects on MuSCs	Key Research Insights	References
role of Growth Factors	IGF-1, FoxOs, PI3K/Akt/mTOR, PI3K/Act/GSK3β, E3 ubiquitin ligases	Enhances protein synthesis, hinders protein degradation, modulates muscle hypertrophy and atrophy	IGF-1 essential for muscle mass maintenance and regeneration. Feedback loops and nutrient availability influence growth.	[26,63]
role of Cytokines	IL-6, TNF-α, IL-1β	modulates inflammation, muscle repair, and regeneration	PE-induced cytokine release essential for muscle repair and systemic functions like glucose metabolism.	[15,96]
Hormones and additional Mediators	Glucocorticoids, catecholamines, cortisol, IL-6, IL-10, IL-1Ra	Alters metabolism, inflammatory responses, impacts MuSCs activities	PE changes hormone levels affecting MuSCs activities and overall health.	[1,97]
Signaling Pathways in MuSCs	Notch, Wnt/β-catenin, TGF-β/Smad, MAPK/ERK	modulates activation, proliferation, differentiation, and self-renewal of MuSCs	Multiple signaling pathways play vital roles in MuSCs fate determination.	[98,99]
Mechanotransduction in MuSCs	Mechanical signals, stretch-activated ion channels, LINC complex, emerin, nesprin	impacts activation and differentiation through mechanotransduction, impacts gene expression and muscle stability	Mechanical loading directly impacts MPS, growth, and differentiation.	[101–102]

5.1.1. Role of growth factors

Role of growth factors is especially significant in the regulation of MuSCs activities by PE-induced molecular signaling. Insulin-like IGF-1, as a pivotal element, plays an essential role in the modulation of both synthetic and degradative metabolic pathways in skeletal muscle. It improves muscle hypertrophy and also

participates in the regulation of atrophy processes. In details, IGF-1 increases skeletal MPS and hinders FoxOs through the activation of the PI3K/Akt/mTOR and PI3K/Act/GSK3β pathways, coupled with modulates the transcription of E3 ubiquitin ligases involved in the UPS-mediated protein degradation. This complex regulatory mechanism illustrates the potential of IGF-1 in sustaining muscle mass and facilitating muscle regeneration, comprising the activation of MuSCs within the muscle [63].

Further analysis of the IGF1-Akt/PKB signaling pathway uncovered its role as a constituent in skeletal muscle growth, affected by feedback loops, growth factors, and nutrient availability [26]. Additionally, the interplay of mechanical signals, inhibition of muscle growth inhibitors, and role of AMPK in governing energy status and muscle fiber size further adds layers to the complexity of modulating muscle growth. These dynamic relationships emphasize potential targets within this signaling pathway for the regulation of muscle growth and atrophy processes [26].

In the context of this framework, the significant effect of PE on IGF-1 signaling cannot be overlooked, particularly in terms of facilitating muscle hypertrophy and function. Evidences indicate that various forms of PE, comprising aerobic and resistance training, can trigger the synthetic metabolic environment conducive to muscle growth by upregulating IGF-1 and IGF-1R levels and activating the PI3K/Akt pathway [70]. These mechanisms positively affect muscle mass and function, in detail, against the backdrop of aging, where role of modulating the IGF-1 signaling pathway becomes more pronounced.

Ultimately, upon these findings, a deeper understanding of roles of IGF-1, FGF, and HGF in the activation, proliferation, and differentiation of MuSCs is essential for a comprehensive understanding of the mechanisms of muscle regeneration following PE. The synergistic action of these growth factors shows a complex network through which PE effectively modulates muscle quality and function.

5.1.2. Role of cytokines

The inflammatory process induced by PE prompts the release of various cytokines, comprising IL-6, TNF-α, and IL-1β, which play crucial roles in the regulation of MuSCs function, providing new perspectives for recognizing muscle repair and regeneration. In details, IL-6 plays multifaceted roles during PE. It is not only pivotal for the anti-inflammatory response during PE but also impacts systemic functions such as glucose metabolism in skeletal muscle and additional tissues. Further evidences have displayed that IL-6 can improve the proliferation of MuSCs and aid in recruiting macrophages, which are critical for muscle regeneration [15,96].

Upon evidences linked to TNF-α, it also supports the proliferation of MuSCs and plays a role in muscle repair and regeneration following injury [15]. Conversely, role of IL-1β is more complex. Its concentration closely enhances profoundly after prolonged or intense PE, showing its role in a more robust inflammatory response [96].

Ultimately, these cytokines are not only key components of the complex interplay between inflammation and muscle repair but also emphasize the significance of inflammatory responses in PE-induced muscle adaptation and

recovery. These findings offer valuable insights into how PE impacts MuSCs activities and muscle health.

5.1.3. Hormones and additional mediators

Evidence has shown how PE profoundly modifies hormone levels, thereby modulating the activity of MuSCs, key to recognizing role of hormones and additional mediators in PE-induced molecular signaling. For instance, the secretion of glucocorticoids and catecholamines enhances during PE, both of which play crucial roles in modulating metabolism and inflammatory responses, thereby affecting MuSCs behavior [1]. In details, acute endurance PE has been uncovered to trigger the concentrations of catecholamines and cortisol in plasma, and notably, these responses display significant differences between exercises played in the morning and evening [97].

In addition, cytokines discharged by muscles during PE, such as IL-6, play a crucial role in modulating metabolism and inflammatory responses. IL-6 can induce anti-inflammatory cytokines, such as IL-10 and IL-1Ra, displaying significant anti-inflammatory effects [96]. Consequently, PE, by modulating levels of hormones and neurofactors, not only impacts metabolism and inflammatory responses but also affects the activity of MuSCs, these synergistic effects being significant for facilitating overall health.

5.1.4. Signaling pathways in MuSCs

The modulation of MuSCs by molecular signaling pathways activated during PE is multifaceted, encompassing several key pathways such as Notch, Wnt/*β*-catenin, TGF-*β*/Smad, and MAPK/ERK. These pathways play a pivotal role in the activation, proliferation, differentiation, and self-renewal of MuSCs.

Taking the Notch signaling pathway as an instance, research within colorectal cancer has revealed that the activity of the Notch pathway is initiated by the binding of Notch ligands to their receptors, causing the cleavage of the receptor's intracellular domain and the release of the NICD, which then enters the nucleus to modulate the expression of target genes. This mechanism is not only vital in cancer research but also stresses the vital role of Notch signaling in the fate determination of MuSCs [98]. Identifying the Wnt/*β*-catenin signaling pathway, evidence mainly centered on pancreatic cancer has found that the activation of the Wnt/*β*-catenin pathway depends on the activation of FZD4 and FZD6. The activation of Wnt ligands improves the accumulation of *β*-catenin in the nucleus and the transcriptional activation of target genes, playing a core role in cell proliferation, migration, and differentiation, further stressing the underlying significance of this pathway in cancer advance and MuSCs regulation [99]. Besides, evidence on the TGF-*β*/Smad signaling pathway has uncovered its role in cardiac fibrosis. TGF-*β* and its receptors regulate cell functions through the activation of Smad2/3 and additional non-Smad pathways (such as MAPKs, PI3K, and Wnt signaling), covering complex mechanisms such as proliferation, differentiation, apoptosis, and survival. The multifaceted regulatory role of TGF-*β* signaling emphasizes its critical significance in both physiological and pathological processes, showing its significance in the regulation of MuSCs function [100]. Additionally, considering the MAPK/ERK signaling pathway, its evidence in fibrosis and cardiac pathological states stresses the

MAPKs (comprising ERK, JNK, and p38 MAPK) as significant mediators of cellular response to external stimuli, involved in the regulation of cell proliferation, differentiation, and survival [100]. These insights not only highlight the core role of these pathways in cellular signal transduction but also stress their potential significance in the regulation of MuSCs activities.

5.1.5. Mechanotransduction in MuSCs

Mechanical loading, a central factor during PE, directly impacts MuSCs through mechanotransduction pathways, acting as a core component in this process. In details, mechanical signals such as stretch-activated ion channels and changes in the ECM play a crucial role in the activation and differentiation of MuSCs.

Article has uncovered that stretch-activated ion channels are not only a vital component of mechanical sensation but also play a core role in converting mechanical stimuli into intracellular signals. This conversion profoundly affects MPS and growth [101]. Additionally, mechanical loading participates in the regulation of cell differentiation and function through different signaling pathways, comprising those linked to osteogenesis, showcasing the diversity and complexity of mechanotransduction in cellular function regulation [102].

Under the impact of mechanical load, cells perceive and respond to mechanical forces through mechanotransduction pathways, a point of particular significance in the MuSCsuloskeletal system. For instance, evidence reveals that in skeletal muscle, the LINC complex and its associated proteins, such as emerin and nesprin, play a core role in mechanical signal transduction between the nucleus and cytoskeleton, impacting nuclear mechanical stability and gene expression [103]. As a result, mechanical loading directly impacts the activation and differentiation of MuSCs through these mechanotransduction pathways, thereby modulating the repair and regeneration processes of muscle.

5.2. Effects of different types and intensities of PE on the function of MuSCs

Various types of training modalities and intensities play a core role in affecting the function of MuSCs. Each training type impacts the activation, proliferation, and differentiation of MuSCs through unique physiological and metabolic mechanisms, thereby causing muscle adaptation and repair. To obtain a deeper understanding of these complex mechanisms, the specific mechanisms of action and effects of endurance training, strength training, high-intensity interval training (HIIT), and different training intensities on MuSCs will be assessed in detail next. **Table 3** illustrates Effects of different types and intensities of PE on the function of MuSCs.

Table 3. Effects of different types and intensities of PE on the function of MuSCs.

PE Type	MuSCs Activation	MuSCs Proliferation	MuSCs Differentiation	Metabolic Impact	muscle Fiber Type	References
Endurance Training	Moderate activation through prolonged mechanical and metabolic stress	enhanced proliferation due to enhanced oxygen delivery and mitochondrial activity	improves differentiation into red muscle fibers (slow-twitch fibers)	Enhances oxidative capacity and mitochondrial function (e.g., PGC-1α, TFAM)	mainly slow-twitch (Type I) fibers, suited for endurance	[104]
Strength Training	High activation due to mechanical overload and muscle tension	Significant proliferation under heavy load conditions	Facilitates differentiation into both red and white fibers (fast-twitch and slow-twitch fibers)	Increases myonuclei number, essential for muscle repair and hypertrophy	mainly fast-twitch (Type II) fibers, focused on strength and power	[1,105]
HIIT	Rapid and robust activation triggered by high mechanical and metabolic stress	Enhanced proliferation due to release of macrophage-derived factors and mechanical forces	improves differentiation into hypertrophic muscle fibers	boosts both anaerobic and aerobic metabolism; increases muscle mass and function	Mixed fiber response, facilitating both fast-twitch and slow-twitch fibers	[4,106]
Training Intensity	High-intensity training improves fast activation; low-intensity training supports steady activation	High intensity supports rapid proliferation; low intensity supports long-term proliferation	High-intensity training favors rapid differentiation for fast muscle repair; low intensity improves long-term stability	High-intensity training enhances metabolic enzymes and energy production; low intensity supports muscle maintenance	Fast-twitch fibers respond to high-intensity; slow-twitch fibers respond to low-intensity	[4,86]
Age and Gender Differences	Reduced activation with age, particularly in type II fibers; males and females exhibit different activation thresholds	Age-related decrease in proliferation capacity; males closely exhibit higher proliferation under training stimuli	Differentiation capacity decreases with age; females may have different hormonal impacts on differentiation	Aging causes mitochondrial dysfunction and oxidative stress; gender differences in metabolic response	Aging preferentially impacts type II fibers (fast-twitch); males and females may exhibit fiber composition differences	[90–91,107–108]
Endurance Training	Moderate activation through prolonged mechanical and metabolic stress	enhanced proliferation due to enhanced oxygen delivery and mitochondrial activity	improves differentiation into red muscle fibers (slow-twitch fibers)	Enhances oxidative capacity and mitochondrial function (e.g., PGC-1α, TFAM)	mainly slow-twitch (Type I) fibers, suited for endurance	[104]
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HIIT	Rapid and robust activation triggered by high mechanical and metabolic stress	Enhanced proliferation due to release of macrophage-derived factors and mechanical forces	improves differentiation into hypertrophic muscle fibers	boosts both anaerobic and aerobic metabolism; increases muscle mass and function	Mixed fiber response, facilitating both fast-twitch and slow-twitch fibers	[4,106]
Training Intensity	High-intensity training improves fast activation; low-intensity training supports steady activation	High intensity supports rapid proliferation; low intensity supports long-term proliferation	High-intensity training favors rapid differentiation for fast muscle repair; low intensity improves long-term stability	High-intensity training enhances metabolic enzymes and energy production; low intensity supports muscle maintenance	Fast-twitch fibers respond to high-intensity; slow-twitch fibers respond to low-intensity	[4,86]

Table 3. (*Continued*).

PE Type	MuSCs Activation	MuSCs Proliferation	MuSCs Differentiation	Metabolic Impact	muscle Fiber Type	References
Age and Gender Differences	Reduced activation with age, particularly in type II fibers; males and females exhibit different activation thresholds	Age-related decrease in proliferation capacity; males closely exhibit higher proliferation under training stimuli	Differentiation capacity decreases with age; females may have different hormonal impacts on differentiation	Aging causes mitochondrial dysfunction and oxidative stress; gender differences in metabolic response	Aging preferentially impacts type II fibers (fast-twitch); males and females may exhibit fiber composition differences	[90–91,107–108]

5.2.1. Endurance training

Different PE modalities and intensities, particularly endurance training such as running and cycling, exert significant effects on the functionality of MuSCs. Such training triggers muscular endurance performance notably by augmenting the quantity of MuSCs and enhancing their oxidative metabolic capacity. In details, endurance training fosters the differentiation of MuSCs into a greater proportion of red muscle fibers (slow-twitch fibers), which are well-suited for prolonged PE.

Research confirms that a combined regimen of running-specific strength and endurance training positively affects the performance and selected body metrics of recreational endurance athletes. Isolated running-specific strength training profoundly enhances maximum strength and explosive power while boosting running economy; on the other hand, endurance training principally triggers maximum oxygen uptake and anaerobic threshold. A 12-week block periodization training program comprising accumulation, transformation, and realization phases yields enhancements in body composition and athletic performance that surpass those from either strength or endurance training alone [104]. Besides, 20 weeks of endurance training in untrained males profoundly increases the average speed over 1500 meters and the running speed at 85% of maximum heart rate. Physiologically, endurance training increases mitochondrial dynamic markers in the biceps femoris muscle, in detail, PGC-1α and TFAM, along with the content and activity of associated enzymes like citrate synthase and cytochrome c oxidase, although it does not profoundly impact the total mitochondrial volume density [104].

Ultimately, endurance training, by enhancing the number of MuSCs and enhancing their oxidative metabolic capabilities, improves the formation and maintenance of red muscle fibers, thereby effectively boosting muscular endurance performance.

5.2.2. Strength training

Strength training, encompassing weightlifting and resistance exercises, plays significant effects on MuSCs, principally by triggering the proliferation and differentiation of MuSCs, thereby augmenting muscle strength and volume. Strength training enhances the number of MuSCs and the nuclei within muscle cells, changes that are essential for muscle repair and regeneration, particularly under the strain of load-bearing strength exercises. The accumulation of MuSCs under such training stimuli plays a pivotal role in the muscle adaptive changes induced by training, in detail, within a load-bearing context [1]. In addition, research has displayed that

strength training, especially with high volume and heavy loads, profoundly impacts muscle damage and recovery processes across various age groups, such as in young and older women, with the response of MuSCs playing a decisive role in this process [105]. Therefore, strength training, by activating MuSCs and facilitating their numerical increase, plays a crucial role in muscle growth and repair, a mechanism vital for enhancing muscle strength and volume.

5.2.3. High intensity interval training

The effect of HIIT on the functionality of MuSCs is manifested in the regulation of their activation, proliferation, and differentiation. This training modality, by modifying the cellular environment, such as the dissociation of muscle fibers or the release of factors from damaged muscle fibers that improve the proliferation and differentiation of MuSCs, can rapidly induce the activation of MuSCs. Macrophage-derived factors are particularly significant in the muscle repair process, as they modulate the proliferation and differentiation of MuSCs [4,106].

Under HIIT, the environment of MuSCs is affected by the complex interactions between mechanical forces, cell signaling pathways, and ECM components, which cause muscle hypertrophy. Mechanical stress and inflammation-induced edema can directly improve the activation and proliferation of MuSCs. Mesenchymal progenitor cells play a vital role in modulating the proliferation of MuSCs, thus promoting muscle growth [4]. Besides, the enhancement of MuSCs function depends on the coordinated balance between pro-inflammatory and anti-inflammatory macrophages, with the former facilitating rapid proliferation of MuSCs and the latter indicating the differentiation of MuSCs and the subsequent regeneration of muscle tissue [106].

Ultimately, HIIT triggers the rapid activation, proliferation, and differentiation of MuSCs through multifaceted regulation, thereby enhancing muscle mass and function. This shows the pivotal role and adaptability of MuSCs in meeting the demands of various types of PE.

5.2.4. Training intensity and MuSCs function

The functional effect of training intensity on MuSCs is significant. Research has illustrated that PE of varying intensities differentially impacts the activation and differentiation of MuSCs. High-intensity training closely increases the activation and differentiation of MuSCs, which is essential for rapid muscle rebuilding and strengthening. Conversely, low-intensity training favors the proliferation and long-term stability of MuSCs, aiding in muscle maintenance and repair.

The response of MuSCs in muscle adaptation and remodeling is modulated by a confluence of factors. The physical properties of the ECM, such as its stiffness, profoundly affect the proliferation and differentiation of MuSCs. ECM stiffness modulates MuSCs activities by modifying cell shape and attachment area, rendering mechanical signaling particularly essential for MuSCs proliferation and differentiation following mechanical loading or muscle injury, and is vital for muscle regeneration and repair [86].

Beyond mechanical stimuli, molecular signals produced by damaged muscle fibers and additional cells also affect the activation and proliferation of MuSCs. For instance, the release of tenascin-C and GAPDH from injured muscle fibers, coupled

with growth factors from macrophages and mesenchymal progenitor cells, can trigger the activation and proliferation of MuSCs [4].

Consequently, the integrated response of MuSCs to mechanical and biochemical signals plays a pivotal role in muscle repair and remodeling. These findings highlight the significance of determining training intensity and its associated mechanical and biochemical stimuli when devising recovery and PE regimens for muscle injury.

5.2.5. Age-related changes and gender differences

Article confirms that age and gender are pivotal factors affecting the function of MuSCs in response to various types and intensities of PE. With advancing age, molecular damage accumulates in cells, impairing their regenerative capacity. This effect is particularly pronounced in muscle tissue, where aging causes a decrease in the proliferative ability and quantity of MuSCs, particularly within type II muscle fibers, likely acting as a primary driver of muscular senescence. Evidences have linked the atrophy of type II muscle fibers with reductions in muscle mass, with a decrease in MuSCs posited as a significant contributor to this atrophy [107]. enhanced age also correlates with a reduction in MuSCs numbers, presaging a diminution in muscle fibers, particularly type II fibers, which impacts the maintenance capacity of elderly muscle [90]. Concurrently, aging muscles exhibit mitochondrial dysfunction, with an accumulation of reactive oxygen species (ROS) and energy deficiency causing a strengthened susceptibility to atrophy [91].

Gender also impacts the tendinous response to PE. For instance, compared to similarly trained male runners, young female runners exhibit lower tendon stiffness, proving that gender may affect the impact of prolonged training on tendon quality [108]. Besides, gender differences in MuSCsulotendinous complex (MTC) adaptability during heavy dynamic resistance training have been revealed, potentially linked to endocrine adaptations of growth factors, such as IGF-I and transforming growth factor β-1 (TGFβ-1) [108].

These findings emphasize the significance of comprehensively recognizing how age and gender impact the PE response of MuSCs, in details, in devising personalized training programs for different ages and genders. Further research into these differences may aid in strengthening PE regimens to promote muscle health and functionality.

6. Future research directions and challenges

6.1. Gaps in current research and potential directions for future studies

Lately, there has been significant progress in recognizing muscle MuSCs and their role in facilitating muscle remodeling during PE. Despite these significant advances, numerous mysteries and challenges remain to be addressed. The following are current gaps in research and underlying directions for future studies: (i) Heterogeneity and functional diversity of MuSCs: While the core role of MuSCs in muscle growth, maintenance, and repair has been established, the heterogeneity of MuSCs and the specific functions of each subtype are not fully determined. Further research should explore the various subgroups of MuSCs and how they respond to various types and intensities of PE. (ii) Mechanisms of MuSCs in muscle fiber type

transition: PE can induce muscle fiber type transition, but the specific role of MuSCs in this process remains unapparent. Investigating how to precisely regulate MuSCs to improve the growth and transition of specific muscle fiber types is essential for designing targeted PE programs and treating muscle degenerative diseases. (iii) Signaling pathways in MuSCs during PE: Although multiple signaling pathways have been determined in modulating MuSCs activities, how these signals are activated and integrated during various forms of PE, and how they cooperate to improve muscle remodeling, requires further study. (iv) The effect of age on MuSCs function: In the context of aging, the regenerative capacity of MuSCs decreases, thus, further research should center on how to boost the function of MuSCs in the elderly through PE or additional interventions is vital for slowing muscle aging and enhancing quality of life.

6.2. Enhancing the understanding of the complex relationship between PE, MuSCs, and muscle remodeling

To better identify the complex relationship between PE, MuSCs, and muscle remodeling, future researches should focus on: (i) Employ multi-omics approaches: Apply transcriptomics, proteomics, and metabolomics to comprehensively assess the response of MuSCs under various PE conditions, displaying the full diagrams of how PE impacts MuSCs function and muscle remodeling. (ii) Develop and apply new technologies: Utilize progressed technologies and strategies, such as single-cell sequencing, CRISPR gene editing, and in vivo imaging to study the behavior of MuSCs in muscle remodeling, and their response to various types and intensities of PE. (iii) Conduct long-term tracking studies: Carry out long-term, cross-age tracking studies to determine the long-term effects of PE on MuSCs function and muscle remodeling. (iv) Trigger interdisciplinary collaboration: Support collaboration between disciplines, including exercise science, cell biology, molecular biology, and geriatric medicine to obtain a deeper understanding of the relationship between PE, MuSCs, and muscle remodeling from various aspects.

6.3. Significance of research in this field and clinical application prospects

Evidences of MuSCs and PE in muscle remodeling are not only of significance to the field of basic biomedical sciences but also plays broad prospects for clinical utilization. With an advanced role of MuSCs in muscle development, maintenance, and regeneration, it may progress targeted treatment strategies for specific muscle diseases, such as muscle atrophy, injury repair, and age-related muscle weakness (e.g., sarcopenia,). Besides, personalized exercise intervention programs could be tailored to an individual’s genetic backdrop and health status, strengthening the advantages of PE while lowering underlying risk. Investigating the interaction between MuSCs and PE not only assists in better recognizing how muscles respond to various types and intensities of PE but also shows the optimal ways to improve muscle health and function through PE. This knowledge will induce the development of new PE intervention strategies, offer a scientific basis for treating muscle diseases,

and supply applications for sustaining muscle health and function in an aging society.

Ultimately, the integrative role of PE and MuSCs in remodeling muscle structure and function stresses the significance of interdisciplinary research in exercise physiology and cell biology. As research advances, we look forward to achieving greater advancements in preventing and treating muscle-related diseases and facilitating the muscle health of the elderly.

7. Conclusion

This review explores how PE improves the remodeling of muscle structure and function through the activation and regulation of MuSCs. The pivotal role of MuSCs in sustaining muscle health, triggering injury repair, and adaptive remodeling is elucidated. PE increases muscle strength and endurance, enhances metabolic functions and the aging process of muscles by facilitating the activation, proliferation, and differentiation of MuSCs. In details, in the elderly, appropriate PE can slow the decrease in muscle function, showcasing the potential of exercise interventions in the prevention and treatment of muscle aging and related diseases.

The unraveling of molecular mechanisms illustrates how PE impacts MuSCs behavior through various signaling pathways, stressing the vital roles of Notch, Wnt/β-catenin, TGF-β, PI3K/Akt, and MAPK/ERK pathways in this process. A deeper understanding of these mechanisms provides possibilities for delving into new therapeutic utilization, particularly for muscle atrophy and age-related muscle dysfunction.

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