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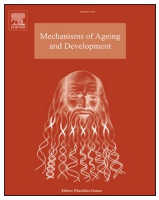

Defective mitochondrial quality control in the aging of skeletal muscle

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ABSTRACT

Age-related skeletal muscle decline is a major contributor to frailty, functional impairment, and loss of independence in advanced age. This process is characterized by selective atrophy of type II fibers, impaired excitation–contraction coupling, and reduced regenerative capacity. Emerging evidence implicates mitochondrial dysfunction as a central mechanism in the disruption of muscle homeostasis with age. Beyond ATP production, mitochondria orchestrate redox signaling, calcium handling, and apoptotic pathways, which are increasingly compromised in aged muscle due to chronic oxidative stress and defective quality control. High-resolution respirometry has revealed intrinsic, lifestyle-independent declines in mitochondrial respiratory capacity, while large-scale phenotyping and transcriptomic profiling have established robust associations between mitochondrial integrity, physical performance, and mobility. These findings have prompted a paradigm shift from static descriptions of mitochondrial decline toward dynamic analyses of mitochondrial signaling networks and stress adaptability. Several quality control mechanisms, including mitochondrial biogenesis, dynamics, mitophagy, and vesicle trafficking, emerge as critical regulators of myocyte integrity. Understanding how these systems deteriorate with age will be pivotal for developing therapeutic targets to preserve muscle function, mitigate sarcopenia, and extend health span.

1. Introduction

Skeletal muscle aging is characterized by a progressive decline in muscle mass, strength, and metabolic efficiency, which increases the risk of physical frailty and loss of independence in late life. These changes begin in early adulthood and accelerate with advancing age (Kirk et al., 2024). At the cellular level, aging muscle exhibits selective atrophy of type II fibers, altered excitation–contraction coupling, and impaired regenerative capacity (Lexell, 1995). Multiple intrinsic and extrinsic drivers, including genetic, metabolic, and environmental stressors, converge to disrupt muscle homeostasis (Picca et al., 2023b).

Mitochondria are central regulators of muscle function and their dysfunction is recognized as a hallmark of aging. Beyond their role in ATP production, mitochondria govern redox balance, calcium homeostasis, and apoptotic signaling. The long-standing mitochondrial free radical theory posits that aging results from cumulative damage driven by mitochondrial reactive oxygen species (ROS) (Barja, 2013). While this concept has evolved, oxidative stress remains a consistent feature of aged muscle, often exceeding antioxidant buffering capacity (Ferrucci et al., 2020), as indicated by elevated levels of oxidative stress markers (e.g., protein carbonyls, lipid peroxidation products) in aged human skeletal muscle and preclinical models (Beltran Valls et al., 2015; Ferrucci et al., 2020). High-resolution respirometry studies confirm that mitochondrial respiratory function declines with age independently of physical activity and changes in body composition, implicating intrinsic organellar dysfunction (Gonzalez-Freire et al., 2018).

Recent large-scale analyses have linked mitochondrial health with key physiological metrics, such as muscle strength, endurance, and mobility (Gonzalez-Freire et al., 2018; Mau et al., 2023; Qiao et al., 2024). Transcriptomic studies in the same cohorts further reveal an inverse correlation between gene expression of markers of mitochondrial quality control (MQC) and physical performance. This has shifted the conceptual framework from “mitochondrial dysfunction” to a broader view emphasizing “mitochondrial signaling and adaptive capacity” during aging (Monzel et al., 2023). In this context, MQC, encompassing mitochondrial proteostasis, biogenesis, dynamics, autophagy, and

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vesicle trafficking, emerges as a central node in the maintenance of myocyte integrity (Picca et al., 2018). Understanding the mechanisms underpinning the dysregulation of these pathways is critical for identifying molecular targets to delay or reverse muscle aging.

2. Mitochondrial quality control mechanisms: hierarchical defense against organelle stress

MQC encompasses a multistep network of surveillance and repair pathways that safeguard mitochondrial integrity and function. These mechanisms act in a coordinated and temporally regulated manner in response to stress-induced damage, ranging from protein misfolding to irreversible membrane depolarization. Through integrated responses, including proteostasis, dynamics, mitophagy, and vesicle formation, MQC adapts mitochondrial output to cellular needs, prevents the accumulation of dysfunctional organelles, and maintains metabolic flexibility.

Under transient or mild stress, adaptive responses such as the mitochondrial unfolded protein response (mtUPR) and antioxidant system activation are engaged (Paasch et al., 2018; Weidberg and Amon, 2018). These pathways promote the expression of chaperones, detoxifying enzymes, and proteases to restore proteome integrity and redox balance. If these responses prove insufficient, mitochondrial dynamics (i.e., fission and fusion) become critical. Fusion supports complementation and dilution of localized damage, while fission facilitates the isolation of defective mitochondrial segments destined for degradation (Archer, 2013).

When damage surpasses a critical threshold, marked by sustained membrane depolarization, impaired ATP production, or leakage of pro-apoptotic factors, mitophagy is activated to eliminate damaged mitochondria (Picca et al., 2023a). In the event of extensive and irreparable injury, apoptotic pathways are engaged to prevent further propagation of dysfunction. Hence, this final stage of MQC acts as a fail-safe mechanism when repair and containment are no longer achievable. Altogether, these time- and damage-dependent processes ensure that cells can dynamically respond to mitochondrial insults, initially favoring recovery and repair, and only resorting to elimination or cell death in case of absolute necessity. Given the central role of MQC for maintaining mitochondrial and cellular homeostasis, its dysfunction has been increasingly implicated in aging, neurodegeneration, cancer, and metabolic disease (Picca et al., 2023a, 2018).

Beyond bulk turnover, mitochondria can also release specialized 100 nm vesicles, termed mitochondria-derived vesicles (MDVs), under mild stress conditions (Sugiura et al., 2014). MDVs transport selected cargo, including oxidized proteins and lipids, to lysosomes and peroxisomes, facilitating localized clearance without sacrificing the entire

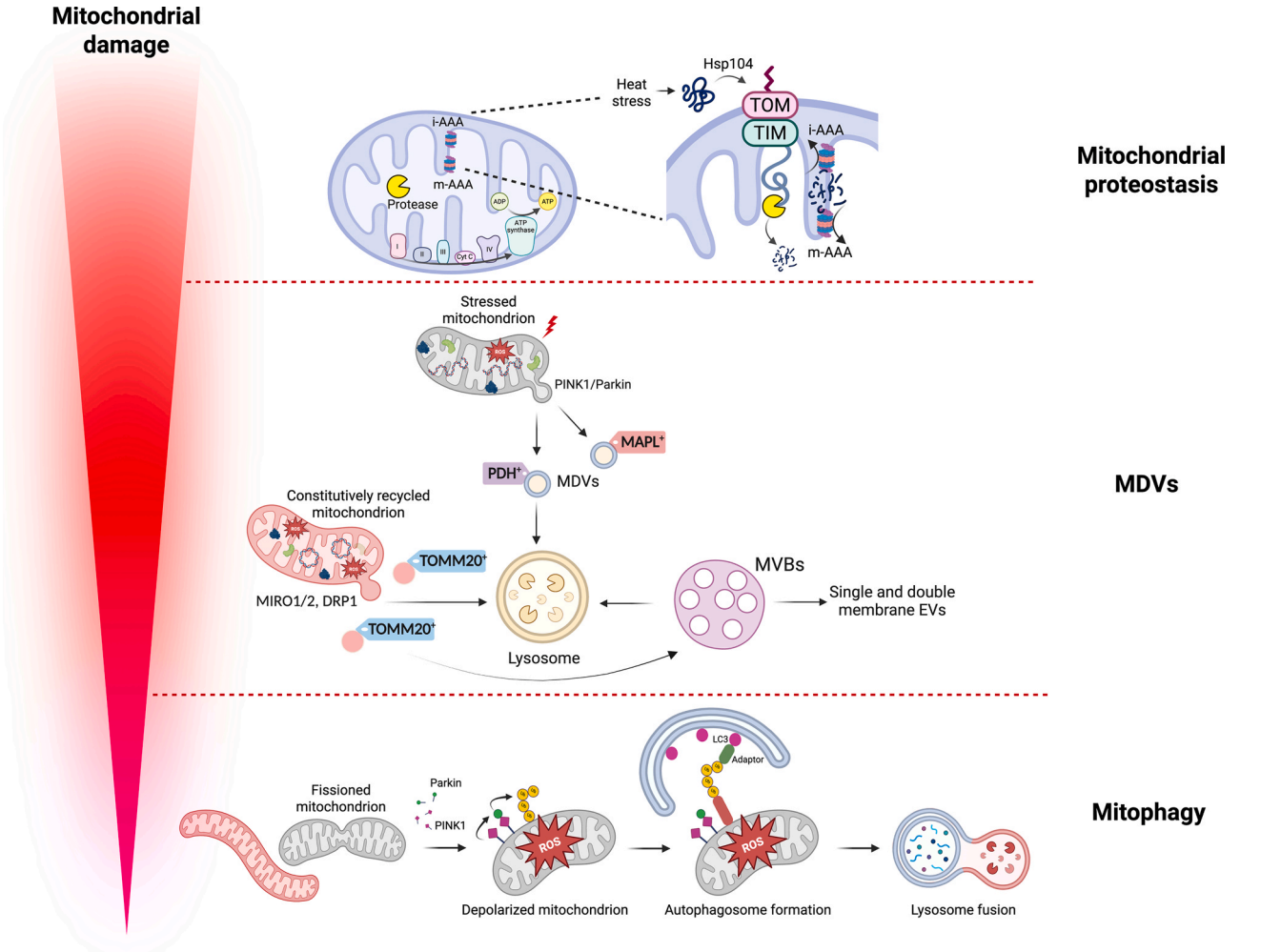

Fig. 1. Schematic representation of the mitochondrial quality control pathways recruited according to varying degree of mitochondrial damage. Abbreviations: DRP1, dynamin related protein 1; EVs, extracellular vesicles; Hsp, heat shock protein; i-AAA, intermembrane space-AAA metalloproteases; LC3, microtubule-associated protein 1 light chain 3; m-AAA, matrix-AAA metalloproteases; MAPL, Mitochondria-Associated Protein Ligase; MDVs, mitochondria-derived vesicles; MIRO1/2, Mitochondrial Rho GTPase 1 and 2; MVBs, multivesicular bodies; PDH, pyruvate dehydrogenase; PINK, phosphatase and tensin homologue-induced putative kinase 1; ROS, reactive oxygen species; TIM, translocase of inner membrane; TOM, translocase of outer membrane.

organelle. Hence, these vesicles serve as an early line of defense, acting prior to mitophagy and providing fine-tuned quality control at the sub-organelle level (Sugiura et al., 2014).

While persistent MQC alterations favor the production of damaged and depolarized mitochondria, transient MQC misalignment is protective to the cell. Indeed, dysfunctional and depolarized organelles are tagged and segregated from the network to allow mitophagy removal (Duvezin-Caubet et al., 2006). This requires rapid inactivation of mitochondrial fusion by stress-induced proteolytic cleavage of the fusion protein optic atrophy 1 (Duvezin-Caubet et al., 2006; Ishihara et al., 2006). As a result, changes in mitochondrial morphology and the activation of mitophagy are considered cytoprotective responses that help alleviate intracellular mitochondrial dysfunction and prevent the initiation of programmed cell death (Fig. 1).

2.1. Ubiquitin–proteasome system in mitochondrial proteostasis

Under conditions of mild mitochondrial stress, the mitochondrial protease–chaperone network acts as a molecular safeguard system (Baker et al., 2011). This preserves mitochondrial protein homeostasis by detecting and removing misfolded or oxidatively damaged proteins (Baker et al., 2011). The mitochondrial proteolytic compartment is auxiliary to the cytosolic counterpart and relies on ATP-dependent Lon proteases of the mitochondrial matrix that import and degrade cytosolic misfolded protein aggregates (Ruan et al., 2017). This functional proteolytic versatility underscores a conserved cross-compartmental mechanism of proteostasis that helps buffer and alleviate proteotoxic stress (Quiles and Gustafsson, 2020).

However, under conditions of elevated cellular energy demand or mitochondrial dysfunction, this machinery may be overwhelmed, leading to cytosolic accumulation of misfolded mitochondrial precursor proteins (Mårtensson et al., 2019; Weidberg and Amon, 2018; Wrobel et al., 2015).

In response, the ubiquitin–proteasome system (UPS) acts as a complementary extramitochondrial quality control pathway. Nuclear-encoded mitochondrial precursor proteins that fail to enter the mitochondrion are ubiquitinated at the outer mitochondrial membrane (OMM) and targeted for degradation by the 26S proteasome (Saeki, 2017). This cascade involves E1 ubiquitin-activating enzymes, E2 conjugating enzymes, and substrate-specific E3 ligases such as mitochondrial E3 ubiquitin protein ligase 1 (MUL1), membrane associated ring-CH-type finger 5 (MARCH5), and ring finger protein 185 (RNF185), all localized to the OMM (Karbowski et al., 2007; Narendra et al., 2008; Yonashiro et al., 2006).

Polyubiquitin chains are recognized by ubiquitin-binding adaptor proteins (e.g., RAD23, p62) or directly by proteasomal receptors (Saeki et al., 2002). The 19S regulatory particle unfolds the substrate in an ATP-dependent manner and translocates it to the 20S core for proteolytic cleavage (Finley, 2009). Deubiquitylating enzymes (DUBs) concurrently recycle ubiquitin moieties to maintain proteostasis flux (Amerik and Hochstrasser, 2004). These degradation pathways not only prevent the accumulation and aggregation of mitochondrial precursors on the organelle surface but also act as a critical surveillance mechanism that preserves mitochondrial import efficiency and organellar integrity under proteotoxic stress (Voos et al., 2016; Wrobel et al., 2015). Importantly, UPS dysfunction has been implicated in age-related muscle decline and neurodegenerative conditions, reinforcing the relevance of proteasomal maintenance for mitochondrial and cellular health (Ruan et al., 2017; Van Acker et al., 2024).

2.2. Mitophagy

Mitophagy is a selective form of autophagy responsible for the removal of dysfunctional or superfluous mitochondria (Picca et al., 2023a). By preventing the accumulation of damaged organelles, mitophagy prevents the buildup of somatic mitochondrial (mtDNA) mutations, limits ROS generation, and preserves bioenergetic efficiency. These functions place mitophagy as a central process in health and disease (Picca et al., 2023a).

Two main mitophagy pathways have been characterized in mammals. The first and best characterized is the phosphatase and tensin homologue (PTEN)-induced putative kinase 1 (PINK1)–Parkin-dependent pathway which is considered the canonical mitophagy route (Palikaras et al., 2018). Under basal conditions, PINK1 is rapidly degraded at the mitochondrial surface. Upon membrane potential loss, PINK1 accumulates at the OMM, recruits Parkin, and catalyzes the formation of phospho-ubiquitin chains on mitochondrial surface proteins. These ubiquitin tags serve as docking sites for autophagy receptors (e.g., p62, optineurin, nuclear dot protein 52) (Lazarou et al., 2015), which in turn engage microtubule-associated protein light chain-3 (LC3) to drive mitophagosome formation and lysosomal degradation.

PINK1–Parkin-independent mitophagy operates through receptor-mediated pathways. Mitophagy receptors, such as BCL-2 and adenovirus E1B 19-kDa-interacting protein 3 (BNIP3), BNIP3-L also referred to as NIX, and FUN14 domain containing 1, are embedded in the mitochondrial membrane and contain LC3-interacting regions (LIRs), allowing direct recruitment of autophagic machinery (Terešak et al., 2022). These alternative routes may dominate in specific tissues or under hypoxic and metabolic stress conditions. Crosstalk between PINK1–Parkin dependent and independent mitophagy pathway. For example, BNIP3 stabilizes PINK1 (Zhang et al., 2016), while both BNIP3 and NIX enhance Parkin recruitment (Lee et al., 2011), suggesting a convergent regulatory architecture.

Spatiotemporal and cell-specific mitophagy dynamics have been described in mouse brain aging (Nikoletopoulou, 2024). Emerging evidence indicates that discrete mitochondrial subdomains can be selectively degraded without complete organelle degradation through process called “piecemeal mitophagy”. This process involves MDV generation and represents an early form of quality control preceding wholesale mitophagy. Such compartmentalized turnover underscores the dynamic and stepwise nature of MQC responses in aging muscle. Molecular details of this recycling machinery and its implications in health and disease are discussed in the next section.

2.3. Mitochondria-derived vesicles

Extracellular vesicles (EVs) are a heterogeneous group of membrane-bound particles that include exosomes, microvesicles, and apoptotic bodies (El Andaloussi et al., 2013). These subtypes are classified based on their size, content, and biogenesis pathways. Exosomes (30–150 nm) arise from the endosomal system, while microvesicles (100–1000 nm) bud from the plasma membrane and apoptotic bodies (0.5–5 μm) are released during programmed cell death (El Andaloussi et al., 2013). Given their diverse origins and cargo, assessing the abundance and function of distinct EV subtypes is crucial, especially in the context of aging, where intercellular communication and damage resolution are disrupted.

The biogenesis of EVs, particularly exosomes, is mediated by the endosomal sorting complex required for transport (ESCRT), which regulates the inward budding of multivesicular bodies (MVBs) and the formation of intraluminal vesicles. This process is tightly regulated and essential for proper sorting of specific cargo into EVs (Jeppesen et al., 2023).

MDVs are a notable subtype of EVs involved in MQC (Sugiura et al., 2014). MDVs form in response to mitochondrial stress, selectively encapsulating damaged mitochondrial components for degradation or secretion (König and McBride, 2024). These vesicles participate in mitochondrial surveillance and are trafficked via pathways involving SNAP receptor (SNARE)-mediated fusion with lysosomes, incorporation into multivesicular bodies (MVBs), or endo–lysosomal sorting.

Several studies have confirmed the presence of mtDNA and other mitochondrial components within circulating EVs (Beatriz et al., 2022;

Lazo et al., 2021). Notably, in neurodegenerative diseases like Huntington's disease, defects in the mitochondria–lysosome axis are linked to increased EV release containing mtDNA, supporting a link between mitochondrial dysfunction and EV-mediated intercellular communication (Beatriz et al., 2022). Beyond MDVs, small EVs (sEVs) with mitochondrial content have been identified. These double-membraned vesicles referred to as mitovesicles are smaller than MDVs and have been shown to carry mtDNA and even intact, functional mitochondria.

Circulating levels of mtDNA-containing EVs decline with age, suggesting that they may possess signaling roles in age-related diseases (Ferrucci et al., 2024; Lazo et al., 2021). Furthermore, some sEVs are capable of transferring bioenergetically functional mitochondria to recipient cells, highlighting their potential for mitochondrial rejuvenation therapies (Thomas et al., 2022).

MicroRNAs (miRNAs) are another key cargo of EVs. Generation of exosome-associated miRNA and EV carrying damage-associated molecular patterns (DAMPs) may converge on pathways critical for MQC, especially under stress. A small set of exosomal miRNAs (e.g., miR-34a, miR-181c, miR-210) has been shown to regulate mitochondrial dynamics, mitophagy, and oxidative stress by targeting genes involved in PINK1–Parkin-mediated mitophagy, dynamin related protein 1-mediated fission, or sirtuin 1 (SIRT1)–peroxisome proliferator-activated receptor gamma coactivator-1alpha (PGC-1α) axis, which are central to mitochondrial biogenesis and repair. For instance, miR-34a promotes endothelial dysfunction and mitochondrial-mediated apoptosis by targeting SIRT1 and facilitating p53 and BAX translocation to mitochondria. Growing evidence has also shown that exosome-associated miRNAs modulate mitochondrial function and stress responses during aging. For example, miR-34a promotes endothelial dysfunction and mitochondrial-mediated apoptosis by repressing SIRT1, activating p53 signaling, and contributing to senescence (Yamakuchi et al., 2008). Moreover, miR-181c targets mitochondrial complex IV genes, altering bioenergetics and enhancing oxidative stress, particularly in cardiac tissue (Das et al., 2012). Finally, miR-210, often upregulated in hypoxia, disrupts mitochondrial respiration via downregulation of iron–sulfur cluster assembly enzyme, affecting iron–sulfur cluster assembly and redox balance (Chan et al., 2009). These miRNAs are intricately linked to mitochondrial fission/fusion, mitophagy (e.g., PINK1–Parkin pathways), and biogenesis (e.g., PGC-1α axis), all of which show altered regulation during aging and contribute to age-associated decline in mitochondrial quality control. In parallel, EVs can transport mitochondrial DAMPS (mtDAMPs), including mtDNA, cardiolipin, and N-formyl peptides, which activate innate immune sensors such as toll-like receptor 9 (TLR9), the NLR family pyrin domain containing 3 (NLRP3) inflammasome, and the cyclic GMP–AMP synthase-stimulator of interferon genes (cGAS–STING) signaling pathway. For instance, the accumulation of damaged mitochondria due to impaired mitophagy leads to NLRP3 inflammasome activation. mtDNA stress can also prime antiviral innate immune responses via the cGAS–STING pathway. Additionally, mitochondrial inner membrane permeabilization enables the release of mtDNA into the cytosol, further eliciting immune responses. These pathways not only reflect the mitochondrial origin of some DAMPs but also signal the need for mitochondrial clearance or repair. Through these mechanisms, both exosomal miRNAs and DAMP-loaded EVs participate in the maintenance and/or disruption of mitochondrial homeostasis, linking cellular communication with mitochondrial quality surveillance.

To support the reproducibility and rigor of EV research, the Minimal Information for Studies of Extracellular Vesicles (MISEV) emphasizes the importance of using complementary methods for EV characterization, including assessing their size, morphology, and molecular markers, while recommending transparent reporting and proper experimental controls (Welsh et al., 2024). In summary, the study of EV subtypes, particularly those containing mitochondrial components, offers valuable insights into cellular communication, disease mechanisms, and potential therapeutic strategies. Adhering to standardized guidelines like MISEV2023 is essential for advancing our understanding and application of EV biology.

3. Evidence of altered mitochondrial quality control processes in muscle aging

Altered MQC signaling may lead to several negative consequences spanning from mitochondrial dysfunction and reduced energy production to overwhelming ROS production and cell death. Indeed, compromised MQC is often associated with accumulation of low-quality organelles that correspond to reduced energy available for cell activities thus compromising cellular function. This is particularly relevant in high energy-demanding tissues, including skeletal muscle, that heavily rely on oxidative metabolism (Coen et al., 2024; Mosharov et al., 2025; Picca et al., 2018). Low-quality mitochondria produce large rates of ROS which can oxidize cellular components and further amplify mitochondrial and cellular damage. Generation of such inefficient organelles has been related to an overall decline of MQC pathways (Fig. 2). The persistence of unresolved mitochondrial damage can trigger cell death and contribute to tissue damage and organ failure.

3.1. Altered proteostasis in muscle aging: mechanisms and therapeutic targets

At the molecular level, amino acid modifications of the myosin globular head have been described in aged skeletal muscles and associated with altered myosin ATPase activity and filament formation (Neal et al., 2024). Accumulation of polyubiquitinated proteins in the muscle, likely indicating disrupted proteostasis, has also been reported (Neal et al., 2024). Decline in protein folding and elimination was linked with reduced muscle functional capacity as evidenced by lack of muscle recovery from disuse in aged rats (Fuqua et al., 2023).

A recent study also described direct and acute inhibitory effects of advanced glycation end-products (AGEs) on protein degradation pathways, including autophagy and the ubiquitin–proteasome system, in isolated murine skeletal muscle fibers (Zhao et al., 2024). Suppression of protein synthesis and inhibition of the mechanistic target of rapamycin signaling (mTOR) were also described. As an effect of AGE administration, endoplasmic reticulum stress and altered expression of inflammatory cytokines were identified (Zhao et al., 2024). Impairment in skeletal muscle proteostasis has also been described in mice on lifelong protein restriction hindering muscle growth and favoring muscle fiber loss (Ersoy et al., 2024). In further support of the contribution of autophagy and proteostasis decline to muscle fiber loss are findings showing that the inhibition of mTOR complex 1 (mTORC1) blunts skeletal muscle protein synthesis in aged rats, with p62 aggregates accumulating over time (Tang et al., 2019). Enhanced mTORC1 activity in aged muscle promotes expression of genes involved muscle catabolism, thus contributing to myofiber loss. Notably, treatment with rapamycin was shown to mitigate these effects and preserve muscle structure and function (Tang et al., 2019).

Physical exercise has been included among the strategies able to counteract the age-associated decline in mitochondrial proteostasis (de Smalen et al., 2023). This effect is mediated, at least partly, by PGC-1α and estrogen-related receptor α signaling pathways. Specifically, an induction of PGC-1α activity was able to ameliorate the age-related reduction of mitochondrial translation and quality control processes (de Smalen et al., 2023). Moreover, the combined administration of metformin and leucine to differentiated myotubes and isolated mice myofibers effectively prevented muscle atrophy by regulating skeletal muscle proteostasis and cellular senescence (Petrocelli et al., 2023) (Table 1).

3.2. Altered mitophagy in muscle aging: mechanisms and therapeutic targets

Via mitophagy cells can limit the accumulation of defective

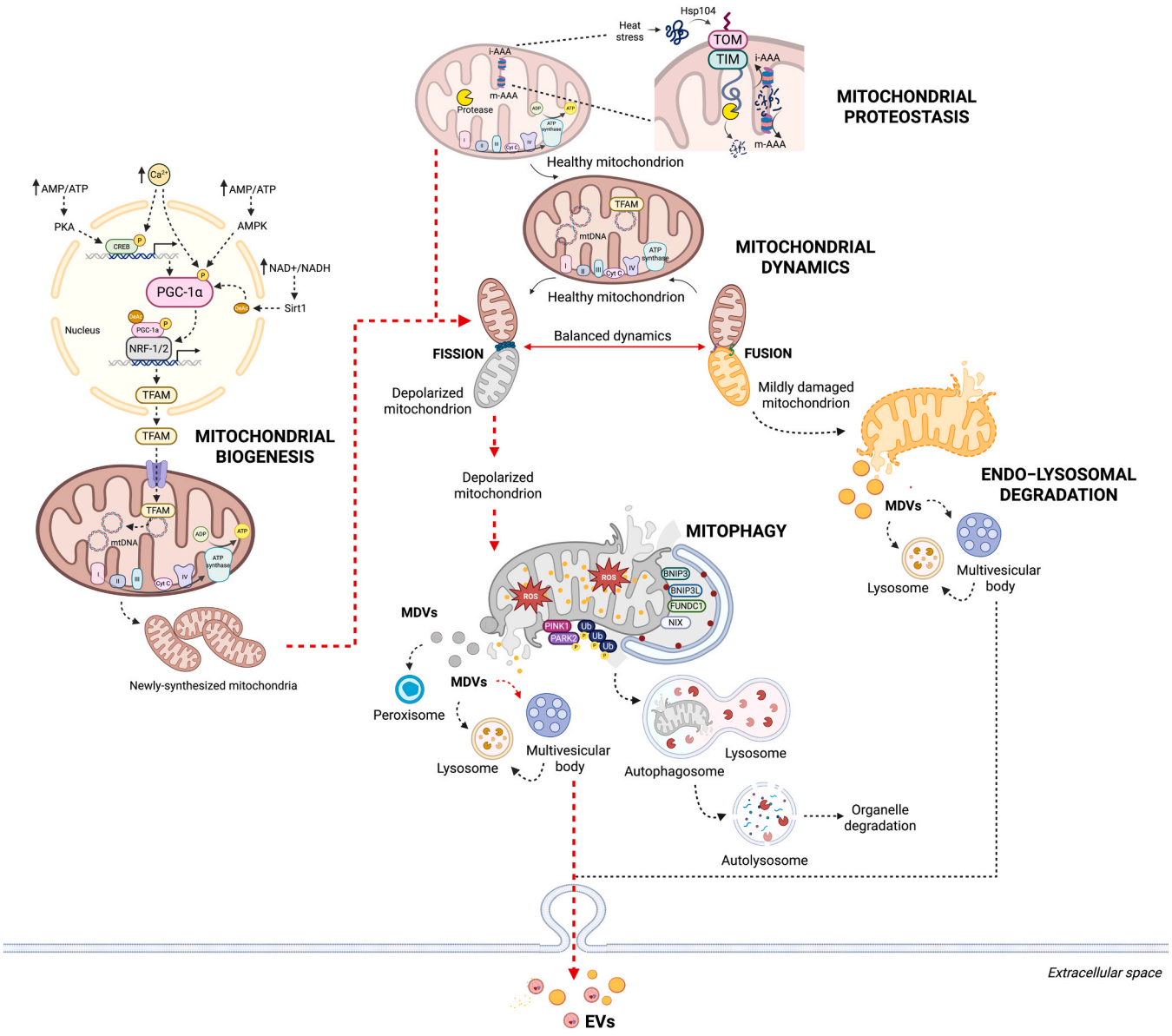

Fig. 2. Schematic representation of the main pathways involved in the age-related decline of mitochondrial quality contributing to muscle aging. Abbreviations: AMPK, adenosine monophosphate-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19 kDa interacting protein 3; BNIP3L, BCL2/adenovirus E1B 19 kDa interacting protein 3-like; CREB, cAMP response element-binding protein; EVs, extracellular vesicles; FUNDC1, FUN14 domain-containing protein 1; Hsp, heat shock protein; i-AAA, intermembrane space-AAA metalloproteases; LC3, microtubule-associated protein light chain-3; m-AAA, matrix-AAA metalloproteases; MDVs, mitochondria-derived vesicles; pyruvate dehydrogenase; mtDNA, mitochondrial DNA; NADH, nicotinamide adenine dinucleotide; NRF, nuclear respiratory factor; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK, phosphatase and tensin homologue-induced putative kinase 1; PKA, protein kinase A; ROS, reactive oxygen species; Sirt1, sirtuin 1; TFAM, mitochondrial transcription factor A; TIM, translocase of inner membrane; TOM, translocase of outer membrane; Ub, ubiquitin.

organelles and, therefore, the generation of large amounts of ROS and/or release of pro-apoptotic/pro-inflammatory factors. Decline in mitophagy compromises also mitochondrial proteostasis and energy metabolism, fostering oxidative stress and myofiber degeneration. While increased expression of mitophagy-associated factors (i.e., PINK1, Parkin, LC3II, p62, Beclin-1, and fission protein 1) may suggest higher mitophagy signaling in aged skeletal muscle, this may actually reflect an accumulation of mitophagy intermediates rather than effective mitochondrial clearance (Yeo et al., 2019).

Overexpression of the biogenesis regulator PGC-1α has been shown to attenuate these alterations in the skeletal muscle of aged mice and to improve mitochondrial quality and function (Yeo et al., 2019). Parallel evidence indicates also BNIP3 as a critical mediator of mitophagy flux and lysosomal homeostasis in aging muscle (Irazoki et al., 2022). BNIP3 deficiency leads to the accumulation of dysfunctional mitochondria also due to impaired lysosomal degradation and triggers TLR9/NLRP3-driven inflammation. These events, while accelerating myofiber atrophy in mice, are associated with reduced muscle inflammation in humans thus indicating a role in modulating skeletal muscle aging (Irazoki et al., 2022). Findings in humans confirm these observation. In skeletal muscle biopsies from frail sedentary older women, a reduced expression (~ 40 %) of BNIP3, Parkin, and other mitophagy-autophagy genes was found which was associated with lower lean mass and poorer physical performance (Drummond et al., 2014). In addition, results from the large Study of Muscle, Mobility and Aging (SOMMA) identified higher expression of genes involved in autophagy in the skeletal muscle of older adults and their association with physical performance, muscle volume, and mitochondrial function (Coen et al.,

Table 1
List of studies describing altered mitochondrial quality control mechanisms in muscle aging.

MQC mechanism	Organism	Key findings	Ref.
Proteostasis	Human and mouse	Age-associated post-translational modifications in myosin reduce are associated with proteostasis collapse and dysfunction and myosin dysfunction	(Neal et al., 2024)
	Rats	Aged muscle recovery is limited by impaired protein degradation but not synthesis	(Fuqua et al., 2023)
	Mouse (ex vivo)	AGEs cause endoplasmic reticulum stress and autophagy inhibition via AGE receptor and proteostasis imbalance	(Zhao et al., 2024)
	Mouse	Long-term protein restriction disrupts mitochondrial and proteostatic networks, promoting atrophy	(Ersoy et al., 2024)
	Mouse (TSC1 KO model)	Chronic activation of mTORC1 induces oxidative damage and alters proteostasis in aging skeletal muscle which is blunted by rapamycin	(Tang et al., 2019)
Mitophagy	Mouse	Aging increases mitophagy markers (PINK1, Parkin, LC3II, etc.); PGC-1α overexpression improves mitochondrial quality	(Yeo et al., 2019)
	Mouse and human	BNIP3 required for mitophagy and lysosomal function; BNIP3 expression in old humans linked to reduced inflammation	(Irazoki et al., 2022)
	Mouse	Aging and sex affect mitophagy response to exercise; TFEB and lysosomal regulation involved	(Triolo et al., 2022)
	Human	Frail older women show ~ 40 % reduction in BNIP3, Parkin, autophagy gene expression which correlate with reduced muscle performance	(Drummond et al., 2014)
	Human	Lifelong exercise allows preserves PGC-1α, LC3II, and BNIP3 levels compared to sedentary older adults	(Dethlefsen et al., 2018)
EVs	H9c2 cardiac myoblasts	MDV release occurs at steady state as a housekeeping process; increases with mitochondrial stressors like antimycin-A; shifts to mitophagy under severe stress	(Cadete et al., 2016)
	Human	Elevated circulating small EVs containing mitochondrial component associated with frailty and sarcopenia	(Picca et al., 2020)
	C2C12 cells and mouse muscle regeneration models	MDVs may remove suboptimal mitochondria during differentiation, ensuring organelle quality	(Todkar et al., 2021)
	Mouse skeletal muscle and satellite cells	EVs from young mice enhance MyoD/desmin, reduce Pax7, improve mitochondria, promote regeneration, deliver Klotho mRNA	(Sahu et al., 2021)

Abbreviations: AGEs, advanced glycation end products; BNIP3, Bcl-2 and adenovirus E1B 19-kDa-interacting protein 3; EVs, extracellular vesicles; LC3II, microtubule-associated protein 1 light chain 3; KO, knockout; MDVs, mitochondria-derived vesicles; MQC, mitochondrial quality control; mTORC1, mammalian target of rapamycin complex 1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PINK1, phosphatase and tensin homologue-induced putative kinase 1; TFEB, transcription factor EB; TSC1 KO, tuberous sclerosis complex 1 knockout.

2024).

Exercise is a potent modulator of mitophagy. In both rodents and humans, endurance training stimulates mitophagy, particularly via transcription factor EB (TFEB) activation, and improves lysosomal biogenesis, with sex-specific differences (Triolo et al., 2022). Lifelong exercise in humans also preserves PGC1α, p53, and p21 expression, and autophagy/mitophagy proteins (LC3II, BNIP3) in older adults, likely mimicking youthful muscle quality profiles (Dethlefsen et al., 2018). A recent study also showed that the SIRT1 activator SRT2104 exerts exercise-mimetic effects and promotes recovery in Duchenne muscular dystrophy by targeting PGC-1α–mediated signaling, thereby supporting the therapeutic potential of pharmacological interventions that mimic exercise-induced mitochondrial adaptations (Giovarelli et al., 2025). Altogether these findings indicate that the PGC-1α, PINK1–Parkin, and BNIP3 axis may be a therapeutic target to counteract age-related mitochondrial dysfunction and muscle loss (Table 1).

3.3. Altered mitochondria-derived vesicle signaling in muscle aging: mechanisms and therapeutic targets

The release of MDVs under steady-state conditions has been described, including in H9c2 cardiac myoblasts whereby it acts as a housekeeping mechanism supporting cell quality more actively than mitophagy (Cadete et al., 2016). This secretion is amplified by treatment with the mitochondrial stressors (i.e., antimycin-A and/or xanthine/xanthine oxidase). This early response is thereafter shifted toward mitophagy following severe or irreversible mitochondrial damage (Cadete et al., 2016). Elevated levels of circulating sEVs enriched with mitochondrial components, have been described in older adults with physical frailty and sarcopenia in whom declines in mitochondrial quality were shown (Picca et al., 2023c, 2020).

MDV generation has been attributed a role in mitochondrial remodeling during myogenesis. Undifferentiated myoblasts display mitochondria with immature cristae and limited β-oxidation; myoblast differentiation, instead, imposes cristae reorganization supporting a shift toward a more oxidative phenotype. This metabolic transition is needed to meet the high ATP demand enabling myotube formation and function (Robinson et al., 2019; Sin et al., 2016). This metabolic transition may be facilitated by MDV-mediated removal of suboptimal mitochondrial components, thus maintaining a pool of metabolically competent organelles during muscle regeneration (Todkar et al., 2021). Circulating EVs seem to play a role in the regulation of skeletal muscle regeneration also via systemic signaling. In vitro studies have shown that aged muscle satellite cells exhibit improved myogenic potential when exposed to serum from young individuals (Brack et al., 2007; Conboy et al., 2005). Expanding on this, Sahu et al. (Sahu et al., 2021) demonstrated that EVs isolated from young mouse serum exerted a rejuvenating influence on aged skeletal muscle stem cells. This includes

upregulation of myogenic markers MyoD and desmin and enhanced mitochondrial function and bioenergetics (Sahu et al., 2021). A concomitant downregulation of Pax7 expression was identified, potentially indicating accelerated progression toward myogenic differentiation (Sahu et al., 2021). Furthermore, systemic administration of young EVs via tail vein injection promoted muscle regeneration in tibialis anterior injured muscle of aged mice, with EVs accumulating at the injury site and increasing local MyoD expression (Sahu et al., 2021). Machine learning analyses further revealed a marked decline in EV heterogeneity with age, including loss of EV subpopulations carrying Klotho mRNA, an anti-aging transcript implicated in mitochondrial maintenance and muscle repair (Sahu et al., 2021). Functional studies confirmed that Klotho-enriched EVs improve mitochondrial function in vitro and facilitate in vivo regeneration of injured aged muscle (Sahu et al., 2021). Collectively, these findings suggest that MDVs and EVs may serve as vital contributors to mitochondrial homeostasis and regenerative signaling in muscle, particularly under physiological and low-grade stress conditions. Although mechanistically distinct, both vesicle systems converge on their capacity to preserve organelle function and cellular integrity. Future investigations are warranted to characterize MDV and EV specific cargo profiles, signaling pathways, and cellular targets in muscle aging. This knowledge could pave the way for novel therapeutic strategies leveraging engineered vesicles as targeted delivery vehicles for restoring mitochondrial and cellular proteostasis and function in the aged muscle (Table 1).

4. Conclusion

MQC is a central determinant of skeletal muscle health and resilience during aging. Dysregulation of MQC pathways contributes to the accumulation of dysfunctional mitochondria, oxidative stress, impaired energy metabolism, and ultimately, myofiber degeneration. These maladaptive changes contribute to the progressive decline in muscle mass and function characteristic of sarcopenia and frailty. While lifestyle interventions, such as regular physical activity and adequate nutrition, remain foundational for maintaining mitochondrial integrity, recent advances highlight a growing repertoire of complementary strategies. These include pharmacological agents that stimulate mitochondrial biogenesis, such as PGC-1α activators resveratrol and 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) as well as exercise mimetics that replicate some benefits of physical activity. In parallel, EVs are emerging as promising delivery vectors for MQC-targeting molecules and/or entire organelle transfer, offering potential for cell type-specific modulation of mitochondrial pathways and improvement of muscle regenerative capacity. Understanding the molecular underpinnings and context-specific regulation of MQC processes will be crucial to identify novel therapeutic targets. Precision approaches that preserve mitochondrial adaptability and inter-organelle communication hold promise to delay muscle aging, reduce late-life disability, and extend health span.

CRediT authorship contribution statement

Francesco Landi: Writing – review & editing. **Anna Picca:** Writing – review & editing, Writing – original draft, Validation, Conceptualization. **Riccardo Calvani:** Writing – review & editing, Validation. **Helio José Coelho-Junior:** Writing – review & editing, Validation. **Emanuele Marzetti:** Writing – review & editing, Writing – original draft, Conceptualization.

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Declaration of Competing Interest

The authors have no conflict of interest to disclose.

Data availability

No data was used for the research described in the article.

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