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Mitophagy in neurodegeneration and aging

Elayne M. Fivenson^a, Sofie Lautrup^{a,b}, Nuo Sun^c, Morten Scheibye-Knudsen^d, Tinna V. Stevnsner^b, Hilde Nilsen^e, Vilhelm A. Bohr^{a,d,*}, and Evandro F. Fang^{a,*}

^aLaboratory of Molecular Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224

^bDanish Aging Research Center, Department of Molecular Biology and Genetics, University of Aarhus, 8000 Aarhus C, Denmark

^cCenter for Molecular Medicine, National Heart Lung and Blood Institute, NIH, Bethesda, MD 20892, USA

^dDanish Center for Healthy Aging, University of Copenhagen, Blegdamsvej 3B, 2200 Copenhagen N, Denmark

^eDepartment of Clinical Molecular Biology, University of Oslo and Akershus University Hospital, 1478 Lørenskog, Norway

Abstract

Mitochondrial dysfunction contributes to normal aging and a wide spectrum of age-related diseases, including neurodegenerative disorders such as Parkinson's disease and Alzheimer's disease. It is important to maintain a healthy mitochondrial population which is tightly regulated by proteolysis and mitophagy. Mitophagy is a specialized form of autophagy that regulates the turnover of damaged and dysfunctional mitochondria, organelles that function in producing energy for the cell in the form of ATP and regulating energy homeostasis. Mechanistic studies on mitophagy across species highlight a sophisticated and integrated cellular network that regulates the degradation of mitochondria. Strategies directed at maintaining a healthy mitophagy level in aged individuals might have beneficial effects. In this review, we provide an updated mechanistic overview of mitophagy pathways and discuss the role of reduced mitophagy in neurodegeneration. We also highlight potential translational applications of mitophagy-inducing compounds, such as NAD⁺ and urolithins.

1. Introduction

Aging is associated with a loss of physiological integrity, including an imbalance in proteostasis and an increase in mitochondrial dysfunction, which can be caused by compromised autophagy and its subtype mitochondrial autophagy, termed mitophagy.

*Co-senior authors: V.A.B. (BohrV@grc.nia.nih.gov) or E.F.F. (evandro.fang@nih.gov).

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Autophagy is the process by which cellular components are degraded and recycled within the cell. Autophagy can refer to the nonspecific, cell-wide degradation of organelles or misfolded proteins in nutrient-starved conditions, as well as the removal of specific damaged or superfluous organelles. Aging and age-related pathologies are associated with reductions in autophagy [1], and emerging evidence suggests that the upregulation of autophagy may delay the onset and ameliorate the symptoms of age-related phenotypes [2]. A reduction in autophagy leads to neurodegeneration in mice [3–5] and is thought to contribute to several neurodegenerative diseases in humans [6]. Mitophagy is a specialized form of autophagy that regulates the turnover of mitochondria. Mitochondria, classically referred to as the “powerhouse” of the cell, produce cellular energy in the form of ATP. However, a large body of work has established additional and synergistic roles of the mitochondria in the regulation of cellular homeostasis [7]. Mitochondrial dysfunction is considered a hallmark of aging [8], and is implicated in apoptosis, senescence, genome instability, inflammation, and metabolic disorders [7, 9]. The term “mitophagy” was first coined by Dr. Lemasters in 2005 [10]. Since then, mitophagy has been linked to various diseases, including neurodegenerative disorders [11] such as Parkinson’s [12], Huntington’s [13], and Alzheimer’s [14], as well as normal physiological aging [15]. In this review, we summarize recent findings linking mitophagy to aging and neurodegeneration. We discuss connections between mitochondrial turnover and genomic stability, explore therapeutic interventions targeting mitophagy pathways, and highlight emerging avenues of research in the field.

2. Overview of mitophagy pathways

Accumulating evidence demonstrates that mitophagy functions throughout life, in fertilization and development, maintaining health throughout life, and preventing age-related disease. Molecular mechanisms of mitophagy have been intensively investigated in multiple species (Figure 1). Mitophagy can either specifically eliminate damaged mitochondria or clear all mitochondria during specialized developmental stages (fertilization and blood cell maturation) or starvation (phosphoinositide 3-kinase/PI3K-dependent). Here we summarize current knowledge of different mitophagy pathways in mammalian cells, *C. elegans*, and yeast.

2.1 Mitophagy in mammals

Under nutrient-rich conditions, damaged and superfluous mitochondria are selectively degraded to maintain mitochondrial homeostasis. One of the most studied pathways in clearing damaged mitochondria in mammalian cells is the PINK1/Parkin pathway (recently reviewed by [16, 17]) (Fig. 1A). PINK1-Parkin-dependent mitophagy is initiated when a decrease in mitochondrial membrane potential caused by mitochondrial damage leads to the stabilization of the ubiquitin kinase (PTEN)-induced kinase 1 (PINK1) on the outer mitochondrial membrane. Here, it phosphorylates ubiquitin, leading to the recruitment of the E3 ubiquitin ligase Parkin. PINK1 phosphorylation activates Parkin, which polyubiquitinates mitochondrial proteins, leading to their association with the ubiquitin-binding domains of autophagy receptors and the formation of the autophagosome. The autophagosome then fuses with the lysosome, leading to degradation of the mitochondria [18]. Alternatively, PINK1 can recruit autophagy receptors directly in a Parkin-independent manner, leading to

low levels of mitophagy [18]. Parkin-mediated mitophagy can be suppressed by deubiquitination of its substrates. USP8 (Ubiquitin Specific Peptidase 8) was found to regulate mitophagy in human cell lines [19], while the reduction of USP30 [20] and USP15 [21] can increase mitophagy and rescue mitochondrial phenotypes in fly models.

Mutations in *Parkin* [22] and *PINK1* [23] lead to the autosomal recessive form of Parkinson's disease. *PINK1*^{-/-} mice exhibit mitochondrial dysfunction, including reduced mitochondrial respiration in the striatum already at 3–4 months of age. This dysfunction was only observed in control mice at 24 months of age, indicating *PINK1*^{-/-} mice are sensitive to age-related damage [24]. While *Parkin*^{-/-} mice exhibit a reduction in proteins involved in mitochondrial function and oxidative stress responses, as well as mild metabolic phenotypes [25], they do not exhibit severe mitochondrial dysfunction or neuronal death, indicating the existence of Parkin-independent mitochondrial clearance pathway(s) [26]. However, when *Parkin*^{-/-} mice are crossed with a PolG mutant mouse, characterized by increased mtDNA damage, the resulting phenotypes include mitochondrial dysfunction and dopaminergic neuronal loss characteristic of Parkinson's disease [27], indicating Parkin-deficient mice are susceptible to increased mtDNA damage.

The PINK1/Parkin-dependent mitophagy pathway has been extensively studied in *Drosophila* [28–32]. Knockout of *Pink1* in *Drosophila* results in sterility, mitochondrial defects, increased sensitivity to stress [33], dopaminergic neuronal loss and locomotive dysfunction [34]. These phenotypes are ameliorated by the overexpression of *Parkin*, suggesting that PINK1 and Parkin function in the same pathway to regulate mitochondrial maintenance [33].

Several mitophagy proteins have been reported to work in a Parkin-independent manner, including AMBRA1, Bcl2-L-13, FUNDC1, MUL1, and Nix/BNIP3L. AMBRA1 (the Activating Molecule in Beclin1-Regulated Autophagy) functions in the autophagy pathway, while also playing a pivotal role in embryogenesis and the development of the nervous system [35]. Interestingly, AMBRA1 induces mitophagy independently of Parkin and p62/SQSTM1 (a major autophagy protein) through direct binding with LC3 [36]. The BH domains of Bcl2-L-13 can independently induce mitochondrial fragmentation, while the WXXI motif binds to LC3 and facilitates mitophagy. In the absence of Parkin, Bcl2-L-13 retains its mitophagy-inducing function [37]. The integral mitochondrial outer membrane protein FUNDC1 was originally reported as a major player in hypoxia-induced mitophagy [38]. FUNDC1 can regulate mitophagy both through recruitment of LC3 via its typical LC3-binding motif Y(18)xxL(21), and by regulation of mitochondrial dynamics through interaction with fission and fusion proteins (DNM1L/DRP1 and OPA1, respectively) [38, 39]. MUL1 (mitochondrial ubiquitin ligase 1) is an E3 protein ligase that localizes onto the mitochondrial outer membrane during mitophagy [40]. In *PINK1* or *parkin* deficient *Drosophila*, MUL1 can ameliorate disease phenotypes through the ubiquitin-dependent degradation of Mitofusin [40]. MUL1 can also cleave sperm-derived mitochondria in a PINK1-dependent manner in zygotes [41] (detailed below). Additionally, Nix/BNIP3L can induce mitophagy in a PINK1/Parkin-independent manner [42] (also shown below). Some proteins involved in Parkin-independent mitophagy pathways, such as Ambra1, Nix, and FUNDC1, also have roles in traditional Parkin-dependent mitophagy [43–45]. Thus, in

mammalian cells, there are several mitophagy pathways which can compensate for the loss of others.

In addition to the clearance of damaged mitochondria, mammals have also developed specialized mitophagy pathways to eliminate mitochondria during developmental stages such as fertilization and blood cell maturation. During the process of reticulocyte maturation into red blood cells, mitochondria are completely cleared by the Nix/BNIP3L-dependent mitophagy pathway [46] (Fig. 1B). Nix is a member of the Bcl-2 family, and it induces mitophagy by decreasing mitochondrial membrane potential. Mitochondria are maternally inherited. After fertilization, paternal mitochondria are selectively degraded leaving only maternally-derived oocyte mitochondria. Deficiency in this process leads to embryonic lethality, signifying its evolutionary significance [41, 42, 47]. Elimination of sperm mitochondria in metazoan cells may require a combined action of p62-dependent autophagy and valosin-containing protein (VCP)-mediated ubiquitination of sperm mitochondria to the 26S proteasome (Fig. 1C).

In addition to the recycling of entire mitochondria, the isolation and digestion of specific damaged proteins within mitochondria can also occur. In this pathway, oxidized proteins in the mitochondrial matrix are engulfed in mitochondrial-derived vesicles (MDVs) and transported to the lysosomes [48, 49] or to peroxisomes [50]. Mitochondria-derived vesicles (MDVs) contain oxidized proteins, which may indicate protein damage or trigger protein aggregation [48]. MDV transport to the lysosome is dependent on PINK1 and Parkin [51]; however, this process is independent of other autophagic proteins such as ATG5 and LC3. MDVs may be an early response to protein damage within the mitochondria in an attempt to correct mitochondrial damage before complete degradation via mitophagy [48] (Fig. 1D).

2.2 Mitophagy in *C. elegans*

Decades of research in cross-species studies suggests that many of the cellular pathways involved in neuronal function and aging are evolutionally conserved. In *C. elegans*, mitophagy plays important roles in lifespan and healthspan [52]. The *C. elegans* mitochondrial protein DCT-1 (DAF-16/FOXO Controlled, germline Tumour affecting-1) is a putative orthologue to the human mitophagy protein Nix/BNIP3L. DCT-1 works downstream of the PINK1-Parkin pathway and is upregulated by the oxidative stress response transcription factor SKN-1 (ortholog of mammalian NRF2) and the FOXO transcription factor DAF-16 (ortholog of mammalian FOXO3) [52] (Fig. 1E). Additionally, as in mammals, *C. elegans* sperm mitochondria are eliminated. Recent work in *C. elegans* suggests that CPS-6, a mitochondrial endonuclease G [42, 47] is required to degrade the paternal mitochondrial genome (Fig. 1F). Further research on the mechanisms of autophagy and mitophagy in *C. elegans* will accelerate both mechanistic and translational studies in the fields of biological aging and neurodegeneration.

3. Mitophagy in neurodegeneration and aging

Mitochondria are key players in a wide range of pathways involved in cellular and tissue homeostasis and aging, including cellular senescence, stem cell function, inflammation, nuclear gene expression, epigenetics, calcium regulation, apoptosis, telomere maintenance,

and genomic stability [9, 15, 53]. Mitochondrial dysfunction is a hallmark of aging [8], demonstrated by the cross-species accumulation of dysfunctional mitochondria with age [54]. Mutations [55, 56] and deletions [57] in the mitochondrial genome accumulate with age, leading to bioenergetic dysfunction and age-related pathologies [58, 59]. Mitochondrial dysfunction can also induce senescence (termed mitochondrial dysfunction-induced senescence (“MiDAS”)), recently shown to contribute extensively to age-related pathologies [60].

In *C. elegans*, mitochondria accumulate with age, which may be due to a reduction in the clearing of damaged mitochondria via mitophagy [61]. Furthermore, induction of mitophagy is required for the lifespan extension of several long-lived *C. elegans* mutants including the IGF/IGF-1 mutants. Lifespan extension in *C. elegans* due to mild mitochondrial dysfunction is also mediated by mitophagy [62]. Sun et al developed the mt-keima mouse to measure mitophagy *in vivo* and demonstrated that mitophagy declines by approximately 70% in the Dentate gyrus, a region of the brain important for memory and learning, between 3 and 21-month old mice [63]. They also observed an increase in mitophagy in the PolG mutator mouse, associating an increase in mtDNA damage [64] with an increase in mitophagy. The authors speculate that it is not an increase in mitochondrial damage that contributes to mitochondrial-driven age-related pathologies, but rather a decline in the cellular capacity to mitigate the damage via mitophagy [63].

Neurons have an exceptionally high demand for ATP, which is needed for axonal transport, maintenance of ion gradients and membrane potential, and generation of synaptic vesicles. ATP production in neurons relies predominately on oxidative phosphorylation. Therefore, mitochondrial health is essential for neuronal function [65]. Given these unique features of neurons, the nervous system may be especially sensitive to mitochondrial damage. Dysfunctional mitophagy is closely linked to Parkinson’s disease (PD) (see section 2.1), a neurodegenerative disorder characterized by a loss of dopaminergic neurons in the substantia nigra as well as the accumulation of Lewy bodies, a form of protein aggregates.

Mitochondrial dysfunction, including reduced membrane potential and respiration, is also associated with Huntington’s disease (HD) [66]. HD is an autosomal dominant neurodegenerative disorder caused by an expansion of CAG repeats in the huntingtin gene, leading to the accumulation of protein aggregates and neuronal death. It has been reported that HD mouse models have reduced activity of PGC-1 α , the master regulator of mitochondrial biogenesis [67] and recently found to be important in the formation of hippocampal dendritic spines and synapses [68]. A reduction in mitophagy may also contribute to mitochondrial dysfunction in HD. Furthermore, human Huntingtin’s transgene (HTT) mice crossed with the mt-keima mouse indicated reduced mitophagy in the dentate gyrus [63]. GAPDH, a protein which catalyzes the sixth step of glycolysis, also functions in the direct engulfment of damaged mitochondria by lysosomes. In normal cells, expression of expanded polyglutamine tracts oxidized inactive GAPDH (iGAPDH) to induce micro-mitophagy. Mechanistically, iGAPDH signals the induction of direct engulfment of damaged mitochondria into lysosomes. However, expanded polyglutamine repeats (mutant Huntingtin) inhibit GAPDH-induced mitophagy through abnormal interaction with GAPDH

[69]. Hwang et al reported a reduction in GAPDH-induced mitophagy in HD cell models due to the inactivation of GAPDH by polyglutamine expansion[69].

Alzheimer's disease is the most prevalent form of neurodegeneration in aging populations. It is characterized by progressive cognitive decline, memory loss, and neuronal death in the cerebral cortex. Brain sections from Alzheimer's patients are characterized by neurofibrillary tangles composed of hyperphosphorylated tau protein and plaques of amyloid beta. Mitochondrial dysfunction is also implicated in the disease pathology [70, 71]. The activation of SIRT1 (See "Sirtuins and Mitophagy") can reduce the amount of beta-amyloid in brain, similar to the reduction mediated by caloric restriction [72].

In addition, compromised mitophagy may also induce amyotrophic lateral sclerosis (ALS), a fatal neurological disease caused by dysfunction of the motor neurons. ALS-related *OPTN* and *TBK1* gene mutations can cause compromised mitophagy [73]. Taken together, these studies suggest that reduced mitophagy contributes to several neuro degenerative diseases and age-related neurogenerative decline.

4. Sirtuins and mitophagy

The conserved sirtuin (silent information regulator) family of proteins are a group of NAD^+ dependent deacetylases that have important roles in metabolism and aging [74]. The mammalian sirtuin family consists of SIRT1-7. SIRT3-5 are predominately targeted to the mitochondria, SIRT1, SIRT6 and SIRT7 are mainly nuclear, and SIRT2 is cytoplasmic. Several excellent reviews have discussed the properties of sirtuins and their role in disease [75–77]. Sirtuin activity is generally correlated with an increase in lifespan and healthspan in yeast [78], flies [79], worms [80], and mice [81, 82]. This is in part due to increased stress response. For example, the increased resistance to oxidative stress in mouse neurons following exercise is mediated by mitochondrial SIRT3 [83]. Furthermore, huntingtin and epilepsy mouse models lacking SIRT3 were more susceptible to neurodegeneration [83]. Sirtuin enzymatic activity is dependent on cellular NAD^+ levels, which decline with age across species [84]. In rats, the NAD^+/NADH ratio decreases in all organs by middle age compared to young rats [85]. Similar findings were reported in human skin samples [86]. Cellular levels of NAD^+ and SIRT1 activity have recently gained attention for their role in regulating mitochondrial biogenesis and mitophagy, and may provide novel therapeutic targets for neurodegeneration and age-related disease.

4.1 Linking energy sensing to mitochondrial homeostasis

Mitochondrial turnover and mitochondrial biogenesis must be tightly balanced in the cell to maintain energy homeostasis. This is in part regulated by the AMP-activated protein kinase (AMPK). AMPK functions as an energy sensor, stimulating ATP production and suppressing ATP consumption in conditions of high cellular AMP/ATP ratio. AMPK promotes mitophagy through multiple mechanisms. First, AMPK phosphorylation of ULK1/ULK2 (mammalian orthologs of yeast Atg1) is required for mitophagy [87]. Since AMPK can increase intracellular NAD^+ levels [88], it may also promote SIRT1-dependent mitophagy [89–91]. SIRT1 activity enhances mitophagy via FOXO signaling and promotes

mitochondrial biogenesis by activating PGC-1 α [90]. This pathway links energy sensing to mitochondrial homeostasis [92].

4.2 Nuclear to Mitochondrial Signaling and Mitophagy

Nuclear to mitochondrial signaling regulates mitochondrial function, and can have profound impacts on aging and disease [93]. This signaling is mediated by a network of sirtuins. NAD⁺ is a key metabolite consumed by sirtuins and by the DNA damage response protein poly(ADP-ribose) polymerase 1 (PARP1). PARP1 detects breaks in DNA and recruits DNA repair proteins through a process called PARylation in which PAR chains are generated and NAD⁺ is consumed [53, 94]. PARP1 may also participate in the detection of G4 structures [95]. The accumulation of nuclear DNA damage, which occurs with age [96], can lead to persistent activation of PARP1, which depletes cellular levels of NAD⁺ and reduces sirtuin activity [97]. In *C. elegans*, when the ortholog of PARP-1, *pme-1*, was knocked down, mitochondrial function improved due to increased NAD⁺ levels and Sir2.1 (the *C. elegans* ortholog of SIRT1) activity and through UPR^{mt} activation. This resulted in lifespan extension and delayed onset of age-related phenotypes [98].

In addition to normal physiological aging, DNA repair-deficient neurodegenerative progeria diseases, including Cockayne Syndrome (CS), Xeroderma Pigmentosum group A (XPA) [99], and Ataxia Telangiectasia (AT) [100], exhibit clinical features similar to classic mitochondrial disorders such as mitochondrial encephalomyopathy, lactic acidosis, stroke-like episodes (MELAS) and Myoclonic epilepsy with ragged-red fibers (MERRF) syndromes [101]. XPA and AT demonstrate mitochondrial dysfunction due to reduced SIRT1 activity, stemming from an increase in DNA damage, persistent activation of PARP1, and depletion of NAD⁺ [91, 102]. For example, treatment with PARP inhibitors and supplementation of NAD⁺ precursors attenuated mitochondrial dysfunction in XPA models and extended lifespan in *xpa-1* worms [99]. Interestingly, similar results were not found in XPC models, a DNA repair disorder not associated with neurodegeneration. Taken together, these results indicate that cellular levels of NAD⁺ can modulate mitochondrial homeostasis and genome stability and may provide therapeutic targets for age-related neurodegeneration and neurodegenerative disease.

SIRT1 can also regulate mitochondrial homeostasis in a PGC-1 α independent manner. Gomes et al demonstrated that when nuclear NAD⁺ declines with age, SIRT1 activity is reduced and the transcription factor HIF-1 α is stabilized [103]. The authors suggest that chronic activation of HIF-1 α leads to a “pseudohypoxic state” in which the transcription of mitochondrially-encoded genes is reduced, leading to an imbalance between nuclear and mitochondrial transcription, and eventually mitochondrial dysfunction. Interestingly, recent work by Jain et al demonstrated that increased HIF activity due to hypoxia ameliorated several features and dramatically increased the lifespan of mouse models of Leigh Syndrome [104]. Thus, the dual role of the HIF pathway to regulate mitochondrial health may be context-dependent and remains to be fully elucidated.

5. Therapeutic interventions that target mitophagy

Given that mitochondrial dysfunction and compromised autophagy/mitophagy can induce a wide spectrum of diseases, including neurodegenerative diseases and premature aging, pharmacological maintenance of mitophagy may have broad translational applications. First, direct activators of mitophagy machinery, such as modulators of PINK1 [105] and Parkin [106] have been shown to increase mitophagy. Activation of sirtuins through sirtuin activating compounds (STACs), has also been shown to be a viable strategy for increasing mitophagy. Drugs such as resveratrol [78] and metformin [107], both of which increase mitophagy, fall into this class. Sirtuin activity can also be mediated through supplementation of NAD⁺ precursors such as NR and NMN, or via inhibitors of NAD⁺-consumers such as PARP, both of which have been found to improve several facets of age-related decline, including neurodegeneration [108]. Recently, Mills et al reported that long term treatment of NMN delayed the onset of age-related decline in wildtype mice through enhanced energy metabolism, suppression of weight increase, and other features [109]. Mitochondrial dysfunction and defective mitophagy contribute to the severe neurodegeneration phenotypes of several DNA repair deficient premature aging diseases, such as CS, XPA, and AT. Intriguingly, NAD⁺ replenishment can ameliorate disease phenotypes and improve both lifespan and healthspan in *C. elegans* and mouse disease models.

Mitophagy can also be induced by bioactive natural compounds, such as antibiotics and plant metabolites. Actinonin is a naturally occurring antibiotic found to increase mitophagy in neuronal stem cells derived from the mt-Keima mouse [63]. The mechanism through which actinonin induces mitophagy may be linked to the depletion of mitochondrial ribosomes and RNA decay [110], although the connection between this pathway and mitochondrial quality control remains to be completely elucidated. Ryu et al recently characterized a novel mitophagy-inducer Urolithin A [4], a metabolite derived from pomegranates. Urolithin A extends the lifespan of *C. elegans* and improves muscle function in mice through mitochondrial maintenance via upregulation of mitophagy [111]. More work remains to be done to deduce the mechanism behind which Urolithin A increases mitophagy. In conclusion, based on the availability of different mitophagy screening animal models, including *C. elegans* and mice, we expect an increase in the discovery of new mitophagy-inducing compounds which will propel further potential clinical studies.

6. Conclusions and future perspectives

A growing body of research implicates mitophagy in neurodegenerative disease and age-related neurological decline, and provides new avenues for therapeutic intervention (Fig. 2). Although mitochondrial dysfunction has long been implicated in the pathology of neurodegenerative diseases such as Parkinson's, Huntington's, Alzheimer's, and others, decreased levels of mitophagy have only recently been recognized as key contributor to disease pathogenesis. Thus, the role of mitochondrial maintenance must be elucidated to better understand the mitochondrial phenotypes in neurodegeneration. Work remains to elucidate the coordination of mitophagy with other mitochondria quality control pathways, such as the UPR^{mt}. For instance, it is interesting to consider the different layers of mitochondrial maintenance in response to stress. In the context of a single mitochondrion,

the UPR^{mt} may serve as a first line of defense against damage, progressing to degradation of damaged proteins via mitochondria-derived vesicles, followed by recycling of the entire organelle via mitophagy. One could even consider mitochondrial dysfunction induced senescence (MiDAS) as the next phase, eventually leading to neurodegeneration and other age-related pathologies. Additionally, the roles and molecular mechanisms of mitophagy in stem cell renewal and function deserve further investigation. In summary, further mechanistic studies of mitophagy may not only improve our understanding of the mechanisms of aging, neurodegeneration, and other diseases, but also suggest novel therapeutic strategies to combat multiple devastating neurodegenerative diseases, and possibly even delay biological aging.

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Highlights

Mitophagy in neurodegeneration and aging

- Mitophagy is essential for the maintenance of mitochondrial quality in neurons
- Compromised autophagy/mitophagy can cause neurodegenerative diseases
- Different molecular pathways of mitophagy have been uncovered
- Mitophagy induction can be a novel approach for the treatment of some neurodegenerative diseases

Figure 1. Overview of Mitophagy Pathways

A. PINK1/Parkin-mediated pathway. PINK1 is stabilized on the outer mitochondrial membrane of damaged mitochondria where it phosphorylates ubiquitin, leading to the activation of parkin. Parkin polyubiquitinates mitochondrial proteins, leading to the association with autophagy receptors and the formation of the autophagosome. The autophagosome then fuses with the lysosome, leading to degradation. Alternatively, PINK1 can recruit autophagy receptors directly in a parkin-independent manner, leading to low levels of mitophagy.

B. Reticulocyte mitophagy. Upon maturation signal, NIX localizes to the outer mitochondrial membrane of reticulocyte mitochondria. NIX binds to LC3, leading to the formation of the autophagosome.

C. Mammalian sperm mitophagy. Ubiquitinated paternal sperm associates with VCP. VCP facilitates the presentation of ubiquitinated (Ub) sperm mitochondrial proteins to the 26S proteasome, leading to degradation. Synchronously, SQSTM1 binds to other ubiquitinated mitochondrial proteins leading to sequestration within an autophagosome.

D. Mitochondria-derived vesicles. Unfolded oxidized proteins lead to aggregation. Cardiolipin is locally oxidized to phosphatidic acid, leading to membrane curvature. PINK1 is localized to the outer mitochondrial membrane where it recruits parkin. The vesicle is formed and the cargo is transported to the lysosome for degradation.

E. *C. elegans* somatic tissue. PINK1 is stabilized on the OMM of damaged/superfluous mitochondria, leading to the recruitment of parkin. Parkin ubiquitinates DCT-1 (homolog of

NIX/BNIP3L), which associates with LGG-1 (homolog of LC3), leading to the formation of the autophagosome.

F. *C. elegans* sperm. Loss of membrane integrity triggers the release of endonuclease G from inner mitochondrial membrane space to the mitochondrial matrix, where it degrades mtDNA.

G. Yeast. Association of OMM protein Atg32 to isolation membrane-bound Atg8 directly or through its interaction with Atg11 recruits targeted mitochondria to the autophagosome.

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Fig 2. Mitophagy in neurodegeneration and aging

Mitophagy can be inhibited by a reduction of autophagic protein activity or by depletion of metabolites such as NAD^+ due to increased DNA damage and consumption or due to a decline in NAD^+ synthesis. A reduction in mitophagy leads to an accumulation of dysfunctional mitochondria, which can induce a variety of damage contributing to neurodegeneration and aging. These pathologies can be restored by targeting mitophagy through genetic editing, mitophagy-inducing compounds, and NAD^+ supplementation.