

Skeletal Muscle Fibrosis: How Fibrotic Mechanisms Limit Muscle Regeneration After Injury

Blaize Haas

Introduction

Skeletal muscle cells are the driving force behind many life functions, such as movement, stability, heat production and amino acid storage. The way they allow organisms to move can be explained through the sliding filament theory, in which the release of Ca^{2+} activates a process where myosin thick filaments grab onto actin thin filaments and pull them toward the center of the sarcomere, thus shortening the muscle fiber; to extend the cell the myosin detaches from the actin and returns its resting state. This highly coordinated process allows skeletal muscle to generate force and perform critical functions throughout the body. Despite skeletal muscle's significant functional support and regenerative capacity, injuries are common and often lead to incomplete recovery due to fibrosis, a process that involves excessive extracellular matrix deposition, particularly collagen, that disrupts normal tissue structure and impairs contractile function. Skeletal muscle fibrosis is common in many disorders such as muscular dystrophy, aging, and injury (Gong et al.). While skeletal muscle possesses a robust regenerative system driven by satellite cells, the process is highly dependent on a regulated and stable cellular environment. When the balance becomes disrupted, fibrotic pathways may dominate over regenerative mechanisms, leading to long term structural abnormalities and a reduced function. As a result, understanding the relationship between fibrosis and regeneration has become increasingly important in muscle biology. Therefore, this paper examines: To what extent do biological mechanisms underlying skeletal muscle fibrosis limit effective regeneration following injury?

Sect 1- Biological mechanisms driving skeletal muscle fibrosis

Transforming growth factor-beta ($\text{TGF-}\beta$) operates as a primary driving molecule in this system, which regulates tissue repair and extracellular matrix production (Yang et al.). When tissue damage occurs, normal wound healing is coordinated by $\text{TGF-}\beta$ through the temporary creation of matrix components. It has been observed that prolonged action of $\text{TGF-}\beta$ causes fibroblasts and fibro-adipogenic progenitors (FAPs) to continue the creation of collagen together with extra matrix proteins even though healing is finished. Structural disorganization of muscle tissue is produced by this excessive matrix gathering, which causes scar creation as time passes. Interactions among defensive immune cells, fibroblasts, satellite cells, and the extracellular matrix influence fibrosis in deep ways (Theret et al.). In times of unhindered regeneration, damaged areas are removed and muscle is reconstructed through collective cellular labor. It has been observed that the extracellular matrix becomes thick and stiff during the advancement of fibrosis (Dewi et al.), which modifies the physical ground where muscle cells operate. Satellite cells are hindered by this dense environment from generating fresh muscle fibers, while scar tissue creation is accelerated. Consequently, fibrosis becomes a primary obstacle against skeletal muscle regeneration when injury takes place.

Sect 2- Muscle Regeneration and satellite cells

Skeletal muscle regeneration relies heavily upon satellite cells, which function as the local stem cells of muscle units (Stepien et al.). Under peaceful resting conditions without injury, satellite cells are kept inactive beneath the basal lamina of muscle fibers. Experts claim that injured tissue releases chemical commands to awaken satellite cells, which makes satellite cells multiply rapidly. Fresh myoblasts—meaning those awakened satellite cells directed toward

muscle growth—are combined with old fibers, so that newly formed muscle fibers restore bodily strength (Relaix et al.).

Complete restoration of muscle needs factors beyond the solitary awakening of satellite cells. Multiple connections among satellite cells, inflammatory units, FAPs, and the extracellular matrix guide the tissue repair sequence (Højfeldt et al.). Harmful waste is cleared away by immune defenders that release activating signals to multiply satellite cells. Structural reinforcement during the growth of muscle fibers is provided by extracellular matrix remodeling that takes place concurrently. It has been observed that these cellular tasks must unfold in an orderly path, because regeneration becomes weak when this sequence is disturbed.

Environmental balance within the tissue is damaged by heavy matrix accumulation and lasting inflammation, which lowers the efficiency of satellite cells during muscle repair (Henze et al.). Accumulation of collagen causes tissue to show severe fibrotic characteristics, shifting healing toward scarring instead of building functional muscle. Many people believe that incomplete muscle healing happens because functional recovery is defeated by dense scar formation.

Sect 3-Fibrosis vs Regeneration

Healing of skeletal muscle after injury depends on an ongoing balance between muscle regeneration and fibrosis. Cooperative action among inflammatory units, satellite cells, and extracellular matrix structures is used to restore broken muscle fibers and re-establish physical performance (Stepien et al.). When inflammatory reactions endure without regulation, healing activity is directed toward fibrosis rather than muscle regeneration. Experts claim that continued stimulation of profibrotic pathways expands matrix growth and collagen accumulation (Mottel et al.), so that scar tissue replaces working muscle fibers.

Cellular communication between defense cells, satellite cells, FAPs, and the surrounding matrix strongly governs this competing relationship. Even though satellite cells possess genuine capacity for rebuilding damaged fibers, extreme fibrotic signals modify the neighborhood and diminish the ability of satellite cells to divide and fuse (Loreti and Sacco). Continuous matrix hardening together with improper tissue shaping creates an escalating cycle where scar formation becomes dominant while regeneration is actively suppressed. It has been observed that muscle regeneration cannot proceed easily when the physical framework becomes excessively rigid.

Scientists suggest that muscle regeneration and fibrosis do not function as separated events, but rather as rival biological paths driven by shared signaling substances. Successful muscle healing is decided by whether regenerative signals overcome ongoing inflammatory and profibrotic signals after physical trauma (Moiseeva et al.). Lost contractile capacity, broken architecture, and partial recovery occur when fibrosis turns into the ruling reaction within muscle tissue. Many people believe that therapies must be built around controlling the equilibrium between fibrosis and muscle regeneration to secure functional repair without uncontrolled scarring.

Section 4-Why Muscle Regeneration Fails

Repeated trauma or extreme damage frequently prevents skeletal muscle from finishing complete recovery, even though skeletal muscle has substantial self-healing ability. Failure occurs primarily because chemical messages meant for brief repair continue operating long past their proper termination time. It has been observed that unchecked signals cause collagen accumulation and extracellular matrix growth (Szlachcikowska et al.), which leads directly to scar creation instead of stopping after muscle replacement. Progressive gathering of scar tissue

causes healthy muscle regeneration to be obstructed because physical space is blocked by dense fibrous matter.

Alteration of the local environment happens steadily as fibrosis moves forward through injured muscle. Density and stiffness within the extracellular matrix are increased, which distorts how cellular units exchange information during tissue crisis (Dewi et al.). Although satellite cells remain present inside the damaged region, their capacity to divide, travel, and merge into fibers is heavily lowered. Ongoing inflammatory activity stimulates fibroblasts and FAPs without interruption, which experts claim will strengthen the pattern of fibrosis instead of muscle regeneration.

Consequently, the internal capacity of skeletal muscle to repair itself is weakened across time. Diminished strength, restricted mobility, and altered functional motion occur when functional muscle units are replaced by dense scar tissue. Chronic destruction of this type is noted in conditions like muscular dystrophy or after repetitive muscle damage, making full physical restoration hard to reach. Many people believe that successful muscle regeneration requires interventions beyond basic satellite cell activation (Szlachcikowska et al.) ; (Dewi et al.). Restoring a balanced biological environment by lowering fibrosis is considered necessary so that natural muscle repair can proceed.

Section 5- Emerging Treatments for Skeletal Muscle Fibrosis

Current medical strategies seek to reduce scar tissue while supporting natural healing, because fibrosis represents a primary cause behind the failure of muscle regeneration. Molecular targeting of particular pathways, especially TGF- β , is investigated by scientists to slow collagen formation and reduce extracellular matrix deposition (Qi et al.). It has been observed that suppression of profibrotic signaling allows satellite cells to restore injured muscle under friendlier conditions.

Tissue engineering combined with regenerative medicine offers an additional route toward healing injured muscle. Synthetic scaffolds and biomaterials are manufactured to copy healthy muscle architecture and provide structural grounding for fresh muscle growth (Wang et al.). Improved cell survival, faster tissue repair, and reduced scarring are produced through the application of these supportive structures. Stem cell interventions and bioengineered muscle implants are explored by investigators for severe trauma, even though experts claim that many of these procedures remain in experimental stages (Awad et al.).

Serious difficulties must be resolved before these therapeutic approaches become standard practice, even though initial reports seem hopeful. Multiple signaling networks and diverse cell groups participate in fibrosis, which is why a single drug is viewed by specialists as insufficient to block scar expansion (Giannone et al.). Many people believe that future clinical approaches must merge anti-fibrotic compounds with therapies that stimulate muscle regeneration.

Re-establishing harmony between fibrosis and muscle regeneration presents the greatest hope for people suffering from muscle injury.

Methods

An extensive literature review is utilized in this paper to investigate how fibrosis hinders skeletal muscle regeneration following physical harm. Material was gathered from PubMed, PubMed Central (PMC), Nature Portfolio journals, Frontiers, and MDPI. Database searches were oriented around terms regarding skeletal muscle fibrosis, muscle regeneration, satellite cells, TGF- β , extracellular matrix, and muscle injury. Examination of both review papers and primary experimental papers was conducted to clarify biological operations and link evidence from different laboratories. Priority was granted to newer publications whenever available, while older

articles were consulted because foundational background had been established by earlier investigators. It has been observed that organizing evidence into core themes—such as mechanisms of fibrosis, satellite cell actions, balance between fibrosis and regeneration, causes of repair failure, and clinical treatments—enables clear synthesis of the material.

Results / Findings

Fibrosis was identified throughout the collected literature as a central barrier that limits skeletal muscle regeneration. Normal muscle repair relies upon inflammatory events, extracellular matrix adjustment, and satellite cell activation, but these identical mechanisms become destructive when their duration is stretched too long

Discussion

These findings help explain why the relationship between fibrosis and regeneration is more complicated than simply viewing one as harmful and the other as beneficial. Many of the processes that eventually contribute to fibrosis are also needed during the early stages of healing. Inflammation, for example, helps remove damaged tissue and initiate repair.

Extracellular matrix production also gives the injured area temporary support. The problem occurs when these responses remain active after they have served their purpose. At that point, a response that originally supported healing can begin to prevent it.

This distinction is important when answering the research question. The evidence suggests that biological mechanisms driving fibrosis can limit regeneration to a large extent, but their effect depends on how long and how strongly they are activated. Persistent TGF- β signaling, inflammation, and collagen deposition can alter the muscle environment enough that satellite cells are no longer able to repair the tissue effectively. Fibrosis can therefore become part of a cycle. Poor regeneration leaves damaged tissue behind, continued injury maintains inflammatory and fibrotic signaling, and the resulting scar tissue makes later regeneration even more difficult.

This also creates a challenge for treatment. Completely blocking inflammation or extracellular matrix production would not necessarily improve healing because both are needed during normal repair. Instead, treatment may need to control when these responses occur and prevent them from becoming chronic. Current research into anti-fibrotic therapies, biomaterials, and regenerative approaches supports this idea, although many treatments remain experimental. Another limitation is that findings from animal models do not always translate directly to human muscle injury. More human studies will be needed to determine which approaches can reduce fibrosis without interfering with the early stages of normal healing.

Conclusion

Skeletal muscle has a strong natural ability to regenerate, but this ability has limits. Based on the literature reviewed, fibrosis can significantly reduce recovery when the normal repair response becomes prolonged or poorly regulated. Persistent inflammation and profibrotic signaling increase collagen and extracellular matrix deposition, which changes the structure of the injured tissue and makes it harder for satellite cells to rebuild functional muscle. Fibrosis is therefore not only a result of failed regeneration. Once established, fibrosis can also contribute to further regenerative failure.

Overall, the biological mechanisms driving skeletal muscle fibrosis limit effective regeneration to a considerable extent, especially following severe, repeated, or chronic injury. However, fibrosis also has a temporary role in normal healing, meaning that simply eliminating the fibrotic response is unlikely to be the best solution. Future treatments may be more successful if they can reduce persistent fibrosis while preserving the early repair processes needed for

regeneration. Understanding where normal healing ends and harmful fibrosis begins remains an important step toward improving recovery after skeletal muscle injury.

Works Cited

1. Awad, K., et al. "Innovations in Skeletal Muscle Regeneration: From Physiology to Bioengineering Approaches for Repair and Restoration." *Frontiers in Physiology*, 2026, <https://doi.org/10.3389/fphys.2026.1789642> .
2. Dewi, N. M., et al. "Targeted Therapy for Skeletal Muscle Fibrosis: Regulation of Myostatin, TGF- β , MMP, and TIMP to Maintain Extracellular Matrix Homeostasis." *Biologics: Targets and Therapy*, vol. 19, 2025, pp. 213–229, <https://doi.org/10.2147/BTT.S508221> .
3. Giannone, A. A., et al. "Deconstruction of Cellular Dynamics after Treatment of Volumetric Muscle Loss Injury with Extracellular Matrix." *npj Regenerative Medicine*, 2025, <https://doi.org/10.1038/s41536-025-00429-8> .
4. Gong, J., et al. "Molecular Mechanisms of Skeletal Muscle Fibrosis and Potential Targeted Therapeutic Strategies." *Frontiers in Immunology*, vol. 17, 2026, article 1714238, <https://doi.org/10.3389/fimmu.2026.1714238> .
5. Henze, H., et al. "Denervation Alters the Secretome of Myofibers and Thereby Affects Muscle Stem Cell Lineage Progression and Functionality." *npj Regenerative Medicine*, vol. 9, 2024, article 10, <https://doi.org/10.1038/s41536-024-00353-3> .
6. Højfeldt, G., et al. "The Repair Capacity Spectrum of Human Skeletal Muscle Injury from Sports to Surgical Trauma Settings." *The Journal of Physiology*, vol. 603, no. 23, 2025, pp. 7441–7454, <https://doi.org/10.1113/JP286507> .
7. Loreti, Matteo, and Alessandra Sacco. "The Jam Session between Muscle Stem Cells and the Extracellular Matrix in the Tissue Microenvironment." *npj Regenerative Medicine*, 2022, <https://doi.org/10.1038/s41536-022-00204-z> .
8. Moiseeva, V., et al. "Senescence Atlas Reveals an Aged-Like Inflamed Niche That Blunts Muscle Regeneration." *Nature*, 2023, <https://doi.org/10.1038/s41586-022-05535-x> .
9. Mottel, L. G., et al. "Immunomodulatory Biomaterials for Vascularized and Innervated Skeletal Muscle Repair." *Frontiers in Immunology*, 2025, <https://doi.org/10.3389/fimmu.2025.1657015> .
10. Parigi, M., et al. "Shining a Light on Skeletal Muscle Regeneration: Red Photobiomodulation Boosts Myoblast Differentiation In Vitro." *The FASEB Journal*, vol. 39, no. 21, 2025, article e71107, <https://doi.org/10.1096/fj.202502477R> .
11. Qi, L., et al. "Advancements in Skeletal Muscle Tissue Engineering: Strategies for Repair and Regeneration of Skeletal Muscle beyond Self-Repair." *Regenerative Biomaterials*, vol. 12, 2025, article rbaf050, <https://doi.org/10.1093/rb/rbaf050> .
12. Relaix, F., et al. "Perspectives on Skeletal Muscle Stem Cells." *Nature Communications*, 2021, <https://doi.org/10.1038/s41467-020-20760-6> .
13. Stepien, D. M., et al. "Tuning Macrophage Phenotype to Mitigate Skeletal Muscle Fibrosis." *The Journal of Immunology*, vol. 204, no. 8, 2020, pp. 2203–2215, <https://doi.org/10.4049/jimmunol.1900814> .
14. Szlachcikowska, D., et al. "Current Insights and Future Directions in Scar Management and Skin Regeneration." *International Journal of Molecular Sciences*, vol. 26, no. 21, 2025, article 10636, <https://doi.org/10.3390/ijms262110636> .
15. Theret, M., et al. "Evolving Roles of Muscle-Resident Fibro-Adipogenic Progenitors in Health, Regeneration, Neuromuscular Disorders, and Aging." *Frontiers in Physiology*, vol. 12, 2021, article 673404, <https://doi.org/10.3389/fphys.2021.673404> .



-
16. Wang, Z., et al. "Adipose Decellularized Matrix: A Promising Skeletal Muscle Tissue Engineering Material for Volume Muscle Loss." *Biomaterials Research*, vol. 29, 2025, article 0174, <https://doi.org/10.34133/bmr.0174> .
 17. Yang, W., et al. "Research Progress on Scar-Free Healing." *Annals of Medicine*, vol. 57, no. 1, 2025, article 2575109, <https://doi.org/10.1080/07853890.2025.2575109> .