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STATE-OF-THE-ART REVIEW

Understanding muscle regenerative decline with aging: new approaches to bring back youthfulness to aged stem cells

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Aging is characterized by the progressive dysfunction of most tissues and organs, which has been linked to the regenerative decline of their resident stem cells over time. Skeletal muscle provides a stark example of this decline. Its stem cells, also called satellite cells, sustain muscle regeneration throughout life, but at advanced age they fail for largely undefined reasons. Here, we discuss current understanding of the molecular processes regulating satellite cell maintenance throughout life and how age-related failure of these processes contributes to muscle aging. We also highlight the emerging field of rejuvenating biology to restore features of youthfulness in satellite cells, with the ultimate goal of slowing down or reversing the age-related decline in muscle regeneration.

Introduction

Stem cells are rare and specialized cells within a fully differentiated tissue that are essential for host-organ repair and renewal. In an adult organism, stem cell populations have the unique capacity both to self-renew and to generate progeny that differentiates to replace lost or damaged cells [1,2]. In most instances, stem cell properties and behavior are determined by the regenerative requirements of the host tissue: High-turnover tissues like the intestine or the hematopoietic system maintain active populations of stem- or progenitor-cell populations, whereas tissues like the skeletal muscle maintain most of their stem cell pool in a

Abbreviations
AMPK, 5′ AMP-activated protein kinase; DMD, Duchene muscle dystrophy; ECM, Extracellular matrix; FAP, Fibro-adipogenic progenitors; FGF, Fibroblast growth factor; GDF11, Growth differentiation factor 11; IL-33, Interleukin 33; JAK, Janus kinases; MAPK, Mitogen-activated protein kinase; NAD, Nicotinamide adenine dinucleotide; NFκB, Nuclear factor kappa-light-chain enhancer of activated B cells; ROS, Reactive oxygen species; STAT, Signal transducer and activator of transcription proteins; TGF, Transforming growth factor; TNF, Tumor necrosis factor; Treg, Regulatory T cell; WISP1, Wnt1-inducible signaling pathway protein 1.

quiescent state, activating it only upon injury [3]. The central role played by stem cells in tissue replacement throughout the human lifespan means that their functional decline often results in compromised organ maintenance and regeneration. At the same time, stem cell-based therapies hold immense potential for regenerative medicine to restore or rejuvenate tissues.

Aging is accompanied by a progressive decline in tissue function and increased vulnerability to disease. Current understanding of the aging process centers on the interplay of cell-intrinsic, intercellular communication and systemic dysregulations. In this context, the adult stem cell is simultaneously an important integrator of multiple age-related alterations and a key contributor to the progression of age-related tissue dysfunction [4,5].

Skeletal muscle harbors a population of quiescent stem cells, called satellite cells, that are essential for its extraordinary regenerative capacity. Upon injury, satellite cells exit quiescence and proliferate, giving rise to a population of committed progenitors capable of engaging the myogenic program to generate new myofibers and replace damaged tissue [6,7]. This remarkable regenerative capacity is greatly affected by the aging process and is associated with an age-related decline in satellite cell numbers and functionality. Moreover, skeletal muscle aging is characterized by a loss of mass and decline in muscle strength, a phenotype that broadly defines sarcopenia. Although the involvement of stem cells in the etiology of sarcopenia is debated [8], the maintenance of a healthy population of satellite cells or the exogenous delivery of a rejuvenated progenitor population to the aging muscle has the potential to correct acquired defects that give rise to age-related muscle wasting. Skeletal muscle is thus an attractive model for the study of stem cell and tissue aging, as well as a potential future target tissue for stem cell-based rejuvenating interventions.

In this review, we examine and discuss our current understanding of the determinants of satellite cell aging and their contribution to age-related loss of regenerative capacity in skeletal muscle. We also highlight recent advances in the field pointing to promising rejuvenating interventions that could help restore skeletal muscle regenerative capacity in the elderly. Finally, we discuss the potential of stem cell-based interventions as rejuvenating strategies to prevent or delay age-related loss of muscle mass and force.

How muscle stem cells age

Skeletal muscle aging is accompanied by a considerable reduction in the size of the satellite cell pool. The decline in satellite cell numbers occurs in the early stages of muscle aging and is likely due to changes affecting the niche and to cell-autonomous alterations that together disturb the proper balance between cell quiescence, proliferation, and apoptosis. Increased expression of myofiber-derived Fibroblast growth factor (FGF)2 in old muscles has been shown to bring satellite cells out of quiescence, causing spontaneous mitogenic activity that can contribute to the exhaustion of the satellite cell pool [9]. Additionally, FGF2 inhibits the expression of sprouty1, an intracellular inhibitor of the Extracellular signal-regulated kinase (ERK)/Mitogen-activated protein kinase (MAPK) signaling pathway, and mouse models with satellite cell-specific deletion of Sprouty1 have defects in the muscle stem cell pool. Sprouty1-null cycling satellite cells are impaired in their capacity to return to quiescence, succumbing instead to apoptosis [10]. Depletion of resident satellite cells after regenerative events in aged muscles also involves deficiencies in the aged niche microenvironment. A recent study revealed that an age-related decline in Notch activators in the niche provokes satellite cell death by mitotic catastrophe, impairing proliferative expansion of muscle stem cell in aged mice [11]. The idea that stem cell survival is an important factor in the maintenance of the satellite cell pool is further supported by the observations that old human satellite cells are susceptible to nuclear apoptosis [12] and that the promotion of anti-apoptotic pathways in aged satellite cells improves muscle regenerative capacity [13].

Although the satellite cell pool diminishes with age, a fraction of the satellite cells survives within the skeletal muscle until very old age. However, even when they are present, these satellite cells have functional defects that undermine their ability to sustain muscle regenerative capacity. The defects in satellite cell proliferative activity in response to regenerative pressure seen in the early stages of the aging process are exacerbated in very old (geriatric) mice. Whereas the early defects are driven by alterations in the environment, at advanced ages quiescent satellite cells are intrinsically changed and become pre-senescent, a state that leads to full senescence in response to regenerative pressure. As a consequence of these defects, old satellite cells show a reduced capacity for activation and expansion after injury and produce insufficient progeny to sustain muscle regeneration. Moreover, the progeny of muscle stem cells that overcome these limitations have a limited differentiation capacity, with poor myogenic potential and a tendency to commit to alternative lineages. The consequence of these defects in old skeletal muscle is an enhanced fibrotic response to injury.

These functional alterations have multiple underlying molecular causes, including altered signaling cues from the aging environment and intrinsic alterations in genomic integrity and metabolic regulation within the satellite cell (Fig. 1 [14–16]).

The aging environment

In a young organism, satellite cell function is tightly regulated by signals originating from the niche and the systemic environment. Alterations to the surrounding milieu have profound effects on satellite cell quiescence, differentiation, and self-renewal, and deterioration of the extracellular environment is one of the main factors determining age-related stem cell dysfunction [17].

The contribution of the aging environment to the decline in satellite cell function was clearly demonstrated by heterochronic tissue transplant studies, which revealed that the age of the host animal was a key determinant factor of the regenerative success of the transplant [18–20]. Subsequent studies employed heterochronic parabiosis, an experimental model involving the surgically pairing and fusion of the circulatory systems of two mice; this approach demonstrated that the regenerative capacity of the muscle is modulated by exposure to blood from an animal of a different age [21,22]. A recent study obtained similar results through direct blood exchange between a young mouse and an aged mouse, supporting the established idea that circulatory factors directly affect satellite cell aging [23].

Since these early discoveries, several signaling molecules, including niche-derived signaling cues and systemic factors, have been identified as mediators of the extrinsic effects of the aging environment on satellite cell function [17]. Changes in the myofiber, the most abundant source of niche signaling, have a significant impact on satellite cell activity: an age-related increase in Transforming growth factor (TGF)β and FGF signaling from the myofiber synergize with a decline in Dl-driven Notch signaling and a decreased deposition of the Extracellular matrix (ECM) protein fibronectin to disrupt satellite cell activity, contributing to impaired regenerative capacity at old age [9,24–28]. Changes in TGFβ and Notch activity contribute to an imbalance in satellite cell activation and differentiation cues [11,24,25], while increased FGF singling breaks satellite cell quiescence leading to stem cell loss [9]. The remaining satellite cells become unresponsive to FGF under regenerative pressure and fail to expand or self-renew [26], a defect that is exacerbated by defective fibronectin deposition in old muscles undergoing regeneration, and the consequent impairment in integrin signaling [27,28]. Aging also impairs the supportive function of fibro-adipogenic progenitors (FAPs), which fail to induce the matricellular protein Wnt1-inducible signaling pathway protein 1 (WISP1), required for satellite cell expansion and commitment [29].

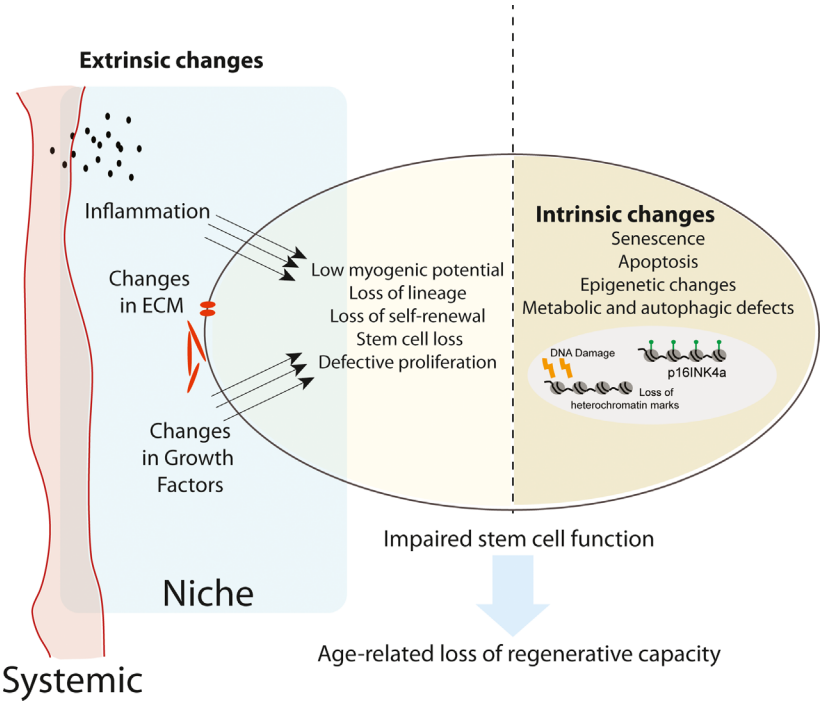

Fig. 1. Extrinsic and intrinsic drivers of satellite cell aging. Changes in niche-derived and systemic signaling molecules, along with intrinsic changes in the satellite cell, contribute to the functional impairments of aged muscle stem cells and the consequent defects in regenerative capacity of the aged skeletal muscle. Changes in the niche and systemic environment include alterations in the inflammatory signaling and changes in secreted and local growth factors that synergize with alterations in ECM signaling to impair satellite cell function. Intrinsic changes to the satellite cell include epigenetic changes and defects in autophagy, leading to increased senescence and apoptosis. These changes manifest in impaired satellite cell function characterized by loss of lineage commitment and low myogenic potential, defects in activation/proliferation that impair self-renewal capacity.

Heterochronic parabiosis has identified systemic factors as key regulators of muscle stem cell function. These include the unconventional Wnt-activating ligand complement component 1q, the TGFβ family member growth differentiation factor 11 (GDF11), and the hormone oxytocin [21,30–32]. Increased Wnt signaling driven by systemic factors promotes aberrant fibrogenic commitment in aged satellite cells, leading to a fibrotic response upon regenerative pressure [21]. Conversely, oxytocin and GDF11 have been identified as rejuvenating factors, decreased in the circulation of old animals, and offer a possible route to improving satellite cell function and muscle regenerative capacity. However, the effects of GDF11 on the muscle and its age-related changes are still debated, with contradictory reports highlighting the need for further investigation [33–37]. Another important circulatory factor affecting satellite cell function in sarcopenic muscles is the exercise-induced myokine apelin [38]. Apelin levels decrease with age, and studies in mice show that this has important consequences for healthspan [39]. A recent study revealed an association between apelin signaling and the beneficial effects of exercise, and also identified a positive effect on the regenerative capacity of aged muscle stem cells [38].

Age-related alterations in the immune environment have also emerged in recent years as important contributors to satellite cell impairments in old muscles. Regenerative success depends on a regulated immune response to muscle injury, involving multiple immune cell types and the coordination of pro-inflammatory and anti-inflammatory signaling [40,41]. Muscle regeneration is critically regulated by macrophages [42,43] and bone marrow transplant from old donors is sufficient to impair satellite cell function in young mice, reducing the number of Pax7+ cells and promoting fibrogenic conversion [44]. A potential mediator of these effects is an age-related increase in myeloid-derived TNFα signaling: TNFα-expressing macrophages are present in aged skeletal muscle, and old TNFα-null mice show improved satellite cell activation and myogenic commitment in response to injury [45]. Consistently with these observations, there is evidence that over-activation of the Nuclear factor kappa-light-chain enhancer of activated B cells (NFκB) pathway (an important TNFα target) in muscle of old mice is sufficient to disrupt satellite cell function and limit regenerative success [46]. In addition to TNFα-NFκB signaling, age-related impairments of satellite cell function are also linked to Janus kinases (JAK)/Signal transducer and activator of transcription proteins (STAT) signaling. Increased STAT3 activation in old satellite cells compromises symmetric expansion by promoting direct myogenic commitment and limits regenerative capacity [47]; however, the source of STAT-activating factors in the old muscles is still unknown. The age-related impairment of satellite cell function is thus likely to be the result of the over-activation of multiple inflammatory pathways acting synergistically. Muscle regenerative capacity is also thought to be limited by age-related impairments to Regulatory T cell (Treg) signaling: Interleukin 33 (IL-33)-dependent recruitment of Tregs during muscle regeneration is decreased in old mice, due to ineffective production of IL-33 by FAP-like cells, and these defects compromise muscle regenerative capacity [48]. Since one of the functions of Tregs during muscle regeneration is to coordinate the transition between pro-inflammatory and anti-inflammatory macrophage states, this age-related impairment may be an additional way in which chronic activation of inflammatory signaling compromises muscle regeneration in old animals.

Epigenetic changes and genomic stability

Satellite cell aging is accompanied by genome-wide epigenetic changes that translate abnormal signaling from the aged environment and a lifelong accumulation of molecular damage into altered gene expression programs. Comparative epigenomic analysis of young and old satellite cells has revealed complex changes with distinct consequences for quiescent and activated stem cells: While in quiescent satellite cells, an age-related increase in repressive chromatin marks can contribute to changes in the expression of genes involved in stem cell self-renewal and lineage commitment [49], in old activated satellite cells permissive chromatin states cause the aberrant induction of developmental pathways that impair stem cell function [50]. Understanding of the impact of these global changes at the level of individual gene expression is still limited; however, epigenetic changes are known to play an important role in the conversion of quiescent satellite cells to a pre-senescent state in geriatric mice [51]. Specific analysis of the p16INK4a locus in satellite cells isolated from geriatric muscles revealed the loss of ubiquitinated H2A, a chromatin repressive mark associated with the polycomb repressor complex 1 [51]. More recently, the transcriptional repressor Slug was also found to be downregulated in aged satellite cells, contributing to the derepression of the p16INK4a gene and the conversion of aged muscle stem cells to a pre-senescent state [52]. Future studies of global chromatin accessibility will likely reveal other changes to specific genomic loci that trigger age-related perturbations in

satellite cell function. It should also be remembered that epigenetic alterations can impact the health of neighboring cells in the satellite cell niche, indirectly contributing to muscle stem cell loss of function. Analysis of histone modifications in whole human skeletal muscle tissues found an age-associated increase in the active enhancer marker H3K27ac. In mouse models, this enhancer activation is associated with the upregulation of ECM genes during aging, contributing to a decline in myogenic capacity and increased fibrogenic conversion of aged satellite cells [53].

The accumulation of DNA damage is a potential source of genomic instability and an important contributor to global changes in the epigenome with aging [54,55]. The quiescent satellite cell combines a low risk of replication-induced DNA damage with highly efficient mechanisms of DNA repair [56]. However, satellite cells isolated from aged mice still have an elevated number of foci containing the DNA damage marker γH2AX [31]. Furthermore, whole-genome sequencing of human satellite cells isolated from individuals of different ages revealed an age-related increase in the somatic mutation burden [57], reinforcing the notion that loss of genomic integrity is an important factor in satellite cell aging. Knowledge remains limited about how age-related environmental changes converge to drive alterations in the satellite cell epigenetic landscape. A better understanding of these processes in aged satellite cells could provide important insights into how to expand the muscle stem cell healthspan.

Autophagic and metabolic defects

The lifelong accumulation of altered or damaged proteins is an important factor in age-related stem cell dysfunction, affecting multiple intracellular signaling pathways and ultimately driving genomic instability, senescence, and apoptosis [58]. Satellite cells, mostly quiescent throughout life, cannot eliminate toxic organelles and protein aggregates through cell division and are therefore particularly susceptible to proteostatic stress [59]. As a consequence, mechanisms of intracellular macromolecular clearance, such as autophagy, play a fundamental role in the maintenance of satellite cell quiescence [58]. Impairment of autophagy causes the accumulation of damaged mitochondria and the generation of high reactive oxygen species (ROS) levels, further propagating protein and DNA damage. During aging, a decline in autophagic flux and the consequent increase in ROS levels are directly linked to the epigenetic derepression of the p16INK4a locus in old satellite cells and their entry into senescence [60]. The observed decline in defective organelle clearance in aged quiescent satellite cells may be related to an oscillatory rewiring that affects the expression of autophagy genes [61].

Autophagy is also required for rapid energy mobilization to meet the metabolic demands of satellite cell activation [62]. The 5' AMP-activated protein kinase (AMPK) signaling pathway seems to play an important role in satellite cell fate decisions when autophagy is unable to meet the energy needs of activated cells. Ectopic activation of the AMPK/p27Kip1 pathway enhances autophagy and reduces markers of cell senescence in aged satellite cells, improving their transplantation potential [13]. The close interconnection between proteostatic and metabolic pathways is well illustrated by a recent study, showing that mitochondrial oxidative respiration is fundamental for the functional maintenance of satellite cells. A reduction in the cellular levels of the oxidized form of cellular nicotinamide adenine dinucleotide (NAD+) affects the normal mitochondrial protein response, ultimately leading to satellite cell senescence [63]. Mitochondrial DNA damage can also affect mitochondrial ultrastructure and cell bioenergetics. Levels of α-Klotho, a membrane-bound and circulating hormonal protein, are decreased in satellite cells derived from aged mice, and genetic knockdown of α-Klotho in young muscle stem cells provokes an aged phenotype, consisting of decreased mitochondrial bioenergetics activity, mitochondrial DNA damage, and increased senescence [64]. Replicative senescence of human satellite cells is also associated with the oxidation of glycolytic enzymes, resulting in impaired glucose metabolism and a metabolic shift of energy substrates in senescent muscle stem cells [65].

Interventions for satellite cell rejuvenation

Considering the combined role of extrinsic and intrinsic determinants on satellite cell aging, interventions that aim to restore the functionality of an aged muscle stem cell are likely to require combinatorial strategies that target age-dependent deregulations in niche signaling and cell-intrinsic alterations simultaneously [66,67]. The studies described in the previous chapter have contributed promising new approaches to the restoration of regenerative capacity in sarcopenic muscles (Fig. 2).

Ex vivo manipulations of aged satellite cells have proven to be effective strategies to reverse some of the intrinsic alterations limiting their regenerative potential (Fig. 2). These manipulations include genetic interventions to silence p16INK4a expression, thereby

restoring quiescence and regenerative capacity to the aged satellite cell [51,52]. Similarly, *ex vivo* pharmacological inhibition of p38 MAPK signaling decreases the expression of cell-cycle inhibitors, such as p16INK4a, and restores asymmetric division in satellite cells, contributing to enhanced regenerative potential of aged satellite cells in muscle transplantation experiments [26,68]. *In vivo*, local and systemic interventions have also shown promise in reversing age-related satellite cell defects (Fig. 2). For example, systemic pharmacological treatments to restore basal autophagy flux preserved quiescence and muscle stem cell regenerative capacity in old muscles [60]. Similarly, systemic delivery of oxytocin restores age-related regenerative capacity in old muscles [32], promoting satellite cell activation and proliferation, while systemic delivery of WISP1 during a regenerative event improves myogenic commitment and regenerative success [29]. Moreover, systemic delivery of exogenous α-Klotho improves muscle stem cell bioenergetics and improves regenerative capacity in aged animals [64]. Local delivery of fibronectin or β1-integrin activators also restores satellite cell responsiveness in old mice, enhancing regenerative capacity [27,28], while intramuscular injection of Wnt inhibitors restore the myogenic potential of old muscle stem cells [21].

Rejuvenating interventions able to target the whole organism have also a positive impact on satellite cell function during aging. Successful interventions include caloric restriction [69], rapamycin treatment [60], supplementation with the NAD+ precursor nicotinamide riboside [63], senescent cell ablation [70], and *in vivo* reprogramming [71]. These studies anticipate the existence of common hallmarks of aging associated with satellite cell loss of function in old animals, which can be considered common targets for intervention. Consistently, targeting chronic inflammation (a shared feature of several age-related pathologies) through systemic treatment with an inhibitor of NFκB activation improves myogenic function in aged satellite cells [46]. The regenerative capacity of old skeletal muscle is also improved by intramuscular or systemic supplementation with IL-33, which reestablishes the recruitment of Tregs into injured muscles [48]. Another

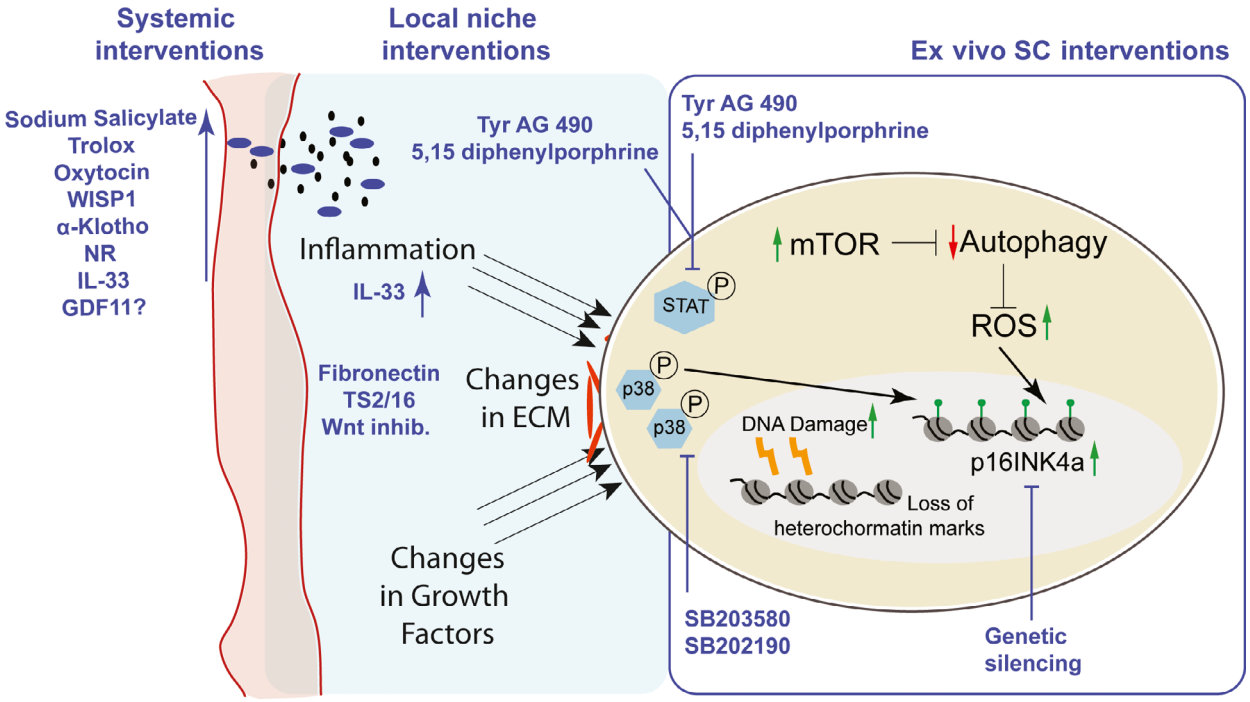

Fig. 2. Interventions for satellite cell rejuvenation. Rejuvenation of the regenerative capacity of aged skeletal muscle can be achieved through multiple interventions, including *ex vivo* rejuvenation of the satellite cell pool prior to transplantation, intramuscular delivery of agents that regulate niche signaling to improve satellite cell function, and systemic treatments that target satellite cell and niche-specific age-related alterations. *Ex vivo* interventions include inhibition of STAT and p38 or genetic repression of the p16INK4a locus. Niche-specific interventions, delivered through intramuscular injections, include inhibition of STAT and Wnt signaling, or supplementation of fibronectin, integrin signaling activators, or Il-33. Systemic interventions include modulators of inflammation, hormones, growth factors, and metabolic regulators targeting specific pathways affected in the aged skeletal muscle and/or the aged satellite cell.

related approach is the inhibition of JAK/STAT pathway: Isolated satellite cells treated *ex vivo* with JAK-STAT inhibitors show improved engraftment in transplantation experiments [47], and intramuscular delivery of STAT inhibitors during regeneration in old mice, also significantly improved muscle regenerative capacity [47]. However, inflammatory pathways are essential regulators of the muscle regenerative response, and pro-inflammatory signaling is essential for the activation phase of satellite cell function; therefore, caution is advised when using these interventions. For example, inhibition of pro-inflammatory mediators impairs the regenerative response in young animals [72], and Interleukin 6-driven STAT activation may be essential for myogenic commitment during regenerative events [73] and satellite cell-dependent muscle growth during hypertrophy [74].

Stem cell-based interventions in muscle aging

The use of stem cells as sources for tissue repair and renewal introduces their potential as rejuvenating interventions [66]. In addition to their primary role as agents of tissue regeneration after injury, satellite cells also contribute to the homeostatic maintenance of muscle fibers [75,76]. However, debate continues about the contribution of satellite cells to the pathogenesis of sarcopenia. Experiments involving lifelong ablation of satellite cells did not produce precocious or exacerbated signs of sarcopenia in sedentary mice [77], leading the authors to conclude that the loss of satellite cells that happens during aging does not contribute the development of sarcopenia. However, in young animals, exercise increases muscle mass through the combined effect on new fiber production in response to exercise-induced fiber damage and the hypertrophy of existing fibers, with both processes depending, at least in part, on satellite cell function [78,79]. It is thus possible that the wear and tear associated with daily activity in humans provides a signal for satellite cell dependent maintenance of muscle mass that was not captured in the ablation study in mice. Moreover, given the functional impairment of satellite cells that persist in the old skeletal muscle, these may be unable to contribute to fiber maintenance in old age. Supporting this view, a recent study showed that preserving functional satellite cells in the old skeletal muscle (through the overexpression of *spry1*) preserves muscle mass and force and attenuates sarcopenia development [80].

Nevertheless, the possible causal relationship of satellite cell loss of function to sarcopenia does not negate the potential of satellite cells as an intervention to restore sarcopenic muscle [81]. The use of healthy muscle stem cells to generate new muscle fibers, and/or to contribute new myonuclei to existing fibers, can be envisioned as a viable strategy to correct the defects that drive age-related muscle wasting, restoring muscle mass and force, and rejuvenating the sarcopenic muscle. In a proof-of-principle study supporting this idea, Hall *et al.* [82] showed that satellite cells transplanted into injured muscle of young mice (along with the associated muscle fiber) contribute to an increase in muscle mass and force that persists as the mice age. In this model, the lifelong persistence of the enhanced muscle mass results from an increase in myofiber numbers and a progressive myofiber hypertrophy, attributed to myonuclear accretion [82].

Satellite cells and other myogenic progenitor-cell types have been successfully used in young animals to ameliorate the effects of degenerative muscle diseases caused by genetic conditions [83]. However, there are no published reports of direct delivery of muscle progenitors into the muscles of old sarcopenic mice. Moreover, while these studies are promising, they have also brought to light several limitations with important implications for the use of cell therapy applied in aged skeletal muscle [66,81]. Successful engraftment with the current methodology used in preclinical settings to deliver progenitor cells to the muscle requires a concurrent injury, which is not a viable strategy for the treatment of sarcopenic muscles. Moreover, the systemic and local environment of chronic inflammation in old organisms presents a further obstacle to the success of these interventions [66] and would likely worsen survival, engraftment, and the myogenic potential of transplanted progenitors. The age-related inflammation and dysregulated immune environment have been consistently demonstrated to have a negative impact on satellite cell function, limiting their myogenic potential and regenerative capacity, contributing significantly to the development of sarcopenia [44–46]. In a model of Duchene muscular dystrophy (DMD), macrophages have been used to deliver pro-activating signals that enable expansion of myoblasts *in situ* before differentiation is initiated [84]. These experiments, together with the use of pharmacological interventions that promote myoblast migration [85], showed that it is possible to modulate muscle progenitor activity *in situ* to promote muscle repair. Successful cell therapies for sarcopenia will likely require the development of concurrent interventions to provide the pro-repair signals elicited by the injury and to promote myogenesis and the subsequent steps of muscle regeneration that are inhibited by the pro-inflammatory environment.

One possible source of such signals is exercise. In DMD models, the injury signal produced by exercise increases the success of muscle progenitor engraftment, removing the need for a concurrent injury induced by toxins or chemicals [86]. However, analysis of muscles subjected to overload induced by synergistic ablation suggests that that physical exercise is insufficient to induce myofiber hypertrophy in the old skeletal muscle [87], but can improve satellite cell responses in injury models [88]. Thus, it is likely that in aged animals, the ability of exercise to induce pro-growth and pro-repair signals is not fully functional. Recent work suggests that this is indeed the case, at least for the exerkine apelin [38]. The authors showed that young but not aged mice or humans increase apelin levels in response to exercise. Since low apelin levels are associated with sarcopenia and apelin signaling promotes fiber hypertrophy and satellite cell-mediated muscle repair [38], it is likely that the lack of such signals in aging would blunt the beneficial effects of exercise in promoting myoblast engraftment. It is therefore critical to identify other factors that mediate the beneficial effects of exercise and that could be used as co-adjuvants in skeletal muscle cell therapy in sarcopenia.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

PMC, JN, and PSV conceived and wrote the manuscript and prepared the figures.

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