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Review

Changes in Communication between Muscle Stem Cells and their Environment with Aging

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Abstract. Aging is associated with both muscle weakness and a loss of muscle mass, contributing towards overall frailty in the elderly. Aging skeletal muscle is also characterised by a decreasing efficiency in repair and regeneration, together with a decline in the number of adult stem cells. Commensurate with this are general changes in whole body endocrine signalling, in local muscle secretory environment, as well as in intrinsic properties of the stem cells themselves. The present review discusses the various mechanisms that may be implicated in these age-associated changes, focusing on aspects of cell-cell communication and long-distance signalling factors, such as levels of circulating growth hormone, IL-6, IGF1, sex hormones, and inflammatory cytokines. Changes in the local environment are also discussed, implicating IL-6, IL-4, FGF-2, as well as other myokines, and processes that lead to thickening of the extra-cellular matrix. These factors, involved primarily in communication, can also modulate the intrinsic properties of muscle stem cells, including reduced DNA accessibility and repression of specific genes by methylation. Finally we discuss the decrease in the stem cell pool, particularly the failure of elderly myoblasts to re-quiesce after activation, and the consequences of all these changes on general muscle homeostasis.

Keywords: Aging, adult stem cells, muscles, skeletal, myoblasts, intercellular signaling peptides and proteins, homeostasis

INTRODUCTION

Over the last 60 years, work performed on animal models, chiefly mouse, rat, and avian, and on human samples, has revealed and explored the capacity of adult stem cells - also called somatic stem cells – to self-renew and to differentiate into unipotent progeny within their residing tissue [1], generally for the purpose of repair. Resident stem cell populations have now been described in most tissues, including bone marrow [2], blood vessels [3], peripheral blood [4], skin [5], teeth [6], gut [7], liver [8], heart [9], brain [10] and skeletal muscle [11]. Once body growth has stopped and adulthood is reached, most of these stem cells become quiescent, and will only be activated for tissue turnover. Although this turnover can be very active as in circulating blood or gut epithelium in other tissues such as liver the stem cells usually remain unsolicited as hepatic damage rarely occurs in healthy adults [8]. Despite this heterogeneity, a decline in number and properties is universally observed in aged stem cells, a phenomenon which alters the maintenance of tissue homeostasis with aging. In aged skeletal muscle, a tissue with low turnover, this decline in the adult stem

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cell (also called satellite cell), which is responsible for muscle repair [12], is associated with muscle atrophy and muscle weakness [13–15], although their depletion in the mouse has differential effects depending on the muscle [12].

Muscle stem cells or satellite cells are localized beneath the basal lamina, peripheral to the muscle fibers [11], and express Pax7 [16] and Notch3 [17]. After muscle injury, satellite cells are driven out of their quiescent state, and start to proliferate. Most of the activated satellite cells rapidly co-express MyoD or Myf5 [16, 18]. The proliferating satellite cells - also called myogenic precursor cells or myoblasts - expand under the control of Notch3 [17] and Notch1/Hey1 pathways [19, 20]. They divide asymmetrically, with self-renewal of the stem cell pool being maintained by a minor population of myogenic precursor cells that down-regulate their expression of MyoD and Myf5 and return to a quiescent state [18, 21–23]. This asymmetrical division involves Numb, an antagonist of the Notch signalling pathway [19, 24]. Numb is asymmetrically localized during myoblast mitosis and it is the cell that has a high level of Numb that goes back to quiescence for self-renewal [19, 24–26]. After several rounds of proliferation, activated myoblasts decrease their expression levels of Pax7, Myf5 [16, 18] and Notch3 [17]. The Notch1 pathway is then repressed by Stra13 [20] through the CBF1 pathway [20, 27]. Simultaneously, the Wnt pathway is activated and promotes myoblast differentiation through β-catenin [28]. Myoblasts exit the cell cycle by expressing p57 [29], and then cyclin inhibitors - p21 and hypophosphorylated pRb [30–32] - together with higher levels MyoD followed by myogenin, a driver which triggers the expression of the differentiation genes [33, 34]. The myoblasts consequently undergo differentiation into myocytes, and fuse either with each other or with existing multi-nucleated myofibers in order to repair injured muscle [35, 36]. The differentiation and maturation process is regulated by MEF2, MEF3, and Mrf4 pathways [37–39], while other factors, such as Myomaker, are involved in fusion [40]. Muscle precursor cell proliferation, fusion and differentiation are tightly orchestrated by circulating hormones (*e.g.* growth hormone [41], testosterone [42, 43] and thyroid hormones [44, 45]), growth factors (*e.g.* IGF system [41], FGF system [46–48], TGF-b [49, 50]), G-CSF [51], chemokines (*e.g.* interleukines [52–55], MPC [55, 56]) and other secreted components (*e.g.* vesicles [57, 58]) present in the muscle stem cell environment.

Aged human [59] or murine [60–62] muscle can regenerate and repair, although the rate of regeneration declines [60–62]. This slower regeneration can be explained by: (1) changes in the muscle stem cell environment (growth factors, growth hormones, inflammation, and extracellular matrix content); (2) a lowered responsiveness of progenitor cells to repair stimuli; and (3) decrease in the number of muscle stem cells with aging. Each of these factors may impact on muscle homeostasis and each may both participate to, and be affected by, age-associated changes in intercellular communication. The subsequent sections will describe the different roles that intercellular communication may play in muscle aging, from hormonal and other circulating endocrine factors to local paracrine and autocrine secretory environment of the stem cell niche that may also modify the intrinsic properties of the stem cells themselves.

HORMONAL AND OTHER CIRCULATING FACTORS: CHANGE IN ENDOCRINE COMMUNICATION WITH AGING

The decline in muscle regenerative capacity with age [63] has been partly attributed to a decline in extrinsic environmental cues (see Fig. 1). Levels of circulating hormones, such as testosterone or IL-6 or growth hormone (GH) or IGF-1, are low in serum samples of aged subjects [64–66].

The endocrine hypothalamic-pituitary axis is altered with aging, leading to changes in hormone secretion that can contribute to cognitive decline or depression. Epidemiological studies have also shown a correlation between the decrease in growth hormone (GH) secretion and sarcopenia as well as other signatures of aging (e.g. intra-abdominal adiposity, osteopenia, etc.) [67]. GH is a stress hormone produced by the hypothalamus. It plays a key role in muscle mass maintenance through life [66]. It acts on myoblasts through its receptor GHR and activates NFATc2 that in turn stimulates the expression and secretion of IL-4 [41, 68, 69] - IL-4 being critical for myoblast fusion [68, 69]. GH also stimulates IGF-1 secretion by both liver and muscle [66]. IGF-1 and its splice variants - IGF-1Ea and IGF-1Eb - modulate myoblast proliferation [70] and differentiation [71] through MAPK and ERK1/2 signalling [70]. The latter regulates myogenesis, for example by interacting with p38αβ MAPK and the asymmetric division and self-renewal of satellite cells [72].

These age-associated changes in the endocrine hypothalamic-pituitary axis can have further effects on the gonadotropic axis. Sex-steroid privation associated with age participates to, among other phenomena,

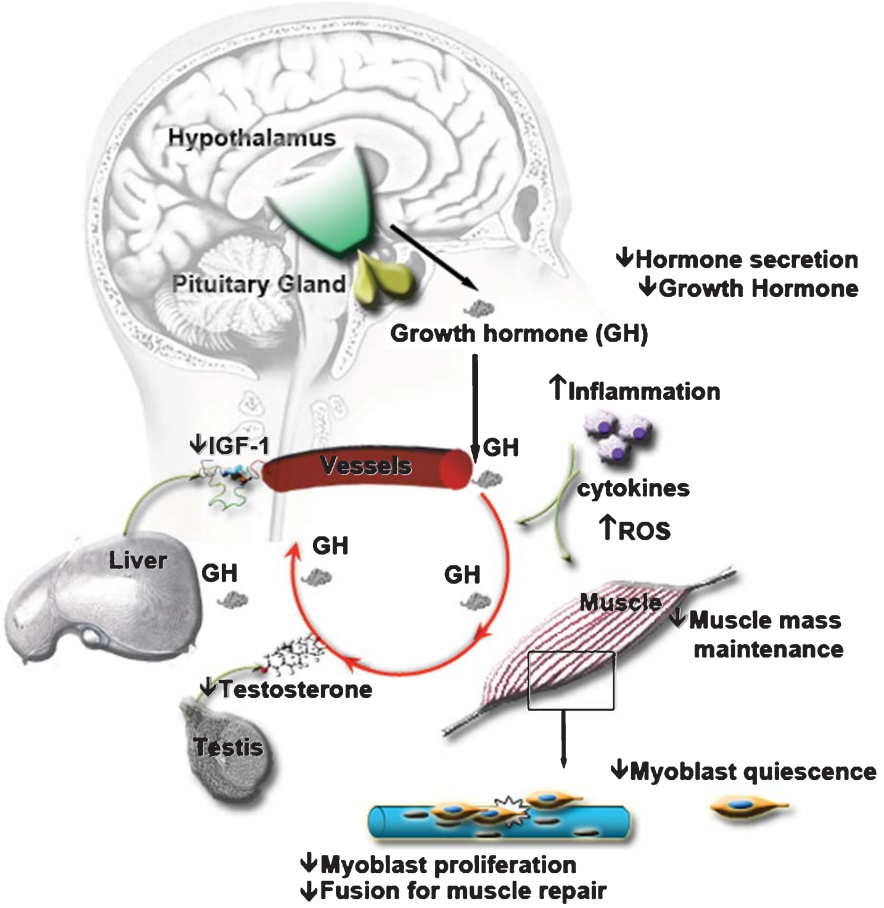

Fig. 1. Age alters serum composition and thereby affects intercellular communication at distance. The endocrine hypothalamic-pituitary axis is altered with aging, affecting the composition of circulating hormones in the serum. For instance, the secretion of growth hormone is decreased, leading to loss of muscle mass. In addition, the lower level of growth hormone will also stimulate less the secretion of IGF-1 - IGF-1 being involved in muscle mass maintenance and in the satellite cell myogenic program. The endocrine hypothalamic-gonadotropic axis is also affected, leading to a decrease of sex steroids such as Testosterone, another hormone involved in muscle mass maintenance. Similarly, a decrease in oestrogen can act on the myogenic program through IGF-1 signaling. The decrease in circulating hormones affects the capacity of the satellite cells to respond to muscle damage. Aging is also associated with an increase in inflammation. The cytokines secretion by aged inflammatory cells as well as their ROS production is modified and can also affect the capacity of the satellite cells to respond to muscle damage. The modification of the entire serum composition with aging has negative effects on muscle mass and on muscle regeneration capacity.

loss of muscle mass [67]. The sex-steroid testosterone, secreted by the testis, has been extensively studied in muscle, and can be considered as a double-sided blade, acting both on myoblast proliferation and differentiation. It acts on myoblasts through the androgen receptor localized in the nucleus [73] or through G protein-coupled receptors [74]. It promotes myoblast proliferation through protein kinase C (PKC) signaling [74] - for instance through nPKCδ and extracellular signal-regulated kinases 1 and 2 (ERK1/2) activation [75]. Once ERK1/2 is phosphorylated, it is accompanied by an increase in cyclin E and Cdk2 – which are involved in myoblast proliferation [76]. Testosterone acts also on myoblast differentiation via protein kinase A (PKA) signaling [74] - PKA being required for myoblast fusion [77, 78]. Interestingly, oestrogens act similarly on the myogenic program through IGF-1 signaling [79].

Aging is associated with an increase in low grade chronic and systemic inflammation, also called inflammaging [80]. Inflammaging could be due to microbial infection, cell debris, over-activated coagulation system, or an increase in cellular senescence with the associated changes in secretion [80]. This increased inflammation is generally attributed to a modified immune partner. Indeed, while young macrophages

have been shown to have a beneficial effect to clear muscle debris after injury and stimulate myogenesis [81–83], aged macrophages can release a higher level of osteopontin that inhibits the muscle regeneration process [84]. Not only macrophages are involved in the muscle regeneration process, but also neutrophils, lymphocytes, dendritic cells, etc. These inflammatory cells secrete numerous chemokines and cytokines, but little is known about the impact of aging on cytokine secretion [85]. In the literature, it is described that IL-6 serum level is decreasing during aging [65]. IL-6 originates from the inflammatory cells, but also from the skeletal muscle itself [86]. It has been shown to be an important regulator of muscle stem cells [53], as it activates janus kinase 2 (Jak2) that will in turn phosphorylate STAT3 [52]. Once STAT3 is phosphorylated, it homodimerizes and translocates to the nucleus to bind to the γ-interferon activation sequence [87] in the promoter regions of genes involved in myoblast proliferation such as c-myc [52]. IL-6 not only regulates myoblast proliferation, but also promotes myoblast differentiation through the p38 MAPK pathway [88]. A decrease in IL-6 serum level could thus impact muscle regeneration efficacy.

The tissues from which circulating factors originate, such as muscle, hypothalamus, gonads, and liver, become atrophic and less active with age [8, 66, 89]. This change in body composition and activity with aging can thus participate to the decrease in circulating hormones (see Fig. 1). Consequently, when muscle damage occurs in an aged person, satellite cells be less prone to activation and differentiation, leading to a less efficient repair. Ten years ago, Conboy et al. elegantly showed that muscle regeneration could be partly rescued in aged mice exposed to serum from young mice through a parabiosis system [90]. Similarly, hormones released during pregnancy rescued the muscle regenerative capacity of aged female mice [91]. When aged subjects are trained, a rejuvenating effect is observed on muscle. This benefit effect could probably be due to a decrease of the inflammation for instance, as observed in exercised patients affected by myositis [92, 93]. When aged muscle stem cells were engrafted into young mice [94], their capacities to proliferate and differentiate were partly restored. Together these data suggest that circulating agents, which can originate from different tissues, impinge on muscle regeneration efficiency. Aging affects both the size and function of each tissue and consequently tissue secretory capacity. This alters the composition of circulating serum effecting intercellular communication at distance.

SECRETORY ENVIRONMENT OF THE STEM CELL NICHE: CHANGE IN PARACRINE AND AUTOCRINE CELL-CELL COMMUNICATION WITH AGING

In addition to its classical role as a locomotive system, skeletal muscle has recently been shown to have a secretory activity. For instance, IL-6 [86] and musculin [95] have been identified to originate from and be secreted by skeletal muscle *in vivo*. *In vitro*, the secretome profile of C2C12 myotubes [55, 56], human myotubes [57] and rat muscle explants [96] suggest that muscle cells secrete numerous growth factors (*e.g.* follistatin like protein 1, IGF-2, TGF, etc) and cytokines. Secreted proteins - also named myokines [95] - may act in an autocrine/paracrine manner on neighboring muscle cells and contribute to muscle growth and regeneration. This local muscle secretome can be altered with aging. For instance, Chakkalakal et al. have shown that an increased secretion of FGF-2 by aged myofibers in mice inhibits sprouty1 expression in satellite cells, and consequently reduces their capacity to go back to quiescence and replenish the pool of the muscle stem cell [47]. The muscle secretome includes not only hormones, but also extracellular matrix components (ECM, *e.g.* TIMP2, fibronectin), miRNAs, and vesicles (exosomes and microvesicles) [57, 58, 97, 98]. Interestingly, exosomes originating from differentiated myocytes stimulate the myogenic program of proliferating myoblasts [58]. Myocyte exosomes contain miRNAs that inhibit Sirtuin expression, and thus stimulate the myoblast differentiation into myotubes [98]. A decrease in muscle mass with aging may thus reduce muscle secretory output. In a transcriptomic analysis performed on quadriceps muscle from young (15–24 years old) and elderly (72–80 years old) subjects, we indeed observed down-regulation of secretome markers in aged muscle [99]. However, little is known about the changes in the composition of the muscle secretome of aged muscle and further investigation is needed.

The local niche of muscle stem cells includes growth factors and cytokines secreted not only by the myofibers themselves, but also potentially by other cell types present within muscle, such as fibroblasts, endothelial or peri-endothelial cells [100, 101]. This local secretome can also be altered with aging (Fig. 2). For instance, fibroblasts present in aged skeletal muscle express a high level of TGF-β [101] – a growth factor that inhibits differentiation of myoblasts [102], and thus slows down the regeneration process. In addition, aging is described to be associated with an increase

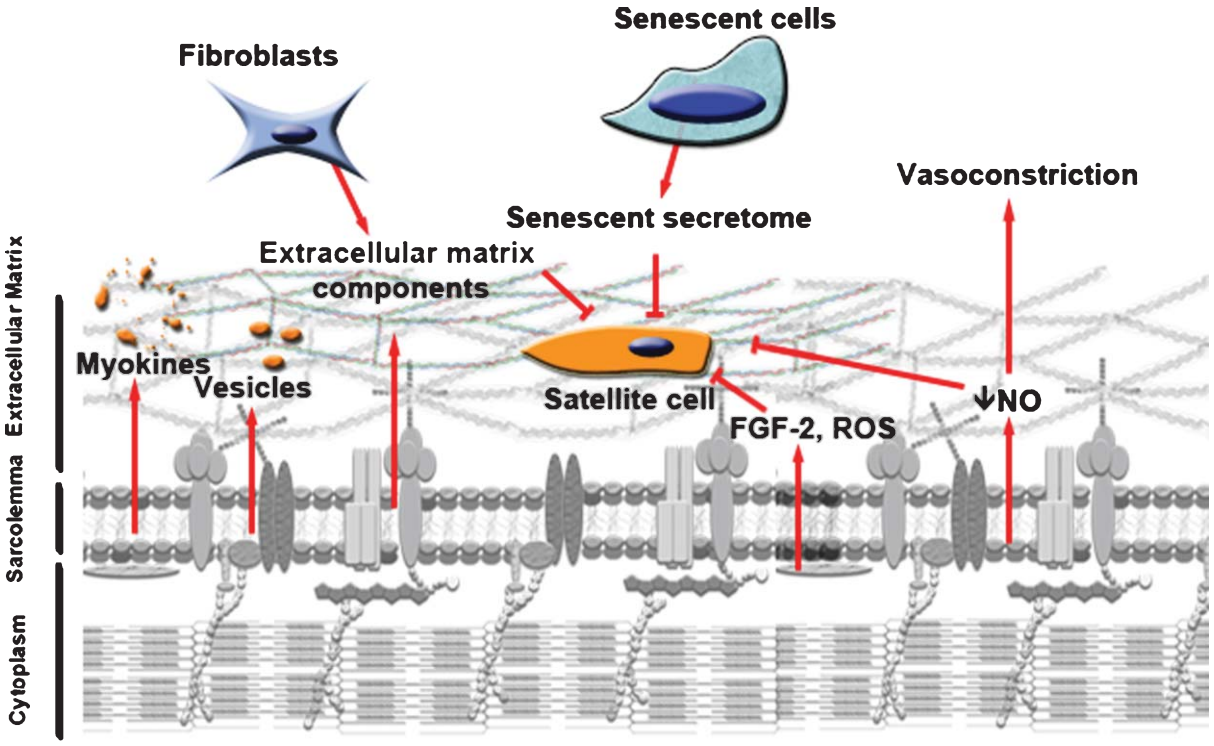

Fig. 2. Aging changes the microenvironment of the satellite cell. Decreased muscle mass can be accompanied by a decrease in myokines and vesicles secreted into the microenvironment of the satellite cells. Aged myofibers produce more ROS and FGF-2, factors that can change epigenetic marking of the satellite cells and shut down their myogenic program and their capacity to re-quiesce. They also release less NO into their environment, stimulating vasoconstriction which may inhibit serum tissue perfusion. Aged fibroblasts present in the muscle can secrete more fibrous proteins, thickening the ECM. In turn, this decreases the diffusion of growth factors toward the satellite cells and thus their responsiveness to muscle repair cues. Increase in senescent cells with age can secrete factors that inhibit tissue regeneration. The microenvironment of the satellite cells is thus altered and affects their capacity to respond to any muscle damage.

in senescent or pre-senescent cells in muscle and other tissue [103, 104]. During the last decade, the secretome of senescent cells from different tissues has been investigated and has been described to have an impact on the inflammatory response (by stimulating it in chronic obstructive pulmonary disease [105]) and to be instrumental in poor tissue regeneration (as observed in aged skin [106]). Altogether, these data suggest that the presence of senescent cells distinct from satellite cells within muscle tissue could alter these microenvironment of the satellite cells, and thus their behavior.

Muscle perfusion is decreased with aging [107], which may render myofibers and satellite cells less accessible to circulating hormones. This loss of perfusion may be maintained by the muscle loss itself. Indeed, sarcopenic muscle presents a disruption of the dystroglycan complex [108], leading to NOS-1 mislocalization, due to the link of NOS-1 to the dystrophin protein [109]. The mis-localization of NOS-1 results in decreased NO production, thereby diminishing muscle perfusion [110]. A second effect of decreased NO production is a reduction in satellite cell activation [111].

Aged skeletal muscle presents a thickening of the ECM and a general increase in fibrosis [112]. Even if muscle fibers can secrete collagens and other components of the ECM [57, 97], little is known about their role in ECM thickening. A recent study shows that fibroblasts present in aged rat muscles express a higher level of collagen IVa2 and laminin 2 – which may participate in the thickening of the ECM [101]. This increase in the ECM thickness can interfere with the muscle regeneration process by modifying myoblast activation, proliferation and migration [48, 113]. Finally, a thickened ECM may act as a partial barrier, reducing the accessibility of the satellite cells to circulating growth factors, as observed for smooth muscle cells [114], and thus impair satellite cell activation and differentiation during muscle repair.

Together, these data suggest that the changes in the secretory composition of the muscle stem cell's local niche with aging can slow down the regeneration process and decrease the replenishment of the pool of reserve cells. Repetitive iterations of this could contribute to the loss of muscle stem cells with aging.

CHANGE IN THE INTRINSIC PROPERTIES OF STEM CELLS WITH AGING

Exposure to a young environment by engraftment into young subjects or by parabiosis experiments only partly rescues the properties of aged satellite cells [90]. For instance their capacity to replenish the pool of reserve cells is not rescued (our unpublished data and [115]). These data suggest that some intrinsic properties of satellite cells are altered with aging and are not easily manipulated by external cues.

Intrinsic properties rely at least partly on DNA methylation, which may regulate gene expression in two ways [116]: (1) the accessibility of methylated enhancer regions to transcription factors is reduced, resulting in gene expression repression; (2) methyl-CpG-binding proteins bind to methylated DNA and alter the activity of histone deacetylases and methyltransferases. Consequently, local histones are hypermethylated, stabilizing the nucleosomes, so that DNA in methylated regions is tightly packed preventing binding of transcription factors or RNA polymerases. A recent study shows that histone methylation patterns are different between aged and young satellite cells in mice [117], and that the methylation profile can be modified by the presence of local growth factors such as FGF-2 [118]. The authors associated this histone methylation profile to a slower capacity of aged satellite cells to re-enter the cell cycle for aged satellite cells [117]. Interestingly, this study [117], as well as our own observations on culture of aged human muscle stem cells, show that once activated, aged satellite cells have a similar myogenic potential to young satellite cells. This indicates that muscle stem cells do not lose their differentiation potency with age, suggesting that the decrease with aging in the differentiation program during muscle regeneration is strongly related to changes in circulating factors.

DNA methylation has been shown to be increased in several tissues with aging, and the skeletal muscle is no exception [119, 120]. We have observed a higher level of DNA methylation in satellite cells of aged subjects (unpublished data). This hypermethylation could impact on the satellite cell fate and interfere with their capacity for self-renewal as observed in previously published studies (our data and [47, 115]). How DNA methylation is regulated with aging is not well known. Repeated stress over time can be one of the parameters implicated [121], involving for instance reactive oxygen species (ROS) [122]. Increased ROS production with age can be due to an increase in inflammation with aging [80] or to mitochondrial dysfunction in aged muscle [123, 124]. A decrease of circulating GH is also associated with a higher level of ROS and a lower level of anti-oxidants [125]. This overproduction of ROS could participate to increased DNA damage observed with aging [126]. Consequently, DNA methyltransferases (DNMT) are recruited to the DNA damage site, potentially inducing DNA silencing of the region nearby [127]. When we re-analyzed the transcriptome data available online (GSE9103), we indeed confirm a significant enrichment in the cellular response to oxidative stress in aged muscles (Fig. 3), suggesting a higher stress in aged muscle. ROS diffuse easily through membranes of fibers, thus potentially affecting DNA damage in neighboring satellite cells, and modifying their methylation status.

Factors discussed above - changes in the composition of circulating hormones in serum, as well as in the microenvironment - could also modify the epigenetic status of satellite cells and thus their behavior during regeneration, slowing satellite cell activation and decreasing their capacity to go back to quiescence

THE LOSS OF MUSCLE STEM CELLS WITH AGING AND ITS CONSEQUENCES ON MUSCLE HOMEOSTASIS

The number of muscle stem cells declines with age in mouse [13, 47, 90, 94] and humans [128, 129]. Although this loss can be caused by an increase in cell death, cellular senescence, or a deficiency in re-quiescence, apoptosis is rarely observed in aged murine and human muscle stem cells [94, 130, 131], suggesting that this cannot by itself explain the loss of muscle stem cells with aging. However, we cannot exclude the fact that apoptosis is a short punctual event that may be missed experimentally. Cellular senescence - also called replicative senescence - is defined as a phenomenon by which normal diploid cells cease to divide. It can be induced by telomere shortening that occurs during cell proliferation, and has been proposed to contribute to the loss of satellite cell function with aging [103]. However, shortened telomere length has not been reported in aged human satellite cells.

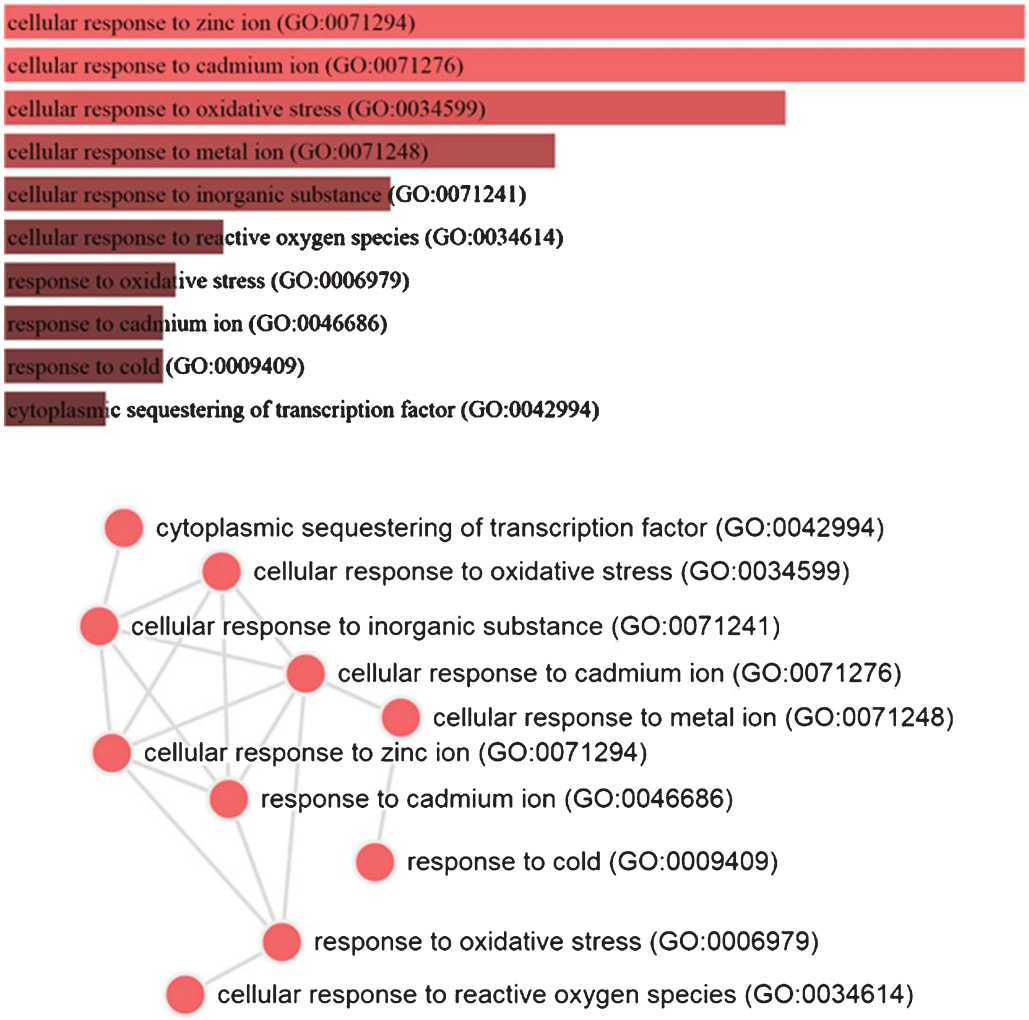

Fig. 3. Increase of oxidative stress response in aged muscles. For this analysis we retrieved the gene expression matrix of old and young muscles of sedentary subjects (series GSE9103 from the Gene Expression Omnibus [139]). We discarded three samples as they did not pass the quality control threshold. To identify differentially expressed genes we used the characteristic direction method [140] followed by gene set enrichment with Enrichr [141]. The top figure depicts a bar graph from the top 10 up-regulated GO Biological Processes (combined score: *p*-value multiplied by z-score) and the bottom figure a network of the same Processes, where each node represents the enriched term and the edges represent the gene content similarity between the nodes.

Furthermore, there may be insufficient activation and turnover of satellite cells to allow senescence to be a major contributor to stem cell decline. Satellite cells are rarely activated in healthy adult human or mouse, and once muscle growth is complete in young human adults [14], subsequent myonuclear turnover is slow, being estimated at 15 years during adulthood [132]. In mouse models, myofiber growth by the addition of new nuclei through satellite cell fusion is completed by 21 days postnatally [133], and there is little evidence to suggest significant turnover. As discussed earlier, the capacity to re-quiesce through the sprouty1 pathway is decreased in aged stem cells [47, 117]. Consequently, when satellite cells are activated for muscle repair in elderly subjects, they do not replenish the pool of reserve cells. This failure of re-quiescence is a likely contributor to stem cell population decline.

The decrease in the number of satellite cells with aging can affect muscle homeostasis by altering the ECM composition. Indeed, aged muscle depleted in satellite cells in a $Pax7^{CreER}$-DTA murine model shows an increase in fibrotic deposition [134], while fiber size was unaffected [135]. Resulting thickening of the ECM may increase myofiber fragility, and reduce the response of satellite cells to muscle damage, as discussed earlier. Therefore a loss of satellite cells could

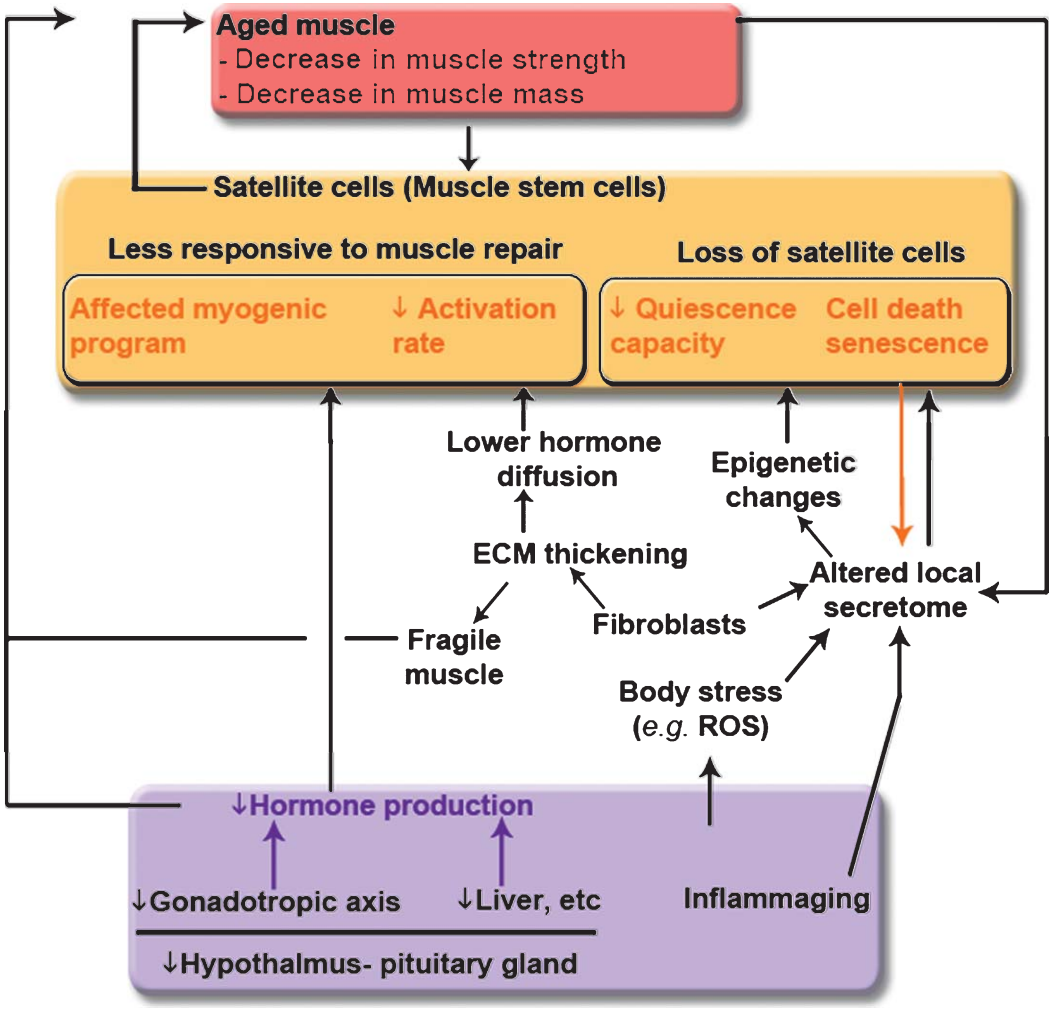

Fig. 4. Links between whole-body composition changes, the decline of muscle size and function, and the loss of muscle stem cells and their functions with aging. Modifications with age of the endocrine systems (hypothalamus-pituitary system, gonad glands, liver, etc.) affect the quantity and the content of circulating serum hormones and impact muscle mass maintenance (atrophy of the muscle fibers and decrease in the regenerative capacity of the muscle). Increased inflammation with age - also called inflammaging - affects whole body stress level and is accompanied by modification in secreted cytokine content. Increased oxidative stress of the muscle leads to DNA damage and epigenetic changes, and consequently affects the regenerative capacity of the muscle. The composition of the microenvironment of the satellite cells is affected with age, through the presence of aged fibroblasts, of senescent cells, and aged myofibers. These local changes contribute to the fragility of the myofibers and to a decrease in the regenerative potency.

impinge directly upon muscle homeostasis, and exacerbate muscle fragility with aging.

CONCLUSION

The interplay between whole-body tissue composition, the quantity and content of circulating serum hormones, and whole-body stress, such as ROS production, changes with age, and contributes to the decline in muscle mass and function (Fig. 4). Increased stress can act through epigenetic marking of satellite cells, changing their intrinsic properties with age - aged satellite cells show a decrease in their activation rate due to epigenetic changes. In addition, satellite cell number is decreased during aging, a loss that can contribute not only to a decreased regenerative capacity, but also to an increase in fibrotic deposition and ECM thickening. Increased muscle stiffness renders myofibers more fragile, requiring the activation of an already reduced and less responsive satellite cell population. Age-associated changes in the local signalling environment can affect the myogenic program causing a lower regeneration efficacy, a decrease in myonuclear

turnover, and a failure in replenishing the pool of reserve cells, further contributing to the loss of muscle mass. Changes in the whole system of intercellular communication – both at the whole-body scale and in muscle microenvironment – may thus act as a vicious circle to exacerbate sarcopenia as the body ages. It is noteworthy that most studies on muscle aging in the literature have been done on muscle stem cells, rather than myofibers, and thus emphasize the role of satellite cells in muscle mass maintenance. The effect of hormones and cytokines and more generally the effect of aging on myofibers is difficult to assess directly and should not be neglected. The myofibers themselves comprise the bulk of the muscle mass and are clearly a key part of the maintenance of their own mass with aging, as indicated by disequilibrium of protein synthesis and degradation or the expression of micropeptides such as myoregulin that have a key role in muscle performance [138].

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CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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