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Muscle stem cell aging: identifying ways to induce tissue rejuvenation

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ABSTRACT

Aging is characterized by the functional and regenerative decline of tissues and organs. This regenerative decline is a consequence of the numerical and functional loss of adult stem cells, which are the corner stone of tissue homeostasis and repair. A palpable example of this decline is provided by skeletal muscle, a specialized tissue composed of postmitotic myofibers that contract to generate force. Skeletal muscle stem cells (satellite cells) are long-lived and support muscle regeneration throughout life, but at advanced age they fail for largely undefined reasons. Here, we discuss recent advances in the understanding of how satellite cells integrate diverse intrinsic and extrinsic processes to ensure optimal homeostatic function and how this integration is perturbed during aging, causing regenerative failure. With this increased understanding, it is now feasible to design and test interventions that delay satellite cell aging. We discuss the exciting new therapeutic potential of integrating and combining distinct anti-aging strategies for regenerative medicine.

1. Introduction

Aging is a complex biological process that affects all the cells of the body and results in a progressive decline in physiological integrity, ultimately leading to organismal death. Research on the biology of aging has made clear the multifactorial nature of the aging process, demonstrating the need to understand the mechanisms that bridge different hallmarks of aging and how their interconnectivity underlies core aging phenotypes (Kennedy et al., 2014).

Adult stem cells are undifferentiated, multipotent progenitor cells residing within a fully differentiated tissue. The physiological function of the stem cell is simple, yet fundamental to the maintenance of tissue homeostasis: stem cells sustain the replacement of somatic cells lost due to tissue injury, or homeostatic pressure from tissue renewal, while simultaneously replenishing the stem cell pool, thereby ensuring that the capacity for tissue homeostasis is maintained for future events of somatic cell loss. As a consequence of their physiological function, stem cells operate mostly in response to stress signals, and proper tissue repair and homeostasis maintenance require a high degree of coordination and integration between extracellular signals and intracellular pathways. Major alterations of tissue function resulting from dysregulations of this process include cancer, when the proliferative activity of stem cells is not properly restricted (Rossi et al., 2008), and tissue loss and fibrosis, when insufficient or inappropriate cell types are formed during the reparative response (Brack et al., 2007; Fry et al., 2015).

Stem cells integrate and manifest many of the biological determinants of aging. Indeed, loss of stem cell function and tissue repair capacity has been consistently identified as a hallmark of organismal aging (Kennedy et al., 2014; Lopez-Otin et al., 2013). A central question in aging research is therefore how stem cells integrate the multiple determinants of age-related loss of repair capacity.

In this review, we discuss the satellite cell as an example of the integrated nature of the diverse biological processes underlying stem cell aging. We will highlight metabolic, proteostatic, genomic and epigenetic mechanisms used by stem cells to cope with the stress signals and examine how aging disrupts the integrity of these diverse mechanisms and their coordinated regulation. We conclude with a perspective on emerging strategies for stem cell rejuvenation, discussing the potential of their combined application to reverse the process of stem cell aging.

2. Biological determinants of satellite cell aging

Skeletal muscle provides a paradigm of tissue aging, involving an age-related decline in tissue function, a phenotype that defines sarcopenia, and a progressive impairment in regenerative capacity at old age, extensively studied to explore the process of stem cell aging. Skeletal

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muscle stem cells are called satellite cells due to their anatomical location adjacent to the muscle fiber, beneath the basal lamina. This stem cell population, characterized by the expression of the paired box transcription factor Pax7, is established early in development and remains mostly quiescent throughout life (Gros et al., 2005; Relaix et al., 2006). Satellite cells are readily activated by injury or stress signals to engage a myogenic program and are essential for skeletal muscle regeneration (Fry et al., 2015; Relaix and Zammit, 2012).

Aging impairs satellite cell function. First, age-related changes in the systemic and local environment diminish the capacity to regulate satellite cells during a regenerative event, thereby compromising activation, proliferation and differentiation, and leading to inefficient repair of the old skeletal muscle (Chakkalakal and Brack, 2012). Second, quiescent satellite cells undergo an intrinsic aging process, manifesting as alterations in stem cell intracellular pathways that render the cells incapable of producing appropriate cellular responses to regenerative cues from the environment (Sousa-Victor et al., 2018).

Research over the past fifteen years has begun to decipher the molecular underpinnings of satellite cell aging, including intercellular communication factors and dysregulated intracellular mechanisms during aging that synergistically contribute to satellite cell aging (Fig. 1). These studies are revealing a landscape of interconnectivity and hierarchical relations among the multiple determinants of satellite cells aging.

2.1. Environmental signaling and inflammation

Aging has a profound effect on the molecular composition of the systemic and local milieux that regulate satellite cell function. Niche-specific alterations identified in the old skeletal muscle include elevated growth–factor signaling associated with FGF and TGFβ ligands, decreased expression of the Notch ligand Delta, and reduced deposition of the extracellular matrix (ECM) protein fibronectin, collectively contributing to impaired satellite-cell function (Carlson et al., 2008; Chakkalakal et al., 2012; Conboy et al., 2003; Lukjanenko et al., 2016; Sousa-Victor et al., 2015). Increased TGFβ signaling synergizes with decreased Notch signaling to impair satellite-cell proliferative capacity (Carlson et al., 2008). Increased FGF signaling disrupts satellite-cell quiescence, resulting in a drop in satellite-cell number (Chakkalakal et al., 2012), and a remnant pool of FGF-unresponsive satellite cells that fail to self-renew. This failed self renewal is due to cell autonomous changes that increase p38-MAPK signaling, intrinsically compromising proliferative activity (Bernet et al., 2014; Cosgrove et al., 2014). Low responsiveness of satellite cells to FGF in old mice is also due to age-related alterations in adhesion between the satellite cell and the ECM, resulting in failure to induce fibronectin-dependent integrin signaling (Lukjanenko et al., 2016; Rozo et al., 2016). The intersections of these pathways provides a good example of how niche signaling alterations are integrated in the satellite cell through an intracellular signaling cascade that intrinsically alters satellite cell behavior over time. Synergizing with the alterations in the muscle local environment, a systemic increase in complement C1q promotes an increase in canonical Wnt signaling within the muscle (Naito et al., 2012), reported to affect satellite cell function in old mice by promoting aberrant fibrogenic commitment and leading to fibrosis (Brack et al., 2007). The effects of systemic environment in age-related muscle regeneration were further demonstrated by heterochronic parabiosis studies showing that several of the defects found in old muscle regenerative capacity can be reversed by exposure to a young systemic environment (Brack et al., 2007; Conboy et al., 2005; Sinha et al., 2014).

Systemic and local alterations in inflammatory signaling are a clear hallmark of tissue and organismal aging and are thought to be important drivers of age-related disease (Furman et al., 2019; Neves and Sousa-Victor, 2019), and to impact satellite cell activity. Increased NF-κB signaling in aged muscle fibers impairs satellite cell function (Oh et al., 2016), whereas JAK-STAT hyperactivation in old satellite cells promotes myogenic commitment at the expenses of symmetric expansion, leading to satellite cell loss (Price et al., 2014).

Immune cells are important integrators of inflammatory signaling, and age-related alterations in immune populations may contribute to the

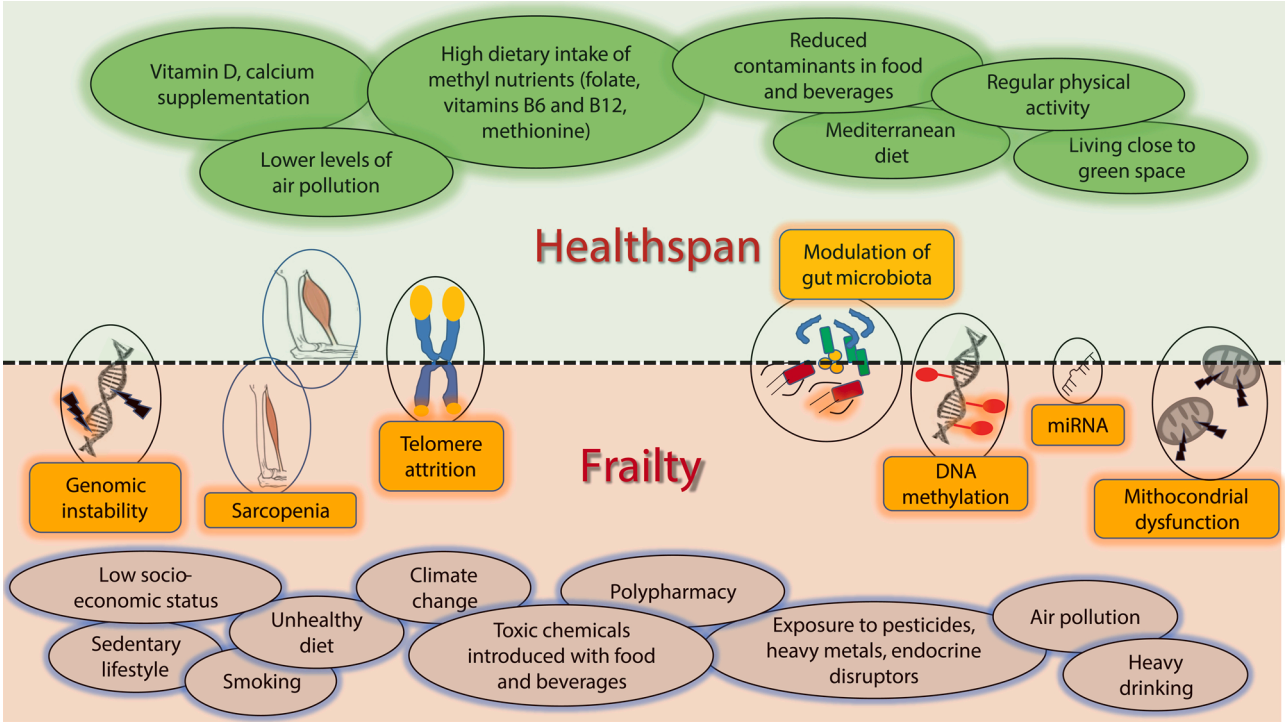

Fig. 1. Extrinsic and intrinsic drivers of satellite cell aging. Age-related alterations in the systemic environment, inflammatory factors derived from senescent cells and myeloid cells synergize with local and systemic alterations in growth factor signaling to drive satellite cell aging. Within the satellite cell, metabolic, proteostatic and stress pathways coordinately drive epigenetic alterations that intrinsically compromise satellite cell function.

disruption of inflammatory signaling in the old skeletal muscle. Reconstitution of the immune system of young mice with bone marrow-derived progenitors isolated from aged mice is sufficient to impair satellite cell function and skeletal muscle regeneration (Wang et al., 2019). At least two different immune cell populations may contribute to these effects. Macrophages in old skeletal muscle have elevated TNFa expression, which contributes to the disruption of satellite cell function (Wang et al., 2018). The other key population is regulatory T cells (Tregs); these cells are important coordinators of inflammatory signaling during muscle regeneration, and their recruitment is limited by loss of niche-derived IL-33 signaling in old muscle (Kuswanto et al., 2016).

2.2. Metabolism and proteostasis

The profound effect of caloric restriction in extending the health span of various stem cell compartments is a clear sign of the importance of metabolic pathways in process of stem cell aging. In skeletal muscle, metabolic processes can simultaneously determine satellite-cell state choices conditioned by bioenergetic availability (thus coordinating the satellite-cell response to tissue repair demands) and function as sources of cellular damage linked to metabolism byproducts, strongly influencing long-term proteostatic maintenance (Garcia-Prat et al., 2017; Ryall et al., 2015a).

Quiescent satellite cells seem to privilege fatty acid oxidation (FAO), only shifting towards glycolytic energetic processes under proliferative pressure (Ryall et al., 2015b). Recent analysis of the metabolic profiles of satellite cells in distinct cell states found this dynamic altered with aging: although mitochondrial numbers are similar in young and old quiescent satellite cells, older cells rely more heavily on glycolysis for ATP production (Pala et al., 2018). These observations suggest that mitochondrial impairment may be a source of satellite cell dysfunction during aging and are consistent with previous results showing that an age-related reduction in the oxidized form of cellular nicotinamide adenine dinucleotide (NAD+) impairs the adaptive mitochondrial unfolded protein response (UPRmt) pathway, resulting in a loss of mitochondrial homeostasis in old satellite cells (Zhang et al., 2016). Beyond the potential bioenergetic consequences, the accumulation of dysfunctional mitochondria is directly linked to higher levels of intracellular reactive oxygen species (ROS), which further propagate macromolecular damage in the aging satellite cell.

Metabolic and proteostatic pathways also intersect at the level of protein and organelle quality control mechanisms. Basal autophagy is a catabolic process that allows the rapid energy mobilization associated with the activation of satellite cells in response to injury (Tang and Rando, 2014); but autophagy also functions as a proteostatic mechanism, essential for the maintenance of organelle homeostasis in quiescent satellite cells. During aging, a decline in autophagic flux leads to the accumulation of dysfunctional mitochondria, with a consequent increase in ROS, and is directly linked to the induction of senescence in geriatric satellite cells (Garcia-Prat et al., 2016). The functional importance of mitochondrial homeostasis in the satellite cell aging process is further supported by the recent discovery that an age-related decline in α-Klotho, a membrane-bound and circulating hormonal protein, disrupts mitochondrial ultrastructure and increases mtDNA damage and ROS accumulation in old satellite cells, resulting in cellular senescence and impaired skeletal muscle regeneration (Sahu et al., 2018).

Many of the metabolic and proteostatic mechanisms maintaining cellular homeostasis are directly regulated by nutrient-sensing pathways, extensively linked to organismal health and life span. The mTOR and AMPK signaling pathways, in particular, play crucial antagonistic roles in the regulation of autophagy. In aged satellite cells, inhibition of mTORC1 can restore basal autophagy (Garcia-Prat et al., 2016) and partially rescue the age-related decline in satellite cell numbers (Haller et al., 2017). Conversely, AMPK signaling enhances autophagy and reduces markers of cell senescence in aged satellite cells (White et al., 2018).

2.3. Epigenetic alterations

The exposure of satellite cells to an altered tissue microenvironment, along with the intrinsic accumulation of damage caused by defects in protein quality control mechanisms and changes in metabolic pathways in the aging organism, ultimately converge in an altered epigenetic landscape in the old stem cell. Thus, epigenetic changes integrate many of the insults and alterations experienced by the organism during aging, constituting a central node of age-related stem cell dysfunction.

Comparative analysis of histone post-translational modifications in aged satellite cells has revealed changes associated with specific progenitor states. Genome-wide analysis of quiescent satellite cells showed that the repressive chromatin mark H3K27me3 increases with aging, possibly contributing to the self-renewal and lineage-commitment defects in the aged satellite cell population (Liu et al., 2013). This shift towards repressive chromatin states in old quiescent satellite cells contrasts with alterations associated with permissive chromatin states observed once the aged satellite cell is activated in response to injury (Schworer et al., 2016). More recently, single-cell transcriptome and DNA methylome profiling of old satellite cells pointed to an age-associated increase in transcriptional heterogeneity and a slight expansion of chromatin DNA methylation (Hernando-Herraez et al., 2019). Consistent with that finding, progenitor cell cultures generated from muscles of elderly individuals show a general increase in methylated DNA, with hypermethylated CpGs distributed throughout the genome (Bigot et al., 2015).

Although the mechanistic links between age-related changes in the global epigenetic landscape and alterations in satellite-cell behavior are still largely unknown, some site-specific changes in chromatin marks have already been shown to be directly responsible for impaired satellite-cell function. Aged quiescent satellite cells are found in a pre-senescent state caused by the epigenetic de-repression of the INK4a locus and consequent expression of the cyclin-dependent kinase inhibitor p16INK4a. In response to injury, p16INK4a-expressing satellite cells fail to activate and expand, entering into a full senescence state (Sousa-Victor et al., 2014). In the case of activated satellite cells, the reported age-related shift towards a permissive chromatin state is directly linked to the induction of the Hox9 gene and a consequent aberrant activation of developmental pathways that contribute to functional decline of aged satellite cells (Schworer et al., 2016).

A potential source of global epigenetic changes in old satellite cells is genomic instability derived from the intracellular accumulation of DNA damage (Behrens et al., 2014; Ermolaeva et al., 2018). Despite their low replication frequency and efficient mechanisms of DNA repair (Vahidi Ferdousi et al., 2014), there is evidence of an increased number of γH2AX foci -indicative of DNA damage- in aged quiescent mouse satellite cells (Sinha et al., 2014). One expected outcome of genomic instability is an increased frequency of somatic mutations. A recent study, analyzing satellite cells isolated from human subjects at different ages, showed evidence for an age-related increase of somatic mutation burden within the satellite cell population that propagates into skeletal muscle tissue, likely contributing to the age-related decline of skeletal muscle function (Franco et al., 2018). Thus, loss of genomic integrity is a potential biological determinant of satellite-cell aging and an example of how stem cell dysfunction can drive overall tissue aging. Important outstanding questions are how these genomic and epigenomic alterations develop in the stem cell throughout life and how the environmental changes that precede these intracellular alterations contribute to intrinsic dysfunctions.

Recent discoveries indicate that cell reprogramming strategies can reset accumulated epigenetic changes, reversing many of the dysfunctional intrinsic alterations that characterize aged stem cells (Kane and Sinclair, 2019). Cyclic induction of the four pluripotency reprogramming Yamanaka factors -Oct3/4, Sox2, Klf4 and c-Myc (OSKM)- can

partially restore satellite-cell numbers and regenerative capacity in progeroid mouse models, pointing to the possible reversible nature of the defects accumulated by satellite cells throughout life (Ocampo et al., 2016).

3. Interaction between intrinsic and extrinsic effects on satellite cell aging

From the studies described above, it is becoming evident that the pathways dysregulated in old satellite cells are interconnected and interdependent, creating a self-amplifying circuit that fuels the aging process.

A common theme among several studies of stem cell aging in muscle is the convergence of many of the age-related alterations on epigenetic changes that compromise satellite-cell function. This interplay is well illustrated by the finding that ROS is a fundamental epigenetic regulator of the senescence-driving gene p16INK4a in aging satellite cells (Garcia-Prat et al., 2016). mTOR and AMPK, key nutrient-sensing pathways, regulate autophagy, a process essential to meet the bioenergetic demands of the activated stem cell and to maintain proteostasis in quiescent satellite cells. The sequential dysregulation of these processes leads to the accumulation of dysfunctional mitochondria and excessive ROS in aged satellite cells, culminating in the senescent satellite-cell phenotype in old organisms. ROS-inducing mitochondrial dysfunctions can also arise from an increase in mtDNA damage or a loss of mitochondrial proteostasis caused by a decline in mtUPR, pointing to mitochondrial homeostasis as another integrator of satellite-cell aging, acting upstream of epigenetic regulation.

Dysregulated signaling pathways within the satellite-cell niche are also likely drivers of intrinsic satellite cell aging. p38-MAPK signaling is chronically activated in satellite cells from aged animals and has been identified as an important contributor to satellite-cell senescence (Bernet et al., 2014; Cosgrove et al., 2014). While there is evidence that MAPK signaling pathways can directly cooperate with polycomb proteins (Voncken et al., 2005), it is yet to be established whether this interaction contributes to the de-repression of the INK4a locus in satellite cells from geriatric mice (Sousa-Victor et al., 2014). Another key advance could come from the identification of the upstream signaling events that lead to the chronic activation of p38-MAPK signaling in old satellite cells. Likely candidates for the increase in p38-MAPK activity are increased cellular stress and inflammation in the aged environment. Moreover, niche-derived dysregulation of FGF-integrin signaling likely synergizes with this pathways to intrinsically compromise the ability of satellite cells to properly regulate their behavior in response to regenerative cues (Bernet et al., 2014; Rozo et al., 2016), providing another example of the interconnectivity among the different determinants of satellite-cell aging.

Thus, there is evidence of a sequential path leading to age-related loss of satellite-cell function, initiating with alterations to the signaling cues that modulate satellite cell function and progressively leading to the accumulation of defects in the satellite cell. In other stem cell populations it has been reported the existence of an epigenetic memory of inflammatory signaling experienced during regenerative events that render stem cells more responsive to a subsequent challenge (Naik et al., 2017). The persistent long-term exposure of old satellite cells to this type of signaling may be a mechanism for the progressive decline of satellite cell function in old organisms.

4. Stem cells and a path to rejuvenation

In the last decade, a number of rejuvenating interventions have emerged with the potential to extend human health span; these include systemic interventions with blood factors, metabolic manipulations, senescent cell ablation and, more recently, cellular reprograming (Mahmoudi et al., 2019). Notably, while the mechanisms underlying the rejuvenating effects of these various interventions are still poorly understood, a common denominator is the rejuvenation of stem cell function, highlighting the importance of reestablishing repair capacity as a path toward organ rejuvenation (Munoz-Canoves et al., 2019; Neves et al., 2017). Indeed, several of these interventions have been shown to improve muscle regenerative capacity (Brack et al., 2007; Cerletti et al., 2012; Chang et al., 2016; Conboy et al., 2005; Garcia-Prat et al., 2016; Ocampo et al., 2016; Zhang et al., 2016).

The rejuvenating potential of blood from young animals was firstly demonstrated in heterochronic parabiosis studies, and improved satellite-cell function and muscle regenerative capacity were among the first reported anti-aging effects (Brack et al., 2007; Conboy et al., 2005). These results were later reproduced by simple heterochronic blood exchanges, confirming that the rejuvenating effects were mediated by blood factors (Rebo et al., 2016). This collection of studies identified molecular targets that have already been validated in a pre-clinical setting as systemic rejuvenating interventions for the satellite cell. These include Wnt inhibitors (Brack et al., 2007), Oxytocin (Elabd et al., 2014) and GDF11 (Sinha et al., 2014). The effects of GDF11 on age-related muscle changes are still debated, with contradictory reports highlighting the need for further research (Egerman et al., 2015; Harper et al., 2016; Hinken et al., 2016; Poggioli et al., 2016; Schafer et al., 2016).

Among the most extensively studied rejuvenating interventions in model organisms are those targeting metabolic pathways, including dietary interventions (e.g. caloric restriction) and dietary restriction mimetics (e.g. rapamycin). Studies in organisms from *C. elegans* to *rhesus monkey*, show consistent benefits in organismal health span (Signer and Morrison, 2013). Short-term caloric restriction is sufficient to increase satellite cell frequency and function in old mice and to enhance the regenerative capacity of stem cells transplanted into recipient mice (Cerletti et al., 2012). Interestingly, the effects can be achieved by applying caloric restriction in either the donor or the recipient mouse, suggesting a synergistic effect of intrinsic satellite cell rejuvenation with systemic effects (Cerletti et al., 2012). The molecular mechanisms underlying the beneficial effects of caloric restriction on satellite cell function are not fully described; however, metabolic and proteostatic pathways are likely candidates for further investigation. Genetic manipulations to attenuate mTOR levels in old satellite cells prevent age-related stem cell loss in the skeletal muscle (Haller et al., 2017). In line with these observations, treatment of aged mice with the mTOR inhibitor, rapamycin, preserves satellite-cell function, averting satellite cell senescence by restoring autophagy (Garcia-Prat et al., 2016). Modulation of mitocondrial UPR by systemic treatment with the NAD^+ precursor nicotinamide riboside (NR) is yet another example of a metabolic intervention that improves heath span and rejuvenates satellite cells by preventing their entry into senescence (Zhang et al., 2016). The benefits of NR treatment may also include stem cell-intrinsic rejuvenating mechanisms (Zhang et al., 2016) and systemic effects (Elhassan et al., 2019), and these effects likely contribute in a combinatorial manner to improved repair capacity. Another rejuvenating intervention targeting a systemic pro-aging molecule is systemic supplementation with alpha-Klotho (Kuro-o et al., 1997), which improves regenerative capacity in aged muscle by regulating stem cell bioenergetics (Sahu et al., 2018).

Senescent-cell ablation and cellular reprograming emerged only in recent years, and these rejuvenating interventions are currently the focus of intense research efforts. Senescent-cell ablation promotes health span and increases life span in mice (Baker et al., 2016; Xu et al., 2018), and satellite cells are one of the target cells ameliorated by this intervention (Chang et al., 2016). Treatment of mice with the senolytic drug ABT263 promotes apoptosis of senescent cells and results in a rejuvenated satellite-cell pool in aged mice, with a reduction in the number of satellite cells with senescent markers. The authors suggest that the effects result from the elimination of senescent satellite cells present in old mice, thus averting the propagation of the senescence phenotype to the surviving satellite cells (Chang et al., 2016). Given the pleiotropic and

non-cell autonomous effects of senescent cells, in particular their ability to secrete pro-inflammatory cytokines, the preservation of satellite cells after senescent cell ablation is likely the result of intrinsic selection of fitter satellite cells in combination with attenuation of the deleterious pro-aging environment created by diverse senescent cells throughout the organism. While promising, senescent-cell ablation should be applied with caution and taking into consideration the physiological status of the organism; in young organisms, senescent cells play important roles in tissue repair (Demaria et al., 2014; Krizhanovsky et al., 2008); and senescent-cell ablation applied during an injury event may compromise regenerative capacity.

Partial reprograming is a rejuvenation intervention capable of erasing aging hallmarks at the cellular level (Ocampo et al., 2016). When applied in vivo, cyclical reprogramming promoted health span in progeria models and regenerative capacity in the skeletal muscle (Ocampo et al., 2016). Reprogramming has been validated in physiological aging models, but only in 12-month-old mice, in which satellite-cell muscle regenerative capacity is not yet impaired by the aging process; however, this intervention to yield similar benefits in older animals and may allay age–related loss of regenerative capacity. Nevertheless, it remains to be determined whether the satellite-cell pool is rejuvenated by the reprograming effects of the satellite cells themselves, by a systemic effect of general organismal rejuvenation, or by a combination of both. It would be interesting to assess rejuvenation of stem cell populations as a possible cellular mechanism of health span extension in animals receiving this intervention.

Another emerging rejuvenating intervention with the potential to allay age-related disease is the regulation of inflammation (Furman et al., 2019; Neves and Sousa-Victor, 2019). An expected outcome of reestablishing a regulated inflammatory response in old organisms is the optimization of tissue repair capacity, which could itself contribute to improved health span (Neves and Sousa-Victor, 2019). There is evidence that systemic interventions targeting inflammatory pathways chronically activated in old skeletal muscle rejuvenate satellite cells and improve repair capacity in the old muscle. These interventions include systemic treatment with an inhibitor of NFκB activation (Oh et al., 2016), systemic supplementation with IL-33 to reestablish the recruitment of Tregs into injured muscles (Kuswanto et al., 2016), and inhibition of the JAK/STAT pathway through intra muscular delivery of STAT inhibitors during regeneration in old mice (Price et al., 2014). Inflammatory pathways are essential regulators of muscle regeneration and growth and are required for the activation phase in satellite cells (Ho et al., 2017; Serrano et al., 2008; Tierney et al., 2014); therefore, interventions targeting inflammatory pathways should aim to modulate rather than to inhibit.

The potential of exercise as a rejuvenating intervention has also been noted, with beneficial effects observed beyond the muscle (Hawley et al., 2014; Leiter et al., 2019). Exercise conditioning can improve the satellite-cell response to injury in old mice (Joanisse et al., 2016). The mechanisms involved in exercise-mediated improvement of organismal health and satellite-cell function are just beginning to be understood and may share common molecular mediators. The exerkine apelin has recently been identified not only as a promoter of satellite-cell-mediated muscle repair (Vinel et al., 2018), but also as a promoter of other aspects of aged muscle health (Vinel et al., 2018) and organismal health span (Rai et al., 2017). Aging has also been found to impair the ability of exercise and injury to promote apelin expression (Vinel et al., 2018), suggesting that therapeutic exercise in the elderly may require additional interventions that can mimick the benefitial effects of exercise.

From the potential therapies discussed above, it is evident that the systemic administration of rejuvenating interventions likely benefits satellite-cell function through a combinatorial action on intrinsic satellite-cell pathways and on the stem cell-supporting environment. Thus, the development of combinatorial molecular interventions to improve muscle repair capacity would benefit from a deep understanding of the molecular mechanisms involved in intrinsic satellite-cell rejuvenation and also affecting other cell types that cooperate with stem cells to optimize tissue repair. Ex-vivo interventions have already identified some pathways that can be targeted in the isolated satellite cell to improve their function, including genetic interventions to silence p16INK4a expression (Sousa-Victor et al., 2014; Zhu et al., 2019) and pharmacological inhibition of p38-MAPK signaling (Bernet et al., 2014; Cosgrove et al., 2014) or of STAT signaling (Price et al., 2014). The next step to optimize rejuvenation would be to identify additional cellular targets for systemic interventions. Candidate strategies in aging animals include targeting immune cells to avert the detrimental effects of chronic inflammation (Neves and Sousa-Victor, 2019). Tregs have already been identified as targets for IL-33 therapy, and other molecular effectors will need to be uncovered. Likely candidates are anti-geronic factors that target macrophages and promote repair (Neves et al., 2016; Sousa-Victor et al., 2019), and their potential in the rejuvenation of muscle repair capacity should be investigated.

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