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REVIEW ARTICLE

CELLULAR AND MOLECULAR MECHANISMS OF MUSCLE REGENERATION

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ABSTRACT

BACKGROUND: Muscle injuries are a common manifestation of exercise and non-mechanical factors such as drugs, genetic defects, and systemic diseases. Despite their clinical importance, the cellular and molecular mechanisms of muscle injury and repair are poorly understood, which hamper development of effective clinical interventions.

OBJECTIVE: This review is an attempt to recognize basic principles of skeletal muscle regeneration process.

METHODS: A thorough systematic review of articles on muscle injury and repair processes was conducted using three reliable search engines for biomedical literature as ScienceDirect, Scopus and PubMed.

REVIEW: Following injury, rapid activation and differentiation of satellite cells is major cellular repair process. At the molecular levels, activation of dysferlin and MG53 proteins help in building the "repair cap" at injury site to initiate repair process. This event is followed by secretion of muscle myokines and subsequent infiltration of macrophages into muscle fibers, which remove cellular debris and activate other repair proteins and satellite cells. This review elaborates cellular and molecular mechanisms regulating these events following muscle injury. Effective therapeutic interventions to counter muscle injury-related atrophy remain elusive.

CONCLUSION: Altogether, this review proposes cellular and molecular targets to accelerate muscle regeneration process following mechanical and non-mechanical injuries. Further investigations are required to elucidate the pathways dictating muscle regeneration process following injury.

KEY WORDS: Skeletal Muscle (MeSH); Regeneration (MeSH); Muscle Injury (MeSH); Satellite cells (Non-MeSH); Dysferlin (MeSH); TRIM proteins (non-MeSH); mg53 (non-MeSH); Myokines (non-MeSH); Inflammation (MeSH); Macrophages (MeSH); Serum Amyloid A (MeSH).

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INTRODUCTION

Skeletal muscle is the largest organ in human body and has an efficient system to repair itself following injury. Multiple factors can induce skeletal muscle damage including extremes of temperatures, toxins, oxidative stress, mechanical strains from eccentric exercises and physical trauma.[1] The muscle repair system primarily includes muscle stem cells or satellite cells which divide and donate extra nuclei to multinuclear skeletal muscle fiber for regeneration.[2] However, in case of extensive damage or deficient repair, degeneration processes step in and result in loss of muscle mass and force, culminating in functional dependency.[3] Surgical procedures often require incisions through the skeletal muscle, and timely and efficient muscle regeneration holds top priority after surgeries. A defective repair and regenerative capacity may prolong recovery and lead to functional compromise with long-term debility and hospitalization.[3]

Many diseases can result in skeletal muscle degeneration and defective regeneration. Dystrophies are a group of inherited muscle diseases, which are due to defect in a gene encoding dystrophin protein and result in repeated muscle injury and fibrosis.[4] Duchene's muscular dystrophy (DMD) is the severe form of genetic muscular dystrophies and results in increased fragility and exhaustion of repair processes in skeletal muscle resulting in replacement of muscle tissues by fibrous tissues.[5] Aging related muscle loss, called sarcopenia also results in degeneration of skeletal muscle.[6] Furthermore, multiple myopathies and drugs can introduce repeated injury and scarring of skeletal muscle with pathological consequences. Developing interventions to boost skeletal muscle repair requires a detailed understanding of the molecular and cellular mechanisms involved in repair and regenerative processes of skeletal muscle following injury.[7] The objective of this review was to examine the repair and regenerative mechanisms that are activated following muscle injury to maintain skeletal muscle homeostasis.

METHODS

A thorough systematic review of articles on muscle injury and repair processes was conducted using three reliable search engines for biomedical literature as ScienceDirect, Scopus and PubMed. The search was performed in May 2020 and specific keywords (skeletal muscle, injury, satellite cells, muscle regeneration, myokines and macrophages) were used. Randomized controlled trials were preferred. Irrelevant papers focusing on body systems other than skeletal muscle were excluded. There was no time constraint for selection of publications although recent publications from last 10 years were generally preferred. Figure 1 describes the flow diagram of the methodology.

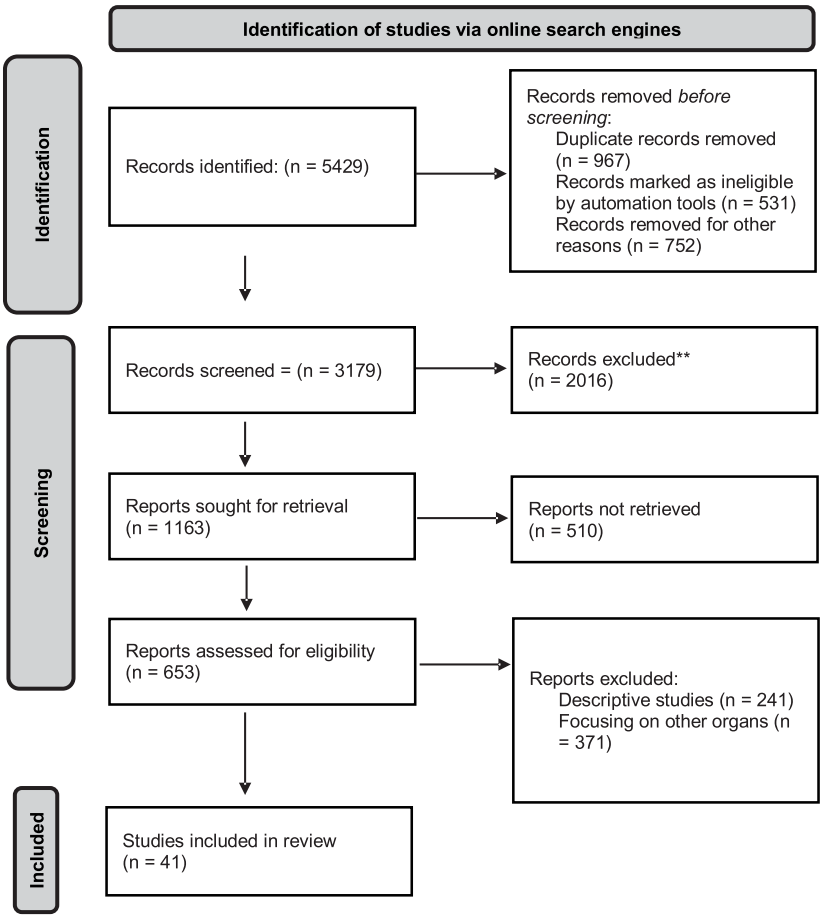

Figure 1: Flow chart of the studies investigated.

REVIEW AND DISCUSSION

The literature search unraveled several studies relevant to the topic of this review. We identified multiple causes of muscle injury through literature search. The causes were generally divided into mechanical factors as due to exercise, and non-mechanical factors such as excessive use of catabolic steroids, systemic inflammation etc. The following sections identify and summarize these causes and their detrimental effects on skeletal muscle at cellular and molecular levels.

Causes of skeletal Muscle Injury

Exercise induced muscle injury

Eccentric contractions often result in excessive stretching and mechanical injuries of the skeletal muscle.[8] These contractions involve excessive stretching of sarcomere and common examples is running downhill or lifting heavy weights. Sarcomere can safeguard itself against these contractions with titin molecules which span across the whole length of sarcomere between successive z-disks.[9] However, excessive, and persistent eccentric contractions often result in damage to sarcomere. Two possible outcomes following such damage are alterations in sarcomere structure and disruption of excitation contraction coupling (EC) machinery. Damaged to sarcomere and its myofibrillar proteins results in of muscle soreness, decreased force generation capacity, and reduce endurance capacity.[10] On the other hand, disruption of EC coupling machinery results in muscle weakness and intracellular calcium dysregulation which can further exacerbate muscle pathology.[6, 11] Fortunately, muscle cell has an efficient repair system to prevent further damage. It involves activation of intracellular protein signaling pathway which result in a cascade of events leading to increased repair and regeneration of skeletal muscle.

Non-exercise induced muscle injury

In addition to mechanical damage, skeletal muscle can also be damaged due to an array of diseases and drugs. Several inherited and acquired myopathies can result in muscle damage.[12] Moreover, multiple drugs including statins and catabolic steroids can induce muscle damage, which leads to reduced muscle strength and mass.[13,14] Skeletal muscle maintenance requires frequent contractions which result in mechanical loading of muscle cell membranes. However, conditions with prolonged inactivity of skeletal muscle such as chronic bed rest, muscle paralysis due to neurological injury, spaceflight as well as acute insult such as surgery, sepsis, and cardiotoxin scan induce muscle wasting and weakness.[15-17] The molecular mechanisms of muscle wasting in these conditions are multifold. These include activation of proteolytic pathways, excessive upregulation of autophagy, mechanical damage to proteins associated with absorbing strains such as dystrophin and titin, and dysfunction of cellular chaperons. However, these mechanisms eventually result in an increased protein degradation and reduced protein synthesis activity inside muscle cells. Further, these conditions lead to alterations in bioenergetics and increased cellular oxidative stress which can exacerbate muscle damage.

Mechanisms of muscle repair

Role of Satellite Cells

Muscle fibers are multinucleated cells and contain hundreds of myonuclei across their length.[18] New myonuclei are added by satellite cells division and donation of myonuclei to the muscle fiber.[19] Additional myonuclei can enhance protein synthesis capacity which can accelerate cellular repair process by providing extra proteins required for repair and regeneration. Mature muscle fibers are post-mitotic and cannot further divide to provide replacement of dead muscle fibers following an injury. Hence the only efficient cellular mechanism of repair is to re-grow existing damaged muscle fiber which requires activation of satellite cells.[2,20]

In resting muscle, satellite cells are in a

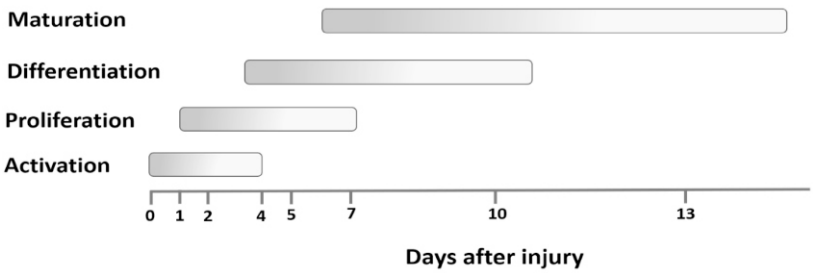

Figure 2: Time frame of muscle satellite cells activation, proliferation, differentiation and maturation following muscle injury.

quiescent state and are localized in the basal lamina of the muscle fibers. Satellite cells are rapidly activated following damage to muscle fiber, and enter the cell cycle phase to proliferate. Following the cell division, one of the daughter cells enter quiescent phase while other fuse with membrane of skeletal muscle fiber, then incorporating its nucleus into muscle fiber.[21] In this way muscle fiber gets an extra nucleus to assist in cellular repair.

The role of satellite cells in muscle hypertrophy is not well defined and is still debated. However, emerging studies show that they have an important role in cellular repair following injury.[21] This is evident in animal models with satellite cells ablation which show some degree of hypertrophy following a stimulus, but no repair capacity when an injury is introduced. For example, when >90% of satellite cells are ablated using tamoxifen injections in Pax7-DTA mouse knockout model, muscle regeneration is severely blunted following an injury.[22] However, some degree of hypertrophy was still possible. These findings suggest that satellite cells play a pivotal role in muscle repair and regeneration after injury.

The activation, differentiation and division of satellite cells following muscle injury is a stepwise process and the timings of these events are summarized in figure 2.

However, a detailed description of these processes is beyond the scope of this review and the readers are encouraged to read some excellent review articles on these processes for further information.[2,21,23] However, their role in muscle repair is well appreciated now. It must be noted that the satellite cells are not the only stem cells involved in muscle repair. Increasing evidence suggests that pericytes and adipocytes stem cells can also help in muscle repair following an injury.[24,25]

Intracellular repair proteins

The extra nuclei donated by muscle satellite cells help in repair process by activating transcription of an array of proteins required for muscle repair and regeneration. Among many proteins required for cellular repair, the role of dysferlin in muscle repair was first recognized in 2003. This was evident by more damage and reduced repair in mouse model of dysferlin deficiency when its muscle were stretched for eccentric contractions.[26] These mice also showed increased cytosolic calcium concentration near the site of injury and the role of elevated calcium concentration in repair process near the site of injury is now well recognized. Calcium can induce cellular repair via multiple mechanisms including induction of vesicles formation and development of a new membrane layer.

In 2009, the role of muscle specific tripartite motif (TRIM) containing family proteins, specifically MG53, was recognized in cellular repair.[27] It was shown that the MG53 knockout mice show extensive damage and deficient repair when an injury is introduced to skeletal muscle.[28] MG53 can assist in cellular repair through multiple mechanisms. For example, it can bind to phosphatidylserine, a lipid in the inner leaflet of the plasma membrane and initiate an assembly of cell membrane repair proteins.[29] A three-step model is proposed to describe the exact mechanism via which MG53 performs its action. First, MG53 recognizes damage to sarcolemma through a molecular mechanism which is poorly understood. Second, MG53 nucleates and interacts with phosphatidylserine on the inner leaflet, forming a repair complex. Third, this process results in local elevation of cytosolic calcium which promotes fusion of the vesicles with the plasma membrane for formation of a repair patch.

Following the discovery of this process, an annexin complex was identified that mediates plasma membrane repair.[30] Similar to MG53, annexins bind to phospholipids and cholesterol rich membranes in the presence of calcium. Using a laser that induces subcellular damage and an FM4-64 fluorescent dye that is triggered in the presence of phosphatidylserine, it was shown that annexin A6 recruits rapidly to the site of FM4-64 fluorescence which shows its affinity to phospholipids.[31]

Based on these findings, a new repair model was proposed where annexin A6 aggregate and form a "repair cap" at the injury site, while dysferlin, MG53 and other repair proteins form the shoulder of repair cup to plug in the damaged site. Thus, following the muscle injury, repair proteins localize to the site of damage where annexin proteins forms a cap to cover the membrane lesion.

Overall, muscle contraction, especially eccentric exercises disrupt the sarcolemma. This activates a series of intracellular processes which work together to minimize the damage and maximize repair.

Endocrine function of skeletal muscle in repair

Skeletal muscle has largely been considered as an organ for contraction. However, increasing evidence suggest that it has an endocrine function which is very relevant in conditions involving exercise and muscle damage. It was previously known that following intense exercises, plasma cytokines levels markedly increase. For example plasma interleukin-6 (IL-6) are secreted from skeletal muscle in response to exercise and other stimuli.[32] It is now widely established that systemic beneficial

effects of exercise are partly due to secretion of cytokines and myokines by contracting skeletal muscle.[33]

Myokines and cytokines are small proteins and assistance of intercellular communications is one of their multiple functions. Myokines as the name indicate are secreted by skeletal muscle and have endocrine, paracrine, and autocrine effects. Apart from their actions on skeletal muscle, myokines also promote metabolic adaptations in various organs following exercise, such as adipose tissues and liver. They are also shown to assist in repair and regeneration of skeletal muscle following traumatic stimuli.[33] Among multiple mechanisms through which myokines can help in skeletal muscle repair, activation of immune signaling by IL-6 is an important mechanism. IL-6 is a pro-inflammatory cytokine and when released from damaged skeletal muscle, it initiates a series of intracellular signaling cascades which activate and accelerate repair and regeneration processes.[32] In agreement with this, a direct association between plasma IL-6 levels and degree of cellular proliferation and muscle fiber regeneration has been proposed.

These findings show that the secretary function of skeletal muscle can contributes to repair and regeneration of muscle fibers following muscle injury. This is primarily achieved through secretion of myokines, such as IL-6 secretion and their subsequent immune activation.

Role of immune response in muscle repair

Activation of immune cells in the skeletal muscle also help in regeneration process after injury. Neutrophils are among the first cell types recruited to site of injury degrade damaged proteins and cellular components by phagocytosis.[34] Neutrophils are followed by macrophages invasion to supplement the small proportion of resident macrophages in skeletal muscle.[35] Macrophages are divided into two categories, pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages. Upon injury, M1 macrophages invade the muscle first and their maximum concentration in the muscle reaches ~24 h after injury.[36] These macrophages are characterized by $CD68^{+}/CD163^{-}$ surface markers and secrete cytokines, such as interleukin (IL-1) and tumor necrosis factor-á (TNF-á), which are responsible for timely and efficient homeostatic response to muscle injury. M2 macrophages are slow to respond and their maximum concentration in skeletal muscle is only achieved 2-4 days after injury.[36] They are characterized by $CD68^{-}/CD163^{+}$ surface markers and secrete anti-inflammatory cytokines, such as IL-10. Emerging evidence suggest that M2 macrophages also contribute to satellite cell proliferation and differentiation following skeletal muscle injury.[37]

Early studies indicated that the satellite cells are activated by growth factors release from injured muscle fibers, such as fibroblast growth factor and insulin like growth factor. However, role of M2 macrophages in activation of satellite cells was later appreciated via studies in cell culture models.[37] For examples, when macrophages were added to mouse and turkey satellite cell cultures, the expressions of markers of proliferation and activation were increased.[38] A direct *in-vivo* role of macrophages in satellite cells activation was later appreciated when it was shown that the muscle regeneration, differentiation and repair was severely blunted in mice subjected to eccentric contractions when macrophages were depleted with an anti-F4/80 immunoglobulin.[39]

Serum amyloid A (SAA) is an acute phase protein and one of the most important downstream target proteins of IL-6 signaling.[32] SAA interacts with several cell surface receptors and mediates many physiological actions by activating various signaling pathways. For example, SAA stimulate matrix metalloproteinase (MMP) which in turn degrade extracellular matrix and facilitates migration and proliferation of satellite cells and macrophages for muscle repair.[40] Studies in cell culture show that MMP's are required for the differentiation, proliferation, and fusion of C2C12 cells to mature myoblasts. Furthermore, myoblasts do not migrate in the absence of MMPs.[41] SAAs also help in mediating inflammation and phagocytosis at the site of injury which facilitates muscle recovery process.

Taken together, a shift from M1 to M2 macrophages seems to play a key role in the microenvironment for muscle tissue regeneration. Macrophage's infiltration is initially required for removing cellular debris after injury. Later infiltration of M2 macrophages help in muscle repair by activating satellite cells. SAAs play an important role in muscle regeneration.

CONCLUSION

Various types of traumas can introduce skeletal muscle injury. However, muscle has tremendous ability to regenerate following an injury. Skeletal muscle repair is a complex process and involves changes at cellular and molecular levels. At cellular levels, infiltration of macrophages and activation of satellite cells are key mediators in skeletal muscle repair. At molecular levels, activation of repair-specific proteins and their downstream signaling pathways facilitate muscle repair and prevention of fibrosis. However, extensive damage and exhaustion of repair machinery results in replacement of contractile tissues with fibrous tissues. This review offers some limitations. The cellular and molecular mechanisms of activation of satellite cells and repair proteins are not discussed in exhaustive details since that will be beyond the scope of this mini review. Several dozen sarcomeric and cytosolic proteins play key role in muscle repair, however their profiling and thorough characterization is overlooked. Emerging role of non-muscle stem cells in muscle repair is not discusses. A thorough understanding of these repair processes will help accelerate muscle repair and prevent formation of unwanted fibrous scars.

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CONFLICT OF INTEREST

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