THE EFFECT OF AEROBIC EXERCISE ON THE MUSCLE STEM CELLS FIBERS

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ABSTRACT

Satellite cells are indispensable for skeletal muscle repair and regeneration and are associated with muscle growth in humans [1]. 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.

1. 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) [2, 3]. Alternatively, aerobic exercise training, including moderate-intensity continuous training (MICT), high-intensity interval training (HIT), and sprint interval training (SIT) [4] 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 [5, 6]. 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 [7, 8]. Specifically, SCs reside between the sarcolemma and the basal lamina, an area referred to as the SC niche [9]. 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 [9]. 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 [8] and growth [10, 11]. It is important to note, however, that on activation, a subset of SCs will revert to quiescence, thereby maintaining the SC pool [12]. 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.
2. THE EFFECT OF AEROBIC EXERCISE ON SC FUNCTION

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 [3, 11]. 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 [13]. 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 [14, 15]. 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 [7] and 14 d of reloading proceeded by 14 d of atrophy induced via hind limb suspension [16]. 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 [17]. 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 [18]. 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 [19]. 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 [17].

Less explored is the effect 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 effect 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](image-url)

Figure 1. Resistance exercise training results in increased muscle fiber crosssectional area (CSA) and SC content. To maintain the myonuclear domain, it is believed that SCs fuse to growing muscle fibers, "donating" their nuclei to support this growth [13].

Aerobic exercise training in rodents consistently results in an increase in SC content [20, 21]. 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 [20, 21, 23].
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 1.

| 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% HRmax followed by 1 min interval @ 80%−95% HRmax, followed by active recovery | ++SC/type II fiber | Charifi, et al. [24] |
| 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% VO2peak followed by 1 min @ 85%−95% VO2peak | ++ SC/total fiber | Murach, et al. [25] |
| 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 | Egner, et al. [18] |
| Human, overweight/obese men (n = 7) and women (n = 7) | Men: 29 ± 9 yr | SIT, 6 wk, 3 d-wk−1 on cycle ergometer: 5x20-s sprint against 0.05 kg·kg−1 body mass interspersed by 2 min low-intensity cycling | No change in SC/type I fiber | Hamai, et al. [26] |
| Wistar rats, male, plantaris (n = 12) | 5 wk | 8 wk, voluntary wheel running | ++ SC/total fibers | Kurosaka, et al. [22] |
| Wistar rats, male (n = 10) and female (n = 10), gastroc | 3.5 mo | END 13 wk, 6 dwk−1 on treadmill, 20-min sessions @ 0.5 km·h−1 (moderate intensity) | ++SC/total fibers | Macaluso and Myburgh [27] |
| Wistar rats, male (n = 9) and female (n = 8), gastroc | Males: 15–17 mo | END 13 wk, 6 dwk−1 on treadmill, 20-min sessions @ 0.5 km·h−1 (moderate intensity) | ++SC/total fibers | Macaluso and Myburgh [27] |
| C57Bl/J male mice, (n = 6) | 24 mo | Progressive END training 8 wk, on treadmill, 3 dwk−1, 40 min/session (speed, 8.5–15 mmin−1). | ++ SC/total fiber | Shefer, et al. [28] |

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 V̇O2max, suggesting that SC may play a role in maintaining muscle fiber health/function in individuals with a high aerobic capacity [27]. However, this study did not take into account fiber CSA, and it may be possible that subjects with a greater V̇O2max also had greater fiber CSA, and this could account for the association between V̇O2max 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 [29]; [24]. 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 [17]; [26]. 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 [17]; [26]. 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 [1]; [31]. 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 [1]. 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 [1].

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 [19].

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.

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.

Although age-associated changes in SC content have been observed, skeletal muscle from old animals retains the ability to positively respond to aerobic exercise [29]; [21]. 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 [28]. 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, 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.

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
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 \[1\]. 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.

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 \[1\].

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 \[1\].

Recent work has demonstrated that endurance exercise training is able to alter the acute SC response to resistance exercise \[2,3\]. 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 \[2,3\].

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.

3. 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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