ARTICLE

The Impact of Aerobic Exercise on the Muscle Stem Cell Response

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JOANISSE, S., T. SNIJDERS, J.P. NEDERVEEN, and G. PARISE. The impact of aerobic exercise on the muscle stem cell response. *Exerc. Sport Sci. Rev.*, Vol. 46, No. 3, pp. 180–187, 2018. *Satellite cells are indispensable for skeletal muscle repair and regeneration and are associated with muscle growth in humans. Aerobic exercise training results in improved skeletal muscle health also translating to an increase in satellite cell pool activation. We postulate that aerobic exercise improves satellite cell function in skeletal muscle.*
Key Words: aerobic exercise, skeletal muscle, satellite cells, regeneration, repair

Key Points

- Skeletal muscle-specific stem cells are termed *satellite cells* and are indispensable for skeletal muscle repair and regeneration.
- In addition to the more traditional studies investigating the impact of resistance exercise on satellite cells, recent studies suggest that satellite cells also may respond to endurance exercise.
- Because satellite cells are imperative to skeletal muscle regeneration, heightened activation of the satellite cell pool after aerobic exercise training may render skeletal muscle repair more efficient after injury.
- We discuss the potential of aerobic exercise to improve the capacity of skeletal muscle to repair and remodel via improved satellite cell function.

Club

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INTRODUCTION

Skeletal muscle is one of the largest organs of the human body and plays an essential role in whole-body locomotion. It also acts as an important nutrient store and serves as a source of glucose disposal, maintaining whole-body homeostasis. Skeletal muscle possesses a remarkable plasticity and can respond to a wide range of stimuli such as injury, damage, and exercise. Regular exercise results in improvements in various metabolic and structural aspects of skeletal muscle health. Resistance exercise training has long been associated with increases in skeletal muscle mass characterized by increases in muscle fiber cross-sectional area (CSA) (1,2). Alternatively, aerobic exercise training, including moderate-intensity continuous training (MICT), high-intensity interval training (HIT), and sprint interval training (SIT) (3), is associated not only with structural remodeling of muscle fibers toward a more oxidative phenotype but also with increases in mitochondrial protein content and function and increased capillary density (4,5). Over the years, extensive research has focused on understanding the molecular basis for structural and functional adaptations that occur in skeletal muscle after exercise training.

Satellite cells (SCs) are muscle-specific stem cells that are essential in skeletal muscle repair and regeneration (6,7). Specifically, SCs reside between the sarcolemma and the basal lamina, an area referred to as the SC niche (8). The muscle fiber to which the SC is associated also composes part of the niche and thus, SCs respond to various signals originating from the muscle fiber (8). When SCs become activated, they proliferate and differentiate, eventually fusing to existing muscle fibers and donating their nuclei and thereby supporting skeletal muscle fiber repair (7) and growth (9–12). It is important to note, however, that on activation, a subset of SCs will revert to quiescence, thereby maintaining the SC pool (13). The extent to which SCs facilitate exercise-induced adaptations is not clear, but further studies are warranted and of keen interest to investigators in the field of exercise science.

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SCs have the ability to fuse to muscle fibers, and because of this reason, it has long been believed that SCs may play a role in mediating increases in muscle fiber size such as those observed after resistance exercise training (2,9–12). This notion is supported by the myonuclear domain theory, which suggests that each myonucleus governs a particular volume of cytoplasm. Once the volume of a cell exceeds the capacity of an individual nucleus (*i.e.*, an increase in muscle fiber size) the addition of new nuclei is necessary to support a larger cell volume (14). Because skeletal muscle fibers are postmitotic in nature, the addition of new nuclei requires fusion of SCs to existing muscle fibers. This theory was originally supported by work in rodent models in which SCs were ablated by gamma irradiation. Skeletal muscle that was void of SCs did not respond to overload-induced hypertrophy, whereas control, nonirradiated, rodents experienced significant hypertrophy (15,16). However, recent work has challenged common dogma that SCs are necessary for inducing muscle fiber hypertrophy. A novel mouse model was developed that achieved near complete ablation of SCs in mature skeletal muscle. In this model, SC-ablated animals maintained the ability to respond to various hypertrophic stimuli such as 2 and 6 wk of overload via synergist ablation (6) and 14 d of reloading proceeded by 14 d of atrophy induced via hind limb suspension (17). This suggests that, at least in rodents, SCs are not necessary for inducing skeletal muscle fiber hypertrophy. However, SCs seem to be required to maintain muscle growth because muscle hypertrophy is attenuated in SC-depleted rodents after 8 wk of overload (18). To further the debate on whether SCs are necessary to mediate this process, a more recent study using the same mouse model as described earlier, albeit in younger mice, reported impaired skeletal muscle hypertrophy after 2 wk of overload-induced hypertrophy (19). Although a highly debated topic when examining data from rodent models, an increase in muscle fiber size has been associated with an expansion of the SC pool in humans (20). This evidence would support the notion that, in humans, nuclear addition is an important part of muscle hypertrophy, consistent with the theory that SCs contribute to muscle growth. It is, however, important to note that recent work in humans has described an increase in muscle fiber CSA without an apparent concomitant increase in the SC pool (18).

Less explored is the impact of aerobic exercise training on the SC pool and the subsequent impact of this event on muscle adaptation in humans. We hypothesize that aerobic exercise training may improve SC function, directly impacting the ability of skeletal muscle to respond to stimuli such as injury and immobilization. The impact of resistance exercise and aerobic exercise training on the SC pool in human skeletal muscle is described in Figure 1. Our review discusses advances regarding the influence of aerobic exercise training on SC function.

AEROBIC EXERCISE TRAINING AND ITS EFFECT ON SC-MEDIATED MUSCLE GROWTH AND REMODELING

Aerobic exercise training in rodents consistently results in an increase in SC content (21–25). In addition, work in rodents suggests that exercise intensity may be important in expanding the SC pool (22). The fact that SC expansion can occur in the absence of increased myofiber CSA and muscle mass in some instances (21–23,25) suggests an important role for SCs in muscle plasticity and adaptation outside the traditional role of promoting muscle growth. The results of studies discussed are summarized in the Table.

The SC response to aerobic exercise in humans has not been as extensively studied, and the results are much less consistent than that observed in rodent models. SC content in skeletal muscle has been observed to be positively correlated with $\dot{V}O_{2max}$, suggesting that SC may play a role in maintaining muscle fiber health/function in individuals with a high aerobic capacity (26). However, this study did not take into account fiber CSA, and it may be possible that subjects with a greater $\dot{V}O_{2max}$ also had greater fiber CSA, and this could account for the association between $\dot{V}O_{2max}$ and SC content. Some studies report an increase in SC content in older adults after 14 wk of interval training, although an increase in type IIa fiber CSA also was observed (27,28). Therefore, the increase in SC content may have occurred to mediate fiber hypertrophy.

More recent work has described an increase in SC associated with type I muscle fibers in middle-aged adults after 12 wk of MICT (18,29). Interestingly, both studies report an increase in CSA of all fiber types, whereas an expansion of the SC pool was only observed in type I fibers (18,29). In addition, an endurance training program that did not induce an increase in muscle fiber size also did not result in an increase in SC content in older participants with type 2 diabetes (30). We have recently demonstrated that there is no apparent expansion in the basal SC pool after 6 wk of various forms of endurance exercise, concomitant with no observed increase in muscle fiber CSA (31,32). Although we did not observe an increase in overall SC content, we demonstrated that after 6 wk of aerobic interval training, there was an increase in SC associated with hybrid muscle fibers, muscle fibers expressing both myosin heavy chain type I and II, only (31). It is, however, important to note that the proportion of hybrid fibers at baseline was very low. After aerobic interval training, there was a trend for an increase in hybrid fibers, and a greater proportion of these fibers had centrally located nuclei, a hallmark of repairing/remodeling fibers. We also observed a high number of SCs associated with fibers expressing neonatal myosin heavy chain (31). To further evaluate the response of SCs to aerobic exercise, we determined the effect of either 6 wk of MICT or 2 different SIT protocols, varying in interval duration. We demonstrated that there was an increase in SC activity (increase in MyoD expression as evidence of activation) without an apparent expansion of the $Pax7^{+}$ pool in the absence of hypertrophy after all three aerobic exercise training programs (32).

Together, these results highlight the capacity for SCs to respond to aerobic exercise and the potential for SCs to engage in a training response appropriate for this type of stimulus. Results from human studies are much more variable than what is observed when rodent models are used, as is highlighted in Table. Any discrepancies observed are likely due to the variable ages of the populations used in addition to a variety of aerobic training programs.

THE IMPACT OF AEROBIC EXERCISE ON SC FUNCTION

SCs are indispensable for skeletal muscle regeneration. Several rodent models have demonstrated severe impairment in muscle regeneration when SCs are abolished from skeletal muscle (6,7) Aerobic exercise results in increased mitochondrial

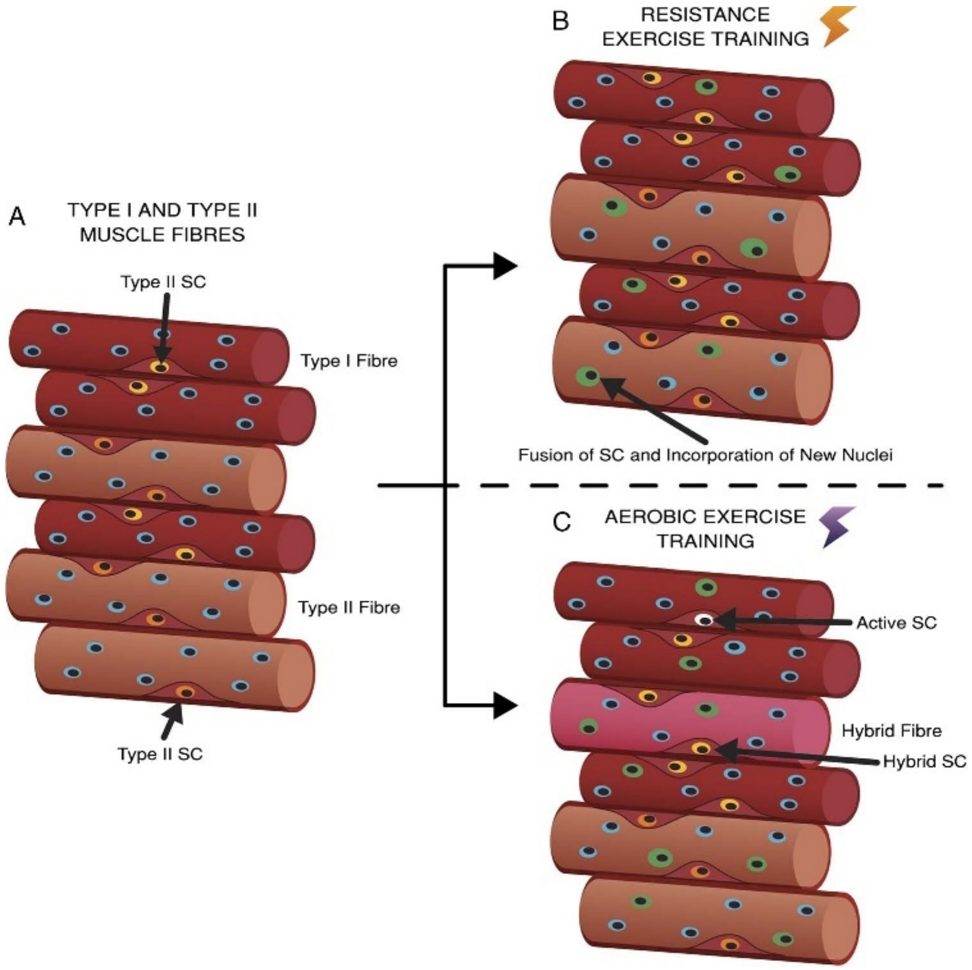

Figure 1. The proposed effect of resistance and aerobic exercise training on the satellite cell (SC) pool in humans. In a homeostatic physiological state (A), each myonucleus governs a set volume of cytoplasm, referred to as the myonuclear domain. Resistance exercise training results in increased muscle fiber crosssectional area (CSA) and SC content (B). To maintain the myonuclear domain, it is believed that SCs fuse to growing muscle fibers, "donating" their nuclei to support this growth. Aerobic exercise training results in a shift toward a more oxidative phenotype characterized by an increased proportion of type I and hybrid muscle fibers, with no increase in muscle fiber CSA (C). An increase in SC content is not observed with aerobic exercise training. However, an increase in the number of active SCs and a greater number of SCs associated with hybrid compared with type I and II muscle fibers is observed after aerobic exercise training (C).

biogenesis and capillary density. The following sections will discuss the potential mechanisms by which aerobic exercise can modulate SC function.

The Importance of Mitochondrial Biogenesis in the Regulation of SC Function

In vitro work has demonstrated impairment in myotube formation when mitochondrial synthesis is inhibited, although gene expression of both MyoD and myogenin, genes related to myogenesis, remained unaffected (33). These early findings suggest that mitochondrial content is important for myoblast differentiation. Mitochondrial biogenesis is increased during skeletal muscle regeneration (34), thus implicating mitochondria as a contributing factor in regeneration. Work in a rat model demonstrated that after gastrocnemius muscle injury, a marked reduction in mitochondrial functionality was observed. However, by restoring mitochondrial function via administration of polycistronic RNAs, which encoded the heavy strand of the rat mitochondrial genome into the injured muscle, SC proliferation was increased accompanied by improved muscle regeneration (34), suggesting that mitochondrial function may have a considerable role in myogenesis. To further support the importance of mitochondrial biogenesis in SC function, isolated SCs demonstrating enhanced activation, defined by cells that entered the cell cycle more quickly after isolation, have higher levels of mitochondrial activity and adenosine triphosphate concentration compared with those with lower activation (35). In addition, SC from mice that underwent a short-term calorie restricted diet had an increased oxygen consumption rate, mitochondrial content, and mitochondrial protein content (36). SCs also experienced improved myogenic function and together, this translated to improved muscle repair (36).

The ablation of SIRT1, a modulator of mitochondrial homeostasis, in skeletal muscle of rodents resulted in impaired skeletal muscle regeneration, further supporting the role of mitochondria in regeneration (37). Supplementation with nicotinamide riboside (NR), a nicotinamide adenine dinucleotide precursor, increased SC content in both young and old rodents and accelerated muscle regeneration after injury; however, this improvement was not observed in rodents in which SIRT1 was not expressed in skeletal muscle, indicating that NR supplementation improved SC function in a SIRT1-dependent manner

TABLE. Summary of studies in human and rodents describing the satellite cell (SC) response to aerobic exercise training.

Species	Age	Exercise Type	SC response	Reference
Human, male (n = 10)	73 ± 4 yr	Concurrent training, 14 wk, 3 d·wk^{-1} END training on cycle ergometer: 3 bouts of 12 min consisting of 2 sequences of 4 min @ 75%–85% HR_{max} followed by 1 min interval @ 80%–95% HR_{max}, followed by active recovery	++ SC/type II fiber ++SC/total fiber	28
Human, male (n = 11)	73 ± 3 yr	Interval training, 14 wk, 4 d·wk^{-1}, on cycle ergometer: 7 bouts of 4 min @ 65%–75% $\dot{V}O_{2peak}$ followed by 1 min @ 85%–95% $\dot{V}O_{2peak}$	++ SC/total fiber	29
Human, obese type 2 diabetic males (n = 15)	61 ± 6 yr	Endurance exercise, 6 mo, 3 d·wk^{-1}, walking, cycling, and cross-country skiing–type exercise: total time of 40 min @ 75% $\dot{V}O_{2peak}$	No change in SC/type I fiber No change in SC/type II fiber	31
Human, overweight females (n = 15)	27 ± 8 yr	HIT, 6 wk, 3 d·wk^{-1}, on cycle ergometer: 10 × 60-s bouts of cycling @ 90% HR_{max} interspersed with 60 s of recovery	No change in SC/type I fiber No change SC/type II fiber ++SC/hybrid fiber	32
Human, overweight males (n = 6) and females (n = 17)	47.6 ± 8 yr	END, 12 wk, 3 d·wk^{-1} on cycle ergometer: 45 min @ 70% HR reserve	No change in SC/type II fiber ++SC/type I fiber ++SC/total fiber	19
Human, overweight/obese men (n = 7) and women (n = 7)	Men: 29 ± 9 yr Women: 29 ± 2 yr	SIT, 6 wk, 3 d·wk^{-1} on cycle ergometer: 3 × 20-s sprint against 0.05 kg·kg^{-1} body mass interspersed by 2 min low-intensity cycling	No change in SC/type I fiber No change in SC/type II fiber ++ Pax7+/MyoD+ cells/fiber (active SC) ++ Pax7-/MyoD+ cells/fiber (differentiating SC)	33
Human, males and females (n = 10)	21 ± 2 yr	SIT, 6 wk, 4 d·wk^{-1} on cycle ergometer: 8 × 20-s intervals at 170% at $\dot{V}O_{2peak}$ interspersed with 10 s of rest	No change in SC/type I fiber No change in SC/type II fiber ++ Pax7+/MyoD+ cells/fiber (active SC) ++ Pax7-/MyoD+ cells/fiber (differentiating SC)	33
Human, males and females (n = 9)	21 ± 4 yr	MICT 6 wk, 4 d·wk^{-1} on cycle ergometer 30 min @ 65% $\dot{V}O_{2peak}$	No change in SC/type I fiber No change in SC/type II fiber ++ Pax7+/MyoD+ cells/fiber (active SC) ++Pax7-/MyoD+ cells/fiber (differentiating SC)	33
Human, females (n = 7)	56 ± 5 yr	END 12 wk, 3 d·wk^{-1} on cycle ergometer 45 min @ 65% $\dot{V}O_{2max}$	No change in SC/type II fiber ++SC/type I fiber ++ SC/total fiber	30
Wistar rats, male, plantaris (n = 12)	5 wk	8 wk, voluntary wheel running	++SC/total fibers	22
Wistar rats, male (n = 10) and female (n = 10), gastroc	3.5 mo	END 13 wk, 6 d·wk^{-1} on treadmill, 20-min sessions @ 0.5 km·h^{-1} (moderate intensity)	++SC/total fibers	26
Wistar rats, male (n = 9) and female (n = 8), gastroc	Males: 15–17 mo Females: 15 mo	END 13 wk, 6 d·wk^{-1} on treadmill, 20-min sessions @ 0.5 km·h^{-1} (moderate intensity)	++SC/total fibers	26
Sprague-Dawley rats, female, plantaris (n = 9)	10 wk	Low-intensity END training 10 wk on treadmill, 30-min sessions 5 d·wk^{-1} graded increase (speed, 25–30 m·min^{-1}; grade 0%–3%).	No change in SC/total fiber	23
Sprague-Dawley rats, female, plantaris (n = 9)	10 wk	Low-intensity END training 10 wk on treadmill, 90-min sessions 5 d·wk^{-1} graded increase (speed, 25–30 m·min^{-1}; grade 0%–3%).	No change in SC/total fiber	23
Sprague-Dawley rats, female, plantaris (n = 9)	10 wk	High-intensity END training 10 wk on treadmill, 30-min sessions 5 d·wk^{-1} graded increase (speed 25–30 m·min^{-1}; grade 0%–18%).	++ SC/total fiber	23
Sprague-Dawley rats, female, plantaris (n = 9)	10 wk	High-intensity END training 10 wk on treadmill, 90-min sessions 5 d·wk^{-1} graded increase (speed, 25–30 m·min^{-1}; grade 0%–18%).	No change in SC/type I fiber ++ SC/total fiber ++ SC/type II fiber	23
NES-GFP heterozygous C57Bl/6 male mice EDL	Young: 4 mo (n = 7) Old: 16 mo (n = 6)	Moderate intensity END 8 wk on treadmill, 30 min·d^{-1}, 6 d·wk^{-1} @ 11.5 m·min^{-1}	++ SC/total fiber	25
C57Bl/J male mice, (n = 6)	24 mo	Progressive END training 8 wk, on treadmill, 3 d·wk^{-1}, 40 min/session (speed, 8.5–15 m·min^{-1}).	++ SC/total fiber	24

EDL indicates extensor digitorum longus; END, endurance; gastroc, gastrocnemius; and HR_{max}, heart rate maximum.

(37). Although not directly using exercise as an intervention, these data further support the role of mitochondria in mediating SC function. These results suggest that aerobic exercise, via increased mitochondrial content and function, may potentially improve SC function. Improved SC function may reestablish muscle fiber structure and function in a more efficient manner.

The Importance of the Vasculature in the Regulation of SC Function

Skeletal muscle perfusion is critical for the maintenance of skeletal muscle health. Adequate fiber perfusion is necessary to provide skeletal muscle with oxygen, nutrients, and various growth factors, while carrying away carbon dioxide and metabolic byproducts (38). A hallmark adaptation associated with aerobic exercise training is an increase in skeletal muscle capillarization (5). In addition to maintenance of muscle health, revascularization is an important part of the regenerative/repair process after injury to skeletal muscle (39). It is well established that there is a spatial relation between SCs and capillaries in humans. Active SCs are located at a closer proximity to capillaries compared with quiescent SCs (40). In addition, it is known that there is "cross-talk" between SCs and endothelial cells (41,42). Therefore, the microvasculature of the skeletal muscle can impact SC function. Not only does the structure of the mircovasculature in skeletal muscle affect SC function but key signaling molecules such as myostatin, vascular endothelial growth factor (VEGF), hepatocyte growth factor, and insulin-like growth factor 1, among others, present in general circulation may interact with the SC niche and impact SC function (43). Exercise has been shown to result in increased circulating levels of various cytokines such as a number of interleukins (IL-1, IL-6, IL-8, IL-10) and tumor necrosis factor α (44). The term *myokine* has recently been coined and describes a cytokine released by skeletal muscle. Myokines are produced after exercise and can act in both a paracrine or endocrine manner, altering the SC microenvironment (45). IL-6 is the most widely studied myokine, and its expression is drastically increased after exercise (44). Interestingly, IL-6 can be classified as both a pro- and antiinflammatory cytokine (46) and has been associated with SC proliferation in humans after eccentric muscle contractions (47). Recent work has demonstrated that basal skeletal muscle capillarization in older adults may be important in promoting skeletal muscle hypertrophy after a resistance exercise training program (48). Older adults were compared based on their extent of type II fiber capillary to fiber perimeter exchange index (CFPE), and only those considered to have a *high* CFPE had an increase in fiber size and SC content after 24 wk of resistance training. Although the results of this study are not directly linked to aerobic exercise, aerobic exercise does result in increased capillary density, thereby potentially reducing the distance between capillaries and SCs and maximizing the outcomes of a resistance exercise training program.

Administration of VEGF, a primary driver of angiogenesis, after injury induced via ischemia results in improved skeletal muscle regeneration in addition to improving angiogenic and myogenic properties of the muscle (49). *In vitro* results have demonstrated that VEGF treatment promotes myotube hypertrophy and facilitates differentiation (50). Aerobic exercise training results in increased VEGF mRNA expression in skeletal muscle (51); therefore, another potential mechanism by which aerobic exercise improves SC function may be by increasing muscle capillarization and VEGF mRNA expression.

Endurance exercise training therefore has the ability to improve SC function in various ways. These proposed mechanisms are summarized in Figure 2. For example, endurance exercise may increase mitochondrial protein content and function within SCs, increase capillarization of skeletal muscle, thereby reducing the distance between SC and capillaries, maximizing the ability of SC to respond to stimuli, and also by inducing changes in the systemic environment, ultimately altering the SC microenvironment (52,53).

FUNCTIONAL IMPLICATIONS OF SATELLITE CELL ADAPTATION TO AEROBIC EXERCISE

Considering the evidence presented earlier, we hypothesize that aerobic exercise improves SC function. The overall health benefits of endurance exercise training are numerous as are the adaptations in skeletal muscle. Although these adaptations are not limited to the SC and its niche, improved SC function also can improve skeletal muscle health and function. Some groups have reported impaired regeneration in old rodents (54–56), whereas others report normal regeneration (57–59). Although age-associated changes in SC content have been observed, skeletal muscle from old animals retains the ability to positively respond to aerobic exercise (23–25). We have recently demonstrated that old mice that have exercise trained before inducing skeletal muscle injury have an improved ability to regenerate skeletal muscle compared with sedentary age-matched animals. The improvement in skeletal muscle regeneration may be due to an increase in the basal SC pool because SCs are indispensable for muscle regeneration (23). Specifically, greater SC content in old exercised compared with sedentary animals may have, in part, been due to an increase in mitochondrial content and function observed in these animals, ultimately improving the muscle's ability to regenerate. Accelerated muscle regeneration in these animals points to not only an increase in SC content and potentially function, but also to an improvement in functional outcome as evidenced by a complete reestablishment of muscle fiber size. Although, translating findings from rodent studies to humans must be done with caution, these results support the notion that aerobic exercise improves SC function.

Disuse models in humans have convincingly demonstrated an inability to reestablish muscle fiber CSA after remobilization and that SC content is reduced after periods of disuse in old adults (60). A reduction in CSA has been reported as early as 7 d after immobilization (61). These results are similarly reflected in rodent models, which demonstrated impaired early muscle regeneration (55,56). Impaired early regeneration may preclude the muscle from ever fully regenerating. Although, the process of reestablishing muscle fiber size after a period of immobilization is different than reestablishing muscle fiber size after injury, the work completed in rodents suggests that older adults that exercise may be able to better recover from periods of immobilization. The ability for an older adult to reestablish muscle fiber size after a period of immobilization is essential in delaying the gradual onset of age-associated muscle loss.

The concept of *muscle memory* has garnered much attention in recent years. Previous work in rodent models has demonstrated that skeletal muscle retains myonuclei acquired during a period of overload-induced hypertrophy when faced with a subsequent period of muscle loss due to denervation. In addition, animals that had previously undergone overload-induced hypertrophy were, to an extent, protected from the denervation-induced muscle loss (62). In line with these findings, rodents that had been previously administered testosterone responded more robustly to a period of overload-induced hypertrophy compared with animals that had not been exposed to testosterone (63). Recent work has explored whether human skeletal muscle possess an enhanced ability to respond to hypertrophic stimuli if it has been exposed to an earlier period of hypertrophy. Here, the authors demonstrate that resistance training results in an increase in lean mass, which is reduced to similar levels to baseline after unloading (64). Interestingly, lean mass is further increased after a subsequent period of resistance training. DNA methylation was assessed after the initial period of resistance training, after the unloading period and again after the subsequent resistance training period. A widespread hypomethylation was observed, suggesting that skeletal muscle seems to possess a "memory" of earlier periods of hypertrophy (64). Taken together, these results highlight that a type of muscle or "myonuclear-memory" may exist and that prior resistance exercise may better enable the muscle to respond to various anabolic stimuli such as reloading after a period of inactivity. To our knowledge, this is the first study to investigate muscle memory after an anabolic stimulus such as resistance training in

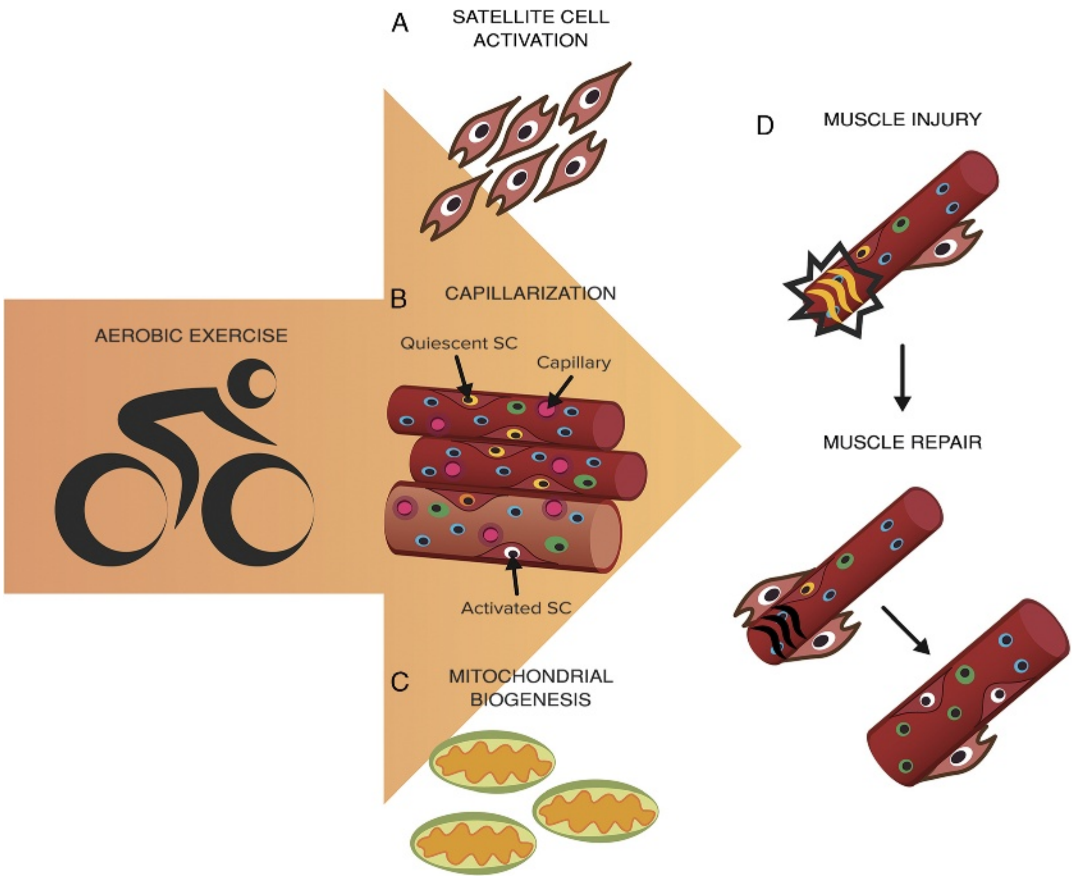

Figure 2. Hypothetical model for the role of aerobic exercise to improve satellite cell (SC) function. We have demonstrated an increase in SC activation after aerobic exercise training (A). Blue cells represent myonuclei, whereas green cells represent fused SCs or newly incorporated nuclei. Aerobic exercise also results in increased skeletal muscle capillarization (B) and mitochondrial biogenesis (C). Active SCs reside in closer proximity to capillaries in comparison with quiescent SC (B). Aerobic exercise has the ability to modulate the circulating systemic environment impacting the SC microenvironment; increased capillarization may increase the exposure of SCs to key signaling molecules found in circulation, depicted as the dotted line surrounding capillaries (B). We propose that aerobic exercise improves SC function via increased skeletal muscle vascularization and mitochondrial biogenesis. Increased SC activation due to aerobic exercise training may improve the ability of muscle to repair itself after injury (D).

humans. How this may affect the ability of humans who have had previous exercise training to better respond to periods of muscle loss such as severe step reduction or immobilization and whether this memory is maintained with age and to what extent remains to be determined but is an interesting avenue for future research.

We have previously demonstrated that the extent of muscle fiber capillarization may be an important factor in mediating the extent of hypertrophy in older adults (48). No observable increase in muscle fiber size or SC content was observed in older adults with a relatively low capillarization of type II muscle fibers before the onset of a resistance training program (48). The results of this study suggest that skeletal muscle perfusion must be adequate to support an increase in muscle fiber size and this may be due to an expansion of the SC pool. Therefore, maximizing skeletal muscle capillarization may better support the ability of skeletal muscle to respond to hypertrophic stimuli such as resistance training. Aerobic exercise training results in an increased capillary density in skeletal muscle, which may improve SC function, ultimately maximizing increases in muscle fiber size after resistance exercise. Although resistance exercise is the criterion standard for increasing muscle mass, aerobic exercise in older individuals may not only improve cardio metabolic health but also may improve skeletal muscle health and its ability to repair/regenerate after periods of disuse — potentially through improved SC function. Recent work has demonstrated that endurance exercise training is able to alter the acute SC response to resistance exercise (29). After a bout of acute resistance exercise, an increase in SCs associated with type I muscle fibers was observed. However, this acute increase after a bout of resistance exercise was no longer observed after 12 wk of endurance training (29). Although this study does not directly address how endurance exercise affects SC biology, it further supports the notion that endurance exercise can directly impact SC function.

CONCLUSIONS

The vast benefits of exercise and its ability to improve health in a wide range of populations are widely accepted. In human work, resistance exercise training has long been associated with an increase in SC content. More recently, a focus has been placed on understanding the effects of aerobic exercise on SC function in skeletal muscle. We postulate that endurance exercise is able to improve SC function via mechanisms described earlier and are outlined in Figure 2. In addition to the canonical role for SC in mediating muscle growth, we hypothesize that endurance exercise is able to improve muscle regeneration in skeletal muscle of rodents likely because of various factors, one of which may be a direct improvement in SC function. The ability of aerobic exercise to modulate SC function is an important finding and may be beneficial in improving skeletal muscle health in various muscle-wasting states such as aging. Future work should be aimed at further understanding the ability of aerobic exercise to improve SC health in skeletal muscle.

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