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Current evidence that exercise can increase the number of adult stem cells

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Abstract The number of adult stem cells (ASCs) is very small, limiting the regenerative potential of tissues. One of the most studied ASCs in humans is the satellite cell (SC), which proliferates and increases pool size under exercise stress and muscle damage. This review examines the growth factor response to specific types of exercise to show the potential of exercise to stimulate not only SC self-renewal, but also other ASCs. We postulate that the same factors that stimulate a high proliferation of SCs in skeletal muscle after physical exercise should also stimulate the proliferation of ASCs in the tissue in which they reside, such as heart, bone, liver and etc. Regular exercise should be promoted, not only for disease prevention, but to maintain a high ASCs reserve and progenitor cell potential for rapid activation in response to future stressors and damage.

Keywords Niche · Self-renewal · Tissue repair · Satellite cell · Endurance training · Resistance training

Introduction

Adult stem cells (ASCs) also known as somatic stem cells, are undifferentiated cells found in many specialised tissues throughout the body after embryonic development. Their primary role is to maintain and repair the tissue in which they are resident. ASCs, have been identified in many tissues and organs, including skeletal muscle, bone, cartilage, skin, blood vessels, teeth, heart, liver, gut, peripheral blood, ovarian epithelium, testis and bone marrow. At least eight different types of ASCs have been isolated: haematopoietic stem cells, mammary stem cells, mesenchymal stem cells, endothelial stem cells, neural stem cell, olfactory ASCs, neural crest stem cells, testicular cells.

ASC pools reside in a specific area called a "stem cell niche", which has been described as a specialised local microenvironment that can be anatomically defined. It includes specific extracellular matrix and supporting cells and is enriched with growth modulating potential to signal stem cell self-renewal or differentiation (Greco and Guo 2010; Di Felice et al. 2009). During daily life a limited number of ASCs need to be activated in order to maintain the homeostasis of the tissue, while the remaining ASCs remain in a quiescent phase; both cells coexist in the same "stem cell zone" (Li and Clevers 2010). This system prevents stem cell exhaustion that will lead to a premature failure of the organ, and enables the regeneration of new tissue to proceed rapidly in the scenario of an injury. Many different aspects of ASCs, such as the physiological role that they play in daily tissue renewal and in regeneration after injury, have been, and are being investigated in scientific models. However, we maintain that there is one aspect of ASCs that seems to be neglected: is it possible to purposefully increase the number of resident ASCs to improve the potential capacity for future episodes of regeneration required in various organs? The myogenic progenitor cell niche, is an ideal system in which to address the question of whether the number of ASCs in the pool can be increased, not only in response to an acute stimulus, but also a chronic stimulus such as endurance and resistance training.

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In this review, molecular mechanisms regulating the satellite cell (SC) niche will be elucidated. Firstly, factors that stimulate self-renewal of SCs will be described and secondly, the effects of acute and chronic physical activity on these factors and hence on SC pool size will be discussed. Finally, we briefly outline new developments on the potential of physical activity to modify the balance of factors in various ASC niches in favour of an increase in the number of ASCs in the specific organs.

The SC niche

Skeletal muscle is a perfect example of a tissue that relies on life-long maintenance of its ASC pool (Mauro 1961). The regeneration abilities of adult skeletal muscle can be attributed almost exclusively to SCs (Hawke and Garry 2001), although other ASCs (such as pericytes, mesoangioblasts, side population cells, muscle-derived stem cells, haematopoietic cells, $CD133^{+}$ cells) are involved in skeletal muscle regeneration (Ten Broek et al. 2010; Schabort et al. 2009). The ability to stimulate myogenesis in human models in order to study muscle regeneration and to access tissue and SCs by muscle biopsy, makes the SC and its niche the most studied adult stem cell population in humans. In fact many studies have been published since 1976 when Schmalbruch and Hellhammer (1976) confirmed that SCs are present in human skeletal muscle at all ages. SC proliferation is influenced by many factors, which directly or indirectly affect the niche. These factors can be divided into three groups: local, mechanical and systemic factors. This division is convenient to explain the factors that modulate self-renewal of SCs more clearly, but in the live niche all these factors interact with each other.

Local factors

The SC niche is delineated by the sarcolemma of the myofibre and the basal membrane (Mauro 1961). The basal side of an SC expresses integrin $\alpha 7\beta 1$, which links the SC with laminin in the basal membrane. The apical side expresses M-cadherin, which attaches the SC to the adjacent myofibre. Different markers have been used to identify SCs in different functional phases (quiescent, activated, proliferating, differentiating), although to date there is no known unique marker of quiescent SCs and our understanding of how SC pool size is maintained is still expanding at both experimental and theoretical levels (Boldrin et al. 2010; Gnocchi et al. 2009).

Two different mechanisms have been proposed for self-renewal of SCs to maintain the same number of this type of ASCs in skeletal muscle: asymmetric and symmetric division (Ten Broek et al. 2010; Cossu and Tajbakhsh 2007; Kuang et al. 2008). During asymmetric division two daughter cells with unequal characteristics are generated: one destined to self-renew and the other to differentiate; in contrast, during symmetric division two identical daughter cells are generated—two self-renewing cells or two differentiating cells (Fig. 1). Although scientific results obtained from in vitro and in vivo animal models seem to indicate that the asymmetric division of SCs is the fundamental self-renewal mechanism (Shinin et al. 2006; Ten Broek et al. 2010), this can only explain the maintenance of SC number but cannot explain the expansion of the SC pool which is observed after an acute bout of strenuous exercise or after training (see "Effect of physical exercise on SC proliferation in humans" section). Therefore, in addition to the highly controlled studies in a cell culture environment, a further understanding of the mechanisms influencing proliferation in vivo is required.

SCs but not muscle fibres express caveolin-1 (Volonte et al. 2005), which maintains a quiescent state by inhibiting the sphingomyelin signaling cascade (Nagata et al. 2006). Sphingomyelin is located in the inner leaflet of the plasma membrane and it has been hypothesised that disruption of laminin–integrin adhesion regulates SC activation/proliferation through the activation of the sphingolipid signaling cascade initiated by the release of hepatocyte growth factor (HGF). Consequently, sphingolipid signaling initiates cell cycle entry but also activates the extracellular signal-regulated kinase/mitogen-activated protein kinase (ERK/MAPK) pathway which may down-regulate caveolin-1 in a feedback loop (Volonte et al. 2005). In fact, Nagata et al. (2006) demonstrated high levels of sphingosine-1-phosphate, after injury, and this may be the stimulus for ERK–MAPK activation, already shown by others to be involved in SC activation (Yablonka-Reuveni et al. 1999; Jones et al. 2005).

Mechanical factors

Recently, Tatsumi et al. (2010) reviewed the results obtained over the last few years by his research group, and by others, on the mechanical factors that trigger activation of SCs, describing a possible mechanism of activation in response to stretch: influx of calcium into the SC and the synthesis of nitric oxide (NO^{-}) radicals by a calcium-calmodulin-dependent mechanism (Tatsumi et al. 2009) that will then activate metallo proteinases (Yamada et al. 2006; 2008). These proteases induce the liberation of HGF from the extracellular matrix with subsequent binding of HGF to its receptor, c-met, which generates a signal for SC activation (Allen et al. 1995; Gal-Levi et al. 1998). HGF is the only growth factor with the established ability to stimulate specifically the activation of quiescent SCs in vitro and in vivo (Allen et al. 1995, 1997; Tatsumi et al. 1998) and its

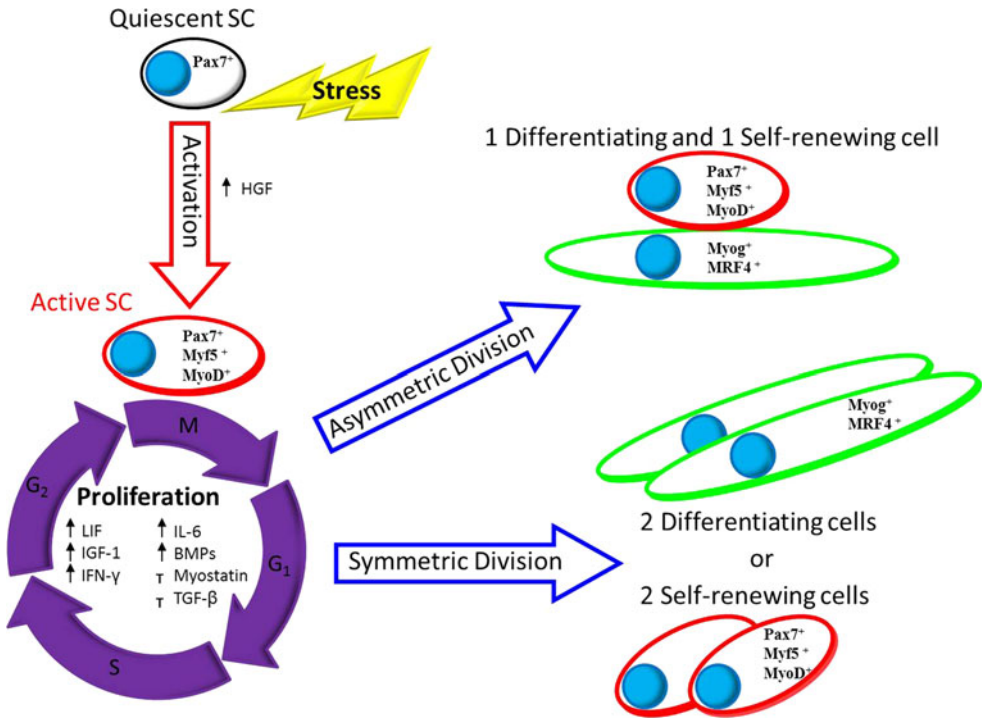

Fig. 1 Satellite cell (SC) cell cycle progression in response to stress. After a stress, such as exercise, quiescent SCs (Pax7 positive; *black circle*) become activated (*red circle*) and undergo proliferation (Pax7, Myf5 and MyoD positive), and ultimately some SCs differentiate (MRF4 and myogenin positive; *green circle*) to repair damaged muscle fibres while others return to quiescence. Different growth factors mediate specific phases of SC behaviour. Growth factors known to modulate SC activation (*HGF* hepatocyte growth factor) and proliferation (leukemia inhibitory factor *LIF*, insulin-like growth factor-1 *IGF-1*, interferon-gamma *IFN-γ*; interleukin-6 *IL-6*, bone morphogenetic proteins *BMPs*, transforming growth factors-beta *TGF-β*) are outlined. The two different mechanisms proposed for self-renewal of SCs (asymmetric and symmetric division) generate either two daughter cells with unequal characteristics (one destined to self-renew and the other to differentiate) during asymmetric division, or, during symmetric division two identical daughter cells are generated (two self-renewing cells or two differentiating cells). (Color figure online)

expression is increased in proportion to the degree of injury during the early proliferation phase of muscle regeneration (Tatsumi et al. 1998, 2001; Suzuki et al. 2002).

Recently it has been discovered that leukemia inhibitory factor (LIF), a member of the interleukin (IL)-6 superfamily known to influence SCs in vitro, is activated by mechanical strain. Broholm et al. (2011) reported an increase in LIF mRNA in response to resistance exercise and further reported that contracting human myotubes produce and secrete LIF in a PI3K-dependent manner, also inducing increased expression of the transcription factors: JunB and c-Myc. These are known to increase myoblast proliferation.

Systemic factors

Besides local and mechanical factors, systemic factors also have to be considered in order to understand the mechanisms underlying SC self-renewal, especially in light of the fact that in older individuals, despite low SC number, their intrinsic myogenic potential and self-renewal capacity remain unaltered (Shefer et al. 2006). In vitro and in vivo experiments have shown that the sera from young animals can restore Notch activation in old SCs restoring their capacity to proliferate and differentiate similarly to young cells; on the other hand old sera rapidly decreased the regenerative response of young SCs (Conboy et al. 2005; Carlson and Conboy 2007; Silva and Conboy 2008). Growth factors, controlling the up- and down regulation of muscle-specific genes, regulate SC behaviour (Charge and Rudnicki 2004). They are secreted by active immune cells, by muscle cells after injury, by the vascular system, by motor neurons and by the SC themselves (Cannon and St Pierre 1998; Hawke and Garry 2001).

Many growth factors have been studied over the last two decades to understand the roles they are playing in muscle regeneration, but overall, insulin-like growth factor-1 (IGF-1) seems to be the main growth factor that stimulates SC proliferation. Administration of IGF-1 to a rat primary SC culture altered the expression of myogenic regulatory factors promoting, first their proliferation, but also subsequently their differentiation (Allen and Boxhorn 1989). In transgenic mice over expressing IGF-1, Chakravarthy et al. (2000) observed high levels of SC proliferation associated

with the activation of the phosphatidylinositol 3-kinase/Akt (PI3K/Akt) signaling pathway, the up-regulation of cyclin-dependent kinase-2 kinase activity and the down-regulation of the cell-cycle inhibitor $p27^{kip1}$. In a feedback loop to control this process, the repression of IGF-1 signaling is also mediated through phosphorylation of Akt, but via its downstream effects on forkhead transcription factor FoxO1 (Machida et al. 2003).

As reviewed by Smith et al. (2008), studies that investigated muscle regeneration after injury provided important information on the role of cytokines in SC proliferation. Several cytokines have been proved to stimulate SC proliferation. For example, interferon-gamma (IFN-γ), an inflammatory cytokine which is released primarily by activated T lymphocytes and natural killer cells, is also released by macrophages and SCs in the injured environment (Cheng et al. 2008). The multi-functional cytokine, interleukin-6 (IL-6), is also released by skeletal muscle fibres and SCs (Serrano et al. 2008) in damaged muscle. IFN-γ and IL-6 activate the Janus kinase 1–signal transducer and activator of transcription (JAK–STAT) pathway (Serrano et al. 2008; Cheng et al. 2008), which is involved in SC proliferation and the prevention of premature differentiation (Sun et al. 2007; Trenerry et al. 2011b). Although bone morphogenetic proteins (BMPs) have been considered, in the past, as inhibitors of SC proliferation (Ten Broek et al. 2010), new evidence suggests that BMPs play a critical role in balancing proliferation and differentiation of SCs and their descendents (Friedrichs et al. 2011). In fact, BMP signals maintain SC descendants in a proliferating state thereby expanding cell numbers, while the daughter cells committed to differentiation up-regulate the expression of chordin, a BMP inhibitor, to support terminal differentiation and myotube formation (Friedrichs et al. 2011).

As underlined by Carlson and Conboy (2007), the self-renewal ability of young SC were negatively affected when exposed to the old sera. It can be hypothesised that SC proliferation is not simply influenced by a lack of proliferating factors but also the presence of inhibitory factors. These include chordin (as mentioned above) and also members of the transforming growth factor superfamily, such as myostatin and transforming growth factor beta 1 (TGF-β1). Myostatin may repress activation and self-renewal of SC by the induction of $p21^{kip}$ (McCroskery et al. 2003), which is an inhibitor of cyclin-dependent protein kinase and a cell cycle inhibitor (Jaumot et al. 1997). High levels of TGF-β1 (in serum and locally in the muscle) induce an excessive expression of CDK inhibitors in SCs, thereby interfering negatively with productive myogenic responses (Carlson et al. 2009). This process may work through the TGF-β receptor and P-Smad signaling in a threshold-dependant manner (Carlson et al. 2009). Different isoforms of TGF-β play a role in the balance between proliferation and differentiation (Schabort et al. 2011). A certain level of TGF-β I is required not only for a normal SC response but also to prevent immune disorders, inflammation and organ dysfunction (Dunker and Krieglstein 2000).

Effect of physical exercise on SC proliferation in humans

Since the first study on SC and exercise, undertaken in 1987 in rats, the connection between an acute bout of exercise that induces muscle damage (discernible at high magnification but not by light microscopy) and SC activation was clear (Darr and Schultz 1987). Exercise-induced activation of SCs can be attributed to specific types of exercise intervention, such as maximal eccentric contraction, that activates the muscle while it is stretched. This type of exercise has been shown to induce a large (over 80 %) increase in SC number 5–8 days after the exercise intervention (Crameri et al. 2004, 2007; O'Reilly et al. 2008). During maximal eccentric contraction the sarcomeres are extended to a range where there is little or no overlap of actin and myosin filaments despite a high external load, leading to severe ultrastructural damage with a very high percentage of hypercontracted myofibrils and necrotic fibre segments (Lauritzen et al. 2009). This type of exercise is frequently prescribed for the purpose of scientific investigation and is not undertaken as a common training method except in bodybuilders. Although downhill running and plyometric jumping, exercise methods commonly used by elite and recreational athletes, the eccentric component is not as extreme as during maximal eccentric resistance exercise and they induce much less severe ultrastructural damage (Macaluso et al. 2012). Moreover preliminary evidence from our laboratory indicated that the skeletal muscle fibre type characteristics influence SC count expansion after a downhill running intervention: a greater SC count expansion was observed in the participants with higher fast twitch fibre percentage (unpublished observations). Therefore, higher mechanical strain experienced in the fast twitch fibres, without extensive damage, was sufficient to activate SC proliferation.

Although, no studies have been conducted to evaluate the acute or chronic effect of stretching or flexibility training on SC behaviour in humans, a few studies in vitro and in animal models suggest that this type of exercise should be able to stimulate SC proliferation through NO-induced mechanisms (Soltow et al. 2010; Leiter and Anderson 2010; Turtikova et al. 2007; Wozniak and Anderson 2007). However, at the moment there is no evidence to support that flexibility exercises may increase

SC pool size in humans. The question therefore arises: is damaging exercise the only method to improve SC pool size?

Recently we pointed out the large variability in SC count between healthy young male individuals irrespective of recent exercise and without the presence of damage or aging-induced changes (Macaluso et al. 2011). Some of these subjects were sedentary and others led an active lifestyle, without training systematically. Those with higher maximal oxygen consumption (VO_2max) had a greater SC pool size. Furthermore, it seems clear from other research that the basal SC pool size makes a difference in the hypertrophic response to a resistance training intervention (Petrella et al. 2008). It is possible that systemic factors may influence basal SC pool size, even in young adults. We showed that the level of stress induced by daily life activities was higher in the individuals with low levels of physical fitness (low VO_2max) and was associated with a higher basal activation of p38-mitogen-activated protein kinase (MAPK), an intracellular stress signaling kinase which enhances the differentiation of SC, which may explain their reduced SC pool size (Macaluso et al. 2011). Higher levels of p38-MAPK activation have been observed in previous studies after a single bout of non-eccentric exercise in untrained humans (Yu et al. 2003) and rat (Lee et al. 2002) compared to trained controls. Together, these results indicate the behavior of SCs, and provide some insight into one of the mechanisms responsible for influencing the SC pool size, despite no acutely damaging events.

One of the adverse effects associated with aging is a progressive loss of muscle mass (loss of muscle fibres and reduced muscle fibre cross-sectional area) (Doherty 2003) and lower regenerative efficiency of muscle (Grounds 1998). Table 1 presents the results of different studies on elderly people showing that SC pool size can be enhanced after endurance (Charifi et al. 2003; Verney et al. 2008) or resistance exercise training (Verney et al. 2008; Verdijk et al. 2009; Mackey et al. 2007), although a few discrepancies are observed due to the type of exercise or subjects' pathology (Snijders et al. 2011). The self-renewal capacity of the SC, reported as the percentage increase in Pax7 or N-CAM positive cells after the training intervention, in elderly individuals in response to resistance training seems to be similar to that reported for younger individuals (Mackey et al. 2010; Kadi et al. 2004; Brooks et al. 2010). These results concur with the idea, developed from studies conducted in animal models and in vitro, that the myogenic potential of SCs remain unaltered with age, despite their lower number (Shefer et al. 2006), but growth factors in sera may influence the proliferation capacity either positively or negatively (Conboy et al. 2005; Carlson and Conboy 2007; Silva and Conboy 2008) with or without the mechanical strain imposed by exercise.

In light of the fact that the systemic growth factors play a key role in SC self-renewal promoting symmetrical division to expand the SC pool size after exercise intervention (Fig. 1), it is essential to study the level of these systemic factors in relation to the physical activity prescribed to the individuals. In other words, it is necessary to test a new hypothesis that any physical activity that will stress the full organism will alter the balance of specific growth factors that directly or indirectly increase the self-renewal capacity of the SCs in skeletal muscle. Since all organs are exposed to systemic stimuli, this hypothesis could also include ASCs in any tissue.

Human ASC classification

Stem cells can be divided into four groups on the basis of their origin: embryonic stem cells, fetal stem cells, umbilical stem cells and ASCs (Schabort et al. 2009). ASCs evolved from embryonic stem cells, and it is believed that they are embryonic stem cells that 'gave up in the race to differentiate', became quiescent and remained in cell niches of organs. Currently, more than 14 subtype of ASCs have been described (Schabort et al 2009): haematopoietic and mesenchymal stem cells residing in bone marrow; gut stem cells located in the crypts of Lieberhahn; liver stem cells; bone and cartilage stem cells (although their niches have not been defined yet); skin and hair stem cells; neuronal stem cells; pancreatic stem cells; retinal stem cells; cardiac stem cells; dental pulp stem cells and skeletal muscle SCs. Other potential muscle progenitors include side population cells and pericytes, whilst cardiovascular stem cells also include mesangioblasts and vascular endothelial progenitor cells.

Much research has been done on the regenerative potential of these ASCs in animal models of tissue damage. Similarly, their ability to trans-differentiate in vitro, has been investigated with a view to ex vivo cell expansion and manipulation for transplant. However, in humans mainly skeletal muscle and dermal ASCs have been studied extensively, but the latter without any emphasis on exercise.

The effects and the potential effect of growth factors released by exercise on ASC

Taking in account the potential capacity of exercise activity to affect the levels of specific growth factors and mitogens positively, we can speculate that physical

Table 1 Human studies investigating the SC pool expansion response to resistance exercise training in elderly and young sedentary male subjects

Age	Wks of training	Markers of SC	Baseline SC [c^+ fibres^{-1}]	Fiber type	Muscle	SC pool expansion	Reference
Elderly							
65–85	12	N-CAM	0.048 ± 0.003	II	Vast	↑ 75.0 %	Verdijk et al. (2009)
70–75	14	N-CAM	0.072 (0.056–0.089)	II	Delt	↑ 62.5 %	Verney et al. (2008)
70–81	12	N-CAM	0.11 ± 0.03	I and II	Vast	↑ 36.4 %	Mackey et al. (2007)
Young							
25 ± 3	12	N-CAM	0.12 ± 0.03†	I and II	Vast	↑ 30.0 % (ns)	Mackey et al. (2010)
20–32	12	N-CAM	0.14 ± 0.01†	I and II	Vast	↑ 31.4 %	Kadi et al. (2004)

Values are mean ± SD or mean (min-max)

c^+ Positive cells, *m* Myonucleus, *Vast vastus lateralis*, *Delt* deltoid, *ns* non significant

† Data obtained by the figure showed in the manuscript

exercise may stimulate many of these different adult stem cell niches promoting ASC proliferation. Increases in the resident pool size would allow the organs a higher potential to maintain and repair themselves. This section examines the current knowledge on the growth factors released during or after different types of exercise, mentioning mainly the in vivo studies in humans, since contradictory results have sometimes been described in animal studies. The focus is on those already reported to have effects on ASCs or with potential to affect ASCs. In view of the fact that the number of these studies is very limited for some of the growth factors, evidence obtained from in vitro studies on primary cell culture of ASCs, treated with different growth factors to stimulate self-renewal, will also be mentioned. The growth factors will be discussed starting from those that have been investigated more in humans to those with a high potential to increase the self-renewal of ASCs in humans, although at the moment only indirect evidence (mainly from in vitro studies) exists. Figure 2 presents a flow diagram of the different ASCs assessed in the studies quoted below.

Vascular endothelial growth factor (VEGF)

VEGF is released by ischemic tissue stimulating the expression of matrix metalloproteinase-9 in the bone marrow, which results in an increased bioavailability of soluble Kit-ligand cytokines (Wahl et al. 2008). These cytokines enhance the mobility of c-kit$^+$ stem cells (c-kit is the receptor for Kit-ligand cytokines), and play a role in translocating them to a vascular-enriched niche thus favouring proliferation and mobilisation to peripheral circulation (Wahl et al. 2008). Endurance exercise induces an increase in VEGF concentration in the circulation, which is sufficient to act as a trigger for release of haematopoietic and endothelial progenitor cells from the bone marrow (Mobius-Winkler et al. 2009). It is important to note that there is a time delay before significant mobilisation is observed. However, it is not only a response to an acute exercise bout, but regular exercise training also increases the numbers of circulating haematopoietic stem and progenitor cells mobilised at the end of the exercise session in healthy individuals, athletes, and in individuals with high risk for cardiovascular disease (Laufs et al. 2004; Steiner et al. 2005; Morici et al. 2005). Moreover it has been shown that individuals who exercise regularly and systematically (training), have a higher level of circulating haematopoietic stem and progenitor cells in the blood stream than sedentary individuals under resting conditions, which may suggest a positive adaptation to the recurrent stress of habitual exercise (Bonsignore et al. 2002).

Declining learning and memory functions have been associated with the attenuation of adult hippocampal neurogenesis. Animal studies suggest that VEGF is an important factor for stimulating adult neurogenesis, and in running animals elevated circulating levels of VEGF as well as a doubling neurogenesis capacity were observed (Cotman et al. 2007; Fabel et al. 2003). In particular, (Fabel et al. 2003) observed that mice with unlimited access to a running wheel presented an increase in proliferative activity of uncommitted neuronal progenitor cells and in accumulation of neuron-committed progenitors compared to the animals caged with a immobilized wheel. Moreover, the blockage of peripheral VEGF, by a single injection of adenovirus encoding for receptor of VEGF, induced a return of neurogenesis to baseline value in running animals but did not suppress neurogenesis below baseline in either running or non-running mice (Fabel et al. 2003) (see further information on neurogenesis in "Brain derived neurotrophic factor (BDNF)" section).

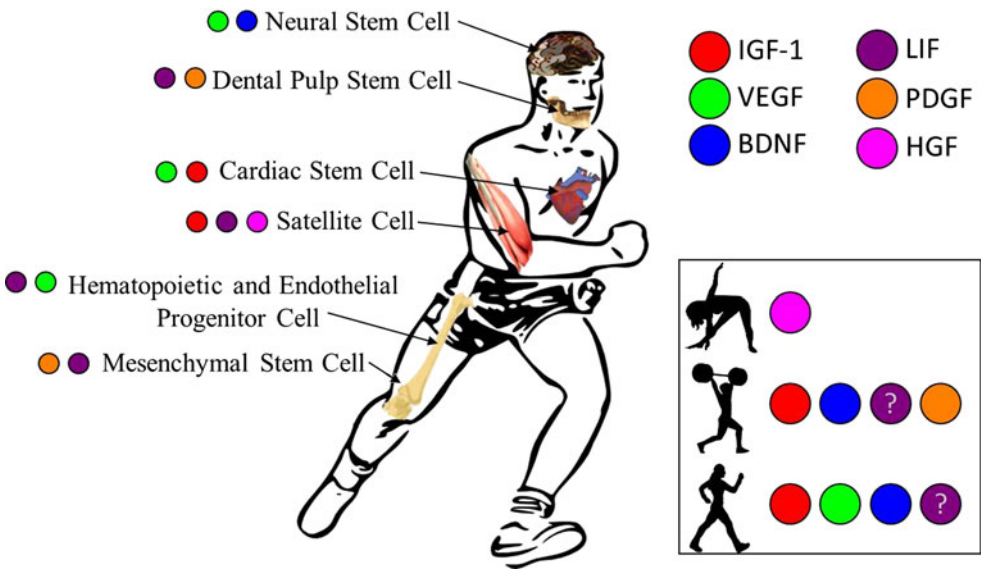

Fig. 2 Hypothetical and potential proliferative effects of growth factors, released by exercise, on specific ASCs. The *black square* indicates the growth factors released by different types of exercise (from the *top to the bottom*: flexibility, resistance and endurance exercise). Insulin-like growth factor-1 *IGF-1*, vascular endothelial growth factor *VEGF*, brain derived neurotrophic factor *BDNF*, leukemia inhibitory factor *LIF*, platelet-derived growth factor PDGF, hepatocyte growth factor *HGF*

IGF-I

IGF-1 regulates skeletal muscle growth by binding to its receptor localised in the sarcolemma, initiating the PI3K/Akt signaling cascade to promote protein synthesis. Circulating concentrations of IGF-1 are affected by many lifestyle factors, such as exercise and nutrition. Resistance exercise increases IGF-1 concentration in the blood stream (Kraemer et al. 1990) and in skeletal muscle (Bamman et al. 2001). Although, recent results seem to suggest that resistance exercise triggers IGF-1 production mainly in muscle cells themselves, without altering the plasma levels (Gundersen 2011), the production of IGF-1 in the liver is dependent on the exercise intensity (Rubin et al. 2005). This growth hormone-induced IGF-1 synthesis can change in relation to the fitness level of the subjects (Hasani-Ranjbar et al. 2011). IGF-1 is encoded by the *igf1* gene, which undergoes alternative splicing producing multiple isoforms (Barton et al. 2010). Three isoforms have been observed in humans and primates (Wallis 2009), while only two in most of the vertebrates (Shimatsu and Rotwein 1987). Human and rodent IGF-1A is virtually identical; human IGF-1C and rodent IGF-1B bear high homology, while human IGF-1B seems to be unique to primates. Each isoform seems to play a different role in tissue growth, in particular, IGF-1A has consistently increased muscle mass (Adams and McCue 1998; Barton 2006; Schertzer and Lynch 2006), whilst human IGF-1C (homologous to rodent IGF-1B) induces hypertrophy only in young animals in the growing phase, where there is an active SC pool (Barton 2006).

IGF-1 appears to have a major role in cardiac adaptation induced by endurance training, namely development of the "athlete's heart" (cardiomyocyte hypertrophy and neoangiogenesis). In fact, it has been hypothesised previously that endurance exercise may determine the formation of new cardiomyocytes through the activation of circulating and resident stem cells, the latter through the IGF-1/AkT pathway (Ellison et al. 2011). In transgenic mice it has been demonstrated that human IGF-1B causes cardiomyocyte proliferation, resulting in cardiomegaly (enlargement of heart) (Reiss et al. 1996). However, these studies are not definitive since an appropriate lineage-tracing model in humans is not currently possible and these observations are limited to the animal model (Beltrami et al. 2003). Nevertheless, human cardiac stem cells (c-kit^{+}) isolated from old patients, still present with the receptor for IGF-1 on their membranes. These cells had a young cell phenotype defined by long telomeres, high telomerase activity, high proliferation rate in vitro, and attenuated apoptosis (Ellison et al. 2011).

Brain derived neurotrophic factor (BDNF)

The term 'neuroplasticity' describes the ability of the brain and cental nervous system (CNS) to adapt to their in vivo environment, respond to injury and acquire information. These responses are mediated by neurotrophins, which stimulate neuronal cell survival, differentiation or growth. Among all neurotrophins, BDNF, produced by neuronal (brain and CNS) and non-neuronal tissues (vascular human endothelial cells, T lymphocytes, B lymphocytes, eosinophils, monocytes, pituitary gland and skeletal muscle fibres), seems to be the most affected by exercise (Knaepen et al. 2010). BDNF can cross the blood–brain barrier and the main cellular origin of BDNF in response to exercise seems to be the brain (estimated to contribute almost 75 % of circulating BDNF). Currently, it is not thought that

muscle-derived BDNF is released into the blood stream. It has been proved that the magnitude of increase in serum BDNF concentration during exercise is dependent on the intensity of the stress induced by exercise (Zoladz and Pilc 2010). Normalisation of the circulating BDNF concentration occurs quite quickly once exercise has stopped, indicating that BDNF enters tissue environments. These may be peripheral tissues or it may be transported back into the brain, once more crossing the blood–brain barrier, and potentially enhancing the health and plasticity of central neural progenitor cells. During endurance or resistance training programs that maintain the same exercise stimulus, the subjects became accustomed to the stress, a homeostatic condition developed again and the specific exercise no longer presented as a stressor of sufficient intensity to increase the level of BDNF in the serum (Zoladz and Pilc 2010).

LIF

Broholm and Pedersen (2010) suggested that the oscillation in Ca^{2+} concentration in skeletal muscle after 3 h of cycling at 60 % of VO_2max (concentric contraction) is responsible for inducing a fourfold increase in muscular LIF mRNA expression measured immediately after and that it declines gradually throughout the post-exercise period. Although the LIF mRNA levels were responsive to this intensity of aerobic exercise, LIF protein levels remained unaltered in the muscle of these subjects (Broholm et al. 2008). A longer duration of aerobic exercise, 6 h of running, also did not change LIF protein levels in the serum of ultra-endurance athletes (Donnikov et al. 2009). In a recent study the same authors showed that 20 min of heavy resistance exercise induced a much higher (about ninefold) increase in the expression of LIF mRNA in the *vastus lateralis* muscle than the aerobic exercise (Broholm and Pedersen 2010). The authors suggested that this difference was not caused by the exercise intensity but rather by the mechanical characteristics of the exercise (Broholm and Pedersen 2010), because of the eccentric phase possibly resulting in structural and ultrastructural damage, thus inducing the calcium influx into the fibre. However, it was observed that LIF protein level remain unaltered in the muscle after an acute bout of downhill running (Malm et al. 2004) which also exploits the eccentric component of muscle contraction, but perhaps not to a sufficient extent in the protocol used. These conflicting data, particularly the apparent lack of translation of LIF mRNA and no assessment of SC responses, lead us to report the in vitro evidence that LIF does indeed influence ASCs. In vitro LIF had a growth stimulating effect on human colony-forming units, both eosinophil and erythroid (Mathieu et al. 2011 Moreau et al. 1987). In contrast, no effect was observed on human neural stem cells treated with LIF (Sun et al. 2008), while rat neural precursor cells proliferated after treatment (Covey and Levison 2007).

Platelet-derived growth factor (PDGF)

PDGF, during early and later development stages, induces the proliferation and migration of mesenchymal stem cells (Hoch and Soriano 2003). Czarkowska-Paczek et al. (2006) reported an increase in PDGF and VEGF level in the circulation of young sportsmen immediately after a strenuous physical exercise session. Similarly, another research group reported a peak in circulating PDGF 3 h after resistance exercise, which also occurred in response to an acute bout after 12 weeks of resistance exercise (Trenerry et al. 2011a).

Endothelial growth factor (EGF)

EGF, seems to be dispensable for human skin-derived mesenchymal stem cell proliferation (Riekstina et al. 2008), while it may be used to induce hepatocyte differentiation in human mesenchymal-derived hepatocyte-like progenitor cells (Lysy et al. 2008).

Basic fibroblast growth factors (bFGF)

Treatment with LIF and bFGF promoted the proliferation of cultured spermatogonial stem cells isolated from human donors (Mirzapour et al. 2011).

Although some growth factors may contribute to ASC regulation, their effects may require additional mitogenic stimulation. For example, human pluripotent stem cells, isolated from dental pulp, required the presence of LIF, EGF and PDGF to ensure proliferation (Atari et al. 2011).

Conclusion

ASCs resident in tissue niches require a stimulus to become activated and to proceed to proliferation. That such stimuli can be provided by localised damage is without doubt. Whether or not exercise may be used to improve the repair process of damaged tissue induced by chronic disease, such as cardiovascular diseases, is currently under investigation. Exercise can, in fact, provide a physiological stimulus to enhance cell signaling to activate resident ASCs and to mobilise haematopoetic stem cells into circulation, with some evidence of myocardial regeneration in patients. The same concept has been used to prescribe exercise to obtain a rejuvenation effect in elderly people.

We propose the following new concept: physical exercise is an important factor to increase the number of ASCs

in various organs without any evidence of localised damage. The exercise stimulus primes the ASC niches and generates a naturally engineered "super hero" with the capacity to easily heal and regenerate body tissue.

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