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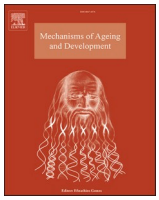

Polyamines and autophagy as a dynamic regulatory network in skeletal muscle regeneration and aging

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ABSTRACT

Autophagy is a core cellular mechanism that preserves tissue homeostasis by removing damaged proteins and organelles. In skeletal muscle, proper regulation of autophagic flux is essential for maintaining metabolic and structural integrity, whereas its disruption contributes to muscle atrophy, metabolic dysfunction, and age-related functional decline. Increasing evidence identifies polyamines, particularly spermidine (Spd), as important modulators of autophagy and cellular resilience, with beneficial effects on stress responses, metabolic regulation, and lifespan extension. Physical exercise likewise acts as a physiological inducer of autophagy, promoting muscle remodelling, mitochondrial quality control, and adaptive responses to stress. Within this framework, spermine oxidase (SMOX) has emerged as a relevant regulator of muscle homeostasis. SMOX expression is maintained in healthy muscle but declines in atrophic conditions. By converting spermine into spermidine, SMOX may help sustain autophagy-related pathways and support muscle mass under physiological conditions. This review explores the interplay between exercise, spermidine, and SMOX, highlighting autophagy as a unifying regulatory axis. We summarize current evidence on their individual and combined roles in preserving muscle function and discuss their potential relevance for promoting healthy muscle aging and counteracting sarcopenia.

1. Introduction

Skeletal muscle is a highly dynamic tissue capable of remarkable structural and functional remodelling in response to environmental, nutritional, and mechanical stimuli. This plasticity depends on a delicate balance between anabolic and catabolic processes, including protein turnover, mitochondrial quality control, and cellular stress responses (Bonaldo and Sandri, 2013; Romanello and Sandri, 2021). Central to these adaptive mechanisms is autophagy, an evolutionarily conserved process that degrades and recycles damaged organelles and proteins, thereby maintaining energy homeostasis and cellular integrity (Masiero et al., 2009; De Mario et al., 2021). During aging or chronic stress, impaired autophagic flux contributes to the accumulation of dysfunctional mitochondria, oxidative stress, and progressive muscle wasting, typical of sarcopenia (Yin et al., 2013; Fanò-Illic and Fulle, 2022). Among the regulatory networks influencing autophagy, Spd has emerged as a key modulator of cellular homeostasis (Pegg, 2016; Casero et al., 2018). Spermidine, along with putrescine and spermine, are the most abundant polyamines in mammals. These small polycationic molecules are involved in nucleic acid stabilization, translation, and stress adaptation. Spermidine has been identified as a physiological inducer of autophagy, capable of extending lifespan and improving metabolic and neuronal health in various models (Minois et al., 2012; Eisenberg et al., 2009; Madeo et al., 2018). Mechanistically, Spd promotes the transcription of autophagy-related genes by modulating acetylation processes (Pietrocola et al., 2015). In skeletal muscle, the polyamine–autophagy axis has gained attention as a potential regulator of muscle regeneration and aging. Experimental studies have shown that Spd supplementation enhances mitochondrial function and counteracts age-related atrophy through the activation of autophagy (Madeo et al., 2018). At a higher level, Spd supplementation suppresses age related decline and extent overall longevity by approximately 10% (Eisenberg et al., 2016). Although spermidine supplementation has been associated with beneficial effects such as enhanced autophagy in experimental

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models, much of the supporting evidence derives from cellular and animal studies (Eisenberg et al., 2016). Moreover, endogenous spermidine levels are tightly regulated by metabolic pathways such as fasting-induced polyamine synthesis, suggesting that physiological regulation may differ from the effects observed with exogenous supplementation (Hofer et al., 2024). In addition, dietary or metabolic interventions may influence overlapping longevity pathways, complicating attribution of observed benefits specifically to spermidine supplementation (Liang et al., 2025). Taken together, these findings suggest that targeting polyamine metabolism represents a promising strategy to sustain muscle health and counteract degenerative processes across lifespan.

2. Autophagy as a central pathway in muscle homeostasis

Autophagy is a cellular process responsible for degradation of protein aggregates and damaged organelles. During autophagy, double membrane vesicles called autophagosomes engulf cargos, which are then degraded after fusion with lysosomes to form autophagolysosomes (Gabandé-Rodríguez et al., 2019). This degradation process recycles amino acids and other by-products for protein synthesis or for the tricarboxylic acid (TCA) cycle to generate energy (Ravikumar et al., 2010). Organelles such as mitochondria can also be selectively degraded through mitophagy (Harper et al., 2018), which is crucial for maintaining cellular homeostasis (Harper et al., 2018). In cardiac and skeletal muscles cells, the ubiquitin-proteasome system and the autophagy-lysosome system are co-regulated to preserve the proper composition of protein and organelles (Sandri, 2010). The autophagy-lysosome system is believed to control long-lived proteins and organelles (Levine and Kroemer, 2008). During autophagy, small ubiquitin-like molecules (LC3, GABARAP, GATE16, and autophagy-related gene (ATG) 12) are transferred from the conjugation system to membranes, aiding in the formation of autophagosomes that engulf cytoplasmic portions (Levine and Kroemer, 2008). This requires recruitment and assembly of autophagy machinery components on phospholipids, where ubiquitin-like components are covalently bound to phosphatidylethanolamine on both autophagosome membranes (Tanida et al., 2004) (Fig. 1). Under normal conditions, autophagy can be induced by fasting and calories restriction, which enhance cellular resistance to various stressors (Madeo et al., 2010). Calories restriction also activates sirtuin 1 (SIRT1), which can induce autophagy (Tang and Rando, 2014) and has been implicated in lifespan extension. Indeed, autophagy has been associated to the promotion of longevity (Madeo et al., 2010). Tight regulation of autophagic flux is crucial for muscle function: excessive autophagy induces atrophy, whereas insufficient autophagy causes weakness and degeneration. In atrophying muscle, autophagy can become overactivated, often in response to elevated production of reactive oxygen species (ROS), including superoxide (O_2^-), hydrogen peroxide (H_2O_2), hydroxyl radicals (•OH), and singlet oxygen, which can damage DNA, proteins, and membrane lipids (Tanida et al., 2004).

Although autophagy inhibitors could theoretically be used to limit muscle wasting, this strategy remains complex. Because autophagy is indispensable for normal muscle physiology, its suppression can paradoxically exacerbate muscle atrophy (Sandri, 2010) (Fig. 1).

2.1. Autophagy as a key regulator of muscle stem cell activation and regeneration

Autophagy also contributes to the activation of quiescent muscle stem cells (satellite cells) (Tang and Rando, 2014). Satellite cells normally remain in a reversible G0 arrest state, but upon tissue injury they activate, re-enter the cell cycle, and either expand to form new myofibres or self-renew to restore the quiescent pool. This activation is sustained primarily by enhanced mitochondrial activity and ATP production, which meet the elevate bioenergetic demands of regeneration. Inhibition of autophagic flux delays satellite cell activation, remarking the importance of this pathway (Tang and Rando, 2014). Mechanistically, autophagy contributes to this process by maintaining mitochondrial quality through mitophagy, thereby preventing the

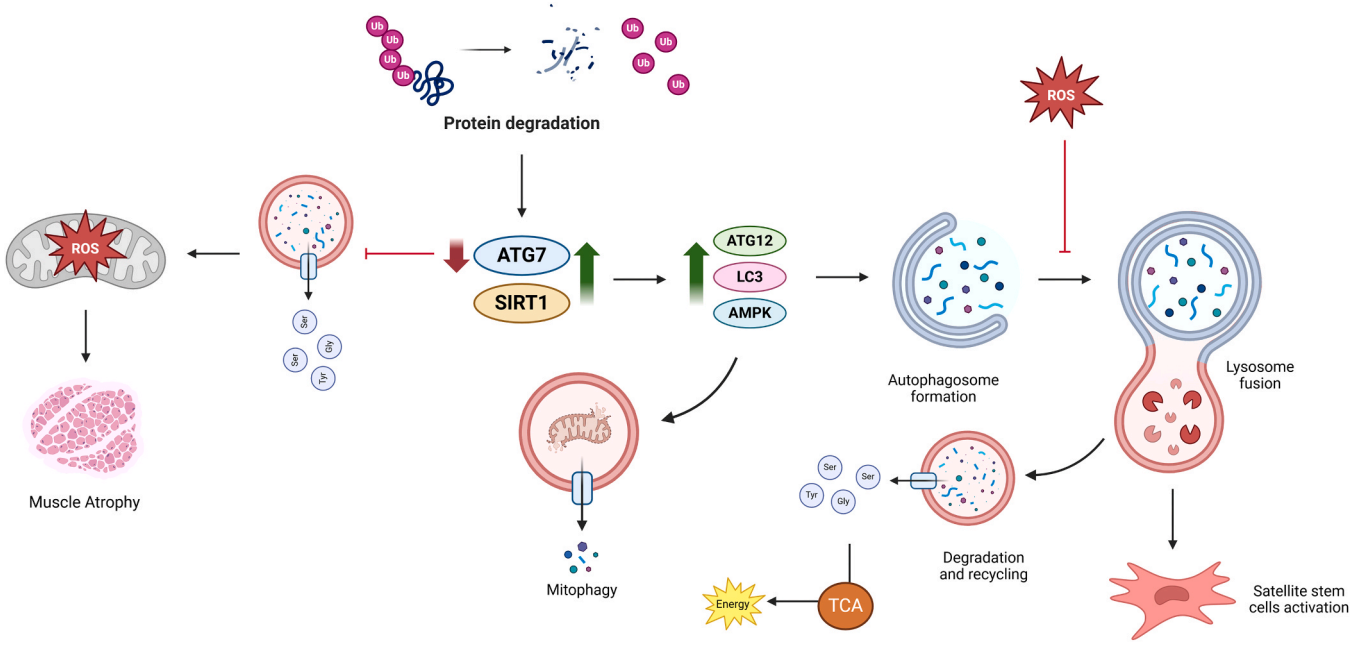

Fig. 1. *Autophagy homeostasis in muscle cells.* This schematic illustrates the actors involved in the regulation of autophagy. Protein degradation activates SIRT1 and ATG7, causing the upregulation of autophagy-related proteins including ATG12, LC3, and AMPK, facilitating the formation of autophagosomes. These structures engulf damaged proteins and organelles, then degraded upon fusion with lysosomes. Autophagic degradation provides amino acids and intermediates for the tricarboxylic acid (TCA) cycle, sustaining energy production. Mitochondrial autophagy (mitophagy) is also enhanced, together with the activation of muscle stem cells. Reactive oxygen species can cause alterations in maintaining the autophagy homeostasis, and the downregulation causes a block of the autophagy machine, leading to abnormal mitochondria and muscle atrophy. Created in https://BioRender.com.

accumulation of dysfunctional mitochondria and limiting excessive ROS production. When autophagy is impaired, defective mitochondria accumulate, leading to oxidative stress and reduced bioenergetic efficiency, which can compromise the metabolic reprogramming required for satellite cell activation (Tang and Rando, 2014). Similarly, García-Prat et al. (2016), investigated the regenerative capacity of skeletal muscle, which relies on long-lived Pax7-expressing satellite cells. They demonstrated that young quiescent satellite cells exhibit constitutive autophagic activity which becomes impaired with aging, as shown using the autophagosome marker GFP–LC3. The autophagic defects in senescent satellite cells were partly due to disrupted autophagosome or lysosomal clearance, tightly linked to altered mitophagy and elevated ROS levels. These alterations contribute to mitochondrial dysfunction and metabolic stress, which can promote the transition from a quiescent state toward cellular senescence rather than productive activation. This research highlights that autophagy plays a pivotal role in determining whether muscle stem cells maintain quiescence or progress toward senescence (García-Prat et al., 2016). Consistently, Fiacco et al. (2016) explored autophagy's role in regulating the regenerative capacity of satellite cells in both normal and dystrophic muscles. They observed a progressive reduction in autophagy during disease progression in mouse models of muscular dystrophy. This failure to activate autophagy was associated with increased fibrosis, exhaustion of regeneration potential, and impaired satellite cell activation (Fiacco et al., 2016). Inefficient autophagic clearance likely exacerbates mitochondrial dysfunction and oxidative stress, further limiting the bioenergetic adaptability required for effective regeneration. Efficient autophagy supports compensatory regeneration in dystrophic muscles by regulating muscle stem cell during repair. Overall, these findings underscore the critical role of autophagy in maintaining optimal muscular function under both physiological and pathologic conditions.

2.2. Impaired autophagy in aging and muscle atrophy

Excessive skeletal muscle protein degradation can lead to a progressive loss of muscle mass and function. In severe conditions, atrophy of respiratory muscles such as the diaphragm and intercostal muscles may occur, potentially resulting in life-threatening complications.

Sandri (2010). Muscle loss conditions often show an induction of muscle-specific, atrophy-related ubiquitin ligases, such as atrogin-1/muscle atrophy F-box (MAFbx) and muscle ring finger-1 (MuRF1), which upregulate several proteasome subunits related to atrophy (Sacheck et al., 2007). Impaired autophagy also promotes synaptic degeneration and premature aging (Carnio et al., 2014). Autophagy declines with age, as evidenced by decreased levels of autophagy markers, contributing to age-related muscle loss (Carnio et al., 2014). In mouse models, Atg7 knockdown, which blocks autophagosome formation, caused deterioration of neuromuscular junctions and the motoneurons innervating degenerated fibers. Restoring Atg7 expression rescued synaptic function. Similarly, in muscle-specific autophagy-knockout mice, deletion of Atg7 led to total inhibition of vesicle formation, resulting in atrophy, weakness, and myopathic features (Meléndez and Neufeld, 2008). The absence of Atg7 genes caused protein aggregate accumulation, abnormal mitochondria, oxidative stress induction, and unfolded protein response activation, leading to myofibre degeneration (Meléndez and Neufeld, 2008). Interestingly, autophagy-null muscles showed significant polyubiquitinated protein accumulation, which was not due to decreased proteasome function since in vivo proteasome activity was not impaired (Sandri, 2010). Ubiquitinated proteins can be delivered to autophagosomes via p62/SQSTM1, which binds both polyubiquitin chains and LC3 (Ichimura et al., 2008). This highlights that impaired autophagy may contribute to the pathogenesis of several myopathies and dystrophies, suggesting that a distinct subset of ubiquitinated proteins is normally targeted to lysosomal rather than proteasomal degradation (Sandri, 2010).

2.3. Interplay between mitochondrial quality control and oxidative stress

Autophagy also plays a significant role in mitochondrial quality control, essential for long-lived cell homeostasis (Fan et al., 2016). The activities of protein kinase AMP dependent (AMPK), mitophagy, and mitochondrial biogenesis are co-ordinately regulated to maintain a healthy pool of mitochondria in cellular homeostasis (Calvani et al., 2013). Mitophagy, which removes damaged mitochondria, is essential for maintaining normal muscle function under both basal conditions and various stress stimuli (Fan et al., 2016). Impaired clearance of damaged mitochondria is thought to be involved in skeletal muscle loss due to oxidative damage and bio-energetic failure (Lee et al., 2012). Moreover, ROS can cause the accumulation of oxidized proteins that tend to aggregate in lysosomes, further promoting ROS production and impairing autophagic function during aging (Terman et al., 2010). The resulting buildup of damaged mitochondria, increased ROS generation, and non-degradable lipofuscin, which is a byproduct of oxidative damage and incomplete degradation of cellular components. Consequently, the failure of mitophagy and the accumulation of dysfunctional mitochondria increased oxidative stress, reduce ATP production, and compromised cellular catabolic machinery, which are responsible for muscle atrophy in aging (Marzetti et al., 2013). Redox homeostasis in muscle relies heavily on glutathione, one of the cell's major antioxidant defences (Aquilano et al., 2014). Glutathione is predominantly present in its reduced form (GSH) and is oxidized to GSSG after exposure to oxidative insult. The GSH/GSSG ratio is therefore a sensitive indicator of cellular redox status (Ceci et al., 2015). Glutathione and autophagy are closely interconnected in maintaining cellular homeostasis. Under physiological conditions, a basal level of autophagy is required for cellular quality control. GSH regulates levels of ROS and thereby restrains excessive autophagy activation, while a drop in GSH and the resulting rise in ROS triggers autophagy as an adaptive response to oxidative stress. In turn, autophagy supports redox balance by removing dysfunctional mitochondria, preventing further ROS production, and helping to preserve the cellular GSH pool (Ceci et al., 2015). Dysfunction of this regulatory circuit leads to the accumulation of oxidative damage and impaired cellular function, with particular relevance in tissues highly sensitive to stress, such as skeletal muscle.

3. Polyamines: metabolic functions and regulation of autophagy

3.1. Polyamine biosynthesis, catabolism, and regulation

The first polyamine to be identified was Spd, discovered more than 330 years ago in human semen (Bachrach, 2010). Since that time, polyamines have been found in all eukaryotes and most prokaryotes. These compounds are low-molecular-weight aliphatic amines that acts as polycations, allowing them to interact with negatively charged molecules, such as DNA, RNA or proteins (Minois et al., 2011; Rea and Bocedi, 2004). Their ability to bind to various molecules grants them pleiotropic functions within the cell. Polyamines are primarily associated with cellular growth, survival and proliferation (Wallace and Fraser, 2004) but they also play roles in the development of different diseases (Cervelli et al., 2014; Pietropaoli et al., 2018; Leonetti et al., 2020; Cervelli et al., 2022). The most abundant polyamines in mammals are putrescine, Spd and spermine; which are produced through a tightly regulated metabolic pathway (Minois et al., 2011). In eukaryotic cells, polyamine synthesis begins with the decarboxylation of ornithine, which is an amino acid derived from arginine via urea cycle, a reaction catalysed by ornithine decarboxylase (ODC) (Soda, 2022). Spermidine and spermine are subsequently synthesized through the sequential addition of aminopropyl groups donated from decarboxylated S-adenosylmethionine (dc-SAM), which itself is derived from S-adenosylmethionine (SAM) via the enzymatic activities of adenosylmethionine decarboxylase (AdoMetDC) (Soda, 2022). Polyamine catabolism is regulated by several enzymes, including Spermidine/spermine

N-(1)-acetyltransferase (SAT1) and N1-acetylpolyamine oxidase (PAOX) (Soda, 2022). SAT1 catalyses the acetylation of spermine and Spd using acetyl-coenzyme A producing N1-acetylated derivatives (Soda, 2022). PAOX then preferentially oxidizes these acetylated polyamines, generating Spd and putrescine along with amino aldehyde and H_2O_2 (Cervelli et al., 2013a) (Fig. 2).

An alternative degradation pathway is mediated by spermine oxidase (SMOX), which directly converts spermine to Spd also releasing an amino aldehyde and hydrogen peroxide (Cervelli et al., 2012). Cellular polyamine levels are highly regulated through coordinated control of their import, export, synthesis, and catabolism. Additionally, cells can import polyamines from the extracellular environment through specialized plasma membrane transporters (Soda, 2022). Polyamines possess several biological activities that may counteract the development of age-related diseases. They have demonstrated anti-inflammatory (Cervelli et al., 2014; Soda et al., 2005) and antioxidant effects (Bellé et al., 2004; Amendola et al., 2005, 2013; Ceci et al., 2022); moreover, polyamines help preserve cellular integrity and genomic stability by protecting against toxic chemicals (Chauhan et al., 2003), and other stressors (Ceci et al., 2022; Sagor et al., 2013). In addition to endogenous biosynthesis, two external sources contribute significantly to systemic polyamine levels: dietary intake and production by intestinal microorganisms (Madeo et al., 2018). Many unprocessed plant-derived foods are naturally rich in polyamines, and bacterial fermentation during food processing can also lead to microbial generation of polyamines (Madeo et al., 2018). Ingested spermine and Spd are efficiently absorbed from the intestine without undergoing degradation (Milovic, 2001). Diet has a notable influence on circulating polyamine levels, and Spd is rich in the Mediterranean diet, that have been associated with improved health outcomes (Zoumas-Morse et al., 2007). Moreover, intestinal luminal Spd availability, is closely linked to the composition of the colonic microbiota (Matsumoto and Benno, 2007). As polyamines levels naturally decline with age, maintaining an adequate intake of polyamines may help counteract this decline and support healthy aging (Hofer et al., 2021). This decline has been associated with alterations in polyamine metabolism during aging, including reduced biosynthesis and changes in catabolic pathways (Soda, 2022). On the other hand, polyamines levels are increased in various diseases, such as cancer and parasites infection. Proliferative cells exhibit high levels of polyamines, presumably to maintain their proliferation (Minois et al., 2011), although it has been proven that increased polyamines levels can't induce cell transformation directly (Soda et al., 2009). In breast cancer, polyamines dysregulation is frequently observed, due to high intracellular polyamines levels, increased ODC1 activity (Meeus et al., 2026) and decreased SMO activity (Cervelli et al., 2010). It has been shown that in mice grafted with a human breast cancer line, polyamine depletion decreased the tumour mass without changes in the cellularity of the tumour tissue (Levêque et al., 1998). Moreover, Kramer et al. (1) observed that ODC inhibitor (DMFO) and AdoMetDC inhibitor (MDL-73811) triggered a slight decrease in cell growth in MALME-3M cells. On the other hand, the combination of both inhibitors led to a rapid cell cycle arrest, with an accumulation of cells in G1 and a reduction in S phase (Polyamine depletion in human melanoma cells leads to G1 arrest associated with induction of p21WAF1/CIP1/SDI1, n.d). They noted a strong p21 induction and a decrease in total Rb level. These changes were prevented by addition of spermidine, concluding that polyamine depletion conferred phenotypes resembling cell senescence (Polyamine depletion in human melanoma cells leads to G1 arrest associated with induction of p21WAF1/CIP1/SDI1, n.d), in accord with the decrease in polyamines levels during aging. Beyond oxidative stress, polyamine metabolism is also modulated by other types of cellular stress. Metabolic stress, such as nutrient deprivation, caloric restriction, or high-fat diets, has been shown to influence intracellular polyamine levels by altering biosynthetic enzyme activity and polyamine catabolism (Eisenberg et al., 2016; Rossi and Cervelli, 2024). Similarly, inflammatory stimuli, including cytokines like TNF-α or

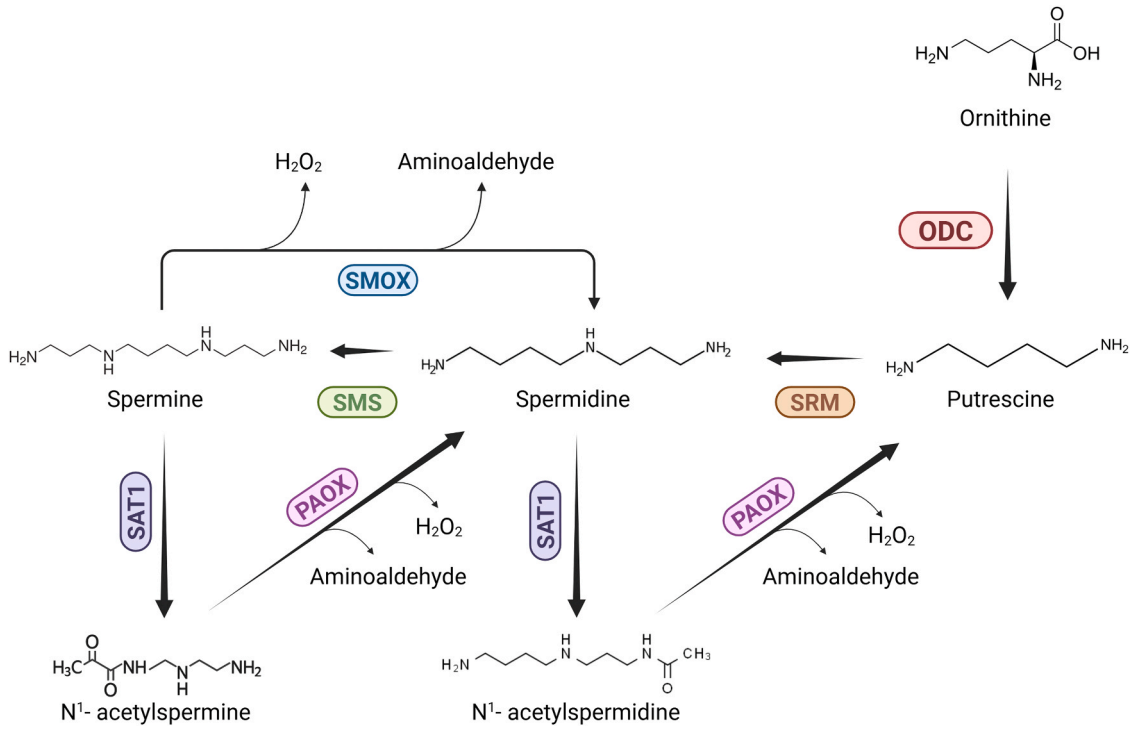

Fig. 2. *Overview of Polyamine Metabolism Pathways.* This diagram depicts the biosynthesis, interconversion, and catabolism of polyamines, including putrescine, spermidine, and spermine. Ornithine decarboxylase (ODC) converts ornithine to putrescine, subsequently converted to spermidine and spermine via spermidine synthase (SRM) and spermine synthase (SMS), respectively. Polyamine catabolism involves acetylation by spermidine/spermine N1-acetyltransferase 1 (SAT1), followed by oxidation via polyamine oxidase (PAOX) and spermine oxidase (SMOX), producing hydrogen peroxide and aldehydes as by-products. The pathway demonstrates that dynamic regulation of polyamine levels is essential for cell growth, differentiation, and stress response. Created in https://BioRender.com.

lipopolysaccharide (LPS), can upregulate polyamine synthesis in immune and epithelial cells, reflecting a role for polyamines in stress adaptation and cellular homeostasis (Pegg, 2016; Madeo et al., 2018). These findings suggest that polyamine metabolism is responsive to a variety of stress signals, not just ROS, and may serve as a common mediator linking different stress types to autophagy and cellular resilience.

3.2. Polyamine-mediated regulation of autophagy: underlying mechanisms

Across the various biological pathways in which polyamines are involved, recent studies have highlighted the role of Spd in promoting autophagy (Eisenberg et al., 2009; Sacitharan et al., 2018). Administration of Spd, either via injection or oral supplementation, enhances autophagy in multiple mouse tissues, including skeletal muscle (Fan et al., 2017). This effect is thought to play a central role in mediating spermidine's beneficial effects on health and longevity. Consistently, inhibition of autophagy abolishes the life span extension induced by Spd in several model organisms (Eisenberg et al., 2009). Mechanistically, Spd promotes autophagy by decreasing cytosolic protein acetylation through inhibition of the acetyltransferase E1A-associated protein p300 (EP300) (Morselli et al., 2011; Cervelli et al., 2018). Inhibition of EP300 is sufficient to induce autophagy (Pietrocola et al., 2015) as it prevents the acetylation of key autophagy-related (ATG) proteins that are required for autophagosome formation (Lee and Finkel, 2009). Additionally, Spd may influence basal autophagic flux by upregulating autophagy-related genes, such as Atg 7, Atg 15, and Atg 11 (Minois et al., 2011). In fact, in wild-type yeast cells expressing EGFP–Atg8p, Spd treatment (4 mM for 48 h), led to the of upregulation of autophagy-related genes such as *ATG7, ATG11* and *ATG15*, as shown via quantitative real-time PCR (Eisenberg et al., 2009). Chromatin immunoprecipitation (ChIP) analysis revealed that Spd increased acetylation at the ATG7 promoter region, suggesting transcriptional activation via promoter hyperacetylation (Eisenberg et al., 2009). Moreover, subcellular localization studies of Atg8p showed that while EGFP–Atg8p was diffusely distributed in control cells, Spd-treated cells displayed clear vacuolar localization of fusion protein in an *ATG7*-dependent manner, indicating enhanced autophagic activity. These findings were further confirmed in human cultured cells and Drosophila models (Eisenberg et al., 2009). The transcription factor FoxO3, negatively regulated by protein kinase B (PKB/Akt), is both necessary and sufficient to induce autophagy in mouse skeletal muscle in vivo (Mammucari et al., 2007), since it drives the expression of autophagy-related genes (Cervelli et al., 2018). In collagen VI–deficient mice, Spd-mediated reactivation of muscle autophagy is associated with the Akt dephosphorylation and its consequent inactivation, which leads to increased transcription of FoxO3-dependent target genes (Chrisam et al., 2015). Furthermore, Spd can reduce acetyl-CoA availability, since its catabolism involves acetylation reactions that consume acetyl-CoA (Madeo et al., 2018). Depletion of the intracellular acetyl-CoA pool has been shown to induce autophagy in cultured mammalian cells as well as in mice, aging yeast, and flies (Mariño et al., 2014). Another mechanism linking Spd to autophagy involves its role in the post-translational modification of eukaryotic initiation factor 5 A (eIF5A) via hypusination. Hypusine is a rare amino acid generated through two enzymatic steps: deoxyhypusine synthase (DHS) transfers a 4-aminobutyl group from Spd to a lysine residue on eIF5A, forming deoxyhypusine, which is subsequently hydroxylated by deoxyhypusine hydroxylase (DOHH) to produce hypusine, thereby activating eIF5A (Tauc et al., 2021). This pathway is highly conserved across species, reflecting its essential biological function. Indeed, hypusinated eIF5A regulates protein synthesis during initiation, elongation, facilitating ribosomal progression at poly-proline and other stalling motifs (Schroeder et al., 2021). Importantly, hypusinated eIF5A promotes the translation of key autophagy-related genes linking this pathway directly to autophagy regulation, such as the autophagy regulator TFEB (Zhang et al., 2019). Loss of eIF5A in cell lines and *Caenorhabditis elegans* reduces autophagosome formation and impairs LC3 lipidation, a crucial step in autophagosome maturation (Lubas et al., 2018). Similarly, pharmacological inhibition of DHS using the Spd-analogue N1-guanyl-1,7-diaminoheptane (GC7) decreases the expression of essential autophagy proteins such as ATG3 (Lubas et al., 2018). Although evidence for the eIF5A–hypusination pathway derives from cell lines and model organisms (Schroeder et al., 2021), this pathway is highly conserved and is thought to operate similarly in mammalian tissues, including skeletal muscle (Luchessi et al., 2009). In muscle cells, efficient protein synthesis and autophagy are tightly coordinated to maintain proteostasis and mitochondrial quality, suggesting that spermidine-dependent hypusination of eIF5A may contribute to the regulation of autophagy in skeletal muscle, although direct in vivo evidence in muscle tissue remains limited (Luchessi et al., 2009). However, negative findings regarding the effects of Spd on muscle have also been reported in literature. Taken together, these molecular mechanisms ranging from transcriptional regulation to posttranslational modification, underscore the central role of Spd in promoting autophagy and thereby contributing to its beneficial effects on health and longevity (Fig. 3).

4. Polyamines in muscle physiology and pathology

4.1. Effects on muscle differentiation

Skeletal muscle differentiation, or myogenesis, is a highly regulated process involving a cascade of muscle-specific genes, whose expression is tightly coordinated with cell cycle withdrawal and the synthesis of muscle contractile proteins. During embryogenesis, muscle fibres are formed through a finely ordered multistep process, that progresses from mononucleated-undifferentiated cells (myoblasts) to polynuclear cells (myotubes) (Hernández-Hernández et al., 2017). The differentiation is primarily regulated by myogenic regulatory factors (MRFs) which belong the basic helix-loop-helix family of transcription factors. These include MyoD, Myf5, myogenin, and MRF4, along with other transcription factors such as paired box 3 (Pax3) and paired box 7 (Pax7) (Soleimani et al., 2012). MyoD and Myf5 are expressed prior to the onset of myogenic differentiation and promote the proliferation and commitment of myogenic progenitor cells into myoblasts (Gianakopoulos et al., 2011). Myogenin drives the differentiation of myoblasts into myotubes while MRF4 is involved in terminal differentiation and cell fate determination (Kassar-Duchossoy et al., 2004) (Fig. 4). Reactive oxygen species, particularly H_2O_2, are key regulators of skeletal muscle physiology. While excessive ROS levels are detrimental, moderate H_2O_2 concentrations function as intracellular messengers that modulate signalling pathways essential for myogenic differentiation (Ji, 1995). One relevant source of H_2O_2 in muscle cells is polyamine catabolism, especially the reaction catalysed by SMOX. Beyond its role in maintaining polyamine homeostasis, SMOX has been implicated in redox-dependent signalling events that accompany muscle differentiation (Cervelli et al., 2009). The link between polyamine metabolism and myogenesis was examined by Cervelli et al. (2009), who assessed SMOX expression during C2C12 differentiation using RT-PCR, polysome mRNP profiling, and enzymatic assays. They reported a rise in SMOX transcripts and activity as myoblasts differentiated, consistent with a parallel decrease in intracellular spermine (Cervelli et al., 2009; Reinoso-Sánchez et al., 2020). This upregulation likely contributes to the controlled production of H_2O_2 required at specific stages of myogenesis. It is plausible that once differentiation progresses and H_2O_2-mediated signalling is no longer needed, the induction of p21 helps repress SMOX expression (Reinoso-Sánchez et al., 2020). Overall, these findings suggest that SMOX functions beyond polyamine catabolism, playing an active role in shaping the redox conditions that support effective muscle differentiation. Its expression dynamics therefore highlight SMOX as a potential functional marker of muscle cell maturation (Reinoso-Sánchez

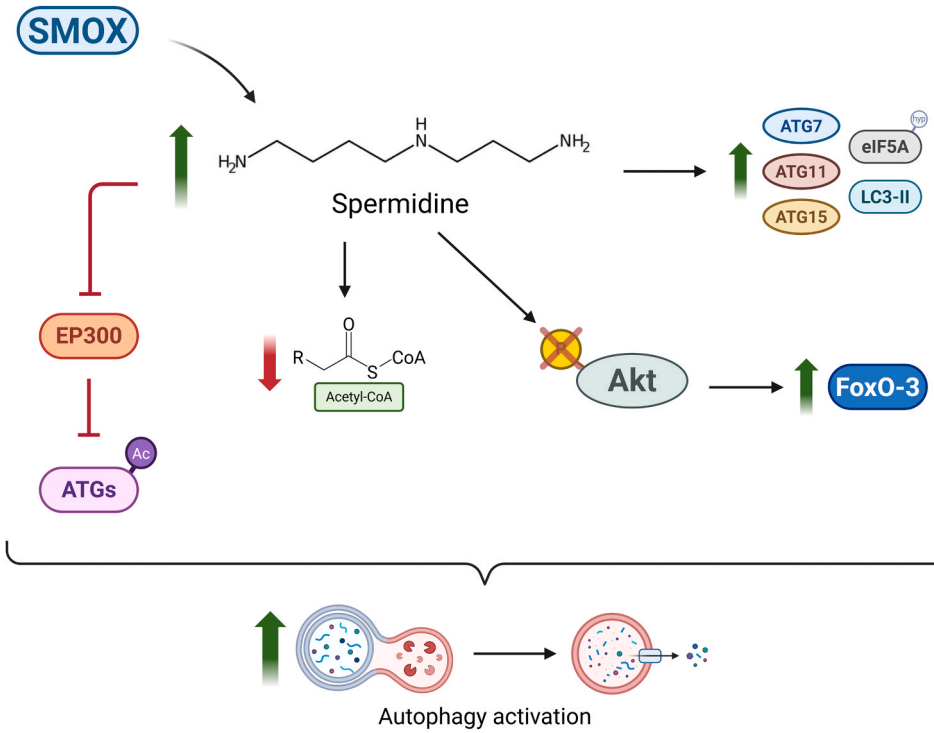

Fig. 3. *Spermidine-induced autophagy*. This scheme illustrates the cellular mechanisms through which Spd promotes autophagy in muscle cells. Spd administration leads to modulation of key molecular pathways, including downregulation of EP300 and ATG's acetylation, Akt dephosphorylation, and upregulation of autophagy-related genes (ATG), FoxO-3, and eIF5A hypusination. These changes converge to induce autophagy, as depicted by the activation of autophagosome formation. Created in https://BioRender.com.

et al., 2020).

4.2. Effects on muscle regeneration

Even if the ability to remodel declines with aging, skeletal muscles retain it to a certain extent due to a specialized population of myogenic progenitors known as satellite cells, which reside beneath the basal lamina of myofibers. These cells are mitotically quiescent, functioning as muscle stem cells, responsible for repair and maintenance of muscle tissue (Cervelli et al., 2018). Following injury or stress events, satellite cells undergo asymmetric division: some replenish the quiescent stem cell pool while others differentiate into myoblasts. The myoblasts then fuse either to form new myotubes or to repair damaged myotubes (Zanou and Gailly, 2013). Protein synthesis is essential for proper skeletal muscle development, and recent studies have highlighted the crucial role of polyamines in this process (Zhou et al., 2022). Spermidine serves as the exclusive substrate for hypusination, a modification essential for efficient protein translation (Zhou et al., 2022). At the cellular level, Ceci et al. (2022) demonstrated that oxidative stress profoundly compromises myoblast function. In C2C12 cells exposed to increasing concentrations of H_2O_2, viability declined sharply within 24 h, cell death increased, and total antioxidant capacity dropped by about 35% after 48 h. Oxidative stress also caused a rapid loss of intracellular polyamines: putrescine and Spd levels fell to 47% and 53% of control values at 6 h, with Spd decreasing further to 40% at 24 h. Supplementation with 10 μM Spd effectively countered these effects, improving the GSH/GSSG ratio previously reduced by nearly 60% and accelerating wound-scratch closure by 34%, indicating enhanced migratory and early regenerative capacity (Ceci et al., 2022). The scratch-wound assay provided clear functional evidence of Spd's pro-regenerative activity. Because this assay mirrors the early phases of muscle repair, where myoblasts must migrate and proliferate at the injury site the restored wound closure in the presence of Spd highlights its ability to sustain key regenerative processes despite oxidative insult (Ceci et al., 2022). Oxidative stress alone reduced total polyamines and upregulated ODC, SAT1, and SMOX, in line with known Nrf2- and NF-κB-mediated stress responses. Given the high polyamine demand of proliferating myoblasts, such depletion likely contributes to impaired regeneration. Restoration of PA levels by Spd paralleled the recovery of scratch-wound performance (Ceci et al., 2022). Taken together, these findings show that Spd strengthens the regenerative potential of skeletal muscle cells by maintaining redox homeostasis, preserving polyamine metabolism, and promoting the myoblast behaviours migration and proliferation required for effective tissue repair (Ceci et al., 2022).

4.3. Effects on muscle atrophy

As previously mentioned, reactive oxygen species (ROS), including H_2O_2, may act as key signalling molecules in muscle differentiation, while also contributing to oxidative stress and subsequent muscle atrophy when dysregulated. Excessive SMOX activity could lead to tissue damage, as demonstrated in an engineered mouse model, conditionally overexpressing SMOX in the neocortical neurons (DACH-SMOX) (Cervelli et al., 2013b). In these mice, chronic SMOX activation in cerebrocortical neurons results in reactive astrocytosis, neuronal loss, persistent oxidative stress, and excitotoxicity (Marcoli et al., 2022).

Recently, Ceci et al. (2017)., developed a transgenic mouse model overexpressing spermine oxidase SMOX, referred to as Total-SMOX, to investigate how alterations in polyamine metabolism affect muscle physiology. SMOX oxidizes spermine to produce H_2O_2, Spd, and 3-aminopropanal, and acts as a positive regulator of muscle gene expression and fiber size (Ceci et al., 2017). However, sustained overproduction of H_2O_2 due to SMOX overexpression disrupts redox homeostasis in skeletal muscle, despite a compensatory increase in antioxidant enzyme activities, such as catalase and glutathione S-transferase, compared to control animals (Ceci et al., 2017). In line with this, muscle from amyotrophic lateral sclerosis (ALS) models exhibits a specific disturbance in polyamine metabolism, and interventions that correct this imbalance

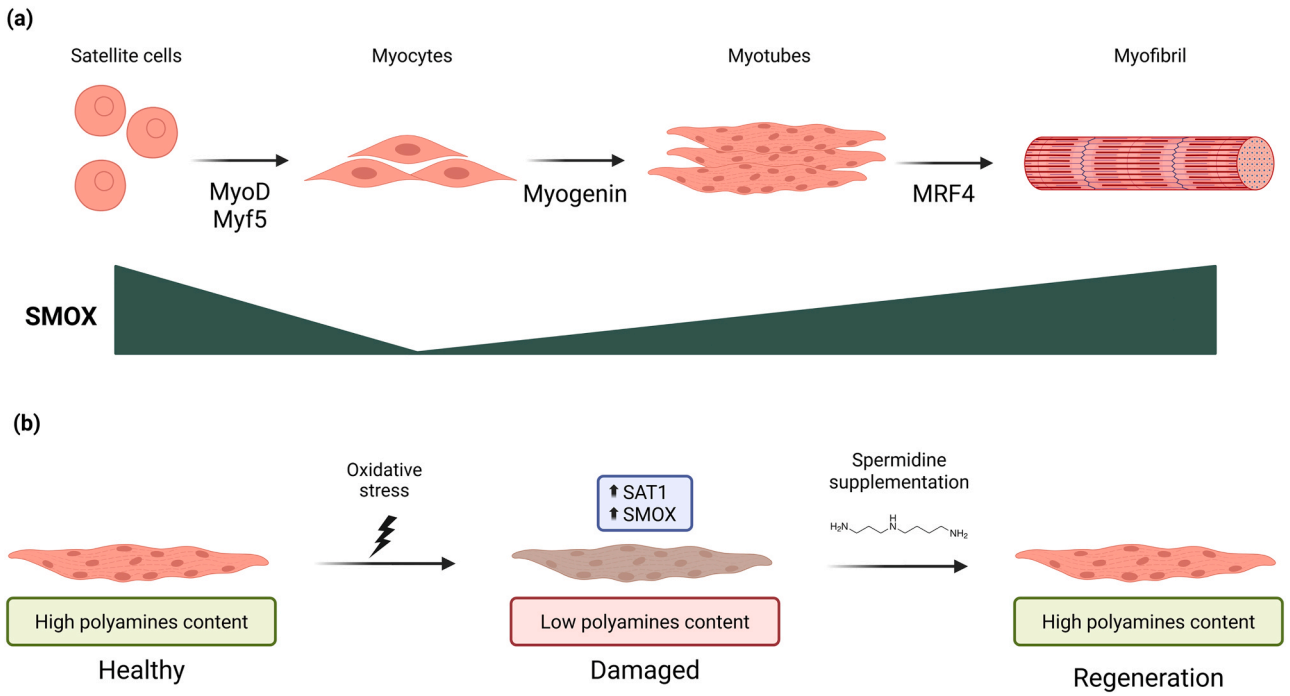

Fig. 4. *SMOX dynamics during myogenesis and its impact on muscle homeostasis and regeneration.* (A).Schematic representation of the sequential stages of skeletal muscle differentiation, from satellite cells to mature myofibrils. Satellite cells activate and commit to the myogenic lineage under the control of MyoD and Myf5, giving rise to proliferating myocytes. As differentiation proceeds, expression of myogenin drives the formation of multinucleated myotubes, which subsequently mature into organized myofibrils under the regulation of MRF4. The gradient below illustrates how SMOX expression and activity fluctuate during myogenesis, decreasing during early commitment and rising progressively during later differentiation stages, suggesting a stage-specific contribution of polyamine catabolism to myogenic maturation. (b) Overview of the role of polyamine metabolism in muscle homeostasis and regeneration. Healthy muscle fibers maintain high polyamine levels, supporting structural and metabolic integrity. Under oxidative stress, upregulation of SAT1 and SMOX leads to dysregulated polyamine turnover and depletion, contributing to muscle damage. Supplementation with spermidine restores polyamine content, thereby supporting the cellular processes necessary for efficient muscle regeneration. Created in https://BioRender.com.

reduces the severity of the atrophic phenotype (Ruggieri et al., 2025).

Across several models of muscle atrophy including immobilization, fasting, denervation, and aging a consistent hallmark is the pronounced decline in SMOX expression (Bongers et al., 2015). Notably, lowering SMOX alone is sufficient to trigger muscle fiber atrophy, whereas its forced overexpression enlarges fiber size in multiple atrophic settings. Mechanistically, this reduction is driven by p21, a cell-cycle–related protein strongly induced during atrophy and actively involved in promoting muscle loss (Bongers et al., 2015). In healthy muscle, low p21 levels allow SMOX to maintain a gene-expression program that preserves fiber size; when p21 rises under atrophic stimuli, SMOX downregulation disrupts this balance, suppressing mRNAs that sustain muscle mass (such as mitofusin-2) and favouring those that promote atrophy (such as myogenin). These findings position SMOX as a positive regulator of muscle homeostasis and identify p21-mediated SMOX repression as a key event in the progression of skeletal muscle atrophy (Bongers et al., 2015).

Consistently, Reinoso-Sánchez et al. (2020) demonstrated a marked reduction of SMOX in a dexamethasone-induced atrophy cellular model and in two distinct ALS mouse models, $SOD1^{G93A}$ and $hFUS^{+/+}$, both characterized by progressive neuromuscular degeneration. The $SOD1^{G93A}$ mouse line carries a pathogenic point mutation in the *superoxide dismutase 1* (SOD1) gene, which promotes oxidative stress and motor neuron degeneration (Gurney et al., 1994), while the $hFUS^{+/+}$ model ubiquitously expresses human the *fused in sarcoma* (FUS) gene and develops early and progressive motor deficits accompanied by muscle weakness (Mitchell et al., 2013). All SMOX transcript variants, including the predominant α isoform and the alternative μ and β forms declined in C2C12 myotubes during dexamethasone-induced atrophy (Reinoso-Sánchez et al., 2020). Interestingly, the authors also identified a circular RNA derived from the SMOX locus, circSMOX, which was significantly upregulated in both *in vitro* and *in vivo* atrophic conditions compared with healthy muscle. This inverse correlation suggests that circSMOX may exert a regulatory influence on its linear counterpart. Given that SMOX converts spermine into Spd, the combined decrease in linear SMOX transcripts and increase in circSMOX suggests a coordinated shift in polyamine catabolism that may actively contribute to muscle wasting. Crucially, if circSMOX acts as a "molecular sponge" or competes for the same pre-mRNA splicing machinery, its upregulation could directly contribute to the depletion of SMOX protein levels (Rossi et al., 2024). By diminishing the available pool of the SMOX enzyme, a known positive regulator of muscle fiber size, circSMOX may provide a distinct, non-linear pathway for accelerating muscle wasting, separate from the p21-mediated transcriptional repression of the linear gene (Reinoso-Sánchez et al., 2020). Complementing these findings, D'Ercole et al. (2022) reported that SMOX, typically enriched in fast 2B fibers, is markedly downregulated after nerve injury, suggesting impaired polyamine turnover during atrophy. Consistent with a functional role, providing SMOX through dietary supplementation in Drosophila improved locomotor performance, mitigating climbing decline (D'Ercole et al., 2022). Collectively, these observations support the view that polyamine metabolism is a key regulatory pathway influencing muscle plasticity. They also highlight circSMOX and SMOX modulation as promising targets for interventions aimed at reducing or preventing muscle atrophy.

Spermidine is generally considered beneficial for muscle homeostasis; however, accumulating evidence indicates that its effects may vary depending on physiological conditions, dosage, and pathological context. Although spermidine has been widely recognized as an inducer of autophagy, its impact on muscle regeneration appears sometimes limited. For example, in a study evaluating spermidine supplementation in a mouse model of cardiotoxin-induced muscle injury, no significant

changes in skeletal muscle mass were observed at any time point, suggesting minimal effects on muscle regeneration following acute damage (Iwata et al., 2024).

Conversely, emerging evidence points to potentially detrimental effects of spermidine under specific conditions. In the context of radiotherapy, spermidine has been implicated in promoting muscle fibrosis and functional decline. Tumour-associated accumulation of arachidonic acid induces ISGylation of spermidine synthase (SRM), facilitating its secretion via extracellular vesicles. These SRM-containing vesicles deliver spermidine to skeletal muscle, where it promotes type I collagen deposition through eIF5A-dependent hypusination. This process contributes to fibrotic remodelling, impairing muscle mechanical properties and leading to weakness. Notably, treatment with Losartan has been shown to counteract this effect by inhibiting SRM ISGylation and secretion, thereby alleviating radiotherapy-induced muscle dysfunction (Zhang et al., 2025).

5. Physical exercise as natural modulator of autophagy

It is widely recognized that physical exercise plays a crucial role in maintaining overall health. Physical activity is defined as any bodily movement produced by skeletal muscles that leads in energy expenditure (Caspersen et al., 1985). It can be classified as occupational, sports, conditioning, household, or other daily life activities. Exercise, in contrast, represents a specific subset of physical activity that is planned, structured, and repetitive with the explicit goal of improving or maintaining physical fitness (Caspersen et al., 1985). Regular physical exercise has been shown to enhance metabolic function, support lipid and glucose homeostasis, and improve oxidative capacity as well as general health and well-being (Vainshtein et al., 2014). Even a relatively short period of endurance exercise, such as six weeks, can markedly increase aerobic capacity and confer cardio protective effects (Brown and Moore, 2007). Furthermore, exercise delays the loss of muscle mass associated with aging and pathological conditions such as sarcopenia (Vainshtein et al., 2014).

Recent studies have explored the molecular mechanisms through

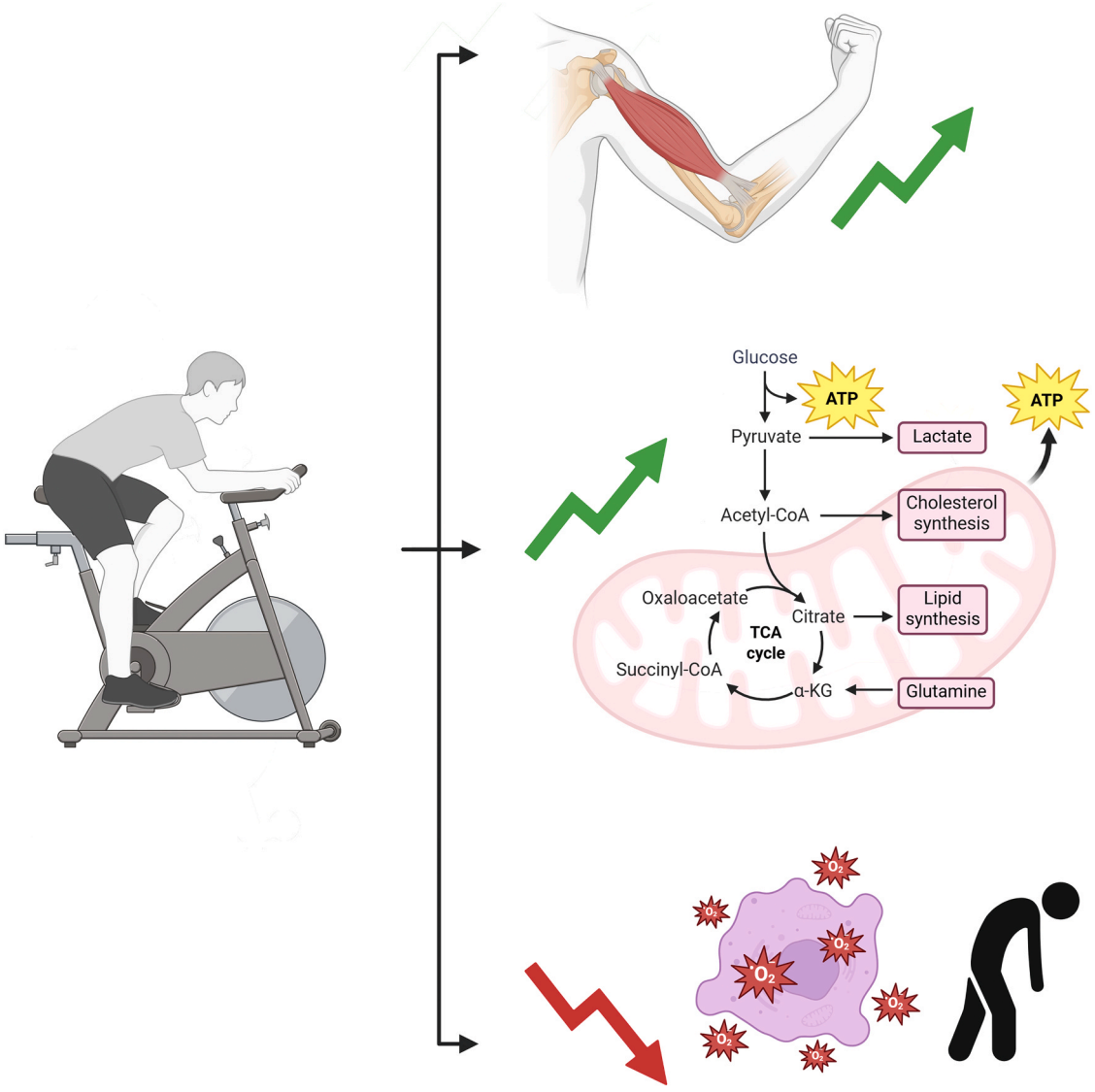

Fig. 5. *Metabolic effects of physical activity on skeletal muscle health.* This representation illustrates the beneficial metabolic adaptations in skeletal muscle induced by physical activity. Exercise promotes muscle hypertrophy and improves mitochondrial function, enhancing the efficiency of the tricarboxylic acid (TCA) cycle and related anabolic processes, including lipid and cholesterol synthesis, as well as glutamine metabolism. Concurrently, physical activity reduces chronic inflammation by lowering ROS levels and attenuating pro-inflammatory signalling. These combined effects contribute to improved muscle performance, energy balance, and long-term tissue health. Created in https://BioRender.com.

which physical exercise promotes muscle health. Since muscle maintenance depends on the balance between protein synthesis and degradation, the process responsible for clearing damaged protein and cellular components, autophagy, the process that removes damaged proteins and cellular components, has been proposed as a key contributor to the beneficial effects of physical exercise (Galasso et al., 2023). Baar et al. (2002) demonstrated that exercise induces mitochondrial biogenesis and remodelling primarily via the transcriptional co-activator PGC-1α (Baar et al., 2002). Overexpression of PGC-1α has been shown to prevent muscle wasting in several pathological contexts (Sandri et al., 2006) and its activity is regulated by p38-MAPK, a signalling molecule activated by muscle contraction, thereby promoting exercise-induced adaptations in skeletal muscle (Akimoto et al., 2005). Muscle contraction increases metabolic demand, resulting in elevated ROS production, a higher AMP/ATP ratio, and increased NAD^+ levels. These changes activate downstream signalling pathways and cellular stress response (Vainshtein et al., 2014). In addition, calcium transients during contraction may cause endoplasmic reticulum stress and trigger the unfolded protein response (Wu et al., 2011). Together, contraction-induced ROS production can result in the accumulation of harmful intermediates, lipid and protein damage, mitochondrial dysfunction, and overall disruption of cellular homeostasis, thereby compromising muscle health. The mechanism that counteracts these effects is fulfilled by autophagy process (Fig. 5).

Evidence indicates that autophagy markers are up regulated following ultra-endurance exercise (Jamart et al., 2012), during acute bouts of treadmill running, and after chronic exercise training (Salminen and Vihko, 1984). He et al. (2012) demonstrated that mice with Bcl2 knock-in mutations (Bcl2AAA), which preserve basal but not stress-induced autophagy, failed to gain exercise-mediated protection against high fat diet induced glucose intolerance. This finding supports the role of stimulus-induced autophagy in the metabolic benefits of physical activity. The link between exercise and autophagy is not surprising giving that acute muscle contraction mimics a form of energy stress and induces transient ROS increases, like nutrient deprivation. Kim et al. (2013) reported that treadmill exercise mitigated age-related declines in autophagy and muscle mass in both extensor digitorum longus and gastrocnemius muscles in male mice, comparing 2- and 10-months old mice. While aging is characterized by a progressive decline in basal autophagic flux, which could theoretically render the elderly more vulnerable to contraction-induced ROS, physical exercise appears to act as a hormetic stressor that recalibrates this system (Powers et al., 2024). In aging muscle, the transient spike in ROS during exercise does not merely accumulate as damage; instead, it serves as a critical signalling trigger for mitohormesis (Powers et al., 2024). By activating redox-sensitive transcription factors, exercise-induced ROS promotes the expression of antioxidant enzymes and stimulates the biogenesis of efficient mitochondria (Wang et al., 2024). Furthermore, the acute metabolic stress of exercise can acutely override the age-related blocks in the autophagic pathway, facilitating the clearance of lipofuscin and protein aggregates that characterize the sedentary aged phenotype (Kim et al., 2013; Lenhare et al., 2017). Thus, rather than exacerbating damage, controlled ROS production during exercise serves as the necessary "wake-up call" to restore cellular quality control mechanisms that have become stagnant with age. In another study, Lenhare et al. (2017), found that acute swimming exercise increased Sestrin 2 (Sesn2) levels and key autophagy markers in aged skeletal muscle. Specifically, 24-months-old C57BL/6 J male mice exposed to a single bout of swimming exercise exhibited increased expression of Sesn2 and alongside enhanced activation of autophagy-related proteins including phosphorylated unc-51-like kinase-1 (Ulk1) and higher of levels of Atg5, Atg7, p62 and LC3-II. Similarly, Li et al. (2018) investigated the effects of 10 weeks of high-intensity interval (HIIT) and moderate-intensity continuous training (MICT) on six-week-old male Sprague–Dawley (SD) rats. Their findings showed that HIIT elicited superior improvements in physical performance and produced greater increases in markers of mitochondrial biogenesis and autophagy in skeletal muscle when compared with both MICT and sedentary controls. Most recently, Von Ruff et al. (2025) conducted an RNA-Seq of muscle biopsies from 8 young (24 ± 3.3 years) and 10 older (72 ± 4.9 years) men before and after 12 weeks of resistance training. Because activating transcription factor 4 (ATF4) contributes to age-related declines in muscle mass and strength, their analysis focused on ATF4-regulated pathways. Resistance training reduced the expression of ATF4-responsive and senescence-associated transcripts in older individuals. Furthermore, increases in lean mass were correlated with higher expression of genes encoding mitochondrial proteins (Von Ruff et al., 2025). In conclusion, physical exercise functions as a powerful hormetic stimulus that triggers transient oxidative and metabolic stress to effectively restart the muscle's quality control systems. By overriding age-related blocks in autophagic flux and mitochondrial turnover, regular physical activity transforms potentially harmful ROS into essential signalling cues that preserve muscle proteostasis and delay the onset of muscle degeneration.

6. Interplay between polyamines and physical exercise in muscle

As previously discussed, both Spd supplementation and physical exercise independently enhance autophagic flux in muscle cells. Their combined effect has recently been investigated in models of muscle atrophy.

One study examined the effects of Spd supplementation and physical exercise in rats treated with D-galactose (D-gal); a widely used model of accelerated aging that also exhibits features of muscle atrophy (Fan et al., 2017). The authors compared the effects of Spd treatment, exercise and their combination on various hallmarks of aging. Remarkably, the combined treatment group exhibited physiological characteristics like those of untreated controls, with most of the detrimental effects induced by D-gal treatment significantly reversed (Fan et al., 2017). D-gal exposure led to a reduction in the ratio of gastrocnemius muscle weight to body weight, altered fibres morphology, and increased β-galactosidase activity, indicating muscle atrophy, oxidative stress, and defective autophagy. Combined treatment effectively counteracted these effects (Fan et al., 2017). Since Spd can induce autophagy through AMPK-dependent signal pathway (Morselli et al., 2011), the study also evaluated the p-AMPK/AMPK ratio. They found that D-gal exposure reduced the phosphorylation of AMPK and the expression of FOXO3a decreased AMPK phosphorylation and FOXO3a expression (by 89.7% and 51%, respectively, compared to controls). Western Blot analysis revealed that combined treatment significantly increased levels of AMPKα and FOXO3a. The study also explored the impact of Spd and exercise on apoptosis. TUNEL staining revealed that the high percentage of apoptotic cells caused from D-gal exposure (52.02%) was reduced to 25.74% with combined treatment. This intervention also restored the D-gal- induced reduction in the Bcl-2/Bax ratio, a critical indicator of a cell's susceptibility to apoptosis, reflecting the balance between pro-survival and pro-death signals (Fan et al., 2017). Additional studies by Laker et al. (2017); Zeng et al. (2020); Wang et al. (2022) demonstrated that exercise induced mitophagy and autophagy in skeletal muscles of mice models through AKT/mTOR, AKT/FOXO3 and AMPK signalling. These signalling cascades can be also modulated by Spd supplementation (Fan et al., 2017; Chrisam et al., 2015), supporting the notion that the combination of Spd and exercise may synergistically enhance muscle health (Fig. 6). Consistent with this hypothesis, Schipke et al. (2019) reported that in different obesity mouse models combined Spd supplementation and exercise resulted in reduced body weight and significantly altered gut microbiota composition, compared to either intervention alone, highlighting the added benefits of the combined approach. The interplay between polyamines and physical exercise were also explored by Rogozkin et al. (2000) who measured the activity of polyamine-synthesising enzymes: ornithine decarboxylase (ODC) and

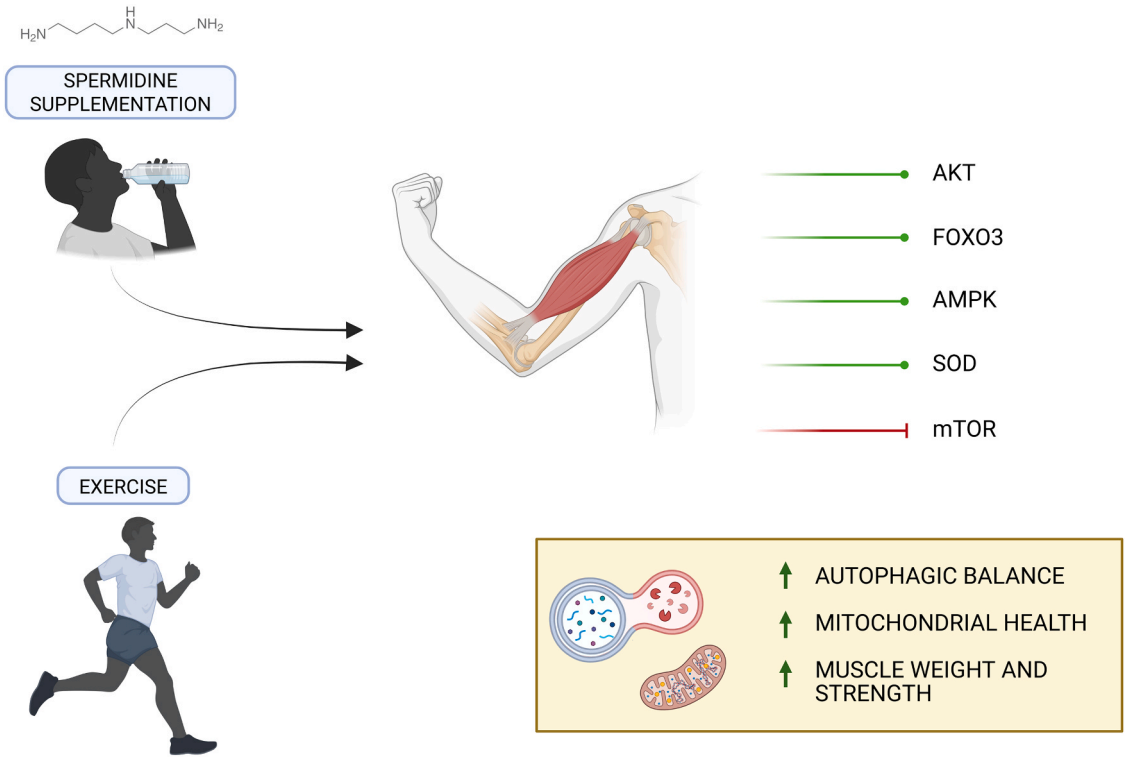

Fig. 6. *Synergistic effects of spermidine supplementation and exercise on skeletal muscle health.* The schematic illustrates the parallel influence of Spd supplementation and physical exercise on skeletal muscle function. Both interventions target skeletal muscle, modulating key signalling pathways including AKT, FOXO3, AMPK, SOD, and mTOR. These molecular changes collectively contribute to enhanced autophagic balance, improved mitochondrial health, and increased muscle mass and strength. Created in https://BioRender.com.

S-adenosylmethionine decarboxylase (SAMDC), as well as polyamine levels in the skeletal muscles of healthy male rats subjected to endurance or resistance exercise, or a single dose of testosterone. ODC activity rose sharply in slow-twitch oxidative fibers two hours after exercise, returning to baseline within 24 h, while SAMDC activity increased more gradually, peaking after eight hours. Polyamine levels increased in both, glycolytic and slow-twitch muscle fibre types, with putrescine concentration rising after 2 h and then decreasing as it was converted into Spd and spermine via SAMDC activity (Rogozkin et al., 2000). Similar enzyme activation and polyamine accumulation were observed following a single dose of 17a-methyltestosterone. Mechanistically, testosterone regulates this process by binding to the androgen receptor (AR), which acts as a transcription factor that directly targets the promoter region of the ODC gene (Betts et al., 1997). This androgen-mediated upregulation of ODC transcription accelerates the conversion of ornithine into putrescine, thereby increasing the pool of available polyamines for muscle hypertrophy and repair (Betts et al., 1997; Thomas, 2001). These findings suggest that exercise-associated increases in endogenous testosterone may contribute to the observed elevation in polyamine levels (Rogozkin et al., 2000). Collectively, these findings suggest that Spd and physical exercise act through converging signalling pathways, specifically the AMPK/FOXO3 and AKT/mTOR axes, to synergistically bolster muscle resilience. By simultaneously stimulating polyamine metabolism and autophagic clearance, this combined approach could offer a superior therapeutic strategy for mitigating muscle wasting and restoring metabolic homeostasis compared to either intervention alone.

7. Conclusions and future perspectives

This review highlights the critical role that polyamines and their associated metabolic pathways play in supporting the physiological functions of skeletal muscle across the lifespan. Central to this role is the link between Spd and the induction of autophagy, a process primarily mediated by the inhibition of the acetyltransferase EP300. By reducing the acetylation levels of key ATG proteins, spermidine effectively bypasses inhibitory signals to stimulate cellular "self-cleaning" and proteostasis.

Through these functions, polyamines contribute to multiple aspects of muscle biology, ranging from embryonic development and cellular differentiation to post-injury repair mechanisms and adaptation to physiological stressors. Through these functions, they help maintain muscle integrity and metabolic homeostasis, particularly during aging, when the regulation of cellular turnover, oxidative balance, and proteostasis becomes increasingly critical.

A central component of this metabolic network is Spd, which can be derived from dietary intake, synthesized endogenously through the activity of spermidine synthase, or produced via polyamine catabolism, including reactions mediated by SMOX. Increasing evidence suggests that SMOX activity may influence skeletal muscle homeostasis by modulating intracellular polyamine levels and by regulating the expression of genes involved in muscle atrophy and stress responses. As Spd levels decline with age, the resulting "autophagic stagnation" contributes to the accumulation of damaged mitochondria and proteins; thus, restoring Spd levels via supplementation or exercise-induced synthesis serves to re-activate these essential clearance pathways. However, the precise molecular mechanisms through which SMOX and spermidine regulate these processes remain incompletely understood. Clarifying how SMOX-derived signals interact with autophagy pathways and exercise-induced adaptations represents a promising direction for future research.

Growing evidence also highlights a potentially synergistic relationship between physical activity and polyamine metabolism. Exercise activates cellular pathways involved in mitochondrial remodelling, redox regulation, and autophagy, processes in which polyamines play an important regulatory role. Specifically, Spd may synergize with exercise-

induced signalling pathways, such as the AMPK–FOXO3a axis, to enhance the transcription of ATG genes and bolster muscle resilience. Recent studies have begun to shed light on the complex molecular interactions between the polyamine metabolic axis and exercise-induced responses in skeletal muscle, an emerging field that holds promise for understanding mechanisms of age-related muscle decline (Fig. 7). Although this field remains relatively underexplored, it offers promising opportunities for advancing our understanding of the mechanisms underlying muscle aging.

Within this context, Spd has attracted increasing attention as a potential therapeutic molecule. In preclinical models, spermidine supplementation has been shown to restore muscle structure and function through mechanisms involving enhanced autophagy, improved mitochondrial quality control, and reduced apoptosis in aging or dystrophic muscle tissues. These findings raise the possibility that combined lifestyle and metabolic interventions, integrating regular physical activity with polyamine supplementation, could enhance therapeutic outcomes in sarcopenia and other muscle disorders. Given its high expression in skeletal muscle and its direct role in regulating intracellular polyamines levels, SMOX therefore represents a promising molecular target for therapeutic intervention. Targeting this enzyme may open new avenues for preserving muscle homeostasis during aging and for treating muscle-related disorders, further underscoring the central importance of the polyamine metabolic network in skeletal muscle biology. However, targeting enzymes involved in polyamine catabolism, such as SMOX, requires caution, as their activity can generate reactive oxygen species and promote oxidative stress under pathological conditions. Therefore, several challenges must be addressed before clinical translation. The bioavailability and pharmacokinetics of orally administered Spd in humans are still incompletely characterized, and optimal dosing strategies have yet to be established. Moreover, the long-term safety of sustained polyamine supplementation requires careful evaluation, particularly given the recognized involvement of polyamines in growth and proliferation.

Future research should prioritize well-controlled clinical studies to evaluate the combined effects of exercise and polyamine-based interventions, alongside mechanistic investigations aimed at elucidating how physical activity influences polyamine metabolism in human skeletal muscle. Such approaches may prove beneficial not only for age-related muscle decline but also for inherited myopathies characterized by progressive degeneration.

CRediT authorship contribution statement

Lavinia Attili: Writing – review & editing, Writing – original draft. **Manuela Cervelli:** Writing – review & editing, Funding acquisition, Conceptualization. **Guglielmo Duranti:** Writing – review & editing, Conceptualization. **Roberta Ceci:** Writing – review & editing, Funding acquisition, Conceptualization. **Marianna Nicoletta Rossi:** Writing – review & editing, Conceptualization. **Rachele Di Santo:** Writing – review & editing.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

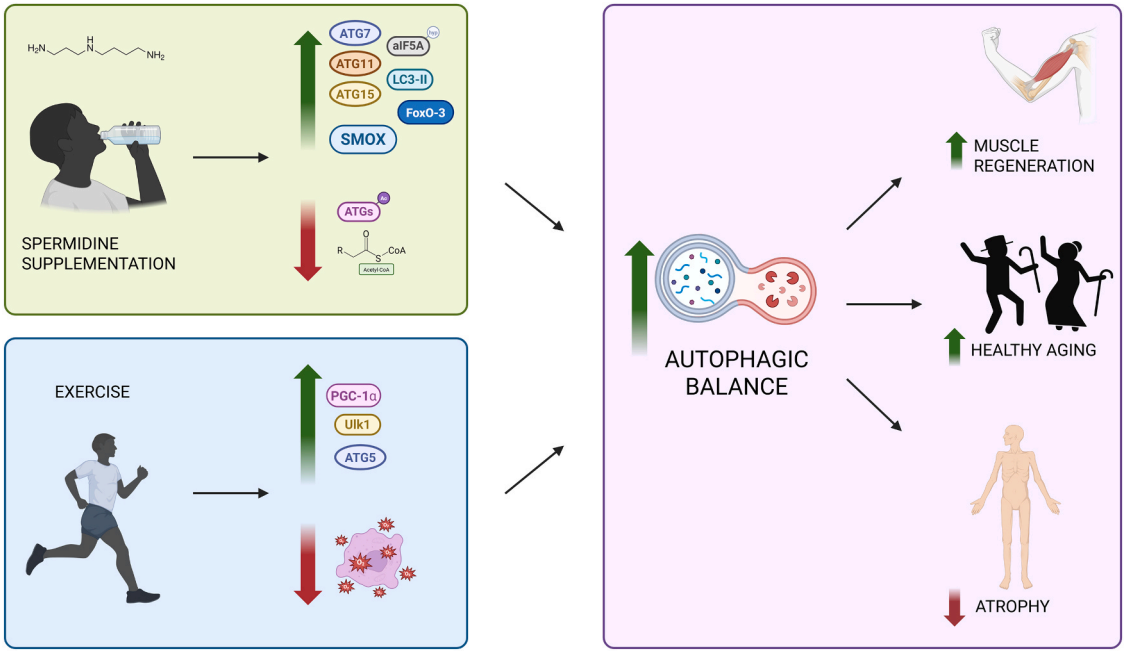

Fig. 7. *Interplay Between Spermidine Supplementation and Exercise in Regulating Autophagy for Muscle Health.* Schematic overview of the complementary roles of spermidine supplementation and physical exercise in promoting muscle health through the activation of autophagy. Spermidine intake upregulates key autophagy-related factors (e.g., ATG proteins, LC3-II, and transcriptional regulators such as FOXO3), while reducing acetylation-dependent inhibition of autophagic machinery. In parallel, exercise stimulates autophagy through pathways involving PGC-1α, ULK1, and ATG5, alongside reductions in cellular stress and damage. Together, these interventions converge to enhance autophagic flux and maintain autophagic balance, ultimately supporting muscle regeneration, preventing atrophy, and promoting healthy aging. Created in https://BioRender.com.

Data availability

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

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