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The Impact of Ageing on Skeletal Muscle: Roles of Mitochondrial Dysregulation, Systemic Communication, and Exercise

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ABSTRACT

Ageing is a major risk factor for degenerative diseases, including sarcopenia, which is characterized by a progressive loss of skeletal muscle mass and function, frailty, and is associated with increased mortality. Skeletal muscle regeneration relies on muscle stem cells and efficient communication with cellular microenvironment. With ageing, skeletal muscle regenerative capacity declines, and sarcopenia results from complex, multitissue dysregulation involving mitochondrial dysfunction, immune ageing, chronic inflammation, senescence, extracellular matrix modification, disruption of neuromuscular junctions and muscle-specific vulnerability. This review summarizes current knowledge contributing to sarcopenia and inefficient muscle repair during ageing from cell-autonomous metabolic dysregulation to age-associated changes in the local and systemic cellular environment. We also explore recent insights into important role of exercise on muscle tissue health. Overall, emerging technologies, including human muscle atlases and spatial transcriptomics, together with exercise-based interventions, will help to identify of novel biomarkers and therapeutic targets to better prevent and treat sarcopenia.

1 | Introduction

Ageing drives the onset of most degenerative pathologies, which are marked by a progressive functional decline at the molecular, cellular, tissue, and organismal levels. The rapid growth of the elderly population in high-income countries is reshaping healthcare systems and exacerbating the burden of age-related diseases, and accordingly, the prevalence of physical performance limitations is expected to rise as societies age (Shreya et al. 2025) (Louie and Ward 2010). Sarcopenia, one of the major hallmark of ageing, is a reduction in skeletal muscle mass and function (Kerr et al. 2024). It negatively impacts force production but it is also a major hallmarks of frailty in elderly individuals and is strongly associated with increased mortality, particularly in chronic diseases (Papadopoulou 2020; J. Xu et al. 2022). Additionally, muscle fat deposition arises during ageing and is negatively associated to survival (Rahemi et al. 2015, Yoshiko et al. 2017, Ahn et al. 2021). Sarcopenia is primarily driven by biological ageing processes including impaired regenerative capacity, metabolic dysregulation and chronic low-grade inflammation. It is considered as pathological condition due to its impact on mobility, autonomy, and overall health (Distefano and Goodpaster 2018). Skeletal muscle is a plastic tissue able to grow under demand such as physical exercise. Skeletal muscle is able to regenerate thanks to the muscle stem cells, called satellite cells (SCs) (Relaix and Zammit 2012). Upon injury, SCs interact with cellular environment to ensure correct tissue repair (Rodríguez

et al. 2024). At homeostasis state, myogenic cells (myofibers and SCs) and surrounding cellular environment are impacted by ageing. Moreover, intrinsic defects of SCs, as well as modifications of extrinsic cues, and micro-environment impair regenerative ability of skeletal muscle. In this review, we describe how sarcopenia impacts muscle function and its capacity to regenerate after injury, with a focus on metabolic dysregulation. Then, we discuss the importance of systemic communication on muscle ageing and health. Finally, we highlight positive impact of exercise on muscle during ageing.

2 | Sarcopenia: The Age-Related Decline of Skeletal Muscle Mass and Function

Physiological changes associated with ageing lead to a progressive loss of skeletal muscle mass, with an estimated annual decline of 0.64%–0.70% in women and 0.80%–0.90% in men (Mitchell et al. 2012). Beyond the structural atrophy of skeletal muscle, age-related muscle loss profoundly contributes to the functional decline observed in the elderly (Wilkinson et al. 2018). Impairments in muscle function not only contribute to frailty but also that diminished muscle strength which is associated with a higher risk of mortality (Gale et al. 2007) (Newman et al. 2006).

A. Impact of ageing on skeletal muscle: global scale.

Dietary protein stimulates muscle protein synthesis (MPS), while insulin suppresses muscle protein breakdown (MPB). This balance is normally maintained an exercise is able to extend the duration of this anabolic response (Cuthbertson et al. 2006). However, physical inactivity rapidly leads to muscle loss by disrupting this balance and results is loss of muscle mass and atrophy (Breen et al. 2013). Age-related muscle loss arises from an imbalance between MPS and MPB though the exact environmental drivers are still under investigation. This disruption of muscle proteostasis is further aggravated by "anabolic resistance" to physical activity and nutritional intake stimuli, that normally promote muscle maintenance (Wilkinson et al. 2018). Older muscles have a blunted growth response to exercise training compared to young muscles (Brook et al. 2016). Older adults exhibit "insulin resistance of protein metabolism," meaning insulin is less effective at suppressing MPB after a meal (Wilkes et al. 2009). The overall result is "anabolic resistance" in older adults.

Skeletal muscle is a highly organized and complex tissue composed of bundles of muscle fibres (myofibers), each representing a single multinucleated muscle cell that contains numerous myofibrils (Mukund and Subramaniam 2020). Proper coordination among these hierarchical components is essential for the generation of contraction, force, and movement (Mukund and Subramaniam 2020) (Lieber 2009). Mass spectrometry–based proteomic studies have revealed an age-associated pathophysiological uncoupling between sarcolemma excitation and the initiation of acto–myosin sliding that drives skeletal muscle fibre contraction (Protasi et al. 2021) (Delbono 2011) (Dowling et al. 2023).

With ageing, there is a progressive reduction in the number of motor units (cell body located in the ventral horn of the spinal cord, the alpha motor neuron, and all the muscle fibersit innervates) in both small (Galea 1996) and large muscles (Piasecki, Ireland, Coulson, et al. 2016) resulting in muscle fibres denervation because motoneuron loss is not adequately compensated by reinnervation of muscle fibres by the remaining motoneurons (Larsson et al. 2019), rendering these fibres more susceptible to structural changes and, ultimately, to degeneration and loss (Piasecki, Ireland, Jones, et al. 2016). Particularly, fast myofibers are more prone to denervation and are reinnervated by sprouting of slow motoneurons. In consequence, there is a conversion of fast-twitch type II muscle fibres into slow-twitch type I muscle fibres (Jang and Van Remmen 2011; Lexell et al. 1988). Indeed, with ageing, the size of slow-twitch type I endurance fibres is largely maintained (Verdijk et al. 2007). In addition, between 50 and 80 years of age in humans, the number of muscle fibres in the large thigh muscle, the vastus lateralis, in men decreases by approximately 50%, (Faulkner et al. 2007) and these changes are closely associated with the age-related decline in motor units including motor unit number reduction, fibre type grouping from denervation-reinnervation cycles, and neuromuscular junction instability, which contribute to decreased strength and coordination (Hepple and Rice 2016).

B. Impact of ageing on skeletal muscle: cellular scale

Numerous modifications of SCs in homeostasis, such as presenescence, lead to defective fate and function upon injury, this will be further developed in following Section 4 of this review. Importantly, necrosis is a rare, if not absent in young and aged homeostatic muscle, raising questions about the long-term requirement for SCs in maintenance of healthy muscle (Lloyd et al. 2023). In 2015, Fry and co-authors used $Pax7^{CreER/+}$; $Rosa26^{DTA/+}$ mice to specifically deplete SCs upon tamoxifen injection. The decrease of myofiber size that naturally occur with age (from 4 to 16-18 month-old in this study) is not impacted by the depletion of SCs, meaning that SC content is not involved in muscle maintenance throughout lifetime (Fry et al. 2015). However, the authors observed an increase of fibrosis in SCs depleted muscle compared to control mice, highlighting the involvement of SCs in limiting ECM accumulation with age (Fry et al. 2015). Similarly, two studies observed that denervation or tenotomy (tendon resection) induces SCs activation without fusion with pre-existing myofibers (Dupont-Versteegden et al. 1999) (McGeachie 1985). Altogether, these studies suggested that, while SCs are necessary for effective skeletal muscle regeneration after injury (Sambasivan et al. 2011), they are dispensable for the maintenance of homeostatic muscle that does not undergo necrosis. However, a study from 2015 that used $Pax7^{Cre}$; $R26R^{tdTomato}$ to follow the fate of SCs in uninjured skeletal muscle found contradictory results. Two weeks after tamoxifen injection in 8 and 12 months-old mice, around 12% of myonuclei from EDL are $tdTomato^{+}$ demonstrating a fusion of SCs within myofibers (Pawlikowski et al. 2015). Identically, while muscle hypertrophy induced by overload in old mice is lost, the depletion of SCs highly decreases myonuclear accretion (J. D. Lee et al. 2016). In 2025, Fressart and co-authors demonstrated that neuromuscular electrical stimulation induces muscle hypertrophy by fusion of SCs with myofibers without signs of necrosis (Fessard et al. 2025). From these recent studies, and SC fate-tracing

murine models, we can hypothesize that in the study of Fry and co-authors, the depletion of $Pax7^+$ was not 100% efficient and the remaining pool of SCs was sufficient, in a resting stage, to cover the function of lost SCs over the progression of ageing. Nevertheless, although the effect of ageing on SCs have been mainly studied in the context of induced necrosis and subsequent regeneration, which remains useful for understanding the impact of ageing on SCs function, some factors have been directly identified as improving muscle mass and function at the resting stage. As example, elevation of prostaglandin 15-PGDH in murine and human muscles during ageing induces a decrease of lipid metabolite PGE2 (prostaglandin E2) (Palla et al. 2021). In accordance, overexpression of 15-PGDH in young mice leads to muscle atrophy and weakness, while its inhibition (using a small inhibitor or shRNA) improves muscle mass, strength and endurance in old mice (Palla et al. 2021). The positive effect of PGE2 is linked to increase of mitochondria number and biogenesis (Palla et al. 2021). The decrease of PGE2 also affects epigenetics and transcriptomic changes occurring in SCs during ageing (Y. X. Wang et al. 2025).

In addition, several non-myogenic cells are part of skeletal muscle: resident macrophages, FAPs (fibro-adipogenic progenitors) or (ECs) endothelial cells. While, resident macrophages are important regulators of tissue homeostasis (Lazarov et al. 2023), they have been poorly studied in both young and old homeostatic muscle. Immunofluorescent analysis on aged human *vastus lateralis* muscle showed a switch toward more anti-inflammatory (CD206+ cells) and less pro-inflammatory (CD86+ cells) phenotype (Cui et al. 2019). On the contrary, two studies realized in aged murine muscle show increase of genes associated to inflammatory response but also cellular detoxification (Kawanishi and Machida 2021) (Krasniewski et al. 2022). Recently, two scRNAseq data sets regarding phenotype of immune cells and, particularly, macrophages have been generated (Krasniewski et al. 2022) (Sousa et al. 2024). However, macrophages are versatile cells highly responsive to the environment, thus proteomic analyses are needed to understand if and how resident macrophages phenotype and function are truly modified during ageing (Guan et al. 2025). Nevertheless, number of resident macrophages appears to be identical between young and aged muscle, suggesting that ageing could impact macrophages function (Guan et al. 2025) (Tobin et al. 2021). Beyond macrophages, other immune cells such as neutrophils, B and T cells are more abundant in aged muscle compared to young counterparts but their effect on sarcopenia still need to be investigated (Kawanishi and Machida 2021) (Sousa et al. 2024). Similarly, the contribution of the extracellular matrix (ECM) to SCs function in young muscle is increasingly recognized, but it remains largely understudied in the context of ageing (Loreti and Sacco 2022). ECM is mainly produced by FAPs that acquire fibrogenic or adipogenic fate depending on the environmental cues (Joe et al. 2010) (Uezumi et al. 2010) (Giuliani et al. 2022). To note, other cells such as macrophages can produce components of ECM (X. Wang and Zhou 2022). Muscle of young mice depleted for FAPs exhibit a loss of SCs and muscle atrophy after only 3 months, however, the authors do not provide information about ECM or impact of FAPs depletion in old animals (Wosczyna et al. 2019). In vitro culture of human SCs on decellularized ECM from muscles of aged mice acquire fibrogenic fate. Same results have been obtained when SCs are cultured on matrix produced in vitro by young or old fibroblasts (Stearns-Reider et al. 2017). In 2021, Schuler et al. performed a quantitative mass spectrometry to characterize proteome of SCs and skeletal muscle during ageing (Schüler et al. 2021). They observed alterations in protein abundances and modified interactions between SCs and their niche during ageing, including an increase in Integrin-related proteins and a decrease in Egfr and Cd44 abundance. Unfortunately, the authors did not investigate the effect of these alterations on the physiology of aged muscle at resting state (Schüler et al. 2021). This resource will be helpful to understand how ECM modifications may impact skeletal muscle health in sarcopenia. Identically, ECs and vasculature have a supportive role in muscle homeostasis and repair (Latroche et al. 2017; Verma et al. 2018). However, whether they are involved in skeletal muscle ageing is unknown (Fukada and Kajiya 2020) (Figure 1). More investigations regarding the skeletal muscle microenvironment and interactions with SCs are still needed to understand how muscle ages and become sarcopenic.

Additionally to this modification of skeletal muscle structure, microenvironment and metabolism, loss of appetite and the resulting decrease of nutriments intake are common issues among old people (Rudzińska et al. 2023). Thus, physiological ageing associated to behavioural changes can induces and/or worsen sarcopenia by impeding muscle capacity to reform or growth, directly or indirectly through inter-organ communications.

3 | Mitochondrial Dysregulation in Aged Skeletal Muscle

Skeletal muscle is one of the primary tissues responsible for maintaining whole-body energy homeostasis, owing to its exceptionally high and continuous demand for ATP to sustain contraction and movement (Gnaiger 2009). This energy reliance makes mitochondria indispensable, as they serve not only as the main producers of ATP through oxidative phosphorylation (OXPHOS) but also as central hubs for metabolic signalling and the synthesis of key anabolic intermediates (Paupe and Prudent 2018). Through this coordinated metabolic network, mitochondria ensure that skeletal muscle meets its substantial energetic needs under both resting and energy-demanding conditions (Gnaiger 2009).

Mitochondria in skeletal muscle are categorized as either subsarcolemmal (SS) or intermyofibrillar (IMF), a distinction defined by their distinct subcellular localizations and morphologies. The SS population, found directly beneath the plasma membrane, is globular and comprises approximately 20% of cellular mitochondria. The IMF population, which accounts for the remaining 80%, is characterized by an elongated, tubular shape and resides between the myofibrils, often aligned at the I-band (Vincent et al. 2019), (Hoppeler 1986) (Rahman and Quadrilatero 2021).

Structural impairments such as swelling, enlargement, and increased branching, alongside internal damage like cristae loss, membrane disruption, matrix dissolution, and vacuolization, are hallmarks of aged skeletal muscle mitochondria (Figure 2) (Pietrangelo et al. 2015) (Bratic and Larsson 2013)

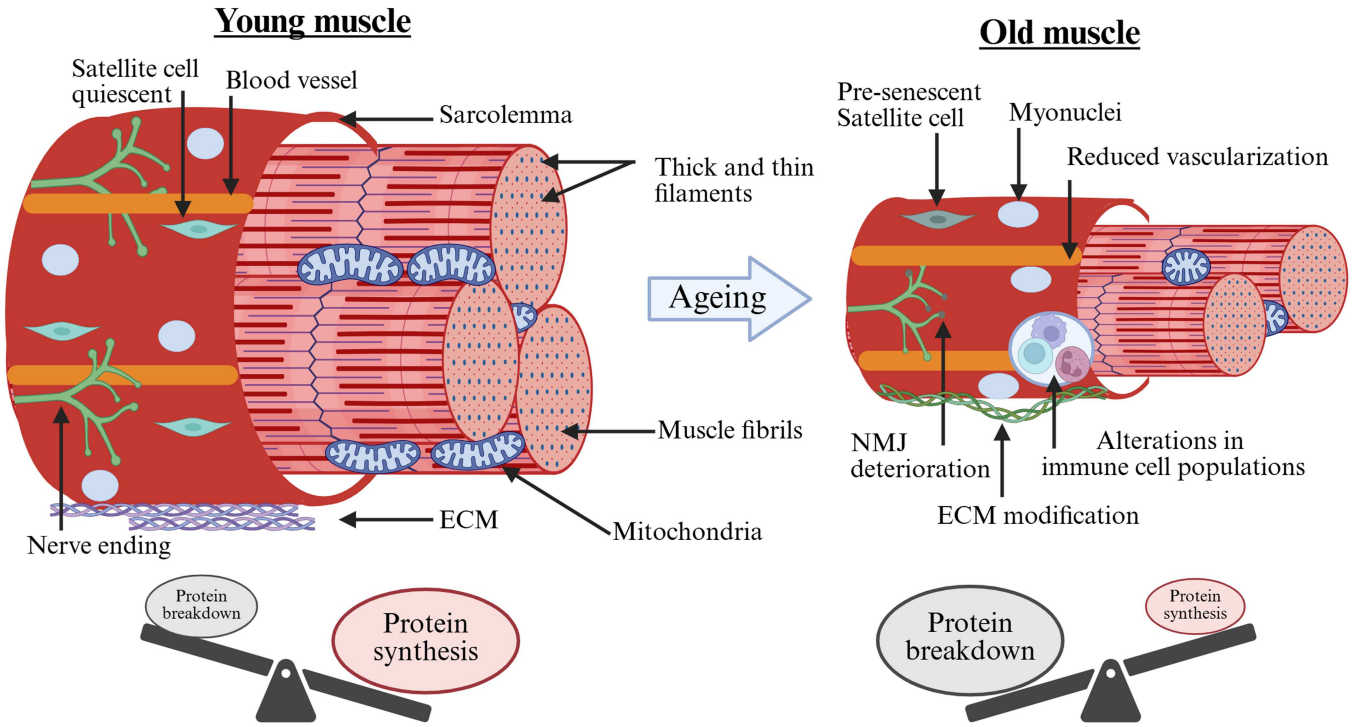

FIGURE 1 | A schematic overview of the effects of ageing on skeletal muscle fibres. Age-related muscle loss is driven by a synergistic failure of proteostasis (imbalanced MPS/MPB), satellite cells (SCs) dysfunction, modifications of extracellular matrix (ECM), and potentially by alterations in immune cells and vascularization.

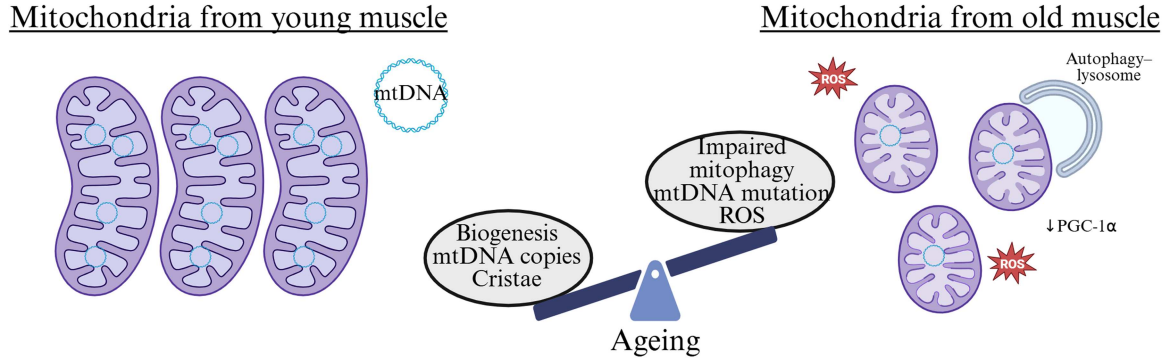

FIGURE 2 | Age-associated alterations in skeletal muscle mitochondria. Ageing disrupts mitochondrial quality control in skeletal muscle through multiple interconnected pathways. This includes ultrastructural changes, impaired dynamics, mtDNA instability, reduced biogenesis due to lower PGC-1α, and defective mitophagy. The resultant accumulation of dysfunctional mitochondria leads to excessive reactive oxygen species (ROS) production, which promotes muscle atrophy, impairs contractile function, and disrupts regeneration. Together, these alterations create a vicious cycle of energetic deficit and proteostatic stress that accelerates the development of sarcopenia.

(Leduc-Gaudet et al. 2015). Mitochondrial networks are maintained by a balance between fusion and fission. Fusion promotes health by sharing components, while fission isolates and facilitates the removal of damaged mitochondria (Gan et al. 2018). Evidence from murine and human studies indicates an age-dependent reduction in the expression of mitochondrial dynamics genes (Sebastián et al. 2016) (Tezze et al. 2017). The pathological importance of this loss is demonstrated by findings that fusion-defective mice develop hallmark features of skeletal muscle ageing, such as elevated ROS, reduced mitochondrial respiration, and pronounced atrophy (Sebastián et al. 2016). Importantly, this phenotype can be mitigated by the overexpression of fusion genes, which confers protection against muscle loss (Romanello 2020). A notable downstream consequence of chronically elevated ROS levels is the accumulation of lipofuscin, an insoluble oxidized protein-lipid aggregate that builds up irreversibly within post-mitotic cells such as skeletal muscle fibres (Jacko et al. 2024). Lipofuscin accumulation is considered a classical histological marker of cumulative oxidative damage and is consistently observed in aged muscle tissue, reflecting the long-term failure of cellular clearance mechanisms and previous oxidative damage (Hütter et al. 2007) (Calvani et al. 2013).

The mitochondrial genome (mtDNA) is a small, circular, double-stranded DNA of maternal origin. Its primary function

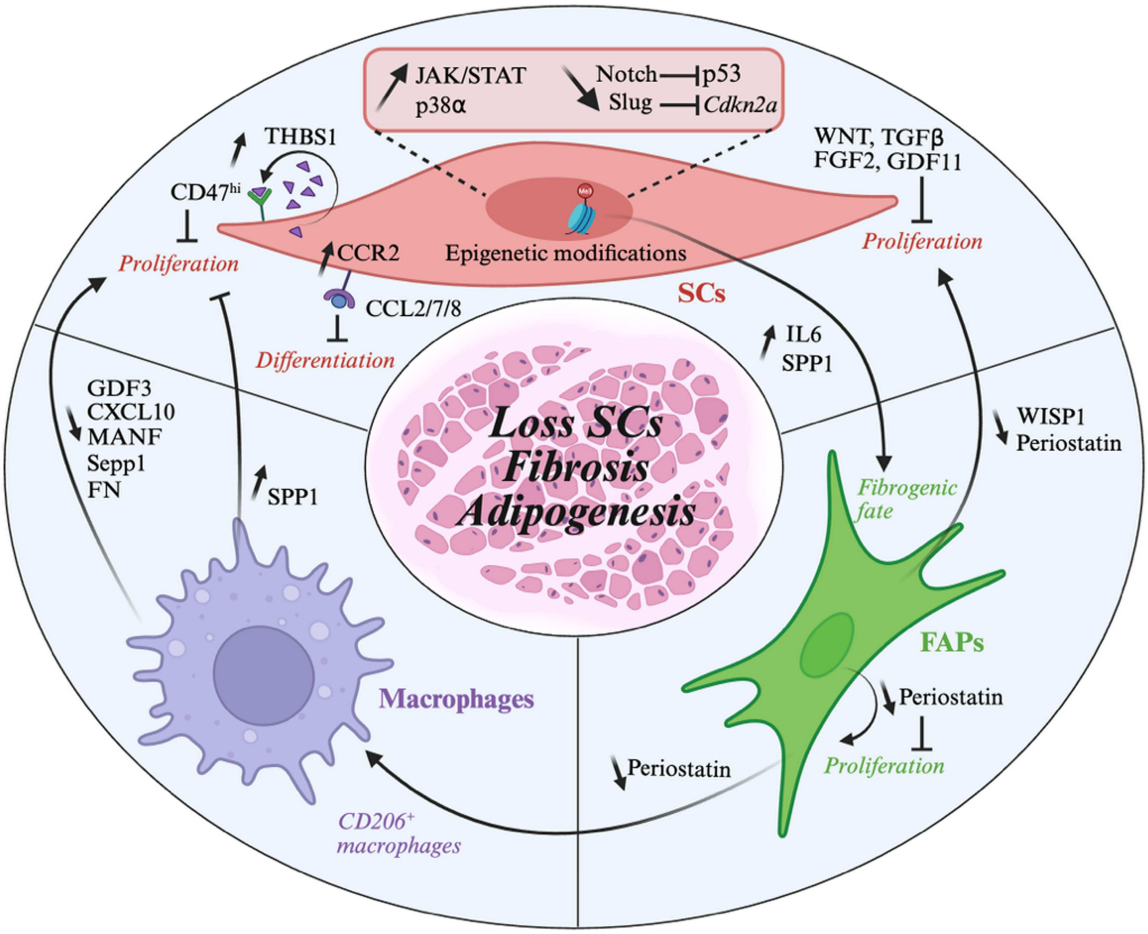

FIGURE 3 | Aged associated changes in SCs and cellular environment. Age-related SCs loss, fibrogenesis and adipogenesis are consequences of intrinsic alterations of SCs, and modifications of communication with surrounding cellular environment. FAPs, fibro-adipogenic progenitors; SCs, satellite cells.

is to encode polypeptides that form essential parts of the respiratory complexes located in the inner mitochondrial membrane, thereby playing a fundamental role in ATP synthesis (Yan et al. 2019) (Sharma and Sampath 2019). Ageing human skeletal muscle exhibits a decline in mtDNA copies and a progressive accumulation of mtDNA mutations that are associated with sarcopenia (Wachsmuth et al. 2016) (Bua et al. 2006) (Wanagat et al. 2001). This mutational burden has a dual detrimental effect: it directly causes atrophy, and it indirectly impairs mitochondrial function by hindering the assembly of respiratory complexes, which decreases oxidative phosphorylation and promotes apoptosis, accelerating muscle decline (Hiona et al. 2010) (Hepple 2014).

The capacity for mitochondrial biogenesis, a process essential for generating new mitochondria, declines in ageing skeletal muscle. This key adaptive mechanism is largely regulated by the master coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), which is vital for maintaining mtDNA homeostasis, managing oxidative stress, and preserving muscle fibre-type balance (Finck 2006) (Scarpulla et al. 2012) (Garcia et al. 2018). The age-related loss of PGC-1α expression contributes to muscle atrophy and chronic systemic inflammation. Conversely, transgenic overexpression of PGC-1α in murine skeletal muscle reduces fatigability and enhances oxidative capacity (Garcia et al. 2018) (Sandri et al. 2006) (S. Yang et al. 2020) (Kerr et al. 2024), underscoring its critical role in maintaining muscle health.

Reactive oxygen species (ROS) encompass radical molecules like superoxide (O_2^-) and hydroxyl radicals (HO•), and non-radical molecules such as hydrogen peroxide (H_2O_2). In skeletal muscle, these species are produced by mitochondria, NADPH oxidases, and through phospholipase A2 (PLA2)-dependent pathways (Lian et al. 2022) (Vasilaki and Jackson 2013). Elevated mitochondrial ROS generation is a hallmark of ageing skeletal muscle and is a key pathophysiological driver of sarcopenia (Venturelli et al. 2014) (Jackson 2016). The detrimental effects of this redox imbalance are multifaceted. Excess ROS can induce atrophy by down-regulating the PI3K-Akt signalling axis (Gomez-Cabrera et al. 2020), impair muscle function by reducing calcium sensitivity and accelerating fatigue (Moopanar and Allen 2005), and promote cellular senescence in SCs (L'honoré et al. 2018). Furthermore, ROS-induced oxidative stress, often coupled with chronic inflammation, inhibits SCs activation, thereby compromising muscle regeneration. Finally, ROS overproduction at neuromuscular junctions disrupts neurotransmission, impairing action potential generation and further contributing to age-related muscle loss (Ivannikov and Van Remmen 2015). Mitophagy is a selective form of autophagy responsible for the removal of damaged mitochondria through the autophagy–

lysosome system. In healthy skeletal muscle, dysfunctional or depolarized mitochondria are efficiently eliminated via mitophagy pathways, thereby maintaining mitochondrial quality and cellular homeostasis (Leduc-Gaudet et al. 2021). Mitophagy is recognized as a crucial mechanism for maintaining muscle homeostasis, as its disruption through genetic knockout results in atrophy, weakness, and dysfunctional mitochondria (Masiero et al. 2009). Thus, strategies aimed at improving mitochondrial biogenesis, dynamics, respiratory chain function, or reducing oxidative stress offer opportunities to counteract age-related decline (Boengler et al. 2017) (Chen et al. 2018) (Salminen and Kaarniranta 2009). Among these, physical exercise remains the most widely studied and effective intervention, as it can simultaneously improve many of the mitochondrial functions that become dysregulated with age (Boengler et al. 2017). Significant knowledge gaps remain regarding the impact of exercise on mitochondrial biology and its effects on skeletal muscle ageing. Notably, the impact of exercise on circulating extracellular mitochondria - whether vesicle-enclosed, freely circulating, or present as mitochondrial components - has yet to be systematically investigated. A clearer understanding of these processes is required to elucidate their potential molecular and physiological relevance (Pedrosa et al. 2025).

4 | Impaired Regenerative Capacity in Aged Skeletal Muscle

In young individuals, skeletal muscle is able to fully regenerate after injury following highly reproducible steps. Skeletal muscle regeneration is mediated by SCs that reside in close association with their microenvironment, also called niche. Upon injury, SCs exit from quiescence (activation), migrate to injury site, proliferate, differentiate and fuse to reform myofibers that will mature to restore tissue integrity (Scharner and Zammit 2011) (Lander et al. 2012) (Relaix and Zammit 2012). During this process, communications between numerous cell types are essential to ensure effective muscle repair, including SCs themselves, FAPs, macrophages and ECs (Rodríguez et al. 2024) (Giuliani et al. 2022) (Theret et al. 2022) (C. Yang et al. 2025). During ageing, the regenerative capacity of skeletal muscle declines: decrease of myofiber size, fibrosis establishment, reduced force and so forth. Intrinsic and extrinsic signals modifying SCs fate and functions, but also skeletal muscle cellular microenvironment explain the defective regenerative capacity that contributes to age-associated muscle dysfunction.

A. Intrinsic effect of ageing on SCs

Cellular senescence is a cellular stress response characterized, among others, by a permanent and irreversible cell cycle arrest and acquisition of a robust secretome termed senescence-associated secretory phenotype (SASP) (Muñoz-Espín and Serrano 2014). In geriatric mice (28-32 months old), quiescent SCs enter pre-senescence by up-regulating *Cdkn2a* gene (cell cycle inhibitor named $p16^{INK4a}$) resulting in defective activation, and a reduced capacity to reform myofibers upon transplantation in injured young muscle host (Sousa-Victor et al. 2014). Ex vivo inhibition of senescence induction in geriatric SCs (by the use of shCdkn2a) restore SCs regenerative capacity by increasing their activation and self-renewal upon transplantation in young host (Sousa-Victor et al. 2014). Similarly, depletion of $p16^{+}$ cells in geriatric injured muscle by treatment with senolytic compounds D + Q (dasatinib and quercetin) improves muscle repair by increasing myofibers size and EDL-specific tetanic force, while decreasing fibrosis and SASP factors (IL-6, CCL2, IFNγ) (Moiseeva et al. 2023). The transcription factor Slug has been identified as direct repressor of *Cdkn2a*, as its expression in SCs decreases with age, and young SCs deleted for Slug exhibit features of senescence. Slug overexpression in old SCs strongly decrease *Cdkn2a* expression and restore self-renewal capacity of aged SCs when transplanted in a dystrophic mouse model (Zhu et al. 2019).

Upon injury, up-regulation of Notch induces exit from quiescence and activation/proliferation of young SCs (Conboy and Rando 2002). Aged SCs exhibit a decrease of Notch activation that induces a decrease of their proliferation. Indeed, activation of Notch increases proliferation of SCs in vitro, and improves skeletal muscle regeneration by increasing percentage of regenerating myofibers in vivo (Conboy et al. 2003). In addition, old SCs undergo higher mitotic catastrophe (cell death following division due to DNA damage) compared to young SCs (Liu et al. 2018). In young SCs, through activation of Hey1/2 L target genes, Notch signalling represses expression of MDM2 (p53 inhibitor). Interestingly, pharmacological activation of p53 (via the inhibition of MDM2) prevent DNA damage and cell death in vitro. Identically, the short pharmacological activation of p53 in old injured mice decrease number of catastrophic mitosis and increase number of SCs per muscle, improving muscle repair (Liu et al. 2018). The decreased proliferation of aged SCs is also explained by an increase of p38α (mitogen-activated protein kinase (MAPK)) and Jak-STAT signalling pathways (Price et al. 2014) (Tierney et al. 2014) (Cosgrove et al. 2014). SCs from young mice deleted for p38α proliferate more than wild type SCs resulting in smaller myofibers formation in vitro and in vivo (Brien et al. 2013; Perdiguero et al. 2007). In vitro, pharmacological inhibition of P-p38α with SB2002190 restore proliferative capacity of aged SCs, and increases their engraftment in muscle of young mice (Cosgrove et al. 2014). When transplanted into muscle of old mice, SB2002190 treated old SCs participate to myofibers formation upon injury, resulting in increased force compared to vehicle treated old SCs (Cosgrove et al. 2014). In the same extend, JAK-STAT signalling pathways are upregulated in old SCs (Price et al. 2014; Tierney et al. 2014). Inhibition of JAK2 or STAT3 by siRNA, or by a STAT3 inhibitor increases their proliferation. Moreover, injured old muscle treated with inhibitor of JAK2 or STAT3 shows improved muscle regeneration compared to control treated old mice by increasing number of SCs, cell proliferation, myofiber size and muscle force (Price et al. 2014; Tierney et al. 2014).

Among the intrinsic factors that influence SC behaviour during ageing, changes in the transcriptional and epigenetic landscape play a key role. At quiescent state, genome of old SCs is enriched in repressor H3K27me3 and deprived of activator H3K4me3 epigenetic modifications compared to young SCs (Liu et al. 2013). A general increase of promoter methylation heterogeneity has also been observed, such as in the promoter of the H3K36me3 repressor (Hernando-Herraez et al. 2019). These alterations lead to modifications in chromatin accessibility and variability of the transcriptome of SCs with age (Hernando-

Herraez et al. 2019) (Shcherbina et al. 2020). Dong et al observed a more open chromatin environment in aged SCs compare to young counterpart, that they called chronic activation chromatin structure (Dong et al. 2022). All these modifications can further impact genes accessibility and expression in old SCs upon injury, resulting in defective function and fate. Indeed, transcriptome variability is higher in old SCs compared to young SCs in regenerative context (decrease of MyoG promoter accessibility resulting in inefficient activation of the myogenic programme) (Hernando-Herraez et al. 2019; Shcherbina et al. 2020). Very recently, a study demonstrated a loss of heterochromatin markers in old SCs, a phenomenon predictive of genome instability, due to the depletion of the S-adenosylmethionine methyl donor SAM (J. Kang, Benjamin, et al. 2024). Authors also identified a decrease of H3K9me3 and HP1a proteins, that maintain and package heterochromatin respectively. Very interestingly, the intraperitoneal injection of SAM in old mice reverse the decrease of H3K9me3 and HP1a. Injured muscle of old treated mice exhibits less SCs cell death, increase of SCs number, larger of myofibers and better grip test force compared to untreated old mice (J. Kang, Benjamin, et al. 2024).

B. Extrinsic effect of ageing on SCs

With ageing, signals received or secreted by SCs change and influence skeletal muscle regenerative capacity (Figure 3). In 2005, parabiotic pairing between young and old mice showed that youthful systemic environment improves muscle regeneration of old mice by, in part, increasing Notch/Delta signalling in SCs (Conboy and Rando 2005). Identically, whole muscle graft (a model of muscle regeneration) into a young muscle show the ability to reform myotubes similarly to whole young muscle graft in young hosts, even if delayed (Shavlakadze et al. 2010). Old systemic environment also exhibits an increase of Wnt signalling, which is inhibited by the young systemic environment. As consequence, the myogenic to fibrogenic conversion of old SCs is reversed and SCs proliferation increases (Brack et al. 2007).

TGFβ is up-regulated in regenerative old muscle compare to young counterpart, inducing an increase of P-Smad3 activation in old SCs and myofibers (Carlson et al. 2008). *In vitro*, the inhibition of TGFb promotes proliferation of old SCs, increasing formation of myofibers. *In vivo*, both inhibition of P-Smad3 by shRNA, and of TGFβ by blocking antibody improves muscle regeneration of old mice (Carlson et al. 2008). Very interestingly, Notch blocks TGFβ signalling, showing a cumulative effect of Notch loss that affects two signalling pathways (Carlson et al. 2008) (Conboy et al. 2003). Similarly, GDF11, a member of TGFβ signalling family, increases in serum of old mice and human. *In vitro*, addition of GDF11 on human myoblasts strongly decreases myotubes formation. In mice, GDF11 treatment impairs muscle regeneration (Egerman et al. 2015).

Ageing also alters SCs niche at structural and molecular levels. Aged myofibers secrete elevated levels of fibroblast growth factor 2 (FGF2) into the SC niche, leading to an increase of spontaneous cycling of SCs in homeostasis. This results in a decrease of old SCs engraftment capacity in young muscle because of self-renewal decline (Chakkalakal et al. 2012). FGF2 has been shown to inhibit SPRY1 activity, a key regulator of SCs quiescence, thereby promoting a shift toward a high-cycling state. Specific long-term deletion of SPRY1 in SCs of aged mice induces a decrease of myofibers size upon injury due to the loss of SCs pool. On the contrary, short deletion improve muscle repair. In the same extend, the pharmacological long term inhibition of FGF2 receptor increase number of self-renew SCs, but impairs growth of myofibers after injury (Chakkalakal et al. 2012). This study highlights the importance of good balance between keeping SCs pool for future needs, and capacity to activate, proliferate and differentiate properly to reform skeletal muscle tissue. Of note, a correlation between risk and severity of sarcopenia and lower methylation of FGF2 DNA region has been observed in whole blood of old human (J.-W. Li et al. 2024).

CCL2/7/8 are chemokines released upon skeletal muscle injury, known principally as attractants for immune cell via CCR2 receptor. The deletion of CCR2 induces a strong decrease of macrophages infiltration that impairs muscle regeneration (Martinez et al. 2010). In 2020, Blanc et al observed that SCs also express CCR2 (Blanc et al. 2020). The activation of CCR2 in SCs induces a defective muscle repair through the inhibition of SCs differentiation. Interestingly, old SCs upregulated CCR2 during muscle repair compared to young counterpart. Identically, CCL2/7/8 are more abundant in old regenerative muscle. Inhibition of CCR2 in old mice improves muscle repair, and notably absolute and specific force, by increasing differentiation of myogenic cells and size of myofibers (Blanc et al. 2020).

As SCs aged, they express more CD47 ($CD47^{hi}$) exhibiting decrease proliferation and regenerative capacity compare to $CD47^{lo}$ SCs (Porpiglia et al. 2022). Through secretion of THBS1, $CD47^{hi}$ directly exert antiproliferative effect on $CD47^{lo}$ SCs. *In vivo* inhibition of THBS1 in old mice improves several features of muscle repair (size of myofibers, grip strength and tetanic force), an effect that is lost in CD47 deleted old mice (Porpiglia et al. 2022). This study shows that SCs themselves differentially secrete factors during ageing that impact their capacity to reform skeletal muscle tissue.

While many negative up-regulated factors have been identified during ageing, few positive ones are known. Klotho is a protein primarily identified as anti-ageing factor that decline with ageing (Prud'homme et al. 2022), and mice deleted for Klotho have reduced lifespan and display several aged related pathologies (Kuro-o et al. 1997). In addition to many organs, Klotho is also present in skeletal muscle (Olauson et al. 2017). It exists as a membrane-bound coreceptor for FGF23 (which further signals through PI3K/Akt, phospholipase Cγ (PLCγ) and Ras/MAPK/ERK) (Prud'homme et al. 2022) and as a soluble form known to inhibit TGFβ pathways (Doi et al. 2011). In vitro, addition of soluble Klotho to aged myofibers increases size of SCs clusters (Sahu et al. 2018). Identically, aged mice supplemented with Klotho through an osmotic pump between 3 and 5 days after muscle injury have improved muscle repair (myofibers size and specific force). Delivery of Klotho between 1 and 3 days increases myofibers size without improving specific force of aged mice (Sahu et al. 2018), showing that the timing of Klotho delivery is very important to ensure correct muscle repair. Additionally, deletion of Klotho in young SCs induces

mitochondrial DNA damage and impairs mitochondrial bioenergetics.

C. Impact of ageing on cellular microenvironment

In addition to SCs, other cell types are impacted by ageing. FAPs number decreases in homeostatic due to a reduced proliferative capacity, but also transiently increases in old regenerative muscle potentially explaining fibrosis establishment in old context (Lukjanenko et al. 2019). Besides quantity, FAPs transcriptome and secretome are modified during ageing (Schüler et al. 2021) (Hoang et al. 2025). Integration of scRNAseq and proteomic data has shown that FAPs exhibit extensive ECM changes with age. Particularly, SPARC Related Modular Calcium Binding 2 (Smoc2) is upregulated during ageing, and its addition to young SCs in culture induces a decrease in self-renewal as observed with old SCs (Schüler et al. 2021). While young FAPs have a paracrine pro-myogenic function to ensure muscle repair (Giuliani et al. 2022), old FAPs have lost this capacity. In injured muscle, old FAPs secrete less WNT1-inducible-signalling pathway protein 1 (WISP1) protein, reducing number of proliferative and committed SCs. Beneficial effect of young FAPs transplanted in old regenerative muscle is lost with WISP1$^{-/-}$ young FAPs. Moreover, systemic injection of WISP in old mice rescue the defective muscle repair (Lukjanenko et al. 2019). A very recent study demonstrated that, upon injury, SCs aged-related epigenetic dysregulation induces proliferation and fibrotic fate of FAPs via secretion of Osteopontin (SPP1) and IL-6 (Riparini et al. 2025). Injured muscle of old mice injected with intramuscular SPP1 and IL-6 antibodies improves muscle repair by increasing of myofibers size and decreasing fibrosis (Riparini et al. 2025). Upon injury in young mice, Periostatin secretion from FAPs inhibits their own proliferation and stimulates the proliferation of SCs at the same time (Garcia-Carrizo et al. 2023). In regenerative aged muscle, Periostatin secretion decreases, participating to defective tissue repair by acting on both FAPs and SCs proliferation. Besides its function toward FAPs and SCs, Periostatin seems to decrease inflammation, as macrophages treated *in vitro* with Periostatin increase CD206^{+} population (Garcia-Carrizo et al. 2023). Altogether, these findings show that ageing modifies multiples functions of FAPs related to niche environment, pro-myogenic functions but also resolution of inflammation.

Upon injury, massive infiltration of macrophages (from blood monocytes) occurs in damaged tissue. In a young context, macrophages are essential all along muscle repair (Oishi and Manabe 2018) (Chazaud 2020) (Theret et al. 2022), and their functions are only beginning to be investigated in old mice. Tobin et al, observed a decrease of macrophages load in injured muscles (both Ly6C^{+} pro-inflammatory and Ly6C^{-} pro-regenerative macrophages) (Tobin et al. 2021). However, other studies shown a modification of inflammatory response with increase of pro-inflammatory and decrease of pro-regenerative populations (Patsalos et al. 2018) (Sousa et al. 2023) (Sousa et al. 2024) (Hoang et al. 2025) (Duong et al. 2021). This discrepancy can be explained by different triggers of damage (barium chloride or cardiotoxin) and time points analysed. Indeed, even if regenerative steps are identical following different injuries, the dynamics can be shifted (Hardy et al. 2016). Moreover macrophages are versatile cells going through numerous phenotypical changes during skeletal muscle regeneration (Varga, Mounier, Horvath, et al. 2016) (Oprescu et al. 2020). Two scRNAseq analysis done on young versus old regenerative muscles highlighted differential transcriptomic signatures and dynamic in macrophages populations (Sousa et al. 2024) (Walter et al. 2024). Particularly, Sousa et al. identified an aged population of macrophages strongly expressing several pro-inflammatory chemokines (Cxcl10, CCL5, CCL8) and pro-fibrotic genes (SPP1, Lgals3) (Sousa et al. 2024). All these studies point out a dysregulated inflammatory response upon injury in aged skeletal muscle.

Compared to young counterparts, bone marrow–derived macrophages (BMDMs) from old mice show higher TNF-α and IFNγ expression after in vitro LPS stimulation (Tobin et al. 2021). On the contrary, other pro-inflammatory cytokines such as IL1b or IL-12b are less expressed, and IL-10 anti-inflammatory cytokine is up-regulated (Tobin et al. 2021). Interestingly, while young pro-inflammatory macrophages sustain myogenic cells proliferation (Saclier et al. 2013), in vitro culture shows that old macrophages have lost this ability and further stimulate myotubes formation (Tobin et al. 2021). Very interestingly, bone marrow transplantation (BMT) from young mice into old mice increases proliferation of SCs and expression of early differentiation marker MyoD (Tobin et al. 2021) improving muscle repair. This point out that old macrophages are not able to respond properly to injury, probably participating in the defective muscle repair occuring during ageing.

In addition to FAPs, macrophages also express SPP1 (Paliwal et al. 2012). While almost absent in infiltrating young macrophages upon injury, the protein is highly found in old macrophages. Coculture of old myofibers containing old SCs with old macrophages (both isolated from injured muscle) shows a decrease of SCs proliferation compared to young coculture. When old myofibers and SCs are culture with young macrophages, there is a rescue of SCs proliferation, similar to that observed in the old coculture with SPP1 bocking antibody. This shows that upregulation of SPP1 secretion by macrophages during ageing inhibits proliferation of SCs (Paliwal et al. 2012). Cxcl10 is a cytokine secreted by macrophages in response to IFNγ stimuli (Groom and Luster 2011) that is downregulated in old macrophages together with genes associated with the IFNγ response (C. Zhang et al. 2020). In vitro , addition of Cxcl10 induces proliferation and differentiation of young SCs. Intramuscular injection of Cxcl10 in regenerative old muscle improves muscle repair by increasing proliferation of SCs, myofiber size and decreasing fibrosis (C. Zhang et al. 2020). Growth Differentiation Factor 3 (GDF3), that is secreted by pro-regenerative macrophages and stimulates the formation of myofibers, decreases in old regenerative muscle (Patsalos et al. 2018) (Varga, Mounier, Patsalos, et al. 2016). A single intramuscular injection is able to increase myofiber size of aged regenerative muscle (Patsalos et al. 2018). Identically, the endoplasmic-reticulum-stress-inducible protein MANF (mesencephalic astrocyte-derived neurotrophic factor) is downregulated in aged macrophages upon injury compared to young macrophages (Sousa et al. 2023). Its deletion in macrophages induces a defect of muscle repair due to an impaired acquisition of pro-regenerative phenotype (Sousa et al. 2023). MANF injection into muscle rescue defective muscle repair in old mice

by improving clearance of dead myofibers and increasing myofibers size (Sousa et al. 2023). Old macrophages also exhibit an altered expression of Selenoprotein P (Sepp1) during muscle repair of aged muscle (Hoang et al. 2025). In young mice, Sepp1 deletion causes a persistence of pro-inflammatory macrophages inducing defective muscle repair. In old mice, BMT of young mice is sufficient to rescue muscle repair, this effect is completely lost when young BM cells deleted for Sepp1 is transplanted (Hoang et al. 2025). Fibronectin (FN) is a component of ECM that is mainly secreted by macrophages, and it expression decreases in ageing (Lukjanenko et al. 2016). Loss of FN increases SCs death by decreasing their adherence capacity, and intramuscular injection of FN improves muscle regeneration of old mice by increasing proliferative SCs and myofiber size (Lukjanenko et al. 2016). This demonstrated that macrophages act on muscle regeneration through SCs niche formation.

Altogether, these studies show the complexity of cell-cell communication during muscle repair (Figure 3). Ageing induces defect in many cell types that in consequence impact tissue homeostasis and ability to repair, thus a full understanding of this dysregulation is necessary for future therapies to counteract sarcopenia.

5 | Impact of the Systemic Communication on Muscle Ageing

One hallmark of ageing is accumulation of senescent cells within tissues, that in consequence, perturb physiological functions (Kaur and Farr 2020). While there is a persistence of senescent cells in regenerative old muscle, senescence is a rare event in resting muscle of geriatric mice (Moiseeva et al. 2023). Biweekly treatment of old mice with senolytics D + Q for 4 months improves both health and lifespan, by notably increasing hanging endurance (M. Xu et al. 2018). Identically, the inducible removal of $p16^{+}$ cells using a systemically expressed senescence-associated "suicide" transgene, INK-ATTAC ($p16^{Ink4a}$-linked apoptosis through targeted activation of caspase) via administrating a synthetic drug (AP20187) in the BubR1 progeroid mouse delays the appearance of age-related pathologies, and increases muscle fiber calibre and exercise ability (Baker et al. 2011). The removal of $p16^{+}$ cells in the INK-ATTAC non progeroid mouse extends healthy lifespan without improving physical condition suggesting another contributor in addition to $p16^{+}$ cells to muscle ageing (Baker et al. 2016). Indeed, Zhang et al observed that some FAPs and myofibers have an up-regulation of the senescence marker p21 by scRNAseq (X. Zhang et al. 2022). The use of D + Q senolytic decreases expression of several senescent related genes and induces improves muscle function and histology. Thus, the general decrease of senescence load during ageing goes along with improvement of skeletal muscle histology and function. However, D + Q is administrated by oral gavage so it could act directly on skeletal muscle cellular environment, or indirectly by alleviating senescence from other tissues (Borghesan et al. 2020).

Through SASP secretion, persistence of senescence induces a chronic low-grade inflammation called inflammaging (X. Li et al. 2023). As example, persistence elevated systemic level of the SASP and cytokine IL-6 promotes muscle atrophy notably during cachexia (Pelosi et al. 2021) (Tsujinaka et al. 1995) (Goodman 1994). Notably, D + Q treatment in old mice reverses the up-regulation of chemokines and cytokines pathways specific to old muscle (X. Zhang et al. 2022). Similarly, treatment of 24-months-old mice for 10 weeks with senolytics ruxolitinib (inhibitor of JAK1 and 2) decreases systemic inflammation and in adipose tissue, leading to physical improvement (M. Xu et al. 2015). Interestingly, centenarians exhibit lower levels of blood inflammation (Arai et al. 2015). As a consequence to chronic inflammation, the immune system, such as resident macrophages, promotes local inflammation disturbing tissue homeostasis (Santoro et al. 2021). This chronic inflammation could also participate to the ageing of the immune system itself, inducing defective support in tissue homeostasis and during repair (Delgado-Pulido et al. 2025). $Vav1^{CRE}$:$Ercc1^{ff}$ mouse (specific depletion of endonuclease repairing DNA damage in hematopoietic cells) display an acceleration of immune system ageing inducing senescence and tissue damage in solids organs such as liver and kidney (Yousefzadeh et al. 2021). Particularly, immune cells from 12-months-old $Vav1^{CRE}$:$Ercc1^{ff}$ mice increase SASP expression reaching a level comparable to 2 years old mice. In consequence, these mice have a decrease grip strength and lifespan (Yousefzadeh et al. 2021). In 2024, Hou and colleagues identifies extracellular vesicles from old bone marrow macrophages (BMM) as driver of senescence and ageing in liver, bone and skeletal muscle when transplanted in young recipient mice. *In vitro*, pretreatment of old BMM with D + Q is sufficient to reverse senescent phenotype, such as SASP expression, and partially improves muscle hanging endurance when transplanted in young recipient mice (Hou et al. 2024). Precisely, the transplantation of old bone marrow (BM) in young recipient mice decreases the number of SCs by promoting their fibrotic fate (Y. Wang et al. 2019). On the contrary, the transplantation of young BM into old recipient mouse restores the inflammatory response within injured muscle and increases number of proliferating SCs. Even if myofiber size remains unchanged, the young BM is sufficient to improve ambulatory distance in old transplanted mice (Tobin et al. 2021). Identically, transplantation of young BM into SAMP10 (senescence accelerated mouse exhibiting accelerate ageing) reduces muscle atrophy and improves physical function such as endurance and grip strength (Inoue et al. 2022). Thus, the specific ageing of the hematopoietic system, and particularly macrophages, is sufficient to drive senescence and aged related failure in non-immune organs, such as skeletal muscle.

Dysregulation of circadian clock in Bmal1 deleted mice is sufficient to induce premature ageing and muscle wasting (Schiaffino et al. 2016), interestingly restauration of clock in both brain and skeletal muscle is sufficient to reverse sarcopenia by preserving muscle mass and force, and decreasing fibrosis and inflammation (Kumar et al. 2024). In zebrafish, the total body deletion of telomerase ($tert^{-/-}$), inducing telomeres shortening, provokes premature ageing phenotype and reduces lifespan (Anchelin et al. 2013). Restauration of telomerase in gut epithelial cells is sufficient to reverse systemic ageing and improves lifespan. Authors observed an increase of muscle thickness in zebrafish having tert only in gut, however, they did not realize any functional analysis (El Maï et al. 2023). Altogether, these studies demonstrated that sarcopenia is not only

linked muscle ageing but is also a consequence of other tissue ageing (Figure 4). Thus, a systemic response is needed to efficiently support whole-body health improvement.

6 | The Role of Exercise in Ameliorating Age-Related Muscle Decline

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure, whereas exercise is a subset of physical activity that is purposeful, planned, structured, and repetitive, performed with the goal of improving or maintaining health, fitness, or performance. Chronic sedentary behaviour and physical inactivity are key mechanistic drivers of sarcopenia and can accelerate the loss of muscle mass and strength, leading to impaired mobility, an increased risk of falls, and higher mortality (Montero-Fernández and Serra-Rexach 2013). Voluntary resistance wheel exercise has been shown to prevent sarcopenia and muscle wasting in aged male and female mice (14.5 months old), particularly in specific hindlimb muscles (White et al. 2016). These improvements were associated with an increased oxidative capacity, reflected by greater mitochondrial mass, and enhanced autophagy, indicated by a higher LC3II/I ratio, in both sexes. Furthermore, this form of exercise also confers benefits to other tissues, such as the heart. In agreement with this metabolic activation of the skeletal muscle in response to exercise, chronic endurance exercise, independently of time and intensity, induces the expression of the PGC-1α, the master regulator of mitochondrial integrity, function, and biogenesis (Moreira et al. 2017). This induction of PGC-1α in response to physical activity (running wheel) in mice is also shown to prevent mitochondrial fragmentation in skeletal muscle during ageing (Halling et al. 2017). An acute endurance and high-intensity interval exercise protocol induces activation of Nrf2 is a critical regulator of the adaptive antioxidant response in recreationally active young males. Beyond mitigating oxidative damage, Nrf2 signalling contributes to improved muscle performance by enhancing mitochondrial biogenesis and function (Islam et al. 2020). Exercise-induced mitophagy may benefit aged muscle by clearing damaged mitochondria, a notion supported by findings that a 6-month combined weight loss and moderate-intensity exercise programme upregulated mRNA expression of mitophagy markers (LC3II, Atg) and the lysosomal protein LAMP-2 in the vastus lateralis of overweight older women (Wohlgemuth et al. 2011). Exercise counteracts key hallmarks of ageing by mitigating oxidative damage and chronic inflammation while enhancing processes such as autophagy, mitochondrial function, and insulin sensitivity. Thus, exercise improves the metabolic decline in skeletal muscle associated to ageing, deaccelerating the deterioration of this tissue during ageing.

Myokines are a class of cytokines and signalling peptides expressed, synthesized, and secreted by skeletal muscle cells following contractions. These molecules, which include IL-6, IGF-1, irisin, myostatin, IL-15, and FGF-21, exhibit pluripotent effects on various tissues (J. H. Lee and Jun 2019). Exercise stimulates a healthy systemic anti-inflammatory environment primarily through myokine release and counteracts the age-related decline in muscle mass and function (Fiuza-Luces et al. 2018). In healthy male, including well-trained lean and physically inactive middle-aged individuals, the systemic concentration of the small leucine-rich proteoglycan decorin, a myokine, rises following both acute and chronic exercise, and is released from contracting human myotubes (Kanzleiter et al. 2014). Decorin appears to counteract muscle loss by inhibiting myostatin, a key negative regulator of muscle growth,

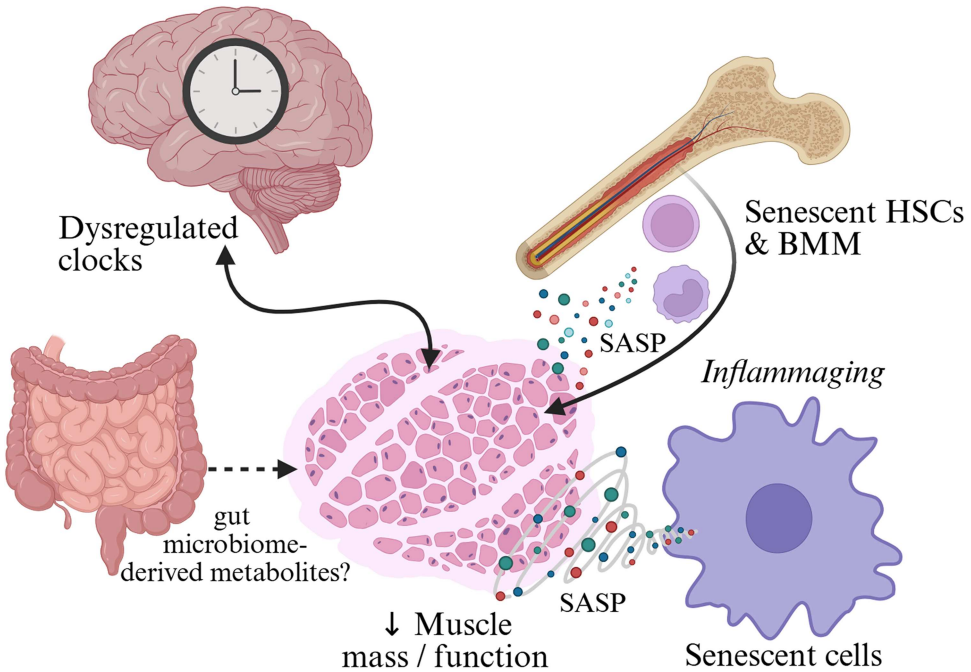

FIGURE 4 | Systemic signals received by aged skeletal muscle. Senescent cells, in particular senescent hematopoietic stem cells (HSCs) and senescent Bone Marrow Macrophages (BMM) promotes inflammaging inducing skeletal muscle dysfunction through Secretory Associated Senescent Phenotype (SASP). Circadian clocks dysregulation favours muscle wasting. Impact of gut ageing on muscle remains to be confirmed.

thereby reducing protein degradation (El Shafey et al. 2016). Similarly, circulating levels of irisin increase in 19-month-old male C57BL/6 mice with exercise (resistance ladder climbing training) and correlate positively with muscle strength measures, such as grip and leg strength (Kim et al. 2015). Apelin, an exercise-induced myokine whose levels normally decrease in an age-dependent manner in humans and rodents, mitigates age-related muscle wasting. It acts by triggering mitochondrial biogenesis, autophagy, and anti-inflammatory pathways in myofibers, and by enhancing regenerative capacity through its effects on SCs. (Vinel et al. 2018). Myokine cardiotrophin-like cytokine factor 1 (CLCF1) declines with age but is upregulated by exercise. Restoring CLCF1 levels in aged male mice (18–24 months old) improved physical performance, glucose tolerance, mitochondrial activity, and bone health, whereas blocking CLCF1 abolished these benefits (J. S. Kang et al. 2025). Higher levels of physical activity correlated with an anti-inflammatory shift in the cytokine profile, characterized by increased adiponectin and IL-10 and decreased pro-inflammatory cytokines (Sallam and Laher 2016). The attenuation of inflammation of age-related muscle changes by resistance exercise may be mediated, in part, by the downregulation of TNF-α expression in skeletal muscle (Gomes et al. 2017). Beyond effect on skeletal muscle, Liu et al observed that 6 weeks of wheel voluntary aerobic exercise in male C57BL/6 J mice of 22-months of age partially reverse transcriptomic changes of SCs toward young counterpart (Liu et al. 2023). They generated massive scRNAseq data from brain, muscle and hematopoietic system in sedentary and trained young and old mice (4 and 22 months of age). Importantly, they observed that beyond myogenic cells, exercise reverses age-induced gene expression modifications toward young profile in many cell types. Particularly, it ameliorates the elevated TNF-α and IFNγ pro-inflammatory pathways occurring with ageing in three analysed tissues (Liu et al. 2023). These findings establish myokines as a critical mediator of the protective effects of exercise on muscle, suggesting its potential as a therapeutic target for age-related musculoskeletal decline. Recently, it has been demonstrated that treadmill exercise prevents fibrosis associated with atrophy (denervation and tendon transection model) by directly promoting apoptosis of FAPs through myofiber secretion of the myokine musclin (X. Kang, Qian, et al. 2024). Moreover, when trained, the ability of old muscle to regenerate is improved (Liu et al. 2023) (X. Kang, Qian, et al. 2024). In frail elderly human (over the age of 75), resistance exercise training decreases TNF-α expression and secretion within skeletal muscle (Greiwe et al. 2001). Recent studies observed that exercise reduces biomarkers of senescence (such as p16, p21, cGAS, and IL-6) in old humans in circulating system and colon mucosa (Englund et al. 2021) (Demaria et al. 2023). Altogether, it means that exercise has a general positive effect on all tissue with the body and can preserve muscle from atrophy and sarcopenia (Table 1).

Beyond skeletal muscle and decrease of inflammatory pathways, exercise also impact neural system ageing. Sarcopenia has been previously associated with neural system deterioration such as impairment of neural transport mechanisms from 18 months of age in male and female C57BL/6 J mice, contributing to morphological and functional muscle deficits (Krishnan et al. 2016). However, voluntary resistance wheel exercise initiated at 15 months of age in C57BL/6 J male and female mice prevented sarcopenia but not the age-related cellular changes in peripheral nerves (Krishnan et al. 2017), indicating that the relationship between this specific exercise protocol and its capacity to modulate age-related neural changes remains unclear. Ageing also impacts spinal cord connectivity, with a selective loss of excitatory synaptic terminals on motor neurons, but no significant changes in inhibitory terminals, observed in sarcopenic mice aged 27 months, influencing their ability to activate muscle properly (Krishnan et al. 2018). Notably, 8 months of voluntary resistance wheel exercise initiated at 15 months of age had no effect on this spinal cord connectivity in male C57BL/6 J mice (V. S. Krishnan et al. 2025). In contrast, voluntary wheel-running exercise beginning in late middle age has been shown to prevent much of the age-associated loss of nerve terminal synaptophysin in female C57BL/6 J aged mice, with exercised animals spending approximately five-fold more time engaged in physical activity compared to sedentary controls (Cheng et al. 2013). Furthermore, a lifelong history of high-level physical activity in 70-year-old men has been associated with a larger population of re-innervated muscle fibres, suggesting that long-term physical activity can attenuate age-related denervation (Mosole et al. 2022). These findings highlight the complexity of the exercise-neural health relationship during ageing, likely reflecting differences in exercise type, protocol, intensity, duration, age of initiation, and interactions with sex and environment. Further studies with standardised protocols are needed to clarify the neuroprotective potential of exercise during ageing.

Furthermore, sarcopenia is associated with enhanced tumorigenesis, attributable to decreased secretion of muscle-derived extracellular vesicles with tumour-suppressive properties. In sarcopenic muscle, diminished extracellular vesicle secretion and altered cargo content attenuate tumour suppression, thereby establishing a muscle-to-tumour communication axis that is responsive to exercise (Goh et al. 2026). Interestingly, muscle response to exercise (resistance training and electrical stimulation) is similar between young and old humans in term of increase of SCs number, regenerating myofibers and myofibers size (Karlsen et al. 2020). Identically, SCs isolated from young and old muscle after 8 weeks of moderate intensity treadmill follow similar expansion capacity *in vitro* (Shefer et al. 2013). Collectively, these findings reveal that aged muscle is able to respond to exercise at the same extend than young muscle. However, the benefit of exercise relies on the positive feedback loop between exercise and muscle function to preserve muscle tissue and function during ageing and in aged-related diseases. The development of state-of-the-art technologies is revealing new factors involved in the effects of exercise on skeletal muscle, such as exercise-dependent post-translational modifications associated with aerobic and resistance training (Pataky et al. 2025). Twelve weeks of high-intensity aerobic exercise leads to alterations in the acetylproteome, including mitochondrial proteins, suggesting post-translational regulation of cellular energy metabolism. In contrast, resistance training over the same period drives changes in phosphoproteomic profiles linked to the contractile and cytoskeletal systems. These newly identified exercise-associated signatures may help uncover novel targets for understanding and preventing sarcopenia and muscle wasting.

TABLE 1 | Summary of evidence on the modulation of skeletal muscle hallmarks of ageing by exercise. References: (White et al. 2016) (Wohlgemuth et al. 2011) (Picard et al. 2013) (Iversen et al. 2011) (Broskey et al. 2014) (Kanzleiter et al. 2014) (Kim et al. 2015) (Seo et al. 2021) (Sáez de Asteasu et al. 2024) (J. S. Kang et al. 2025) (Marzuca-Nassr et al. 2024) (Latimer et al. 2022) (M. Zhang et al. 2024).

Hallmark of ageing modulated by exercise	Exercise type used in the intervention	Experimental model	References
Prevents sarcopenia and induces hypertrophy via enhanced mitochondrial biogenesis and autophagy.	34-week voluntary resistance wheel exercise	Aged C57BL/6 J mice (male and female)	White et al. (2016)
Mitochondrial membrane dynamics remodelling in skeletal muscle	3-h single bout of voluntary wheel running	C57BL/6 J female mice	Picard et al. (2013)
Decorin myokine mediates muscle hypertrophy and prevents muscle loss	Mice: 4-week treadmill (5×/week); Humans: acute resistance exercise + 12-week intervention	Mice and middle-aged men	Kanzleiter et al. (2014)
Irisin-induced improvements in muscle strength and function	Mice: 12-week ladder climbing (3×/week, tail weight) Humans: 12-week elastic band training (2×/week, 1 h/session)	Mice: 19 months, males (C57BL/6); Womens: > 65 years	Kim et al. (2015)
Glucose uptake, glycolytic flux, and mitochondrial metabolism	Aerobic and resistance for humans Treadmill for mice	Young, adult and elderly male and female participants Young and age mice	Kang et al. (2025)
VO2peak increased, along with an increase in muscle mitochondrial ATP production rate from palmitate after training.	An 8-week fully supervised aerobic cycling programme was performed, consisting of three 30-min sessions per week at 65% of VO2peak.	Healthy older adults aged 60–80 years	Latimer et al. (2022)
Enhanced skeletal muscle oxidative capacity	Cycling exercise bout at 75% VO2max	Older male and female adults (67-75 years old)	Iversen et al. (2011)
Improvements in mitochondrial function and content	16-week aerobic training (bike, walk, run, row), 3×/week at 75–80% HR	Sedentary and phy[sical...] male and female [participants...] years old	Broskey et al. (2014)
Muscle functional capacity	Resistance training, balance and walking exercises	Male and female aged over 75 years	Sáez de Asteasu et al. (2024)
Increases muscle mass, strength, and physical performance	Whole-body resistance training three times per week for 12 weeks, including lower- and upper-body exercises. Training intensity progressively increased from 60% to 80% of 1RM.	Two age groups (65–75 years and ≥ 85 years) including male and female human participants.	Marzuca-Nassr et al. (2024)
Improved physical function and muscle strength, accompanied by increased levels of muscle growth factors.	Resistance training: body weight-based and elastic band RT, 3x/week, 1 h per session, for 16 weeks	Adult women aged over 65 years	Seo et al. (2021)
Activation of autophagy and cellular quality control	6-month moderate-intensity exercise (aerobic, strength, flexibility)	Older adult women (55-79 years old)	Wohlgemuth et al. (2011)
Improved body composition, muscle strength and physical performance, blood pressure, lipid profile, and SF-36 health survey scores.	Progressive high-intensity resistance training over 12 weeks, increasing intensity	Older male and female individuals (≥ 65 years) diagnosed with sarcopenia.	Zhang et al. (2024)

In the field of exercise science, the development of novel training methods could further enhance our understanding of skeletal muscle physiological responses during ageing. One example is low-load resistance training with blood flow restriction, which has already shown promising effects on muscle strength and on sarcopenia-related blood biomarkers, including growth hormone, IG-F-1, myostatin, and follistatin (M. Zhang et al. 2024).

Overall, benefits of exercise are mediated through distinct exercise modalities—including resistance, aerobic, balance, and flexibility training—each targeting specific aspects of physical function (Angulo et al. 2020). Thus, exercise should be continuously performed across entire life, and actively implemented in older adults to counteract the skeletal muscle deterioration and sarcopenia. However, several considerations should be considered when performing exercise studies, including the inclusion of both sexes and appropriately aged sedentary controls. In addition, the impact of exercise may be muscle-specific, as certain training programmes may not prevent the loss of muscle mass or function in some muscles.

7 | Future Perspectives/Knowledge Gaps

Sarcopenia is driven by many molecular alterations and cellular dysregulation within the skeletal muscle itself, and from other tissues. This complexity and the size of muscle make it difficult to treat. While we have now some insights regarding effect of ageing on SCs, interactions with others cell types are far to be understood, especially in homeostasis. Identically, impact of low chronic inflammation is not elucidated yet, and we could hypothesize a feedback effect of skeletal muscle that potentially support the inflammaging process. As example, where are located senescent cells, what cell types? Where is the source of up-regulated/down-regulated factors during ageing? Moreover and unfortunately, many studies included only old male mice (Granic et al. 2023), research on female mice is needed as during ageing women mainly undergo sarcopenia induced menopause (Shrikhande et al. 2025), and a recent study-observed a phenotypic and molecular differences between old male and female mice (Kerr et al. 2024). There are muscle-specific differences in the extent to which sarcopenia affects skeletal muscles. In both quadrupedal and bipedal mammals, alterations are more pronounced in the lower (hind) limbs compared with the upper (fore) limbs (Larsson et al. 2019). This distinction should be taken into account when diagnostic criteria for sarcopenia rely primarily on measurements of upper-limb muscle mass or function. Exercise appears to be beneficial preserving and reversing sarcopenia, not only through direct effect on skeletal muscle but also on other tissues. Single-cell and single-nucleus RNA sequencing technologies have been increasingly applied to aged skeletal muscle, revealing complex cell type–specific regulatory mechanisms underlying muscle plasticity. These emerging approaches have identified age- and frailty-associated transcriptional changes across multiple cellular populations within mature skeletal muscle, including subsets of nuclei expressing senescence-related markers in aged human muscle (Perez et al. 2022). Such findings are improving the characterization of distinct cellular subpopulations associated with aging and sarcopenia. Collectively, these technologies are paving the way for the development of cell type–specific and targeted therapeutic strategies aimed at enhancing exercise responsiveness during aging and in the context of chronic disease (Murach and Peterson 2023). These new technologies lead to recent atlas realized on aged human skeletal muscle at homeostasis (Lai et al. 2024) and during regeneration (Brorson et al. 2025) combined with spatial transcriptomics will surely help to improve our comprehension of sarcopenia and identified new targets and biomarkers to counteract muscle decline providing a better care of frailty.

Author Contributions

Juan Diego Hernández-Camacho: funding acquisition, writing – original draft, writing – review and editing, **Marielle Saclier:** funding acquisition, writing – original draft, writing – review and editing.

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Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The authors have nothing to report.

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