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INFLUENCE OF AEROBIC EXERCISE ON THE BRAWN STEM CELLS FIBERS

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ABSTRACT: Satellite cells are indispensable for skeletal brawn repair and regeneration and are associated with brain growth in humans (Sophie Joanisse, et al, 2017). Aerobic exercise training results in improved skeletal brawn health also translating to an increase in satellite cell pool activation. We postulate that aerobic exercise improves satellite cell function in skeletal brawn.

KEYWORDS: Influence, Aerobic, Exercise

I. INTRODUCTION

The skeletal brawn 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 brawn possesses 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 brawn health. Resistance exercise training has long been associated with increases in skeletal brawn mass characterized by increases in brawn fiber cross-sectional area (CSA) (Kosek DJ, et al, 2006; Petrella JK, et al, 2006). Alternatively, aerobic exercise training, including moderate-intensity continuous training (MICT), high-intensity interval training (HIT), and sprint interval training (SIT) (MacInnis MJ, et al, 2016), is associated not only with the structural remodeling of brawn fibers toward a more oxidative phenotype but also with increases in mitochondrial protein content and function and increased capillary density (Gibala MJ, et al, 2012). Over the years, extensive research has focused on understanding the molecular basis for structural and functional adaptations that occur in skeletal brawn after exercise training.

Satellite cells (SCs) are brawn-specific stem cells that are essential in skeletal brawn repair and regeneration (McCarthy JJ, et al, 2011; Sambasivan R, et al, 2011). Specifically, SCs reside between the sarcolemma and the basal lamina, an area referred to as the SC niche (Kuang S, et al, 2008). The brawn fiber to which the SC is associated also composes part of the niche and thus, SCs respond to various signals originating from the brawn fiber (Kuang S, et al, 2008). When SCs become activated, they proliferate and differentiate, eventually fusing to existing brawn fibers and donating their nuclei and thereby supporting skeletal brawn fiber repair (Sambasivan R, et al, 2011) and growth (Petrella JK, et al, 2008). It is important to note, however, that on activation, a subset of SCs will revert to quiescence, thereby maintaining the SC pool (Rudnicki MA, et al, 2008). 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.

The influence of aerobic exercise on sc function

SCs can fuse to brawn fibers, and because of this reason, it has long been believed that SCs may play a role in mediating increases in brawn fiber size such as those observed after resistance exercise

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training (Petrella JK, et al, 2008). This notion is supported by the myonuclear domain theory, which suggests that each myonucleus governs a particular volume of the cytoplasm. Once the volume of a cell exceeds the capacity of an individual nucleus (i.e., an increase in brawn fiber size) the addition of new nuclei is necessary to support a larger cell volume (Allen DL, et al, 1999). Because skeletal brawn fibers are postmitotic, the addition of new nuclei requires a fusion of SCs to existing brawn fibers. This theory was originally supported by work in rodent models in which SCs were ablated by gamma irradiation. Skeletal brawn that was void of SCs did not respond to overload-induced hypertrophy, whereas control, nonirradiated, rodents experienced significant hypertrophy (Adams GR, et al, 2002). However, recent work has challenged the common dogma that SCs are necessary for inducing brawn fiber hypertrophy. A novel mouse model was developed that achieved near-complete ablation of SCs in mature skeletal brawn. 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 (McCarthy JJ, et al, 2011) and 14 d of reloading proceeded by 14 d of atrophy induced via hind limb suspension (Jackson JR, et al, 2012). This suggests that, at least in rodents, SCs are not necessary for inducing skeletal brawn fiber hypertrophy. However, SCs seem to be required to maintain brawn growth because brawn hypertrophy is attenuated in SC-depleted rodents after 8 wk of overload (Fry CS, et al, 2014). 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 brawn hypertrophy after 2 wk of overload-induced hypertrophy (Egner IM, et al, 2016). Although a highly debated topic when examining data from rodent models, an increase in brawn fiber size has been associated with an expansion of the SC pool in humans (Snijders T, et al, 2015). This evidence would support the notion that, in humans, nuclear addition is an important part of brawn hypertrophy, consistent with the theory that SCs contribute to brawn growth. It is, however, important to note that recent work in humans has described an increase in brawn fiber CSA without an apparent concomitant increase in the SC pool (Fry CS, et al, 2014).

Less explored is the influence of aerobic exercise training on the SC pool and the subsequent impact of this event on brawn adaptation in humans. We hypothesize that aerobic exercise training may improve SC function, directly impacting the ability of skeletal brawn to respond to stimuli such as injury and immobilization.

The influence of resistance exercise and aerobic exercise training on the SC pool in human skeletal brawn is described in Figure 1. Our review discusses advances regarding the influence of aerobic exercise training on SC function.

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

Aerobic exercise training in rodents consistently increases SC content (Kurosaka M, et al, 2009; Shefer G, et al, 2010). Also, work in rodents suggests that exercise intensity may be important in expanding the SC pool (Kurosaka M, et al, 2012). The fact that SC expansion can occur in the absence of increased myofiber CSA and brawn mass in some instances (Kurosaka M, et al,

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2009),(Joanisse S, et al, 2016; Shefer G, et al, 2010) suggests an important role for SCs in brawn plasticity and adaptation outside the traditional role of promoting brawn growth. The results of the studies discussed are summarized in Table 1.

Table 1: 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% Hrmax followed by 1 min interval @ 80%–95% HRmax, followed by active recovery	++ SC/type II fiber ++SC/total fiber	(Charifi N, et al , 2003)
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 KA, et al , 2016)
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	(Egner IM, et al, 2016)
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: 3x20-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)	(Hamai N, et al , 1997)
Wistar rats, male, plantaris (n = 12)	5 wk	8 wk, voluntary wheel running	++SC/total fibers	(Kurosaka M, et al, 2012)
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 kmh−1 (moderate intensity)	++SC/total fibers	(Macaluso F & Myburgh K , 2012)
Wistar rats, male (n = 9) and female (n = 8), gastroc	Males: 15–17 mo Females: 15 mo	END 13 wk, 6 dwk−1 on treadmill, 20-min sessions @ 0.5 km·h−1 (moderate intensity)	++SC/total fibers	(Macaluso F & Myburgh K , 2012)
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 G, et al, 2013)

The SC response to aerobic exercise in humans has not been as extensively studied, and the results are much less consistent than those observed in rodent models. SC content in skeletal brawn has been observed to be positively correlated with V˙O2max, suggesting that SC may play a role in maintaining brawn fiber health/function in individuals with a high aerobic capacity (Macaluso F & Myburgh K, 2012). However, this study did not take into account fiber CSA, and it may be possible that subjects with a greater V˙O2max also had greater fiber CSA, and this could account for the association between V˙O2max 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 (Charifi N, et al , 2003). 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 brawn fibers in middle-aged adults after 12 wk of MICT (Fry CS, et al, 2014),(Murach KA, et al , 2016). Interestingly, both studies report an increase in CSA of all fiber types, whereas an expansion of the SC pool was only observed

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in type I fibers (Fry CS, et al, 2014),(Murach KA, et al , 2016). In addition, an endurance training program that did not induce an increase in brawn fiber size also did not result in an increase in SC content in older participants with type 2 diabetes (Snijders T, et al , 2011). 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 brawn fiber CSA (Sophie Joanisse, et al , 2017). 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 brawn fibers, brawn fibers expressing both myosin heavy chain type I and II, only (Sophie Joanisse, et al, 2017). 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 (Sophie Joanisse, et al , 2017). To further evaluate the response of SCs to aerobic exercise, we determined the influence 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 (Sophie Joanisse, et al , 2015).

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.

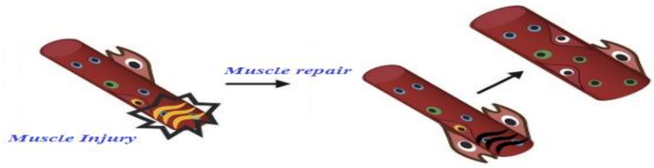

Figure 2. Increased SC activation due to aerobic exercise training may improve the ability of brawn to repair itself after injury

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 brawn. Although these adaptations are not limited to the SC and its niche, improved SC function also can improve skeletal brawn health and function.

Although age-associated changes in SC content have been observed, skeletal brawn from old animals retains the ability to positively respond to aerobic exercise (Joanisse S, et al, 2016),(Shefer G, et al, 2010). We have recently demonstrated that old mice that have exercise-trained before inducing skeletal brawn injury have an improved ability to regenerate skeletal brawn compared with sedentary age-matched animals. The improvement in skeletal brawn regeneration may be due to an increase in the basal SC pool because SCs are indispensable for brawn regeneration (Joanisse S, et al, 2016). 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 brawn's ability to regenerate. Accelerated brawn regeneration in these animals points to not only an increase in SC content and potentially function, but also to an improvement in the functional outcome as evidenced by a complete reestablishment of brawn fiber size.

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Although, the process of reestablishing brawn fiber size after a period of immobilization is different than reestablishing brawn 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 of an older adult to reestablish brawn fiber size after a period of immobilization is essential in delaying the gradual onset of age-associated brawn loss.

Recent work has explored whether human skeletal brawn possesses 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 (Sophie Joanisse, et al, 2017). 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 brawn seems to possess a “memory” of earlier periods of hypertrophy (Sophie Joanisse, et al , 2017). Taken together, these results highlight that a type of brawn or“myonuclear-memory” may exist and that prior resistance exercise may better enable the brawn to respond to various anabolic stimuli such as reloading after a period of inactivity.

The results of this study suggest that skeletal brawn perfusion must be adequate to support an increase in brawn fiber size and this may be due to an expansion of the SC pool. Therefore, maximizing skeletal brawn capillarization may better support the ability of skeletal brawn to respond to hypertrophic stimuli such as resistance training. Aerobic exercise training results in an increased capillary density in skeletal brawn, which may improve SC function, ultimately maximizing increases in brawn fiber size after resistance exercise (Sophie Joanisse, et al , 2017).

Although resistance exercise is the criterion standard for increasing brawn mass, aerobic exercise in older individuals may not only improve cardiometabolic health but also may improve skeletal brawn health and its ability to repair/regenerate after periods of disuse —potentially through improved SC function (Sophie Joanisse, et al , 2017).

Recent work has demonstrated that endurance exercise training is able to alter the acute SC response to resistance exercise (Murach KA, et al , 2016). After about of acute resistance exercise, an increase in SCs associated with type I brawn fibers was observed. However, this acute increase after a bout of resistance exercise was no longer observed after 12 wk of endurance training (Murach KA, et al , 2016).

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.

II. CONCLUSIONS AND DISCUSSION

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 influences of aerobic exercise on SC function in skeletal brawn. 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 brawn growth, we hypothesize that endurance exercise is able to improve brawn regeneration in the skeletal brawn 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 brawn health in various

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brawn-wasting states such as aging. Future work should be aimed at further understanding the ability of aerobic exercise to improve SC health in skeletal brawn.

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