From autophagy to mitophagy: *Quality control mechanisms in skeletal muscle*

Eduardo Antuña[a,b,c,*], Nerea Menéndez-Coto[a,b,c], Paula Fernández-Guisasola[a,c], and Ana Coto-Montes[a,b,c]
[a]Department of Morphology and Cell Biology, University of Oviedo, Oviedo, Spain
[b]Research Group OSKAR, Instituto de Investigación Sanitaria del Principado de Asturias (ISPA), Oviedo, Spain
[c]Instituto de Neurociencias del Principado de Asturias (INEUROPA), Oviedo, Spain
*Corresponding author. e-mail address: edugan.97@gmail.com

Contents

Abstract

Autophagy is a process which is responsible for the maintenance of cellular homeostasis. This is achieved through the orchestration of both highly selective and non-selective degradation pathways, the purpose of which is the elimination of damaged structures. Recent findings have revealed that, in addition to its intracellular function, this organelle exhibits a remarkable "social life" and forms relationships with other cellular organelles. This has led to the discovery that mitochondrial quality is maintained not only through mitophagy, but also through extracellular mechanisms between cells. This has significantly expanded our understanding of tissue integrity. In skeletal muscle, autophagy, or autophagy, is a finely tuned process that plays a crucial role in maintaining physiological performance and adaptation. Disruption of

International Review of Cell and Molecular Biology
ISSN 1937-6448, https://doi.org/10.1016/bs.ircmb.2025.11.006

autophagy has been linked to accelerated degeneration, metabolic dysfunction, and frailty. Although therapeutic manipulation of autophagy and mitophagy shows promise in restoring muscle health, major translational barriers persist. A more profound and nuanced exploration of autophagy flux in human muscle is imperative, underpinned by novel advanced cell biology technologies and predicated on satellite cells as the primary agents in muscle regeneration. The full therapeutic potential of autophagy could be harnessed to redefine interventions against muscle ageing and associated diseases. However, this would still require critical scrutiny of the long-term effects and systemic consequences.

1. Introduction

Cells are the essential functional units responsible for essential functions for cell viability including the execution of the processes of energy production, signal transduction, gene expression, and maintenance of structural integrity. To fulfil these functions effectively, cells must maintain homeostasis, defined as a precise balance of biochemical mechanisms that ensure optimal performance and survival under changing environmental conditions (Valls & Esposito, 2022). This balance is facilitated by a complex network of regulatory systems, including the ubiquitin-proteasome system (UPS), which coordinates the maintaining of proteostasis and preventing cytotoxic stress (Ballabio & Bonifacino, 2020). UPS is a low-capacity degradation system that degrades protein to protein. In a similar manner, redox homeostasis plays a critical role in regulating reactive oxygen species (ROS), which are essential for signaling, but deleterious in excess (Ernst et al. 2018; Ray et al. 2012), being crucial for preventing oxidative damage to DNA, proteins, and lipids (Holmström & Finkel, 2014). The plasma membrane is also involved in the maintenance of homeostasis through the preservation of ion gradients and the sensing of extracellular cues, which in turn trigger adaptive responses (Ernst et al. 2018).

The cellular interactome is defined as the complex network of interconnected pathways that govern cell behavior and ensure proper function. This network integrates proteostasis, mitochondrial dynamics, signaling cascades, and autophagy, coordinating responses to internal and external stimuli to maintain homeostasis (Coto-Montes et al. 2021). The ability to regulate these mechanisms is critical for the adaptation of cells, their survival, and the prevention of dysfunction, particularly in metabolically active tissues such as skeletal muscle. In the event of system failure or dysregulation, there is a corresponding deterioration in cellular function, giving rise

to pathological conditions including metabolic disorders, cancer, and age-related diseases, in addition to central nervous system (CNS)-related diseases such as mental disorders and neurodegeneration (Gómez-Virgilio et al., 2022; Höhn et al. 2020; Li et al. 2025; Menéndez-Valle et al., 2023). Therefore, it can be concluded that a comprehensive understanding and preservation of cellular homeostasis is of paramount importance for both the maintenance of basic biological processes and the development of therapeutic interventions.

It is evident that organelles such as the endoplasmic reticulum (ER) and lysosomes play a pivotal role in these homeostatic processes. For instance, the unfolded protein response (UPR) modulates ER activity to manage the stress associated with improper protein folding (Ron & Walter, 2007). In addition, lysosomes integrate nutrient signals and coordinate catabolic responses (Ballabio & Bonifacino, 2020; Settembre & Perera, 2024). The combined functionality of these systems is pivotal in ensuring the preservation of cellular functionality, adaptability, and survival capacity. This, in turn, is essential for maintaining the health of both tissue and organisms as a whole.

The text places particular emphasis on delineating the molecular and cellular pathways involved in the maintenance of proteostasis, organelle turnover and structural integrity of skeletal muscle tissue. The objective of this study is to integrate the most recent findings in the field to identify potential therapeutic targets that promote healthy muscle ageing and mitigate the pathological consequences associated with dysregulated cellular quality control systems in muscle-related diseases.

2. What is autophagy and quality control mechanisms?

Autophagy, a term derived from the Greek words “auto” (self) and “phagos” (to eat), refers to a conserved intracellular degradation process by which cells remove damaged organelles, misfolded proteins, and other cytoplasmic components through lysosomal degradation. This catabolic pathway plays a crucial role in maintaining cellular homeostasis, energy balance, and functional integrity under both physiological and pathological conditions (Lei & Klionsky, 2021). The maintenance of cellular homeostasis is contingent upon a meticulously orchestrated network of regulatory mechanisms that guarantee the optimal function, structure, and survival of the cell. These systems have been demonstrated to regulate protein folding, organelle integrity, and metabolic balance in response to

intracellular and environmental signals. Autophagy, the UPS and mitochondrial quality control are of particular significance in this regard, working in synergy to prevent the accumulation of damaged or dysfunctional components (Mizushima & Levine, 2020; Paez et al. 2023). Autophagy is a highly regulated process that is typically activated in response to various stress signals, including nutrient deprivation, oxidative stress, hypoxia, and organelle dysfunction (Glick et al. 2010; Gómez-Virgilio et al., 2022; Parzych & Klionsky, 2014). Autophagy, therefore, as a cellular quality control mechanism, is vital for maintaining homeostasis, as well as for enabling adaptive responses to stress, preserving tissue function and organismal health (González-Blanco et al. 2022). Autophagy's role in quality control ensures the viability and functionality of cells, thus contributing to tissue and organismal health and preventing related pathologies, including neurodegeneration, metabolic syndromes and muscle disorders (Chen et al. 2022; Klionsky et al. 2021; Mizushima, 2018). Moreover, autophagy is increasingly recognized not only as a survival mechanism but also as a critical modulator of cell fate and inter-organelle communication, thus highlighting its relevance as a target for therapeutic interventions in multiple diseases.

2.1 Autophagy: Cell viability must be ensured by recycling

Autophagy can be defined as the process of degradation and recycling of damaged or dysfunctional molecules within the cell, as previously outlined. Furthermore, it is a highly conserved mechanism in eukaryotes, based on their ATG proteins, which, although not constant, show strong homology between organisms and tissues (Levine & Kroemer, 2019). This cellular mechanism can be selective or non-selective in terms of the cellular material it degrades. In selective autophagy, the encapsulation of the cargo by the phagophore is achieved through the binding of the phagophore to specific surface markers. The formation of the phagophore is contingent on the presence of surface markers, which, when recognized, initiate the process of the autophagosome engulfing the cargo. This process occurs through a zipper-like mechanism, resulting in an object of a size and shape corresponding to that of the cellular structure, without the occurrence of cytoplasmic uptake (Norell et al. 2024). However, in non-selective autophagy, the formation of the phagophore is facilitated by a coordinated mechanism involving numerous molecules, which enable its elongation and encapsulation of damaged or dysfunctional molecules with part of the circulating cytoplasm (Vargas et al. 2023). Notwithstanding the selectivity

of the autophagy process, three well-defined types of autophagy are currently distinguished according to the cellular components they degrade. These are macroautophagy, microautophagy and chaperone-mediated autophagy.

Macroautophagy is the most extensively studied and best-known autophagy mechanism at present. It is responsible for the selective or non-selective elimination of large molecules, such as organelles and protein aggregates, through the formation of autophagosomes, which engulf part of the cell cytoplasm in the process, and lead the cargos to the lysosomes, which are full of acid hydrolases (Gómez-Virgilio et al., 2022). The cellular stimuli that activate this autophagy pathway is energy deficiency due to nutrient deprivation and cellular stress. The ER plays a special role in the formation of autophagosomes, since it has specific domains, the omegasomes, which will establish contact with other molecules facilitating the synthesis of the phagophores that will give rise to autophagosomes after the elongation stage (Karanasios et al. 2013).

Microautophagy is defined as a non-selective mechanism of degradation of small molecules and small cytoplasmic portions. This process of degradation is facilitated by the internalization of small cytosolic cargoes into lysosomes (Yamamoto & Matsui, 2024). In contrast to macroautophagy, microautophagy does not necessitate the formation of autophagosomes. This type of autophagy is commonly performed by the cell under stress and starvation as in macroautophagy, but it also has functions as a cell and organelle function and size regulator (Li et al. 2012; Wang, Klionsky, et al. 2023).

Chaperone-mediated autophagy (CMA) is a selective process that occurs in a context-dependent manner, whereby damaged, obsolete, or regulatory proteins are removed from the cellular interior. The selectivity of molecules for CMA is such that only molecules containing a KFERQ-like sequence can be degraded by this pathway, as this is the sequence recognized by the Hsp70 chaperone in the cytosol (Kaushik & Cuervo, 2018). Of the total number of cytosolic soluble proteins, approximately 30 % of them can be recognized for CMA (Massey et al. 2006). The complex of KFERQ-like motif substrate and Hsp70 subsequently binds to other co-chaperone proteins, such as Hsp40, Hsp90, HIP, HOP, and Bag-1, and, finally, binds to the lysosomal receptor LAMP2A for degradation (Kaushik & Cuervo, 2018; Wang et al. 2024). CMA, the selective lysosomal degradation pathway, is imperative for cellular homeostasis, contributing to proteostasis, metabolic adaptation and stress responses (Cuervo & Wong, 2014) (Table 1).

Table 1 Summary of the main autophagy pathways in mammals.

	Macroautophagy	Microautophagy	Chaperone-Mediated Autophagy (CMA)
Selectivity	Selective and Non-Selective	Non-Selective	Selective
Cargo	Damaged organelles, cytoplasm and molecular aggregates	Cytosolic small molecules	Specific KFERQ peptides-like proteins
Cellular Mechanism	Autophagosomes formation and its fusion with lysosomes	Lysosomal membrane to engulf cytoplasmic content	Selective translocation of KFERQ-motif proteins through binding and complex formation of Hsp70, cochaperones and LAMP−2A
Markers	AMPK, ULK1, ATG5, ATG12, LC3I-II, p62/ SQSTM1	ESCRT components (TSG101, VPS4, CHMP4B), LAMPs	KFERQ sequence, Hsp70, LAMP−2A
Triggering factors	Cellular stress and nutrient deprivation	Cellular stress and basal turnover	Oxidative stress and prolonged starvation
Cellular function	''Cell cleaning'', bulk degradation and energy homeostasis	Organelle size regulation and membrane turnover	Cellular quality control and metabolic regulation

The mechanism of macroautophagy, more commonly referred to as autophagy in mammals, consists of different phases with different specific molecules in each stage. Firstly, the mechanism is induced by signals of

nutrient deprivation or cellular stress. In such conditions, the mechanistic target of rapamycin complex 1 (mTORC1) is inhibited, thus allowing the activation of AMP-activated protein kinase (AMPK) and the subsequent phosphorylation and activation of a protein complex known as ULK1 (Deretic & Kroemer, 2022; Kim et al. 2011). The complex under discussion comprises the ULK1/2 kinases (homologue of ATG1 in yeast), ATG13, ATG101 and FIP200 (RB1CC1) (Hosokawa et al. 2009; Zachari & Ganley, 2017). In basal conditions, the Activating Molecule in Beclin-1-Regulated Autophagy (AMBRA1) has been observed to associate with BCL2 at the mitochondrial membrane, thereby inhibiting autophagy (Rubinstein & Kimchi, 2012; Strappazzon et al. 2011). Upon receiving a signal to initiate the process of autophagy, and in the absence of inhibition by mTORC1 (Nazio et al., 2013), AMBRA1 dissociates from BCL2 and translocates to the endoplasmic reticulum (ER). In this location, it ubiquitinises Beclin-1 (a homologue of ATG6 in yeast), thereby activating it and facilitating its binding to the subsequent PI3KC3 complex, which is essential for the formation of the autophagosome (Sun, 2016).

The next step in the macroautophagy mechanism is the formation of the autophagosome by the omegasome in the ER. The activation of ULK1 and its binding to the ER (or to its cargo in the case of selective autophagy), allows the attraction of PI3KC3, a complex composed of Beclin-1, ATG14L, VSP15 and VSP34 (Sanchez-Martin et al. 2020). The PI3KC3 complex will be phosphorylated by ULK1 kinase complex to bind DFCP1 and recruit ATG9 and WIPI2 (ATG18 in yeast) to the ER membrane to synthesize the autophagosome (Nähse et al. 2023; Olivas et al. 2023).

Once the nucleation of the phagophore in the omegasome is generated, it will undergo a process of elongation and recruitment of the cytosolic cargo. To this end, the cytosolic form of LC3 (LC3-I, homologue of ATG8 in yeast) undergoes a series of enzymatic modifications to become LC3-II, which associates with the phagophore membrane (Wild et al. 2014). This process begins with the cleavage of pro-LC3 by ATG4, generating LC3-I, which is activated by the E1-like enzyme ATG7 and transferred to the E2-like enzyme ATG3. Finally, with the assistance of the E3-like ligase complex ATG12–ATG5–ATG16L1, LC3-I is conjugated to phosphatidylethanolamine (PE), forming LC3-II (Fang et al. 2021; Wang et al. 2024). This lipidation is crucial for the expansion and closure of the autophagosomal membrane. p62/SQSTM1 serves as an autophagic adaptor protein, recognizing and binding to ubiquitinated cargo through its ubiquitin-associated

domain and simultaneously interacting with LC3 via its LC3 interaction region (LIR) motif. This binding is essential for the correct functioning of the autophagic machinery (Gallagher & Holzbaur, 2023; Runwal et al. 2019). LC3-II remains attached to the autophagosome until it fuses with a lysosome, where LC3-II is degraded along with the autophagic cargo. Additionally, recent studies have shown that during the formation and stabilization of the cup-like shape of phagophores, an intimate interplay is established between LC3-II, which is gradually attaching lipids contributing to the formation of the phagophore, and the ATG5-ATG12-ATG16L1 complex (Campisi et al. 2025; Mohan et al. 2024; Yu & Klionsky, 2024).

Following the completion of the formation and loading of the autophagosome, the process of maturation is initiated. This process involves the dissociation of early autophagy-related proteins and the recruitment of factors necessary for the fusion of the autophagosome with lysosomes. Key players in this maturation include Rab7, a small GTPase that regulates late endosomal trafficking, and the HOPS complex, which acts as a tethering factor facilitating the docking of autophagosomes to lysosomes (McEwan et al. 2015; Nguyen & Yates, 2021). The process of fusion between autophagosomes and lysosomes is facilitated by SNARE complex proteins, which regulate the convergence of the two membranes. Syntaxin 17 (STX17), located on the autophagosomal membrane, pairs with SNAP29 and VAMP8 on the lysosomal membrane to form a trans-SNARE complex that drives membrane fusion (Jiang et al. 2014; Shen et al. 2021). Moreover, research has indicated that ATG14L, an early-acting factor, may facilitate efficient SNARE complex assembly, thereby promoting the fusion of autophagosomes with lysosomes (Reggiori & Ungermann, 2017). The SNARE complex, located in the autophagosomal membrane, facilitates the fusion of lysosomes with autophagosomes. Upon completion of the process of autophagy, the resultant fusion gives rise to the formation of an autolysosome. Within this autolysosome, the enclosed cargos are subject to degradation by lysosomal hydrolases, thus giving rise to fundamental biomolecules, including fatty acids, nucleotides and amino acids. These recycled building blocks can be reused for energy production, biosynthesis, and cellular repair, especially under cellular stress conditions such as starvation or damage.

2.2 Selective mechanisms of organelle degradation

A preliminary review of autophagy has been conducted from a general perspective, with a focus on the processes of destruction and recycling of

damaged or dysfunctional macromolecules. However, cells are also capable of degrading organelles and structural components in a organelle-dependent form. This specific form of autophagy is imperative for sustaining cellular homeostasis, as it facilitates the precise elimination of dysfunctional organelles that could otherwise compromise cellular function (Anding & Baehrecke, 2017). Through a series of meticulously regulated processes, cells are able to identify and degrade specific organelles via dedicated molecular machinery, ensuring not only metabolic balance but also structural and functional integrity.

2.2.1 Reticulophagy

The ER plays a central role in protein folding, calcium storage, and lipid synthesis within the cell. To maintain ER proteostasis under both physiological and stress conditions, cells rely on several quality control mechanisms. Among the most studied are the UPR and ER-associated degradation (ERAD) pathways. Under homeostatic conditions, the coordinated function of UPR and autophagy ensures proper ER function. However, during ER stress, dysregulation of autophagy may occur, leading to cell death via apoptosis (Song, Tan, et al. 2017).

In these scenarios, the ERAD pathway is activated to recognize misfolded proteins, targeting them for ubiquitination and subsequent proteasomal degradation. Nevertheless, when ERAD is overwhelmed, the cell initiates a broader strategy known as reticulophagy (also referred to as ER-phagy), a form of selective autophagy directed at dysfunctional regions of the ER. Unlike bulk autophagy, reticulophagy involves specialized receptors containing LIRs or GABARAP-interacting motifs (GIMs), which mediate the direct engagement of ER subdomains with the autophagosomal machinery (Liang et al. 2020).

In yeast, this selective process is mechanistically simpler, proceeding via microautophagy and not requiring the full autophagosome formation machinery (Schäfer et al. 2020; Schuck et al. 2014). The tight coordination among UPR, ERAD, and reticulophagy ensures that reticulophagy is only activated when canonical pathways are insufficient to restore ER homeostasis.

In mammals, reticulophagy is mediated by at least eleven identified receptors (Mochida & Nakatogawa 2022b), four of which are considered core components of this selective autophagy pathway: reticulophagy regulator 1 (RETREG1/FAM134B), reticulon 3 (RTN3), SEC62 (a protein involved in translational regulation), and cell cycle progression 1 (CCPG1). Although each receptor operates within distinct ER-phagy pathways, they

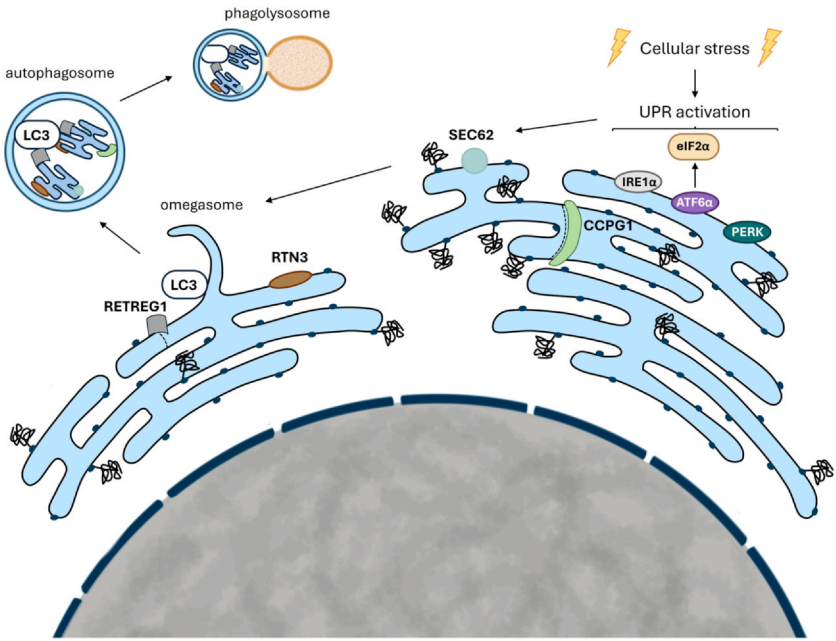

Fig. 1 Overview of the reticulophagy process. Under endoplasmic reticulum (ER) stress, when the unfolded protein response (UPR) and endoplasmic reticulum associated degradation (ERAD) pathways are insufficient to restore homeostasis, reticulophagy is activated. This selective form of autophagy targets dysfunctional ER subdomains through specific receptors (RETREG1/FAM134B, RTN3, SEC62, and CCPG1). Reticulophagy operates in coordination with UPR and ERAD as part of a hierarchical quality control system that preserves ER function and prevents apoptosis.

all share a functional LIR motif, which facilitates their recruitment to autophagosomes and engagement with the autophagic machinery (Yao et al. 2021) (Fig. 1).

RETREG1/FAM134B was the first ER-phagy receptor to be identified and remains the most extensively characterized. It is predominantly localized to ER sheets, where it plays a pivotal role in initiating fragmentation of the ER membrane into vesicles competent for autophagosome incorporation (Khaminets et al. 2015). RETREG1 contains a reticulon homology domain (RHD) that induces membrane curvature, a critical step in vesicle formation. Importantly, its expression is regulated by ATF4, a downstream transcription factor of the PERK branch of the UPR, establishing a direct mechanistic link between ER stress and ER-phagy induction (Luhr et al. 2019; Mu et al. 2024).

RTN3 serves a similar function to RETREG1 but is specialized in the remodeling of ER tubules, contributing to their fragmentation and turnover (Grumati et al. 2017). RTN3-mediated ER-phagy is particularly critical for neuronal homeostasis, and its disruption has been associated with neurodegenerative disorders (Liang et al. 2020).

SEC62 is implicated in the recovery phase following acute ER stress, functioning in post-translational protein translocation, calcium homeostasis, and the selective clearance of ER subdomains enriched in misfolded proteins through ER-phagy (Linxweiler & Müller 2022; Wilkinson, 2019).

Finally, CCPG1 plays a crucial role in secretory tissues such as the exocrine pancreas, where it maintains ER proteostasis under conditions of chronic stress. CCPG1 acts as a scaffold by interacting with both LC3 and FIP200, effectively integrating upstream stress signals with autophagosome biogenesis (Ishii et al. 2023; Smith et al. 2018; Zhou et al. 2021).

Altogether, the interplay between ERAD, the UPR, and ER-phagy receptors constitutes a hierarchical and tightly regulated defense system that safeguards cellular homeostasis under conditions of stress. While ER-phagy primarily serves a protective and adaptive function by selectively removing dysfunctional ER components, its dysregulation can disrupt this delicate balance, tipping the cellular response towards apoptosis. This dynamic offers promising therapeutic potential, as targeting ER-phagy pathways may provide novel strategies to restore proteostasis and mitigate disease progression in disorders associated with chronic ER stress.

2.2.2 Nucleophagy

The nucleus is a fundamental organelle essential for cell viability, serving as the repository of genetic material and orchestrating gene expression, thereby governing virtually all vital cellular functions. Nucleophagy refers to the selective autophagic degradation of superfluous or damaged nuclear components to preserve nuclear integrity and sustain cellular homeostasis (Mochida et al. 2015). Cells employ several surveillance mechanisms to detect genomic instability and maintain nuclear health, including key regulators such as p53 and p21, which play critical roles in the prevention of DNA damage and the facilitation of rapid DNA repair (Galluzzi et al. 2014; Williams & Schumacher, 2016).

In yeast, nucleophagy occurs through two distinct pathways: macronucleophagy and micronucleophagy. In *Saccharomyces cerevisiae*, two forms of micronucleophagy have been characterized: piecemeal nucleophagy (PMN) and late nucleophagy (LN), both of which mediate the degradation of

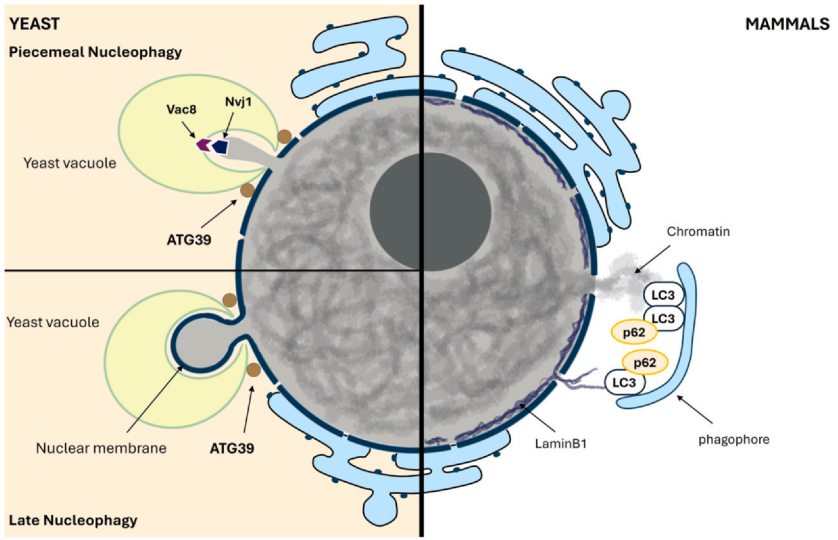

Fig. 2 Overview of the nucleophagy process in yeast and in mammals. Nucleophagy is a selective form of autophagy that degrades damaged or excess nuclear components to maintain nuclear integrity. In yeast, it occurs via piecemeal or late nucleophagy, involving ATG39. In mammals, nucleophagy is less defined but involves autophagic machinery contributing to senescence, genome stability, and stress responses.

nuclear material under stress conditions (Papandreou & Tavernarakis, 2019) (Fig. 2). PMN involves the direct sequestration of non-essential regions of the nucleus into the vacuole via nuclear-vacuole junctions. This process is dependent on the interaction of two key proteins, Nvj1 and Vac8, which are required for the formation and maintenance of these junctions (Bo Otto & Thumm, 2020; Dawaliby & Mayer, 2010). Additionally, the autophagy receptor ATG39, localized to the perinuclear endoplasmic reticulum, contributes to this process by inducing curvature and deformation of the nuclear envelope to facilitate autophagic sequestration (Mochida & Nakatogawa 2022a; Mochida et al. 2022). These mechanisms are particularly important for survival during the early stages of nutrient deprivation (Bo Otto & Thumm, 2020; Dawaliby & Mayer, 2010).

Late nucleophagy, by contrast, is mediated exclusively by ATG39 and is associated with significant morphological alterations of the nucleus. LN is activated under conditions of prolonged nitrogen starvation or pharmacological inhibition of the mechanistic target of rapamycin (mTOR) pathway (Otto & Thumm, 2021). Together, these nucleophagic pathways

provide a multilayered strategy for maintaining nuclear quality control and promoting cell survival during stress.

In mammals, the molecular mechanisms underlying nucleophagy remain less well characterized compared to yeast; however, several parallels between the two systems have been proposed. Autophagy-related proteins such as LC3B and p62 have been shown to interact with nuclear lamina components, particularly lamin B1, as well as with chromatin, thereby promoting their selective degradation during cellular senescence (Luo et al. 2016) (Fig. 2). When properly activated, nucleophagy has the capacity to eliminate excess DNA content in polyploid tumor cells (cells with more than two complete copies of the same chromosome), thus favoring homeostasis. In these cellular contexts, selective activation can play a protective role against tumor development by contributing to the maintenance of cellular and tissue integrity. However, as it involves the selective degradation of an essential organelle such as the nucleus, nucleophagy can also act as a mechanism of cell death. Therefore, when this pathway is deregulated or excessively activated, it can compromise the viability of healthy cells, generating unexpected and potentially harmful cytotoxicity (Fu et al. 2018). This targeted degradation contributes to the remodeling of nuclear architecture and supports the clearance of damaged or redundant nuclear materia. Notably, age-related pathologies and senescence are frequently associated with profound alterations in nuclear structure, which may impair nucleophagic activity and contribute to nuclear dysfunction (Pathak et al. 2021).

Although a direct mammalian homologue of the yeast-specific nucleophagy receptor ATG39 has yet to be identified, the existence of functionally analogous mechanisms is strongly suggested by emerging evidence (Boyle & Wilfling, 2023; Papandreou & Tavernarakis, 2019), such as the translocon subunit SEC62 (Kucińska et al. 2023). This knowledge gap presents a valuable opportunity for further investigation into the regulation of nucleophagy in mammals and its broader implications for nuclear quality control, ageing, and age-associated diseases.

2.2.3 Pexophagy

Peroxisomes are multifunctional organelles involved in diverse metabolic processes, including lipid metabolism, detoxification of ROS, and plasmalogen biosynthesis. Preserving peroxisomal homeostasis is essential for cellular viability and function (Wanders et al. 2023). Pexophagy, a selective form of autophagy, facilitates the targeted degradation of dysfunctional or

surplus peroxisomes, thereby mitigating cellular damage and preventing the onset of ROS-associated pathologies (Cho et al. 2018). This process can be triggered by a range of cellular stressors, such as nutrient deprivation, hypoxia, and oxidative stress. However, tight regulation of pexophagy is crucial, as recent findings suggest that its excessive activation may interfere with other selective autophagy pathways (Germain et al. 2024).

Pexophagy displays notable mechanistic differences between yeast and mammalian systems (Fig. 3). In yeast, two distinct modalities have been described. In macropexophagy, the peroxisome is recognized and enclosed by a phagophore that matures into an autophagosome before fusing with the lysosome. In contrast, micropexophagy involves the direct engulfment of the peroxisome by the lysosomal membrane through invagination (Manjithaya et al. 2010). In *Pichia pastoris*, pexophagy is mediated by Atg30, whereas in *Saccharomyces cerevisiae*, the functional homologue is Atg36.

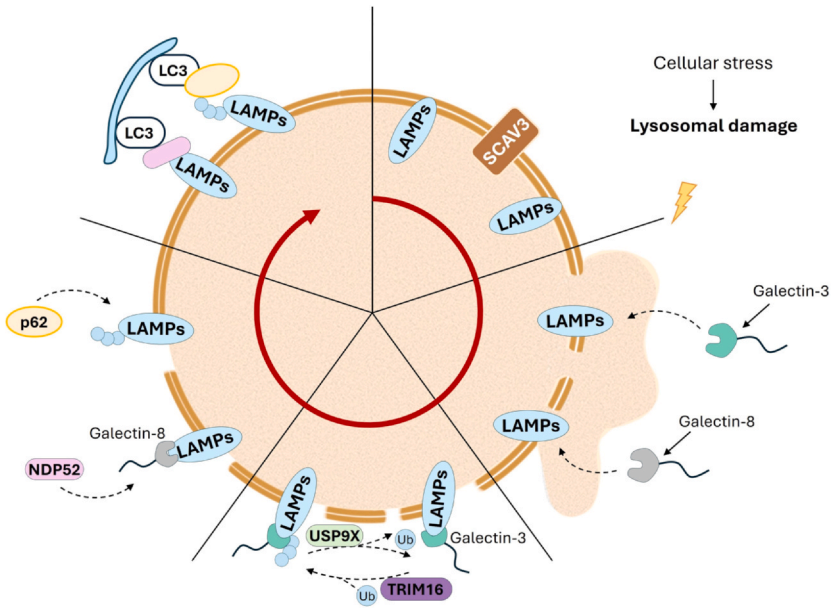

Fig. 3 Overview of the pexophagy process in yeast and in mammals. Pexophagy in yeast involves receptors like Atg30 or Atg36; a mechanism initiated by a sequence of protein interactions that result in the degradation of the damaged peroxisomes. In mammals the selective degradation of peroxisomes occurs via ubiquitin-dependent or ubiquitin-independent pathways, engaging receptors such as p62, NBR1, or direct LC3–PEX14 interactions. Both systems converge on autophagosome formation and lysosomal degradation of peroxisomes.

These receptors interact with peroxisomal membrane proteins PEX3 and PEX14, initiating the recruitment of autophagic machinery (Burnett et al. 2015; Motley et al. 2012). Phosphorylation of Atg30 is required for its interaction with scaffold proteins Atg11 and Atg17, both of which are key components of the pre-autophagosomal structure (PAS) (Mao et al. 2014). This complex promotes the assembly of the core autophagy machinery, including Atg1, Atg8, Atg9, and the PI3KC3 complex (Farré & Subramani, 2016). Furthermore, Atg26 contributes to phagophore membrane elongation through its binding to phosphatidylinositol-4-phosphate (Nazarko et al. 2007).

In mammals, pexophagy proceeds through both ubiquitin-dependent and ubiquitin-independent mechanisms. In the ubiquitin-dependent route, the peroxisomal import receptor PEX5 can undergo monoubiquitination at specific residues such as Cys11 or Lys209 in response to oxidative stress (Demers et al. 2023). This post-translational modification is recognized by autophagy receptors p62/SQSTM1 and NBR1, which contain ubiquitin-binding domains and LIRs, thereby facilitating the recruitment of peroxisomes to autophagosomes. Although PEX3 does not directly mediate ubiquitination, it plays a structural role in anchoring components of the E3 ligase complex, which comprises PEX2, PEX10, and PEX12, and is responsible for catalyzing PEX5 ubiquitination (Okumoto et al. 2014; Yamashita et al. 2014). The deubiquitinase USP30 counteracts this process, thereby modulating the rate of pexophagy (Riccio et al. 2019).

In the ubiquitin-independent pathway, LC3 can directly bind to PEX14, competing with PEX5 and enabling peroxisome sequestration into autophagosomes without the need for ubiquitin tagging (Jiang et al. 2015). Additionally, the tankyrase enzymes TNKS1 and TNKS2 have been shown to associate with PEX14 and ATG9A, particularly under conditions of amino acid starvation, further promoting this non-canonical mode of pexophagy (Zamudio-Martinez et al. 2021).

2.2.4 Lysophagy

Lysosomes are pivotal organelles for cellular degradation and recycling, orchestrating the breakdown of damaged proteins, lipids, and organelles through the process of autophagy. Lysosomes, which are replete with hydrolytic enzymes, function optimally under acidic conditions (internal pH ~5.0) and are fundamental for sustaining cellular homeostasis (Settembre et al. 2013). Nevertheless, given their potent enzymatic content and role in autophagy by processing cytotoxic macromolecules, lysosomal

damage or membrane permeabilization represents a significant threat to cell viability. To mitigate the deleterious effects associated with lysosomal dysfunction, cells have evolved lysophagy, a selective, ubiquitin-dependent form of autophagy that targets compromised lysosomes for degradation, thereby preventing the release of harmful components and preserving organellar integrity (Bi et al. 2025; Li et al. 2015).

Lysophagy is initiated upon lysosomal membrane permeabilization (LMP), an event that may arise from oxidative stress or pathogenic infection (Papadopoulos et al. 2020). Following LMP, intraluminal glycoproteins, including LAMP1 and LAMP2, become exposed to the cytosol, where they are recognized by galectin family members, most notably Galectin-3 (LGALS3) and Galectin-8 (LGALS8), which function as molecular sensors of lysosomal damage (Jia et al. 2020; Kuma & Yoshimori, 2025). These galectins bind to β-galactosidase residues exposed to the cytoplasmic side of damaged lysosomes, effectively labelling them for selective removal via autophagy. Galectin-3 has been demonstrated to promote lysophagy by recruiting the E3 ubiquitin ligase tripartite motif containing 16 (TRIM16), facilitating the ubiquitination of lysosomal membrane proteins (Chauhan et al. 2016; Jia et al. 2020) and the subsequent engagement of the autophagy receptor p62/SQSTM1 (Gallagher & Holzbaur, 2023), thereby initiating the autophagic clearance cascade (Chauhan et al. 2016; Jia et al. 2020). In a similar manner, Galectin-8 has been shown to directly interact with the autophagy cargo receptor NDP52, which links damaged lysosomes to LC3 by LIR, thereby coordinating the formation of autophagosomes, particularly during antibacterial autophagy (Li et al. 2013). Following the ubiquitination of lysosomal membrane proteins such as LAMP1 or SCAV-3, receptors including p62, NBR1, and the AAA-ATPase valosin-containing protein p97 (VCP/p97) recognize and target the compromised organelles for sequestration by the ubiquitin-LC3 autophagic machinery (Eapen et al. 2021; Papadopoulos et al. 2017). The process of lysophagy is subject to fine-tuning by deubiquitinating enzymes, such as USP9X, in conjunction with modulators, including MAP3K7, which have the capacity to remove ubiquitin chains and adjust the threshold for lysophagy initiation (Shariq et al. 2024) (Fig. 4). In summary, lysophagy represents a highly coordinated quality control pathway integrating damage sensing via galectins, ubiquitination of lysosomal proteins, recruitment of selective autophagy receptors, and autophagy receptor-mediated biogenesis of the autophagy vacuoles to ensure the efficient clearance of defective lysosomes. Dysfunctional lysophagy has

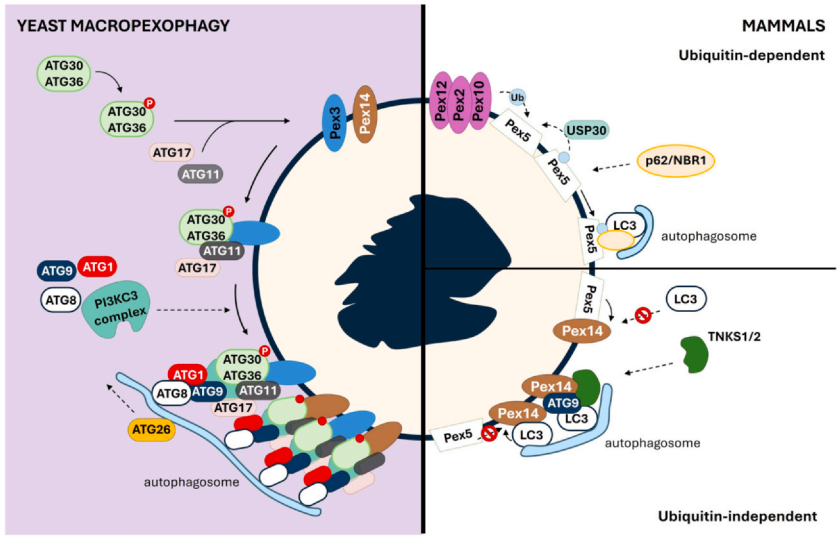

Fig. 4 Overview of the lysophagy process. Lysophagy is a selective autophagy pathway that removes damaged lysosomes to prevent cellular toxicity. Upon lysosomal membrane permeabilization, galectins detect exposed glycoproteins, triggering ubiquitination and recruitment of autophagy receptors (p62, NDP52). This process ensures lysosomal quality control and removes the damaged lysosomes.

been implicated in the process of aging and a range of pathological conditions, thereby underscoring its essential role in maintaining organellar and cellular homeostasis.

2.2.5 Mitophagy

Mitochondria are essential, pleiotropic organelles that play a central role in sustaining cell viability and function. They are primarily responsible for the production of adenosine triphosphate (ATP) and the oxidation of fatty acids.

In mitochondria, ATP is generated by the mitochondrial respiratory chain and oxidative phosphorylation (OXPHOS) complexes. The electron transport chain is the process by which electrons are transferred from protein donors, such as $FADH_2$ and NADH, to the final acceptor, which is typically O_2, through protein complexes (complexes I-IV). These electrons generate a proton gradient in the intermembrane space of the mitochondria, which is utilized by complex V (ATP synthase) to produce ATP by pumping protons into the mitochondrial matrix. During the event of OXPHOS inefficacy, whether due to mitochondrial impairment or stress, there is an attendant

decline in ATP levels, an increase in ROS, and the activation of dysfunctional mitochondria removal (Ebanks & Chakrabarti, 2022; Zong et al. 2024). Consequently, ATP generation is not merely an energetic outcome, but rather a pivotal factor in determining mitochondrial fate through the process of autophagy surveillance pathways (Yun et al. 2020).

Additionally, mitochondria regulate key processes such as apoptosis, calcium homeostasis via their interaction with the ER at membrane-associated membranes (MAMs), and the generation of ROS, which serve as signaling molecules in pathways controlling cell proliferation and death. The selective degradation of mitochondria via autophagy, known as mitophagy, is fundamental for maintaining mitochondrial quality control and, by extension, overall cellular homeostasis (D'Arcy, 2024; Wang, Long, et al. 2023).

Mitophagy is typically initiated by receptors located on the outer mitochondrial membrane (OMM) and can proceed via two functionally distinct pathways: the Parkin-dependent and Parkin-independent mechanisms. In the classical, Parkin-dependent pathway, mitophagy is triggered by the loss of mitochondrial membrane potential (Narendra et al. 2008), while the Parkin-independent pathway responds to broader cues such as mitochondrial dysfunction, hypoxia, iron depletion, or activation of AMP-activated protein kinase (AMPK) (Seabright et al. 2020; Terešak et al. 2022). These stimuli lead to the recruitment of pathway-specific receptors to damaged mitochondria (Palikaras et al. 2018), though the downstream engagement of autophagic effectors, including autophagosomal markers such as LC3, remains consistent across both pathways (Fig. 5).

In the Parkin-dependent mitophagy pathway, the core components include PTEN-induced putative kinase 1 (PINK1) and the E3 ubiquitin ligase Parkin. Under physiological conditions, PINK1 is imported into healthy mitochondria and rapidly degraded. However, in depolarized mitochondria, PINK1 accumulates on the OMM due to impaired import and proteolytic processing, thereby acting as a sensor of mitochondrial damage. Once stabilized, PINK1 phosphorylates pre-existing ubiquitin molecules and initiates the recruitment of MARCH5/MITOL, another mitochondrial E3 ubiquitin ligase that facilitates polyubiquitination of various OMM proteins (Koyano et al. 2019; Yoo et al. 2019). Parkin is then recruited to the mitochondria, where it amplifies the ubiquitin signaling cascade by further ubiquitinating OMM proteins and phosphorylating ubiquitin itself, forming phosphorylated ubiquitin chains (p-Ub).

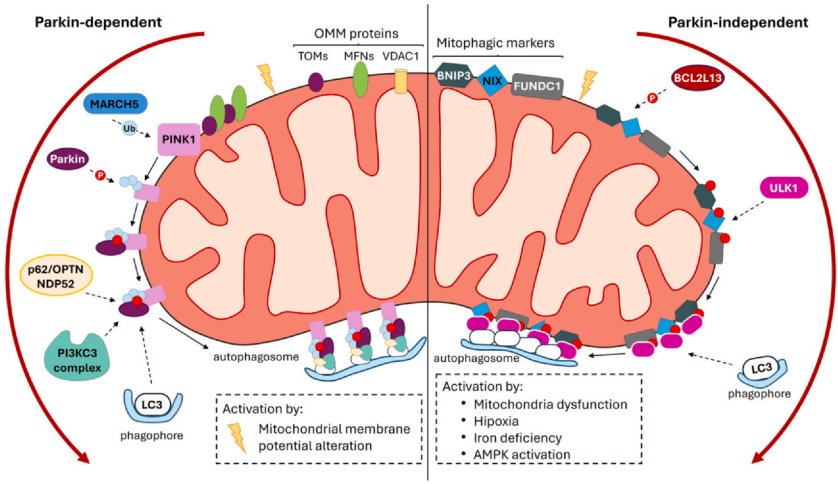

Fig. 5 Overview of the mitophagy process. Mitophagy is a selective autophagy pathway that eliminates damaged mitochondria to preserve cellular homeostasis. It proceeds via Parkin-dependent and Parkin-independent mechanisms, involving key sensors like PINK1, Parkin, and receptors such as BNIP3, NIX, and FUNDC1. Both pathways converge on LC3-mediated autophagosome formation and lysosomal degradation of dysfunctional mitochondria.

These serve as docking platforms for mitophagy receptors such as optineurin (OPTN), NDP52, and p62/SQSTM1 (Ordureau et al. 2015). These adaptors, in turn, bind to autophagic effectors including LC3, ATG9A, ULK1, and the PI3KC3 complex, thereby initiating the de novo formation of autophagosomes around the damaged mitochondrion, which ultimately fuses with lysosomes to enable degradation.

In contrast, the Parkin-independent mitophagy pathway is activated when Parkin is absent or functionally impaired (Villa et al. 2018; Wang, Long, et al. 2023). In this pathway, mitochondrial degradation relies on a distinct set of OMM-localized receptors, including BNIP3 (BCL2/adenovirus E1B 19kDa-interacting protein 3), NIX/BNIP3L, FUNDC1, BCL2L13 (a mammalian homologue of yeast ATG32) and FKBP8. Additional regulatory factors include AMBRA1, which can serve as a mitophagy receptor and interact with the E3 ubiquitin ligase HUWE1, thereby facilitating mitophagy in a ubiquitin-dependent manner even in the absence of Parkin (Di Rita et al. 2018; Michel et al. 2017).

Upon cellular stress such as hypoxia or energy deprivation, transcriptional upregulation of BNIP3 and NIX occurs, and these proteins are

inserted into the OMM. BCL2L13 has been shown to recruit ULK1 to mitochondria, where it stabilizes BNIP3 by protecting it from proteasomal degradation mediated by the SKP1–CUL1–FBXL4 ubiquitin ligase complex (Murakawa et al. 2019; Poole et al. 2021). Once localized, ULK1 phosphorylates BNIP3, NIX, and FUNDC1 at residues near their LIR motifs (Poole et al. 2021; Wu et al. 2014), enhancing their affinity for LC3 and facilitating their incorporation into forming autophagosomes (Liu et al. 2012). This phosphorylation step is critical for the efficient sequestration and degradation of damaged mitochondria.

3. *Cellular security area*: Additional quality control mechanisms

Cell viability is sustained by an intricate network of surveillance and repair systems that collectively ensure the structural and functional integrity of the cell under various physiological and pathological conditions. Each organelle and cellular process is supported by its own set of quality control mechanisms, operating not in isolation but as components of an interdependent network that preserves homeostasis and promotes cell survival. As highlighted throughout this review, autophagy plays a central role in maintaining cellular function, though it operates in close coordination with other adaptive systems.

The cellular microenvironment is subject to constant stressors, many of which threaten protein homeostasis. In response, cells activate protective pathways such as the heat shock response, mediated by heat shock proteins (HSPs). These molecular chaperones assist in protein folding, prevent aggregation, and promote the degradation of misfolded proteins, thereby limiting proteotoxic stress (Alagar Boopathy et al. 2022). HSPs are grouped by molecular weight into distinct families, including HSP100, HSP90, HSP70, HSP60, and small HSPs. Their expression is largely governed by heat shock factor 1 (HSF1), a transcription factor maintained in an inactive state under homeostatic conditions through association with HSP70 and HSP90. Upon cellular stress, HSF1 dissociates from these complexes, trimerizes, and translocates to the nucleus, where it initiates the transcription of HSP genes (Gomez-Pastor et al. 2018; Masser et al. 2020). Beyond protein folding, chaperones such as HSP70, HSP90, and HSP60 also participate in regulating apoptosis and modulating immune responses (Gu et al. 2025).

The UPR is another key adaptive mechanism that counteracts proteostatic disruption. It is activated when misfolded proteins accumulate in the ER, triggering a coordinated transcriptional and translational program to restore homeostasis or, in cases of unresolved stress, to induce apoptosis. Notably, recent evidence suggests that UPR activation in one cell can influence neighboring cells through intercellular signaling, highlighting its role in tissue-level coordination of stress responses (Imanikia et al. 2018). The UPR comprises three principal branches, each controlled by a distinct ER transmembrane sensor: activating transcription factor 6 alpha (ATF6α), inositol-requiring enzyme 1 alpha (IRE1α), and PKR-like ER kinase (PERK). Under non-stress conditions, these sensors remain inactive through their association with the ER-resident chaperone BiP (HSPA5), a member of the HSP70 family. Upon ER stress, BiP dissociates to assist in protein folding, leading to the activation of the three UPR sensors (Kopp et al. 2019). These branches differ in both activation kinetics and functional outcomes. ATF6α is typically the earliest responder, followed by IRE1α, which is activated only under more severe stress and acts in synergy with ATF6α. Both are considered adaptive responses aimed at promoting cellular tolerance to chronic ER stress. PERK, by contrast, is activated later and, depending on stress intensity, may induce apoptotic signaling when damage is irreparable (Coto-Montes et al. 2021; Senft & Ronai, 2015). In parallel, the ERAD pathway eliminates misfolded proteins via proteasomal degradation, and its integration with the UPR is critical for sustaining ER proteostasis (Hwang & Qi, 2018).

The integrated stress response (ISR) is a broader, evolutionarily conserved pathway that orchestrates cellular adaptation to diverse stressors, including nutrient scarcity, hypoxia, oxidative imbalance, and viral infection (Costa-Mattioli & Walter, 2020). Activation of the ISR is mediated by phosphorylation of eukaryotic initiation factor 2 alpha (eIF2α) at Ser51, catalyzed by one of four specialized kinases: PERK (ER stress), GCN2 (amino acid deprivation) (Jin et al. 2021), PKR (viral double-stranded RNA sensing) (Dabo & Meurs, 2012), and HRI (heme deficiency, oxidative stress, and hypoxia) (Chen, 2025). This phosphorylation event globally suppresses protein synthesis but selectively enhances the translation of transcription factors such as ATF3, ATF4, ATF5, and CHOP (Münch & Harper, 2016; Palam et al. 2011; Slavin et al. 2022; Vattem & Wek, 2004), which in turn regulate genes involved in survival, mitochondrial metabolism, redox balance, and cellular repair. In mammals, the ISR is functionally linked to the mitochondrial UPR (mtUPR), forming a shared quality control axis that safeguards mitochondrial function and integrates with broader

stress responses (Arnould et al. 2015). Nonetheless, persistent ISR activation and dysregulated proteostasis have been associated with pathological processes and chronic disease (Costa-Mattioli & Walter, 2020; Hipp et al. 2014).

Mitochondria, owing to their central role in energy metabolism and apoptotic regulation, are frequent targets of these stress response systems. Beyond mitophagy and the mtUPR, mitochondria employ a spectrum of quality control mechanisms that adapt dynamically to the cellular context. One such mechanism is mitochondrial dynamics, which encompasses fission, fusion, and intracellular trafficking. These processes are essential not only for organelle maintenance but also for the selective removal and functional redistribution of mitochondrial components (Tábara et al. 2025).

Mitochondrial fission is regulated primarily by dynamin-related protein 1 (DRP1) and mitochondrial fission 1 protein (FIS1). Upon phosphorylation at Ser616, DRP1 becomes activated and is recruited to the OMM via receptors such as FIS1, mitochondrial fission factor (MFF), and mitochondrial dynamics proteins MID49 and MID51 (Forte et al., 2021). Once localized, DRP1 oligomerizes in a GTP-dependent manner, constricting the mitochondrial membrane and facilitating division (Tilokani et al. 2018). Fission is essential not only for mitochondrial biogenesis but also for the removal of damaged mitochondrial segments via mitophagy. In contrast, mitochondrial fusion is mediated by the mitofusins MFN1 and MFN2 on the OMM and optic atrophy 1 (OPA1) on the inner mitochondrial membrane (IMM). MFN1 and MFN2 tether adjacent mitochondria and catalyze outer membrane fusion through GTP hydrolysis. Subsequent inner membrane fusion is regulated by OPA1 in a cardiolipin-dependent manner (Ban et al. 2017; Noone et al. 2022; Tábara et al. 2025). Fusion events contribute to the dilution of damaged mitochondrial content and support the preservation of mitochondrial membrane potential under metabolic stress.

Mitochondrial fission dynamics encompass two spatially distinct pathways, according to the mitochondrial region to be fractionated and with unique biological outcomes: midzone fission and peripheral fission. Mitochondrial midzone fission has been observed to target the central region of the mitochondrion and is associated with mitochondrial biogenesis and proliferation processes (Colpman et al. 2023; Kleele et al. 2021). These processes supply the energy needs of healthy cells. Midzone fission has been described as orchestrated by DRP1 together with MFF, and ER and actin-mediated pre-constriction to the mitochondria (Kleele et al. 2021).

Conversely, peripheral fission, which occurs at the mitochondrial viability ends, is associated with mitophagy and degradation. As with midzone

fission, this mechanism is mediated by DRP1, but regulated by FIS1, often preceded by lysosomal tethering, and serves to isolate dysfunctional mitochondrial units (with loss of membrane potential and a reduction in structural proteins (e.g., OPA1)), or damaged mitochondria (Kleele et al. 2021; Twig et al. 2008). Moreover, recent studies have identified a crucial regulator, MTFP1, which further elucidates the degradation dynamics of defective mitochondrial fragments. This regulator facilitates the fission of MTFP1-enriched mitochondrial zones at the periphery, resulting in the formation of smaller mitochondria that are more amenable to removal via autophagy. This process maintains the number of copies of mitochondrial DNA (mtDNA) and serves to minimize imbalances in cellular homeostasis (Tábara et al. 2024).

While traditionally confined to intracellular processes, mitochondrial quality control also involves intercellular mechanisms. When intrinsic pathways such as mitophagy or mitochondrial biogenesis are insufficient, cells may engage alternative routes such as mitochondrial transfer. This process entails the transfer of whole or fragmented mitochondria between donor and recipient cells and has been observed in settings including pulmonary injury, ischemia, neurodegeneration, and cancer (Wen et al. 2025). Among the most studied donors are mesenchymal stem cells (MSCs), likely due to their regenerative and immunomodulatory properties (Gopalarethinam et al. 2023; Han et al. 2022). Mitochondrial trafficking during transfer is mediated by Miro1, a Rho-GTPase that anchors mitochondria to the microtubule cytoskeleton, guiding them toward tunnelling nanotubes (TNTs) (Li et al. 2024). TNTs are narrow, actin-rich cytoplasmic extensions (approximately 50–200 nm in diameter) that connect adjacent cells and enable direct exchange of organelles, proteins, and even ionic signals (Ahmad et al. 2014; Rustom et al. 2004; Zurzolo, 2021). This intercellular transport mechanism allows metabolically active cells to support compromised neighbors under stress (Han et al. 2016; Wang & Gerdes, 2015). Conflicting studies have proposed both unidirectional disposal of dysfunctional mitochondria (Liu et al. 2023) and bidirectional exchange models whereby organelle elimination and functional rescue occur concurrently (Chakraborty et al. 2023).

A more recently described mitochondrial clearance mechanism is mitochondrial extrusion, also referred to as mitocytosis. Unlike transfer, this process involves the expulsion of damaged mitochondria from the cytoplasm into the extracellular space, often without engaging a recipient cell or traditional vesicular trafficking. This

phenomenon has been particularly observed in migratory cells during regeneration or tumor invasion (Lyamzaev et al. 2022; Unuma et al. 2015). One key structure involved in extrusion is the migrasome, a vesicular body deposited along the migration path of cells, which acts as a reservoir for damaged mitochondria (Ma et al. 2015). These migrasomes enable spatial segregation and clearance of dysfunctional organelles outside the cell (Tang et al. 2024). This pathway may act as a compensatory mechanism in conditions where mitophagy is insufficient or impaired, highlighting the growing complexity and adaptability of mitochondrial quality control systems.

4. Skeletal muscle: An organ adjustable to suit the situation

Skeletal muscle comprises approximately 40 % of total body mass, although this proportion is dynamically modulated in response to physiological stimuli such as exercise or pathological conditions (Mukund & Subramaniam, 2020; Sartori et al. 2021). Its highly specialized structure reflects functional demands related to mechanical force generation, metabolic capacity, and spatial organization. Skeletal muscle is composed predominantly of elongated, multinucleated fibers formed through the developmental fusion of mononucleated, postmitotic myoblasts (Yamakawa et al. 2020; Zhou et al. 2022). These fibers are embedded within a complex and well-organized network of connective tissue, extracellular matrix (ECM), and vascular structures that support both mechanical function and metabolic exchange (Loreti & Sacco, 2022).

Two main fiber types are recognized: type I fibers, characterized by oxidative, slow-twitch metabolism, and type II fibers, which are glycolytic and fast-twitch. Both types favor catabolic over anabolic metabolism for energy production, contributing to the metabolic versatility of skeletal muscle (Anderson, 2022). The muscle's structural framework consists of a hierarchical organization of three concentric connective tissue layers. The outermost epimysium is composed of dense irregular connective tissue that encloses the entire muscle, transmitting contractile force to tendons and bones. The perimysium, located beneath the epimysium, subdivides the muscle into fascicles (bundles of muscle fibers that coordinate contraction across functional units). The innermost layer, the endomysium, comprises areolar connective tissue enriched with capillaries and nerves, and plays a

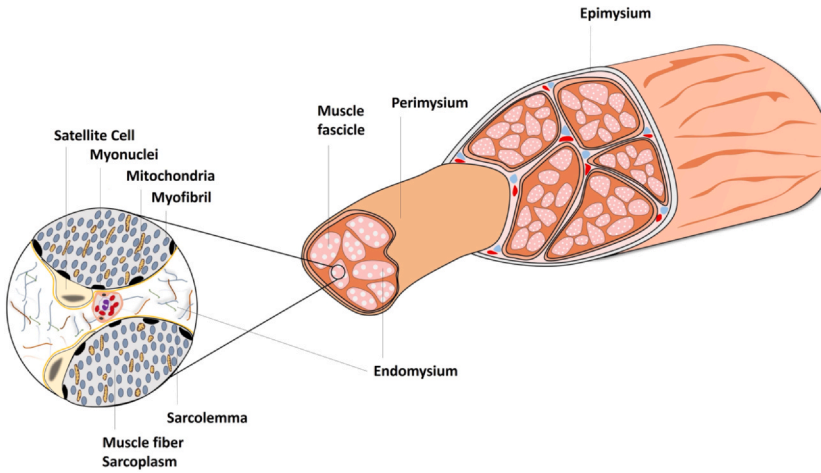

Fig. 6 Skeletal muscle morphology: from anatomy to histology. The diagram shows the main histological structures of skeletal muscle.

critical role in maintaining ionic balance for excitation–contraction coupling, as well as contributing to the viscoelastic properties of muscle tissue (Mukund & Subramaniam, 2020) (Fig. 6). Together, these layers enable precise alignment of myofibers, facilitate mechanotransduction, and support compartmentalized force transmission, all of which are essential for optimal skeletal muscle performance (Frontera & Ochala, 2015).

The identification of satellite cells in 1961, following the advent of electron microscopy, marked a milestone in skeletal muscle biology. These adult muscle stem cells reside in a quiescent state between the sarcolemma and the basal lamina of mature fibers. Although generally inactive in homeostasis, satellite cells are rapidly activated in response to muscle injury or mechanical stress. Upon activation, they proliferate and differentiate into myogenic precursors, thereby playing a pivotal role in muscle regeneration and repair (Anderson, 2022; Cai et al. 2022; Chen et al. 2022; Englund et al. 2021; Loreti & Sacco, 2022; Zhou et al. 2022).

Functionally, skeletal muscle is specialized for voluntary contraction, a process mediated by sarcomeres, the fundamental contractile units composed of interdigitating actin and myosin filaments. Sarcomere contraction is regulated by excitation–contraction coupling, a calcium-dependent signaling mechanism that ensures precise temporal control of muscle fiber shortening (Calderón et al. 2014). However, beyond its biomechanical functions, skeletal muscle is now recognized as a major regulator of

systemic metabolism. It represents the largest reservoir of amino acids in the body, supporting protein turnover and providing substrates during catabolic states such as fasting, infection, or trauma (Wolfe, 2006). Moreover, skeletal muscle is the primary site of insulin-stimulated glucose uptake and glycogen storage, placing it at the center of glycemic regulation and whole-body metabolic homeostasis (Argilés et al. 2016; Fu et al. 2024).

Recent findings have redefined skeletal muscle as a pleiotropic endocrine organ, capable of secreting bioactive peptides termed myokines. Notable examples include interleukin-6 (IL-6), irisin, and myostatin, which exert autocrine, paracrine, and endocrine effects. These myokines influence multiple distant tissues, including adipose tissue, liver, brain, pancreas, and bone, modulating energy expenditure, insulin sensitivity, inflammation, and even neuroplasticity (Rai & Demontis, 2016; Severinsen & Pedersen, 2020). Muscle-derived signals are now recognized as essential components of systemic communication networks, regulating physiological processes such as immunity, ageing, and adaptive responses to physical and metabolic stress (Antuña et al. 2022; Chow et al. 2022; Tokizane & Imai, 2024). Thus, the maintenance of skeletal muscle integrity is not only essential for locomotion but also for the prevention of chronic diseases including sarcopenia, obesity, type 2 diabetes, and cardiovascular disorders.

4.1 Prime muscle years

As previously discussed, skeletal muscle is a highly plastic tissue that continuously adapts to mechanical, metabolic, and environmental stimuli under physiological conditions. The preservation of muscle integrity and function critically depends on the precise regulation of intracellular quality control mechanisms, particularly those governing organelle maintenance. Due to its dynamic functional demands, skeletal muscle experiences substantial fluctuations in energy requirements between contraction and rest. Remarkably, during active contraction, pre-existing ATP stores are sufficient to sustain activity for only approximately two seconds, thereby necessitating rapid and sustained ATP regeneration to maintain contractile function (Gaitanos et al. 1993). In addition to mechanical work, a consistent energy supply is required to support vital cellular maintenance and quality control processes; when energy availability becomes limited, these processes are compromised, leading to disruption of cellular homeostasis.

Mitochondria are central to skeletal muscle physiology, acting both as principal ATP producers and as significant sources and targets of ROS. Mitochondria-derived ROS play a dual role in skeletal muscle biology: at

physiological concentrations, they act as signaling molecules that facilitate adaptive responses such as hypertrophy and regeneration (Powers et al. 2010). However, excessive ROS production (typically observed during strenuous exercise, inflammation, or injury) can result in oxidative damage to proteins, lipids, and nucleic acids, ultimately impairing muscle function. Emerging data highlights the essential role of regulated ROS signaling in satellite cell activation and proliferation, processes critical to effective muscle regeneration (Lian et al. 2022; Potes et al. 2024).

Autophagy represents a fundamental component of skeletal muscle homeostasis. While the field has primarily focused on macroautophagy, the roles of microautophagy and CMA remain poorly understood in this tissue (Franco-Romero et al. 2024). Basal autophagy is required to prevent the accumulation of dysfunctional organelles and protein aggregates, whereas stress-induced autophagy facilitates repair and remodeling following damage (Franco-Romero et al. 2024; Paré et al. 2017). Even under homeostatic conditions, skeletal muscle undergoes continuous structural renewal; during hypertrophic growth, transient activation of autophagy contributes to fiber adaptation by removing organelles and proteins damaged by mechanical stress (de Gonzalo-Calvo et al., 2012; Sartori et al. 2021; Xia et al. 2021). Notably, ROS can activate redox-sensitive kinases such as AMPK and p38 MAPK, which regulate autophagic flux during adaptation and remodeling (Rodney et al. 2016).

Autophagy in skeletal muscle is also finely tuned by nutritional signals. Following nutrient intake, elevated levels of amino acids (AAs) and branched-chain amino acids (BCAAs) activate mTORC1, which suppresses autophagy while promoting protein synthesis and muscle growth (Zhang et al. 2014). Similarly, increased glucose availability inhibits autophagy through a reduction in the AMP/ATP ratio, further activating mTORC1 and reinforcing anabolic pathways (Efeyan et al. 2013; Sebastián & Zorzano, 2020). In contrast, the regulation of autophagy by lipid levels remains ambiguous; current evidence provides no consensus on whether high or low lipid concentrations stimulate or suppress autophagy in skeletal muscle (Sebastián & Zorzano, 2020). During nutrient deprivation, particularly under conditions of low glucose or AAs, autophagy is activated via inhibition of AKT and mTORC1, along with the phosphorylation of Beclin-1, AMPK, and the ULK1 complex, initiating autophagosome formation.

Mitophagy has emerged as a critical regulator of metabolic reprogramming and cell fate decisions within skeletal muscle (Esteban-Martínez et al. 2017). During regenerative phases, enhanced mitophagy is required

for satellite cell activation and progression through the myogenic program (Hong et al. 2022a; Picca et al. 2023). Mitochondrial dynamics, specifically the balance between fission and fusion, are tightly coupled with metabolic status and coordinate the redistribution of mitochondria following satellite cell division to ensure proper energy supply (Youle & van der Bliek, 2012). Proper regulation of these dynamics is essential for maintaining mitochondrial function and promoting efficient myofiber recovery following injury (Yasuda et al. 2023). Conversely, disruption of mitochondrial fission, for instance, through DRP1 inhibition, impairs regenerative efficiency and exacerbates atrophy in injured muscle (Hong et al. 2022b).

Collectively, these interconnected mechanisms (autophagy, mitophagy, and mitochondrial dynamics) constitute an integrated quality control system that enables young and healthy skeletal muscle to maintain homeostasis, respond to physiological challenges, and recover effectively following injury or hypertrophic stimulation.

4.2 Power turns to frailty

Although skeletal muscle possesses robust mechanisms to maintain cellular homeostasis and support regeneration under physiological conditions, the disruption of these quality control systems is increasingly recognized as a central contributor to muscle pathology. In muscle-related disorders, such as muscular dystrophies and age-associated muscle loss, dysregulation of essential cellular processes leads to the accumulation of molecular damage, a decline in regenerative capacity, and ultimately, tissue degeneration and functional impairment.

One of the earliest and most prominent perturbations in diseased muscle is the imbalance between ROS production and antioxidant defense mechanisms (González-Blanco et al. 2022; Potes et al. 2017). Excessive ROS accumulation damages cellular components, including DNA, proteins, and lipids, while simultaneously interfering with key regulatory signaling pathways. Overproduction of ROS can suppress the activity of autophagy-promoting kinases such as AMPK and sirtuin 1 (SIRT1), thereby impairing cellular repair and metabolic flexibility (Hong et al. 2024). Moreover, mitochondria damaged by oxidative stress can release mitochondrial damage-associated molecular patterns (mtDAMPs) into the cytosol, where they are detected by pattern recognition receptors of the innate immune system. This recognition triggers pro-inflammatory cascades, notably the activation of the NLRP3 inflammasome, further propagating inflammation and muscle fiber atrophy (Antuña et al. 2022).

These maladaptive responses establish a self-perpetuating cycle of injury, inflammation, and degeneration.

A consistent hallmark across a broad spectrum of myopathies is the dysfunction of the autophagy–lysosome system. Impaired autophagic flux results in the accumulation of defective mitochondria and toxic protein aggregates, intensifying ROS generation and metabolic stress. Defective mitophagy has been identified as a key pathological feature in degenerating muscle fibers (Kubat et al. 2023) and is implicated in diverse models of muscular dystrophies and metabolic myopathies (Di Leo et al. 2023; Mito et al. 2022; Mucha et al. 2021). These observations underscore the indispensable role of mitochondrial quality control in the maintenance of muscle tissue integrity.

Mitochondrial dynamics are similarly disrupted in degenerative muscle states. Abnormal mitochondrial fragmentation and impaired fusion, often linked to decreased expression or functional deficiency of key regulatory proteins such as DRP1, mitofusins (MFN1/2), and OPA1, compromise mitochondrial morphology, connectivity, and function (Potes et al. 2019; 2019). As a result, affected mitochondria exhibit reduced oxidative phosphorylation capacity, exacerbated oxidative stress, and impaired bioenergetic output. Dysfunctional mitochondrial networks are particularly detrimental in regenerating muscle, where metabolic support is essential for satellite cell activation and differentiation.

The regenerative potential of skeletal muscle, which depends largely on the function of satellite cells, is also markedly impaired when cellular quality control mechanisms are compromised. In pathological settings, satellite cells display heightened sensitivity to oxidative damage and mitochondrial dysfunction, coupled with impaired autophagic clearance. These insults lead to a reduction in their proliferative and differentiation potential, and are frequently associated with premature senescence (Gao et al. 2024; González-Blanco et al. 2022). Such dysfunction in the satellite cell compartment is a major contributor to progressive muscle wasting and the decline in tissue functionality observed in both muscular disorders and physiological ageing.

4.2.1 Cancer-cachexia

Cancer cachexia is a multifactorial and debilitating syndrome characterized by involuntary weight loss, profound skeletal muscle wasting, and systemic inflammation. These alterations contribute to a significantly worsened prognosis and elevated mortality in patients with cancer (Peixoto da Silva et al., 2020). Although the clinical presentation of cachexia is well

established, the underlying molecular mechanisms remain incompletely elucidated. At the cellular level, skeletal muscle catabolism in cachexia is closely associated with severe mitochondrial dysfunction. Increased ROS generation, altered mitochondrial dynamics, and impaired autophagic clearance converge to drive progressive muscle degradation and energy failure (Beltrà et al., 2021; Carson et al. 2016).

A fundamental mitochondrial perturbation linked to cancer is the metabolic reprogramming of tumor cells themselves. By reducing mitochondrial oxidative phosphorylation and favoring aerobic glycolysis, a phenomenon known as the Warburg effect, tumor cells disrupt systemic metabolic homeostasis (Lu et al. 2015). This reconfiguration of cellular energy metabolism profoundly affects peripheral tissues, particularly skeletal muscle, inducing a state of energetic stress and redox imbalance that promotes catabolic activity and muscle breakdown.

Muscle wasting in cancer cachexia results primarily from an imbalance between protein synthesis and degradation, with proteolytic activity significantly outweighing anabolic processes. While the ubiquitin–proteasome and autophagy–lysosome systems are hyperactivated in cachexia, pharmacological interventions targeting these individual proteolytic pathways have shown only limited efficacy in preserving muscle mass and function (Penna et al. 2016; Pin et al. 2017). This limited therapeutic impact suggests that cancer cachexia is not solely a disorder of proteostasis, but rather involves a broader collapse of cellular homeostasis.

Recent studies have identified impaired mitophagy as a key pathological feature in the progression of muscle wasting. Inefficient clearance of damaged mitochondria leads to sustained mitochondrial dysfunction, which, in turn, exacerbates oxidative stress, impairs bioenergetic output, and activates stress-responsive catabolic pathways. These events culminate in the degeneration and loss of muscle fibers (Brown et al. 2017). Given the essential role of mitochondrial quality control in muscle maintenance, therapeutic strategies aimed at restoring autophagic and mitophagic flux have emerged as particularly promising. Preclinical models of cancer cachexia have demonstrated that enhancing autophagy or promoting mitochondrial turnover can significantly attenuate muscle atrophy and improve functional performance (Hardee et al. 2020).

Collectively, these findings mark a conceptual shift in our understanding of cancer cachexia, moving beyond a traditional focus on proteolysis to encompass the critical contributions of mitochondrial dysfunction, defective autophagy, and systemic metabolic derangement. Addressing this interconnected network

of pathological mechanisms offers a more comprehensive framework for therapeutic development and may yield novel approaches to preserve muscle mass, enhance physical performance, and ultimately improve quality of life and survival in cancer patients.

4.2.2 Muscle dystrophies

Muscular dystrophies (MD) constitute a heterogeneous group of approximately 30 inherited disorders caused by mutations in over 40 genes, all of which result in progressive skeletal muscle weakness and degeneration. The clinical presentation of MD varies markedly depending on the subtype, with differences in age of onset, rate of progression, and distribution of affected muscle groups (Mercuri et al. 2019). Nonetheless, all forms share a common endpoint: significant loss of mobility, independence, and quality of life.

Among the various subtypes, calpainopathies represent a clinically and genetically defined subgroup of limb-girdle muscular dystrophies (LGMDs), characterized by progressive, symmetrical weakness that predominantly affects proximal muscles of the pelvic and shoulder girdles. These disorders result from mutations in the CAPN3 gene, which encodes calpain-3, a muscle-specific, calcium-dependent protease. Although its full physiological function remains incompletely elucidated, accumulating evidence supports its key role in maintaining sarcomere integrity and regulating mitochondrial homeostasis (Gallardo et al. 2011; Jahnke et al. 2020; Sáenz et al. 2008).

The pathological consequences of CAPN3 deficiency extend beyond sarcomeric disruption. In murine models of LGMDR1 (Limb-Girdle Muscular Dystrophy Recessive 1), loss of CAPN3 function impairs muscle cell proliferation and differentiation, both of which are essential for effective regeneration (Casas-Fraile et al. 2020). A hallmark of CAPN3-deficient muscle is dysregulated mitogenesis, which leads to the accumulation of dysfunctional mitochondria. This mitochondrial impairment compromises bioenergetic capacity and exacerbates the muscle's inability to regenerate following damage (Jahnke et al. 2020). Moreover, studies in patient-derived muscle biopsies have revealed broader organelle disorganization, including aberrant centrosome positioning and nuclear architectural defects (Valls et al. 2025), suggesting that CAPN3 deficiency perturbs global cellular architecture and organization. These structural abnormalities correlate with impaired autophagic flux, a feature shared across multiple forms of muscular atrophy and cellular senescence

(Dziewulska et al. 2018; Park et al. 2009; Taranum et al. 2012). The convergence of mitochondrial dysfunction, altered organelle architecture, and autophagy impairment underscores the fundamental role of quality control mechanisms in skeletal muscle maintenance.

Duchenne muscular dystrophy (DMD) is a severe X-linked disorder caused by mutations in the dystrophin gene. It typically manifests in early childhood and leads to progressive muscle weakness, severe disability, and premature death. Under physiological conditions, dystrophin anchors the intracellular cytoskeleton to the extracellular matrix, thereby stabilizing the sarcolemma during mechanical stress associated with contraction (Duan et al. 2021; Keefe & Kardon, 2015). In its absence, the sarcolemmal membrane becomes increasingly fragile, leading to recurrent damage, inflammation, and necrosis. Chronic oxidative stress, mitochondrial dysfunction, and impaired autophagy are key pathological features in DMD (Bellissimo et al. 2022; Casati et al. 2024). Recent data show a significant disruption of mitophagy in DMD muscle tissue, including defective Parkin translocation to damaged mitochondria and impaired lysosomal degradation, leading to the accumulation of dysfunctional organelles and exacerbation of fiber necrosis (Chassagne et al., 2024; Kang et al. 2018). In parallel, DMD satellite cells exhibit reduced regenerative potential, further accelerating disease progression (Granet et al. 2025). These findings are consistent with data from mdx mouse models, which demonstrate muscle degeneration associated with the dysregulation of autophagy and inflammatory pathways, mitochondrial bioenergetic failure, and excessive ROS production (van Westering et al. 2020). Additionally, proteomic studies reveal an upregulation of the ubiquitin–proteasome system in DMD (Bonuccelli et al. 2003; Carmignac et al. 2011), reinforcing the critical role of autophagy–lysosome and proteasomal systems in muscle proteostasis and degeneration.

Considering the shared pathogenic mechanisms across these muscle dystrophies, the preservation or restoration of autophagic flux and cellular quality control emerges as a compelling therapeutic strategy. Targeting defective autophagy and mitochondrial dysfunction may not only halt or delay the progression of muscle degeneration but also improve regenerative potential, offering hope for more effective treatment approaches.

4.2.3 Sarcopenia and aging

In recent decades, human lifespan has markedly increased, driven by advances in medicine, public health, and socioeconomic conditions.

However, this extension of lifespan is not always accompanied by a proportional improvement in healthspan, the period of life spent in good health. As a result, there is growing scientific interest in the mechanisms underlying healthy aging and how to preserve physiological function over time. As discussed throughout this review, skeletal muscle acts not only as an effector of movement but also as a sensor organ, responding dynamically to systemic and intracellular signals. During aging, this adaptability is progressively lost as cellular homeostasis becomes deregulated and quality control mechanisms decline in efficiency, ultimately promoting cellular senescence and death (López-Otín et al. 2023).

Aging is characteristically associated with a progressive decline in muscle mass and function, a condition known as sarcopenia. Sarcopenia is one of the most disabling geriatric syndromes, as the deterioration of muscle integrity severely compromises mobility, autonomy, and overall quality of life (Sayer & Cruz-Jentoft, 2022). Central to the pathogenesis of sarcopenia is the gradual breakdown of intracellular quality control systems, including those governing mitochondrial function, proteostasis, autophagy, and inflammation. This breakdown results in increased catabolic activity, mitochondrial dysfunction, elevated apoptosis, maladaptive immune responses, and impaired regenerative potential. These intrinsic alterations are further exacerbated by extrinsic factors such as reduced physical activity and increased sedentary behavior, which commonly accompany aging (Antuña et al. 2022; Liu et al. 2021; Luo et al. 2025; Raffin et al. 2023; Spendiff et al. 2016).

A hallmark of aging skeletal muscle is the decline in autophagic efficiency, leading to the accumulation of dysfunctional proteins and organelles, which intensifies cellular stress and activates compensatory pathways such as the unfolded protein response (UPR) (González-Blanco et al. 2022). Impairments in mitophagy, particularly via defective PINK1–Parkin signaling and disrupted mitochondrial dynamics, further accelerate muscle degeneration and loss of function in sarcopenia (Peker et al. 2018) (Antuña et al. under peer review). Compounding this decline is the well-documented reduction in both the number and functionality of satellite cells, muscle-resident stem cells essential for tissue regeneration. This decline is largely attributable to chronic oxidative stress, low-grade inflammation, and defective autophagic clearance (Antuña et al. 2024; Chinvattanachot et al. 2024; Englund et al. 2021; González-Blanco et al. 2022). In sarcopenic muscle, dysregulation of the autophagy–lysosome axis is closely associated with organelle dysfunction, aberrant myofiber morphology, and the

progressive decline in muscle strength and mass (González-Blanco et al. 2022; Pathak et al. 2021; Wiedmer et al. 2021). Consequently, interventions aimed at restoring autophagic flux and preserving mitochondrial quality have emerged as promising strategies for mitigating the effects of sarcopenia.

The maintenance of skeletal muscle homeostasis depends on highly coordinated quality control systems that regulate ROS balance, mitochondrial dynamics, and autophagic–mitophagic processes. In inherited disorders such as Duchenne muscular dystrophy (DMD) and Limb-Girdle Muscular Dystrophy Recessive 1 (LGMDR1), mutations directly impair mitophagy and exacerbate muscle degeneration. Similarly, in cancer cachexia, mitochondrial fragmentation and impaired autophagic flux drive severe muscle wasting. Age-related sarcopenia further exemplifies how cumulative decline in quality control capacity leads to mitochondrial dysfunction, regenerative failure, and tissue loss.

Altogether, these findings underscore the centrality of mitochondrial quality control, autophagic regulation, and oxidative stress management in the preservation of muscle health. A deeper understanding of how failures in these systems contribute to muscle pathology may inform the development of novel therapeutic strategies. Targeting these core mechanisms could not only help maintain muscle mass and function in aging and disease but also improve systemic health, mobility, and overall quality of life.

5. Science to prevent muscle dysfunction

Maintaining muscle mass and function throughout life constitutes one of the most relevant biomedical challenges in the promotion of healthy aging. Although the mechanisms of muscle dysfunction, such as altered cell quality control and progressive loss of mitophagy, have been widely described, new therapeutic strategies with promising results are also emerging. Although we have described molecular alterations of autophagy during muscle dysfunction due to pathologies and aging, there is scientific evidence of novel preventive therapies to obtain a correct maintenance of muscle function and structure, delaying physiological aging. Among the scientific community, studies that postulate physical activity and exercise as possible non-invasive impact therapies in favor of healthy aging. Physical exercise, nutritional interventions and bioactive molecules such as melatonin have been shown to improve muscle homeostasis through the stimulation of controlled regeneration and degradation pathways.

5.1 Exercise and physical training

Physical exercise represents a critical window for optimizing skeletal muscle growth, functionality, and resilience. Resistance training (RT) induces muscle hypertrophy through mechanical and metabolic stimuli that activate satellite cells, essential for myonuclear accretion and fiber growth (Wackerhage et al. 2019). Satellite cell activation is tightly coordinated with the local and systemic inflammatory milieu, mechanical loading, and nutrient availability, integrating signals that culminate in enhanced regenerative capacity and muscle expansion. Importantly, exercise-induced hypertrophy in youth is not solely the result of protein accretion but is paralleled by profound remodeling of mitochondrial networks. Long-term training increases mitochondrial content as well as enhances OXPHOS activity by an increase of the density cristae shape for mitochondrial respiration, reducing ROS release (Jacobs & Lundby, 2013; Schytz et al. 2024).

Moreover, regular exercise promotes efficient turnover of cellular components via activation of autophagy and mitophagy pathways. During resistance training exercises, AMP/ATP ratio increases, activating AMPK and downstream ULK1, while mTORC1 is inhibited (Memme et al. 2021; Song, Moore, et al. 2017). Additionally, mitochondrial turnover is not a passive consequence, but a regulated response intricately connected with anabolic signaling pathways such as mTORC1, which orchestrate the balance between growth and quality control. However, when people only pure resistance training is performed, changes in mitophagy are not as robust as when a combination of resistance training and endurance exercises is performed (Picca et al. 2023). Enhanced mitochondrial biogenesis, driven by upregulation of PGC-1α and related transcriptional coactivators, ensures sufficient energy supply to sustain anabolic demands and preserve redox homeostasis during and after training stimuli (Summermatter et al. 2013).

This dynamic renewal process prevents the accumulation of dysfunctional organelles and proteotoxic aggregates, sustaining muscle quality and function. Emerging evidence suggests that exercise-induced mitophagy is not merely a housekeeping mechanism but an essential contributor to hypertrophic adaptation, ensuring that expanding muscle fibers maintain metabolic flexibility and oxidative capacity (Roberts & Markby, 2021). The coordinated activation of satellite cells, enhancement of mitochondrial content, and fine-tuning of autophagy highlight exercise as a multifaceted intervention that shapes muscle health at a cellular and molecular level.

In the face of aging, there is research that sees the promotion of physical exercise in elderly populations as essential, demonstrating its beneficial effect on balance performance (Thomas et al. 2019). In sarcopenia, as the most pronounced aging mechanism in skeletal muscle decline, RT has been described in numerous studies as one of the most effective strategies, preserving its physical function and preventing frailty. During this type of training, older adults gain strength and muscle mass (Mcleod et al. 2024), as well as enhanced their aerobic capacity, mobility and independence and quality of life (Phu et al. 2015) in a comparable way to younger individuals (Landi et al. 2014). However, more studies related to physical exercise are needed because of the difficulty of this population in adhering to frequent training and, as in young people, the variety of types of training.

5.2 Nutritional ergogenic aid supplementation

Skeletal muscle is an energetically demanding tissue, a characteristic that directly intersects with the regulation of autophagy and cellular quality control mechanisms. As previously discussed, under conditions of nutrient scarcity, particularly reduced glucose and amino acid availability, skeletal muscle activates autophagic pathways as a compensatory energy source. While nutritional supplementation has traditionally been associated with high-performance athletes, it is now increasingly recognized as a viable strategy to support muscle health across broader populations (Beck et al. 2015). Numerous studies support the utility of nutritional interventions, particularly protein and creatine monohydrate supplementation, for enhancing muscle function and recovery in aging and disease contexts.

To appreciate the relevance of protein supplementation in older adults, it is essential to recognize that aging is frequently accompanied by malnutrition, which leads to the depletion of energy reserves and muscle mass loss (Calcaterra et al. 2024; Roberts et al. 2021). Several clinical studies have demonstrated that protein-based nutritional strategies improve muscle strength and function in elderly and sarcopenic individuals, particularly when combined with RT (Kemmler et al. 2018; Liao et al. 2019; Shen et al. 2023; Zhou et al. 2024). For instance, muscle-strengthening exercise (MSE) in combination with protein supplementation has been shown to enhance lean body mass, mobility, and muscular strength in frail older populations. However, the results across trials remain heterogeneous, with some reporting only modest or inconsistent improvements in parameters such as gait speed and handgrip strength, particularly when exercise is absent (Anton et al. 2018; Bauer & Diekmann, 2015; Deutz et al. 2014; Tieland et al. 2017).

In addition to anabolic benefits, whey and soy proteins have demonstrated anti-inflammatory effects by reducing circulating pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α). These effects are particularly relevant in the context of "inflammaging", the chronic low-grade inflammation observed during aging and in functionally dependent individuals (Antuña et al. 2022; Antuña et al. 2024; Prokopidis, Mazidi, et al. 2023). This systemic impact suggests that protein supplementation may improve not only muscular outcomes but also broader inflammatory and metabolic health. Nonetheless, critical questions remain regarding optimal dosing, timing, and population-specific responses, particularly in frail or critically ill patients (Bels et al. 2023).

Amino acids (AAs), as essential biomolecules, play central roles in protein synthesis, redox regulation, immune modulation, and intracellular signaling (Ling et al. 2023). Among them, essential amino acids (EAAs) (especially BCAAs such as leucine, isoleucine, and valine) have been extensively studied for their pivotal role in promoting muscle protein synthesis and cellular homeostasis (Nie et al. 2018; Wolfe, 2017). Experimental and clinical research has consistently shown that amino acid supplementation stimulates anabolic pathways, counters muscle atrophy, and inhibits proteolysis. Notably, leucine is a direct activator of the mTORC1 pathway, a key regulator of muscle hypertrophy and recovery (Suryawan et al. 2020). Supplementation with leucine-enriched EAAs has been shown to enhance muscle protein synthesis post-exercise and during periods of immobilization, particularly in older adults with anabolic resistance (Azhar et al. 2021; Glover et al. 2008; Pasiakos et al. 2011; Wall et al. 2016; Waskiw-Ford et al. 2020).

In parallel, several trials link amino acid intake to reductions in inflammatory biomarkers such as C-reactive protein (CRP) and IL-6, offering additional pathways through which muscle function and systemic health may be improved in aging populations (Aquilani et al. 2021). Beyond their anabolic properties, BCAAs have also been implicated in enhancing insulin sensitivity and glucose uptake through PI3K-AKT pathway activation, although chronic elevation of BCAAs has paradoxically been associated with insulin resistance in certain metabolic contexts (Lynch & Adams, 2014), warranting a personalized approach to supplementation.

Emerging evidence also suggests a role for amino acids in regulating stem cell function. Experimental models show that leucine and arginine promote satellite cell proliferation and differentiation via mTORC1 and

nitric oxide pathways, enhancing muscle regeneration following injury (Dai et al. 2015; Gong et al. 2021; Wang et al. 2022). Moreover, in vitro studies have demonstrated that amino acid supplementation supports the maintenance and expansion of human mesenchymal stem cells, reinforcing their utility in regenerative therapies (Higuera et al. 2012). These findings point toward a dual role for amino acids in both preserving existing muscle and augmenting intrinsic regenerative potential. Additionally, certain amino acids such as arginine and citrulline have been shown to support mitochondrial function and oxidative metabolism, likely through enhanced nitric oxide production and PGC-1α-mediated mitochondrial biogenesis, improving endurance and reducing fatigue (Villareal et al. 2018).

Creatine (Cr) is a nitrogen-containing organic compound synthesized endogenously in the kidneys and liver from arginine, glycine, and methionine. It is primarily transported to energy-demanding tissues such as skeletal muscle and brain via the SLC6A8 creatine transporter, where it is stored in high concentrations (Brosnan & Brosnan, 2007; Guzun et al. 2011). Creatine enters cells through a sodium-chloride symport, independent of ATP consumption (Bonilla et al. 2021). Within mitochondria, mitochondrial creatine kinase (mtCK) uses ATP from oxidative phosphorylation to generate phosphocreatine (PCr), which is then shuttled to the cytosol to rapidly regenerate ATP via cytosolic creatine kinase (CK), particularly during high-intensity, short-duration activity (Burke et al. 2023). Because skeletal muscle stores 3–4 times more PCr than ATP, this system provides a fast but short-lived energy buffer, sustaining maximal effort for ∼10 s (Baker et al. 2010; Kreider et al. 2017). Thus, the Cr–PCr system is critical for energy homeostasis, especially in skeletal and cardiac muscle, supporting muscular performance, recovery, and neuromuscular resilience.

In addition to its energetic role, creatine exerts antioxidant, anti-apoptotic, and mitochondrial stabilizing effects, suggesting broader applications in muscle-wasting and neurodegenerative disorders (Adhihetty & Beal, 2008; Marshall et al. 2022). Clinically, creatine monohydrate supplementation has demonstrated benefits for muscle hypertrophy, mitochondrial function, and cognitive performance, including in aging-related disorders such as sarcopenia, heart failure, multiple sclerosis, and others marked by creatine deficiency (Burke et al. 2023; Candow & Moriarty, 2024; Del Franco et al. 2022; Hall et al. 2021; Ostojic, 2022; Prokopidis, Giannos, et al. 2023).

Nevertheless, not all evidence is favorable. Some studies suggest that creatine supplementation may promote metastasis in specific cancer

models, urging caution in oncological settings (Zhang & Bu, 2022). Conversely, research with cyclocreatine, a synthetic creatine analogue, has shown potential anti-proliferative effects in prostate cancer, indicating that the relationship between creatine and cancer is complex and context-dependent (Patel et al. 2022). Moreover, creatine has shown anti-inflammatory and anti-catabolic effects, including reductions in muscle protein breakdown and bone resorption, supporting its potential role in the treatment of frailty and cachexia (Cordingley et al. 2022). In summary, creatine represents a promising adjunct therapy for age-related musculoskeletal decline and cognitive dysfunction, but its application must be carefully tailored to individual health conditions and clinical settings (Hall et al. 2021).

5.3 Drugs: Melatonin treatment

Targeting molecular regulators of autophagy, as previously discussed in the context of nutritional supplementation, can exert beneficial effects on skeletal muscle homeostasis and cellular quality control. In line with these strategies, increasing attention has been directed toward therapies that specifically target mitochondrial function and integrity, with melatonin emerging as a particularly promising candidate.

Melatonin is an endogenously produced indoleamine classically associated with the regulation of circadian rhythms and predominantly secreted by the pineal gland. However, it is now widely recognized as a ubiquitous molecule synthesized by virtually all cells, including skeletal muscle (Manchester et al. 2015). Beyond its chronobiological roles, melatonin functions as a potent antioxidant, acting both directly by scavenging reactive oxygen and nitrogen species, and indirectly, by upregulating endogenous antioxidant enzymes. Its amphiphilic structure enables rapid diffusion across biological membranes and preferential accumulation within mitochondria, where it limits oxidative damage and preserves mitochondrial function (Boga et al. 2019). These properties are particularly relevant for skeletal muscle, which is not only highly metabolically active but also particularly susceptible to mitochondrial dysfunction during aging and in pathological states (Pahal et al. 2025).

Melatonin plays a crucial role in maintaining mitochondrial membrane stability, preserving membrane potential, and supporting ATP synthesis, thereby contributing to muscle homeostasis across the lifespan (Coto-Montes et al. 2016). Importantly, melatonin biosynthesis is closely tied to amino acid metabolism, as it derives from tryptophan via a multi-step enzymatic

pathway that includes serotonin as an intermediate (Tan et al. 2015). Consequently, the availability of tryptophan represents a limiting factor in melatonin production, highlighting a nutritional–neuroendocrine interface that influences both circadian biology and skeletal muscle physiology.

A growing body of experimental and clinical evidence supports the therapeutic potential of melatonin for maintaining skeletal muscle health in both young and aged organisms. Melatonin supplementation has been shown to enhance mitochondrial efficiency, reduce oxidative stress, and accelerate muscle regeneration following injury (Yao et al. 2025). In aged muscle, where mitochondrial fragmentation, increased ROS, and impaired regeneration are hallmarks of sarcopenia, melatonin administration mitigates muscle atrophy, improves mitochondrial architecture, and restores contractile capacity (Ramírez-Casas et al. 2025). These effects appear to be mediated, at least in part, through modulation of autophagy and mitophagy, both of which are essential for mitochondrial quality control and proteostasis (Coto-Montes et al. 2012; Vega-Naredo et al. 2012).

Recent findings from our group further support these observations, demonstrating that melatonin supplementation in obese murine models not only reduces oxidative burden but also enhances mitochondrial biogenesis and dynamics, improves glucose and mitochondrial metabolism, and partially restores cellular proteostasis in skeletal muscle (Potes et al., 2023). Moreover, melatonin facilitates satellite cell proliferation and differentiation, processes essential for effective muscle regeneration (Su et al. 2023; Zhu et al. 2024) (Bermejo-Millo et al. under peer review).

Given its favorable safety profile, antioxidant capacity, and broad spectrum of biological actions, melatonin emerges as a compelling therapeutic agent for preserving skeletal muscle integrity and optimizing regenerative processes across the lifespan (Andersen et al. 2016; Coto-Montes et al. 2016). Its mitochondrial-protective effects, ability to regulate autophagy and oxidative stress, and capacity to stimulate muscle repair mechanisms position it as a valuable intervention for mitigating muscle decline in aging and disease. Moreover, its biosynthetic dependence on tryptophan links its efficacy to nutritional status, further highlighting the integrative nature of metabolic and regenerative muscle health. In conclusion, melatonin supplementation, whether through direct administration or enhanced endogenous synthesis via dietary precursors, holds significant promise as a multifactorial strategy to promote healthy skeletal muscle aging (Fig. 7).

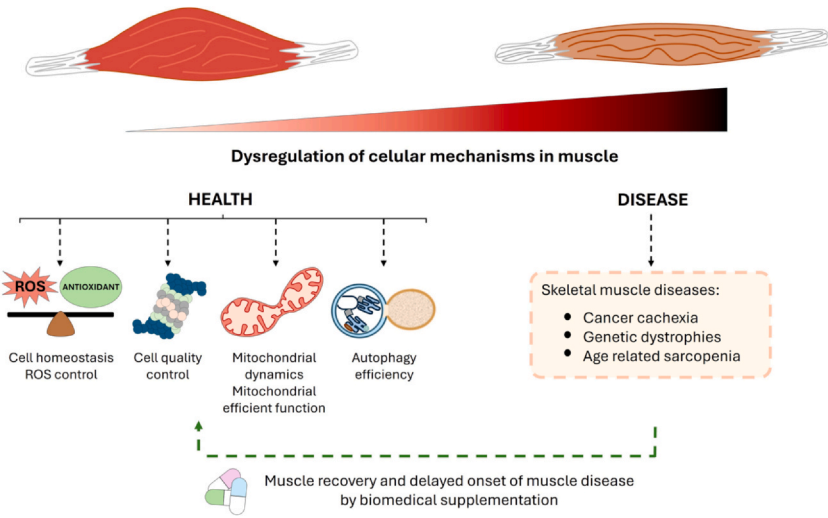

Fig. 7 Overview of cellular alterations identified in skeletal muscle, from health to disease, and how science can improve cellular control mechanisms.

6. Future perspectives and conclusions

Recent advances in our understanding of autophagy and cellular quality control mechanisms have significantly reshaped current perspectives on the pathogenesis of metabolic, muscular, and degenerative diseases. While preclinical studies have provided encouraging evidence for the therapeutic modulation of autophagy, substantial barriers remain before these findings can be translated into clinical practice. Among the most promising avenues is the exploration of autophagy-targeted interventions to preserve or restore skeletal muscle function. Existing evidence supports that autophagic modulation and stimulation of muscle growth are attainable objectives through strategic approaches. However, there remains considerable uncertainty regarding the long-term effects of sustained autophagy activation or suppression in skeletal muscle. Although autophagy is indispensable for cellular homeostasis, chronic modulation, either upregulation or inhibition, may carry adverse consequences, potentially impairing muscle regeneration and function (Sebastián & Zorzano, 2020). Excessive activation may induce the degradation of vital cellular constituents, while prolonged inhibition promotes the accumulation of dysfunctional organelles and exacerbates muscle degeneration (Wang et al. 2024).

Controlled activation of mitophagy has been proposed as a dual mechanism: facilitating the selective clearance of damaged mitochondria while promoting mitochondrial renewal, ultimately preserving both metabolic and contractile functions (Wang, Long, et al. 2023). Furthermore, the assessment of autophagy, especially mitophagy, as a diagnostic and prognostic biomarker in muscular disorders represents an innovative direction that may refine patient stratification, disease monitoring, and therapeutic responsiveness.

Traditionally, mitochondrial quality control was believed to be orchestrated exclusively by intracellular processes such as mitophagy. However, emerging evidence has revealed a more complex reality involving extracellular mitochondrial quality control mechanisms. These include intercellular mitochondrial transfer, the formation of TNTs, the release of mitochondria-containing extracellular vesicles, and even the physical extrusion of damaged mitochondria. These non-canonical mechanisms allow cells to share or eliminate mitochondria in response to physiological or pathological stress, thereby maintaining tissue energy homeostasis and integrity through intercellular cooperation. This conceptual shift, the so-called "social life" of mitochondria, challenges the traditional view of cellular autonomy and underscores the importance of intercellular mitochondrial dynamics in maintaining musculoskeletal and systemic health. Understanding these mechanisms opens novel therapeutic windows in diseases such as neurodegeneration, cardiovascular pathologies, and cancer, where mitochondrial dysfunction plays a central role.

Despite these insights, a critical bottleneck in clinical translation remains: the discrepancy between in vitro models and the complex in vivo physiology of human skeletal muscle. A lack of animal or cellular models that fully recapitulate human muscle architecture, fiber-type composition, and metabolic heterogeneity limits the direct applicability of preclinical findings. Thus, in-depth characterization of selective autophagy in human muscle is urgently required. To date, inconsistent and highly heterogeneous results from human studies represent a major barrier to the development of clinical therapies for muscle damage and atrophy.

In this context, combined strategies involving exercise and targeted nutritional supplementation represent the most effective and well-supported interventions currently available. Nonetheless, long-term safety remains insufficiently studied. Moreover, the heterogeneity in study design, population characteristics, and supplementation protocols highlights the need for personalized interventions to maximize efficacy while avoiding adverse outcomes. Interventions that combine nutritional

strategies (e.g., AAs, creatine, melatonin) with physical training appear particularly promising in restoring mitochondrial quality, redox balance, and promoting muscle regeneration, especially in conditions of age-related or disease-induced degeneration. Tailored nutritional supplementation further enhances anabolic and energetic capacity, particularly in settings of age-associated malnutrition.

To bridge the translational gap, future research must adopt cutting-edge methodologies. Advanced molecular tools, such as single-cell transcriptomics, imaging-based autophagy flux assays, and mitochondrial functional profiling, offer new opportunities to assess muscle biology in vivo. However, key questions remain unanswered. Furthermore, the integration of longitudinal, high-quality clinical studies that account for individual variability, including age, sex, genetics, metabolic status, and lifestyle, will be essential to inform personalized therapies.

In summary, although targeting autophagy and quality control pathways offers transformative potential for the treatment of muscle-related diseases, several scientific and translational challenges must still be overcome. Future research must not only delineate the fundamental mechanisms involved but also validate these findings in physiologically relevant human systems and rigorously evaluate the safety and efficacy of proposed interventions. The successful clinical translation of these concepts will require an interdisciplinary, technology-driven approach. Only through such coordinated efforts can we fully harness the regenerative potential of autophagy biology to promote muscle health, resilience, and quality of life across the lifespan.

Acknowledgments

This work was supported by the Instituto de Salud Carlos III (Ministry of Science, Innovation and Universities (MCIU)) and co-founded by the European Union, grant reference PI21/01596; by Government of the Principado de Asturias through the Fundación para el Fomento en Asturias de la Investigación Científica Aplicada y a la Tecnología (FICYT), SEKUENS and also co-founded by the European Union, GRUPIN (IDI/2024/000719 and IDE/2024/000719). E.A. thanks his predoctoral fellowships to Instituto de Salud Carlos III, grant number FI22/00286.

References

Adhihetty, P. J., & Beal, M. F. (2008). Creatine and its potential therapeutic value for targeting cellular energy impairment in neurodegenerative diseases. *Neuromolecular Medicine, 10*, 275–290.

Ahmad, T., Mukherjee, S., Pattnaik, B., Kumar, M., Singh, S., Kumar, M., ... Agrawal, A. (2014). Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *The EMBO Journal, 33*, 994–1010.

Alagar Boopathy, L. R., Jacob-Tomas, S., Alecki, C., & Vera, M. (2022). Mechanisms tailoring the expression of heat shock proteins to proteostasis challenges. *The Journal of Biological Chemistry, 298*, 101796.

Andersen, L. P. H., Gögenur, I., Rosenberg, J., & Reiter, R. J. (2016). The safety of melatonin in humans. *Clinical Drug Investigation, 36*, 169–175.

Anderson, J. E. (2022). Key concepts in muscle regeneration: Muscle "cellular ecology" integrates a gestalt of cellular cross-talk, motility, and activity to remodel structure and restore function. *European Journal of Applied Physiology, 122*, 273–300.

Anding, A. L., & Baehrecke, E. H. (2017). Cleaning house: Selective autophagy of organelles. *Developmental Cell, 41*, 10–22.

Anton, S. D., Hida, A., Mankowski, R., Layne, A., Solberg, L. M., Mainous, A. G., & Buford, T. (2018). Nutrition and exercise in sarcopenia. *Current Protein & Peptide Science, 19*, 649–667.

Antuña, E., Cachán-Vega, C., Bermejo-Millo, J. C., Potes, Y., Caballero, B., Vega-Naredo, I., ... Garcia-Gonzalez, C. (2022). Inflammaging: Implications in sarcopenia. *International Journal of Molecular Sciences, 23*, 15039.

Antuña, E., Potes, Y., Baena-Huerta, F. J., Cachán-Vega, C., Menéndez-Coto, N., Álvarez Darriba, E., ... Garcia-Gonzalez, C. (2024). NLRP3 contributes to sarcopenia associated to dependency recapitulating inflammatory-associated muscle degeneration. *International Journal of Molecular Sciences, 25*, 1439.

Aquilani, R., Zuccarelli, G. C., Maestri, R., Boselli, M., Dossena, M., Baldissarro, E., ... Verri, M. (2021). Essential amino acid supplementation is associated with reduced serum C-reactive protein levels and improved circulating lymphocytes in post-acute inflamed elderly patients. *International Journal of Immunopathology and Pharmacology, 35* 20587384211036823.

Argilés, J. M., Campos, N., Lopez-Pedrosa, J. M., Rueda, R., & Rodriguez-Mañas, L. (2016). Skeletal muscle regulates metabolism via interorgan crosstalk: Roles in health and disease. *Journal of the American Medical Directors Association, 17*, 789–796.

Arnould, T., Michel, S., & Renard, P. (2015). Mitochondria retrograde signaling and the UPR mt: Where are we in mammals? *International Journal of Molecular Sciences, 16*, 18224–18251.

Azhar, G., Wei, J. Y., Schutzler, S. E., Coker, K., Gibson, R. V., Kirby, M. F., ... Wolfe, R. R. (2021). Daily consumption of a specially formulated essential amino acid-based dietary supplement improves physical performance in older adults with low physical functioning. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 76*, 1184–1191.

Baker, J. S., McCormick, M. C., & Robergs, R. A. (2010). Interaction among Skeletal muscle metabolic energy systems during intense exercise. *Journal of Nutrition and Metabolism, 2010*, 905612.

Ballabio, A., & Bonifacino, J. S. (2020). Lysosomes as dynamic regulators of cell and organismal homeostasis. *Nature Reviews. Molecular Cell Biology, 21*, 101–118.

Ban, T., Ishihara, T., Kohno, H., Saita, S., Ichimura, A., Maenaka, K., ... Ishihara, N. (2017). Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. *Nature Cell Biology, 19*, 856–863.

Bauer, J. M., & Diekmann, R. (2015). Protein supplementation with aging. *Current Opinion in Clinical Nutrition and Metabolic Care, 18*, 24–31.

Beck, K. L., Thomson, J. S., Swift, R. J., & von Hurst, P. R. (2015). Role of nutrition in performance enhancement and postexercise recovery. *The Open Access Journal of Sports Medicine, 6*, 259–267.

Bellissimo, C. A., Garibotti, M. C., & Perry, C. G. R. (2022). Mitochondrial stress responses in Duchenne muscular dystrophy: Metabolic dysfunction or adaptive reprogramming? *American Journal of Physiology. Cell Physiology, 323*, C718–C730.

Bels, J. L. M., Ali Abdelhamid, Y., & van de Poll, M. C. G. (2023). Protein supplementation in critical illness: Why, when and how? *Current Opinion in Clinical Nutrition and Metabolic Care, 26*, 146–153.

Beltrà, M., Pin, F., Ballarò, R., Costelli, P., & Penna, F. (2021). Mitochondrial dysfunction in cancer cachexia: Impact on muscle health and regeneration. *Cells, 10*, 3150.

Bi, J., Sun, Y., Guo, M., Sun, X., Sun, J., Jiang, R., ... Huang, G. (2025). Lysosomes: Guardians and healers within cells- multifaceted perspective and outlook from injury repair to disease treatment. *Cancer Cell International, 25*, 136.

Bo Otto, F., & Thumm, M. (2020). Nucleophagy-implications for microautophagy and health. *International Journal of Molecular Sciences, 21*, 4506.

Boga, J. A., Caballero, B., Potes, Y., Perez-Martinez, Z., Reiter, R. J., Vega-Naredo, I., & Coto-Montes, A. (2019). Therapeutic potential of melatonin related to its role as an autophagy regulator: A review. *Journal of Pineal Research, 66*, e12534.

Bonilla, D. A., Kreider, R. B., Stout, J. R., Forero, D. A., Kerksick, C. M., Roberts, M. D., & Rawson, E. S. (2021). Metabolic basis of creatine in health and disease: A bioinformatics-assisted review. *Nutrients, 13*, 1238.

Bonuccelli, G., Sotgia, F., Schubert, W., Park, D. S., Frank, P. G., Woodman, S. E., ... Lisanti, M. P. (2003). Proteasome inhibitor (MG-132) treatment of mdx mice rescues the expression and membrane localization of dystrophin and dystrophin-associated proteins. *The American Journal of Pathology, 163*, 1663–1675.

Boyle, E., & Wilfling, F. (2023). Autophagy as a caretaker of nuclear integrity. *FEBS Letters, 597*, 2728–2738.

Brosnan, J. T., & Brosnan, M. E. (2007). Creatine: Endogenous metabolite, dietary, and therapeutic supplement. *Annual Review of Nutrition, 27*, 241–261.

Brown, J. L., Rosa-Caldwell, M. E., Lee, D. E., Blackwell, T. A., Brown, L. A., Perry, R. A., ... Greene, N. P. (2017). Mitochondrial degeneration precedes the development of muscle atrophy in progression of cancer cachexia in tumour-bearing mice. *The Journal of Cachexia, Sarcopenia and Muscle, 8*, 926–938.

Burke, R., Piñero, A., Coleman, M., Mohan, A., Sapuppo, M., Augustin, F., ... Schoenfeld, B. J. (2023). The effects of creatine supplementation combined with resistance training on regional measures of muscle hypertrophy: A systematic review with meta-analysis. *Nutrients, 15*, 2116.

Burnett, S. F., Farré, J.-C., Nazarko, T. Y., & Subramani, S. (2015). Peroxisomal Pex3 activates selective autophagy of peroxisomes via interaction with the pexophagy receptor Atg30. *The Journal of Biological Chemistry, 290*, 8623–8631.

Cai, Z., Liu, D., Yang, Y., Xie, W., He, M., Yu, D., ... Li, Y. (2022). The role and therapeutic potential of stem cells in skeletal muscle in sarcopenia. *Stem Cell Research & Therapy, 13*, 28.

Calcaterra, L., Abellan van Kan, G., Steinmeyer, Z., Angioni, D., Proietti, M., & Sourdet, S. (2024). Sarcopenia and poor nutritional status in older adults. *Clinical Nutrition (Edinburgh, Scotland), 43*, 701–707.

Calderón, J. C., Bolaños, P., & Caputo, C. (2014). The excitation-contraction coupling mechanism in skeletal muscle. *Biophysical Reviews, 6*, 133–160.

Campisi, D., Hawkins, N., Bonjour, K., & Wollert, T. (2025). The role of WIPI2, ATG16L1 and ATG12-ATG5 in selective and nonselective autophagy. *Journal of Molecular Biology*, 169138.

Candow, D. G., & Moriarty, T. (2024). Effects of creatine monohydrate supplementation on muscle, bone and brain- hope or hype for older adults? *Current Osteoporosis Reports, 23*(1).

Carmignac, V., Quéré, R., & Durbeej, M. (2011). Proteasome inhibition improves the muscle of laminin α2 chain-deficient mice. *Human Molecular Genetics, 20*, 541–552.

Carson, J. A., Hardee, J. P., & VanderVeen, B. N. (2016). The emerging role of skeletal muscle oxidative metabolism as a biological target and cellular regulator of cancer-induced muscle wasting. *Seminars in Cell & Developmental Biology, 54*, 53–67.

Casas-Fraile, L., Cornelis, F. M., Costamagna, D., Rico, A., Duelen, R., Sampaolesi, M. M., ... Sáenz, A. (2020). Frizzled related protein deficiency impairs muscle strength, gait and calpain 3 levels. *Orphanet Journal of Rare Diseases, 15*, 119.

Casati, S. R., Cervia, D., Roux-Biejat, P., Moscheni, C., Perrotta, C., & De Palma, C. (2024). Mitochondria and reactive oxygen species: The therapeutic balance of powers for duchenne muscular dystrophy. *Cells, 13*, 574.

Chakraborty, R., Nonaka, T., Hasegawa, M., & Zurzolo, C. (2023). Tunnelling nanotubes between neuronal and microglial cells allow bi-directional transfer of α-Synuclein and mitochondria. *Cell Death & Disease, 14*, 329.

Chassagne J., Silva N.D., Akrouf I., Cadot B., Julien L., Barthélémy I., … Benkhelifa-Ziyyat S. (2024). Early endosome disturbance and endolysosomal pathway dysfunction in Duchenne muscular dystrophy. 2024.12.16.628552. Available at: https://www.biorxiv.org/content/10.1101/2024.12.16.628552v1 [Accessed May 6, 2025].

Chauhan, S., Kumar, S., Jain, A., Ponpuak, M., Mudd, M. H., Kimura, T., ... Deretic, V. (2016). TRIMs and galectins globally cooperate and TRIM16 and Galectin-3 Co-direct autophagy in endomembrane damage homeostasis. *Developmental Cell, 39*, 13–27.

Chen, J.-J. (2025). HRI protein kinase in cytoplasmic heme sensing and mitochondrial stress response: relevance to hematological and mitochondrial diseases. *The Journal of Biological Chemistry*, 108494.

Chen, W., Chen, Y., Liu, Y., & Wang, X. (2022). Autophagy in muscle regeneration: Potential therapies for myopathies. *The Journal of Cachexia, Sarcopenia and Muscle*.

Chinvattanachot, G., Rivas, D., & Duque, G. (2024). Mechanisms of muscle cells alterations and regeneration decline during aging. *Ageing Research Reviews, 102*, 102589.

Cho, D.-H., Kim, Y. S., Jo, D. S., Choe, S.-K., & Jo, E.-K. (2018). Pexophagy: Molecular mechanisms and implications for health and diseases. *Molecules and Cells, 41*, 55–64.

Chow, L. S., Gerszten, R. E., Taylor, J. M., Pedersen, B. K., van Praag, H., Trappe, S., ... Snyder, M. P. (2022). Exerkines in health, resilience and disease. *Nature Reviews Endocrinology, 18*, 273–289.

Colpman, P., Dasgupta, A., & Archer, S. L. (2023). The role of mitochondrial dynamics and mitotic fission in regulating the cell cycle in cancer and pulmonary arterial hypertension: Implications for dynamin-related protein 1 and mitofusin2 in hyperproliferative diseases. *Cells, 12*, 1897.

Cordingley, D. M., Cornish, S. M., & Candow, D. G. (2022). Anti-Inflammatory and anti-catabolic effects of creatine supplementation: A brief review. *Nutrients, 14*, 544.

Costa-Mattioli, M., & Walter, P. (2020). The integrated stress response: From mechanism to disease. *Science (New York, N. Y.), 368*, eaat5314.

Coto-Montes, A., Boga, J. A., Rosales-Corral, S., Fuentes-Broto, L., Tan, D.-X., & Reiter, R. J. (2012). Role of melatonin in the regulation of autophagy and mitophagy: a review. *Molecular and Cellular Endocrinology, 361*, 12–23.

Coto-Montes, A., Boga, J. A., Tan, D. X., & Reiter, R. J. (2016). Melatonin as a potential agent in the treatment of sarcopenia. *International Journal of Molecular Sciences, 17*, E1771.

Coto-Montes, A., González-Blanco, L., Antuña, E., Menéndez-Valle, I., Bermejo-Millo, J. C., Caballero, B., ... Potes, Y. (2021). The Interactome in the evolution from frailty to sarcopenic dependence. *Frontiers in Cell and Developmental Biology, 9*, 792825.

Cuervo, A. M., & Wong, E. (2014). Chaperone-mediated autophagy: Roles in disease and aging. *Cell Research, 24*, 92–104.

Dabo, S., & Meurs, E. F. (2012). dsRNA-dependent protein kinase PKR and its role in stress, signaling and HCV infection. *Viruses, 4*, 2598–2635.

Dai, J.-M., Yu, M.-X., Shen, Z.-Y., Guo, C.-Y., Zhuang, S.-Q., & Qiu, X.-S. (2015). Leucine promotes proliferation and differentiation of primary preterm rat satellite cells in part through mTORC1 signaling pathway. *Nutrients, 7*, 3387–3400.

D'Arcy, M. S. (2024). Mitophagy in health and disease. Molecular mechanisms, regulatory pathways, and therapeutic implications. *Apoptosis: An International Journal on Programmed Cell Death, 29*, 1415–1428.

Dawaliby, R., & Mayer, A. (2010). Microautophagy of the nucleus coincides with a vacuolar diffusion barrier at nuclear-vacuolar junctions. *Molecular Biology of the Cell, 21*, 4173–4183.

Del Franco, A., Ambrosio, G., Baroncelli, L., Pizzorusso, T., Barison, A., Olivotto, I., ... Vergaro, G. (2022). Creatine deficiency and heart failure. *Heart Failure Reviews, 27*, 1605–1616.

Demers, N. D., Riccio, V., Jo, D. S., Bhandari, S., Law, K. B., Liao, W., ... Kim, P. K. (2023). PEX13 prevents pexophagy by regulating ubiquitinated PEX5 and peroxisomal ROS. *Autophagy, 19*, 1781–1802.

Deretic, V., & Kroemer, G. (2022). Autophagy in metabolism and quality control: Opposing, complementary or interlinked functions? *Autophagy, 18*, 283–292.

Deutz, N. E. P., Bauer, J. M., Barazzoni, R., Biolo, G., Boirie, Y., Bosy-Westphal, A., ... Tipton, K., Calder, P. C. (2014). Protein intake and exercise for optimal muscle function with aging: recommendations from the ESPEN Expert Group. *Clinical Nutrition (Edinburgh, Scotland), 33*, 929–936.

Di Leo, V., Bernardino Gomes, T. M., & Vincent, A. E. (2023). Interactions of mitochondrial and skeletal muscle biology in mitochondrial myopathy. *The Biochemical Journal, 480*, 1767–1789.

Di Rita, A., Peschiaroli, A., Acunzo, D., Strobbe, P., Hu, D., Gruber, Z., ... Cecconi, F. (2018). HUWE1 E3 ligase promotes PINK1/PARKIN-independent mitophagy by regulating AMBRA1 activation via IKKα. *Nature Communications, 9*, 3755.

Duan, D., Goemans, N., Takeda, S., Mercuri, E., & Aartsma-Rus, A. (2021). Duchenne muscular dystrophy. *Nature Reviews Disease Primers, 7*, 13.

Dziewulska, D., Nycz, E., Rajczewska-Oleszkiewicz, C., Bojakowski, J., & Sulejczak, D. (2018). Nuclear abnormalities in vascular myocytes in cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL). *Neuropathology: Official Journal of the Japanese Society of Neuropathology, 38*, 601–608.

Eapen, V. V., Swarup, S., Hoyer, M. J., Paulo, J. A., & Harper, J. W. (2021). Quantitative proteomics reveals the selectivity of ubiquitin-binding autophagy receptors in the turnover of damaged lysosomes by lysophagy. *Elife, 10*, e72328.

Ebanks, B., & Chakrabarti, L. (2022). Mitochondrial ATP synthase is a target of oxidative stress in neurodegenerative diseases. *Frontiers in Molecular Biosciences, 9*, 854321.

Efeyan, A., Zoncu, R., Chang, S., Gumper, I., Snitkin, H., Wolfson, R. L., ... Sabatini, D. M. (2013). Regulation of mTORC1 by the Rag GTPases is necessary for neonatal autophagy and survival. *Nature, 493*, 679–683.

Englund, D. A., Zhang, X., Aversa, Z., & LeBrasseur, N. K. (2021). Skeletal muscle aging, cellular senescence, and senotherapeutics: Current knowledge and future directions. *Mechanisms of Ageing and Development, 200*, 111595.

Ernst, R., Ballweg, S., & Levental, I. (2018). Cellular mechanisms of physicochemical membrane homeostasis. *Current Opinion in Cell Biology, 53*, 44–51.

Esteban-Martínez, L., Sierra-Filardi, E., McGreal, R. S., Salazar-Roa, M., Mariño, G., Seco, E., ... Boya, P. (2017). Programmed mitophagy is essential for the glycolytic switch during cell differentiation. *The EMBO Journal, 36*, 1688–1706.

Fang, D., Xie, H., Hu, T., Shan, H., & Li, M. (2021). Binding features and functions of ATG3. *Frontiers in Cell and Developmental Biology, 9*, 685625.

Farré, J.-C., & Subramani, S. (2016). Mechanistic insights into selective autophagy pathways: Lessons from yeast. *Nature Reviews. Molecular Cell Biology, 17*, 537–552.

Forte, M., Schirone, L., Ameri, P., Basso, C., Catalucci, D., Modica, J., ... Italian Society of Cardiology Working group on Cellular and Molecular Biology of the Heart (2021). The role of mitochondrial dynamics in cardiovascular diseases. *British Journal of Pharmacology, 178*, 2060–2076.

Franco-Romero, A., Sandri, M., & Schiaffino, S. (2024). Autophagy in Skeletal Muscle. *Cold Spring Harb Perspect Biola*041565.

Frontera, W. R., & Ochala, J. (2015). Skeletal muscle: A brief review of structure and function. *Calcified Tissue International, 96*, 183–195.

Fu, N., Yang, X., & Chen, L. (2018). Nucleophagy plays a major role in human diseases. *Current Drug Targets, 19*, 1767–1773.

Fu, S., Gong, X., Liang, K., Ding, K., Qiu, L., Cen, H., & Du, H. (2024). KLF3 impacts insulin sensitivity and glucose uptake in skeletal muscle. *American Journal of, 327*, C1219–C1235.

Gaitanos, G. C., Williams, C., Boobis, L. H., & Brooks, S. (1993). Human muscle metabolism during intermittent maximal exercise. *Journal of Applied Physiology (1985), 75*, 712–719.

Gallagher, E. R., & Holzbaur, E. L. F. (2023). The selective autophagy adaptor p62/SQSTM1 forms phase condensates regulated by HSP27 that facilitate the clearance of damaged lysosomes via lysophagy. *Cell Reports, 42*, 112037.

Gallardo, E., Saenz, A., & Illa, I. (2011). Limb-girdle muscular dystrophy 2A. *Handbook of Clinical Neurology, 101*, 97–110.

Galluzzi, L., Bravo-San Pedro, J. M., & Kroemer, G. (2014). Organelle-specific initiation of cell death. *Nature Cell Biology, 16*, 728–736.

Gao, T., Zhang, Y., Zhang, D., & Zeng, P. (2024). Skeletal muscle stem cells and the microenvironment regulation in sarcopenia:A review. *Zhongguo Yi Xue Ke xue Yuan xue Bao. Acta Academiae Medicinae Sinicae, 46*, 958–964.

Germain, K., So, R. W. L., DiGiovanni, L. F., Watts, J. C., Bandsma, R. H. J., & Kim, P. K. (2024). Upregulated pexophagy limits the capacity of selective autophagy. *Nature Communications, 15*, 375.

Glick, D., Barth, S., & Macleod, K. F. (2010). Autophagy: Cellular and molecular mechanisms. *The Journal of Pathology, 221*, 3–12.

Glover, E. I., Phillips, S. M., Oates, B. R., Tang, J. E., Tarnopolsky, M. A., Selby, A., ... Rennie, M. J. (2008). Immobilization induces anabolic resistance in human myofibrillar protein synthesis with low and high dose amino acid infusion. *The Journal of Physiology, 586*, 6049–6061.

Gomez-Pastor, R., Burchfiel, E. T., & Thiele, D. J. (2018). Regulation of heat shock transcription factors and their roles in physiology and disease. *Nature Reviews. Molecular Cell Biology, 19*, 4–19.

Gómez-Virgilio, L., Silva-Lucero, M.-D.-C., Flores-Morelos, D.-S., Gallardo-Nieto, J., Lopez-Toledo, G., Abarca-Fernandez, A.-M., ... Cardenas-Aguayo, M.-D.-C. (2022). Autophagy: A key regulator of homeostasis and disease: An overview of molecular mechanisms and modulators. *Cells, 11*, 2262.

Gong, L., Zhang, X., Qiu, K., He, L., Wang, Y., & Yin, J. (2021). Arginine promotes myogenic differentiation and myotube formation through the elevation of cytoplasmic calcium concentration. *Animal Nutrition, 7*, 1115–1123.

González-Blanco, L., Bermúdez, M., Bermejo-Millo, J. C., Gutiérrez-Rodríguez, J., Solano, J. J., Antuña, E., ... Coto-Montes, A. (2022). Cell interactome in sarcopenia during aging. *The Journal of Cachexia, Sarcopenia and Muscle, 13*, 919–931.

de Gonzalo-Calvo, D., Fernández-García, B., de Luxán-Delgado, B., Rodríguez-González, S., García-Macia, M., Suárez, F. M., ... Coto-Montes, A. (2012). Long-term training induces a healthy inflammatory and endocrine emergent biomarker profile in elderly men. *Age (Melbourne, Vic.), 34*, 761–771.

Gopalarethinam, J., Nair, A. P., Iyer, M., Vellingiri, B., & Subramaniam, M. D. (2023). Advantages of mesenchymal stem cell over the other stem cells. *Acta Histochemica, 125*, 152041.

Granet, J.A., Robertson, R., Cusmano, A.A., Filippelli, R.L., Lorenz, T.O., Li, S., … Chang, N.C. (2025). Muscle stem cells in Duchenne muscular dystrophy exhibit molecular impairments and altered cell fate trajectories impacting regenerative capacity. 2024.07.24.604963. Available at: https://www.biorxiv.org/content/10.1101/2024.07.24.604963v3 [Accessed June 2, 2025].

Grumati, P., Morozzi, G., Hölper, S., Mari, M., Harwardt, M.-L. I. E., Yan, R., ... Dikic, I. (2017). Full length RTN3 regulates turnover of tubular endoplasmic reticulum via selective autophagy. *Elife, 6*, e25555.

Gu, J., He, Y., He, C., Zhang, Q., Huang, Q., Bai, S., ... Wang, L. (2025). Advances in the structures, mechanisms and targeting of molecular chaperones. *Signal Transduction and Targeted Therapy, 10*, 84.

Guzun, R., Timohhina, N., Tepp, K., Gonzalez-Granillo, M., Shevchuk, I., Chekulayev, V., ... Saks, V. A. (2011). Systems bioenergetics of creatine kinase networks: physiological roles of creatine and phosphocreatine in regulation of cardiac cell function. *Amino Acids, 40*, 1333–1348.

Hall, M., Manetta, E., & Tupper, K. (2021). Creatine supplementation: An update. *Current Sports Medicine Reports, 20*, 338–344.

Han, H., Hu, J., Yan, Q., Zhu, J., Zhu, Z., Chen, Y., ... Zhang, R. (2016). Bone marrow-derived mesenchymal stem cells rescue injured H9c2 cells via transferring intact mitochondria through tunneling nanotubes in an in vitro simulated ischemia/reperfusion model. *Molecular Medicine Reports, 13*, 1517–1524.

Han, Y., Yang, J., Fang, J., Zhou, Y., Candi, E., Wang, J., ... Shi, Y. (2022). The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. *Signal Transduction and Targeted Therapy, 7*, 92.

Hardee, J. P., Fix, D. K., Koh, H.-J., Wang, X., Goldsmith, E. C., & Carson, J. A. (2020). Repeated eccentric contractions positively regulate muscle oxidative metabolism and protein synthesis during cancer cachexia in mice. *Journal of Applied Physiology (1985), 128*, 1666–1676.

Higuera, G. A., Schop, D., Spitters, T. W. G. M., van Dijkhuizen-Radersma, R., Bracke, M., de Bruijn, J. D., ... van Blitterswijk, C. A. (2012). Patterns of amino acid metabolism by proliferating human mesenchymal stem cells. *Tissue Engineering. Part A, 18*, 654–664.

Hipp, M. S., Park, S.-H., & Hartl, F. U. (2014). Proteostasis impairment in protein-misfolding and -aggregation diseases. *Trends in Cell Biology, 24*, 506–514.

Höhn, A., Tramutola, A., & Cascella, R. (2020). Proteostasis failure in neurodegenerative diseases: Focus on oxidative stress. *Oxidative Medicine and Cellular Longevity, 2020*, 5497046.

Holmström, K. M., & Finkel, T. (2014). Cellular mechanisms and physiological consequences of redox-dependent signalling. *Nature Reviews. Molecular Cell Biology, 15*, 411–421.

Hong, C., Li, X., Zhang, K., Huang, Q., Li, B., Xin, H., ... Wang, S. (2024). Novel perspectives on autophagy-oxidative stress-inflammation axis in the orchestration of adipogenesis. *Front Endocrinol (Lausanne), 15*, 1404697.

Hong, X., Isern, J., Campanario, S., Perdiguero, E., Ramírez-Pardo, I., Segalés, J., ... Muñoz-Cánoves, P. (2022a). Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy. *Cell Stem Cell, 29*, 1506–1508.

Hong, X., Isern, J., Campanario, S., Perdiguero, E., Ramírez-Pardo, I., Segalés, J., ... Muñoz-Cánoves, P. (2022b). Mitochondrial dynamics maintain muscle stem cell regenerative competence throughout adult life by regulating metabolism and mitophagy. *Cell Stem Cell, 29*, 1298–1314.e10.

Hosokawa, N., Hara, T., Kaizuka, T., Kishi, C., Takamura, A., Miura, Y., ... Mizushima, N. (2009). Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. *Molecular Biology of the Cell, 20*, 1981–1991.

Hwang, J., & Qi, L. (2018). Quality control in the endoplasmic reticulum: Crosstalk between ERAD and UPR pathways. *Trends in Biochemical Sciences, 43*, 593–605.

Imanikia, S., Sheng, M., & Taylor, R. C. (2018). Cell Non-autonomous UPRER Signaling. *Current Topics in Microbiology and Immunology, 414*, 27–43.

Ishii, S., Chino, H., Ode, K. L., Kurikawa, Y., Ueda, H. R., Matsuura, A., ... Itakura, E. (2023). CCPG1 recognizes endoplasmic reticulum luminal proteins for selective ER-phagy. *Molecular Biology of the Cell, 34*, ar29.

Jacobs, R. A., & Lundby, C. (2013). Mitochondria express enhanced quality as well as quantity in association with aerobic fitness across recreationally active individuals up to elite athletes. *Journal of Applied Physiology (1985), 114*, 344–350.

Jahnke, V. E., Peterson, J. M., Van Der Meulen, J. H., Boehler, J., Uaesoontrachoon, K., Johnston, H. K., ... Nagaraju, K. (2020). Mitochondrial dysfunction and consequences in calpain-3-deficient muscle. *Skelet Muscle, 10*, 37.

Jia, J., Claude-Taupin, A., Gu, Y., Choi, S. W., Peters, R., Bissa, B., ... Deretic, V. (2020). Galectin-3 Coordinates a Cellular System for Lysosomal Repair and Removal. *Developmental Cell, 52*, 69–87.e8.

Jiang, L., Hara-Kuge, S., Yamashita, S.-I., & Fujiki, Y. (2015). Peroxin Pex14p is the key component for coordinated autophagic degradation of mammalian peroxisomes by direct binding to LC3-II. *Genes to Cells: Devoted to Molecular & Cellular Mechanisms, 20*, 36–49.

Jiang, P., Nishimura, T., Sakamaki, Y., Itakura, E., Hatta, T., Natsume, T., & Mizushima, N. (2014). The HOPS complex mediates autophagosome-lysosome fusion through interaction with syntaxin 17. *Molecular Biology of the Cell, 25*, 1327–1337.

Jin, H.-O., Hong, S.-E., Kim, J.-Y., Jang, S.-K., & Park, I.-C. (2021). Amino acid deprivation induces AKT activation by inducing GCN2/ATF4/REDD1 axis. *Cell Death & Disease, 12*, 1127.

Kang, C., Badr, M. A., Kyrychenko, V., Eskelinen, E.-L., & Shirokova, N. (2018). Deficit in PINK1/PARKIN-mediated mitochondrial autophagy at late stages of dystrophic cardiomyopathy. *Cardiovascular Research, 114*, 90–102.

Karanasios, E., Stapleton, E., Manifava, M., Kaizuka, T., Mizushima, N., Walker, S. A., & Ktistakis, N. T. (2013). Dynamic association of the ULK1 complex with omegasomes during autophagy induction. *Journal of Cell Science, 126*, 5224–5238.

Kaushik, S., & Cuervo, A. M. (2018). The coming of age of chaperone-mediated autophagy. *Nature Reviews. Molecular Cell Biology, 19*, 365–381.

Keefe, A. C., & Kardon, G. (2015). A new role for dystrophin in muscle stem cells. *Nature Medicine, 21*, 1391–1393.

Kemmler, W., Kohl, M., Freiberger, E., Sieber, C., & von Stengel, S. (2018). Effect of whole-body electromyostimulation and/or protein supplementation on obesity and cardiometabolic risk in older men with sarcopenic obesity: The randomized controlled FranSO trial. *BMC Geriatrics, 18*, 70.

Khaminets, A., Heinrich, T., Mari, M., Grumati, P., Huebner, A. K., Akutsu, M., ... Dikic, I. (2015). Regulation of endoplasmic reticulum turnover by selective autophagy. *Nature, 522*, 354–358.

Kim, J., Kundu, M., Viollet, B., & Guan, K.-L. (2011). AMPK and mTOR regulate autophagy through direct phosphorylation of Ulk1. *Nature Cell Biology, 13*, 132–141.

Kleele, T., Rey, T., Winter, J., Zaganelli, S., Mahecic, D., Perreten Lambert, H., ... Manley, S. (2021). Distinct fission signatures predict mitochondrial degradation or biogenesis. *Nature, 593*, 435–439.

Klionsky, D. J., Petroni, G., Amaravadi, R. K., Baehrecke, E. H., Ballabio, A., Boya, P., ... Pietrocola, F. (2021). Autophagy in major human diseases. *The EMBO Journal, 40*, e108863.

Kopp, M. C., Larburu, N., Durairaj, V., Adams, C. J., & Ali, M. M. U. (2019). UPR proteins IRE1 and PERK switch BiP from chaperone to ER stress sensor. *Nature Structural & Molecular Biology, 26*, 1053–1062.

Koyano, F., Yamano, K., Kosako, H., Tanaka, K., & Matsuda, N. (2019). Parkin recruitment to impaired mitochondria for nonselective ubiquitylation is facilitated by MITOL. *The Journal of Biological Chemistry, 294*, 10300–10314.

Kreider, R. B., Kalman, D. S., Antonio, J., Ziegenfuss, T. N., Wildman, R., Collins, R., ... Lopez, H. L. (2017). International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. *Journal of the International Society of Sports Nutrition, 14*, 18.

Kubat, G. B., Bouhamida, E., Ulger, O., Turkel, I., Pedriali, G., Ramaccini, D., ... Pinton, P. (2023). Mitochondrial dysfunction and skeletal muscle atrophy: Causes, mechanisms, and treatment strategies. *Mitochondrion, 72*, 33–58.

Kucińska, M. K., Fedry, J., Galli, C., Morone, D., Raimondi, A., Soldà, T., ... Molinari, M. (2023). TMX4-driven LINC complex disassembly and asymmetric autophagy of the nuclear envelope upon acute ER stress. *Nature Communications, 14*, 3497.

Kuma, A., & Yoshimori, T. (2025). Pathways to repair or remove lysosomes damaged by extracellular fine particles. In Y. Baba, R. Hanayama, H. Akita, & T. Yasui (Eds.). *Extracellular fine particles* (pp. 169–184). Singapore: Springer Nature. https://doi.org/10.1007/978-981-97-7067-0_13 [Accessed May 6, 2025].

Landi, F., Marzetti, E., Martone, A. M., Bernabei, R., & Onder, G. (2014). Exercise as a remedy for sarcopenia. *Current Opinion in Clinical Nutrition and Metabolic Care, 17*, 25–31.

Lei, Y., & Klionsky, D. J. (2021). The emerging roles of autophagy in human diseases. *Biomedicines, 9*, 1651.

Levine, B., & Kroemer, G. (2019). Biological functions of autophagy genes: A disease perspective. *Cell, 176*, 11–42.

Li, C., Yuan, Y., Jia, Y., Zhou, Q., Wang, Q., & Jiang, X. (2025). Cellular senescence: From homeostasis to pathological implications and therapeutic strategies. *Frontiers in Immunology, 16*, 1534263.

Li, M., Rong, Y., Chuang, Y.-S., Peng, D., & Emr, S. D. (2015). Ubiquitin-dependent lysosomal membrane protein sorting and degradation. *Molecular Cell, 57*, 467–478.

Li, S., Wandel, M. P., Li, F., Liu, Z., He, C., Wu, J., ... Randow, F. (2013). Sterical hindrance promotes selectivity of the autophagy cargo receptor NDP52 for the danger receptor galectin-8 in antibacterial autophagy. *Science Signaling, 6*, ra9.

Li, W., Li, J., & Bao, J. (2012). Microautophagy: Lesser-known self-eating. *Cellular and Molecular Life Sciences: CMLS, 69*, 1125–1136.

Li, Y., Yang, Z., Zhang, S., & Li, J. (2024). Miro-mediated mitochondrial transport: A new dimension for disease-related abnormal cell metabolism? *Biochemical and Biophysical Research Communications, 705*, 149737.

Lian, D., Chen, M.-M., Wu, H., Deng, S., & Hu, X. (2022). The role of oxidative stress in skeletal muscle myogenesis and muscle disease. *Antioxidants (Basel), 11*, 755.

Liang, J. R., Lingeman, E., Luong, T., Ahmed, S., Muhar, M., Nguyen, T., ... Corn, J. E. (2020). A genome-wide ER-phagy screen highlights key roles of mitochondrial metabolism and ER-resident UFMylation. *Cell, 180*, 1160–1177.e20.

Liao, C.-D., Chen, H.-C., Huang, S.-W., & Liou, T.-H. (2019). The role of muscle mass gain following protein supplementation plus exercise therapy in older adults with sarcopenia and frailty risks: A systematic review and meta-regression analysis of randomized trials. *Nutrients, 11*, 1713.

Ling, Z.-N., Jiang, Y.-F., Ru, J.-N., Lu, J.-H., Ding, B., & Wu, J. (2023). Amino acid metabolism in health and disease. *Signal Transduction and Targeted Therapy, 8*, 345.

Linxweiler, M., & Müller, C. S. L. (2022). Role of the SEC62 gene in dermato-oncology - impact on tumor cell biology, prognostication, and personalized therapy management. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology: JDDG, 20*, 1187–1199.

Liu, D., Fan, Y.-B., Tao, X.-H., Pan, W.-L., Wu, Y.-X., Wang, X.-H., ... Li, Y.-S. (2021). Mitochondrial quality control in sarcopenia: updated overview of mechanisms and interventions. *Aging and disease, 12*, 2016–2030.

Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P., ... Chen, Q. (2012). Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nature Cell Biology, 14*, 177–185.

Liu, Y., Fu, T., Li, G., Li, B., Luo, G., Li, N., & Geng, Q. (2023). Mitochondrial transfer between cell crosstalk - An emerging role in mitochondrial quality control. *Ageing Research Reviews, 91*, 102038.

López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M., & Kroemer, G. (2023). Hallmarks of aging: An expanding universe. *Cell, 186*, 243–278.

Loreti, M., & Sacco, A. (2022). The jam session between muscle stem cells and the extracellular matrix in the tissue microenvironment. *NPJ Regen Med, 7*, 16.

Lu, J., Tan, M., & Cai, Q. (2015). The Warburg effect in tumor progression: mitochondrial oxidative metabolism as an anti-metastasis mechanism. *Cancer Letters, 356*, 156–164.

Luhr, M., Torgersen, M. L., Szalai, P., Hashim, A., Brech, A., Staerk, J., & Engedal, N. (2019). The kinase PERK and the transcription factor ATF4 play distinct and essential roles in autophagy resulting from tunicamycin-induced ER stress. *The Journal of Biological Chemistry, 294*, 8197–8217.

Luo, M., Zhao, X., Song, Y., Cheng, H., & Zhou, R. (2016). Nuclear autophagy: An evolutionarily conserved mechanism of nuclear degradation in the cytoplasm. *Autophagy, 12*, 1973–1983.

Luo, X., Wang, J., Ju, Q., Li, T., & Bi, X. (2025). Molecular mechanisms and potential interventions during aging-associated sarcopenia. *Mechanisms of Ageing and Development, 223*, 112020.

Lyamzaev, K. G., Zinovkin, R. A., & Chernyak, B. V. (2022). Extrusion of mitochondria: Garbage clearance or cell-cell communication signals? *Journal of Cellular Physiology, 237*, 2345–2356.

Lynch, C. J., & Adams, S. H. (2014). Branched-chain amino acids in metabolic signalling and insulin resistance. *Nature Reviews Endocrinology, 10*, 723–736.

Ma, L., Li, Y., Peng, J., Wu, D., Zhao, X., Cui, Y., ... Yu, L. (2015). Discovery of the migrasome, an organelle mediating release of cytoplasmic contents during cell migration. *Cell Research, 25*, 24–38.

Manchester, L. C., Coto-Montes, A., Boga, J. A., Andersen, L. P. H., Zhou, Z., Galano, A., ... Reiter, R. J. (2015). Melatonin: An ancient molecule that makes oxygen metabolically tolerable. *Journal of Pineal Research, 59*, 403–419.

Manjithaya, R., Nazarko, T. Y., Farré, J.-C., & Subramani, S. (2010). Molecular mechanism and physiological role of pexophagy. *FEBS Letters, 584*, 1367–1373.

Mao, K., Liu, X., Feng, Y., & Klionsky, D. J. (2014). The progression of peroxisomal degradation through autophagy requires peroxisomal division. *Autophagy, 10*, 652–661.

Marshall, R. P., Droste, J.-N., Giessing, J., & Kreider, R. B. (2022). Role of creatine supplementation in conditions involving mitochondrial dysfunction: A narrative review. *Nutrients, 14*, 529.

Masser, A. E., Ciccarelli, M., & Andréasson, C. (2020). Hsf1 on a leash - controlling the heat shock response by chaperone titration. *Experimental Cell Research, 396*, 112246.

Massey, A. C., Zhang, C., & Cuervo, A. M. (2006). Chaperone-mediated autophagy in aging and disease. *Current Topics in Developmental Biology, 73*, 205–235.

McEwan, D. G., Popovic, D., Gubas, A., Terawaki, S., Suzuki, H., Stadel, D., ... Dikic, I. (2015). PLEKHM1 regulates autophagosome-lysosome fusion through HOPS complex and LC3/GABARAP proteins. *Molecular Cell, 57*, 39–54.

Mcleod, J. C., Currier, B. S., Lowisz, C. V., & Phillips, S. M. (2024). The influence of resistance exercise training prescription variables on skeletal muscle mass, strength, and physical function in healthy adults: An umbrella review. *The Journal of Sport and Health Science, 13*, 47–60.

Memme, J. M., Erlich, A. T., Phukan, G., & Hood, D. A. (2021). Exercise and mitochondrial health. *The Journal of Physiology, 599*, 803–817.

Menéndez-Valle, I., Cachán-Vega, C., Boga, J. A., González-Blanco, L., Antuña, E., Potes, Y., ... Coto-Montes, A. (2023). Differential cellular interactome in schizophrenia and bipolar disorder-discriminatory biomarker role. *Antioxidants (Basel), 12*, 1948.

Mercuri, E., Bönnemann, C. G., & Muntoni, F. (2019). Muscular dystrophies. *Lancet, 394*, 2025–2038.

Michel, M. A., Swatek, K. N., Hospenthal, M. K., & Komander, D. (2017). Ubiquitin linkage-specific affimers reveal insights into K6-Linked ubiquitin signaling. *Molecular Cell, 68*, 233–246.e5.

Mito, T., Vincent, A. E., Faitg, J., Taylor, R. W., Khan, N. A., McWilliams, T. G., & Suomalainen, A. (2022). Mosaic dysfunction of mitophagy in mitochondrial muscle disease. *Cell Metabolism, 34*, 197–208.e5.

Mizushima, N. (2018). A brief history of autophagy from cell biology to physiology and disease. *Nature Cell Biology, 20*, 521–527.

Mizushima, N., & Levine, B. (2020). Autophagy in human diseases. *The New England Journal of Medicine, 383*, 1564–1576.

Mochida, K., & Nakatogawa, H. (2022a). Atg39 binding to the inner nuclear membrane triggers nuclear envelope deformation in piecemeal macronucleophagy. *Autophagy, 18*, 3046–3047.

Mochida, K., & Nakatogawa, H. (2022b). ER-phagy: Selective autophagy of the endoplasmic reticulum. *EMBO Reports, 23*, e55192.

Mochida, K., Oikawa, Y., Kimura, Y., Kirisako, H., Hirano, H., Ohsumi, Y., & Nakatogawa, H. (2015). Receptor-mediated selective autophagy degrades the endoplasmic reticulum and the nucleus. *Nature, 522*, 359–362.

Mochida, K., Otani, T., Katsumata, Y., Kirisako, H., Kakuta, C., Kotani, T., & Nakatogawa, H. (2022). Atg39 links and deforms the outer and inner nuclear membranes in selective autophagy of the nucleus. *The Journal of Cell Biology, 221*, e202103178.

Mohan, J., Moparthi, S. B., Girard-Blanc, C., Campisi, D., Blanchard, S., Nugues, C., ... Wollert, T. (2024). ATG16L1 induces the formation of phagophore-like membrane cups. *Nature Structural & Molecular Biology, 31*, 1448–1459.

Motley, A. M., Nuttall, J. M., & Hettema, E. H. (2012). Pex3-anchored Atg36 tags peroxisomes for degradation in Saccharomyces cerevisiae. *The EMBO Journal, 31*, 2852–2868.

Mu, W., Zhi, Y., Zhou, J., Wang, C., Chai, K., Fan, Z., & Lv, G. (2024). Endoplasmic reticulum stress and quality control in relation to cisplatin resistance in tumor cells. *Front Pharmacol, 15*, 1419468.

Mucha, O., Kaziród, K., Podkalicka, P., Rusin, K., Dulak, J., & Łoboda, A. (2021). Dysregulated autophagy and mitophagy in a mouse model of duchenne muscular dystrophy remain unchanged following heme oxygenase-1 Knockout. *International Journal of Molecular Sciences, 23*, 470.

Mukund, K., & Subramaniam, S. (2020). Skeletal muscle: A review of molecular structure and function, in health and disease. *Wiley Interdisciplinary Reviews: Systems Biology and Medicine, 12*, e1462.

Münch, C., & Harper, J. W. (2016). Mitochondrial unfolded protein response controls matrix pre-RNA processing and translation. *Nature, 534*, 710–713.

Murakawa, T., Okamoto, K., Omiya, S., Taneike, M., Yamaguchi, O., & Otsu, K. (2019). A mammalian mitophagy receptor, Bcl2-L-13, recruits the ULK1 complex to induce mitophagy. *Cell Reports, 26*, 338–345 e6.

Nähse, V., Raiborg, C., Tan, K. W., Mørk, S., Torgersen, M. L., Wenzel, E. M., ... Stenmark, H. (2023). ATPase activity of DFCP1 controls selective autophagy. *Nature Communications, 14*, 4051.

Narendra, D., Tanaka, A., Suen, D.-F., & Youle, R. J. (2008). Parkin is recruited selectively to impaired mitochondria and promotes their autophagy. *The Journal of Cell Biology, 183*, 795–803.

Nazarko, T. Y., Farré, J.-C., Polupanov, A. S., Sibirny, A. A., & Subramani, S. (2007). Autophagy-related pathways and specific role of sterol glucoside in yeasts. *Autophagy, 3*, 263–265.

Nguyen, J. A., & Yates, R. M. (2021). Better together: Current insights into phagosome-lysosome fusion. *Frontiers in Immunology, 12*, 636078.

Nie, C., He, T., Zhang, W., Zhang, G., & Ma, X. (2018). Branched chain amino acids: Beyond nutrition metabolism. *International Journal of Molecular Sciences, 19*, 954.

Noone, J., O'Gorman, D. J., & Kenny, H. C. (2022). OPA1 regulation of mitochondrial dynamics in skeletal and cardiac muscle. *Trends in Endocrinology and Metabolism: TEM, 33*, 710–721.

Norell, P. N., Campisi, D., Mohan, J., & Wollert, T. (2024). Biogenesis of omegasomes and autophagosomes in mammalian autophagy. *Biochemical Society Transactions, 52*, 2145–2155.

Okumoto, K., Noda, H., & Fujiki, Y. (2014). Distinct modes of ubiquitination of peroxisome-targeting signal type 1 (PTS1) receptor Pex5p regulate PTS1 protein import. *The Journal of Biological Chemistry, 289*, 14089–14108.

Olivas, T. J., Wu, Y., Yu, S., Luan, L., Choi, P., Guinn, E. D., ... Melia, T. J. (2023). ATG9 vesicles comprise the seed membrane of mammalian autophagosomes. *The Journal of Cell Biology, 222*, e202208088.

Ordureau, A., Heo, J.-M., Duda, D. M., Paulo, J. A., Olszewski, J. L., Yanishevski, D., ... Harper, J. W. (2015). Defining roles of PARKIN and ubiquitin phosphorylation by PINK1 in mitochondrial quality control using a ubiquitin replacement strategy. *Proceedings of the National Academy of Sciences of the United States of America, 112*, 6637–6642.

Ostojic, S. M. (2022). Creatine and multiple sclerosis. *Nutritional Neuroscience, 25*, 912–919.

Otto, F. B., & Thumm, M. (2021). Mechanistic dissection of macro- and micronucleophagy. *Autophagy, 17*, 626–639.

Paez, H. G., Pitzer, C. R., & Alway, S. E. (2023). Age-related dysfunction in proteostasis and cellular quality control in the development of sarcopenia. *Cells, 12*, 249.

Pahal, S., Mainali, N., Balasubramaniam, M., Shmookler Reis, R. J., & Ayyadevara, S. (2025). Mitochondria in aging and age-associated diseases. *Mitochondrion, 82*, 102022.

Palam, L. R., Baird, T. D., & Wek, R. C. (2011). Phosphorylation of eIF2 facilitates ribosomal bypass of an inhibitory upstream ORF to enhance CHOP translation. *The Journal of Biological Chemistry, 286*, 10939–10949.

Palikaras, K., Lionaki, E., & Tavernarakis, N. (2018). Mechanisms of mitophagy in cellular homeostasis, physiology and pathology. *Nature Cell Biology, 20*, 1013–1022.

Papadopoulos, C., Kirchner, P., Bug, M., Grum, D., Koerver, L., Schulze, N., ... Meyer, H. (2017). VCP/p97 cooperates with YOD1, UBXD1 and PLAA to drive clearance of ruptured lysosomes by autophagy. *The EMBO Journal, 36*, 135–150.

Papadopoulos, C., Kravic, B., & Meyer, H. (2020). Repair or lysophagy: Dealing with damaged lysosomes. *Journal of Molecular Biology, 432*, 231–239.

Papandreou, M.-E., & Tavernarakis, N. (2019). Nucleophagy: From homeostasis to disease. *Cell Death and Differentiation, 26*, 630–639.

Paré, M. F., Baechler, B. L., Fajardo, V. A., Earl, E., Wong, E., Campbell, T. L., ... Quadrilatero, J. (2017). Effect of acute and chronic autophagy deficiency on skeletal muscle apoptotic signaling, morphology, and function. *Biochim Biophys Acta Mol Cell Res, 1864*, 708–718.

Park, Y.-E., Hayashi, Y. K., Goto, K., Komaki, H., Hayashi, Y., Inuzuka, T., ... Nishino, I. (2009). Nuclear changes in skeletal muscle extend to satellite cells in autosomal dominant Emery-Dreifuss muscular dystrophy/limb-girdle muscular dystrophy 1B. *Neuromuscular Disorders: NMD, 19*, 29–36.

Parzych, K. R., & Klionsky, D. J. (2014). An overview of autophagy: Morphology, mechanism, and regulation. *Antioxidants & Redox Signaling, 20*, 460–473.

Pasiakos, S. M., McClung, H. L., McClung, J. P., Margolis, L. M., Andersen, N. E., Cloutier, G. J., ... Young, A. J. (2011). Leucine-enriched essential amino acid supplementation during moderate steady state exercise enhances postexercise muscle protein synthesis. *The American Journal of Clinical Nutrition, 94*, 809–818.

Patel, R., Ford, C. A., Rodgers, L., Rushworth, L. K., Fleming, J., Mui, E., ... Leung, H. Y. (2022). Cyclocreatine suppresses creatine metabolism and impairs prostate cancer progression. *Cancer Research, 82*, 2565–2575.

Pathak, R. U., Soujanya, M., & Mishra, R. K. (2021). Deterioration of nuclear morphology and architecture: A hallmark of senescence and aging. *Ageing Research Reviews, 67*, 101264.

Peixoto da Silva, S., Santos, J. M. O., Costa, E., Silva, M. P., Gil da Costa, R. M., & Medeiros, R. (2020). Cancer cachexia and its pathophysiology: links with sarcopenia, anorexia and asthenia. *The Journal of Cachexia, Sarcopenia and Muscle, 11*, 619–635.

Peker, N., Donipadi, V., Sharma, M., McFarlane, C., & Kambadur, R. (2018). Loss of Parkin impairs mitochondrial function and leads to muscle atrophy. *American Journal of Physiology, 315*, C164–C185.

Penna, F., Bonetto, A., Aversa, Z., Minero, V. G., Rossi Fanelli, F., Costelli, P., & Muscaritoli, M. (2016). Effect of the specific proteasome inhibitor bortezomib on cancer-related muscle wasting. *The Journal of Cachexia, Sarcopenia and Muscle, 7*, 345–354.

Phu, S., Boersma, D., & Duque, G. (2015). Exercise and sarcopenia. *Journal of Clinical Densitometry: The Official Journal of the International Society for Clinical Densitometry, 18*, 488–492.

Picca, A., Faitg, J., Auwerx, J., Ferrucci, L., & D'Amico, D. (2023). Mitophagy in human health, ageing and disease. *Nature Metabolism, 5*, 2047–2061.

Pin, F., Minero, V. G., Penna, F., Muscaritoli, M., De Tullio, R., Baccino, F. M., & Costelli, P. (2017). Interference with Ca2+-dependent proteolysis does not alter the course of muscle wasting in experimental cancer cachexia. *Frontiers in Physiology, 8*, 213.

Poole, L. P., Bock-Hughes, A., Berardi, D. E., & Macleod, K. F. (2021). ULK1 promotes mitophagy via phosphorylation and stabilization of BNIP3. *Sci Reports, 11*, 20526.

Potes, Y., Bermejo-Millo, J. C., Mendes, C., Castelão-Baptista, J. P., Díaz-Luis, A., Pérez-Martínez, Z., ... Vega-Naredo, I. (2024). p66Shc signaling and autophagy impact on C2C12 myoblast differentiation during senescence. *Cell Death & Disease, 15*, 200.

Potes, Y., Díaz-Luis, A., Bermejo-Millo, J. C., Pérez-Martínez, Z., de Luxán-Delgado, B., Rubio-González, A., ... Coto-Montes, A. (2023). Melatonin alleviates the impairment of muscle bioenergetics and protein quality control systems in leptin-deficiency-induced obesity. *Antioxidants (Basel), 12*, 1962.

Potes, Y., de Luxán-Delgado, B., Rodriguez-González, S., Guimarães, M. R. M., Solano, J. J., Fernández-Fernández, M., ... Coto-Montes, A. (2017). Overweight in elderly people induces impaired autophagy in skeletal muscle. *Free Radical Biology & Medicine, 110*, 31–41.

Potes, Y., Pérez-Martinez, Z., Bermejo-Millo, J. C., Rubio-Gonzalez, A., Fernandez-Fernández, M., Bermudez, M., ... Coto-Montes, A. (2019). Overweight in the elderly induces a switch in energy metabolism that undermines muscle integrity. *Aging and Disease, 10*, 217–230.

Powers, S. K., Duarte, J., Kavazis, A. N., & Talbert, E. E. (2010). Reactive oxygen species are signalling molecules for skeletal muscle adaptation. *Experimental Physiology, 95*, 1–9.

Prokopidis, K., Giannos, P., Triantafyllidis, K. K., Kechagias, K. S., Forbes, S. C., & Candow, D. G. (2023). Effects of creatine supplementation on memory in healthy individuals: a systematic review and meta-analysis of randomized controlled trials. *Nutrition Reviews, 81*, 416–427.

Prokopidis, K., Mazidi, M., Sankaranarayanan, R., Tajik, B., McArdle, A., & Isanejad, M. (2023). Effects of whey and soy protein supplementation on inflammatory cytokines in older adults: a systematic review and meta-analysis. *The British Journal of Nutrition, 129*, 759–770.

Raffin, J., de Souto Barreto, P., Le Traon, A. P., Vellas, B., Aubertin-Leheudre, M., & Rolland, Y. (2023). Sedentary behavior and the biological hallmarks of aging. *Ageing Research Reviews, 83*, 101807.

Rai, M., & Demontis, F. (2016). Systemic nutrient and stress signaling via myokines and myometabolites. *Annual Review of Physiology, 78*, 85–107.

Ramírez-Casas, Y., Fernández-Martínez, J., Martín-Estebané, M., Aranda-Martínez, P., López-Rodríguez, A., Esquivel-Ruiz, S., ... Acuña-Castroviejo, D. (2025). Melatonin and exercise restore myogenesis and mitochondrial dynamics deficits associated with sarcopenia in iMS-Bmal1-/- Mice. *Journal of Pineal Research, 77*, e70049.

Ray, P. D., Huang, B.-W., & Tsuji, Y. (2012). Reactive oxygen species (ROS) homeostasis and redox regulation in cellular signaling. *Cellular Signalling, 24*, 981–990.

Reggiori, F., & Ungermann, C. (2017). Autophagosome Maturation and Fusion. *Journal of Molecular Biology, 429*, 486–496.

Riccio, V., Demers, N., Hua, R., Vissa, M., Cheng, D. T., Strilchuk, A. W., ... Kim, P. K. (2019). Deubiquitinating enzyme USP30 maintains basal peroxisome abundance by regulating pexophagy. *The Journal of Cell Biology, 218*, 798–807.

Roberts, F. L., & Markby, G. R. (2021). New insights into molecular mechanisms mediating adaptation to exercise; A review focusing on mitochondrial biogenesis, mitochondrial function, mitophagy and autophagy. *Cells, 10*, 2639.

Roberts, S. B., Silver, R. E., Das, S. K., Fielding, R. A., Gilhooly, C. H., Jacques, P. F., ... Booth, S. (2021). Healthy aging-nutrition matters: Start early and screen often. *Advances in Nutrition, 12*, 1438–1448.

Rodney, G. G., Pal, R., & Abo-Zahrah, R. (2016). Redox regulation of autophagy in skeletal muscle. *Free Radical Biology & Medicine, 98*, 103–112.

Ron, D., & Walter, P. (2007). Signal integration in the endoplasmic reticulum unfolded protein response. *Nature Reviews. Molecular Cell Biology, 8*, 519–529.

Rubinstein, A. D., & Kimchi, A. (2012). Life in the balance - a mechanistic view of the crosstalk between autophagy and apoptosis. *Journal of Cell Science, 125*, 5259–5268.

Runwal, G., Stamatakou, E., Siddiqi, F. H., Puri, C., Zhu, Y., & Rubinsztein, D. C. (2019). LC3-positive structures are prominent in autophagy-deficient cells. *Scientific Reports, 9*, 10147.

Rustom, A., Saffrich, R., Markovic, I., Walther, P., & Gerdes, H.-H. (2004). Nanotubular highways for intercellular organelle transport. *Science (New York, N. Y.), 303*, 1007–1010.

Sáenz, A., Azpitarte, M., Armañanzas, R., Leturcq, F., Alzualde, A., Inza, I., ... López de Munain, A. (2008). Gene expression profiling in limb-girdle muscular dystrophy 2A. *PLoS One, 3*, e3750.

Sanchez-Martin, P., Lahuerta, M., Viana, R., Knecht, E., & Sanz, P. (2020). Regulation of the autophagic PI3KC3 complex by laforin/malin E3-ubiquitin ligase, two proteins involved in Lafora disease. *Biochimica et Biophysica Acta: Molecular Cell Research, 1867*, 118613.

Sartori, R., Romanello, V., & Sandri, M. (2021). Mechanisms of muscle atrophy and hypertrophy: Implications in health and disease. *Nature Communications, 12*, 330.

Sayer, A. A., & Cruz-Jentoft, A. (2022). Sarcopenia definition, diagnosis and treatment: consensus is growing. *Age and Ageing, 51*, afac220.

Schäfer, J. A., Schessner, J. P., Bircham, P. W., Tsuji, T., Funaya, C., Pajonk, O., ... Schuck, S. (2020). ESCRT machinery mediates selective microautophagy of endoplasmic reticulum in yeast. *The EMBO Journal, 39*, e102586.

Schuck, S., Gallagher, C. M., & Walter, P. (2014). ER-phagy mediates selective degradation of endoplasmic reticulum independently of the core autophagy machinery. *Journal of Cell Science, 127*, 4078–4088.

Schytz, C. T., Ørtenblad, N., Lundby, A.-K. M., Jacobs, R. A., Nielsen, J., & Lundby, C. (2024). Skeletal muscle mitochondria demonstrate similar respiration per cristae surface area independent of training status and sex in healthy humans. *The Journal of Physiology, 602*, 129–151.

Seabright, A. P., Fine, N. H. F., Barlow, J. P., Lord, S. O., Musa, I., Gray, A., ... Lai, Y.-C. (2020). AMPK activation induces mitophagy and promotes mitochondrial fission while activating TBK1 in a PINK1-Parkin independent manner. *The FASEB Journal, 34*, 6284–6301.

Sebastián, D., & Zorzano, A. (2020). Self-eating for muscle fitness: Autophagy in the control of energy metabolism. *Developmental Cell, 54*, 268–281.

Senft, D., & Ronai, Z. A. (2015). UPR, autophagy, and mitochondria crosstalk underlies the ER stress response. *Trends in Biochemical Sciences, 40*, 141–148.

Settembre, C., Fraldi, A., Medina, D. L., & Ballabio, A. (2013). Signals from the lysosome: A control centre for cellular clearance and energy metabolism. *Nature Reviews. Molecular Cell Biology, 14*, 283–296.

Settembre, C., & Perera, R. M. (2024). Lysosomes as coordinators of cellular catabolism, metabolic signalling and organ physiology. *Nature Reviews. Molecular Cell Biology, 25*, 223–245.

Severinsen, M. C. K., & Pedersen, B. K. (2020). Muscle-organ crosstalk: The emerging roles of myokines. *Endocrine Reviews, 41*, 594–609.

Shariq, M., Khan, M. F., Raj, R., Ahsan, N., & Kumar, P. (2024). PRKAA2, MTOR, and TFEB in the regulation of lysosomal damage response and autophagy. *The Journal of Molecular Medicine (Berl), 102*, 287–311.

Shen, Q., Shi, Y., Liu, J., Su, H., Huang, J., Zhang, Y., ... Liu, W. (2021). Acetylation of STX17 (syntaxin 17) controls autophagosome maturation. *Autophagy, 17*, 1157–1169.

Shen, Y., Shi, Q., Nong, K., Li, S., Yue, J., Huang, J., ... Hao, Q. (2023). Exercise for sarcopenia in older people: A systematic review and network meta-analysis. *The Journal of Cachexia, Sarcopenia and Muscle, 14*, 1199–1211.

Slavin, M. B., Kumari, R., & Hood, D. A. (2022). ATF5 is a regulator of exercise-induced mitochondrial quality control in skeletal muscle. *Molecular Metabolism, 66*, 101623.

Smith, M. D., Harley, M. E., Kemp, A. J., Wills, J., Lee, M., Arends, M., ... Wilkinson, S. (2018). CCPG1 Is a non-canonical autophagy cargo receptor essential for ER-Phagy and pancreatic ER proteostasis. *Developmental Cell, 44*, 217–232.e11.

Song, S., Tan, J., Miao, Y., Li, M., & Zhang, Q. (2017). Crosstalk of autophagy and apoptosis: Involvement of the dual role of autophagy under ER stress. *Journal of Cellular Physiology, 232*, 2977–2984.

Song, Z., Moore, D. R., Hodson, N., Ward, C., Dent, J. R., O'Leary, M. F., ... Philp, A. (2017). Resistance exercise initiates mechanistic target of rapamycin (mTOR) translocation and protein complex co-localisation in human skeletal muscle. *Scientific Reports, 7*, 5028.

Spendiff, S., Vuda, M., Gouspillou, G., Aare, S., Perez, A., Morais, J. A., ... Hepple, R. T. (2016). Denervation drives mitochondrial dysfunction in skeletal muscle of octogenarians. *The Journal of Physiology, 594*, 7361–7379.

Strappazzon, F., Vietri-Rudan, M., Campello, S., Nazio, F., Florenzano, F., Fimia, G. M., ... Cecconi, F. (2011). Mitochondrial BCL-2 inhibits AMBRA1-induced autophagy. *The EMBO Journal, 30*, 1195–1208.

Su, C.-M., Tsai, C.-H., Chen, H.-T., Wu, Y.-S., Chang, J.-W., Yang, S.-F., & Tang, C.-H. (2023). Melatonin improves muscle injury and differentiation by increasing Pax7 expression. *International Journal of Biological Sciences, 19*, 1049–1062.

Summermatter, S., Santos, G., Pérez-Schindler, J., & Handschin, C. (2013). Skeletal muscle PGC-1α controls whole-body lactate homeostasis through estrogen-related receptor α-dependent activation of LDH B and repression of LDH A. *Proceedings of the National Academy of Sciences of the United States of America, 110*, 8738–8743.

Sun, W.-L. (2016). Ambra1 in autophagy and apoptosis: Implications for cell survival and chemotherapy resistance. *Oncology Letters, 12*, 367–374.

Suryawan, A., Rudar, M., Fiorotto, M. L., & Davis, T. A. (2020). Differential regulation of mTORC1 activation by leucine and β-hydroxy-β-methylbutyrate in skeletal muscle of neonatal pigs. *Journal of Applied Physiology (1985), 128*, 286–295.

Tábara, L. C., Burr, S. P., Frison, M., Chowdhury, S. R., Paupe, V., Nie, Y., ... Prudent, J. (2024). MTFP1 controls mitochondrial fusion to regulate inner membrane quality control and maintain mtDNA levels. *Cell, 187*, 3619–3637.e27.

Tábara, L.-C., Segawa, M., & Prudent, J. (2025). Molecular mechanisms of mitochondrial dynamics. *Nature Reviews. Molecular Cell Biology, 26*, 123–146.

Tan, D.-X., Manchester, L. C., Esteban-Zubero, E., Zhou, Z., & Reiter, R. J. (2015). Melatonin as a potent and inducible endogenous antioxidant: Synthesis and metabolism. *Molecules (Basel, Switzerland), 20*, 18886–18906.

Tang, H., Huang, Z., Wang, M., Luan, X., Deng, Z., Xu, J., ... Zhou, J. (2024). Research progress of migrasomes: From genesis to formation, physiology to pathology. *Frontiers in Cell and Developmental Biology, 12*, 1420413.

Taranum, S., Vaylann, E., Meinke, P., Abraham, S., Yang, L., Neumann, S., ... Noegel, A. A. (2012). LINC complex alterations in DMD and EDMD/CMT fibroblasts. *European Journal of Cell Biology, 91*, 614–628.

Terešak, P., Lapao, A., Subic, N., Boya, P., Elazar, Z., & Simonsen, A. (2022). Regulation of PRKN-independent mitophagy. *Autophagy, 18*, 24–39.

Thomas, E., Battaglia, G., Patti, A., Brusa, J., Leonardi, V., Palma, A., & Bellafiore, M. (2019). Physical activity programs for balance and fall prevention in elderly: A systematic review. *Medicine, 98*, e16218.

Tieland, M., Franssen, R., Dullemeijer, C., van Dronkelaar, C., Kyung Kim, H., Ispoglou, T., ... de Groot, L. C. P. G. M. (2017). The Impact of dietary protein or amino acid supplementation on muscle mass and strength in elderly people: Individual Participant Data and Meta-Analysis of RCT's. *The Journal of Nutrition, Health & Aging, 21*, 994–1001.

Tilokani, L., Nagashima, S., Paupe, V., & Prudent, J. (2018). Mitochondrial dynamics: Overview of molecular mechanisms. *Essays in Biochemistry, 62*, 341–360.

Tokizane, K., & Imai, S.-I. (2024). Inter-organ communication is a critical machinery to regulate metabolism and aging. *Trends in Endocrinology and Metabolism: TEM, S1043-2760*(24), 00320–00325.

Twig, G., Elorza, A., Molina, A. J. A., Mohamed, H., Wikstrom, J. D., Walzer, G., ... Shirihai, O. S. (2008). Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. *The EMBO Journal, 27*, 433–446.

Unuma, K., Aki, T., Funakoshi, T., Hashimoto, K., & Uemura, K. (2015). Extrusion of mitochondrial contents from lipopolysaccharide-stimulated cells: Involvement of autophagy. *Autophagy, 11*, 1520–1536.

Valls, A., Ruiz-Roldán, C., Immanuel, J., Alonso-Martín, S., Gallardo, E., Fernández-Torrón, R., ... Sáenz, A. (2025). The role of integrin β1D mislocalization in the pathophysiology of calpain 3-related limb-girdle muscular dystrophy. *Cells, 14*, 446.

Valls, P. O., & Esposito, A. (2022). Signalling dynamics, cell decisions, and homeostatic control in health and disease. *Current Opinion in Cell Biology, 75*, 102066.

Vargas, J. N. S., Hamasaki, M., Kawabata, T., Youle, R. J., & Yoshimori, T. (2023). The mechanisms and roles of selective autophagy in mammals. *Nature Reviews. Molecular Cell Biology, 24*, 167–185.

Vattem, K. M., & Wek, R. C. (2004). Reinitiation involving upstream ORFs regulates ATF4 mRNA translation in mammalian cells. *Proceedings of the National Academy of Sciences of the United States of America, 101*, 11269–11274.

Vega-Naredo, I., Caballero, B., Sierra, V., García-Macia, M., de Gonzalo-Calvo, D., Oliveira, P. J., ... Coto-Montes, A. (2012). Melatonin modulates autophagy through a redox-mediated action in female Syrian hamster Harderian gland controlling cell types and gland activity. *Journal of Pineal Research, 52*, 80–92.

Villa, E., Marchetti, S., & Ricci, J.-E. (2018). No Parkin Zone: Mitophagy without Parkin. *Trends in Cell Biology, 28*, 882–895.

Villareal, M. O., Matsukawa, T., & Isoda, H. (2018). l-Citrulline supplementation-increased skeletal muscle PGC-1α expression is associated with exercise performance and increased skeletal muscle weight. *Molecular Nutrition & Food Research, 62*, e1701043.

Wackerhage, H., Schoenfeld, B. J., Hamilton, D. L., Lehti, M., & Hulmi, J. J. (2019). Stimuli and sensors that initiate skeletal muscle hypertrophy following resistance exercise. *Journal of Applied Physiology (1985), 126*, 30–43.

Wall, B. T., Dirks, M. L., Snijders, T., van Dijk, J.-W., Fritsch, M., Verdijk, L. B., & van Loon, L. J. C. (2016). Short-term muscle disuse lowers myofibrillar protein synthesis rates and induces anabolic resistance to protein ingestion. *American Journal of Physiology Endocrinology and Metabolism, 310*, E137–E147.

Wanders, R. J. A., Baes, M., Ribeiro, D., Ferdinandusse, S., & Waterham, H. R. (2023). The physiological functions of human peroxisomes. *Physiological Reviews, 103*, 957–1024.

Wang, H., Li, X., Zhang, Q., Fu, C., Jiang, W., Xue, J., ... Liang, W. (2024). Autophagy in disease onset and progression. *Aging and Disease, 15*, 1646–1671.

Wang, L., Klionsky, D. J., & Shen, H.-M. (2023). The emerging mechanisms and functions of microautophagy. *Nature Reviews. Molecular Cell Biology, 24*, 186–203.

Wang, R., Li, K., Sun, L., Jiao, H., Zhou, Y., Li, H., ... Lin, H. (2022). L-Arginine/nitric oxide regulates skeletal muscle development via muscle fibre-specific nitric oxide/mTOR pathway in chickens. *Animal Nutrition, 10*, 68–85.

Wang, S., Long, H., Hou, L., Feng, B., Ma, Z., Wu, Y., ... Zhao, G. (2023). The mitophagy pathway and its implications in human diseases. *Signal Transduction and Targeted Therapy, 8*, 304.

Wang, X., & Gerdes, H.-H. (2015). Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. *Cell Death and Differentiation, 22*, 1181–1191.

Waskiw-Ford, M., Hannaian, S., Duncan, J., Kato, H., Abou Sawan, S., Locke, M., ... Moore, D. (2020). Leucine-enriched essential amino acids improve recovery from post-exercise muscle damage independent of increases in integrated myofibrillar protein synthesis in young men. *Nutrients, 12*, 1061.

Wen, H., Deng, H., Li, B., Chen, J., Zhu, J., Zhang, X., ... Zhou, Y. (2025). Mitochondrial diseases: From molecular mechanisms to therapeutic advances. *Signal Transduction and Targeted Therapy, 10*(9).

van Westering, T. L. E., Johansson, H. J., Hanson, B., Coenen-Stass, A. M. L., Lomonosova, Y., Tanihata, J., ... Roberts, T. C. (2020). Mutation-independent proteomic signatures of pathological progression in murine models of duchenne muscular dystrophy. *Molecular & Cellular Proteomics: MCP, 19*, 2047–2068.

Wiedmer, P., Jung, T., Castro, J. P., Pomatto, L. C. D., Sun, P. Y., Davies, K. J. A., & Grune, T. (2021). Sarcopenia - Molecular mechanisms and open questions. *Ageing Research Reviews, 65*, 101200.

Wild, P., McEwan, D. G., & Dikic, I. (2014). The LC3 interactome at a glance. *Journal of Cell Science, 127*, 3–9.

Wilkinson, S. (2019). ER-phagy: shaping up and destressing the endoplasmic reticulum. *The FEBS Journal, 286*, 2645–2663.

Williams, A. B., & Schumacher, B. (2016). p53 in the DNA-Damage-Repair Process. *Cold Spring Harb Perspect Med, 6*, a026070.

Wolfe, R. R. (2017). Branched-chain amino acids and muscle protein synthesis in humans: myth or reality? *Journal of the International Society of Sports Nutrition, 14*, 30.

Wolfe, R. R. (2006). The underappreciated role of muscle in health and disease. *The American Journal of Clinical Nutrition, 84*, 475–482.

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W., ... Feng, D. (2014). ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Reports, 15*, 566–575.

Xia, Q., Huang, X., Huang, J., Zheng, Y., March, M. E., Li, J., & Wei, Y. (2021). The role of autophagy in skeletal muscle diseases. *Frontiers in Physiology, 12*, 638983.

Yamakawa, H., Kusumoto, D., Hashimoto, H., & Yuasa, S. (2020). Stem cell aging in skeletal muscle regeneration and disease. *International Journal of Molecular Sciences, 21*, E1830.

Yamamoto, H., & Matsui, T. (2024). Molecular mechanisms of macroautophagy, microautophagy, and chaperone-mediated autophagy. *Journal of Nippon Medical School = Nihon Ika Daigaku Zasshi, 91*, 2–9.

Yamashita, S., Abe, K., Tatemichi, Y., & Fujiki, Y. (2014). The membrane peroxin PEX3 induces peroxisome-ubiquitination-linked pexophagy. *Autophagy, 10*, 1549–1564.

Yao, R.-Q., Ren, C., Xia, Z.-F., & Yao, Y.-M. (2021). Organelle-specific autophagy in inflammatory diseases: a potential therapeutic target underlying the quality control of multiple organelles. *Autophagy, 17*, 385–401.

Yao, Y., Luo, Y., Liang, X., Zhong, L., Wang, Y., Hong, Z., ... Zhang, M. (2025). The role of oxidative stress-mediated fibro-adipogenic progenitor senescence in skeletal muscle regeneration and repair. *Stem Cell Research & Therapy, 16*, 104.

Yasuda, T., Ishihara, T., Ichimura, A., & Ishihara, N. (2023). Mitochondrial dynamics define muscle fiber type by modulating cellular metabolic pathways. *Cell Reports, 42*, 112434.

Yoo, Y.-S., Park, Y.-J., Lee, H.-S., Oanh, N. T. K., Cho, M.-Y., Heo, J., ... Cho, H. (2019). Mitochondria ubiquitin ligase, MARCH5 resolves hepatitis B virus X protein aggregates in the liver pathogenesis. *Cell Death & Disease, 10*, 938.

Youle, R. J., & van der Bliek, A. M. (2012). Mitochondrial fission, fusion, and stress. *Science (New York, N. Y.), 337*, 1062–1065.

Yu, G., & Klionsky, D. J. (2024). In vitro and in vivo reconstitution systems reveal the membrane remodeling ability of LC3B and ATG16L1 to form phagophore-like membrane cups. *Autophagy, 20*, 2359–2360.

Yun, H. R., Jo, Y. H., Kim, J., Shin, Y., Kim, S. S., & Choi, T. G. (2020). Roles of autophagy in oxidative stress. *International Journal of Molecular Sciences, 21*, 3289.

Zachari, M., & Ganley, I. G. (2017). The mammalian ULK1 complex and autophagy initiation. *Essays in Biochemistry, 61*, 585–596.

Zamudio-Martinez, E., Herrera-Campos, A. B., Muñoz, A., Rodríguez-Vargas, J. M., & Oliver, F. J. (2021). Tankyrases as modulators of pro-tumoral functions: molecular insights and therapeutic opportunities. *Journal of Experimental & Clinical Cancer Research: CR, 40*, 144.

Zhang, L., & Bu, P. (2022). The two sides of creatine in cancer. *Trends in Cell Biology, 32*, 380–390.

Zhang, Y., Nicholatos, J., Dreier, J. R., Ricoult, S. J. H., Widenmaier, S. B., Hotamisligil, G. S., ... Manning, B. D. (2014). Coordinated regulation of protein synthesis and degradation by mTORC1. *Nature, 513*, 440–443.

Zhou, H.-H., Liao, Y., Zhou, X., Peng, Z., Xu, S., Shi, S., ... Yang, W. (2024). Effects of timing and types of protein supplementation on improving muscle mass, strength, and physical performance in adults undergoing resistance training: A network meta-analysis. *International Journal of Sport Nutrition and Exercise Metabolism, 34*, 54–64.

Zhou, S., Han, L., & Wu, Z. (2022). A long journey before cycling: Regulation of quiescence exit in adult muscle satellite cells. *International Journal of Molecular Sciences, 23*, 1748.

Zhou, Z., Liu, J., Fu, T., Wu, P., Peng, C., Gong, X., ... Pan, L. (2021). Phosphorylation regulates the binding of autophagy receptors to FIP200 Claw domain for selective autophagy initiation. *Nature Communications, 12*, 1570.

Zhu, G.-Z., Zhao, K., Li, H.-Z., Wu, D.-Z., Chen, Y.-B., Han, D., ... Zhong, Z.-M. (2024). Melatonin ameliorates age-related sarcopenia by inhibiting fibrogenic conversion of satellite cell. *Molecular Medicine (Cambridge, Mass.), 30*, 238.

Zong, Y., Li, H., Liao, P., Chen, L., Pan, Y., Zheng, Y., ... Gao, J. (2024). Mitochondrial dysfunction: Mechanisms and advances in therapy. *Signal Transduction and Targeted Therapy, 9*, 124.

Zurzolo, C. (2021). Tunneling nanotubes: Reshaping connectivity. *Current Opinion in Cell Biology, 71*, 139–147.