Invited Review

Skeletal muscle repair and regeneration: Focusing on the role of satellite cells and myogenic regulatory networks

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Abstract

Understanding the mechanisms of skeletal muscle regeneration is crucial for advancing therapeutic strategies to manage muscle injuries and prevent muscle-related degenerative diseases. Skeletal muscle regeneration is a tightly regulated process involving structural, cellular, and molecular components, which provide mechanical stability and facilitate vascular and neural integration. Muscle fibers are multinucleated and contain organized myofibrils composed of actin and myosin, enabling contraction. In addition, muscle stem cells, known as satellite cells, are essential for muscle regeneration, and the balance between their quiescent and activated states has been widely investigated in regenerative biology. Upon activation, satellite cells exit quiescence, proliferate, differentiate into myoblasts, and fuse to form new myofibers. This regenerative process proceeds through three distinct stages: destruction, repair, and remodeling, coordinated by immune cells, cytokines, and growth factors. Transcription factors such as Pax7, MyoD, and MyoG play critical roles in regulating myogenesis. Effective muscle regeneration relies on the dynamic interplay between satellite cells, fibroblasts, and extracellular matrix remodeling to restore functional integrity.

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Introduction

Skeletal muscle makes up a significant portion of our body weight, around 30-40% in both men and women.[1] It serves several crucial functions. First, skeletal muscles are responsible for movement and force production in a wide variety of activities, such as maintaining posture, controlling locomotion, and breathing.[2] Second, skeletal muscles are metabolically active. They act as a major storage site for amino acids and muscle glycogen, which are vital energy sources. These reserves become particularly important for producing ATP (adenosine triphosphate) during exercise, when the muscles' energy requirements increase. Next, muscles play a key role in regulating body temperature. For instance, when exposed to cold, our body triggers involuntary muscle contractions, or shivering, to generate heat and maintain our core body temperature. Finally, beyond their roles in movement and posture, skeletal muscles also function as dynamic endocrine organs. When they contract, they release various signaling molecules called myokines. These myokines have systemic effects, influencing inflammation, metabolism, and communication between different organs throughout the body.[2] Upon injury, skeletal muscles activate a well-orchestrated regenerative process to restore normal functions.

In this review article, we explore the general structure of skeletal muscles, the ultrastructure of muscle fibers, and the roles of cytoskeletal and contractile proteins in muscle function. Special emphasis is placed on the biology of satellite cells, their involvement in skeletal muscle regeneration, and the molecular mechanisms governing adult myogenesis, providing an integrated view of how skeletal muscle maintains its integrity and functionality in response to injury.

Physiological Anatomy of Skeletal Muscle

There are three layers of connective tissue that surround and protect skeletal muscle fibers: epimysium, perimysium, and endomysium. 1) Epimysium, the outer layer that surrounds the entire muscle, provides structural integrity and protection. The connection between the epimysium and bone is the tendon. 2) The middle layer, perimysium, that wraps bundles of muscle fibers (fascicles). In addition, blood vessels, lymphatics, and nerves are all found in this layer. 3) The inner layer, endomysium, surrounds the individual muscle fibers or muscle cells. This layer also has capillaries and nerve fibers. These connective tissue layers work together to support muscle function, force transmission, and structural stability.[2,3]

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The Ultrastructure of Muscle Fibers

Skeletal muscle fibers are elongated in shape with a length of about 25-30 cm and a diameter of 10-80 μm. The cell is multinucleated and contains numerous mitochondria with striated characteristics. The sarcolemma represents the plasma membrane connected with the neuromuscular junction of motor neurons and is surrounded by the basal lamina and muscle stem cells known as satellite cells.[2,3] These cells play a crucial role in muscle repair and regeneration in adult skeletal muscles.[2,4] Sarcoplasmic reticulum is the calcium ion storage organelle that is responsible for excitation-contraction coupling.[5] The basic unit of muscle contraction is the sarcomere which has an average length of about 2 μm.[6] The contractile machinery proteins or myofilaments (myofibrils) that play a critical role in muscle contraction are thick filaments and thin filaments known as myosin and actin, respectively.[6] The striated appearance of muscle fibers, observable under both light and electron microscopes, arises from the organized arrangement of myosin and actin filaments, which differ in their refractive indices and form alternating light and dark bands The area between two Z lines is called sarcomere that presents the M-line in the middle position of the sarcomeres. Dark bands are composed of A bands, a group of myosin overlaps with actin filaments. Light bands, I bands represent only actin filaments. H bands contain only myosin filaments.[6]

Cytoskeletons and Contractile Proteins In Muscle Fibers

The actin filaments or F-actins have a diameter ranging from 5 to 8 nm and a length of 1 μm. A couple of F-actins form a double helical structure that becomes one actin filament. The formation of F-actin involves globular actin (G-actin) molecules which are connected into one F-actin filament with nebulin, a cytoskeletal protein controlling the length of F-actin. In addition, tropomyosin and troponin have an important role in the off and on sliding filament mechanism orchestrated to the calcium ion presentation and regulating actin-myosin binding to provide skeletal muscle fiber contraction force and morphological alterations. Moreover, tropomodulin also controls actin length, while a-actinin and capZ anchor actin filaments to the Z line. The desmin connects Z line across sarcomeres.[6-9]

The Skeletal Muscles Can Repair Themselves After Injuries

Adult skeletal muscular tissues can repair themselves after stressor activations and muscle injuries, such as burns, incision, crush injury, and ischemia. The skeletal muscle growth, repair, and regeneration are caused by the function of muscle stem cells (MuSCs) or myogenic precursors known as satellite cells.[10] In the resting state, satellite cells are maintained in quiescence (inactive state) in their niche.[11,14]

In general terms, quiescence is a reversible, non-proliferative state of the stem cells that benefits the somatic stem cells to preserve their long-term regenerative capacity. In skeletal muscle, satellite cells remain in a quiescent state under homeostatic conditions, residing between the basal lamina and the sarcolemma of muscle fibers. This dormant state is characterized by low metabolic activity, a tightly regulated cell cycle arrest (G_0 phase), and a transcriptional program that maintains stemness while preventing premature activation or differentiation. The quiescent satellite cells express specific markers, most notably paired box protein 7 (Pax7), which is essential for their maintenance and identity. In contrast, they lack the expression of activation and differentiation markers, such as MyoD and myogenin. The quiescent state is actively maintained by niche signals from the surrounding micro-environment, including Notch signaling, fibroblast growth factors (FGFs), and Wnt pathways, as well as epigenetic regulators that suppress cell cycle entry.[11,14]

In contrast, after satellite cells are activated from muscle injuries, these cells undergo proliferation, and differentiation into myoblasts, myotubes, and muscle fibers, respectively. Therefore, the skeletal muscle repair and growth are present from this process.[11,12]

The Satellite Cells Characteristics

The location of satellite cells is uniquely placed between the surroundings of basal lamina and the sarcolemma. This specific location facilitates the satellite cells to adequately monitor and respond to the skeletal muscle cell environment alteration.[11-13] The number of satellite cells accounts for 2-10% of total myonuclei per muscle fibers[11]. Satellite cells exhibit a distinctly different morphology compared to myofiber, and other adjacent cells. Under phase-contrast microscopy, these cells are located on a single myofiber. In addition, their characteristics under electron microscopic investigation are 1) mononucleated myogenic cells, 2) a large nucleus-to-cytoplasmic ratio, and 3) few organelles, small nuclei, and condensed interphase chromatin.[11-13] There are specific markers of satellite cells, the paired box proteins Pax7 and Pax3 in the nucleus. Other transcription factors are, for instance, the myogenic regulatory factor 5 (Myf5) and homeobox transcription factor Barx2. In addition, biomarkers on their plasma membrane or surface makers are β1-integrin, α7-integrin, syndecan-4, M-cadherin, calcitonin-receptor (CALCR), C-X-C chemokine receptor type-4 (CXCR4), vascular cell adhesion molecule 1 (VCAM1), and CD34.[13,14] After satellite cells proliferation, some of them return to quiescence (self-renewal). The importance of the quiescent state of

satellite cells is to preserve stem cell properties. The quiescent state also prevents excessive activation, DNA damage, cellular aging (senescence), and depletion of the stem cells reservoir.[14,20] Therefore, satellite cell multiplication involves asymmetric division. This refers to the process of muscle stem cells undergoing mitotic division, producing one self-renewing stem cell and one committed progenitor cell. This mechanism is essential for maintaining the stem cell pool while enabling muscle regeneration for future activation from the stressors. Dysregulation of this process can lead to stem cell exhaustion or impaired muscle regeneration, contributing to muscle degeneration in aging or diseases.[20]

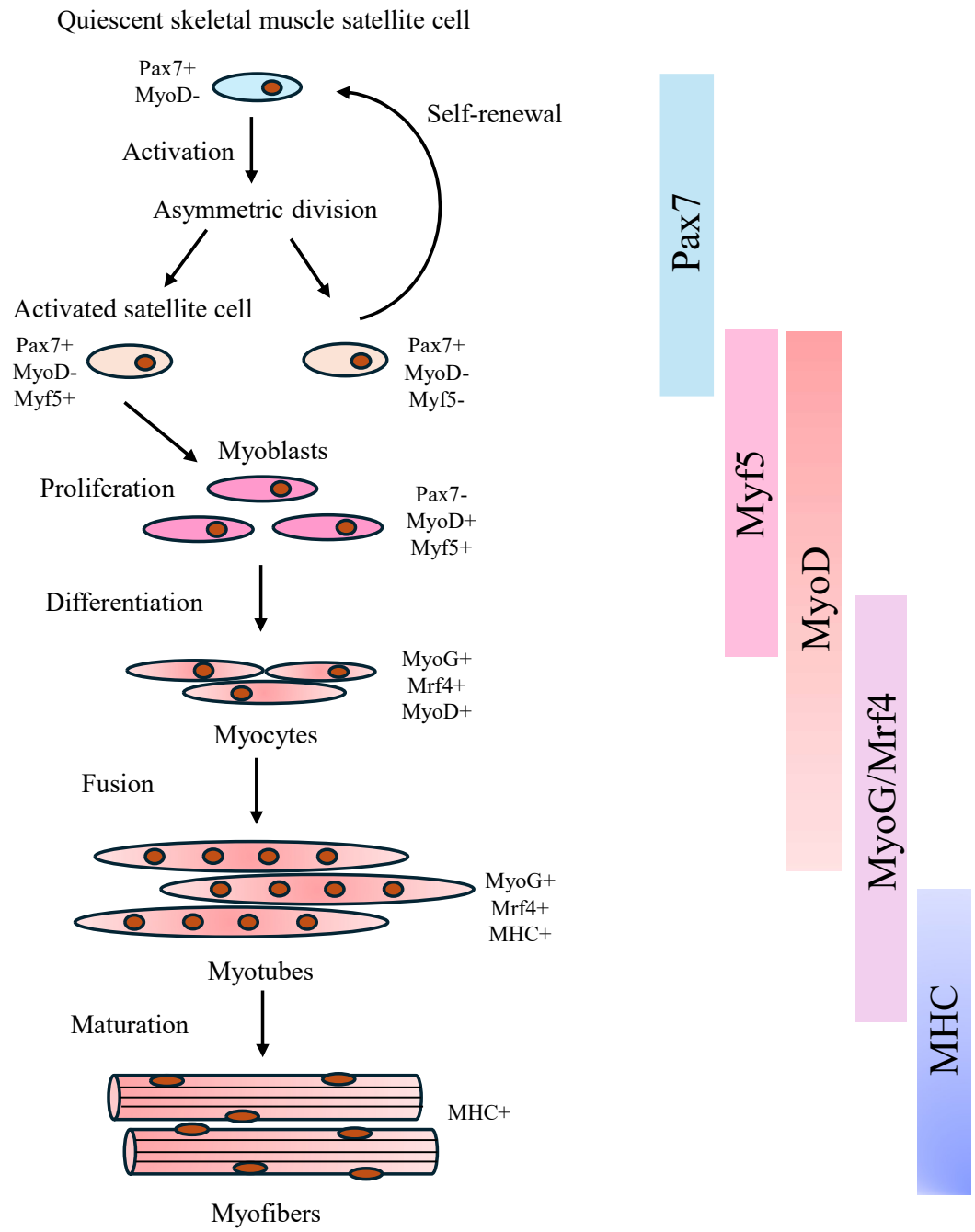

Figure 1 The illustration of skeletal muscle regeneration.
In response to muscle injury, quiescent satellite cells (Pax7+ and MyoD−) become activated and begin differentiating into myoblasts (Pax7+, Myf5+, and MyoD+). Some of them revert to quiescent state (Pax7+, MyoD−, and Myf5−) to maintain the satellite cell population. Numerous myoblasts differentiate into myocytes (MyoD+, MyoG+, and Mrf4+). Myocytes fused to form multinucleated myotubes (MyoG+, Mrf4+, and MHC+), which subsequently mature into functional myofibers (MHC+).

The Regeneration of Skeletal Muscle

The regenerative process is typically divided into three main stages: 1) destruction, 2) repair, and 3) remodeling. Each stage involves specific cellular and molecular mechanisms that are critical for effective muscle healing.

The first stage, destruction or inflammatory stage, occurs immediately after muscle injury, typically resulting from contusions, strains, or lacerations. These injuries lead to myofiber damage and are accompanied by increased calcium ion flux as well as calcium ion release from the sarcoplasmic reticulum, leading to proteolysis and myofiber necrosis.[13] The necrotic muscle fibers release damage-associated molecular patterns (DAMPs), which activate the infiltration of immune cells. Within six hours after muscle injury, neutrophils are among the first inflammatory cells that are responsible in this phase. In this phase, neutrophils release pro-inflammatory cytokines, for example tumor necrosis factor-alpha (TNF-α) and interleukin-1 (IL-1), cytokines, chemokines, and reactive oxygen species (ROS) that amplify the inflammatory response and recruit additional immune cells, such as monocytes and macrophages, to the injury sites.[13,15] Therefore, the first stage provides clearance of cellular debris and prepares for the subsequent repair mechanisms.

Next, the repair phase is the activation and proliferation of satellite cells. In this phase, the quiescent satellite cells are activated to proliferate and differentiate into myoblasts, which then fuse to form new myofibers or repair existing ones. The transition from pro-inflammatory to anti-inflammatory cytokines is crucial during this phase.[16] Macrophages release anti-inflammatory chemicals including interleukin-10, interleukin-4, and interleukin-3 (IL-10, IL-4, and IL-3) to facilitate satellite cells proliferation and differentiation into myoblasts.[17] In addition, regulatory T cells promote the conversion of pro-inflammatory macrophages to anti-inflammatory macrophages, release growth factors, and stimulate satellite cell proliferation and differentiation in muscle regeneration.[18] Moreover, several growth factors play pivotal roles in satellite cell activation and proliferation. Hepatocyte growth factor (HGF) is released early after injury and binds to c-Met receptors on satellite cells, leading to their activation. The upregulation of insulin-like growth factor-1 (IGF-1) promotes satellite cell proliferation and differentiation through the PI3K/Akt/mTOR signaling pathway.[19] In addition, regulatory T cells secrete a specific growth factor amphiregulin (Areg), which promotes satellite cell differentiation into myoblasts and facilitates muscle repair and regeneration.[13,16,18]

The last phase or remodeling phase involves the maturation and remodeling of newly formed myofibers and the re-establishment of the muscle's contractile architecture. During this phase, myoblasts differentiate and fuse to form multinucleated myotubes, which further mature into functional myofibers.[16]

The Molecular Mechanism of Myogenesis

Regeneration of skeletal muscles involves the activation and differentiation of satellite cells (Figure 1). There are many factors involved, which regulate and coordinate this process to produce significant morphological changes. In the resting state, satellite cells stay in quiescence, (G0 phase of the cell cycle)[21] and express paired box protein 7 (Pax7) to maintain quiescence. They do not show myoblast determination protein 1 (MyoD).[11,14,22] In addition, other key regulators in this state are Notch signaling, which supports self-renewal and cyclin-dependent kinase (CDK) inhibitors, such as p21, p27, and p57. These inhibitors prevent satellite cells from entering the cell cycle.

After muscular injuries, activated satellite cells migrate to the injured site. Ephrin and Wnt7a are responsible for this cell migration and induction to leave quiescent stage into G1 phase of cell cycle.[11,22] In addition, other regulators of satellite cells exit quiescence and enter the G1 phase to prepare for proliferation. These include, HGF/c-Met signaling to trigger activation, fibroblast growth factor-2 (FGF-2) to promote cell cycle entry, cyclin D1/CDK4 to drive G1 progression and myogenic factor 5 (Myf5).[23] During the S Phase (DNA replication), the key regulators are cyclin E/CDK2 which promote S phase entry. In the G2 phase, the satellite cells prepare for mitosis. This phase requires cyclin A/CDK2 and p38 MAPK to enhance myogenic commitment.[23] For the M phase or mitosis, satellite cells divide into two daughter cells. One cell may return to quiescence to maintain the stem cell pool.[23] In the proliferation period, some satellite cells increase the expression of muscle-specific transcription factors MyoD and myogenic factor 5 (Myf5), which initiate differentiation and become myogenic progenitor cells or myoblasts. Therefore, MyoD and Myf5 play a crucial role in the early stages, promoting the determination of myoblasts.[12,24] Moreover, to facilitate the terminal differentiation from myoblasts fusion into multinucleated myotubes, this process requires myogenin (MyoG) and myogenic regulatory factor 4 (Mrf4).[24,25] In addition, the functions of myogenic regulatory factors (MRF) not only involve the myogenesis regulation, but also contribute to satellite cells to be in a quiescent, activated, committed or differentiated state.[26,27]

The transcription factors including Myf5, MyoD, MyoG, and Mrf4 belong to the MRF family. As a key regulator, MyoD stimulates MyoG expression. This induction of MyoG initiates the terminal differentiation of myoblasts, transforming them into myocytes and subsequently fusing into multinucleated myotubes.[28] The important marker of

newly formed myofibers is presented by myosin heavy chain (MHC) which is expressed at the central nuclei of myofibers, the contractile units of skeletal muscles.[12]

Conclusion and Future Directions

The skeletal muscle is a highly organized and dynamic tissue, composed of multi-layered connective structures, complex contractile machinery, and specialized stem cells known as satellite cells. These anatomical and cellular components provide contraction, structural stability, and regenerative capabilities following injury. The intricate architecture of muscle fibers, including the sarcomere and cytoskeletal proteins, such as actin, myosin, and desmin, facilitates efficient force generation and transmission. The regenerative potential of skeletal muscle is largely attributed to satellite cells, which remain quiescent under normal conditions but become activated upon injury. These cells undergo proliferation, differentiation, and fusion to repair or replace damaged muscle fibers, governed by tightly regulated molecular pathways.

Insights into the cellular mechanisms underlying muscle regeneration, particularly the activity of muscle stem cells, may facilitate the identification of novel therapeutic targets for regenerative medicine. Furthermore, understanding the key proteins and signaling pathways involved in muscle repair can advance research focused on monitoring their alterations in response to extracellular insults. This knowledge is essential for establishing mechanistic links between molecular changes and clinical outcomes, ultimately guiding the development of targeted interventions for muscle-related disorders.

Future research should focus on the enhancement of muscle regeneration in pathological conditions, such as aging (sarcopenia), muscular dystrophies, and pharmacological action of medicinal plants and active compounds on myogenesis. Understanding the molecular signaling that governs satellite cell quiescence and activation can open new therapeutic pathways.

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