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INVITED REVIEW

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Selective autophagy pathways in ageing and neurodegeneration: Emerging roles for mitophagy and nucleophagy

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Ageing is characterized by the progressive accumulation of molecular and cellular damage, driven by both genetic and nongenetic factors and ultimately leading to functional decline and an increased risk of disease. Convergent evidence indicates that many of the mechanisms influencing ageing are intimately related to the ability of the organism to cope with intrinsic and extrinsic stress. Key determinants of this capacity are the molecular pathways that coordinate stress responses throughout life. Among these, general and cargo-specific autophagy have emerged as integral components of cellular and systemic adaptation to stress. Here, we focus on mitophagy, a selective form of autophagy targeting mitochondria, and nucleophagy, the selective autophagic recycling of nuclear material. These processes help safeguard the integrity of two organelles that are central to long-term cellular

Abbreviations
AD, Alzheimer's disease; AIM, Atg8-family interacting motif; ALS, amyotrophic lateral sclerosis; AMBRA1, autophagy/Beclin-1 regulator 1; ANC-1, abnormal nuclear anchorage protein 1; ATG8, autophagy-related protein 8; ATP13A2, ATPase 13A2, lysosomal type 5; BECN1, beclin 1; BNIP3, BCL2/adenovirus E1B 19 kDa protein-interacting protein; C9ORF72, chromosome 9 open reading frame 72; CALCOCO2/NDP52, calcium-binding and coiled-coil domain-containing protein 2/nuclear dot protein 52; CCFs, cytoplasmic chromatin fragments; cGAS/STING, cyclic GMP-AMP synthase/stimulator of interferon genes; CMA, chaperone-mediated autophagy; DAF-2, dauer formation-2, an insulin/IGF-1 receptor homologue; DCT-1, DAF-16/FOXO-controlled, germline tumour affecting-1; DJ-1, Parkinsonism-associated deglycase (PARK7); DRP1, dynamin-related protein 1; DRPLA, dentatorubral-pallidoluysian atrophy; EAT-2, eating abnormal-2, nicotinic acetylcholine receptor subunit; ER, endoplasmic reticulum; FBXO7, F-box only protein 7; FOXO3α, forkhead box O3 alpha; FTD, frontotemporal dementia; FUNDC1, FUN14 domain-containing protein 1; FUS, RNA-binding protein; FXTAS, fragile X-associated tremor/ataxia syndrome; GABARAP, GABA type A receptor-associated protein; HD, Huntington's disease; HTT, huntingtin; IMM, inner mitochondrial membrane; INM, inner nuclear membrane; INMDV, INM-derived vesicle; LC3, microtubule-associated protein 1 light chain 3; LGG-1, GABA type A receptor-associated protein (GABARAP) homologue; LIR, LC3-interacting region; LN, late nucleophagy; LRRK2, leucine-rich repeat kinase 2; MICOS, mitochondrial contact site and cristae organizing system; MPP, mitochondrial processing peptidase; MTX1, metaxin 1; NAD^+, nicotinamide adenine dinucleotide; NBR1, neighbour of BRCA1 gene 1; NIX/BNIP3L, BCL2 interacting protein 3 like; NPC, nuclear pore complex; NRF2, nuclear factor erythroid 2–related factor 2; OMA1, Overlapping activity with m-AAA protease 1 homologue; OMM, outer mitochondrial membrane; ONM, outer nuclear membrane; OPTN, optineurin; PABPN1, poly(A) binding protein nuclear 1; PAM, presequence translocase-associated import motor; PARL, presenilin-associated rhomboid-like protein; PARP1, poly(ADP-ribose) polymerase 1; PARPi, PARP inhibitor; PD, Parkinson's disease; PDR-1, Parkinson disease related-1; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 α; PINK1, PTEN-induced putative kinase 1; PMN, piecemeal micronucleophagy; PRKN, parkin RBR E3 ubiquitin protein ligase; ROS, reactive oxygen species; SAM, sorting and assembly machinery; SAMM50, stands for sorting and assembly machinery component 50 homologue; SCA1, spinocerebellar ataxia type 1; SIRT1, sirtuin 1; SIRT3, sirtuin 3; SKN-1, skinhead-1; SOD1, superoxide dismutase 1; SQSTM1, sequestosome 1; TARDBP, TAR DNA-binding protein 43; TBK1, TANK-binding kinase 1; TEX264, testis expressed gene 264; TIM23, translocase of the inner membrane 23; TOM, translocase of the outer membrane; TORC1, target of rapamycin complex 1; Ub, ubiquitin; ULK1, unc-51-like autophagy activating kinase 1; USP15, ubiquitin specific peptidase 15; USP30, ubiquitin specific peptidase 30; USP8, ubiquitin specific peptidase 8; VPS35, vacuolar protein sorting 35 homologue; XPO-1, exportin-1.

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survival and function. Such homeostatic mechanisms are vital in long-lived neurons, where they mediate damage removal during ageing to protect against neurodegeneration. We further discuss how perturbations in these autophagic pathways may contribute to ageing and neurodegenerative disorders. Finally, we outline key open questions and future challenges in the field, including the largely unexplored possibility of functional connections between mitophagy and nucleophagy, which we identify as an important direction for future research.

Introduction

Ageing in diverse species ranging from yeast to humans is driven by the gradual accumulation of molecular and cellular damage over time that eventually compromises physiological function and increases susceptibility to disease [1,2]. Although this process is partially stochastic, studies in model organisms have revealed that ageing is also regulated by evolutionarily conserved genetic pathways and biochemical processes [3]. In addition, nongenetic factors, including dietary interventions and extrinsic stressors, have a substantial impact on ageing outcomes [4]. A key feature of ageing is the limited capacity of maintenance, repair and turnover pathways, resulting in the accumulation of damaged macromolecules and organelles. Among these pathways, autophagy plays a central role in maintaining cellular and organismal homeostasis [5–7].

Autophagy is a conserved lysosome-dependent degradation pathway involved in the elimination of injured or dysfunctional organelles, protein aggregates and intracellular pathogens, among others. Operating under basal conditions as well as in response to stress, autophagy is essential for maintaining cellular quality control and enabling adaptation to fluctuating physiological environments [8–10]. Three distinct classes of autophagy have been described: microautophagy, chaperone-mediated autophagy (CMA) and macroautophagy [11]. Macroautophagy, hereafter referred to as autophagy, is the major type of autophagic recycling and differs from the other two types in that substrates are sequestered by an isolation membrane (the phagophore), which elongates and eventually seals to engulf cargo, forming a double-membrane structure, the autophagosome. Autophagosomes then fuse with lysosomes to form autolysosomes, in which hydrolytic degradation of autophagosome contents occurs [11].

In addition to bulk degradation of cytosolic proteins and macromolecular complexes, autophagy selectively targets superfluous and damaged organelles, including mitochondria, peroxisomes and the nucleus, as well as lipids and invasive microbes. These forms of selective autophagy are known as mitophagy, pexophagy, nucleophagy, lipophagy and xenophagy, respectively, and are vital for protecting against cellular damage associated with ageing [12]. The core autophagy machinery includes the ATG8 family of ubiquitin-like proteins, which become lipidated and associate with the phagophore and autophagosome membranes to facilitate cargo sequestration and autophagosome maturation. In mammals, the ATG8 family comprises the LC3 and GABARAP subfamilies, which perform overlapping yet distinct functions in autophagosome biogenesis and selective cargo degradation. During selective autophagy, substrate specificity is conferred by selective autophagy receptors, such as p62/SQSTM1 (sequestosome 1) and NBR1 (neighbour of BRCA1 gene 1), which bind ubiquitinated cargo while simultaneously interacting with ATG8 proteins through LC3-interacting region (LIR) motifs [10,13–17].

Beyond the core autophagy machinery, regulation at the transcriptional level enables cells to adjust autophagic capacity in response to changing physiological and environmental demands [18–20]. By inducing the expression of genes involved in autophagy and cellular stress responses, transcriptional programmes promote the clearance of damaged cellular components while supporting the metabolic adaptations required for survival under stress [21]. In *Caenorhabditis elegans*, for example, the transcription factor SKN-1, an orthologue of mammalian NRF2, regulates the expression of genes involved in proteostasis, detoxification and autophagy, thereby promoting stress resistance and longevity [18].

Despite these regulatory mechanisms, autophagic activity generally declines with age and impaired autophagy often correlates with accelerated ageing and numerous age-associated diseases [22]. Age-related alterations have also been reported in multiple forms of selective autophagy. Among these, mitophagy and nucleophagy have attracted considerable attention in recent years because of their important roles in maintaining mitochondrial and nuclear integrity,

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respectively. Mitochondria coordinate cellular energy production, support biosynthetic processes and act as signalling hubs that orchestrate cellular stress responses [23,24]. The nucleus safeguards genome integrity and controls gene expression, while alterations in nuclear morphology and architecture have emerged as conserved features of ageing [25,26]. Thus, preserving organelle integrity through mitophagy and nucleophagy, together with other quality control mechanisms, is crucial for sustaining cellular fitness during ageing. These pathways are particularly important in long-lived neurons, where they mediate the removal of damaged mitochondria and nuclear components, thereby supporting neuronal homeostasis and protecting against neurodegeneration.

Mitochondria and the nucleus communicate extensively through bidirectional signalling pathways that coordinate cellular responses to stress [27]. Whether the selective autophagy pathways that maintain these organelles are similarly coordinated, however, remains largely unknown. Although recent studies have substantially advanced our understanding of mitophagy and its roles in ageing and numerous neurodegenerative disorders, nucleophagy remains comparatively understudied, despite emerging evidence implicating it in nuclear maintenance, cellular senescence, ageing and disease. In this review, we discuss recent advances in mitophagy and nucleophagy research, placing emphasis on their roles in ageing and age-related neurodegeneration. Given their distinct biological functions and the current state of mechanistic understanding, we examine these pathways separately rather than focusing on their potential crosstalk. Finally, we highlight key open questions that need to be addressed before modulation of these organelle-specific autophagy pathways can be considered as a therapeutic strategy for age-related pathologies.

Mitophagy pathways in the context of ageing and neurodegeneration

Besides their well-established roles as bioenergetic and biosynthetic organelles, mitochondria also function as signalling hubs in eukaryotic cells [28], participating in processes, such as reactive oxygen species (ROS) production [29], apoptosis [30], regulation of Ca^{2+} signalling [31], innate immunity [32,33] and fatty acid metabolism [34]. Thus, maintaining a healthy mitochondrial population is essential for cellular and organismal homeostasis. Mitochondrial content, distribution and function vary across cell types in accordance with their specific energetic and metabolic needs. In polarized cells such as neurons, mitochondrial transport along cytoskeletal filaments is essential for matching mitochondrial localization to local energy requirements in the cell body, axons and dendrites [35].

Beyond cell-type-specific requirements, mitochondrial homeostasis must be dynamically regulated to support cellular function and organismal metabolic adaptation to both intrinsic and extrinsic cues. At the cellular level, maintenance of a proper mitochondrial pool depends on the balance between mitochondrial biogenesis and degradation through mitophagy, together with fusion and fission processes that shape mitochondrial network organization. Mitophagy is a critical mitochondrial quality control mechanism whose efficiency and regulation during ageing appear to be context-dependent [36–38]. This is particularly relevant to postmitotic cells such as neurons and cardiomyocytes, which must persist throughout the organism's lifespan. Determining the contribution of defective or dysregulated mitophagy to ageing and age-related pathologies is therefore of considerable importance, given the central role of mitochondria in neuronal function and survival, as well as the broader contribution of neurons to whole-body energy homeostasis [39]. Despite substantial progress, the molecular mechanisms governing mitophagy, particularly under physiological conditions, remain incompletely understood. Nevertheless, recent advances in the characterization of mitophagy regulators, together with the development of improved experimental models, have provided critical insights into the pathways that mediate mitochondrial turnover under both basal and stress conditions. These pathways are broadly classified as ubiquitin (Ub)-dependent and receptor-mediated pathways (Fig. 1), which together contribute to mitochondrial quality control. Dysregulation of these pathways has been implicated in ageing and several neurodegenerative disorders. Comprehensive reviews of these mechanisms are available elsewhere [40–44].

The best-characterized Ub-dependent mitophagy pathway is the PTEN-induced putative kinase 1 (PINK1)–Parkin pathway (Fig. 1A). Notably, homologues of PINK1 and Parkin have not yet been identified in yeast [45]. Under physiological conditions, the PINK1 precursor is targeted to mitochondria via the translocase of the outer membrane (TOM) complex and subsequently imported through the translocase of the inner membrane 23 (TIM23) complex. Its N-terminal mitochondrial targeting sequence (MTS) is cleaved by the mitochondrial processing peptidase (MPP), followed by cleavage within its transmembrane (TM) domain by the inner mitochondrial membrane (IMM) protease PARL (presenilin-associated rhomboid-like protein). The PARL-cleaved PINK1

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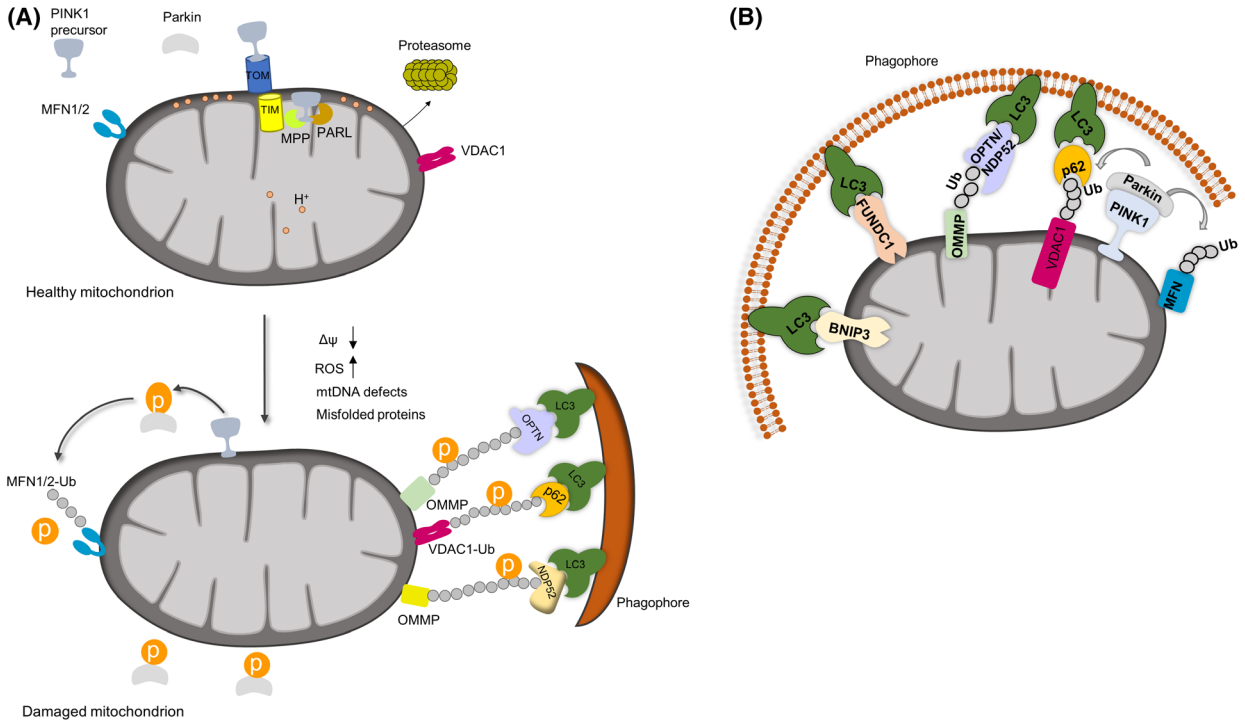


Fig. 1. Schematic overview of major mitophagy pathways. (A) Phosphatase and tensin homologue-induced putative kinase 1 (PINK1)/Parkin-dependent mitophagy. Under physiological conditions, the PINK1 precursor is targeted to mitochondria via the translocase of the outer membrane (TOM) complex and subsequently imported through the translocase of the inner membrane 23 (TIM23) complex. Its N-terminal mitochondrial targeting sequence reaches the mitochondrial matrix, where it is cleaved by the mitochondrial processing peptidase (MPP) followed by cleavage within the transmembrane domain by the inner mitochondrial membrane protease PARL (presenilin-associated rhomboid-like protease). The resulting processed PINK1 fragment is retro-translocated to the cytosol and degraded by the ubiquitin–proteasome system. Upon mitochondrial depolarization, mitochondrial import and processing of PINK1 are impaired, resulting in the stabilization and accumulation of full-length PINK1 on the outer mitochondrial membrane (OMM), where it undergoes autophosphorylation and phosphorylates ubiquitin at Ser65 and Parkin at Ser65 within its ubiquitin-like domain. Phosphorylation of ubiquitin generates phospho-ubiquitin signals that promote Parkin recruitment to the damaged mitochondrial surface, while phosphorylation of Parkin contributes to its activation. Activated Parkin ubiquitinates OMM proteins, including mitofusins (MFN1, MFN2) and voltage-dependent anion-selective channel protein 1 (VDAC1), generating ubiquitin chains that are recognized by autophagy receptors, including Optineurin (OPTN) and NDP52. These receptors bind both ubiquitinated cargo and microtubule-associated protein 1 light chain 3 (LC3) on forming autophagic membranes, thereby promoting mitophagy. (B) Receptor-mediated mitophagy. OMM receptors, such as FUN14 domain-containing 1 (FUNDC1), BCL2/adenovirus E1B 19-kDa interacting protein 3 (BNIP3) and Nip-3-like protein X (NIX), among others, directly interact with LC3 through LC3 interacting region (LIR) motifs, thereby mediating mitophagy.

fragment is retro-translocated to the cytosol, where it is degraded by the ubiquitin–proteasome system via the N-end rule pathway [46,47]. Upon mitochondrial depolarization, mitochondrial import and processing of PINK1 are impaired, resulting in the accumulation and stabilization of full-length PINK1 on the outer mitochondrial membrane (OMM). Stabilized PINK1 undergoes autophosphorylation and phosphorylates ubiquitin at Ser65 and Parkin at Ser65 within its ubiquitin-like domain. Phosphorylated ubiquitin (p-Ub) functions as a signal for Parkin recruitment, and importantly, as a critical activator of Parkin. Binding of p-Ub induces conformational changes that relieve Parkin autoinhibition and enable its E3 ubiquitin ligase activity [48,49]. Once activated, Parkin ubiquitinates additional mitochondrial substrates, generating ubiquitin chains that can be phosphorylated by PINK1. This feedforward mechanism progressively amplifies the p-Ub signal on the mitochondrial surface [49,50]. The accumulation of ubiquitin and p-Ub promotes the recruitment of autophagy receptors and downstream components of the autophagic machinery [51,52]. Recent work has shed new light on the reciprocal roles of Tom7, a component of the translocase of the TOM complex and OMA1, a mitochondrial metallopeptidase, in regulating PINK1 import and activation. Tom7 promotes PINK1 import arrest and accumulation at the OMM, whereas OMA1 selectively degrades improperly

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localized PINK1, thereby limiting its activation [53]. Importantly, PINK1-dependent mitophagy can also be triggered by defects in mitochondrial protein import and the accumulation of misfolded proteins. In this context, loss or inactivation of the presequence translocase-associated import motor (PAM) complex is sufficient to trigger mitophagy independently of mitochondrial depolarization [54].

Several alternative pathways have been described that operate independently of PINK1/Parkin, contributing to the maintenance of mitochondrial quality and quantity. These include receptor-mediated pathways (Fig. 1B) involving mitochondrial outer membrane proteins such as BNIP3 (BCL2/adenovirus E1B 19 kDa protein-interacting protein), NIX/BNIP3L (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3-like), FUNDC1 (FUN14 domain-containing protein 1) and AMBRA1 (autophagy/beclin-1 regulator-1). Under mitophagy-inducing conditions, these receptors directly interact with LC3 via their LIR motifs, promoting autophagosome recruitment to mitochondria. Further details regarding these pathways, as well as other mitophagy regulators, have been extensively reviewed elsewhere [41,45,55–58].

Although mitophagy is commonly viewed as a stress-responsive mechanism for eliminating damaged mitochondria, accumulating evidence indicates that basal mitophagy occurs under physiological conditions and is crucial for maintaining mitochondrial homeostasis and protecting against cellular senescence and ageing [59,60]. Indeed, a recent study showed that basal mitophagy is highly active in human primary cells and is diminished upon immortalization. Its regulation is mediated by the PINK1-PRKN-SQSTM1 pathway, in which SQSTM1/p62 senses superoxide-enriched mitochondria via its redox-sensitive cysteine residues, promoting its oligomerization and subsequent activation of mitophagy. Treatment with the SQSTM1-targeting small molecule STOCK1N–57 534 stimulates mitophagy in both senescent cells and primary cells derived from naturally aged donors, where mitophagy is reduced, and attenuates cellular ageing phenotypes, highlighting the potential of enhancing basal mitophagy as a strategy to promote healthy ageing [59].

A specialized form of basal mitochondrial quality control is piecemeal mitophagy, which selectively removes individual mitochondrial proteins, protein complexes or mitochondrial fragments rather than entire organelles. This housekeeping process can occur independently of mitochondrial depolarization. The OMM protein metaxin 1 (MTX1) and the sorting and assembly machinery (SAM) component SAMM50 have been implicated in piecemeal mitophagy. MTX1 interacts with LC3C and p62 to promote phagophore-mediated sequestration of mitochondrial fragments, whereas SAMM50 acts as a mitophagy receptor by recruiting ATG8 family proteins and cooperating with p62 to mediate basal piecemeal mitophagy of SAM and MICOS (mitochondrial contact site and cristae organizing system) components [61,62].

Taken together, these findings support the notion that mitophagy extends well beyond mitochondrial turnover. Indeed, efficient mitophagy preserves organelle quality surveillance and cellular homeostasis, whereas age-associated impairment of mitophagy promotes mitochondrial dysfunction and contributes to the development of several neurodegenerative disorders (Fig. 2).

Mitophagy in ageing

Mitophagy is a key mitochondrial quality control mechanism under both physiological and stress conditions. As such, it is tightly regulated to maintain a functional mitochondrial pool and support cellular and organismal homeostasis. When mitophagy is impaired or dysregulated, damaged mitochondria accumulate, leading to elevated ROS production and increased susceptibility to oxidative stress, which can contribute to cellular senescence and ageing (Fig. 2). Over the past decade, studies in model organisms have shown that mitophagy is extensively remodelled during ageing, although the direction and magnitude of these changes vary across tissues and experimental contexts [36–38]. Interestingly, recent findings challenge the assumption that mitophagy necessarily declines with ageing. Indeed, mitophagy was found to increase or remain unchanged in several organs of aged mice compared with young animals, suggesting that age-associated changes in mitophagy may differ from the broader decline in autophagy and may reflect an adaptive response to increasing mitochondrial stress and damage [63].

Consistent with a beneficial role for mitophagy in longevity, ubiquitous overexpression of Parkin extends lifespan in *Drosophila melanogaster*. Interestingly, neuron-specific overexpression of Parkin during adulthood is sufficient to prolong lifespan without compromising fertility, locomotion or feeding behaviour. Notably, long-lived Parkin-overexpressing flies exhibit reduced levels of insoluble ubiquitinated proteins, indicating improved proteostasis during ageing. They also display decreased levels of the mitochondrial fusion factor Mitofusin, a known Parkin substrate, together with enhanced mitochondrial function at advanced ages. In total, these findings suggest that Parkin overexpression enhances organismal healthspan and lifespan, likely through modulation of mitochondrial dynamics and activity [64].

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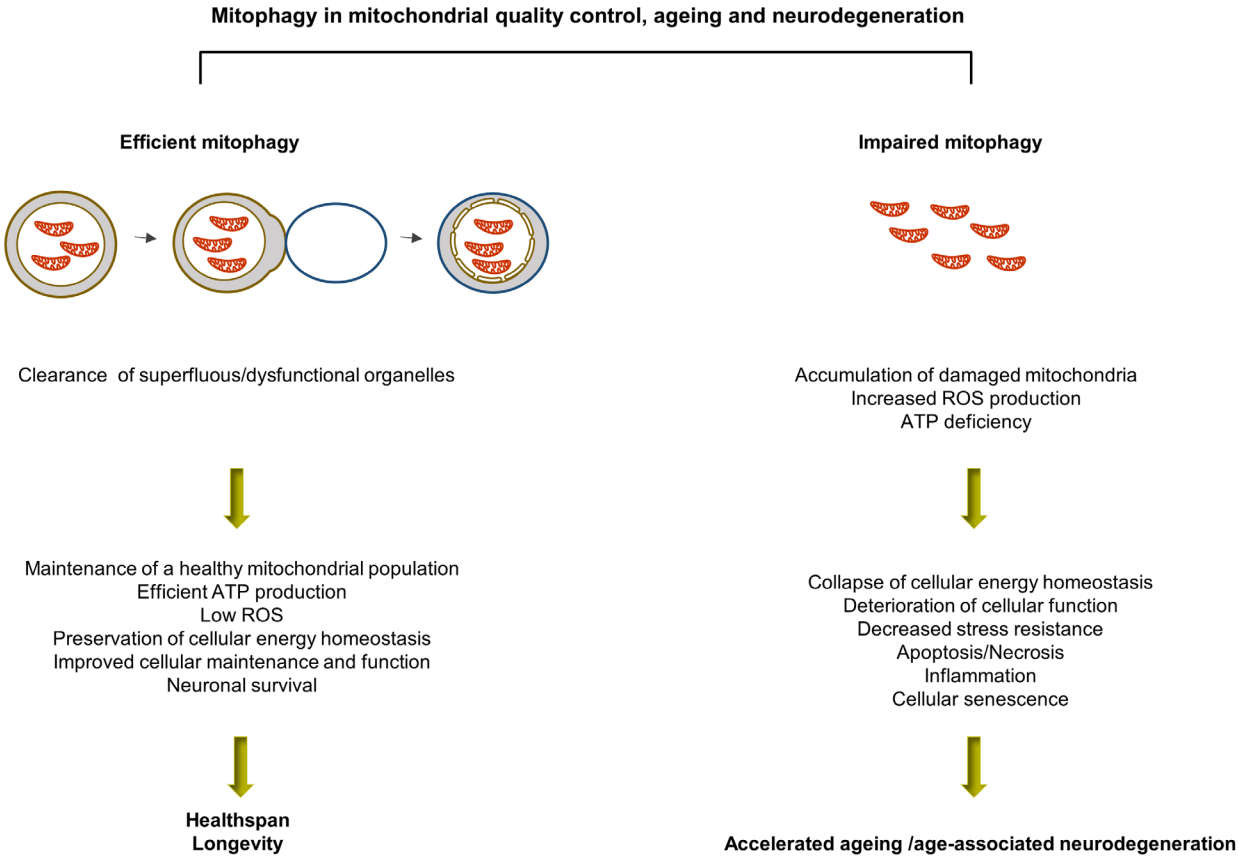


Fig. 2. Mitophagy in mitochondrial quality control, ageing and neurodegeneration. Under physiological conditions, damaged or dysfunctional mitochondria are selectively removed through mitophagy, involving their sequestration within autophagic membranes and subsequent lysosomal degradation. Efficient mitophagy preserves mitochondrial quality, limits reactive oxygen species (ROS) production, maintains cellular homeostasis and supports healthy ageing. In contrast, age-associated impairment of mitophagy leads to the progressive accumulation of dysfunctional mitochondria, resulting in mitochondrial dysfunction, increased oxidative stress, bioenergetic deficits and chronic inflammation. These alterations may promote cellular senescence, accelerate the ageing process and increase susceptibility to age-associated neurodegeneration.

Further evidence that mitophagy can increase during ageing comes from a study in *Drosophila*, which showed that mitophagy increases with age and that this increase is abolished by depletion of PINK1 or Parkin [65]. In this context, activation of mitophagy may represent a compensatory response to the progressive accumulation of mitochondrial damage during ageing. Together with the findings in aged mice described above, these observations suggest that age-associated changes in mitophagy are context-dependent and may reflect an adaptive response to mitochondrial stress rather than a uniform decline in mitophagic activity.

These findings also highlight the importance of maintaining balanced PINK1-Parkin-dependent ubiquitin signalling for mitochondrial quality control and organismal survival. In line with this, the mitochondrial deubiquitinase USP30 antagonizes Parkin function *in vivo*. Genetic inhibition of USP30 restores mitochondrial integrity in *pink1* and *parkin* mutant flies and confers organismal benefits [66]. Similarly, USP8 and USP15 localize to mitochondria, where they remove ubiquitin from Parkin substrates, thereby opposing Parkin-mediated mitophagy [67]. Taken together, these findings suggest that mitochondrial quality control during ageing depends not only on the capacity to initiate mitophagy but also on the appropriate regulation and termination of ubiquitin signalling.

In *C. elegans*, mitophagy and mitochondrial biogenesis are coordinated by DCT-1 (the orthologue of mammalian BNIP3/NIX), PDR-1/Parkin and PINK-1. Both processes are required for lifespan extension in insulin signalling-defective (*daf-2*) and dietary restriction (*eat-2*) mutants, highlighting mitophagy as a shared

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component of multiple longevity pathways. Defects in mitophagy activate SKN-1-dependent retrograde signalling. However, the coordination between mitophagy and mitochondrial biogenesis becomes disrupted with age, contributing to mitochondrial dysfunction and organismal decline [68]. Collectively, these findings suggest that healthy ageing requires appropriate coordination between mitochondrial biogenesis, turnover and stress responses rather than sustained activation of mitophagy *per se*.

Mitophagy in neurodegenerative diseases

Since neurons have large bioenergetic demands and limited regenerative capacity, maintaining a healthy mitochondrial pool is essential for neuronal function. Conversely, failure to eliminate dysfunctional mitochondria leads to energetic collapse, oxidative stress, inflammation and proteotoxicity (Fig. 2). A wealth of reports in the literature link defective mitophagy to several neurodegenerative disorders, including Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) [44,57,69,70].

In PD, mutations in PINK1 and Parkin are strongly associated with impaired mitochondrial clearance, especially in dopaminergic neurons, resulting in the accumulation of damaged mitochondria and contributing to neuronal loss. In addition, oxidative stress and impaired respiration further drive neurodegeneration, while α-synuclein aggregates interfere with mitochondrial trafficking and autophagic flux. Beyond PINK1 and Parkin, several other PD-associated proteins, including LRRK2, FBXO7, VPS35, DJ-1 and ATP13A2 have also been implicated in mitochondrial quality control [71–75]. For example, mutations in the *LRRK2* gene inhibit the degradation of the OMM protein Miro that anchors mitochondria to microtubule motors. Retention of Miro on damaged mitochondria prolongs mitochondrial motility and delays mitophagic elimination. Such defects lead to increased susceptibility to oxidative damage and neuronal deterioration, as observed in induced pluripotent stem cell-derived neurons from patients with inherited or sporadic PD [76]. Collectively, genetic, molecular and preclinical model-based evidence supports the therapeutic potential of targeting mitophagy in neurodegenerative diseases. Consistent with this concept, small-molecule-based approaches for mitophagy enhancement—namely, USP30 inhibitors and PINK1 activators—are now entering Phase I clinical trials [77]. However, the potential benefits of enhancing mitophagy may depend on disease stage and cellular context.

AD, the most common neurodegenerative disorder, is characterized by the extracellular accumulation of amyloid-β (Aβ) plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated forms of the microtubule-associated protein tau [78]. AD is strongly associated with mitochondrial dysfunction and bioenergetic deficits [79,80]. Impaired mitophagy has been reported in postmortem hippocampal samples of patients with AD, induced pluripotent stem cell-derived human AD neurons, and mouse and nematode models of the disease [81]. Moreover, pharmacological interventions that restore mitophagy, including NAD^+ (nicotinamide adenine dinucleotide) supplementation and urolithin A treatment, have been shown to ameliorate cognitive decline in experimental models of AD. In *C. elegans*, these beneficial effects depend on the PINK-1, PDR-1 or DCT-1 pathways. Mitophagy activation also enhances microglial phagocytosis of Aβ plaques, mitigates neuroinflammation in APP/PS1 mice and reduces AD-related tau hyperphosphorylation in human neuronal cells [81]. Although these compounds act through distinct molecular mechanisms, they converge on promoting mitochondrial homeostasis. Specifically, NAD^+ supplementation is thought to restore intracellular NAD^+ pools, thereby activating NAD^+-dependent sirtuins. Among these, SIRT3, a major mitochondrial sirtuin, enhances mitochondrial quality control by regulating mitochondrial dynamics, antioxidant defences and FOXO3α-dependent activation of the PINK1/Parkin mitophagy pathway. In parallel, SIRT1 primarily promotes mitochondrial biogenesis through activation of PGC-1α (peroxisome proliferator-activated receptor gamma coactivator-1 α) [82]. Urolithin A, in turn, activates conserved mitochondrial stress-response pathways that enhance mitophagic clearance of dysfunctional mitochondria [83]. More recently, urolithin A has been shown to suppress age-associated cGAS/STING-mediated inflammation by enhancing mitophagy, thereby limiting the cytosolic accumulation of mitochondrial DNA and improving neurological function in aged mice, providing additional mechanistic support for its therapeutic potential in age-related disorders [63]. Beyond NAD^+ and urolithin A, USP30 inhibitors and small-molecule PINK1 activators are also being evaluated as pharmacological enhancers of mitophagy, with several compounds now progressing through preclinical development and early-phase clinical testing [77]. Despite encouraging efficacy in preclinical models, the clinical translation of mitophagy-enhancing therapies remains challenging owing to limited human data and uncertainties regarding optimal dosing, long-term safety and patient selection.

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HD is an autosomal dominant neurodegenerative disorder caused by an increased number of CAG repeats in the huntingtin (*HTT*) gene, resulting in an abnormally elongated polyglutamine tract within the huntingtin protein (HTT). Mutant HTT (mHTT) has been strongly associated with mitochondrial dysfunction, in part through disruption of calcium homeostasis [84,85]. Consistent with a role for impaired mitochondrial quality control in HD pathogenesis, mouse models expressing the human *HTT* transgene together with the mt-Keima mitophagy reporter exhibit markedly reduced mitophagy, suggesting that boosting mitophagy could be an effective treatment for HD [38]. Mechanistically, HTT has been shown to interact with ULK1 (Unc-51–like kinase 1), a key initiator of autophagy, and the selective autophagy receptor SQSTM1/p62 involved in cargo recognition [86,87]. In addition, HTT associates with several components of the mitophagy machinery, including BECN1, NBR1, OPTN and CALCOCO2/NDP52, facilitating their physical proximity and promoting mitophagy activation. Importantly, these interactions are disrupted by mHTT, resulting in defective mitophagy, accumulation of damaged mitochondria, reduced mitochondrial respiration, and increased ROS production [88]. Thus, mutant HTT may disrupt mitochondrial quality control at several stages of the selective autophagy pathway in HD, contributing to the accumulation of damaged mitochondria and mitochondrial dysfunction.

ALS is a progressive neurodegenerative disorder characterized by the loss of upper and lower motor neurons and subsequent muscle atrophy. A growing body of evidence implicates mitochondrial dysfunction and impaired mitochondrial quality control in ALS pathogenesis. Several ALS-associated genes, including *OPTN*, *TBK1*, *SOD1*, *TARDBP*, *FUS* and *C9ORF72*, have been linked to the regulation of mitochondrial quality control and homeostasis [89]. For example, mutations in *OPTN* impair mitophagy and mitochondrial clearance, whereas ALS-associated *TBK1* mutations can impair the phosphorylation of OPTN and p62, thereby disrupting mitophagy [90]. Along similar lines, mutations in *SOD1*, *TARDBP* and *FUS* have been associated with mitochondrial fragmentation, oxidative stress and defective mitochondrial trafficking [89]. In addition, the pathogenic GGGGCC hexanucleotide repeat expansion in *C9ORF72*, the most common genetic cause of ALS, disrupts autophagy–lysosomal function and has been associated with mitochondrial dysfunction [91]. Because motor neurons have exceptionally high energy demands and long axons that require efficient mitochondrial transport and turnover, they are particularly vulnerable to defects in mitochondrial quality control [92]. Collectively, these findings support the view that impaired mitochondrial homeostasis contributes to ALS pathogenesis and is not merely a secondary consequence of neurodegeneration. Nevertheless, emerging evidence suggests that the role of mitophagy in ALS may be highly context-dependent. Indeed, it has been recently shown that Parkin ablation delays disease progression and prolongs survival in SOD1-G93A mice, highlighting the complex role of mitophagy in ALS [93]. Together, these findings suggest that therapeutic modulation of mitophagy in ALS may require personalized approaches that consider disease stage, genetic background and cellular context, rather than indiscriminate activation or inhibition of the pathway.

While the molecular mechanisms and disease relevance of mitophagy are comparatively well established (Figs 1 and 2), nucleophagy has only recently emerged as an important pathway linking nuclear quality control with ageing and neurodegeneration (Fig. 3).

Nucleophagy

Overview of nucleophagy as a nuclear quality control pathway

Ageing is accompanied by genomic instability and alterations in nuclear organization and architecture [7]. Because the nucleus safeguards genome integrity and controls gene expression, cells have evolved sophisticated surveillance and quality control systems that maintain the fidelity of DNA replication and transcription while preserving a functional nuclear proteome and overall nuclear homeostasis [94]. Emerging evidence suggests that selective autophagic degradation of nuclear components, broadly referred to as nucleophagy, contributes to nuclear homeostasis and quality control during ageing and in response to cellular stress [95,96]. Compared with the extensively characterized pathways of mitophagy, nucleophagy is considerably less well understood. To date, several nuclear substrates have been reported to undergo macronucleophagy, including nucleus-derived vesicles, nuclear pore complex (NPC) assemblies and nucleoporins in yeast, and nuclear lamins and Sirtuin 1 (SIRT1) in mammalian cells [97–99]. These proposed nucleophagic substrates and their potential links to cellular senescence and neurodegeneration are illustrated in Fig. 3. Most mechanistic insights into nucleophagy have been derived from yeast, although several evolutionarily conserved components have subsequently been identified in mammals.

In yeast, nuclear material can be degraded through distinct nucleophagic pathways, including piecemeal

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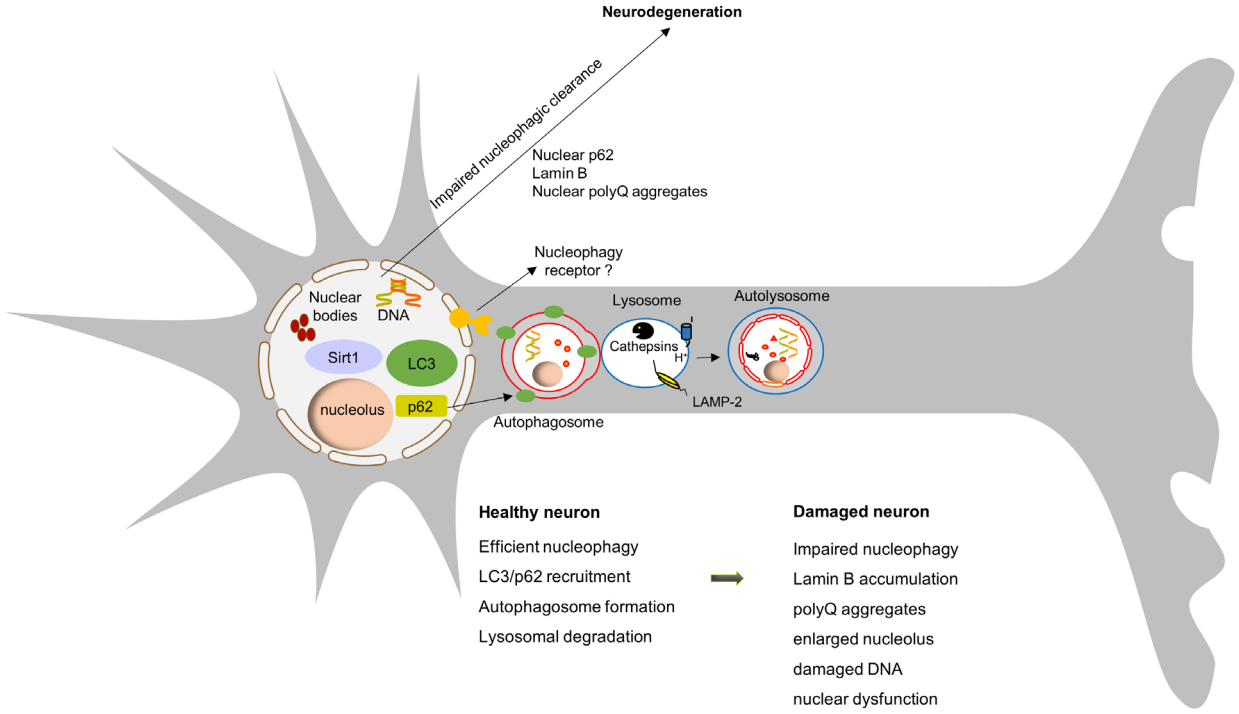


Fig. 3. Proposed model of neuronal macronucleophagy in health and disease. Under physiological conditions, selected nuclear components, including nuclear proteins, ribosomal components, rRNA and DNA-containing nuclear material may undergo degradation through macronucleophagy. This process may involve direct interaction of nuclear cargo with nuclear LC3, association with autophagy receptors such as p62, or engagement of putative nucleophagy receptors at the nuclear envelope, leading to sequestration of nuclear material within autophagic membranes. Following autophagosome–lysosome fusion, nucleophagic cargo is degraded by lysosomal hydrolases (e.g. cathepsins). Sirtuin 1 (SIRT1) has been identified as a selective substrate of nucleophagy in mammalian cells during cellular senescence and ageing, suggesting that related mechanisms may contribute to nuclear quality control in neurons. Under pathological conditions, impaired or dysregulated nucleophagy may compromise the clearance of damaged or aggregation-prone nuclear material (e.g. p62, Lamin B and nuclear polyQ aggregates), thereby contributing to disruption of nuclear homeostasis and neurodegeneration. LAMP-2, lysosome-associated membrane protein 2.

micronucleophagy (PMN) and late nucleophagy (LN), which are activated under different nutritional conditions and rely on partially overlapping components of the core autophagy machinery. In contrast to macronucleophagy, these pathways involve the direct sequestration of nuclear cargo at the vacuole–nucleus interface rather than its prior enclosure within conventional autophagosomes [100,101].

The discovery of Atg39 provided the first mechanistic insight into receptor-mediated nucleophagy in the budding yeast *Saccharomyces cerevisiae* [102]. Atg39 abundance is markedly increased under stress conditions, including nitrogen starvation and endoplasmic reticulum (ER) stress, as well as following rapamycin treatment, which mimics aspects of nitrogen starvation through inhibition of target of rapamycin complex 1 (TORC1) activity [103]. Similar to what is known for other selective autophagy receptors, Atg39 interacts with Atg11 through its cytoplasmic domain, recruiting the core autophagy machinery to the nuclear envelope, while its interaction with Atg8 on expanding isolation membranes facilitates the sequestration of nuclear-envelope-derived vesicles into autophagosomes [102,104,105].

Beyond its role as a nucleophagy receptor, Atg39 also coordinates the membrane remodelling required for macronucleophagy. Remodelling of the nuclear envelope generates nucleus-derived double-membrane vesicles containing intranuclear components, which are subsequently engulfed by autophagosomes. Atg39 associates with both the outer nuclear membrane (ONM) and the inner nuclear membrane (INM). Its N-terminal transmembrane region anchors to the ONM, while C-terminal amphipathic helices extending into the perinuclear space interact with the INM, linking the two membranes [104,106]. This interaction is essential not only for retaining Atg39 at the nuclear envelope but also for facilitating nuclear envelope remodelling and the sequestration of INM fragments into nucleus-derived double-membrane vesicles [104,106]. However,

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the precise mechanisms by which Atg39 contributes to membrane remodelling remain incompletely understood. Given that amphipathic helices can sense and induce membrane curvature by inserting hydrophobic residues into one leaflet of the lipid bilayer [107,108], Atg39 may directly contribute to INM deformation through its amphipathic helices [104].

More recent work has provided further mechanistic insight into the kinetics and ultrastructural features of nucleophagy, revealing that the process can proceed without compromising nuclear envelope integrity. Specifically, it was shown that the generation of nucleus-derived vesicles during Atg39-dependent nucleophagy involves two consecutive membrane fission steps: an initial INM fission, giving rise to an INM-derived vesicle (INMDV) in the perinuclear space, and a subsequent fission event at the ONM, which then releases a double-membraned vesicle into the cytosol. Importantly, this study also uncovered an unexpected role for the dynamin-like protein 1 (Dnm1), an orthologue of the DRP1 GTPase, in mediating the ONM fission events. Although Dnm1 has previously been implicated in mitophagy and pexophagy, these findings provide evidence for its involvement in nuclear envelope remodelling events. Similar to mitophagy and pexophagy, Dnm1 recruitment at the ONM pinching site is mediated by Atg11, which is itself recruited by Atg39 [109]. Collectively, these observations suggest that Atg39 coordinates sequential INM and ONM remodelling events to promote the formation and cytosolic release of nucleus-derived double-membrane vesicles while preserving overall nuclear envelope integrity.

Further supporting a functional link between ER and nuclear envelope remodelling, the ER autophagy receptor Atg40 has been shown to contribute, at least in part, to macronucleophagy [102]. Furthermore, yeast cells lacking Atg39 exhibit abnormal nuclear morphology and reduced survival under nitrogen starvation compared with wild-type cells, suggesting that nucleophagy contributes to the maintenance of nuclear integrity and cellular fitness under stress conditions [102]. Despite these advances, several key questions remain unanswered. For example, it remains unclear how nucleophagic cargo is selected and whether specific classes of nuclear components, such as proteins, RNAs or lipids, are preferentially enriched in nucleus-derived vesicles during their clearance through nucleophagy.

In addition to bulk turnover of nuclear envelope fragments, nucleophagy can also selectively target distinct nuclear substructures. In Atg39-deficient yeast cells, the nucleoporin Nup159 interacts with Atg8 through its AIM (Atg8-family interacting motif), promoting selective turnover of NPC components through a process referred to as nucleoporinophagy [110]. Detailed mechanistic descriptions of NPC-phagy and related nucleophagic pathways are provided in recent specialized reviews [95,98]. Together, these findings highlight the diversity of nucleophagic pathways identified in yeast and provide a framework for investigating their conservation in mammals.

Recent studies in mammalian systems have revealed both conserved and divergent mechanisms linking nucleophagy to cellular stress and disease [111]. Notably, no mammalian orthologue of Atg39 has been identified. Instead, mammalian nucleophagy involves distinct selective autophagy receptors, including TEX264, which has been shown to mediate the nucleophagic clearance of poly(ADP-ribose) polymerase 1 (PARP1) trapped on chromatin, following PARP inhibitor (PARPi) treatment. In this context, TEX264, in cooperation with the p97 AAA+ ATPase, promotes the recognition and clearance of trapped PARP1 by facilitating its engagement with LC3 and subsequent autophagic degradation. Disruption of this pathway increases PARP1 trapping, resulting in the accumulation of trapped PARP1, increased genome instability and cell death, including in PARPi-resistant cancer cells [112]. Although initially characterized in the context of cancer therapy resistance, this pathway provides further evidence for selective nuclear component clearance in mammalian cells and reinforces the emerging role of nucleophagy in maintaining nuclear homeostasis. These findings support the view that mammalian cells possess specialized mechanisms for nuclear quality control while also highlighting substantial mechanistic differences from the yeast pathways described above. How these mechanisms are regulated during ageing and whether their dysregulation contributes to age-associated nuclear dysfunction remain important questions for future investigation.

Nucleophagy in cellular senescence and ageing

Unlike mitophagy, which has been extensively characterized as a mechanism of organelle quality control during ageing, nucleophagy remains comparatively understudied in the context of nuclear homeostasis. Given that nuclear dysfunction, including altered nuclear architecture, impaired chromatin organization, nucleolar abnormalities and disrupted nuclear proteostasis, is increasingly recognized as a prominent feature of ageing and age-associated diseases, nucleophagy may represent an important component of nuclear quality control during ageing. In mammals, studies of nucleophagy have primarily focused on the selective autophagic degradation of nuclear components in

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pathological contexts, including progeroid syndromes, neurodegeneration and cancer [95,96]. Emerging evidence, however, indicates that nucleophagy also contributes to physiological processes associated with cellular senescence, organismal longevity and reproductive maintenance, as discussed below.

A well-characterized substrate of mammalian nucleophagy is lamin B1, a major component of the nuclear lamina, a filamentous network underlying the INM that is unique to metazoans and is essential for maintaining nuclear architecture and function. The nuclear lamina is primarily composed of A-type and B-type lamins [113]. Among these, B-type lamins have emerged as crucial regulators of cellular senescence. Mechanistically, LC3 is present not only in the cytoplasm but also in the nucleus [15], where it directly interacts with lamin B1 and associates with lamin-associated domains (LADs) on chromatin. In contrast, lamins A/C and lamin B2 exhibit little or no binding to LC3. Importantly, the LC3–lamin B1 interaction mediates lamin B1 degradation in response to oncogenic and genotoxic insults, including activated RAS, through nucleus-to-cytoplasm transport and subsequent lysosomal degradation. Inhibition of either autophagy or the LC3–lamin B1 interaction attenuated oncogene-induced senescence in primary human cells, revealing a previously unrecognized role for autophagy in safeguarding cells against tumorigenesis [97]. Together, these findings indicate that selective nucleophagic degradation of lamin B1 contributes to the nuclear reorganization that accompanies oncogene-induced senescence.

A complementary mechanism of autophagy-mediated processing of nuclear material has also been described during cellular senescence. Senescent cells generate cytoplasmic chromatin fragments (CCFs), which arise through nuclear remodelling events associated with loss of lamin B1. These chromatin-containing fragments are subsequently processed through the autophagy–lysosome pathway, contributing to the remodelling and turnover of nuclear material during senescence. Although CCF clearance is mechanistically distinct from the selective autophagic degradation of nuclear components that characterizes nucleophagy, these findings support a broader role for autophagy in nuclear material turnover and the maintenance of nuclear homeostasis during cellular senescence [114].

More recently, studies in model organisms have expanded the physiological relevance of nucleophagy beyond cellular senescence by uncovering mechanistic links with ageing and longevity. In this context, the nuclear envelope anchor protein Nesprin-2 and its *C. elegans* orthologue ANC-1 were identified as regulators of nucleophagy. Nesprin-2/ANC-1-mediated nucleophagy functions to restrain nucleolar expansion, thereby preserving nuclear homeostasis [115]. This observation is particularly significant because the nucleolus is the site of ribosome biogenesis, one of the most energy-demanding processes in eukaryotic cells [116]. Consequently, nucleolar structure and activity are highly responsive to growth-promoting signals and diverse cellular insults, collectively encompassed by the evolving concept of nucleolar stress. Dysregulation of nucleolar homeostasis has emerged as a hallmark of numerous human disorders, including cancer and neurodegenerative diseases, while increased nucleolar size is a recognized biomarker of ageing and metabolic dysfunction [117,118].

Autophagy-mediated regulation of nucleolar homeostasis provides an additional link between nuclear quality control and longevity. Independent studies have shown that inhibition of the nuclear export receptor XPO-1 reduces nucleolar size, fibrillarin abundance and protein synthesis through an LGG-1/GABARAP-dependent mechanism, linking autophagy-mediated ribosomal protein surveillance to nucleolar homeostasis and longevity [119]. Together, these findings and the growing interest in pharmacological strategies targeting nucleolar function and ribosome biogenesis highlight nucleolar homeostasis as a promising therapeutic target in age-related diseases [117].

Beyond regulating nucleolar size, Nesprin-2/ANC-1-dependent nucleophagy also preserves nuclear architecture by limiting nuclear shape abnormalities and the accumulation of lamins. Importantly, this pathway also contributes to longevity and germline immortality under stress conditions. In this context, conserved signalling pathways and longevity regulating conditions, such as low insulin-IGF1 signalling and dietary restriction, interface with molecular mechanisms controlling nuclear architecture. Notably, ANC-1-mediated nucleophagy was shown to be crucial for the clearance of aberrant germ cells during their differentiation in the *C. elegans* gonad. Perturbation of this clearance pathway causes tumour-like structures in the *C. elegans* germline and progressive sterility over several generations, indicating loss of germline immortality. Likewise, genetic ablation of *nesprin-2* in female mice has been associated with ovarian tumour development. Overall, these findings underscore the importance of nucleophagy in regulating nuclear homeostasis, longevity and reproductive fitness. Given the evolutionary conservation of the regulatory factors involved, similar pathways may impinge on human ageing as well [115].

Collectively, studies in mammalian systems and model organisms indicate that nucleophagy contributes

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to multiple aspects of ageing biology through the selective turnover of nuclear components. Depending on the cellular and physiological context, nucleophagy has been implicated in senescence-associated nuclear remodelling, longevity, germline maintenance and reproductive fitness [97,114,115,119]. An important unresolved question is whether an age-dependent decline in nucleophagic flux contributes causally to these biological processes and outcomes, or instead arises as a consequence of broader cellular dysfunction.

Nucleophagy in neurodegenerative diseases and related disorders

Perturbations in nuclear integrity and architecture underlie a broad spectrum of human pathologies. These include nuclear envelope disorders, defects in nucleocytoplasmic transport, diseases characterized by the accumulation of intranuclear aggregates and disorders associated with dysregulated nucleophagy, among others. Nucleophagy contributes to nuclear homeostasis by selectively targeting nuclear components for lysosomal degradation [13,120]. As shown in Fig. 3, impaired nucleophagic clearance may lead to the accumulation of damaged nuclear material, potentially contributing to age-associated neurodegeneration. Consequently, diseases characterized by persistent nuclear damage, abnormal nuclear envelope architecture or the accumulation of intranuclear aggregates may increase the need for nucleophagy-mediated quality control.

Nuclear envelope disorders

Mutations in lamins have been linked to muscular dystrophies, neurodegeneration and premature ageing syndromes, collectively referred to as laminopathies [121]. Although laminopathies predominantly affect skeletal muscle and cardiac tissue, their neurological manifestations, together with evidence that nuclear lamins are essential for neuronal function and survival, highlight the importance of nuclear envelope integrity in the nervous system [122]. Studies of these disorders provide evidence that nucleophagy and related autophagy-mediated mechanisms contribute to nuclear quality control by removing damaged nuclear material and limiting its accumulation [97]. Likewise, mutations in *EMD* cause emerinopathies, in which muscular dystrophy and severe cardiac abnormalities are among the most clinically significant features. *EMD* encodes emerin, a nuclear envelope protein involved in the regulation of transcription factor activity, cell signalling, nuclear architecture, chromatin organization and epigenetic regulation, nucleo-cytoskeletal mechanotransduction and cellular polarity [123,124]. Interestingly, perinuclear autophagosomes/autolysosomes containing nuclear components have been detected in several cases of nuclear envelopathies, including in mouse models deficient in lamins or emerin and in skeletal and cardiac muscles derived from affected individuals. Blockage of autophagy leads to the accumulation of nuclear damage and reduced cell survival, suggesting a protective role of autophagy/nucleophagy in these cells [125]. Although observed at a low frequency, similar autophagosomal structures have been observed in wild-type cells, suggesting that nucleophagy serves a housekeeping function under physiological conditions [125].

Defective nucleocytoplasmic transport

Several aggregation-prone neurodegenerative diseases have also been linked to the loss of nuclear homeostasis. One notable example is the GGGGCC (G4C2) repeat expansion in a noncoding region of C9ORF72, which is the most common genetic cause of sporadic and familial forms of ALS and frontotemporal dementia (FTD). This repeat expansion disrupts nucleocytoplasmic transport by impairing NPC function [126]. Such defects are expected to compromise nuclear quality control and may increase reliance on pathways that remove damaged nuclear components. Although direct evidence linking nucleophagy to C9ORF72-associated ALS remains limited, disruption of nuclear homeostasis and nuclear pore function may increase the demand for selective nuclear quality control pathways, including nucleophagy.

Intranuclear aggregation

The accumulation of intranuclear protein aggregates represents another form of nuclear damage that may place increased demands on nuclear quality control pathways, including nucleophagy. This is illustrated by spinocerebellar ataxia type 1 (SCA1), a polyglutamine disorder caused by expansion of a CAG repeat in the *ATXN1* gene. The mutant protein localizes to a single nuclear structure in the Purkinje cells of patients or mammalian disease models, in contrast to normal ataxin-1 that localizes to several smaller nuclear structures. SCA1 pathogenesis is believed to involve the disruption of a nuclear matrix-associated domain [127]. Along similar lines, two additional adult-onset diseases may also involve defects in autophagy-mediated nuclear turnover. Oculopharyngeal muscular dystrophy is caused by an expansion of alanine in the PABPN1

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protein and is characterized by nuclear filament inclusions in skeletal muscle fibres [128]. Similarly, the RNA-mediated fragile X-associated tremor ataxia syndrome (FXTAS) is caused by CGG-repeat-containing FMR1 transcripts and is characterized by intranuclear inclusions in neurons and astrocytes. Notably, the number of CGG repeats is closely related to the number of intranuclear inclusions, suggesting that CGG-repeat length may serve as a predictor of neurological involvement and neuropathological burden in FXTAS [129]. Although direct evidence for nucleophagy in these disorders remains limited, the persistence of intranuclear inclusions raises the possibility that impaired nuclear quality control pathways, including nucleophagy, may be insufficient to efficiently eliminate damaged or aggregation-prone nuclear material. Whether these inclusions are directly recognized as substrates for nucleophagy, however, remains unknown.

Dysregulated nucleophagy

Further evidence for the importance of balanced nucleophagy comes from studies of dentatorubral-pallidoluysian atrophy (DRPLA), a polyglutamine disease caused by a CAG-repeat expansion in the *ATN1* gene [130]. In DRPLA, impairment of canonical autophagy leads to nuclear degeneration through a Golgi membrane-associated nucleophagy pathway that promotes lamin B1 degradation and excretion. These alterations result in motor behaviour defects and severe cerebellar pathology [131].

Overall, these findings suggest that both impaired clearance and dysregulated activation of nuclear quality control pathways may compromise nuclear integrity and neuronal function. Maintaining appropriately regulated nuclear turnover may therefore be essential for neuronal homeostasis and long-term brain health (Fig. 3).

Concluding remarks

Accumulating findings indicate that autophagy declines with age and that impaired autophagic function contributes substantially to ageing and age-related pathologies. Conversely, genetic, pharmacological and dietary interventions that stimulate autophagy can improve healthspan and lifespan across diverse model organisms. The studies discussed herein focus on two forms of organelle-specific autophagy, mitophagy and nucleophagy. Growing evidence supports the view that both processes are altered during ageing, with age-related changes likely to be tissue- and context-dependent rather than uniformly declining. Given the extensive bidirectional communication between the nucleus and mitochondria (Fig. 4), further dissection of the mechanisms governing these selective autophagic pathways will provide crucial insights into the cellular and molecular underpinnings of healthspan and organismal ageing [132–135]. In particular, determining whether and how mitophagy and nucleophagy are coordinated to preserve mitochondria–nucleus communication represents an important direction for future research. Accordingly, strategies aimed at preserving or enhancing these pathways, as well as their interplay during aging, may offer opportunities to promote healthy ageing and improve quality of life in later years.

Outstanding questions and future perspectives

Converging lines of evidence suggest that different cell types have evolved distinct mechanisms to regulate organelle-specific autophagy. Similar to bulk autophagy, these pathways are vital in postmitotic cells such as neurons, where organelle quality control must be tightly regulated across time and space.

With regard to mitophagy, evidence for its physiological significance in cellular function, and especially in neuronal physiology, is steadily increasing, with implications for organismal homeostasis. However, the molecular mechanisms that regulate basal mitophagy remain poorly understood. As mitophagy rates vary between and within tissues [38], the question arises as to how mitophagy is coordinated across tissues. For example, mitochondrial perturbation in one tissue can activate the mitochondrial stress response pathway in a distal tissue [132], raising the possibility that systemic signals contribute to the regulation of mitophagy at the organismal level.

In contrast, nucleophagy remains comparatively understudied. Many aspects of this process remain elusive. How is nucleophagy executed under basal conditions? What determines cargo specificity? Are there dedicated receptors that function specifically during basal nucleophagy? How is this selective form of autophagy regulated in physiological settings? Does its efficiency decline during normal ageing, and what are the consequences for healthspan and lifespan? These are only some of the relevant questions that remain open.

An additional consideration is the remarkable cell-type complexity of the brain. In addition to non-neuronal cells, such as astrocytes, oligodendrocytes and microglia, neurons themselves comprise numerous subtypes and they are organized in networks and spatially distinct structures that are dedicated to different functions [136]. Future work should therefore aim at

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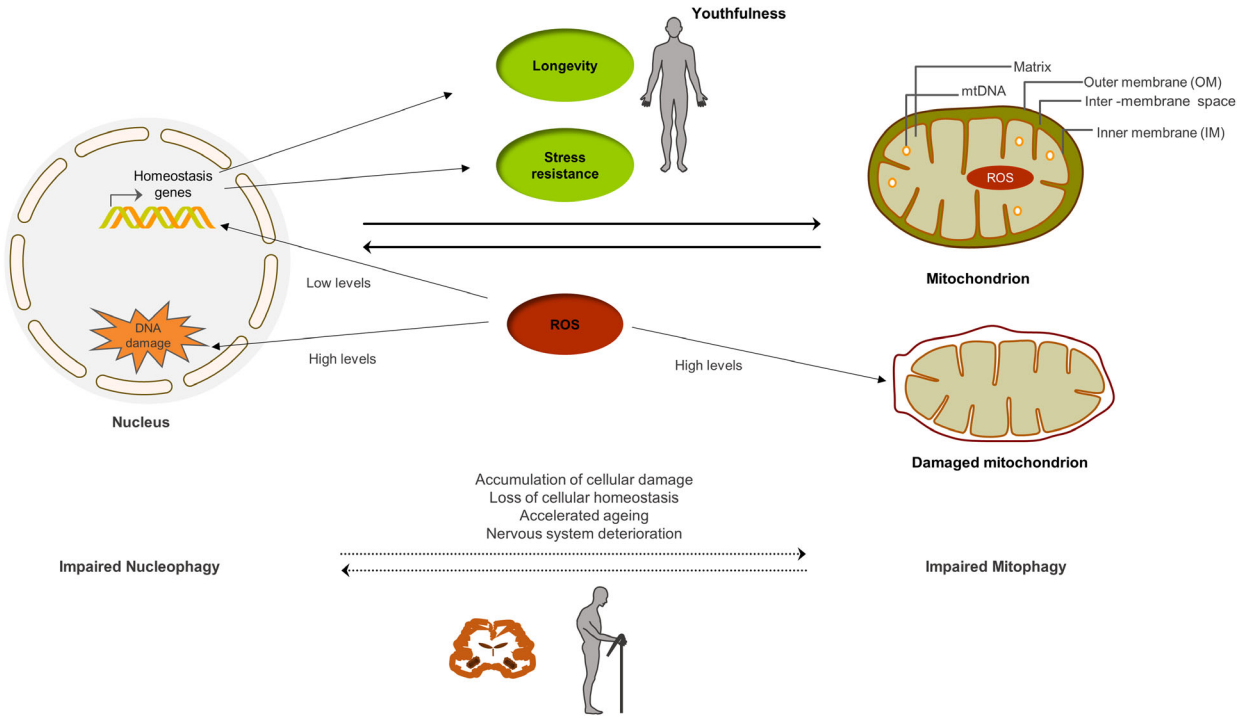


Fig. 4. Mitochondria–nucleus communication. Coordination between mitochondria and the nucleus is essential for maintaining cellular homeostasis under physiological and stress conditions. Low levels of mitochondrial ROS activate signalling pathways that promote adaptive stress responses and longevity. In contrast, excessive ROS and other insults can compromise mitochondrial and nuclear integrity and function. Impairment of organelle quality control mechanisms, including mitophagy and nucleophagy, leads to the progressive accumulation of cellular damage, disruption of cellular homeostasis and accelerated ageing. Arrows indicate stimulatory interactions. Dashed lines indicate the putative interplay between mitophagy and nucleophagy. mtDNA, mitochondrial DNA; ROS, reactive oxygen species.

investigating basal and induced selective autophagy within defined neuronal populations to better understand how these pathways contribute to neuronal function, vulnerability and ageing.

Conflict of interest

The authors declare no conflict of interest.

Author contributions

MM and NT contributed to the conceptualization, writing—original draft and writing—review and editing.

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