Mitophagy and the Brain

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Abstract

Stress mechanisms have long been associated with neuronal loss and neurodegenerative diseases. The origin of cell stress and neuronal loss likely stems from multiple pathways. These include (but are not limited to) bioenergetic failure, neuroinflammation, and loss of proteostasis. Cells have adapted compensatory mechanisms to overcome stress and circumvent death. One mechanism is mitophagy. Recent studies have implicated mitophagy in several neurodegenerative diseases and clinical trials are underway which target mitophagy pathways. Here, we review mitophagy pathways, the role of mitophagy in neurodegeneration, potential therapeutics, and the need for further study.

Key Words: Mitochondria, Alzheimer’s Disease, mitophagy, neurodegeneration, aging
1. Introduction

Mitochondria are essential organelles that regulate energy homeostasis, cell signaling, and cell death [1-3]. During threatened cell death or nutrient starvation mitochondria can be degraded and recycled through mitophagy. Mitophagy is a specific form of autophagy, a process where cell contents are degraded and recycled. In a broad sense, mitophagy involves tagging mitochondria for removal, engulfment of the organelle by an autophagosome, and degradation in a lysosome. There are several pathways which control, initiate, and facilitate mitophagy. The many facets of mitochondrial function control and contribute to mitophagy pathways.

Mitochondria coordinate and balance energy production through beta oxidation, the citric acid cycle (TCA cycle), and oxidative phosphorylation at the electron transport chain (ETC). Beta oxidation is a catabolic pathway were free fatty acids are converted to acetyl coA, which enter the TCA cycle and ultimately oxidative phosphorylation. In the TCA cycle, either pyruvate (from glycolysis) or acetyl coA are oxidized to generate the high energy electron carriers, NADH and FADH₂. NADH and FADH₂ enter the ETC at complex I and complex II, respectively. These high energy electron carriers undergo oxidation/reduction reactions in the ETC in order to pump protons into the matrix. These protons ultimately power ATP synthase (or Complex V) for the generation of ATP from ADP. These bioenergetic reactions maintain the mitochondrial electrochemical gradient, or mitochondrial membrane potential. Mitochondrial membrane potential is the main signal which either inhibits or initiates mitophagy.

Synaptic loss is strongly correlated to cognitive deficits and motor dysfunction [4-7]. Mitochondria are essential for synaptic function and neurotransmitter synthesis, release, and uptake[8,9] [10]. Accumulation of damaged mitochondria could lead to synaptic dysfunction and neurodegeneration. Mitophagy may play a role in ensuring synaptic mitochondrial integrity by degrading damaged mitochondria.

Disruption of mitophagy is observed with aging and in many neurodegenerative diseases. Recent advances have described novel mechanisms of mitophagy within the central nervous system (CNS). Here we will review current knowledge of mitophagy regulation, its role in neurodegenerative disease, and therapeutic potential.

2. Mitophagy: Autophagy for Mitochondria

Autophagosomes can be derived from membranes of endoplasmic reticulum (ER), golgi, mitochondria, or plasma membrane [11-15]. The biogenesis of autophagosomes involves the formation of the isolation membrane (IM), elongation and maturation, closure and then fusion with the lysosome to form the autolysosome. The first step in autophagosome biogenesis is the activation of the Unc-51-like kinase 1 complex (ULK1; pre-initiation complex) which contains ULK1, autophagy related proteins 13 and 101 (Atg13, Atg101), and focal adhesion kinase family interacting partner 200 (FIP200)[16-19]. This complex recruits the class III phosphatidylinositol 3-kinase (PI3K) Vps34 complex (Beclin1, autophagy related protein 14 (Atg14), autophagy and beclin 1 regulator 1 (Ambra1), vascular protein sorting 34 and 15 (Vps34 and Vps15)) to produce phosphatidylinositol 3-phosphate (PI3P); also called the initiation complex [16,18,20,21]. PI3P binding proteins, FYVE domain containing proteins (DFCP1) and WD repeat protein interacting with phosphoinositide (WIPIs) localize to the IM [17]. All of this culminates in the formation of the omegasome and IM. Autophagy related proteins 12, 5, 16 (Atg12, Atg5, Atg16)
and LC3-phosphatidylethanolamine (PE) facilitate the elongation and closure of the IM, following fusion with the lysosome[16,17,22].

There are several forms of autophagy (Figure 1); macroautophagy, non-selective/bulk autophagy, selective autophagy/microautophagy, or chaperone-mediated autophagy. Macroautophagy and non-selective/bulk mitophagy serves to degrade non-specific parts of the cytoplasm that are a mixture of contents. Selective autophagy is specific to cargo type, such as peroxisomes (pexophagy), ER (ER-phagy), pathogens (xenophagy), and mitochondria (mitophagy)[23,24].

Mitochondrial quality control mechanisms include mitochondrial chaperones, the mitochondrial unfolded protein response (UPR\textsuperscript{mt}), degradation of mitochondrial proteins in the cytoplasm via the proteasome (p97, 26S proteasome), removal of damaged proteins via mitochondrial derived vesicles (MDVs), and mitophagy [25]. Misfolded mitochondrial proteins can be refolded by mitochondrial chaperone proteins (heat shock proteins 22, 60, and 70) or cleaved/degraded by mitochondrial proteases Lon and Clp through the UPR\textsuperscript{mt} [26-30]. Damaged mitochondrial proteins can also be targeted specifically for proteasome degradation by p97 through the proteasome [31]. MDVs bud off mitochondria after engulfing damaged mitochondrial macromolecules. MDVs are associated with impaired mitochondrial import channels. These MDVs are either degraded by lysosomes, peroxisomes, or exocytosed [32,33]. Mitophagy (reviewed extensively below) functions to remove damaged mitochondria with the goal of preventing cell death.

2.1 Non-Receptor Mediated Mitophagy

Non-receptor mediated mitophagy (Figure 2) or classical mitophagy involves PTEN-induced kinase 1 (PINK1) and Parkin. PINK1 is normally degraded in the inner mitochondrial membrane (IMM) by PARL (presenilin-associated rhomboid-like protease) [34,35]. During mitophagy induction, PINK1 becomes active and accumulates on the outer mitochondrial membrane (OMM) where it recruits Parkin and ubiquitin through phosphorylation [36-44]. Parkin accumulates and polyubiquitinates mitochondrial proteins triggering proteasomal degradation. Parkin ubiquitination of OMM proteins leads to more PINK1 activity and phosphorylation of substrates, including recruitment of additional Parkin proteins at the OMM, creating a positive feedback loop. OMM proteins mitofusins 1 and 2 (MFN1/2), voltage dependent anion channel 1 (VDAC1), and translocase of the outer mitochondrial membrane 20 (TOM20) are ubiquitinated by Parkin [37,39-48]. Ubiquitination of MFN1/2 blocks mitochondrial fusion allowing for the isolation of damaged mitochondria and smaller mitochondria facilitate autophagosome targeting [25,42,49,50].

Autophagy adaptor proteins are recruited to the OMM by ubiquitinated proteins. These adaptors include neighbor BRCA1 gene (NBR1), nuclear dot protein 52 (NDP52), optineurin (OPTN), sequestosome-1 (SQSTM1/p62), and Tax1-binding protein (TAX1BP1) [14,23,45,51-57]. Adaptor proteins recruit and interact with autophagosome proteins; gamma-aminobutyric acid receptor-associated protein (GABARAP) or microtubule-associated protein 1A/1B-light chain 3 (LC3) to mediate the formation of the mitophagosome and lysosomal fusion/degradation. These adaptor proteins interact with LC3 and GABARAP through LC3 interacting regions (LIR) motifs (W/F/YxxL/I) [14,25,50,58]. The importance of different adaptor proteins has been up for debate and often their involvement in mitophagy is context dependent. The same is true for Parkin, as
there are some pathways of mitophagy which are Parkin independent, these are discussed below [14,37].

2.2 Receptor Mediated Mitophagy

Receptor mediated mitophagy (Figure 2) is driven by mitochondrial receptor proteins which contain LIR motifs (W/F/YxxL/I) [14,43]. OMM proteins, autophagy and Beclin 1 regulator 1 (AMBRA1), Bcl-2 interacting partner 3 (BNIP3), FUN14 domain-containing protein 1 (FUNDC1), Nip3-like protein X (NIX); and IMM proteins cardiolipin and prohibitin 2 (PHB2) are the most studied receptors which mediate mitophagy [14,43,59-64].

Receptor mediated mitophagy is activated under specific conditions. For example, during hypoxia BNIP3 and NIX transcription are activated by hypoxia inducible factor 1 alpha (HIF1α) [64-67]. BNIP3 and NIX activity are regulated by phosphorylation where increased phosphorylation increases their binding affinity for LC3 [68,69]. Hypoxia also promotes FUNDC1 binding to LC3 through dephosphorylation via phosphoglycerate mutase family member 5 phosphatase (PGAM5) [59,61,70,71]. Conversely, FUNDC1 phosphorylation by ULK1 is also a mitophagy activating event. Ultimately ubiquitination of FUNDC1 by E3 ubiquitin protein ligase 5 (UBR5) promotes lysosomal degradation of mitochondria [59,61,72]. The IMM receptors, PHB2 and cardiolipin have been shown to interact the LC3, especially during times of mitochondrial permeabilization [73,74]. AMBRA1 is sequestered and inhibited by B-cell lymphoma protein 2 (Bcl-2) on the OMM but upon mitophagy activation AMBRA1 binds LC3 in a Parkin dependent or independent manner [75].

Receptor mediated mitophagy culminates in the elongation of and closure of phagophore membranes, resulting in engulfment of the mitochondria. The elongation and closure of the phagophore is driven by the mitochondrial receptor binding LCR and/or GABARAP, leading to closure of the phagophore by GABARAP [14,43]. Last, the autophagosome fuses with a lysosome for degradation.

2.3 Mitoptosis

Separate from mitophagy pathways, damaged mitochondria can be partitioned and removed through mitoptosis. This phenomenon was first proposed in 1992 [76]. Mitoptosis has several proposed definitions. One possible process of mitoptosis occurs when damaged mitochondria gather around the nucleus, are selectively partitioned into lipid membranes and extruded from the cell [77]. A separate definition is when mitochondria undergo condensation with swelling and fragmentation of cristae. This leads to the bursting of the OMM and fragmented cristae are extruded into the cytoplasm. In other forms of mitoptosis the OMM can remain intact and the cristae deteriorate through refraction and coalescence [50,77-81]. The main benefit of mitoptosis is to prevent opening of the mitochondrial permeability transition pore (MPTP) and apoptosis. Overall, the method of which cells dispose of damaged mitochondria or part of mitochondria can vary and requires further study. There might be cell and tissue type specific pathways which evolved to provide the least devastating consequences based on cell and tissue function.

Mitoptosis does not require any extramitochondrial signaling or protein complexes, according to current knowledge. Some argue that PINK1 and Parkin might be involved, but no
consensus exists [50,77-82]. Situations which likely activate mitoptosis include mitochondrial membrane depolarization, increased ROS production and degradation of mitochondrial DNA (mtDNA).

2.4 Transcellular Mitophagy

Recent studies have described exocytosis of mitochondria from cells followed by endocytosis or phagocytosis of these extracellular mitochondria. In the brain, it was observed that neurons release mitochondria at synapses and these extracellular mitochondria were taken up by glial cells for phagocytosis [83,84]. This phenomenon will be referred to as transcellular mitophagy moving forward (Figure 3). A recent study showed retinal ganglion axons shed mitochondria which were then then degraded by adjacent astrocytes in mice [83]. Mitochondria might undergo degradation in the axoplasm (cytoplasm of nerve axon) with the assistance of axonal lysosomes [84]. Essentially, instead of being degraded in the soma, transcellular mitophagy describes the fact that axonal mitochondria are instead enclosed by axoplasmic membranes that are shed and degraded by neighboring cells.

The notion that transcellular mitophagy occurs is logical, given that it is not energetically favorable for neurons to bring mitochondria from dendrites back to the cell body for mitophagy. The process of transcellular mitophagy requires more study and understanding at the basic level and with regards to disease.

In addition to transcellular mitophagy, the observation of glial cells transferring mitochondria to neurons has been documented. In stroke models, glial cells transfer mitochondria to neurons as a likely means to protect neurons from energy stress and hypoxia [85,86]. The specific pathways which facilitate mitochondrial transfer between cells are unknown. However, some studies suggest in astrocytes, glial acidic fibrillary protein (GFAP) and in neurons, uncoupling protein 2 (UCP2) may play a role [87,88].

In mesenchymal stem cells connexins (particularly connexin 43) oligomerize to form GAP junctions. These GAP junctions may facilitate the formation of tunneling nanotubules which allow the exchange of cellular contents like mitochondria [89]. Other studies suggest Miro1, a protein which connects cytoskeletal motor proteins to mitochondria is involved in mitochondrial transfer between cells [90]. Finally, S100A4 has been shown to guide tunneling nanotubule growth [91]. The phenomenon of mitochondrial transfer between cells has been documented in a wide variety of models and tissue types [84-86,88-97]. An important question remains regarding what initiates mitochondrial transfer and the specific mechanisms which control this process.

3. Mitophagy in aging and neurodegeneration

Changes in mitophagy flux, signaling, and mitochondrial function are observed with aging and in neurodegenerative diseases. It is imperative to understand the role mitophagy could contribute to brain aging and neurodegeneration. We discuss these implications below.

3.1 Aging

Aging is associated with a loss of proteostasis, mitochondrial dysfunction, genome instability, inflammation, and metabolic deficits [25]. Reduced autophagy and mitophagy are observed in models of aging [25,98].
Mitochondrial homeostasis and function are altered in aging. However, the exact mechanisms and findings are not consistent across models and studies. Brain cytochrome oxidase (COX; complex IV) and complex I activity are reduced while ROS production and oxidized proteins are increased in aged rats [99,100]. Calcium homeostasis is changed in aged rat brain mitochondria and synaptosomes, neither were able to take up calcium at a rate equivalent to young rats [101]. Aged mice have altered proteomic expression of glycolytic, TCA, and oxidative phosphorylation pathways in brain but mitochondrial function is unchanged [102]. This suggests a compensatory mechanism with aging.

Altered brain mitochondrial morphology is observed in aged rats and monkeys [103,104]. Other findings suggest a change to mtDNA epigenetic markers and increased mtDNA deletions in aged mouse brain [105,106]. Oxidative damage to brain mtDNA is related to reduced lifespan across numerous species (birds and mammals) [107,108]. mtDNA in aged human brain shows increased somatic mutation burden and oxidative damage [109-111].

In multiples organisms, mitophagy is associated with longevity and lifespan. Pink1 knockout causes a shorter lifespan while Parkin overexpression in neurons specifically increases lifespan in D. melanogaster [38,112,113]. C. elegans models with induction of mild mitochondrial stress and up regulated mitophagy have extended lifespan [114,115]. Urolithin A (UA), tomatidine, and catechinic acid induce mitophagy and increase the lifespan of C. elegans models [116-118]. In an aging mouse model, stimulation of mitophagy with NAD⁺ prolongs lifespan [119].

Mitochondrial quality control emerges as a central theme in most neurodegenerative diseases, including AD, PD, and ALS. Mitophagy stimulation has shown positive effects in models of these diseases.

### 3.2 Alzheimer’s Disease

AD is the most common form of dementia diagnosed upon autopsy with neuropathological examination [120,121]. The pathological hallmarks which lead to AD diagnosis postmortem are considerable Aβ plaques and tau tangles throughout the brain [120-123]. Recent advances in neuroimaging have allowed the determination of Aβ plaque and tau tangle load in living subjects, showing these proteins accumulate in the brain decades before clinical signs of cognitive decline [122,124-126].

One of the earlier observations in AD subjects was reduced glucose uptake/utilization in the brain via fluorodeoxyglucose (FDG)-positron emission tomography (PET) [124-129]. Accumulation of evidence has ensued the last several decades showing an overall metabolic deficit in AD subjects, both within the brain and systemically [130]. The mitochondrial ETC enzyme, COX (or complex IV), has reduced Vmax in AD brain, fibroblasts, and blood samples [128,131-142]. AD like changes can be transferred to other cell types when AD patient mitochondria (mtDNA) are transferred [135,143-147]. This process of creating cytoplasmic hybrid cells (cybrids) allows for the determination of the contribution of mtDNA on disease and cell physiological processes [146].

Mitochondria in AD autopsy brain samples have fragmented cristae and vary widely in size compared to age matched ND brain samples [148]. Mitochondria within dendritic spines and presynaptic terminals show the most fragmented and disorganized cristae. Alterations to
mitochondrial ultrastructure were observed in areas of the brain with and without Aβ and tau pathology (cerebellar cortex, hypothalamus, cerebellum, and visual cortex). In addition to altered mitochondrial morphology, presynaptic terminals had reduced synaptic vesicles and fragmentation of golgi cisternae was observed [148].

mtDNA inheritance confers risk to AD. Studies show that offspring of maternal AD subjects have a higher risk of AD diagnosis than offspring of paternal AD subjects. Nearly all mitochondria are inherited maternally. Offspring from maternal AD subjects show metabolic and neuroimaging changes earlier in life than offspring of paternal AD subjects [125,149-152]. Furthermore, inherited mtDNA haplogroups are associated with both increased and decreased AD risk [153-160]. These inherited mtDNA haplogroups also interact with the nuclear DNA encoded risk factor, ApoE (apolipoprotein E) to influence AD risk [155,160,161]. Thus, it is important to understand the role of mitochondria, mitophagy, and metabolism in AD.

AD mouse models have disrupted mitophagy[162]. This is observed in human tau transgenic mice and AD postmortem brain with accumulated tau aggregates [163]. Mutant APP (Swedish mutant) mice show increased mitochondrial fission proteins, decreased mitochondrial fusion and mitophagy protein expression in hippocampal neurons [164]. APPsw /PS1dE9 transgenic mice show increased LC3, PINK1, and Parkin expression [165]. Cortical neurons derived from AD transgenic mice (J20; Swedish and Indiana APP mutations) also show increased mitophagy protein expression with depolarized mitochondrial membrane potential [166].

In AD postmortem brain samples accumulation of damaged mitochondria and autophagosome vacuoles are observed [167-169]. The UPRmt pathway is upregulated at the gene level, with reduced proteasomal activity through the 26S proteasome. Parkin, SQSTM1/p62, and LCR mitochondrial localization are increased [168-172]. Mitophagy pathways are altered in human postmortem AD brain. Cytosolic Parkin is depleted, lysosomal deficits are observed. Impaired Parkin recruitment to mitochondria is suggested to be caused by tau mediated sequestration of Parkin in the cytosol [166,173]. Defects in the activation of ULK1 and TBK1 lead to impaired mitophagy [173]. In AD, mitophagy increases or decreases depending on the part of the cell. Although it is increased in lysosomes, other parts of the cell fail at completing mitophagy.

Mechanisms of altered mitophagy and mitochondrial function warrant further study in AD. Specifically given the strong association of mitochondria and mitophagy with synapse health and function.

3.3 Parkinson’s Disease

PD is a neurodegenerative disease with both cognitive and neuromuscular changes. Motor deficits, tremors, rigidity, bradykinesia, dyssomnia, and depression are clinical hallmarks of PD. In some cases, PD can cause cognitive impairment. Within the brain, PD causes degeneration of dopaminergic neurons in the substantia nigra, with Lewy body accumulation (composed of aggregating α-synuclein) [174-176].

Mitochondrial dysfunction is observed in PD. A complex I deficiency is noted in brain (substantia nigra) but not in skeletal muscle [177,178]. The complex I deficiency might be brain specific, but some studies suggest deficits in platelets of PD subjects [179,180]. These findings are dependent on methodology used. Mitochondrial dysfunction is also observed in cybrid cell
lines derived from transfer of PD subject mtDNA, suggesting mtDNA may play a role [146,181-183]. Furthermore, PD patients have increased rates of mtDNA deletion in the substantia nigra [184,185].

PD has been associated with mitophagy dysfunction since the discovery of mutations in genes involved in mitophagy causing familial PD. Mutations in PARK6 (encodes for PINK1), PARK2 (encodes for Parkin), PARK1/4 (α-synuclein), PARK7 (DJ1), PARK8 (LRRK2), PARK17 (Vsp35), and PARK9 (ATP13A2) genes are linked to familial PD [173,186-191]. The role of PINK1, Parkin, and Vsp35 in mitophagy are well known and reviewed above. DJ1 and α-synuclein have been shown to modulate mitophagy either through direct interactions with PINK1 and Parkin, or by causing mitochondrial fragmentation. Loss of function of LRRK2 and ATP13A2 genes are linked to familial PD [173,186-191].

Despite these genetic studies, most PD cases are sporadic with no known genetic cause. Inhibition of complex I function with rotenone (a pesticide) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) induces PD in rodent and non-human primates [192-196]. Dopaminergic neurons form many synapses (up to one million per neuron) and thus have a high bioenergetic demand to maintain these unmyelinated synapses [4,197]. In human postmortem brain, mitophagy markers (phosphorylated S65 ubiquitin) increase across age and with PD diagnosis [198]. This mitophagy marker also associated with Lewy Bodies, showing an increase of mitophagy in early PD stages and decrease in late PD stages [198]. α-synuclein is also associated with an increase in Miro expression in post-mortem brain tissue, human neurons, and fly models of PD [199]. Reducing Miro in the human neuronal and fly models rescued neurodegeneration and mitophagy [199].

Overall, PD patients and disease models consistently show mitochondrial and mitophagy dysfunction.

3.4 ALS

ALS is a neurodegenerative disease marked by the loss of alpha motor neurons in the lumbar spinal cord and motor cortex [200,201]. The lifespan post ALS diagnosis is short, often 2-3 years because the progressive muscle wasting leads to lung paralysis. In some cases of ALS dementia is present [202]. Most ALS cases are sporadic, with a rare subset (less than 5% of total cases) being familial. These familial cases are caused by mutations in genes including Tdp43, Fus, Fig4, Ang, Vapb, and C9orf72 [203-206]. Mutations in the Optn gene which encodes an autophagy protein, optineurin, were found to be causative of ALS in 2010. [207-209]. After discovery of mutations in Sod1 and Tdp43, transgenic mouse models were developed [210-212].

Changes to mitochondrial ultrastructure in human ALS subjects were revealed several decades ago[213-215]. Cytoplasmic inclusions that may represent mitochondria-containing autophagic vacuoles are observed in ALS motor neurons[216,217]. Although ALS neurodegeneration is anatomically specific, mitochondrial abnormalities are found systemically [200,201,213,215,218,219]. Mitochondrial dysfunction is present in platelet and muscle mitochondria from ALS subjects [213,215,220-224]. MtDNA may contribute to ALS pathologies, as cybrid cells harboring mtDNA from ALS subjects often show mitochondrial abnormalities and increased cell death [146,215,225,226].

ALS is modeled using rodents that express human mutant SOD1 or mutant TDP43 [210,212]. SOD1 is a cytoplasmic enzyme which was identified within mitochondrial membranes
This is the case for both mutant SOD1 and to a lesser extent wild type SOD1. Mutant SOD1 ALS transgenic mice have altered mitochondrial morphology and mitochondrial SOD1 accumulation. This raises the possibility that mutant SOD1 may drive neurodegeneration by damaging mitochondria. TDP43 mutants are also observed within mitochondria and appear to induce mitochondrial dysfunction. Both TDP43 and SOD1 are known to aggregate within motor neurons and muscle; TDP43 interacts with proteins critical to mitophagy in an inhibitory manner.

Impaired mitophagy was proposed to be involved in the denervation of neuromuscular junctions in an ALS mouse model. Lysosomal dysfunction has also been implicated in ALS. Specifically, lysosomal deficits result in an abnormal accumulation of autophagic vacuoles that engulf damaged mitochondria within the motor neuron axons of G93A SOD1 ALS mice. Impaired mitochondrial turnover along with the accumulation of misfolded proteins and protein aggregates contributes to ALS linked mitochondrial dysfunction and motor neuron death. Mitochondrial and mitophagy ultrastructure are varied across compartments of motor neurons. Parkin, Miro1, and Mfn2 are depleted in an ALS mouse model (G93A SOD1) motor neurons, however mitochondrial localized p62 is upregulated. Mutant forms of optineurin interfere with Parkin ubiquitin ligase function.

In human post-mortem samples, increased autophagic vesicles are observed in lumbar spinal cord motor neurons. Induced pluripotent stem cell (iPSC) derived motor neurons from familial ALS subjects with C9orf72 mutations or haploinsufficiency have dysfunction of autophagy pathways.

As discussed above mitochondrial dysfunction and mitophagy alterations are prevalent in human AD, PD, and ALS samples as well as cell and animal models of disease. We discuss below methods being investigated to modulate mitophagy in these diseases below.

### 4. Modulating Mitophagy in Neurodegeneration

Increasing mitophagy in transgenic mouse models of neurodegeneration have shown mostly beneficial effects. In AD models (iPSC derived, transgenic mice, and C. elegans) increasing mitophagy using nicotinamide mononucleotide (NMN), UA, or actinonin (AC) reduced Aβ and tau aggregation. In AD transgenic mice mitophagy induction benefited cognition. These compounds are NAD+ precursors which may drive mitophagy through alterations in redox balance (NAD+/NADH). UA likely drives mitophagy through a PINK1/Parkin/Nix axis.

Broad autophagy induction with Rilmenidine in the G93A mutant SOD1 mouse model of ALS did not change disease progression. The mechanism(s) of Rilmenidine autophagy/mitophagy induction are currently unknown. Rapamycin (an mTOR inhibitor) treatment of this same mouse model was detrimental unless mature lymphocytes were depleted. These studies highlight the importance of understanding the non-cell autonomous effects of autophagy and mitophagy pathways.

In PD rodent models (MPTP injection) a drug, Salidroside, increased Parkin and PINK1 expression and preserved dopaminergic neurons in the substantia nigra. A cell permeable form of Parkin rescued cells from aggregating α-synuclein, partially restored motor function,
and protected dopaminergic neurons in the 6-ODHA PD (6-hydroxydopamine) mouse model [251].

UA has been shown safe and well tolerated in elderly adults, with plasma concentrations detectable at a range of doses. Furthermore, UA affected mitochondrial gene expression in muscle [252]. A separate study in healthy adults is registered for UA (NCT04160312) but no results have been posted. Clinical trials for NMN (NCT04228640 safety trial) are recruiting or ongoing (NCT03151239 effects on cardiometabolic health). In Japan, the first human clinical trial of NMN showed no deleterious effects suggesting NMN is tolerable and safe [253,254]. No clinical trials for these NAD⁺ precursor mitophagy modulators are currently registered for neurodegenerative diseases.

Lifestyle interventions could be useful tools to boost mitophagy. Exercise and diet have been shown to induce mitophagy [255-259]. In both AD animal models and human clinical trials exercise has shown cognitive benefit [258,260-264]. Exercise effects in ALS and PD are more controversial but overall seem to improve physical and cognitive outcomes [265-270]. Intermittent fasting and ketogenic diets have also been shown to induce mitophagy and improve cognition/motor performance [271-277].

Current clinical trials aimed at increasing autophagy, mitophagy, or mitochondrial function are ongoing or recently completed. For AD, these include treatment with nicotinamide riboside (NR; NCT04430517; NAD⁺ precursor), Dimebon (NCT00675623, NCT00829374; stimulates mTOR dependent mitophagy), resveratrol (NCT00678431; mTOR inhibitory), ketogenic diets (NCT03860792), and caloric restriction diets (NCT02460783). In PD, these include nicotinamide supplementation (NCT03568968; NAD⁺ precursor), ubiquinol/Coenzyme Q10 (NCT03061513; autophagy mechanism unknown), ketogenic diets and ketone esters (NCT01364545, NCT04477161). In ALS one clinical trial for ubiquinol/Coenzyme Q10 (NCT00243932; autophagy mechanism unknown) was completed. Overall, the clinical trials directly modulating mitophagy are lacking and require more attention. The majority of mitophagy inducers in clinical trials have unknown mechanisms and pleotropic affects. These pleotropic affects could be beneficial or deleterious.

Targeting specific pathways and tissues could be advantageous in avoiding deleterious or off target effects. Designing new therapeutic strategies should focus on modulating specific mitophagy targets while also enhancing mitochondrial function and biogenesis.

5. Concluding Remarks

Mitophagy and mitochondrial quality control are important mechanisms which should be further studied in the context of brain aging and neurodegeneration. Novel mechanisms of mitochondrial quality control in neurons and glia have illuminated the knowledge gaps in this field of study. Mitochondria are dynamic and multifaceted organelles at the forefront of pathways associated with aging and neurodegeneration (proteostasis, metabolism, inflammation, synapse loss). Thus, targeting mitochondrial health and mitochondrial quality control will target the most common pathological mechanisms in neurodegeneration.
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References

1. Wilkins, H.M.; Swerdlow, R.H. Relationships Between Mitochondria and Neuroinflammation: Implications for Alzheimer’s Disease. Curr Top Med Chem 2016, 16, 849-857, doi:10.2174/1568026615666150827095102.
2. Eisner, V.; Picard, M.; Hajnoczky, G. Mitochondrial dynamics in adaptive and maladaptive cellular stress responses. Nat Cell Biol 2018, 20, 755-765, doi:10.1038/s41556-018-0133-0.
3. Swerdlow, R.H.; Koppel, S.; Weidling, I.; Hayley, C.; Ji, Y.; Wilkins, H.M. Mitochondria, Cybrids, Aging, and Alzheimer’s Disease. Prog Mol Biol Transl Sci 2017, 146, 259-302, doi:10.1016/bs.pmbts.2016.12.017.
4. Pissadaki, E.K.; Bolam, J.P. The energy cost of action potential propagation in dopamine neurons: clues to susceptibility in Parkinson’s disease. Front Comput Neurosci 2013, 7, 13, doi:10.3389/fncom.2013.00013.
5. Robinson, J.L.; Molina-Porcel, L.; Corrada, M.M.; Raible, K.; Lee, E.B.; Lee, V.M.; Kawas, C.H.; Trojanowski, J.Q. Perforant path synaptic loss correlates with cognitive impairment and Alzheimer’s disease in the oldest-old. Brain 2014, 137, 2578-2587, doi:10.1093/brain/awu190.
6. Kashyap, G.; Bapat, D.; Das, D.; Gowaikar, R.; Amritkar, R.E.; Rangarajan, G.; Ravindranath, V.; Ambika, G. Synapse loss and progress of Alzheimer’s disease -A network model. Sci Rep 2019, 9, 6555, doi:10.1038/s41598-019-43076-y.
7. Lepeta, K.; Lourenco, M.V.; Schweitzer, B.C.; Martino Adami, P.V.; Banerjee, P.; Catuara-Solarz, S.; de La Fuente Revenga, M.; Guillem, A.M.; Haidar, M.; Ijomone, O.M., et al. Synaptopathies: synaptic dysfunction in neurological disorders - A review from students to students. J Neurochem 2016, 138, 785-805, doi:10.1111/jnc.13713.
8. Manji, H.; Kato, T.; Di Prospero, N.A.; Ness, S.; Beal, M.F.; Krams, M.; Chen, G. Impaired mitochondrial function in psychiatric disorders. Nat Rev Neurosci 2012, 13, 293-307, doi:10.1038/nrr3229.
9. Sheng, Z.H.; Cai, Q. Mitochondrial transport in neurons: impact on synaptic homeostasis and neurodegeneration. Nat Rev Neurosci 2012, 13, 77-93, doi:10.1038/nrr3156.
10. Han, S.; Jeong, Y.Y.; Sheshadri, P.; Su, X.; Cai, Q. Mitophagy regulates integrity of mitochondria at synapses and is critical for synaptic maintenance. EMBO Rep 2020, 10.15252/embr.201949801, e201949801, doi:10.15252/embr.201949801.
11. Hailey, D.W.; Rambold, A.S.; Satpute-Krishnan, P.; Mitra, K.; Sougrat, R.; Kim, P.K.; Lippincott-Schwartz, J. Mitochondria supply membranes for autophagosome biogenesis during starvation. Cell 2010, 141, 656-667, doi:10.1016/j.cell.2010.04.009.
12. Ravikumar, B.; Moreau, K.; Jareiss, L.; Puri, C.; Rubinsztein, D.C. Plasma membrane contributes to the formation of pre-autophagosomal structures. Nat Cell Biol 2010, 12, 747-757, doi:10.1038/ncb2078.
13. Hayashi-Nishino, M.; Fujita, N.; Noda, T.; Yamaguchi, A.; Yoshimori, T.; Yamamoto, A. A subdomain of the endoplasmic reticulum forms a cradle for autophagosome formation. Nat Cell Biol 2009, 11, 1433-1437, doi:10.1038/ncb1991.
14. Feng, D.; Liu, L.; Zhu, Y.; Chen, Q. Molecular signaling toward mitophagy and its physiological significance. *Exp Cell Res* **2013**, *319*, 1697-1705, doi:10.1016/j.yexcr.2013.03.034.

15. Ge, L.; Zhang, M.; Kenny, S.J.; Liu, D.; Maeda, M.; Saito, K.; Mathur, A.; Xu, K.; Schekman, R. Remodeling of ER-exit sites initiates a membrane supply pathway for autophagosome biogenesis. *EMBO Rep* **2017**, *18*, 1586-1603, doi:10.15252/embr.201744559.

16. Tanida, I. Autophagosome formation and molecular mechanism of autophagy. *Antioxid Redox Signal* **2011**, *14*, 2201-2214, doi:10.1089/ars.2010.3482.

17. Itakura, E.; Mizushima, N. Characterization of autophagosome formation site by a hierarchical analysis of mammalian Atg proteins. *Autophagy* **2010**, *6*, 764-776, doi:10.4161/auto.6.6.12709.

18. Hurley, J.H.; Young, L.N. Mechanisms of Autophagy Initiation. *Annu Rev Biochem* **2017**, *86*, 225-244, doi:10.1146/annurev-biochem-061516-044820.

19. Hosokawa, N.; Haras, T.; Kaizuka, T.; Takamura, A.; Miura, Y.; Iemura, S.; Natsume, T.; Takehana, K.; Yamada, N., et al. Nutrient-dependent mTORC1 association with the ULK1-Atg13-FIP200 complex required for autophagy. *Mol Biol Cell* **2009**, *20*, 1981-1991, doi:10.1091/mbc.E08-12-1248.

20. Funderburk, S.F.; Wang, Q.J.; Yue, Z. The Beclin 1-VPS34 complex—at the crossroads of autophagy and beyond. *Trends Cell Biol* **2010**, *20*, 355-362, doi:10.1016/j.tcb.2010.03.002.

21. Tassa, A.; Roux, M.P.; Attaix, D.; Bechet, D.M. Class III phosphoinositide 3-kinase--Beclin1 complex mediates the amino acid-dependent regulation of autophagy in C2C12 myotubes. *Biochem J* **2003**, *376*, 577-586, doi:10.1042/BJ20030826.

22. Romanov, J.; Walczak, M.; Ibiriciu, I.; Schuchner, S.; Ogris, E.; Kraft, C.; Martens, S. Mechanism and functions of membrane binding by the Atg5-Atg12/Atg16 complex during autophagosome formation. *EMBO J* **2012**, *31*, 4304-4317, doi:10.1038/emboj.2012.278.

23. Mizushima, N.; Komatsu, M. Autophagy: renovation of cells and tissues. *Cell* **2011**, *147*, 728-741, doi:10.1016/j.cell.2011.10.026.

24. Knuppertz, L.; Osiewacz, H.D. Orchestrating the network of molecular pathways affecting aging: Role of nonselective autophagy and mitophagy. *Mech Ageing Dev* **2016**, *153*, 30-40, doi:10.1016/j.mad.2016.01.003.

25. Fivenson, E.M.; Lautrup, S.; Sun, N.; Scheibye-Knudsen, M.; Stevnsner, T.; Nilsen, H.; Bohr, V.A.; Fang, E.F. Mitophagy in neurodegeneration and aging. *Neurochem Int* **2017**, *109*, 202-209, doi:10.1016/j.neuint.2017.02.007.

26. Lin, Y.F.; Haynes, C.M. Metabolism and the UPR(mt). *Mol Cell* **2016**, *61*, 677-682, doi:10.1016/j.molcel.2016.02.004.

27. Haynes, C.M.; Ron, D. The mitochondrial UPR - protecting organelle protein homeostasis. *J Cell Sci* **2010**, *123*, 3849-3855, doi:10.1242/jcs.075119.

28. Pellegrino, M.W.; Nargund, A.M.; Haynes, C.M. Signaling the mitochondrial unfolded protein response. *Biochim Biophys Acta* **2013**, *1833*, 410-416, doi:10.1016/j.bbamcr.2012.02.019.

29. Voos, W.; Rottgers, K. Molecular chaperones as essential mediators of mitochondrial biogenesis. *Biochim Biophys Acta* **2002**, *1592*, 51-62, doi:10.1016/s0167-4889(02)00264-1.

30. Ryan, M.T.; Naylor, D.J.; Hoj, P.B.; Clark, M.S.; Hoogenraad, N.J. The role of molecular chaperones in mitochondrial protein import and folding. *Int Rev Cytol* **1997**, *174*, 127-193, doi:10.1016/s0074-7696(08)62117-8.

31. Xu, S.; Peng, G.; Wang, Y.; Fang, S.; Karbowsk, M. The AAA-ATPase p97 is essential for outer mitochondrial membrane protein turnover. *Mol Biol Cell* **2011**, *22*, 291-300, doi:10.1091/mbc.E10-09-0748.

32. Cadete, V.I.; Deschenes, S.; Cuillerier, A.; Brisebois, F.; Sugiuira, A.; Vincent, A.; Turnbull, D.; Picard, M.; McBride, H.M.; Burelle, Y. Formation of mitochondrial-derived vesicles is an active
33. Sugiura, A.; McLelland, G.L.; Fon, E.A.; McBride, H.M. A new pathway for mitochondrial quality control: mitochondrial-derived vesicles. *EMBO J* 2014, 33, 2142-2156, doi:10.15252/embj.201488104.

34. Meissner, C.; Lorenz, H.; Weihofen, A.; Selkoe, D.J.; Lemberg, M.K. The mitochondrial intramembrane protease PARL cleaves human Pink1 to regulate Pink1 trafficking. *J Neurochem* 2011, 117, 856-867, doi:10.1111/j.1471-4159.2011.07253.x.

35. Jin, S.M.; Lazarou, M.; Wang, C.; Kane, L.A.; Narendra, D.P.; Youle, R.J. Mitochondrial membrane potential regulates PINK1 import and proteolytic destabilization by PARL. *J Cell Biol* 2010, 191, 933-942, doi:10.1083/jcb.201008084.

36. Matsuda, N.; Sato, S.; Shiba, K.; Okatsu, K.; Saisho, K.; Gautier, C.A.; Sou, Y.S.; Saiki, S.; Kawajiri, S.; Sato, F., et al. PINK1 stabilized by mitochondrial depolarization recruits Parkin to damaged mitochondria and activates latent Parkin for mitophagy. *J Cell Biol* 2010, 189, 211-221, doi:10.1083/jcb.200910140.

37. Geisler, S.; Holmstrom, K.M.; Skujat, D.; Fiesel, F.C.; Rothfuss, O.C.; Kahle, P.J.; Springer, W. PINK1/Parkin-mediated mitophagy involves ubiquitination of mitofusins 1 and 2: Implications for Parkinson disease pathogenesis. *Autophagy* 2011, 7, 243-245, doi:10.4161/auto.7.2.14332.

38. Wei, H.; Liu, L.; Chen, Q. Selective removal of mitochondria via mitophagy: distinct pathways for different mitochondrial stresses. *Biochim Biophys Acta* 2015, 1853, 2784-2790, doi:10.1016/j.bbamcr.2015.03.013.

39. Durcan, T.M.; Fon, E.A. The three 'P's of mitophagy: PARKIN, PINK1, and post-translational modifications. *Genes Dev* 2015, 29, 989-999, doi:10.1101/gad.262758.115.
48. Tanaka, A.; Cleland, M.M.; Xu, S.; Narendra, D.P.; Suen, D.F.; Karbowski, M.; Youle, R.J. Proteasome and p97 mediate mitophagy and degradation of mitofusins induced by Parkin. *J Cell Biol* **2010**, *191*, 1367-1380, doi:10.1083/jcb.201007013.

49. Chan, N.C.; Salazar, A.M.; Pham, A.H.; Sweredoski, M.J.; Kolawa, N.J.; Graham, R.L.; Hess, S.; Chan, D.C. Broad activation of the ubiquitin-proteasome system by Parkin is critical for mitophagy. *Hum Mol Genet* **2011**, *20*, 1726-1737, doi:10.1093/hmg/ddr048.

50. Mijaljica, D.; Prescott, M.; Devenish, R.J. Mitophagy and mitoptosis in disease processes. *Methods Mol Biol* **2010**, *648*, 93-106, doi:10.1007/978-1-60761-756-3_6.

51. Shi, J.; Fung, G.; Deng, H.; Zhang, J.; Fiesel, F.C.; Springer, W.; Li, X.; Luo, H. NBR1 is dispensable for PARK2-mediated mitophagy regardless of the presence or absence of SQSTM1. *Cell Death Dis* **2015**, *6*, e1943, doi:10.1038/cddis.2015.278.

52. Richter, B.; Sliter, D.A.; Herhaus, L.; Stolz, A.; Wang, C.; Beli, P.; Zaffagnini, G.; Wild, P.; Martens, S.; Wagner, S.A., et al. Phosphorylation of OPTN by TBK1 enhances its binding to Ub chains and promotes selective autophagy of damaged mitochondria. *Proc Natl Acad Sci U S A* **2016**, *113*, 4039-4044, doi:10.1073/pnas.1523926113.

53. Yamada, T.; Dawson, T.M.; Iijima, M.; Sesaki, H. SQSTM1/p62 promotes mitochondrial ubiquitination independently of PINK1 and PRKN/parkin in mitophagy. *Cell Death Dis* **2019**, *15*, 2012-2018, doi:10.1080/15548627.2019.1643185.

54. Whang, M.I.; Tavares, R.M.; Benjamin, D.I.; Kattah, M.G.; Nomura, D.K.; Debnath, J.; Malynn, B.A.; Ma, A. The Ubiquitin Binding Protein TAX1BP1 Mediates Autophagosome Induction and the Metabolic Transition of Activated T Cells. *Immunity* **2017**, *46*, 405-420, doi:10.1016/j.immuni.2017.02.018.

55. Yoo, S.M.; Jung, Y.K. A Molecular Approach to Mitophagy and Mitochondrial Dynamics. *Mol Cells* **2018**, *41*, 18-26, doi:10.14348/molcells.2018.2277.

56. Liu, L.; Feng, D.; Chen, G.; Chen, M.; Zheng, Q.; Song, P.; Ma, Q.; Zhu, C.; Wang, R.; Qi, W., et al. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. *Nat Cell Biol* **2012**, *14*, 177-185, doi:10.1038/ncb2422.

57. Novak, I.; Kirkin, V.; McEwan, D.G.; Zhang, J.; Wild, P.; Rozenknop, A.; Rogov, V.; Lohr, F.; Popovic, D.; Occhipinti, A., et al. Nix is a selective autophagy receptor for mitochondrial clearance. *EMBO Rep* **2010**, *11*, 45-51, doi:10.1038/embr.2009.256.

58. Wu, W.; Tian, W.; Hu, Z.; Chen, G.; Huang, L.; Li, W.; Zhang, X.; Xue, P.; Zhou, C.; Liu, L., et al. ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. *EMBO Rep* **2014**, *15*, 566-575, doi:10.1002/embr.201438501.

59. Zhang, J.; Ney, P.A. NIX induces mitochondrial autophagy in reticulocytes. *Autophagy* **2008**, *4*, 354-356, doi:10.4161/auto.5552.

60. Sandoval, H.; Thiagarajan, P.; Dasgupta, S.K.; Schumacher, A.; Prchal, J.T.; Chen, M.; Wang, J. Essential role for Nix in autophagic maturation of erythroid cells. *Nature* **2008**, *454*, 232-235, doi:10.1038/nature07006.
64. Zhang, J.; Ney, P.A. Role of BNIP3 and NIX in cell death, autophagy, and mitophagy. *Cell Death Differ* **2009**, *16*, 939-946, doi:10.1038/cdd.2009.16.

65. Sowter, H.M.; Ratcliffe, P.J.; Watson, P.; Greenberg, A.H.; Harris, A.L. HIF-1-dependent regulation of hypoxic induction of the cell death factors BNIP3 and NIX in human tumors. *Cancer Res* **2001**, *61*, 6669-6673.

66. Guo, K.; Seearfoss, G.; Krolikowski, D.; Pagnoni, M.; Franks, C.; Clark, K.; Yu, K.T.; Jaye, M.; Ivashchenko, Y. Hypoxia induces the expression of the pro-apoptotic gene BNIP3. *Cell Death Differ* **2001**, *8*, 367-376, doi:10.1038/sj.cdd.4400810.

67. Bellot, G.; Garcia-Medina, R.; Gounon, P.; Chiche, J.; Roux, D.; Pouyssegur, J.; Mazure, N.M. Hypoxia-induced autophagy is mediated through hypoxia-inducible factor induction of BNIP3 and BNIP3L via their BH3 domains. *Mol Cell Biol* **2009**, *29*, 2570-2581, doi:10.1128/MCB.00166-09.

68. Liu, K.E.; Frazier, W.A. Phosphorylation of the BNIP3 C-Terminus Inhibits Mitochondrial Damage and Cell Death without Blocking Autophagy. *PLoS One* **2015**, *10*, e0129667, doi:10.1371/journal.pone.0129667.

69. Rogov, V.V.; Suzuki, H.; Marinkovic, M.; Lang, V.; Kato, R.; Kawasaki, M.; Buljubasic, M.; Sprung, M.; Rogova, N.; Wakatsuki, S., et al. Phosphorylation of the mitochondrial autophagy receptor Nix enhances its interaction with LC3 proteins. *Sci Rep* **2017**, *7*, 1131, doi:10.1038/s41598-017-01258-6.

70. Ma, K.; Zhang, Z.; Chang, R.; Cheng, H.; Mu, C.; Zhao, T.; Chen, L.; Zhang, C.; Luo, Q.; Lin, J., et al. Dynamic PGAM5 multimers dephosphorylate BCL-xL or FUNDC1 to regulate mitochondrial and cellular fate. *Cell Death Differ* **2020**, *27*, 1036-1051, doi:10.1038/s41418-019-0396-4.

71. Chen, G.; Han, Z.; Feng, D.; Chen, Y.; Chen, L.; Wu, H.; Huang, L.; Zhou, C.; Cai, X.; Fu, C., et al. A regulatory signaling loop comprising the PGAM5 phosphatase and CK2 controls receptor-mediated mitophagy. *Mol Cell* **2014**, *54*, 362-377, doi:10.1016/j.molcel.2014.02.034.

72. Chen, Z.; Liu, L.; Cheng, Q.; Li, Y.; Wu, H.; Zhang, W.; Wang, Y.; Sehgal, S.A.; Siraj, S.; Wang, X., et al. Mitochondrial E3 ligase MARCH5 regulates FUNDC1 to fine-tune hypoxic mitophagy. *EMBO Rep* **2017**, *18*, 495-509, doi:10.15252/embr.201643309.

73. Yan, C.; Gong, L.; Chen, L.; Xu, M.; Abou-Hamdan, H.; Tang, M.; Desaubry, L.; Song, Z. PHB2 (prohibitin 2) promotes PINK1/PRKN/Parkin-dependent mitophagy by the PARL-PGAM5-PINK1 axis. *Autophagy* **2020**, *16*, 419-434, doi:10.1080/15548627.2019.1628520.

74. Li, X.X.; Tsoi, B.; Li, Y.F.; Kurihara, H.; He, R.R. Cardiolipin and its different properties in mitophagy and apoptosis. *J Histochem Cytochem* **2015**, *63*, 301-311, doi:10.1369/0022155415574818.

75. Strappazzon, F.; Nazio, F.; Corrado, M.; Cianfanelli, V.; Romagnoli, A.; Fimia, G.M.; Campello, S.; Nardacci, R.; Placentini, M.; Campanella, M., et al. AMBRA1 is able to induce mitophagy via LC3 binding, regardless of PARKIN and p62/SQSTM1. *Cell Death Differ* **2015**, *22*, 517, doi:10.1038/cdd.2014.190.

76. Zorov, D.B.; Kinnally, K.W.; Tedeschi, H. Voltage activation of heart inner mitochondrial membrane channels. *J Bioenerg Biomembr* **1992**, *24*, 119-124, doi:10.1007/BF00769538.

77. Lyamzaev, K.G.; Nepryaikhina, O.K.; Saprunova, V.B.; Bakeeva, L.E.; Pletjushkina, O.V.; Chernyak, B.V.; Skulachev, V.P. Novel mechanism of elimination of malfunctioning mitochondria (mitoptosis): formation of mitoptotic bodies and extrusion of mitochondrial material from the cell. *Biochim Biophys Acta* **2008**, *1777*, 817-825, doi:10.1016/j.bbabio.2008.03.027.

78. Skulachev, V.P. Bioenergetic aspects of apoptosis, necrosis and mitoptosis. *Apoptosis* **2006**, *11*, 473-485, doi:10.1007/s10495-006-5881-9.
79. Skulachev, V.P. Mitochondrial physiology and pathology; concepts of programmed death of organelles, cells and organisms. *Mol Aspects Med* 1999, 20, 139-184, doi:10.1016/s0098-2997(99)00008-4.

80. Jangamreddy, J.R.; Los, M.J. Mitoptosis, a novel mitochondrial death mechanism leading predominantly to activation of autophagy. *Hepat Mon* 2012, 12, e6159, doi:10.5812/hepatmon.6159.

81. Tinari, A.; Garofalo, T.; Sorice, M.; Esposti, M.D.; Malorni, W. Mitoptosis: different pathways for mitochondrial execution. *Autophagy* 2007, 3, 282-284, doi:10.4161/auto.3924.

82. Skulachev, V.P. Programmed death phenomena: from organelle to organism. *Ann N Y Acad Sci* 2002, 959, 214-237, doi:10.1111/j.1749-6632.2002.tb02095.x.

83. Davis, C.H.; Kim, K.Y.; Bushong, E.A.; Mills, E.A.; Boassa, D.; Shih, T.; Kinebuchi, M.; Phan, S.; Zhou, Y.; Bihlmeyer, N.A., et al. Transcellular degradation of axonal mitochondria. *Proc Natl Acad Sci U S A* 2014, 111, 9633-9638, doi:10.1073/pnas.1404651111.

84. Davis, C.H.; Marsh-Armstrong, N. Discovery and implications of transcellular mitophagy. *Autophagy* 2014, 10, 2383-2384, doi:10.4161/15548627.2014.981920.

85. Hayakawa, K.; Esposito, E.; Wang, X.; Terasaki, Y.; Liu, Y.; Xing, C.; Ji, X.; Lo, E.H. Corrigendum: Transfer of mitochondria from astrocytes to neurons after stroke. *Nature* 2016, 539, 123, doi:10.1038/nature19805.

86. Hayakawa, K.; Esposito, E.; Wang, X.; Terasaki, Y.; Liu, Y.; Xing, C.; Ji, X.; Lo, E.H. Transfer of mitochondria from astrocytes to neurons after stroke. *Nature* 2016, 535, 551-555, doi:10.1038/nature18928.

87. Hass, D.T.; Barnstable, C.J. Mitochondrial Uncoupling Protein 2 Knock-out Promotes Mitophagy to Decrease Retinal Ganglion Cell Death in a Mouse Model of Glaucoma. *J Neurosci* 2019, 39, 3586-3596, doi:10.1523/JNEUROSCI.2702-18.2019.

88. Gao, L.; Zhang, Z.; Lu, J.; Pei, G. Mitochondria Are Dynamically Transferring Between Human Neural Cells and Alexander Disease-Associated GFAP Mutations Impair the Astrocytic Transfer. *Front Cell Neurosci* 2019, 13, 316, doi:10.3389/fncel.2019.00316.

89. Islam, M.N.; Das, S.R.; Emin, M.T.; Wei, M.; Sun, L.; Westphalen, K.; Rowlands, D.J.; Quadri, S.K.; Bhattacharya, S.; Bhattacharya, J. Mitochondrial transfer from bone-marrow-derived stromal cells to pulmonary alveoli protects against acute lung injury. *Nat Med* 2012, 18, 759-765, doi:10.1038/nm.2736.

90. Ahmad, T.; Mukherjee, S.; Pattnaik, B.; Kumar, M.; Singh, S.; Kumar, M.; Rehman, R.; Tiwari, B.K.; Jha, K.A.; Barhanpurkar, A.P., et al. Miro1 regulates intercellular mitochondrial transport & enhances mesenchymal stem cell rescue efficacy. *EMBO J* 2014, 33, 994-1010, doi:10.1002/embj.201386030.

91. Torralba, D.; Baixauli, F.; Sanchez-Madrid, F. Mitochondria Know No Boundaries: Mechanisms and Functions of Intercellular Mitochondrial Transfer. *Front Cell Dev Biol* 2016, 4, 107, doi:10.3389/fcell.2016.00107.

92. Han, H.; Hu, J.; Yan, Q.; Zhu, J.; Zhu, Z.; Chen, Y.; Sun, J.; Zhang, R. Bone marrow-derived mesenchymal stem cells rescue injured H9c2 cells via transferring intact mitochondria through tunneling nanotubes in an in vitro simulated ischemia/reperfusion model. *Mol Med Rep* 2016, 13, 1517-1524, doi:10.3892/mmr.2015.4726.

93. Liu, K.; Ji, K.; Guo, L.; Wu, W.; Lu, H.; Shan, P.; Yan, C. Mesenchymal stem cells rescue injured endothelial cells in an in vitro ischemia-reperfusion model via tunneling nanotube like structure-mediated mitochondrial transfer. *Microvasc Res* 2014, 92, 10-18, doi:10.1016/j.mvr.2014.01.008.

94. Cho, Y.M.; Kim, J.H.; Kim, M.; Park, S.J.; Koh, S.H.; Ahn, H.S.; Kang, G.H.; Lee, J.B.; Park, K.S.; Lee, H.K. Mesenchymal stem cells transfer mitochondria to the cells with virtually no mitochondrial
function but not with pathogenic mtDNA mutations. PLoS One 2012, 7, e32778, doi:10.1371/journal.pone.0032778.

95. Konari, N.; Nagaishi, K.; Kikuchi, S.; Fujimiya, M. Mitochondria transfer from mesenchymal stem cells structurally and functionally repairs renal proximal tubular epithelial cells in diabetic nephropathy in vivo. Sci Rep 2019, 9, 5184, doi:10.1038/s41598-019-40163-y.

96. Spees, J.L.; Olson, S.D.; Whitney, M.J.; Prockop, D.J. Mitochondrial transfer between cells can rescue aerobic respiration. Proc Natl Acad Sci U S A 2006, 103, 1283-1288, doi:10.1073/pnas.0510511103.

97. Wang, X.; Gerdes, H.H. Transfer of mitochondria via tunneling nanotubes rescues apoptotic PC12 cells. Cell Death Differ 2015, 22, 1181-1191, doi:10.1038/cdd.2014.211.

98. Hansen, M.; Rubinsztein, D.C.; Walker, D.W. Autophagy as a promoter of longevity: insights from model organisms. Nat Rev Mol Cell Biol 2018, 19, 579-593, doi:10.1038/s41580-018-0033-y.

99. Petrosillo, G.; De Benedictis, V.; Ruggiero, F.M.; Paradies, G. Decline in cytochrome c oxidase activity in rat-brain mitochondria with aging. Role of peroxidized cardiolipin and beneficial effect of melatonin. J Bioenerg Biomembr 2013, 45, 431-440, doi:10.1007/s10863-013-9505-0.

100. Petrosillo, G.; Matera, M.; Casanova, G.; Ruggiero, F.M.; Paradies, G. Mitochondrial dysfunction in rat brain with aging Involvement of complex I, reactive oxygen species and cardiolipin. Neurochem Int 2008, 53, 126-131, doi:10.1016/j.neuint.2008.07.001.

101. Leslie, S.W.; Chandler, L.J.; Barr, E.M.; Farrar, R.P. Reduced calcium uptake by rat brain mitochondria and synaptosomes in response to aging. Brain Res 1985, 329, 177-183, doi:10.1016/0006-8993(85)90523-2.

102. Stauch, K.L.; Purnell, P.R.; Villeneuve, L.M.; Fox, H.S. Proteomic analysis and functional characterization of mouse brain mitochondria during aging reveal alterations in energy metabolism. Proteomics 2015, 15, 1574-1586, doi:10.1002/pmc.201400277.

103. Bertoni-Freddari, C.; Fattoretti, P.; Casoli, T.; Spagna, C.; Meier-Ruge, W.; Ulrich, J. Morphological plasticity of synaptic mitochondria during aging. Brain Res 1993, 628, 193-200, doi:10.1016/0006-8993(93)90955-m.

104. Bertoni-Freddari, C.; Balietti, M.; Giorgetti, B.; Grossi, Y.; Casoli, T.; Di Stefano, G.; Perretta, G.; Fattoretti, P. Selective decline of the metabolic competence of oversized synaptic mitochondria in the old monkey cerebellum. Rejuvenation Res 2008, 11, 387-391, doi:10.1089/rej.2008.0659.

105. Tanhauser, S.M.; Laipis, P.J. Multiple deletions are detectable in mitochondrial DNA of aging mice. J Biol Chem 1995, 270, 24769-24775, doi:10.1074/jbc.270.42.24769.

106. Dzitoyeva, S.; Chen, H.; Manev, H. Effect of aging on 5-hydroxymethylcytosine in brain mitochondria. Neurobiol Aging 2012, 33, 2881-2891, doi:10.1016/j.neurobiolaging.2012.02.006.

107. Herrero, A.; Barja, G. 8-oxo-deoxyguanosine levels in heart and brain mitochondrial and nuclear DNA of two mammals and three birds in relation to their different rates of aging. Aging (Milano) 1999, 11, 294-300, doi:10.1007/BF03339803.

108. Barja, G.; Herrero, A. Oxidative damage to mitochondrial DNA is inversely related to maximum life span in the heart and brain of mammals. FASEB J 2000, 14, 312-318, doi:10.1096/fasebj.14.2.312.

109. Mecocci, P.; MacGarvey, U.; Kaufman, A.E.; Koontz, D.; Shoffner, J.M.; Wallace, D.C.; Beal, M.F. Oxidative damage to mitochondrial DNA shows marked age-dependent increases in human brain. Ann Neurol 1993, 34, 609-616, doi:10.1002/ana.410340416.

110. Wallace, D.C. Mitochondrial DNA in aging and disease. Sci Am 1997, 277, 40-47, doi:10.1038/scientificamerican0897-40.

111. Cortopassi, G.A.; Shibata, D.; Soong, N.W.; Arnheim, N. A pattern of accumulation of a somatic deletion of mitochondrial DNA in aging human tissues. Proc Natl Acad Sci U S A 1992, 89, 7370-7374, doi:10.1073/pnas.89.16.7370.
112. Clark, I.E.; Dodson, M.W.; Jiang, C.; Cao, J.H.; Huh, J.R.; Seol, J.H.; Yoo, S.J.; Hay, B.A.; Guo, M. Drosophila pink1 is required for mitochondrial function and interacts genetically with parkin. 
*Nature 2006*, *441*, 1162-1166, doi:10.1038/nature04779.

113. Rana, A.; Rera, M.; Walker, D.W. Parkin overexpression during aging reduces proteotoxicity, alters mitochondrial dynamics, and extends lifespan. *Proc Natl Acad Sci U S A 2013*, *110*, 8638-8643, doi:10.1073/pnas.1216197110.

114. Palikaras, K.; Lionaki, E.; Tavernarakis, N. Coordination of mitophagy and mitochondrial biogenesis during ageing in C. elegans. *Nature 2015*, *521*, 525-528, doi:10.1038/nature14300.

115. Schiavi, A.; Maglioni, S.; Palikaras, K.; Shaik, A.; Strappazzon, F.; Brinkmann, V.; Torgovnick, A.; Castelein, N.; De Henau, S.; Braeckman, B.P., et al. Iron-Starvation-Induced Mitophagy Mediates Lifespan Extension upon Mitochondrial Stress in C. elegans. *Curr Biol 2015*, *25*, 1810-1822, doi:10.1016/j.cub.2015.05.059.

116. Wu, X.; Al-Amin, M.; Zhao, C.; An, F.; Wang, Y.; Huang, Q.; Teng, H.; Song, H. Catechinic acid, a natural polyphenol compound, extends the lifespan of Caenorhabditis elegans via mitophagy pathways. *Food Funct 2020*, *11*, 5621-5634, doi:10.1039/d0fo00694g.

117. Fang, E.F.; Waltz, T.B.; Kassahun, H.; Lu, Q.; Kerr, J.S.; Morevati, M.; Fivenson, E.M.; Wollman, B.N.; Marosi, K.; Wilson, M.A., et al. Tomatidine enhances lifespan and healthspan in C. elegans through mitophagy induction via the SKN-1/Nrf2 pathway. *Sci Rep 2017*, *7*, 46208, doi:10.1038/srep46208.

118. Ryu, D.; Mouchiroud, L.; Andreux, P.A.; Katsyuba, E.; Moullan, N.; Nicolet-Dit-Felix, A.A.; Williams, E.G.; Jha, P.; Lo Sasso, G.; Hузard, D., et al. Urolithin A induces mitophagy and prolongs lifespan in C. elegans and increases muscle function in rodents. *Nat Med 2016*, *22*, 879-888, doi:10.1038/nm.4132.

119. Fang, E.F.; Hou, Y.; Lautrup, S.; Jensen, M.B.; Yang, B.; SenGupta, T.; Caponio, D.; Khezri, R.; Demarest, T.G.; Aman, Y., et al. NAD(+) augmentation restores mitophagy and limits accelerated aging in Werner syndrome. *Nat Commun 2019*, *10*, 5284, doi:10.1038/s41467-019-13172-8.

120. Braak, H.; Braak, E. Diagnostic criteria for neuropathologic assessment of Alzheimer's disease. *Neuropathol Aging 1997*, *18*, 585-88, doi:10.1016/s0197-4580(97)00062-6.

121. Powers, J.M. Diagnostic criteria for the neuropathologic assessment of Alzheimer's disease. *Neuropathol Aging 2013*, *18*, 553-54, doi:10.1016/s0197-4580(97)00070-5.

122. Jack, C.R., Jr.; Barrio, J.R.; Kepe, V. Cerebral amyloid PET imaging in Alzheimer's disease. *Acta Neuropathol 2013*, *126*, 643-657, doi:10.1007/s00401-013-1185-7.

123. Dubois, B.; Feldman, H.H.; Jacova, C.; Dekosky, S.T.; Barberger-Gateau, P.; Cummings, J.; Delacourte, A.; Galasko, D.; Gauthier, S.; Jicha, G., et al. Research criteria for the diagnosis of Alzheimer's disease: revising the NINCDS-ADRDA criteria. *Lancet Neurol 2007*, *6*, 734-746, doi:10.1016/S1474-4422(07)70178-3.

124. Marcus, C.; Mena, E.; Subramaniam, R.M. Brain PET in the diagnosis of Alzheimer's disease. *Clin Nucl Med 2014*, *39*, e413-422; quiz e423-416, doi:10.1097/RLU.0000000000000547.

125. Mosconi, L.; McHugh, P.F. FDG- and amyloid-PET in Alzheimer's disease: is the whole greater than the sum of the parts? *Q J Nucl Med Mol Imaging 2011*, *55*, 250-264.

126. Suppiah, S.; Didier, M.A.; Vinjamuri, S. The Who, When, Why, and How of PET Amyloid Imaging in Management of Alzheimer's Disease-Review of Literature and Interesting Images. *Diagnostics (Basel) 2019*, *9*, doi:10.3390/diagnostics9020065.

127. Herholz, K.; Salmon, E.; Perani, D.; Baron, J.C.; Holthoff, V.; Frolich, I.; Schonknecht, P.; Ito, K.; Mielke, R.; Kalbe, E., et al. Discrimination between Alzheimer dementia and controls by automated analysis of multicenter FDG PET. *Neuroimage 2002*, *17*, 302-316, doi:10.1006/nimg.2002.1208.
128. Valla, J.; Berndt, J.D.; Gonzalez-Lima, F. Energy hypometabolism in posterior cingulate cortex of Alzheimer's patients: superficial laminar cytochrome oxidase associated with disease duration. J Neurosci 2001, 21, 4923-4930.

129. Messa, C.; Perani, D.; Lucignani, G.; Zenorini, A.; Zito, F.; Rizzo, G.; Grassi, F.; Del Sole, A.; Franceschi, M.; Gilardi, M.C., et al. High-resolution technetium-99m-HMPAO SPECT in patients with probable Alzheimer's disease: comparison with fluorine-18-FDG PET. J Nucl Med 1994, 35, 210-216.

130. Morris, J.K.; Honea, R.A.; Vidoni, E.D.; Swerdlow, R.H.; Burns, J.M. Is Alzheimer's disease a systemic disease? Biochim Biophys Acta 2014, 1842, 1340-1349, doi:10.1016/j.bbadis.2014.04.012.

131. Bosetti, F.; Brizzi, F.; Barogi, S.; Mancuso, M.; Siciliano, G.; Tendi, E.A.; Murri, L.; Rapoport, S.I.; Solaini, G. Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. Neurobiol Aging 2002, 23, 371-376, doi:10.1016/s0197-4580(01)00314-1.

132. Fukui, H.; Diaz, F.; Garcia, S.; Moraes, C.T. Cytochrome c oxidase deficiency in neurons decreases both oxidative stress and amyloid formation in a mouse model of Alzheimer's disease. Proc Natl Acad Sci U S A 2007, 104, 14163-14168, doi:10.1073/pnas.0705738104.

133. Parker, W.D., Jr.; Parks, J.K. Cytochrome oxidase in Alzheimer's disease brain: purification and characterization. Neurology 1995, 45, 482-486, doi:10.1212/wnl.45.3.482.

134. Cardoso, S.M.; Proenca, M.T.; Santos, S.; Santana, I.; Oliveira, C.R. Cytochrome c oxidase is decreased in Alzheimer's disease platelets. Neurobiol Aging 2004, 25, 105-110, doi:10.1016/s0197-4580(03)00033-2.

135. Khan, S.M.; Cassarino, D.S.; Abramova, N.N.; Keeney, P.M.; Borland, M.K.; Trimmer, P.A.; Krebs, C.T.; Bennett, J.C.; Parks, J.K.; Swerdlow, R.H., et al. Alzheimer's disease cybrids replicate beta-amyloid abnormalities through cell death pathways. Ann Neurol 2000, 48, 148-155.

136. Kish, S.J.; Bergeron, C.; Rajput, A.; Dozic, S.; Mastroiaccono, F.; Chang, L.J.; Wilson, J.M.; DiStefano, L.M.; Nobrega, J.N. Brain cytochrome oxidase in Alzheimer's disease. J Neurochem 1992, 59, 776-779, doi:10.1111/j.1471-4159.1992.tb09439.x.

137. Kish, S.J. Brain energy metabolizing enzymes in Alzheimer's disease: alpha-ketoglutarate dehydrogenase complex and cytochrome oxidase. Ann N Y Acad Sci 1997, 826, 218-228, doi:10.1111/j.1749-6632.1997.tb48473.x.

138. Mutisya, E.M.; Bowling, A.C.; Beal, M.F. Cortical cytochrome oxidase activity is reduced in Alzheimer's disease. J Neurochem 1994, 63, 2179-2184, doi:10.1046/j.1471-4159.1994.63062179.x.

139. Parker, W.D., Jr. Cytochrome oxidase deficiency in Alzheimer's disease. Ann N Y Acad Sci 1991, 640, 59-64, doi:10.1111/j.1749-6632.1991.tb00191.x.

140. Parker, W.D., Jr.; Filley, C.M.; Parks, J.K. Cytochrome oxidase deficiency in Alzheimer's disease. Neurology 1990, 40, 1302-1303, doi:10.1212/wnl.40.8.1302.

141. Alberts, M.J.; Ioannou, P.; Deucher, R.; Gilbert, J.; Lee, J.; Middleton, L.; Roses, A.D. Isolation of a cytochrome oxidase gene overexpressed in Alzheimer's disease brain. Mol Cell Neurosci 1992, 3, 461-470, doi:10.1016/1044-7431(92)90057-9.

142. Curti, D.; Rognoni, F.; Gasparini, L.; Cattaneo, A.; Paolillo, M.; Racchi, M.; Zani, L.; Bianchetti, A.; Trabucchi, M.; Bergamaschi, S., et al. Oxidative metabolism in cultured fibroblasts derived from sporadic Alzheimer's disease (AD) patients. Neurosci Lett 1997, 236, 13-16, doi:10.1016/s0304-3940(97)00741-6.

143. Silva, D.F.; Selfridge, J.E.; Lu, J.; E, L.; Roy, N.; Hutflies, L.; Burns, J.M.; Michaelis, E.K.; Yan, S.; Cardoso, S.M., et al. Bioenergetic flux, mitochondrial mass and mitochondrial morphology...
dynamics in AD and MCI cybrid cell lines. *Hum Mol Genet* **2013**, *22*, 3931-3946, doi:10.1093/hmg/ddt247.

144. Sheehan, J.P.; Swerdlow, R.H.; Miller, S.W.; Davis, R.E.; Parks, J.K.; Parker, W.D.; Tuttle, J.B. Calcium homeostasis and reactive oxygen species production in cells transformed by mitochondria from individuals with sporadic Alzheimer’s disease. *J Neurosci* **1997**, *17*, 4612-4622.

145. Cardoso, S.M.; Santana, I.; Swerdlow, R.H.; Oliveira, C.R. Mitochondria dysfunction of Alzheimer’s disease cybrids enhances Abeta toxicity. *J Neurochem* **2004**, *89*, 1417-1426, doi:10.1111/j.1471-4159.2004.02438.x.

146. Swerdlow, R.H. Mitochondria in cybrids containing mtDNA from persons with mitochondrialopathies. *J Neurosci Res* **2007**, *85*, 3416-3428, doi:10.1002/jnr.21167.

147. Trimmer, P.A.; Keeney, P.M.; Borland, M.K.; Simon, F.A.; Almeida, J.; Swerdlow, R.H.; Parks, J.P.; Parker, W.D., Jr.; Bennett, J.P., Jr. Mitochondrial abnormalities in cybrid cell models of sporadic Alzheimer’s disease worsen with passage in culture. *Neurobiol Dis* **2004**, *15*, 29-39, doi:10.1016/j.nbd.2003.09.011.

148. J, B.S. Mitochondria in Alzheimer’s disease: An Electron Microscopy Study *Alzheimer’s Disease & Treatment* **2019**, DOI: 10.5772/intechopen.84881, doi:10.5772/intechopen.84881.

149. Berti, V.; Mosconi, L.; Glodzik, L.; Li, Y.; Murray, J.; De Santi, S.; Pupi, A.; Tsui, W.; De Leon, M.J. Structural brain changes in normal individuals with a maternal history of Alzheimer’s disease. *Neurobiol Aging* **2011**, *32*, e2317-e2326, doi:10.1016/j.neurobiolaging.2011.01.001.

150. Mosconi, L. Glucose metabolism in normal aging and Alzheimer’s disease: Methodological and physiological considerations for PET studies. *ClinTransl Imaging* **2013**, *1*, doi:10.1007/s40336-013-0026-y.

151. Mosconi, L.; Mistur, R.; Switalski, R.; Brys, M.; Glodzik, L.; Rich, K.; Pirraglia, E.; Tsui, W.; De Santi, S.; de Leon, M.J. Declining brain glucose metabolism in normal individuals with a maternal history of Alzheimer disease. *Neurology* **2009**, *72*, 513-520, doi:10.1212/01.wnl.0000333247.51383.43.

152. Mosconi, L.; Rinne, J.O.; Tsui, W.H.; Murray, J.; Li, Y.; Glodzik, L.; McHugh, P.; Williams, S.; Cummings, M.; Pirraglia, E., et al. Amyloid and metabolic positron emission tomography imaging of cognitively normal adults with Alzheimer’s parents. *Neurobiol Aging* **2013**, *34*, 22-34, doi:10.1016/j.neurobiolaging.2012.03.002.

153. Swerdlow, R.H.; Hui, D.; Chalise, P.; Sharma, P.; Wang, X.; Andrews, S.J.; Pa, J.; Mahnken, J.D.; Morris, J.; Wilkins, H.M., et al. Exploratory analysis of mtDNA haplogroups in two Alzheimer’s longitudinal cohorts. *Alzheimers Dement* **2020**, *16*, 1164-1172, doi:10.1002/alz.12119.

154. Andrews SJ, S.R., McInerney T, Fulton-Howard B, Gross A, McFall P, Patterson C, Goate A, Michaelis E, Pa J. Mitochondrial haplogroups & a nuclear encoded mitochondrial polygenic risk score interact to influence dementia risk. *Alzheimer’s and Dementia AAIC 2018* 2018.

155. Carriero, G.; Bonafe, M.; De Luca, M.; Rose, G.; Varcasia, O.; Bruni, A.; Maletta, R.; Nacmias, B.; Sorbi, S.; Corsonello, F., et al. Mitochondrial DNA haplogroups and APOE4 allele are non-independent variables in sporadic Alzheimer’s disease. *Hum Genet* **2001**, *108*, 194-198, doi:10.1007/s004390100463.

156. Coto, E.; Gomez, J.; Alonso, B.; Corao, A.I.; Diaz, M.; Menendez, M.; Martinez, C.; Calatayud, M.T.; Moris, G.; Alvarez, V. Late-onset Alzheimer’s disease is associated with mitochondrial DNA 7028C/haplogroup H and D310 poly-C tract heteroplasm. *Neurogenetics* **2011**, *12*, 345-346, doi:10.1007/s10048-011-0295-4.
157. Fesahat, F.; Houshmand, M.; Panahi, M.S.; Gharagozli, K.; Mirzajani, F. Do haplogroups H and U act to increase the penetrance of Alzheimer's disease? *Cell Mol Neurobiol* **2007**, *27*, 329-334, doi:10.1007/s10571-006-9126-9.

158. Takasaki, S. Mitochondrial haplogroups associated with Japanese Alzheimer's patients. *J Bioenerg Biomembr* **2009**, *41*, 407-410, doi:10.1007/s10863-009-9240-8.

159. van der Walt, J.M.; Dementieva, Y.A.; Martin, E.R.; Scott, W.K.; Nicodemus, K.K.; Kroner, C.C.; Welsh-Bohmer, K.A.; Saunders, A.M.; Roses, A.D.; Small, G.W., et al. Analysis of European mitochondrial haplogroups with Alzheimer disease risk. *Neurosci Lett* **2004**, *365*, 28-32, doi:10.1016/j.neulet.2004.04.051.

160. Zhou, X.; Chen, Y.; Mok, K.Y.; Kwok, T.C.Y.; Mok, V.C.T.; Guo, Q.; Ip, F.C.; Chen, Y.; Mullapudi, N.; Alzheimer's Disease Neuroimaging, I., et al. Non-coding variability at the APOE locus contributes to the Alzheimer's risk. *Nat Commun* **2019**, *10*, 3310, doi:10.1038/s41467-019-10945-z.

161. Lakatos, A.; Derbeneva, O.; Younes, D.; Keator, D.; Bakken, T.; Lvova, M.; Brandon, M.; Guffanti, G.; Reglodi, D.; Saykin, A., et al. Association between mitochondrial DNA variations and Alzheimer's disease in the ADNI cohort. *Neurobiol Aging* **2010**, *31*, 1355-1363, doi:10.1016/j.neurobiolaging.2010.04.031.

162. Reddy, P.H.; Oliver, D.M. Amyloid Beta and Phosphorylated Tau-Induced Defective Autophagy and Mitophagy in Alzheimer's Disease. *Cells* **2019**, *8*, doi:10.3390/cells8050488.

163. Hu, Y.; Li, X.C.; Wang, Z.H.; Luo, Y.; Zhang, X.; Liu, X.P.; Feng, Q.; Wang, Q.; Yue, Z.; Chen, Z., et al. Tau accumulation impairs mitophagy via increasing mitochondrial membrane potential and reducing mitochondrial Parkin. *Oncotarget* **2016**, *7*, 17356-17368, doi:10.18632/oncotarget.7861.

164. Manczak, M.; Kandimala, R.; Yin, X.; Reddy, P.H. Hippocampal mutant APP and amyloid beta-induced cognitive decline, dendritic spine loss, defective autophagy, mitophagy and mitochondrial abnormalities in a mouse model of Alzheimer's disease. *Hum Mol Genet* **2018**, *27*, 1332-1342, doi:10.1093/hmg/ddy042.

165. Wang, X.; Zhao, X.L.; Xu, L.L.; Wang, C.F.; Wei, L.F.; Liu, Z.; Yang, H.; Wang, P.; Xie, Z.H.; Bi, J.Z. Mitophagy in APPsw/PS1dE9 transgenic mice and APPsw stably expressing in HEK293 cells. *Eur Rev Med Pharmacol Sci* **2015**, *19*, 4595-4602.

166. Ye, X.; Sun, X.; Starovoytov, V.; Cai, Q. Parkin-mediated mitophagy in mutant hAPP neurons and Alzheimer's disease patient brains. *Hum Mol Genet* **2015**, *24*, 2938-2951, doi:10.1093/hmg/ddv056.

167. Bordi, M.; Berg, M.J.; Mohan, P.S.; Peterhoff, C.M.; Alldred, M.J.; Che, S.; Ginsberg, S.D.; Nixon, R.A. Autophagy flux in CA1 neurons of Alzheimer hippocampus: Increased induction overburdens failing lysosomes to propel neuritic dystrophy. *Autophagy* **2016**, *12*, 2467-2483, doi:10.1080/15548627.2016.1239003.

168. Kerr, J.S.; Adriaanse, B.A.; Greig, N.H.; Mattson, M.P.; Cader, M.Z.; Bohr, V.A.; Fang, E.F. Mitophagy and Alzheimer's Disease: Cellular and Molecular Mechanisms. *Trends Neurosci* **2017**, *40*, 151-166, doi:10.1016/j.tins.2017.01.002.

169. Nixon, R.A. The role of autophagy in neurodegenerative disease. *Nat Med* **2013**, *19*, 983-997, doi:10.1038/nm.3232.

170. Kurosawa, M.; Matsumoto, G.; Sumikura, H.; Hatsuta, H.; Murayama, S.; Sakurai, T.; Shimogori, T.; Hattori, N.; Nukina, N. Serine 403-phosphorylated p62/SQSTM1 immuno-reactivity in inclusions of neurodegenerative diseases. *Neurosci Res* **2016**, *103*, 64-70, doi:10.1016/j.neures.2015.08.002.

171. Bharadwaj, P.; Martins, R.N. PRKAG2 Gene Expression Is Elevated and its Protein Levels Are Associated with Increased Amyloid-beta Accumulation in the Alzheimer's Disease Brain. *J Alzheimers Dis* **2020**, *74*, 441-448, doi:10.3233/JAD-190948.
172. Lonskaya, I.; Shekoyan, A.R.; Hebron, M.L.; Desorges, N.; Algarzaz, N.K.; Moussa, C.E. Diminished parkin solubility and co-localization with intraneuronal amyloid-beta are associated with autphagic defects in Alzheimer’s disease. *J Alzheimers Dis* **2013**, *33*, 231-247, doi:10.3233/JAD-2012-121141.

173. Yan, X.; Wang, B.; Hu, Y.; Wang, S.; Zhang, X. Abnormal Mitochondrial Quality Control in Neurodegenerative Diseases. *Front Cell Neurosci* **2020**, *14*, 138, doi:10.3389/fncel.2020.00138.

174. Poewe, W.; Seppi, K.; Tanner, C.M.; Halliday, G.M.; Brundin, P.; Volkmann, J.; Schrag, A.E.; Lang, A.E. Parkinson disease. *Nat Rev Dis Primers* **2017**, *3*, 17013, doi:10.1038/nrdp.2017.13.

175. Gibb, W.R.; Lees, A.J. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson’s disease. *J Neurol Neurosurg Psychiatry* **1988**, *51*, 745-752, doi:10.1136/jnnp.51.6.745.

176. Clarke, C.E. Parkinson’s disease. *BMJ* **2007**, *335*, 441-445, doi:10.1136/bmj.39289.437454.AD.

177. Mann, V.M.; Cooper, J.M.; Krige, D.; Daniel, S.E.; Schapira, A.H.; Marsden, C.D. Brain, skeletal muscle and platelet homogenate mitochondrial function in Parkinson’s disease. *Brain* **1992**, *115*(Pt 2), 333-342, doi:10.1093/brain/115.2.333.

178. Gatt, A.P.; Duncan, O.F.; Attems, J.; Francis, P.T.; Ballard, C.G.; Bateman, J.M. Dementia in Parkinson’s disease is associated with enhanced mitochondrial complex I deficiency. *Mov Disord* **2016**, *31*, 352-359, doi:10.1002/mds.26513.

179. Blake, C.I.; Spitz, E.; Leehey, M.; Hoffer, B.J.; Boyson, S.J. Platelet mitochondrial respiratory chain function in Parkinson’s disease. *Mov Disord* **1997**, *12*, 3-8, doi:10.1002/mds.870120103.

180. Krige, D.; Carroll, M.T.; Cooper, J.M.; Marsden, C.D.; Schapira, A.H. Platelet mitochondrial function in Parkinson’s disease. The Royal Kings and Queens Parkinson Disease Research Group. *Ann Neurrol* **1992**, *32*, 782-788, doi:10.1002/ana.410320612.

181. Arduino, D.M.; Esteves, A.R.; Swerdlow, R.H.; Cardoso, S.M. A cybrid cell model for the assessment of the link between mitochondrial deficits and sporadic Parkinson’s disease. *Methods Mol Biol* **2015**, *1265*, 415-424, doi:10.1007/978-1-4939-2288-8_31.

182. Esteves, A.R.; Domingues, A.F.; Ferreira, I.L.; Januario, C.; Swerdlow, R.H.; Oliveira, C.R.; Cardoso, S.M. Mitochondrial function in Parkinson’s disease cybrids containing an nt2 neuron-like nuclear background. *Mitochondrion* **2008**, *8*, 219-228, doi:10.1016/j.mito.2008.03.004.

183. Esteves, A.R.; Lu, J.; Rodova, M.; Onyango, I.; Lezi, E.; Dubinsky, R.; Lyons, K.E.; Pahwa, R.; Burns, J.M.; Cardoso, S.M., et al. Mitochondrial respiration and respiration-associated proteins in cell lines created through Parkinson’s subject mitochondrial transfer. *J Neurochem* **2010**, *113*, 674-682, doi:10.1111/j.1471-4159.2010.06631.x.

184. Dolle, C.; Fones, I.; Nido, G.S.; Miletic, H.; Osuagwu, N.; Kristoffersen, S.; Lilleg, P.K.; Larsen, J.P.; Tysnes, O.B.; Haugarvoll, K., et al. Defective mitochondrial DNA homeostasis in the substantia nigra in Parkinson disease. *Nat Commun* **2016**, *7*, 13548, doi:10.1038/ncomms13548.

185. Gu, G.; Reyes, P.E.; Golden, G.T.; Woltjer, R.L.; Hulette, C.; Montine, T.J.; Zhang, J. Mitochondrial DNA deletions/rearrangements in parkinson disease and related neurodegenerative disorders. *J Neuropathol Exp Neurol* **2002**, *61*, 634-639, doi:10.1093/jnen/61.7.634.

186. Valente, E.M.; Abou-Sleiman, P.M.; Caputo, V.; Muquit, M.M.; Harvey, K.; Gispert, S.; Ali, Z.; Del Turco, D.; Bentivoglio, A.R.; Healy, D.G., et al. Hereditary early-onset Parkinson’s disease caused by mutations in PINK1. *Science* **2004**, *304*, 1158-1160, doi:10.1126/science.1096284.

187. Polymeropoulos, M.H.; Lavedan, C.; Leroy, E.; Ide, S.E.; Dehejia, A.; Dutra, A.; Pike, B.; Root, H.; Rubenstein, J.; Boyer, R., et al. Mutation in the alpha-synuclein gene identified in families with Parkinson’s disease. *Science* **1997**, *276*, 2045-2047, doi:10.1126/science.276.5321.2045.

188. Lee, J.Y.; Nagano, Y.; Taylor, J.P.; Lim, K.L.; Yao, T.P. Disease-causing mutations in parkin impair mitochondrial ubiquitination, aggregation, and HDAC6-dependent mitophagy. *J Cell Biol* **2010**, *189*, 671-679, doi:10.1083/jcb.201001039.
189. Lesage, S.; Condroyer, C.; Klebe, S.; Honore, A.; Tison, F.; Brefel-Courbon, C.; Durr, A.; Brice, A.; French Parkinson's Disease Genetics Study. Identification of VPS35 mutations replicated in French families with Parkinson disease. *Neurology* 2012, 78, 1449-1450, doi:10.1212/WNL.0b013e318253d5f2.

190. Kitada, T.; Asakawa, S.; Hattori, N.; Matsumine, H.; Yamamura, Y.; Minoshima, S.; Yokochi, M.; Mizuno, Y.; Shimizu, N. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. *Nature* 1998, 392, 605-608, doi:10.1038/33416.

191. Chen, Y.; Chen, K.; Song, W.; Chen, X.; Cao, B.; Huang, R.; Zhao, B.; Guo, X.; Burgunder, J.; Li, J., et al. VPS35 Asp620Asn and EIF4G1 Arg1205His mutations are rare in Parkinson disease from southwest China. *Neurobiol Aging* 2013, 34, 1709 e1707-1708, doi:10.1016/j.neurobiolaging.2012.11.003.

192. Saravanan, K.S.; Sindhu, K.M.; Mohanakumar, K.P. Acute intranigral infusion of rotenone in rats causes progressive biochemical lesions in the striatum similar to Parkinson's disease. *Brain Res* 2005, 1049, 147-155, doi:10.1016/j.brainres.2005.04.051.

193. Duty, S.; Jenner, P. Animal models of Parkinson's disease: a source of novel treatments and clues to the cause of the disease. *Br J Pharmacol* 2011, 164, 1357-1391, doi:10.1111/j.1476-5381.2011.01426.x.

194. Betarbet, R.; Sherer, T.B.; MacKenzie, G.; Garcia-Osuna, M.; Panov, A.V.; Greenamyre, J.T. Chronic systemic pesticide exposure reproduces features of Parkinson's disease. *Nat Neurosci* 2000, 3, 1301-1306, doi:10.1038/81834.

195. Zeng, X.S.; Geng, W.S.; Jia, J.J. Neurotoxin-Induced Animal Models of Parkinson Disease: Pathogenic Mechanism and Assessment. *ASN Neuro* 2018, 10, 1759091418777438, doi:10.1177/1759091418777438.

196. von Wrangel, C.; Schwabe, K.; John, N.; Krauss, J.K.; Alam, M. The rotenone-induced rat model of Parkinson's disease: behavioral and electrophysiological findings. *Behav Brain Res* 2015, 279, 52-61, doi:10.1016/j.bbr.2014.11.002.

197. Bolam, J.P.; Pissadaki, E.K. Living on the edge with too many mouths to feed: why dopamine neurons die. *Mov Disord* 2012, 27, 1478-1483, doi:10.1002/mds.25135.

198. Hou, X.; Fiesel, F.C.; Truban, D.; Castanedes Casey, M.; Lin, W.L.; Soto, A.I.; Tacik, P.; Rousseau, L.G.; Diehl, N.N.; Heckman, M.G., et al. Age- and disease-dependent increase of the mitophagy marker phospho-ubiquitin in normal aging and Lewy body disease. *Autophagy* 2018, 14, 1404-1418, doi:10.1080/15548627.2018.1461294.

199. Hsieh, C.H.; Shaltouki, A.; Gonzalez, A.E.; Bettencourt da Cruz, A.; Burbulla, L.F.; St Lawrence, E.; Schule, B.; Krainc, D.; Palmer, T.D.; Wang, X. Functional Impairment in Miro Degradation and Mitophagy Is a Shared Feature in Familial and Sporadic Parkinson's Disease. *Cell Stem Cell* 2016, 19, 709-724, doi:10.1016/j.stem.2016.08.002.

200. Smith, E.F.; Shaw, P.J.; De Vos, K.J. The role of mitochondria in amyotrophic lateral sclerosis. *Neurosci Lett* 2019, 710, 132933, doi:10.1016/j.neulet.2017.06.052.

201. Swerdlow, R.H.; Parks, J.K.; Pattee, G.; Parker, W.D., Jr. Role of mitochondria in amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord* 2000, 1, 185-190, doi:10.1080/14660820050515179.

202. Beeldman, E.; Raaphorst, J.; Klein Twennaar, M.; de Visser, M.; Schmand, B.A.; de Haan, R.J. The cognitive profile of ALS: a systematic review and meta-analysis update. *J Neurol Neurosurg Psychiatry* 2016, 87, 611-619, doi:10.1136/jnnp-2015-310734.

203. Gubbay, S.S.; Kahana, E.; Zilber, N.; Cooper, G.; Pintov, S.; Leibowitz, Y. Amyotrophic lateral sclerosis. A study of its presentation and prognosis. *J Neurol* 1985, 232, 295-300, doi:10.1007/bf00313868.
204. Norris, F.; Shepherd, R.; Denys, E.; U, K.; Mukai, E.; Elias, L.; Holden, D.; Norris, H. Onset, natural history and outcome in idiopathic adult motor neuron disease. J Neurol Sci 1993, 118, 48-55, doi:10.1016/0022-510X(93)90245-t.

205. Rothstein, J.D. Current hypotheses for the underlying biology of amyotrophic lateral sclerosis. Ann Neurol 2000, 65 Suppl 1, S3-9, doi:10.1002/ana.21543.

206. Rowland, L.P.; Shneider, N.A. Amyotrophic lateral sclerosis. N Engl J Med 2001, 344, 1688-1700, doi:10.1056/NEJM200105313442207.

207. Deng, H.X.; Bigio, E.H.; Zhai, H.; Fecto, F.; Ajroud, K.; Shi, Y.; Yan, J.; Mishra, M.; Ajroud-Driss, S.; Heller, S., et al. Differential involvement of optineurin in amyotrophic lateral sclerosis with or without SOD1 mutations. Arch Neurol 2011, 68, 1057-1061, doi:10.1001/archneurol.2011.178.

208. van Blitterswijk, M.; van Vuught, P.W.; van Es, M.A.; Schelhaas, H.J.; van der Kooi, A.J.; de Visser, M.; Veldink, J.H.; van den Berg, L.H. Novel optineurin mutations in sporadic amyotrophic lateral sclerosis patients. Neurobiol Aging 2012, 33, 1016 e1011-1017, doi:10.1016/j.neurobiolaging.2011.05.019.

209. Sakaguchi, T.; Irie, T.; Kawabata, R.; Yoshida, A.; Maruyama, H.; Kawakami, H. Optineurin with amyotrophic lateral sclerosis-related mutations abrogates inhibition of interferon regulatory factor-3 activation. Neurosci Lett 2011, 505, 279-281, doi:10.1016/j.neulet.2011.10.040.

210. Gurney, M.E.; Pu, H.; Chiu, A.Y.; Dal Canto, M.C.; Polchow, C.Y.; Alexander, D.D.; Caliendo, J.; Hentati, A.; Kwon, Y.W.; Deng, H.X., et al. Motor neuron degeneration in mice that express a human Cu,Zn superoxide dismutase mutation. Science 1994, 264, 1772-1775, doi:10.1126/science.8209258.

211. Kong, J.; Xu, Z. Massive mitochondrial degeneration in motor neurons triggers the onset of amyotrophic lateral sclerosis in mice expressing a mutant SOD1. J Neurosci 1998, 18, 3241-3250.

212. Wegorzewska, I.; Bell, S.; Cairns, N.J.; Miller, T.M.; Baloh, R.H. TDP-43 mutant transgenic mice develop features of ALS and frontotemporal lobar degeneration. Proc Natl Acad Sci U S A 2009, 106, 18809-18814, doi:10.1073/pnas.0908767106.

213. Vielhaber, S.; Kunz, D.; Winkler, K.; Wiedemann, F.R.; Kirches, E.; Heinze, H.J.; Elger, C.E.; Schubert, W.; Kunz, W.S. Mitochondrial DNA abnormalities in skeletal muscle of patients with sporadic amyotrophic lateral sclerosis. Brain 2000, 123 ( Pt 7), 1339-1348, doi:10.1093/brain/123.7.1339.

214. Duffy, L.M.; Chapman, A.L.; Shaw, P.J.; Grierson, A.J. Review: The role of mitochondria in the pathogenesis of amyotrophic lateral sclerosis. Neuropathol Appl Neurobiol 2011, 37, 336-352, doi:10.1111/j.1365-2990.2011.01166.x.

215. Swerdlow, R.H.; Parks, J.K.; Cassarino, D.S.; Trimmer, P.A.; Miller, S.W.; Maguire, D.J.; Sheehan, J.P.; Maguire, R.S.; Pattee, G.; Juel, V.C., et al. Mitochondria in sporadic amyotrophic lateral sclerosis. Exp Neurol 1998, 153, 135-142, doi:10.1006/exnr.1998.6866.

216. Hart, M.N.; Cancilla, P.A.; Frommes, S.; Hirano, A. Anterior horn cell degeneration and Bunina-type inclusions associated with dementia. Acta Neuropathol 1977, 38, 225-228, doi:10.1007/bf00688069.

217. Mizuno, Y.; Amari, M.; Takatama, M.; Aizawa, H.; Mihara, B.; Okamoto, K. Immunoreactivities of p62, an ubiquitin-binding protein, in the spinal anterior horn cells of patients with amyotrophic lateral sclerosis. J Neurol Sci 2006, 249, 13-18, doi:10.1016/j.jns.2006.05.060.

218. Rodriguez, G.E.; Gonzalez, D.M.; Monachelli, G.M.; Costa, J.J.; Nicola, A.F.; Sica, R.E. Morphological abnormalities in mitochondria of the skin of patients with sporadic amyotrophic lateral sclerosis. Arq Neuropsiquiatr 2012, 70, 40-44, doi:10.1590/s0004-282x2012000100010.

219. Swerdlow, R.H. The neurodegenerative mitochondriopathies. J Alzheimers Dis 2009, 17, 737-751, doi:10.3233/JAD-2009-1095.
220. Catalan-Garcia, M.; Garrabou, G.; Moren, C.; Guitart-Mampel, M.; Hernando, A.; Diaz-Ramos, A.; Gonzalez-Casacuberta, I.; Juarez, D.L.; Bano, M.; Enrich-Bengoa, J., et al. Mitochondrial DNA disturbances and deregulated expression of oxidative phosphorylation and mitochondrial fusion proteins in sporadic inclusion body myositis. Clin Sci (Lond) 2016, 130, 1741-1751, doi:10.1042/CS20160080.

221. Horvath, R.; Fu, K.; Johns, T.; Genge, A.; Karpati, G.; Shoubridge, E.A. Characterization of the mitochondrial DNA abnormalities in the skeletal muscle of patients with inclusion body myositis. J Neuropathol Exp Neurol 1998, 57, 396-403, doi:10.1097/00005072-199805000-00003.

222. Wiedemann, F.R.; Manfredi, G.; Mawrin, C.; Beal, M.F.; Schon, E.A. Mitochondrial DNA and respiratory chain function in spinal cords of ALS patients. J Neurochem 2002, 80, 616-625, doi:10.1046/j.0022-3042.2001.00731.x.

223. Borthwick, G.M.; Johnson, M.A.; Ince, P.G.; Shaw, P.J.; Turnbull, D.M. Mitochondrial enzyme activity in amyotrophic lateral sclerosis: implications for the role of mitochondria in neuronal cell death. Ann Neurol 1999, 46, 787-790, doi:10.1002/1531-8249(199911)46:5<787::aid-ana17>3.0.co;2-8.

224. Fujita, K.; Yamauchi, M.; Shibayama, K.; Ando, M.; Honda, M.; Nagata, Y. Decreased cytochrome c oxidase activity but unchanged superoxide dismutase and glutathione peroxidase activities in the spinal cords of patients with amyotrophic lateral sclerosis. J Neurosci Res 1996, 45, 276-281, doi:10.1002/(SICI)1097-4547(19960801)45:3<276::AID-JNR9>3.0.CO;2-A.

225. Shrivastava, M.; Subbiah, V. Elevated caspase 3 activity and cytosolic cytochrome c in NT2 cybrids containing amyotrophic lateral sclerosis subject mtDNA. Int J Neurosci 2016, 126, 839-849, doi:10.3109/00207454.2015.1074902.

226. Wilkins, H.M.; Carl, S.M.; Swerdlow, R.H. Cytoplasmic hybrid (cybrid) cell lines as a practical model for mitochondriopathies. Redox Biol 2014, 2, 619-631, doi:10.1016/j.redox.2014.03.006.

227. Wong, P.C.; Pardo, C.A.; Borchelt, D.R.; Lee, M.K.; Copeland, N.G.; Jenkins, N.A.; Sisodia, S.S.; Cleveland, D.W.; Price, D.L. An adverse property of a familial ALS motor neuron disease characterized by vacuolar degeneration of mitochondria. Neuron 1995, 14, 1105-1116, doi:10.1016/0896-6273(95)00259-7.

228. Mattiazzi, M.; D'Aurelio, M.; Gajewski, C.D.; Martushova, K.; Kiaei, M.; Beal, M.F.; Manfredi, G. Mutated human SOD1 causes dysfunction of oxidative phosphorylation in mitochondria of transgenic mice. J Biol Chem 2002, 277, 29626-29633, doi:10.1074/jbc.M203065200.

229. Tafuri, F.; Ronchi, D.; Magri, F.; Comi, G.P.; Corti, S. SOD1 misplacing and mitochondrial dysfunction in amyotrophic lateral sclerosis pathogenesis. Front Cell Neurosci 2015, 9, 336, doi:10.3389/fncel.2015.00336.

230. Davis, S.A.; Itaman, S.; Khalid-Janney, C.M.; Sherard, J.A.; Dowell, J.A.; Cairns, N.J.; Gitcho, M.A. TDP-43 interacts with mitochondrial proteins critical for mitophagy and mitochondrial dynamics. Neurosci Lett 2018, 678, 8-15, doi:10.1016/j.neulet.2018.04.053.

231. Huntley, M.L.; Gao, J.; Termarsarasab, P.; Wang, L.; Zeng, S.; Thammongkolchai, T.; Liu, Y.; Cohen, M.L.; Wang, X. Association between TDP-43 and mitochondria in inclusion body myositis. Lab Invest 2019, 99, 1041-1048, doi:10.1038/s41374-019-0233-x.

232. Wang, P.; Deng, J.; Dong, J.; Liu, J.; Bigio, E.H.; Mesulam, M.; Wang, T.; Sun, L.; Wang, L.; Lee, A.Y., et al. TDP-43 induces mitochondrial damage and activates the mitochondrial unfolded protein response. PLoS Genet 2019, 15, e1007947, doi:10.1371/journal.pgen.1007947.

233. Blokhuis, A.M.; Groen, E.J.; Koppers, M.; van den Berg, L.H.; Pasterkamp, R.J. Protein aggregation in amyotrophic lateral sclerosis. Acta Neuropathal 2013, 125, 777-794, doi:10.1007/s00401-013-1125-6.
234. Johnson, B.S.; Snead, D.; Lee, J.J.; McCaffery, J.M.; Shorter, J.; Gitler, A.D. TDP-43 is intrinsically aggregation-prone, and amyotrophic lateral sclerosis-linked mutations accelerate aggregation and increase toxicity. *J Biol Chem* **2009**, *284*, 20329-20339, doi:10.1074/jbc.M109.010264.

235. Nogalska, A.; D'Agostino, C.; Terracciano, C.; Engel, W.K.; Askanas, V. Impaired autophagy in sporadic inclusion-body myositis and in endoplasmic reticulum stress-provoked cultured human muscle fibers. *Am J Pathol* **2010**, *177*, 1377-1387, doi:10.2353/apjpath.2010.100050.

236. Vattemi, G.; Nogalska, A.; King Engel, W.; D'Agostino, C.; Checler, F.; Askanas, V. Amyloid-beta42 is preferentially accumulated in muscle fibers of patients with sporadic inclusion-body myositis. *Acta Neuropathol* **2009**, *117*, 569-574, doi:10.1007/s00404-009-0511-6.

237. Watanabe, M.; Dykes-Hoberg, M.; Culotta, V.C.; Price, D.L.; Wong, P.C.; Rothstein, J.D. Histological evidence of protein aggregation in mutant SOD1 transgenic mice and in amyotrophic lateral sclerosis neural tissues. *Neurobiol Dis* **2001**, *8*, 933-941, doi:10.1006/nbdi.2001.0443.

238. Rogers, R.S.; Tungtur, S.; Tanaka, T.; Nadeau, L.L.; Badawi, Y.; Wang, H.; Ni, H.M.; Ding, W.X.; Nishimune, H. Impaired Mitophagy Plays a Role in Denervation of Neuromuscular Junctions in ALS Mice. *Front Neurosci* **2017**, *11*, 473, doi:10.3389/fnins.2017.00473.

239. Natale, G.; Lenzi, P.; Lazzeri, G.; Falleni, A.; Biagioni, F.; Ryskalin, L.; Fornai, F. Compartment-dependent mitochondrial alterations in experimental ALS, the effects of mitophagy and mitochrondriogenesis. *Front Cell Neurosci* **2015**, *9*, 434, doi:10.3389/fnsc.2015.00434.

240. Ruffoli, R.; Bartalucci, A.; Frati, A.; Fornai, F. Ultrastructural studies of ALS mitochondria connect altered function and permeability with defects of mitophagy and mitochrondriogenesis. *Front Cell Neurosci* **2015**, *9*, 341, doi:10.3389/fnsc.2015.00341.

241. Palomo, G.M.; Granatiero, V.; Kawamata, H.; Konrad, C.; Kim, M.; Arreguin, A.J.; Zhao, D.; Milner, T.A.; Manfredi, G. Parkin is a disease modifier in the mutant SOD1 mouse model of ALS. *EMBO Mol Med* **2018**, *10*, doi:10.15252/emmm.201808888.

242. Wong, Y.C.; Holzbaur, E.L. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. *Proc Natl Acad Sci U S A* **2014**, *111*, E4439-4448, doi:10.1073/pnas.1405752111.

243. Sasaki, S. Autophagy in spinal cord motor neurons in sporadic amyotrophic lateral sclerosis. *J Neuropathol Exp Neurol* **2011**, *70*, 349-359, doi:10.1097/NEN.0b013e3182160690.

244. Almeida, S.; Gascon, E.; Tran, H.; Chou, H.J.; Gendron, T.F.; Degroot, S.; Tapper, A.R.; Sellier, C.; Charlet-Berguerand, N.; Karydas, A., et al. Modeling key pathological features of frontotemporal dementia with C9ORF72 repeat expansion in iPS-derived human neurons. *Acta Neuropathol* **2013**, *126*, 385-399, doi:10.1007/s00401-013-1149-y.

245. Webster, C.P.; Smith, E.F.; Bauer, C.S.; Moller, A.; Hautbergue, G.M.; Ferraiuolo, L.; Myszczynska, M.A.; Higginbottom, A.; Walsh, M.J.; Whitworth, A.J., et al. The C9orf72 protein interacts with Rab1a and the ULK1 complex to regulate initiation of autophagy. *EMBO J* **2016**, *35*, 1656-1676, doi:10.15252/embj.201694401.

246. Fang, E.F. Mitophagy and NAD(+) inhibit Alzheimer disease. *Autophagy* **2019**, *15*, 1112-1114, doi:10.1080/15548627.2019.1596497.

247. Fang, E.F.; Hou, Y.; Palikaras, K.; Adriaanse, B.A.; Kerr, J.S.; Yang, B.; Lautrup, S.; Hasan-Olive, M.M.; Caponio, D.; Dan, X., et al. Mitophagy inhibits amyloid-beta and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. *Nat Neurosci* **2019**, *22*, 401-412, doi:10.1038/s41593-018-0332-9.

248. Perera, N.D.; Sheean, R.K.; Lau, C.L.; Shin, Y.S.; Beart, P.M.; Horne, M.K.; Turner, B.J. Rilmenidine promotes MTOR-independent autophagy in the mutant SOD1 mouse model of amyotrophic lateral sclerosis without slowing disease progression. *Autophagy* **2018**, *14*, 534-551, doi:10.1080/15548627.2017.1385674.
249. Staats, K.A.; Hernandez, S.; Schonefeldt, S.; Bento-Abreu, A.; Dooley, J.; Van Damme, P.; Liston, A.; Robberecht, W.; Van Den Bosch, L. Rapamycin increases survival in ALS mice lacking mature lymphocytes. *Mol Neurodegener* **2013**, *8*, 31, doi:10.1186/1750-1326-8-31.

250. Li, R.; Chen, J. Salidroside Protects Dopaminergic Neurons by Enhancing PINK1/Parkin-Mediated Mitophagy. *Oxid Med Cell Longev* **2019**, *2019*, 9341018, doi:10.1155/2019/9341018.

251. Chung, E.; Choi, Y.; Park, J.; Nah, W.; Park, J.; Jung, Y.; Lee, J.; Lee, H.; Park, S.; Hwang, S., et al. Intracellular delivery of Parkin rescues neurons from accumulation of damaged mitochondria and pathological alpha-synuclein. *Sci Adv* **2020**, *6*, eaba1193, doi:10.1126/sciadv.aba1193.

252. Andreux, P.A.; Blanco-Bose, W.; Ryu, D.; Burdet, F.; Ibberson, M.; Aebischer, P.; Auwerx, J.; Singh, A.; Rinsch, C. The mitophagy activator urolithin A is safe and induces a molecular signature of improved mitochondrial and cellular health in humans. *Nat Metab* **2019**, *1*, 595-603, doi:10.1038/s42255-019-0073-4.

253. Irie, J.; Inagaki, E.; Fujita, M.; Nakaya, H.; Mitsuishi, M.; Yamaguchi, S.; Yamashita, K.; Shigaki, S.; Ono, T.; Yukioka, H., et al. Effect of oral administration of nicotinamide mononucleotide on clinical parameters and nicotinamide metabolite levels in healthy Japanese men. *Endocr J* **2020**, *67*, 153-160, doi:10.1507/endocrj.EJ19-0313.

254. Tsubota, K. The first human clinical study for NMN has started in Japan. *NPJ Aging Mech Dis* **2016**, *2*, 16021, doi:10.1038/njpjamd.2016.21.

255. Yoo, S.Z.; No, M.H.; Heo, J.W.; Park, D.H.; Kang, J.H.; Kim, J.H.; Seo, D.Y.; Han, J.; Jung, S.J.; Kwak, H.B. Effects of Acute Exercise on Mitochondrial Function, Dynamics, and Mitophagy in Rat Cardiac and Skeletal Muscles. *Int Neurourol J* **2019**, *23*, S22-31, doi:10.5213/inj.1938038.019.

256. Kwon, I.; Jang, Y.; Lee, Y. Endurance Exercise-Induced Autophagy/Mitophagy Coincides with a Reinforced Anabolic State and Increased Mitochondrial Turnover in the Cortex of Young Male Mouse Brain. *J Mol Neurosci* **2020**, 10.1007/s12031-020-01624-6, doi:10.1007/s12031-020-01624-6.

257. Guan, Y.; Drake, J.C.; Yan, Z. Exercise-Induced Mitophagy in Skeletal Muscle and Heart. *Exerc Sport Sci Rev* **2019**, *47*, 151-156, doi:10.1249/JES.0000000000000192.

258. Bernardo, T.C.; Marques-Aleixo, I.; Beleza, J.; Oliveira, P.J.; Ascensao, A.; Magalhaes, J. Physical Exercise and Brain Mitochondrial Fitness: The Possible Role Against Alzheimer’s Disease. *Brain Pathol* **2016**, *26*, 648-663, doi:10.1111/bpa.12403.

259. Vainshtein, A.; Tryon, L.D.; Pauly, M.; Hood, D.A. Role of PGC-1alpha during acute exercise-induced autophagy and mitophagy in skeletal muscle. *Am J Physiol Cell Physiol* **2015**, *308*, C710-719, doi:10.1152/ajpcell.00380.2014.

260. Morris, J.K.; Vidoni, E.D.; Johnson, D.K.; Van Sciver, A.; Mahnken, J.D.; Honea, R.A.; Wilkins, H.M.; Brooks, W.M.; Billinger, S.A.; Swerdlow, R.H., et al. Aerobic exercise for Alzheimer’s disease: A randomized controlled pilot trial. *PLoS One* **2017**, *12*, e0170547, doi:10.1371/journal.pone.0170547.

261. Baker, L.D.; Frank, L.L.; Foster-Schubert, K.; Green, P.S.; Wilkinson, C.W.; McTiernan, A.; Cholerton, B.A.; Plymate, S.R.; Fishel, M.A.; Watson, G.S., et al. Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer’s disease. *J Alzheimers Dis* **2010**, *22*, 569-579, doi:10.3233/JAD-2010-100768.

262. Vidoni, E.D.; Johnson, D.K.; Morris, J.K.; Van Sciver, A.; Greer, C.S.; Billinger, S.A.; Donnelly, J.E.; Burns, J.M. Dose-Response of Aerobic Exercise on Cognition: A Community-Based, Pilot Randomized Controlled Trial. *PLoS One* **2015**, *10*, e0131647, doi:10.1371/journal.pone.0131647.

263. Tomporowski, P.D. Effects of acute bouts of exercise on cognition. *Acta Psychol (Amst)* **2003**, *112*, 297-324, doi:10.1016/s0001-6918(02)00134-8.
264. Nichol, K.; Deeny, S.P.; Seif, J.; Camacho, K.; Cotman, C.W. Exercise improves cognition and hippocampal plasticity in APOE epsilon4 mice. *Alzheimers Dement* **2009**, *5*, 287-294, doi:10.1016/j.jalz.2009.02.006.

265. Kiernan, M.C. Amyotrophic lateral sclerosis and the neuroprotective potential of exercise. *J Physiol* **2009**, *587*, 3759-3760, doi:10.1113/jphysiol.2009.177022.

266. de Almeida, J.P.; Silvestre, R.; Pinto, A.C.; de Carvalho, M. Exercise and amyotrophic lateral sclerosis. *Neurol Sci* **2012**, *33*, 9-15, doi:10.1007/s10072-011-0921-9.

267. David, F.J.; Robichaud, J.A.; Leurgans, S.E.; Poon, C.; Kohrt, W.M.; Goldman, J.G.; Comella, C.L.; Vaillancourt, D.E.; Corcos, D.M. Exercise improves cognition in Parkinson's disease: The PRET-PD randomized, clinical trial. *Mov Disord* **2015**, *30*, 1657-1663, doi:10.1002/mds.26291.

268. Armon, C. A randomized controlled trial of resistance exercise in individuals with ALS. *Neurology* **2008**, *71*, 864-865; author reply 865-866, doi:10.1212/01.wnl.0000327290.13342.0a.

269. Dalbello-Haas, V.; Florence, J.M.; Kloos, A.D.; Scheirbecker, J.; Lopate, G.; Hayes, S.M.; Pioro, E.P.; Mitsumoto, H. A randomized controlled trial of resistance exercise in individuals with ALS. *Neurology* **2007**, *68*, 2003-2007, doi:10.1212/01.wnl.0000264418.92308.a4.

270. Ari, C.; Murdun, C.; Goldhagen, C.; Koutnik, A.P.; Bharwani, S.R.; Diamond, D.M.; Kindy, M.; D'Agostino, D.P.; Kovacs, Z. Exogenous Ketone Supplements Improved Motor Performance in Preclinical Rodent Models. *Nutrients* **2020**, *12*, doi:10.3390/nu12082459.

271. Hernandez, A.R.; Hernandez, C.M.; Campos, K.; Truckenbrod, L.; Federico, Q.; Moon, B.; McQuail, J.A.; Maurer, A.P.; Bizon, J.L.; Burke, S.N. A Ketogenic Diet Improves Cognition and Has Biochemical Effects in Prefrontal Cortex That Are Dissociable From Hippocampus. *Front Aging Neurosci* **2018**, *10*, 391, doi:10.3389/fnagi.2018.00391.

272. A randomized controlled trial of resistance exercise in individuals with ALS. *Neurology* **2008**, *71*, 864-865; author reply 865-866, doi:10.1212/01.wnl.0000327290.13342.0a.

273. Brownlow, M.L.; Benner, L.; D'Agostino, D.; Gordon, M.N.; Morgan, D. Ketogenic diet improves motor performance but not cognition in two mouse models of Alzheimer's pathology. *PLoS One* **2013**, *8*, e75713, doi:10.1371/journal.pone.0075713.

274. Koppel, S.J.; Swerdlow, R.H. Neuroketotherapeutics: A modern review of a century-old therapy. *Neurochem Int* **2018**, *117*, 114-125, doi:10.1016/j.neuint.2017.05.019.

275. Li, L.; Wang, Z.; Zuo, Z. Chronic intermittent fasting improves cognitive functions and brain structures in mice. *PLoS One* **2013**, *8*, e66069, doi:10.1371/journal.pone.0066069.

276. Krikorian, R.; Shidler, M.D.; Dangelo, K.; Couch, S.C.; Benoit, S.C.; Clegg, D.J. Dietary ketosis enhances memory in mild cognitive impairment. *Neurobiol Aging* **2012**, *33*, 425 e419-427, doi:10.1016/j.neurobiolaging.2010.10.006.
Figures and Legends

Figure 1. Autophagy Types. Created with BioRender.com
Figure 2. Mitophagy. A. Non-Receptor Mediated Mitophagy or Classical Mitophagy. Activation of PINK1 leads to recruitment of ubiquitin and Parkin. Parkin ubiquitinates and phosphorylates mitochondrial proteins (such as VDAC, MFN1/2, TOM20) and this initiates receptor adaptor protein recruitment (p62, NDP52, OPTN, TAX1BP1, NBR1). These adaptor proteins interact with LC3 to form the autophagosome. The Vps34 and Atg5/12/16 complex facilitate autophagosome maturation, closure, and lysosome fusion. B. Receptor Mediated Mitophagy. Mitochondrial receptor proteins (BNIP3, NIX, FUNC1, AMBRA1, PHB2, or cardiolipin) are ubiquitinated and phosphorylated. This facilitates their interaction with LC3 and GABARAP for autophagosome formation. The Vps34 and Atg5/12/16 complex facilitate autophagosome maturation, closure, and lysosome fusion. Created with BioRender.com
Figure 3. Transcellular Mitophagy. Mitochondria are released at neuronal synapses where they are taken up by glial cells (astrocytes and/or microglia) for degradation. Created with BioRender.com