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REVIEW ARTICLE

Skeletal Muscle Loading Changes its Regenerative Capacity

Eduardo Teixeira[1] · **José Alberto Duarte**[1]

Abstract Whenever skeletal muscle insults occur, both by functional impositions or other injury forms, skeletal muscle repair (SMR) follows. The SMR succeeds when proper skeletal muscle regeneration and limited fibrosis ensue. Muscle fiber replenishment by fibrosis negatively affects the tissue quality and functionality and, furthermore, represents the worst post-injury phenotypic adaptation. Acute muscle injury treatment commonly follows the RICE method—rest, ice, compression, and elevation. This immediate immobilization seems to be beneficial to preserving the tissue structure and avoiding further destruction; however, if these interventions are delayed, the risk of muscle atrophy and its deleterious-related effects increase, with resultant impaired SMR. Moreover, a growing body of evidence shows positive skeletal muscle loading (SML) effects during SMR since it seems to effectively increase satellite cells (SCs) in their activation, proliferation, self-renewal, and differentiation capacities. Additionally, recent data show that SML may also influence the functions of other participants in SMR, compelling SMR to achieve less fibrotic accretion and accelerated muscle mass recovery. Moreover, given the SML effects on SCs, it is plausible to consider that these can increase the myofibers' basal myogenic potential. Thus, it seems relevant to scrutinize the possible acute and chronic SML therapeutic and prophylactic effects regarding the SMR process.

Key Points

Acute immobilization upon injury may be beneficial but can compromise proper skeletal muscle repair (SMR).

Skeletal muscle loading (SML) may increase the number of satellite cells, their proliferation, and their differentiation capacities, which enhance proper SMR.

SML increases vascularization and collagen turnover and should therefore be promoted during SMR.

1 Introduction

The skeletal muscle potency to respond to different stimuli such as exercise, immobilization, trauma, or chemical insult, relies on its regenerative capacity due to the presence of a myogenic stem cell population known as satellite cells (SCs) [1]. The SCs, resting between the sarcolemma and the skeletal muscle basal lamina, first described by Alexander Mauro [2], are the prime source of myogenic cells. Nonetheless, the fact that stem cells from other tissues may effectively migrate, incorporate the SC pool, or acquire its properties and myogenic potential [3–5] reveals that skeletal muscle regeneration (SMReg) may be affected by other stem cells and chemoattractants released by skeletal muscle fibers. SMReg is defined when damaged myofibers, or their segments, are replaced by new ones, without modifying the original tissue structure. However,

✉ Eduardo Teixeira
edsilvateixeira@hotmail.com

[1] Centro de Investigação em Atividade Física e Saúde, Faculdade de Desporto da Universidade do Porto (CIAFEL-FADEUP), Rua Dr. Plácido Costa 91, 4200-450 Porto, Portugal

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skeletal muscle repair (SMR), depending on the injury's intricate nature, i.e. insult type and severity, does not only occur by SMReg but also by the total or partial substitution of damaged fibers by connective tissue (fat and scar tissue) with loss of original structure and functional impairment [6, 7]. Ideally, in order to maintain skeletal muscle structure and functionality, the SMR should always be achieved by SMReg.

Muscle injuries may range from: (1) mild (focal intracellular damage, i.e. sarcoplasm rupture or myofibril disruption); (2) moderate (myofibril complete or segmental injury or necrosis); and (3) severe (affecting one or more muscle bundles, blood vessels and interstitial tissues). To cope appropriately with these different insults, various participants execute numerous functions composing the SMR per se, which can be characterized by either (1) SMReg through activation, proliferation, and differentiation of SCs into myoblasts, during mild injuries and day-to-day wear and tear; (2) activation of mononucleated cells (fibroblasts, myogenic, and resident inflammatory cells), promoting both SMReg and extracellular matrix (ECM) remodeling (fibrotic accretion or degradation) during moderate injuries or, finally, during severe insults; (3) activation of all the cells mentioned in points (2) and (3) and, through chemotactic signaling released into the blood stream, infiltration of an additional variety of inflammatory and myogenic cells [6, 8–10]. During moderate-to-severe insults, SMR also embraces inflammatory response, characterized by a complex cellular and molecular event that interacts with the activity of SCs throughout the process [10]. Considering these wide interactions, knowledge regarding SMReg cellular and molecular mechanisms is pivotal when analyzing SMR. Nonetheless, recent studies show that both ECM characteristics [11] and their constituents [12] seem to be fundamental for proper SMR and SC behavior, indicating that the ECM is another important participant during SMR. Moreover, since skeletal muscle loading (SML) effectively modulates ECM turnover [13], it seems relevant to analyze its SMR-related interactions.

Curiously, therapeutic approaches such as surgical techniques for scar tissue removal, biologic scaffold grafting, and use of nonsteroidal anti-inflammatory drugs (NSAIDs) and antifibrotic agents [14] have been used to accomplish effective SMR. Additionally, RICE (rest, ice, compression, and elevation) continues to be the most used procedure to acutely treat muscle injuries. Although RICE may effectively reduce the injury bleeding, preventing further tissue damage during the initial post-injury hours [15], if the forced immobilization continues, as it usually does, it may also contribute to an increased skeletal muscle atrophy through muscular unloading, which exacerbates many adverse consequences such as increased proteolysis, through activation of ubiquitin-proteasome, lysosomal, and calpain proteolytic pathways, and increased myonuclei loss through nuclear apoptosis [16], impairing a proper SMReg and, therefore, the SMR.

This raises a pertinent issue for those seeking a faster and less fibrotic SMR, and highlights a plausible SML importance during the process. Indeed, previous studies showed favorable SML effects during SMR [17]. As addressed in Sect. 2.1.1, recent data show that SML seems to efficiently stimulate the activation [18] and proliferation capacities [19] of SCs. These advantageous effects seem to be important during animal growth [20], and seem to be conserved during human aging [19], which putatively ensures an increased basal myogenic potential (BMP). The BMP concept, i.e. the putative SC reserve that will turn into new muscle fibers if necessary, is supported by (1) recent animal studies that, although relatively controversial, indicate SCs as absolutely necessary for SMReg after muscle injury [21, 22]; (2) evidence supporting the fact that the number and functionality of SCs are critical to preventing muscle tissue substitution by fat or fibrosis after muscle damage [7]; and (3) data showing that reduced muscle regeneration, after immobilization-related atrophy in elderly humans, was related to a blunted response in SC proliferation [23].

Consequently, it seems appealing to scrutinize (1) the SML effects on the skeletal muscle BMP, i.e. its ability to acutely and chronically increase the number of SCs; (2) its ability to induce milieu alterations on both SCs and ECM; (3) its capacity to modulate SMR outcomes; and (4) its likely prophylactic role against skeletal muscle insults.

In order to provide the framework for this article's discussion, we define SML as muscle requirements equal to or higher than those used in day-to-day wear and tear, while, conversely, skeletal muscle unloading occurs during prolonged bed rest or limb immobilization, and favors muscle deconditioning and atrophy.

2 Skeletal Muscle Loading (SML) Effects on Skeletal Muscle Stem Cells and Their Milieu

Recent evidence indicates that the ability of stem cells to proliferate, self-renew, or differentiate into a specific phenotype may be controlled by their particular mechanical environment, i.e. stiffness alterations of their milieu, since they are able to perceive and react to external mechanical forces [24–26]. Experiments with cultured mesenchymal stem cells showed that stiffness manipulation of the collagen-coated gels was able to determine their specific lineage and phenotype and, subsequently, that soft gels simulating brain matrices were neurogenic, rigid gels simulating muscle were myogenic, and the denser gels were osteogenic [27]. Moreover, this study also showed the

importance of the chemical milieu of stem cells since manipulation of soluble factors was able to reprogram cell lineage specification in the early phases of differentiation. Therefore, both mechanical and chemical factors seem to be important in governing the function and fate of stem cells. Like other stem cells, SCs are located in a very specific physical environment, comprising the ECM, vascular and neural tissues, different cell types, and numerous diffusible molecules. All these constituents interact with each other in order to precisely regulate the quiescence, self-renewal, proliferation, and differentiation of SCs. Collectively, the immediate niche, local milieu, and systemic milieu may stimulate the activity of SCs. Briefly, the immediate niche comprises the regulatory signaling pathways (Wnt, Notch, and sphingolipid signaling), the myofiber niche (secretion of stromal cell-derived factor-1 [SDF-1], transmembrane Notch ligand Delta), and the ECM and related factors (hepatocyte growth factor [HGF], fibroblast growth factor [FGFs], insulin growth factor [IGF] and matrix metalloproteinases [MMPs]). The local milieu comprises interstitial cells (fibroblasts, myogenic precursors, and fibro/adipogenic precursors), motor neurons (secrete the neurotrophins nerve growth factor [NGF] and brain-derived neurotrophic factor [BDNF]), and vasculature (secrete vascular endothelial growth factor [VEGF]). Finally, the systemic milieu comprises immune cells, interleukin (IL)-6, androgens, and nitric oxide ($^{\cdot}$NO) [4]. The effects of SML on the SCs niche are addressed in Sect. 2.1.3.

Recently, some studies showed that muscle tissue is able to produce, upon SML, several myokines, i.e. cytokines that exert numerous effects by endocrine, paracrine, or autocrine signaling [28–30]. This may indicate that SML, in addition to the loading-derived mechanical factor, also produces chemical signals that may be critical to either the behavior of the SCs or the incorporation of other myogenic stem cells. The effects of SML on the SC pool are addressed in Sect. 2.1.

2.1 SML Effects on Satellite Cells

The skeletal muscle adaptation concept, regarding the functionality of the SCs, continues to embrace different features of skeletal muscle plasticity such as growth, hypertrophy, atrophy, nuclear turnover, aging, and SMReg. Recently, the interaction between the biology of SCs and skeletal muscle adaptation has been the subject of intense debate [31–34]. Human studies examining the functionality of SCs during different features of muscle fiber adaptation (e.g. exercise during aging [35, 36], skeletal muscle responses following resistance [36, 37], endurance training [35], remodeling [38]) are defining new perspectives for the study of SC functions during muscle plasticity. This section will highlight the current data regarding the response of SCs to SML.

2.1.1 Acute Effects

A very precise myogenic program, coordinated by key transcription factors, the myogenic regulatory factors (MRFs), controls the quiescence, activation, proliferation, and differentiation or self-renewal activities of SCs. First, SCs are mitotically quiescent (G_0 phase of cell cycle) and express Pax7 but not MyoD or myogenin. Extrinsic factors, such as damage or exercise, may activate SCs, i.e. they enter the cell cycle. Activated SCs start to proliferate, creating progeny (the myogenic precursor cells or myoblasts) that express MyoD and MYF5. After proliferation, SCs can either self-renew (maintaining the SC pool), or differentiate into adult myoblasts, initiating differentiation by downregulating Pax7 expression. Finally, the fusion and the terminal differentiation begin with the expression of myogenin and MyoD [4].

In normal, undamaged muscles, 2–7 % of each of the fiber's nuclei are SCs that are mitotically quiescent (expressing Pax7; at G_0 phase); however, as described, when exposed to loading, trauma or injury signals, they activate, proliferate, and either self-renew (maintaining the SC pool), or differentiate into myoblasts that follow terminal differentiation [39]. In order to expand the number of SCs, their withdrawal from quiescence is mandatory. Immunohistochemical (IHC) analysis from the middle region of the vastus lateralis from young men, subjected to one bout of combined endurance and resistance exercises, showed that SCs from both type I and II fibers were able to enter the cell cycle (increased delta-like 1 homolog [DLK1] expression) within 9 h post-exercise [18]. However, although SML may be effective in promoting the activation of SCs, their pool will only increase if they proliferate efficiently. Again, loading through a single bout of voluntary running was able to either promote dynamic changes in rat plantaris muscle messenger RNA (mRNA) expression (increased expression of cell-cycle-related genes 24 h post-exercise) or increased cell proliferation, confirmed by 5-bromo-2-deoxyuridine (BrdU; a thymidine analog nucleoside that labels DNA-replicating nuclei) immunohistochemistry [40]. Another study analyzing the effects of a single bout of high-intensity eccentric exercise showed that after 4 and 8 days the SCs from the vastus lateralis of young sedentary males increased their expression of neural cell adhesion molecule (NCAM) and the fetal antigen 1 (FA1) [41], indicating again that SML was able to potentiate the activation and proliferation of SCs. Curiously, a more recent study was able to detect an increase in both the SC number and expression of cell-cycle-related components (DLK1 for activation, and

proliferating cell nuclear antigen for proliferation), in vastus lateralis muscles of nine young men, only 24 h after an intensive eccentric exercise protocol (300 eccentric knee contractions) [42]. These results suggest a possible fiber-type-specific response to different types and loading intensities. Indeed, data regarding the acute effects of resistance exercise in human skeletal muscle showed an increase in the number of SCs, specifically in the type II fiber type [43]. Nonetheless, others, despite an SC-specific response to the type of contraction mode (concentric or eccentric; SCs increase only upon eccentric contractions), have not described a fiber-type-specific response to acute resistance exercise [44].

Extensive data show that aging specifically reduces the content of SCs in type II skeletal muscle fibers [36, 45]; however, the following studies show that SCs seem to be able to either increase in number or increase mRNA expression of important MRFs following SML. Both situations may be important during SMR. For instance, SCs (expressing NCAM in IHC labeling) from the human vastus lateralis of older adults were able to increase in number 24 h after a single bout of eccentric exercise; however, this increase was clearly diminished when compared with younger men [46]. Moreover, others have also demonstrated that age reduces the ability of vastus lateralis SCs to activate and increase in number following a single bout of resistance exercise, specifically in type II muscle fibers [47]. A more recent study, also using a single bout of resistance exercise, showed that SCs from the vastus lateralis of older adults took longer (72 h) to increase in number, in the type II muscle fibers, when compared with younger men (48 h) [48]. However, an interesting study analyzing the human skeletal muscle response to an unloading/reloading event (skeletal muscle atrophy through limb cast, and loading through cast removal and resistance exercise training), also documented reduced SC activity in older individuals despite no differences being found regarding the mRNA expression of main MRFs [23].

Despite this data collection pointing out the acute activation, proliferation, and increase in the number of SCs promoted by SML, some controversy has been documented in the literature regarding the unloading effects on the number of SCs. Interestingly, a study analyzing the atrophy process using rat hindlimb suspension also indicated, using BrdU staining, that SCs from the gastrocnemius muscle seem to acutely proliferate 6 h after hindlimb suspension, but after 1 week in this condition the number of SCs significantly decreased when compared with weight-bearing controls [49]. Curiously, this increase in the number of SCs during unloading (2 weeks of unilateral whole-leg casting) was also found in human vastus lateralis muscles (on both type I and II fibers) of young males but not in older individuals [23]. Nonetheless, a more recent study analyzing the effects of 2 weeks of a full-leg cast in 12 young men, evinced that the number of SCs did not change despite an increase in myogenin mRNA, which may indicate some activity in the SC pool [50]. Additionally, another study analyzing the effect of neuromuscular electrical stimulation (NMES) on the vastus lateralis of young males subjected to 5 days of muscle unloading (full-leg cast) also showed that the number of SCs did not change; nevertheless, an increase in MyoD and myogenin mRNA may be indicative of the activity of SCs [51]. However, another relevant study analyzing the molecular regulators of the activity of SCs in human vastus lateralis muscles following unloading (2 weeks of full-leg cast) and reloading (exercise after cast removal) also showed that aging deteriorates the ability of SCs to proliferate [52]. All these data regarding the behavior of SCs during unloading suggest different responses between animal and human studies, indicating that methodological frailties or other particularities of this condition (e.g. the underlying cause) may influence the results [53]. Moreover, it is worth mentioning that the discrepancies shown in the different studies might be due to the fact that apoptotic cells in the skeletal muscle promote the fusion of healthy myoblasts, as reported in an animal study by Hochreiter-Hufford et al. [54]. Considering that skeletal muscle atrophy may, per se, induce an acute pro-apoptotic environment both inside and outside myofibers [53], one might consider that this event may transitorily increase myonuclei turnover. The increased mRNA expression of important MRFs may be indicative of this increased SC turnover rate. The reported data clearly support the concept that unloading transiently stimulates the proliferation of SCs; nonetheless, further investigation is warranted to clearly demonstrate its occurrence [55].

In summary, irrespective of the atrophy-related controversy, solid data indicate that SML is an effective way to acutely increase the activation, proliferation, and number of SCs, enabling a transient increase in BMP.

2.1.2 Chronic Effects

Considering the acute SML effects in the SC pool, it seems appealing to explore their long-term consequences to determine whether the more active musculature, the greater its number of SCs, and therefore the greater its BMP.

Again, several chronic SML conditions seem to effectively maintain the elevated number of SCs [37, 43, 56–62]. Nevertheless, debate continues regarding the requirement of the presence and fusion of SCs during muscle hypertrophy [63] and regrowth following atrophy [64]. For instance, an animal study analyzing the mechanical overload effect in SC-depleted plantaris muscle showed that the

addition of SCs is not necessary for muscle hypertrophy [65]. Moreover, the muscle regrowth capacity, following atrophy (hindlimb suspension), in SC-depleted mice soleus was also independent of the presence of SCs [64]. These animal studies simply suggest that the myonuclear domain is dynamic. Solid data indicate that the acquisition of new myonuclei for further hypertrophy is only mandatory when the myonuclear domain size exceeds a certain threshold [66]. Curiously, both animal studies showed a significant reduction in muscle turnover (BrdU-positive myonuclei) of SC-depleted muscles [64, 65]. Additionally, a recent study analyzing the role of human muscle SCs during 6 weeks of aerobic interval training (nonhypertrophic stimulus) demonstrated that SCs intensely contribute to muscle remodeling [38]. Considering this, one can consider that the depletion of muscle SCs and therefore the loss of myonuclei turnover and further hypertrophy, may be decisive for a proper SMReg, i.e. to maintain muscle tissue structure and functionality during SMR, as has already been mentioned [7, 22].

Despite this controversy, a recent study analyzing the effect of 16 weeks of resistance exercise showed that SCs from the quadriceps muscles increased in number in both type I and II fibers. Additionally, a correlation between the relative changes in the number of SCs and the percentage increase in the lean muscle mass was observed [43]. Interestingly, a study using cluster analysis to evaluate the relationship between myofiber hypertrophy and SC pool in the vastus lateralis of 66 humans showed that those who had larger SC pools in basal conditions had greater capacity to increase SC number, to increase fiber nuclei addition and to achieve greater fiber hypertrophy in response to 16 weeks of knee extensor resistance training [37]. These results indicate the importance of a larger SC pool during a stressful event such as resistance exercise. However, reduced basal SC pools, such as those seen in type II fibers of elderly human skeletal muscles, are also able to increase their number of SCs (and their fiber size) in response to 12 weeks of resistance exercise [36]. Therefore, the association between the content of basal SCs and muscle fiber hypertrophy following resistance exercise continues to be debatable.

Another study analyzing the effect of 10-week resistance training in 18 women with trapezius myalgia also showed an increase in the number of SCs in both type I and II muscle fibers, conjugated with an increase in SCs expressing Ki-67 (indication of cell cycle activity), demonstrating enhanced proliferation [60]. This type of chronic SC pool adaptation to resistance training has been previously described in nine adult women in the same muscle group, but without myalgia [56]. Remarkably, even during a 12-week, light-loading resistance training, SCs from vastus lateralis of 12 young men were able to increase their pool [61], suggesting that SML can be an interesting way to increase the BMP in situations where solid resistance training is not possible, e.g. during moderate skeletal muscle injuries or to prevent atrophy during limb casting. In addition, 12 weeks of aerobic training (three sessions of 45 min per week at 70 % heart rate reserve) performed by sedentary adults (6 males and 17 females) resulted in increased content of SCs in type I fibers (but not type II fibers) [62], indicating again that a fiber-type-specific response and a less demanding type of SML seem to be effective in enhancing the muscle BMP.

As described, some studies show that the capacity of SCs to respond to acute SML seems to be preserved during aging, mainly in type I muscle fibers. Likewise, the SC pool of both elderly men and women maintains its ability to increase during both endurance [57, 67] and resistance training [59, 67, 68]. A study analyzing the effect of 14 weeks of intermittent endurance cycling (45 min daily, 4 days per week) in the vastus lateralis of 11 men (aged 70–80 years) showed that the SC (NCAM-positive) pool effectively increases [57]. Similarly, the SC (NCAM-positive) pool of vastus lateralis of 13 older men (average 72 years of age) increased following 12 weeks of resistance training, wherein a dramatic fiber type II-specific response occurred [59]. Additionally, both elderly men and women were also able to increase their number of SCs in type II muscle fibers from the vastus lateralis in response to 6 months of resistance training [68]. Finally, a study specifically analyzing both lower body endurance (intermittent cycling) and upper body resistance (three sets of three strength-training exercises) SML potential to increase the SC pool in elderly men over a 14-week period (three times per week) revealed that simultaneous lower body endurance and upper body resistance training effectively increased the SC pool of the vastus lateralis and deltoid muscles, respectively, solely in type II muscle fibers [67]. Curiously, endurance training (6 months) in obese male type 2 diabetes patients (61 $\pm$ 6 years) did not change the content of the SCs in the vastus lateralis muscle [69]. One can consider that either the condition or the training intensity (much lower than that used by others [57, 67]) possibly blunted muscle growth and response of the SCs.

Once again, these results demonstrate the SML potential to mitigate the specific age-dependent decline of SCs [36], specifically seen in type II muscle fibers [45].

Finally, it is important to acknowledge that the SC pool is highly plastic, i.e. it proficiently adapts to SML but also adapts to unloading, as reported in a study analyzing the SC pool from the vastus lateralis of 15 young men who, despite an increase in SCs due to 90 days of resistance training, their number of SCs returned to pre-training values within 90 days of detraining [58]. This study also indicated that only 3 days after detraining, SCs seemed to

suddenly decrease their proliferation capacity, as suggested from the mRNA values of the cell-cycle marker p21.

In summary, these studies collectively indicate that SML seems to ensure a greater BMP that is maintained in the active musculature, even throughout the aging process. This important feature may be a determinant in the success of SMR.

2.1.3 Satellite Cell Niche Modulation

The microenvironment (i.e. their surroundings and everything within, contacting and influencing stem cell behavior) in which the stem cells reside is their niche [70, 71], and although there are many unanswered questions regarding the characteristics of this milieu, like its molecular regulatory aspects on different organs, it is becoming apparent that in the skeletal muscle this microenvironment plays a major role in the fate of SCs [72]. The behavior of SCs can be severely altered by growth factors, cytokines, and other diffusible molecules produced by adjoining cells and surrounding ECM [72, 73]. Briefly, as described, molecules from the immediate niche and the local or systemic milieu of the SCs, may alter their state. SCs seem to (1) activate, in an autocrine-fashion, upon contact with HGF and epidermal growth factor (EGF), from SCs, myofibers, and interstitial cells, or present in serum in the immediate niche and nitric oxide (˙NO), a diffusible molecule (produced by diverse cell types, including epithelial cells, endothelial cells, fibroblasts, macrophages and muscle cells) from the systemic niche; (2) proliferate with FGF, IGF-1, tumor necrosis factor (TNF)-like weak inducer apoptosis (TWEAK) and delta-1 protein, a Notch ligand; and (3) differentiate with IGF-1. Their quiescence is maintained mostly in the presence of calcitonin and laminin. The main functional inhibitors are myostatin (activation and self-renewal), BDNF, TWEAK, and FGF (differentiation). The Wnt proteins affect the fate of the cell; the SDF-1 (or CXCL12) acts in the migration process, and the integrin α4β1 (VLA4) acts in the myoblast fusion [4, 74]. These intricate interactions between these different molecules and growth factors, which can be modulated during diverse physiological or pathological situations, unmask the niche complexity that governs the fate of SCs, and therefore it seems important to unveil the modulatory effects of SML.

Recently, data addressing which myokines seem to be produced and released by the contracting skeletal muscle (postulating a conceptual foundation that emphasizes the skeletal muscle as a 'secretory organ' capable of communicating and inducing effects in an autocrine, paracrine, or endocrine fashion) showed that some myokines (IL-6, BDNF, IL-7, and IL-15) might exert specific actions on the proliferation and differentiation of SCs [75]. Nonetheless, SML effects are broader with respect to changing the niche molecular characteristics of SCs since they seem to influence the production, expression, and release of different mediators in different tissue cells [75].

As described, in addition to SCs, SMReg may include stem cells from other tissues, such as circulating endothelial progenitor cells (EPCs) and circulating bone marrow progenitor cells (cBMPs) that effectively recognize, migrate, and contribute to the SC pool, and regenerate injured skeletal muscle [3–5]. Curiously, when comparing amateur runners with sedentary controls, the number of cBMPs ($CD34^+$, $CD38^+$, $CD33^+$) was three- to fourfold higher in runners [76]. Additionally, regarding other stem cells with myogenic potency, i.e. the EPCs or blood vessel stem cells ($CD34^+$, $CD133^+$, KDR^+), SML seems to be a determinant in increasing their numbers [77]. These two examples support the likely capacity that SML seems to have on increasing the availability of stem cells, which, along with the migration capacities, also have myogenic potency that can be important during SMR.

The likely skeletal muscle chemotactic capacity seems to be supported by its own myokines and other chemical mediators produced by the surrounding tissue cells, as shown by one study, using transgenic mice, genetically marked cells, cell cultures, and immunostained human muscle, evaluating the relationship between the EPCs and the niches of the SCs [78]. Its main findings were that SCs were markedly associated with capillaries, their numbers correlated with muscle capillarization, and both stem cell groups seemed to communicate in a paracrine faction through the release of VEGF, IGF-1, HGF, and FGF, reciprocally promoting angiogenesis and the proliferation of SCs, mainly through VEGF production of SCs, and culminating in a spatiotemporal relationship between myogenesis and angiogenesis [78]. Irrespective of the VEGF central role in angiogenesis and which were the main cells expressing it, it is clear that SML increases the number of muscle capillaries and VEGF expression [79], and this niche alteration, together with the proliferation effect of SCs, provided a possible means of achieving an improved SMR. Actually, as already demonstrated, VEGF infusion in regenerating mice tibialis anterior muscles not only promotes proper SMReg but also protects SCs from apoptosis [80].

Finally, because interactions between SML, SMReg and IGFs have been recently reviewed [81], this issue will not be addressed further. Nonetheless, as reviewed, since SML increases IGF-1 expression and this growth factor enhances SMReg [82], it is reasonable to consider SML as a positive SMR modulator.

3 SML and Skeletal Muscle Repair

Considering that SML effectively increases skeletal muscle myogenic potential, i.e., induces SCs pool growth, in both acute and chronic conditions, it seems appealing to

scrutinize its therapeutic and prophylactic effects during SMR. Nonetheless, as described, SMR characteristics and outcomes depend upon the type of muscle injuries that are highly heterogenic in severity, making human studies scarce.

3.1 SML Therapeutic Effects

Upon muscle injury, the most common acute treatment adheres to the RICE procedure. This widely used approach, using immobilization as the fundamental principle, attempts to acutely reduce blood flow and edema, minimizing inflammation and, afterwards, gradual increases in SML (within pain restrictions), as well as other therapeutic options (medication, ultrasound, and hyperbaric oxygen therapy), are recommended [15]. Interestingly, growing data indicate a crucial role for inflammation in achieving proper SMReg [83], and heat application may accelerate the proliferation and differentiation of SCs [84]. Consequently, despite the acute benefits of RICE in controlling further tissue damage, it seems relevant to acknowledge that if the forced immobilization continues, it will ablate the potential of SML to increase the activation and proliferation of SCs, and possibly impair SMR.

In the particular case of hamstring injuries, the lack of studies analyzing different types of rehabilitation protocols shows that common practice is based on empirical knowledge and cannot either be favored or disproved [85]. However, two recent studies showed that rehabilitation protocols accentuating active eccentric exercises during recovery from hamstring injuries are more effective than those with usual protocols, i.e., with less emphasis on eccentric SML [86, 87]. These results may elucidate the importance of a more intense SML protocol when compared with protocols emphasizing flexibility exercises. An interesting animal study analyzing the adjuvant effect of SML on muscle-derived stem cell (MDSC) transplantation during SMR might elucidate a possible explanation for these outcomes [88]. The results of this study showed that in addition to an increased proliferation on mechanically-stimulated MDSCs, SML (5 weeks of treadmill running) enhanced MDSC transplantation after injury, prevented fibrosis accretion, and increased skeletal muscle vascularity [88]. Curiously, a former study analyzing marked bone marrow cells transplanted into mice that were submitted to both forced running exercise (downhill running) and EDL overload (surgical tibialis anterior removal) also showed an increased incorporation of bone marrow-derived cells into skeletal muscle [89]. Both studies suggested that in addition to the mentioned increase in the SC pool, SML may be an effective way of enhancing SMR by stem cell chemotactic attraction. In addition, during SMR following notexin injury in the soleus muscles of female rats, recovery of muscle mass and decreased fibrosis was also shown in active (caged with access to running wheel and performing treadmill running 5 days/week) compared with sedentary (kept in normal cages) animals [17]. This study also showed that active rats recovered their muscle mass to pre-injury values within 21 days of post-injury whereas sedentary rats failed to restore muscle mass to pre-injury values even after 42 days. Moreover, SCs from active rats had better and faster proliferation (measured by proliferator cell nuclear antigen and MyoD) and increased differentiation (higher expression of myogenin) [17]. Decreases in fibrosis accretion also occurred using stretching exercises (passive mobilization) in the first 2, 7, and 14 days after laceration injury in the gastrocnemius muscle of male rats [90]. Interestingly, despite the lack of studies regarding SML influence in ECM dynamics during SMR, it is known that both collagen production and MMP (proteases that mainly degrade ECM collagen) activity acutely increase with loading and, chronically, SML increases both collagen content and turnover [13]. More recently, a study analyzing the acute and chronic effects of endurance training (45 min/10 days/5 weeks) in the vastus lateralis of ten men, showed acute (2 h after exercise bout) increases in MMP-9 (modulates collagen turnover and growth factor availability) activity and chronic (10 days of training) increases in MMP-2 (cleaves ECM and basal lamina in angiogenesis and is implicated in successful SMR) and tissue inhibitor of MMP-1 mRNA expression [91]. This ECM enzymatic modulation may determine the favorable, less fibrotic, skeletal muscle phenotype seen in loaded muscle during SMR.

Finally, as described, SMR is also influenced by an important contribution of the inflammatory system. Curiously, increases in macrophage content during SML (10 weeks of resistance training in 18 women identified as having trapezius myalgia) [60], have been reported. Furthermore, improved phagocytic activity in macrophages from rats submitted to 1 h of swimming [92] may demonstrate a possible acute improvement of SML on macrophage function that may also be important for removing cellular debris during SMR. Despite the fact that some macrophage functions (antigen presentation, major histocompatibility complex II expression and antiviral activity) may be hindered by SML, others, such as tumor cytotoxicity, chemotaxis, and phagocytosis functions, are enhanced by both acute and chronic SML [93]. Nonetheless, many aspects regarding the interaction between the cellular innate immune function and exercise continue to be unknown [94].

3.2 SML Prophylactic Effects

As elucidated, acute SML compels SCs to activate and proliferate, and these effects possibly justify the increased

number of SCs in muscles loaded chronically. Thus, one could speculate that SML effectively increases the BMP of muscles. It is therefore plausible that this theoretical prophylactic effect may be significant in medical conditions that either force muscle unloading (such as limb casting) or damage skeletal muscle (surgery). Disregarding the accidental injuries, this prophylactic effect should be considered in programmed interventions that imply skeletal muscle unloading or injury. Evidence in animal studies indicates that NMES may prevent loss of myonuclei and SCs by apoptosis, preserving the SC pool for further SMR, and attenuate decreases in muscle size and force production [95, 96]. Similar results were also found in young human skeletal muscle, subjected to disuse atrophy (5 days of one-leg casting), with or without NMES sessions. Their data showed that NMES prevented loss of muscle mass and mRNA expression of important regulators of muscle protein breakdown, but neither preserved muscle strength nor altered the number of myonuclei and SCs [51]. Nonetheless, during conditions characterized by impaired limb movement, electrical stimulation should be considered since it may be a potential strategy to avoid loss of muscle mass.

4 Conclusion and Further Perspectives

This review highlights the possible role of SML in increasing the myogenic potential that possibly drives the SMR toward a more functional phenotype. The data presented also evince the SML therapeutic effect upon injury, increasing and stimulating proper SMReg and inhibiting excessive fibrotic deposition. Thus, SML seems to promote (1) acute and chronic increases in the number of SCs; (2) increased activation, proliferation, and terminal differentiation of SCs; (3) increased migration of other myogenic stem cells; (4) increased angiogenesis; (5) inhibition of excessive fibrosis deposition during SMR; and, collectively, (6) a faster and proficient SMReg. Moreover, SML efficiently promotes milieu alterations through myokines released by myofibers upon contraction, which induce the production and release of cytokines from surrounding cells. This milieu molecular alteration may support the muscular chemotactic activity that increases stem cell migration during SMR, and promote a chemical environment more suitable to successfully react upon injury. Other important, but less clear, SML features may be hidden in the physical and mechanical force-related imposition, upon contraction, to all cells within the skeletal muscle and its ECM. Possibly, this physical cellular stress, perceived by all cells, is as effective in altering cellular function as the chemical and molecular milieu alterations.

This data collection suggests that active skeletal muscles might be better prepared to effectively respond to a muscle injury. This prophylactic effect should be contemplated in clinical situations where muscle atrophy or injury intentionally occurs. This review also evinces the lack of studies analyzing the cellular and molecular alterations promoted by SML during SMR, particularly regarding the ECM alterations. Finally, we seek to encourage physical therapists, sports medicine specialists, and muscle physiologists to deliberately promote, as soon as possible, a more active therapeutic approach to SMR.

Compliance with Ethical Standards

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References

1. Otto A, Collins-Hooper H, Patel K. The origin, molecular regulation and therapeutic potential of myogenic stem cell populations. J Anat. 2009;215(5):477–97.
2. Mauro A. Satellite cell of skeletal muscle fibers. J Biophys Biochem Cytol. 1961;9:493–5.
3. Biressi S, Rando TA. Heterogeneity in the muscle satellite cell population. Semin Cell Dev Biol. 2010;21(8):845–54.
4. Yin H, Price F, Rudnicki MA. Satellite cells and the muscle stem cell niche. Physiol Rev. 2013;93(1):23–67.
5. Bentzinger CF, Wang YX, Dumont NA, et al. Cellular dynamics in the muscle satellite cell niche. EMBO Rep. 2013;14(12):1062–72.
6. Moyer AL, Wagner KR. Regeneration versus fibrosis in skeletal muscle. Curr Opin Rheumatol. 2011;23(6):568–73.
7. Sciorati C, Clementi E, Manfredi AA, et al. Fat deposition and accumulation in the damaged and inflamed skeletal muscle: cellular and molecular players. Cell Mol Life Sci. 2015;72(11):2135–56.
8. Charge SB, Rudnicki MA. Cellular and molecular regulation of muscle regeneration. Physiol Rev. 2004;84(1):209–38.
9. Pillon NJ, Bilan PJ, Fink LN, et al. Cross-talk between skeletal muscle and immune cells: muscle-derived mediators and metabolic implications. Am J Physiol Endocrinol Metab. 2013;304(5):E453–65.
10. Tidball JG, Villalta SA. Regulatory interactions between muscle and the immune system during muscle regeneration. Am J Physiol Regul Integr Comp Physiol. 2010;298(5):R1173–87.
11. Sicari BM, Rubin JP, Dearth CL, et al. An acellular biologic scaffold promotes skeletal muscle formation in mice and humans with volumetric muscle loss. Sci Transl Med. 2014;6(234):234ra58.
12. Urciuolo A, Quarta M, Morbidoni V, et al. Collagen VI regulates satellite cell self-renewal and muscle regeneration. Nat Commun. 2013;4:1964.
13. Kjaer M, Magnusson P, Krogsgaard M, et al. Extracellular matrix adaptation of tendon and skeletal muscle to exercise. J Anat. 2006;208(4):445–50.
14. Danna NR, Beutel BG, Campbell KA, et al. Therapeutic approaches to skeletal muscle repair and healing. Sports Health. 2014;6(4):348–55.
15. Jarvinen TA, Jarvinen TL, Kaariainen M, et al. Muscle injuries: optimising recovery. Best Pract Res Clin Rheumatol. 2007;21(2):317–31.

16. Powers SK, Kavazis AN, DeRuisseau KC. Mechanisms of disuse muscle atrophy: role of oxidative stress. Am J Physiol Regul Integr Comp Physiol. 2005;288(2):R337–44.
17. Richard-Bulteau H, Serrurier B, Crassous B, et al. Recovery of skeletal muscle mass after extensive injury: positive effects of increased contractile activity. Am J Physiol Cell Physiol. 2008;294(2):C467–76.
18. Snijders T, Verdijk LB, Beelen M, et al. A single bout of exercise activates skeletal muscle satellite cells during subsequent overnight recovery. Exp Physiol. 2012;97(6):762–73.
19. Mackey AL, Esmarck B, Kadi F, et al. Enhanced satellite cell proliferation with resistance training in elderly men and women. Scand J Med Sci Sports. 2007;17(1):34–42.
20. Smith HK, Merry TL. Voluntary resistance wheel exercise during post-natal growth in rats enhances skeletal muscle satellite cell and myonuclear content at adulthood. Acta Physiol (Oxf). 2012;204(3):393–402.
21. Relaix F, Zammit PS. Satellite cells are essential for skeletal muscle regeneration: the cell on the edge returns centre stage. Development. 2012;139(16):2845–56.
22. Wang YX, Rudnicki MA. Satellite cells, the engines of muscle repair. Nat Rev Mol Cell Biol. 2012;13(2):127–33.
23. Suetta C, Frandsen U, Mackey AL, et al. Ageing is associated with diminished muscle re-growth and myogenic precursor cell expansion early after immobility-induced atrophy in human skeletal muscle. J Physiol. 2013;591(Pt 15):3789–804.
24. Lee DA, Knight MM, Campbell JJ, et al. Stem cell mechanobiology. J Cell Biochem. 2011;112(1):1–9.
25. Reilly GC, Engler AJ. Intrinsic extracellular matrix properties regulate stem cell differentiation. J Biomech. 2010;43(1):55–62.
26. Discher DE, Janmey P, Wang YL. Tissue cells feel and respond to the stiffness of their substrate. Science. 2005;310(5751):1139–43.
27. Engler AJ, Sen S, Sweeney HL, et al. Matrix elasticity directs stem cell lineage specification. Cell. 2006;126(4):677–89.
28. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. Physiol Rev. 2008;88(4):1379–406.
29. Pedersen BK, Edward F. Adolph distinguished lecture: muscle as an endocrine organ: IL-6 and other myokines. J Appl Physiol (1985). 2009;107(4):1006–14.
30. Pedersen BK, Fischer CP. Beneficial health effects of exercise—the role of IL-6 as a myokine. Trends Pharmacol Sci. 2007;28(4):152–6.
31. Hvid LG. Early plasticity of human skeletal muscle in response to disuse. Acta Physiol (Oxf). 2014;210(3):460–1.
32. Persson PB. Skeletal muscle satellite cells as myogenic progenitors for muscle homoeostasis, growth, regeneration and repair. Acta Physiol (Oxf). 2015;213(3):537–8.
33. Parise G. Satellite cells: promoting adaptation over a lifetime. Acta Physiol (Oxf). 2014;210(3):462–4.
34. Verdijk LB. Satellite cell activation as a critical step in skeletal muscle plasticity. Exp Physiol. 2014;99(11):1449–50.
35. Mackey AL, Karlsen A, Couppe C, et al. Differential satellite cell density of type I and II fibres with lifelong endurance running in old men. Acta Physiol (Oxf). 2014;210(3):612–27.
36. Verdijk LB, Snijders T, Drost M, et al. Satellite cells in human skeletal muscle; from birth to old age. Age (Dordr). 2014;36(2):545–7.
37. Petrella JK, Kim JS, Mayhew DL, et al. Potent myofiber hypertrophy during resistance training in humans is associated with satellite cell-mediated myonuclear addition: a cluster analysis. J Appl Physiol. 2008;104(6):1736–42.
38. Joanisse S, Gillen JB, Bellamy LM, et al. Evidence for the contribution of muscle stem cells to nonhypertrophic skeletal muscle remodeling in humans. FASEB J. 2013;27(11):4596–605.
39. Rudnicki MA, Le Grand F, McKinnell I, et al. The molecular regulation of muscle stem cell function. Cold Spring Harb Symp Quant Biol. 2008;73:323–31.
40. Choi S, Liu X, Li P, et al. Transcriptional profiling in mouse skeletal muscle following a single bout of voluntary running: evidence of increased cell proliferation. J Appl Physiol (1985). 2005;99(6):2406–15.
41. Crameri RM, Langberg H, Magnusson P, et al. Changes in satellite cells in human skeletal muscle after a single bout of high intensity exercise. J Physiol. 2004;558(Pt 1):333–40.
42. Cermak NM, Snijders T, McKay BR, et al. Eccentric exercise increases satellite cell content in type II muscle fibers. Med Sci Sports Exerc. 2013;45(2):230–7.
43. Bellamy LM, Joanisse S, Grubb A, et al. The acute satellite cell response and skeletal muscle hypertrophy following resistance training. PLoS One. 2014;9(10):e109739.
44. Hyldahl RD, Olson T, Welling T, et al. Satellite cell activity is differentially affected by contraction mode in human muscle following a work-matched bout of exercise. Front Physiol. 2014;5:485.
45. Verdijk LB, Koopman R, Schaart G, et al. Satellite cell content is specifically reduced in type II skeletal muscle fibers in the elderly. Am J Physiol Endocrinol Metab. 2007;292(1):E151–7.
46. Dreyer HC, Blanco CE, Sattler FR, et al. Satellite cell numbers in young and older men 24 hours after eccentric exercise. Muscle Nerve. 2006;33(2):242–53.
47. McKay BR, Ogborn DI, Bellamy LM, et al. Myostatin is associated with age-related human muscle stem cell dysfunction. FASEB J. 2012;26(6):2509–21.
48. Snijders T, Verdijk LB, Smeets JS, et al. The skeletal muscle satellite cell response to a single bout of resistance-type exercise is delayed with aging in men. Age (Dordr). 2014;36(4):9699.
49. Ferreira R, Neuparth MJ, Ascensao A, et al. Skeletal muscle atrophy increases cell proliferation in mice gastrocnemius during the first week of hindlimb suspension. Eur J Appl Physiol. 2006;97(3):340–6.
50. Snijders T, Wall BT, Dirks ML, et al. Muscle disuse atrophy is not accompanied by changes in skeletal muscle satellite cell content. Clin Sci (Lond). 2014;126(8):557–66.
51. Dirks ML, Wall BT, Snijders T, et al. Neuromuscular electrical stimulation prevents muscle disuse atrophy during leg immobilization in humans. Acta Physiol (Oxf). 2014;210(3):628–41.
52. Carlson ME, Suetta C, Conboy MJ, et al. Molecular aging and rejuvenation of human muscle stem cells. EMBO Mol Med. 2009;1(8–9):381–91.
53. Brooks NE, Myburgh KH. Skeletal muscle wasting with disuse atrophy is multi-dimensional: the response and interaction of myonuclei, satellite cells and signaling pathways. Front Physiol. 2014;5:99.
54. Hochreiter-Hufford AE, Lee CS, Kinchen JM, et al. Phosphatidylserine receptor BAI1 and apoptotic cells as new promoters of myoblast fusion. Nature. 2013;497(7448):263–7.
55. Yu SF, Baylies MK. Cell biology: death brings new life to muscle. Nature. 2013;497(7448):196–7.
56. Kadi F, Thornell LE. Concomitant increases in myonuclear and satellite cell content in female trapezius muscle following strength training. Histochem Cell Biol. 2000;113(2):99–103.
57. Charifi N, Kadi F, Feasson L, et al. Effects of endurance training on satellite cell frequency in skeletal muscle of old men. Muscle Nerve. 2003;28(1):87–92.
58. Kadi F, Schjerling P, Andersen LL, et al. The effects of heavy resistance training and detraining on satellite cells in human skeletal muscles. J Physiol. 2004;558(Pt 3):1005–12.
59. Verdijk LB, Gleeson BG, Jonkers RA, et al. Skeletal muscle hypertrophy following resistance training is accompanied by a

fiber type-specific increase in satellite cell content in elderly men. J Gerontol A Biol Sci Med Sci. 2009;64(3):332–9.
60. Mackey AL, Andersen LL, Frandsen U, et al. Strength training increases the size of the satellite cell pool in type I and II fibres of chronically painful trapezius muscle in females. J Physiol. 2011;589(Pt 22):5503–15.
61. Mackey AL, Holm L, Reitelseder S, et al. Myogenic response of human skeletal muscle to 12 weeks of resistance training at light loading intensity. Scand J Med Sci Sports. 2011;21(6):773–82.
62. Fry CS, Noehren B, Mula J, et al. Fibre type-specific satellite cell response to aerobic training in sedentary adults. J Physiol. 2014;592(Pt 12):2625–35.
63. O'Connor RS, Pavlath GK. Point:Counterpoint: satellite cell addition is/is not obligatory for skeletal muscle hypertrophy. J Appl Physiol (1985). 2007;103(3):1099–100.
64. Jackson JR, Mula J, Kirby TJ, et al. Satellite cell depletion does not inhibit adult skeletal muscle regrowth following unloading-induced atrophy. Am J Physiol Cell Physiol. 2012;303(8):C854–61.
65. McCarthy JJ, Mula J, Miyazaki M, et al. Effective fiber hypertrophy in satellite cell-depleted skeletal muscle. Development. 2011;138(17):3657–66.
66. Van der Meer SF, Jaspers RT, Degens H. Is the myonuclear domain size fixed? J Musculoskelet Neuronal Interact. 2011;11(4):286–97.
67. Verney J, Kadi F, Charifi N, et al. Effects of combined lower body endurance and upper body resistance training on the satellite cell pool in elderly subjects. Muscle Nerve. 2008;38(3):1147–54.
68. Leenders M, Verdijk LB, van der Hoeven L, et al. Elderly men and women benefit equally from prolonged resistance-type exercise training. J Gerontol A Biol Sci Med Sci. 2013;68(7):769–79.
69. Snijders T, Verdijk LB, Hansen D, et al. Continuous endurance-type exercise training does not modulate satellite cell content in obese type 2 diabetes patients. Muscle Nerve. 2011;43(3):393–401.
70. Watt FM, Hogan BL. Out of Eden: stem cells and their niches. Science. 2000;287(5457):1427–30.
71. Moore KA, Lemischka IR. Stem cells and their niches. Science. 2006;311(5769):1880–5.
72. Pannerec A, Marazzi G, Sassoon D. Stem cells in the hood: the skeletal muscle niche. Trends Mol Med. 2012;18(10):599–606.
73. Cornelison DD. Context matters: in vivo and in vitro influences on muscle satellite cell activity. J Cell Biochem. 2008;105(3):663–9.
74. Kuang S, Gillespie MA, Rudnicki MA. Niche regulation of muscle satellite cell self-renewal and differentiation. Cell Stem Cell. 2008;2(1):22–31.
75. Pedersen BK. Muscle as a secretory organ. Compr Physiol. 2013;3(3):1337–62.
76. Bonsignore MR, Morici G, Santoro A, et al. Circulating hematopoietic progenitor cells in runners. J Appl Physiol (1985). 2002;93(5):1691–7.
77. Ribeiro F, Ribeiro IP, Alves AJ, et al. Effects of exercise training on endothelial progenitor cells in cardiovascular disease: a systematic review. Am J Phys Med Rehabil. 2013;92(11):1020–30.
78. Christov C, Chretien F, Abou-Khalil R, et al. Muscle satellite cells and endothelial cells: close neighbors and privileged partners. Mol Biol Cell. 2007;18(4):1397–409.
79. Yan Z, Okutsu M, Akhtar YN, et al. Regulation of exercise-induced fiber type transformation, mitochondrial biogenesis, and angiogenesis in skeletal muscle. J Appl Physiol (1985). 2011;110(1):264–74.
80. Arsic N, Zacchigna S, Zentilin L, et al. Vascular endothelial growth factor stimulates skeletal muscle regeneration in vivo. Mol Ther. 2004;10(5):844–54.
81. Zanou N, Gailly P. Skeletal muscle hypertrophy and regeneration: interplay between the myogenic regulatory factors (MRFs) and insulin-like growth factors (IGFs) pathways. Cell Mol Life Sci. 2013;70(21):4117–30.
82. Musaro A, Giacinti C, Borsellino G, et al. Stem cell-mediated muscle regeneration is enhanced by local isoform of insulin-like growth factor 1. Proc Natl Acad Sci USA. 2004;101(5):1206–10.
83. Grounds MD. The need to more precisely define aspects of skeletal muscle regeneration. Int J Biochem Cell Biol. 2014;56:56–65.
84. Hatade T, Takeuchi K, Fujita N, et al. Effect of heat stress soon after muscle injury on the expression of MyoD and myogenin during regeneration process. J Musculoskelet Neuronal Interact. 2014;14(3):325–33.
85. Mason DL, Dickens VA, Vail A. Rehabilitation for hamstring injuries. Cochrane Database Syst Rev. 2012;(12):Art.-No:CD004575. doi:10.1002/14651858.CD004575.pub3.
86. Askling CM, Tengvar M, Tarassova O, et al. Acute hamstring injuries in Swedish elite sprinters and jumpers: a prospective randomised controlled clinical trial comparing two rehabilitation protocols. Br J Sports Med. 2014;48(7):532–9.
87. Askling CM, Tengvar M, Thorstensson A. Acute hamstring injuries in Swedish elite football: a prospective randomised controlled clinical trial comparing two rehabilitation protocols. Br J Sports Med. 2013;47(15):953–9.
88. Ambrosio F, Ferrari RJ, Distefano G, et al. The synergistic effect of treadmill running on stem-cell transplantation to heal injured skeletal muscle. Tissue Eng Part A. 2010;16(3):839–49.
89. Palermo AT, LaBarge MA, Doyonnas R, et al. Bone marrow contribution to skeletal muscle: a physiological response to stress. Dev Biol. 2005;279(2):336–44.
90. Hwang JH, Ra YJ, Lee KM, et al. Therapeutic effect of passive mobilization exercise on improvement of muscle regeneration and prevention of fibrosis after laceration injury of rat. Arch Phys Med Rehabil. 2006;87(1):20–6.
91. Rullman E, Norrbom J, Stromberg A, et al. Endurance exercise activates matrix metalloproteinases in human skeletal muscle. J Appl Physiol (1985). 2009;106(3):804–12.
92. Silveira EM, Rodrigues MF, Krause MS, et al. Acute exercise stimulates macrophage function: possible role of NF-kappaB pathways. Cell Biochem Funct. 2007;25(1):63–73.
93. Woods J, Lu Q, Ceddia MA, et al. Special feature for the Olympics: effects of exercise on the immune system: exercise-induced modulation of macrophage function. Immunol Cell Biol. 2000;78(5):545–53.
94. Walsh NP, Gleeson M, Shephard RJ, et al. Position statement. Part one: immune function and exercise. Exerc Immunol Rev. 2011;17:6–63.
95. Guo BS, Cheung KK, Yeung SS, et al. Electrical stimulation influences satellite cell proliferation and apoptosis in unloading-induced muscle atrophy in mice. PLoS One. 2012;7(1):e30348.
96. Zhang BT, Yeung SS, Liu Y, et al. The effects of low frequency electrical stimulation on satellite cell activity in rat skeletal muscle during hindlimb suspension. BMC Cell Biol. 2010;11:87.