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Therapeutic Approaches to Skeletal Muscle Repair and Healing

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Context: Skeletal muscle is comprised of a highly organized network of cells, neurovascular structures, and connective tissue. Muscle injury is typically followed by a well-orchestrated healing response that consists of the following phases: inflammation, regeneration, and fibrosis. This review presents the mechanisms of action and evidence supporting the effectiveness of various traditional and novel therapies at each phase of the skeletal muscle healing process.

Evidence Acquisition: Relevant published articles were identified using MEDLINE (1978-2013).

Study Design: Clinical review.

Level of Evidence: Level 3.

Results: To facilitate muscle healing, surgical techniques involving direct suture repair, as well as the implantation of innovative biologic scaffolds, have been developed. Nonsteroidal anti-inflammatory drugs may be potentially supplanted by nitric oxide and curcumin in modulating the inflammatory pathway. Studies in muscle regeneration have identified stem cells, myogenic factors, and β-agonists capable of enhancing the regenerative capabilities of injured tissue. Furthermore, transforming growth factor-β1 (TGF-β1) and, more recently, myostatin and the rennin-angiotensin system have been implicated in fibrous tissue formation; several antifibrotic agents have demonstrated the ability to disrupt these systems.

Conclusion: Effective repair of skeletal muscle after severe injury is unlikely to be achieved with a single intervention. For full functional recovery of muscle there is a need to control inflammation, stimulate regeneration, and limit fibrosis.

Strength-of-Recommendation Taxonomy (SORT): B

Keywords: skeletal muscle; injury; repair

Skeletal muscle injuries commonly occur during participation in sports and often present a treatment challenge. These injuries are frequently associated with significant morbidity and prolonged loss of function. Up to 50% of sporting injuries are isolated to skeletal muscle and affect a wide spectrum of individuals ranging from high-level athletes to the average "weekend warrior."[22,27] The classic treatment follows the acronym RICE (rest, ice, compression, elevation). These principles have been used successfully to treat low-severity muscle injury but have proven ineffective for the treatment of high-grade muscle strains, especially in individuals requiring full return to high-intensity competition.[63]

Skeletal muscle injury can result from a myriad of external insults, including contusions, lacerations, burns, and exposure to toxins. In addition to these mechanisms of injury, the application of force that surpasses the load capacity of the muscle during routine use may also contribute to injury. Specifically, skeletal muscle is capable of generating stresses exceeding 0.3 MPa at frequencies over 10 Hz without succumbing to injury.[58] The magnitude of such stresses, however, can be increased significantly under certain loading conditions, such as when the muscle is eccentrically contracting, resulting in trauma. Irrespective of the mechanism, muscle injury and the mechanical trauma itself disrupts the basal lamina and plasma membrane of affected myofibers, allowing for an unregulated influx of extracellular calcium.[26,28] Necrosis of the injured myofibers ensues through an autodigestion process mediated by various proteases, such as calpain.[26,58] Swelling and hematoma formation then occur and facilitate further muscle degeneration.[24,59] Skeletal muscle response to injury proceeds through overlapping phases, beginning with inflammation, progressing to regeneration, and concluding

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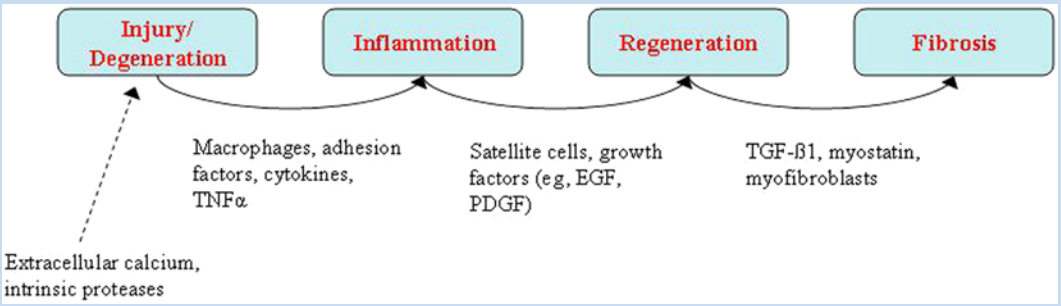

Figure 1. Phases of skeletal muscle healing. These general phases are precipitated by a variety of cell types, cytokines, and growth factors, ultimately leading to muscle regeneration and fibrosis. TNFα, tumor necrosis factor α; EGF, epidermal growth factor; PDGF, platelet-derived growth factor; TGF-β1, transforming growth factor-β1.

with fibrosis (Figure 1). Neither the controls to orchestrate this process nor the regulators of the transitions among phases are fully understood.

MUSCLE INJURY AND DIRECT REPAIR

Trauma to the intrasubstance of a muscle, in particular, often impairs functional capacity by disrupting the musculotendinous complex.[30] In the setting of volumetric muscle loss greater than 20%, the defect typically is not repaired through intrinsic healing mechanisms, resulting in a decrease in function.[1] In such cases, surgery may be the only intervention capable of restoring partial or full function. Therefore, the indications for surgical repair of an intrasubstance muscle laceration generally include a partial or full transection that, left unrepaired, could result in weakness and/or loss of function.[30]

Suture Repair

While surgery may alter the local anatomy and underlying biomechanics at the injury site, it has remained a common mode of muscle repair.[55] Historically, suture repair of muscle injuries has been the primary intervention, and various techniques have been described.[2,25,42] Kragh et al conducted a biomechanical analysis of muscle repaired with incorporation of perimysium versus epimysium.[33] Figure-of-eight stitches were placed in the lacerated quadriceps bellies of a euthanized pig, and sutures were tensioned on a biomechanical device. The maximum strain and load for repairs with epimysium were greater than those with perimysium, indicating that incorporation of epimysium into muscle suture repair yields superior biomechanical stability. Another biomechanical study compared Kessler stitches with a combination of perimeter and Mason-Allen stitches in a cadaveric pig quadriceps femoris model.[34] Combination suturing was found to have a lower failure rate and greater mean load and strain maximums compared with Kessler stitches. Additionally, a nonrandomized outcomes analysis was carried out on paratroopers with acute traumatic closed transection of the biceps brachii muscle and compared nonoperative management with muscle repair that consisted of suturing the muscle fibers and epimysium with both running interlocked stitches and modified Mason-Allen stitches.[32] This study showed that those patients who underwent surgical repair had statistically significantly higher function, satisfaction, and appearance scores than those who had nonoperative treatment at a mean of 11 years follow-up.

Biologic Scaffolds

In addition to direct suture repair, innovative work involving biologics and regenerative medicine has led to the advent of biologic scaffolds. These biomaterials are developed from various species of origin, such as bovine and porcine tissue and tissue such as dermis, submucosa, and pericardium. Although frequently xenogeneic, these scaffolds are prepared and processed so that they do not generate a proinflammatory reaction when implanted.[3,31] Biologic scaffolds preserve the composition and 3-dimensional structure of the extracellular matrix of their tissue of origin and promote remodeling of injured tissues.[4] Certain biologic scaffolds transition the macrophage phenotype from the proinflammatory M1 state to the more tissue-regenerating M2 type and stimulate the release of latent growth factors.[59]

Given its regenerative capabilities, several studies have sought to adapt the biologic scaffold for use in skeletal muscle reconstruction. A muscle-derived biologic scaffold was implanted into a full-thickness defect in rat gastrocnemius muscle.[44] After 1 week, mesenchymal stem cells were injected into the scaffold, and at 6 weeks, the scaffold had regenerated a mean 85.4% of the muscle with a mean specific tension of 94% compared with the contralateral limb. To further characterize its potential, Turner et al[60] implanted an extracellular matrix–based scaffold into a canine model that had undergone complete resection of the distal gastrocnemius muscle. After 6 months, the scaffold had facilitated the formation of innervated, vascularized skeletal muscle similar to native tissue. This repaired muscle had a contractile force of 48% of the contralateral muscle. Additionally, a histomorphologic study by Valentin et al[62] reconstructed a rodent abdominal wall defect with a noncrosslinked porcine small intestinal mucosa biologic scaffold. Six months after

Table 1. Potential therapies for inflammation: agents and their corresponding effects on mitigating the inflammatory phase of skeletal muscle healing

Agent	Effect(s)
Nitric oxide	Increase inflammatory cytokines through HGF mediator
NSAIDs	Inhibit COX to suppress prostaglandin synthesis
Curcumin	Inhibit NF-κB transcription factor

HGF, hepatocyte growth factor; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells.

surgery, this acellular scaffold was replaced by sheets of skeletal muscle. The regenerated tissue demonstrated increased resistance to fatigue and achieved approximately 80% of the contractile force of native muscle. Similarly, Crow et al[15] utilized a small intestinal mucosa scaffold to repair lacerations of the extensor digitorum longus muscle bellies in rabbits. In this investigation, lacerations were either left unrepaired (group 1) or were treated with a modified Kessler stitch (group 2). The biologic scaffold was sutured into half of the specimens in each group. Suture repair with augmentation by the scaffold yielded tissue with the greatest similarity to native muscle with regard to function and morphology. These studies illustrate the potential of biologic scaffolds to serve as novel treatments for the regeneration of skeletal muscle.

THE INFLAMMATION PATHWAY

The inflammation stage involves a balance between further injury to myofibrils, mediated by neutrophil-produced free radical species,[40,53] and macrophage-mediated removal of necrotic cells and pro-healing cytokine production.[43,65] Soon after skeletal muscle injury, inflammatory mediators (serotonin, histamine, thromboxane A2, etc) saturate the area, released by platelets that were activated by the injured muscle's exposed collagen.[53] These mediators attract other platelets, controlling local hemorrhage, and encourage extravasation of peripheral immune cells (neutrophils, macrophages, T lymphocytes). These cells defend the host from foreign organisms as well as facilitate cellular "clean-up" and progression of muscle repair. A variety of factors have been investigated to aid in modulating inflammation (Table 1).

Nitric Oxide

Nitric oxide (NO) may increase inflammation and serve as an activator of satellite cells after skeletal muscle trauma.[18] Hepatocyte growth factor (HGF) may be a mediator for NO action.[18] Studies in rats have demonstrated that inhibition of NO leads to decreased inflammatory reaction on histology at 24 hours after injury. At 7 days postinjury, increased collagen deposition has been seen on histology and by morphometric image analysis. In the same rat model, significantly increased expression (by RT-PCR assay) of inflammatory cytokines IL-1β and IL-6 was observed at both 1 and 7 days post-trauma.[19] This expression was suppressed in the presence of an NO inhibitor (L-NAME), suggesting that NO plays a pivotal role in the inflammatory cascade.

Nonsteroidal Anti-inflammatory Drugs

Nonsteroidal anti-inflammatory drugs (NSAIDs) seem a logical selection for curbing inflammation. Designed to target cyclooxygenase (COX), NSAIDs suppress prostaglandin synthesis, a key step in the inflammation pathway. NSAIDs, however, have not affected functional recovery of muscle tissue after injury.[57,64] In fact, COX-2 activity is essential for normal growth of regenerating myofibers in a mouse model of muscle injury.[9] During the acute phase of healing (generally days 3-7 after injury), a short-term course of NSAIDs is beneficial and resulted in no adverse effects on the healing process or muscle strength, but care should be taken when using NSAIDs because emerging evidence suggests that long-term use may have adverse effects on muscle healing.[38]

Curcumin

Curcumin, a compound that inhibits the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) transcription factor, may slow the inflammatory cascade. Murine studies have demonstrated faster regeneration of myofibers with organization into their normal architecture after trauma with intraperitoneal curcumin therapy.[56] The same group also performed in vitro studies on myoblasts treated with an NF-κB inhibitor to show that the effect is the same as if curcumin itself were applied, indicating curcumin's action on regenerating muscle through NF-κB. Additionally, they demonstrated failure of IL-1β (which stimulates NF-κB 5-fold in their reporting construct) to produce a response after curcumin treatment in vitro. Although further animal studies and eventually human trials are needed, curcumin has the potential to play a pivotal role in a multimodal approach to treating muscle injuries in the future.

Table 2. Potential therapies for regeneration: agents and their corresponding effects on the regeneration phase of skeletal muscle healing

Agent	Effect(s)
Muscle-derived stem cells	Enhance angiogenesis by VEGF secretion
Adipose-derived stem cells	Promote regeneration, mechanism poorly understood but thought to be through a paracrine mediator; more easily harvested, less immunogenic
Human muscle myogenic factor	Stimulate satellite cells to re-enter the cell cycle after injury
Brain-derived neurotrophic factor	Thought to be involved in satellite cell activation and proliferation
β-agonists	Increase in protein synthesis and decrease in degradation resulting from increase in intracellular cAMP

cAMP, cyclic adenosine monophosphate; VEGF, vascular endothelial growth factor.

ENGINEERING MYOFIBER REGENERATION

Satellite cells are muscle stem cells located between the basal lamina and sarcolemma of individual myofibers and supply the injured muscle with their regenerative capacity.[8,51] These cells serve as the reserve of myogenic precursors and may have the potential for complete repair of injured muscles. However, it is not clear what cellular signals are responsible for orchestrating the transition from quiescence to regeneration in satellite cells.[8] When stimulated, satellite cells differentiate into myoblasts. These myoblasts subsequently fuse to one another or to injured myofibers.[8,29] The regenerative potential of satellite cells is limited by scar tissue formation. The scar replaces normal muscle architecture with tissue that lacks innervation and contractile properties and therefore significantly limits the ability of the injured muscle to regain all of its preinjury function.[29,51] Various therapies and targets have been studied to better control this regenerative process (Table 2).

Muscle-Derived Stem Cells

Muscle-derived stem cells (MDSCs) are postnatal stem cells (distinct from satellite cells) with the capacity to differentiate into multiple lineages.[49,61] These MDSCs were isolated in a Duchenne muscular dystrophy model, in which they restored dystrophin expression after transplantation.[52] In the context of muscle injury, their reparative capacity is thought to be related to their ability to secrete the angiogenic protein vascular endothelial growth factor (VEGF).[7,49] This relationship highlights the close association between the regenerative phase of muscle repair and angiogenesis.[7,49,50]

Ota et al[49] injected MDSCs into injured mouse muscles and yielded increased angiogenesis, muscle fiber regeneration, and muscle strength and decreased fibrosis compared with controls. They found that muscle regeneration after MDSC transplantation is time dependent and concluded that postinjury day 4 transplantation significantly aids muscle recovery. A significant limitation of this treatment is the need to harvest MDSCs of patients 2 weeks prior to the muscle injury to ensure adequate time for culture expansion. Clinical viability of MDSCs is being established with human trials for urinary stress incontinence.[11]

Adipose-Derived Stem Cells

A stem cell population derived from adipose tissue may be more clinically relevant than bone marrow–derived mesenchymal stem cells because of their "accessibility, abundance, and higher proliferation rates."[51] Additionally, they are less immunogenic than their bone marrow–derived counterparts.[16] In a rat model, adipose-derived stem cells were injected directly into lacerated soleus muscles and appeared to accelerate muscle repair, but their promise showed limitations.[51] There was an increase in strength and number of regenerating myofibers at 2 weeks but not at 4 weeks. Interestingly, the cells themselves were not found in the host tissue at 2 or 4 weeks. Furthermore, fibrosis was not inhibited by the intervention. In light of the rapid disappearance of the adipose-derived stem cells, the mechanism of action may be by a paracrine mediator.

Novel Intrinsic Human Muscle Myogenic Factor

There may be myogenic factors that stimulate satellite cells to re-enter the cell cycle after muscle injury. These theoretical factors are of interest for their potential ability to recruit a cadre of satellite cells for muscle repair after injury. Li et al[35] isolated one such factor (fraction H) from human soleus muscle biopsies and confirmed its ability to promote myogenic cell alignment and fusion. When the novel protein was tested on injured muscles in rats, regenerated muscle fibers were found where the control muscles showed fibrosis.

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is a protein expressed in satellite cells as well as nonmuscle tissue.[13] After

Table 3. Potential therapies to treat fibrosis: agents and their corresponding effects on mitigating the fibrosis phase of skeletal muscle healing

Agent	Effect(s)
Suramin	Inhibits TGF-β1 and myostatin via follistatin up-regulation, decreases fibroblast proliferation and fibrosis
Relaxin	Antagonizes TGF-β1, decreases type I and III collagen deposition to minimize fibrosis
Decorin	Inhibits TGF-β1 and myostatin via follistatin, mitigates fibrosis and recovers contractile strength
Gamma interferon	Disrupts TGF-β1 signal transduction, stunts fibroblast growth, diminishes fibrotic protein expression
IGF-1/FGF	Prevents SMAD phosphorylation by TGF-β1, decreases fibronectin expression and extracellular matrix accumulation, also aids in regeneration
ARBs/ACE inhibitors	Antagonizes CTGF, limits extracellular matrix accumulation

ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; CTGF, connective tissue growth factor; SMAD, a portmanteau of MAD ("mothers against decapentaplegic") and SMA (a nematode protein, "small body size"); TGF-β1, transforming growth factor-β1.

injury, BDNF can be detected, coinciding with satellite cell activation and proliferation, leading to speculation about the involvement of BDNF in that process. Transgenic mice with a selective absence of skeletal muscle BDNF had a depleted satellite cell population (inferred by decreased satellite cell markers), disturbed proliferation and differentiation of myoblasts, and delayed regeneration of myofibers after muscle injury.[13] Exogenous BDNF could "rescue" regenerating knockout-mouse–derived myotubes in vitro.

β-agonists

β-agonist therapy has shown potential in skeletal muscle repair.[5] Animals receiving β-adrenoceptor agonist therapy have an increase in both size and force-producing capacity of injured muscles.[5] Two days after injury to the extensor digitorum longus muscle, experimental rats showed approximately 3.5-fold up-regulation of β-adrenoceptors. Effects of β-adrenoceptor agonist therapy are not dependent upon this up-regulation, however. Muscle mass and fiber cross-sectional area was increased in rats injected with fenoterol (a β-adrenoceptor agonist)—both those that had suffered injury and those that had not. An interesting effect of this treatment is that the up-regulation of receptor density is attenuated by approximately 40% with β-adrenoceptor agonist therapy. The clinical significance of this attenuation is still not known.[6]

FIBROSIS AND ANTIFIBROTIC AGENTS

Following the regeneration phase of healing, skeletal muscle often transitions into a fibrotic phase. This process commonly commences 2 to 3 weeks after injury.[23,26] Characterized by the abnormal accumulation of extracellular matrix, fibrosis results from the activation of myofibroblasts by a variety of factors, including adult muscle stem cells, inflammatory or perivascular cells, myostatin, and resident fibroblasts.[37] Transforming growth factor-β1 (TGF-β1) is essential to this process.[39] This cytokine is a member of the TGF-β superfamily, which is released from traumatized muscle fibers. Ligands from this group initially bind to a TGF-β2 receptor, which in turn phosphorylates a TGF-β1 receptor. The type 1 receptor then catalyzes the activation of the intracellular protein SMAD, a portmanteau of the protein "mothers against decapentaplegic" (MAD) and a nematode protein (SMA, for "small body size"), which stimulates the transcription of specific target genes leading to extracellular matrix neogenesis and, ultimately, fibrosis. The extent of these fibrotic changes is determined by the total collagen content of the connective tissue, measured by the amount of hydroxyproline, with elevated levels of collagen associated with increased mechanical stiffness of muscle fiber bundles.[37] Prolonged extracellular matrix deposition and the resulting scar formation impede muscle regeneration and may interfere with function.[23]

Suramin and Relaxin

Given the impairments associated with skeletal muscle fibrosis resulting from injury, or in disease states such as Duchenne muscular dystrophy, various agents have been investigated to modulate this healing phase (Table 3).[14] Because of the aforementioned critical role that TGF-β1 has in the development of fibrosis, research has emphasized identifying therapies that target this cytokine or its signaling pathway. Suramin, a heparin analog, has been used as an antineoplastic and antiparasitic drug.[47] By binding to heparin proteins, it competitively inhibits various growth factors, including epidermal growth factor (EGF) and TGFβ1.[48] This effect was confirmed in a strain injury model of murine gastrocnemius muscles, whereby suramin antagonized the stimulatory effect

of TGF-β1 on the proliferation of muscle-derived fibroblasts.[12] The muscle treated with suramin also generated significantly less fibrotic tissue, indicating that suramin can reduce scar formation. Additionally, suramin reduced myostatin expression in a contusion injury model of murine tibialis anterior muscles and was associated with decreased fibrosis formation.[47]

Myostatin is a member of the TGF-β superfamily that impedes muscle growth by stimulating fibrosis.[48] Furthermore, like suramin, relaxin can interact with and antagonize TGF-β1.[36] Specifically, it inhibits TGF-β1's stimulating effect on type I and type III collagen deposition and, in doing so, reduces the production of fibrous tissue. Relaxin also decreases myofibroblast proliferation and scar formation in a dose-dependent manner.[46]

Decorin, Gamma Interferon, and Growth Factors

Similar to suramin and relaxin, a variety of other agents demonstrate a capacity to combat skeletal muscle fibrosis. Decorin, a small and predominantly leucine-based proteogylcan, interferes with TGF-β1 activity to create an antifibrotic effect.[23] To illustrate this, Fukushima et al[21] injected human recombinant decorin into lacerated murine hindlimb gastrocnemius muscles and performed a histologic analysis to assess healing after 2 weeks. Muscle treated with decorin had significantly decreased fibrosis and a level of strength similar to uninjured muscle. Moreover, much like suramin, decorin also minimizes fibroblast development by inhibiting myostatin through up-regulation of follistatin.[66] In addition, researchers have investigated the antifibrotic potential of gamma interferon. As a cytokine, gamma interferon blocks the TGF-β1 signaling pathway and, in a murine laceration model, stunted the growth rate of fibroblasts and diminished fibrotic protein expression.[20] The area of fibrosis was decreased in those mice injected with gamma interferon, and they exhibited improved tetanic and fast-twitch muscle strength. Furthermore, while growth factors have been predominantly associated with enhanced muscle regeneration, there is evidence to suggest that they may have antifibrotic effects as well. For example, insulin-like growth factor-1 (IGF-1) inhibits SMAD phosphorylation by TGF-β1 and the expression of fibronectin, which in turn modulates extracellular matrix accumulation and could prevent skeletal muscle fibrosis.[17] Fibroblast growth factor (FGF) may also decrease scar tissue formation in lacerated muscle.[41]

Angiotensin II Receptor Blocker and Angiotensin-Converting Enzyme Inhibitors

Although most often associated with blood pressure regulation, the rennin-angiotensin system (RAS) has also been implicated in fibrous tissue and scar development in a variety of tissues, principally through angiotensin II and the angiotensin-converting enzyme (ACE).[23] Considering this, studies have investigated how the RAS can be manipulated to mitigate fibrosis. Angiotensin II receptor blockers (ARBs) antagonize the connective tissue growth factor (CTGF)–mediated increase of extracellular matrix molecules and fibrotic proteins in a tibialis anterior muscle model.[10] CTGF is a cysteine-rich protein that contributes to extracellular matrix production, and its level correlates with the severity of tissue fibrosis. Consequently, by inhibiting its function, ARBs can decrease fibrosis in skeletal muscle. ARBs, such as losartan, may also serve as an adjunct to platelet-rich plasma (PRP) therapy for treating muscle contusion injuries.[54] The combination of the supply of growth factors provided by PRP with the antifibrotic effects of ARBs has the potential to enhance muscle injury treatment. Additionally, ACE inhibitors have also been shown to exhibit antifibrotic effects. In a murine model of Duchenne muscular dystrophy, Morales et al[45] revealed that enalapril decreases both CTGF expression and its profibrotic activity without affecting TGF-β1. The mice treated with this ACE inhibitor boasted increased skeletal muscle strength and decreased fibrosis.

SUMMARY AND FUTURE DIRECTIONS

Skeletal muscle injury leads to the initiation of a well-coordinated cascade that attempts to contain the damage and also repair the injured muscle. However, based on the severity of the muscle injury, this response to injury may not be sufficient to return the injured muscle to its preinjury function and may therefore require further treatment to enhance the repair process.

Suture repair of muscle injuries, historically the primary surgical modality, has focused on incorporation of the epimysium into the repair and the use of combination suturing, which may yield superior results. Biologic scaffolds, however, are emerging as a novel, alternative therapy. A product of the growing field of applied biomaterials, these scaffolds bridge the gap between direct repair and regenerative medicine by preserving the extracellular matrix of the tissue of origin and stimulating the migration and production of progenitor cells. They show promise in regenerating skeletal muscle and recovering contractile strength after injury. Additionally, characterizing the effects of biomechanical loading scaffolds to promote regeneration and studies comparing scaffolds from different xenogeneic origins will aid in identifying the optimal conditions under which these therapies function.

NSAIDs were the most promising intervention to target inflammation but have not been clinically proven beneficial for more substantial muscle injuries and are only effective when used short term. NO inhibitors have shown promise in an animal model of skeletal injury, but no projections about the safety of NO inhibitors in human subjects have been made, and it is unlikely that they will be clinically relevant. The anti-inflammatory properties of curcumin have been targeted for many clinical applications, and studies have been positive in both in vitro and in vivo models.

Myofiber regeneration after injury is central to, though not sufficient for, skeletal muscle repair. Stem cell research, while both promising and enticing, is several years away from clinical utility. Also, unanswered questions regarding the long-term effects of β-adrenoceptor agonist therapy may temper enthusiasm for their use. Continued investigation of myogenic

factors that have been isolated from human muscle and elucidation of their effects on satellite cells are the next step in muscle regeneration.

Fibrosis resulting from injury can also impair functional outcomes. TGF-β1 serves a critical role in fibrous tissue formation after skeletal muscle injury, and continued research is revealing myostatin to be another key factor. Consequently, several therapies are aimed at inhibiting these factors or disrupting their signaling pathways. These antifibrotic agents, such as suramin, relaxin, decorin, and gamma interferon, reduce skeletal muscle fibrosis and facilitate recovery. No reliable formulations exist, however, for the administration of many of these antifibrotic therapies. Growth factors, such as IGF-1 and FGF, may also have antifibrotic potential, but more research is needed to validate preliminary studies. Additionally, ACE inhibitors and ARBs, previously used almost exclusively for modulating blood pressure, are also emerging as a therapy to decrease muscle fibrosis and increase strength in injured or dystrophic skeletal muscle.

Effective repair of skeletal muscle after severe injury is unlikely to be achieved with a single intervention. For full functional recovery of muscle, there is a need to control inflammation, stimulate regeneration, and limit fibrosis.

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