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Mitochondrial quality in aging and neurodegeneration: The emerging role of mitochondria-derived vesicles

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ABSTRACT

Mitochondria are central to cellular energy metabolism, redox balance, and signaling, and their integrity is maintained by a multilayered mitochondrial quality control (MQC) system. This system includes proteostasis, dynamics, biogenesis, and mitophagy, which together repair or remove damaged organelles. Mitochondria-derived vesicles (MDVs) have emerged as an additional MQC component. MDVs are small vesicles that bud from mitochondria and selectively transport damaged mitochondrial proteins, lipids, and nucleic acids to endolysosomal compartments or other intracellular destinations, enabling rapid and localized responses to mitochondrial stress. Acting upstream of or in parallel with mitophagy, MDVs can avoid or delay irreversible mitochondrial damage and help preserve cellular homeostasis. Aging and age-associated disorders are characterized by progressive mitochondrial dysfunction and chronic inflammation. Age-related changes in intracellular trafficking, lysosomal function, and vesicle dynamics may impair MDV formation, cargo selection, and targeting. Under conditions of defective degradation, mitochondrial components may also appear in extracellular vesicles, potentially contributing to altered intercellular signaling and inflammation. In the nervous system, where energetic demands are high and mitochondrial turnover requires tight regulation, such alterations may be especially harmful. This review summarizes MQC mechanisms in neurons, with a focus on MDVs, their dysregulation during aging and neurodegeneration, and implications for biomarkers and therapeutic strategies.

1. Introduction

Mitochondria maintain their fidelity through a multilayered quality control system that includes proteostasis, biogenesis, dynamics (fusion and fission), and mitophagy. The selective extrusion of damaged components within mitochondria-derived vesicles (MDVs) has also been described in conditions of mitochondrial stress (Ferrucci et al., 2024; König and McBride, 2024; Gagliardi et al., 2024). MDVs are small (70–150 nm) membrane-bound carriers that bud from the outer and/or inner mitochondrial membrane to deliver specific cargo, such as oxidized proteins, lipids, or mitochondrial DNA (mtDNA), to late endosomes, lysosomes, or peroxisomes for degradation (Ferrucci et al., 2024; König and McBride, 2024). When these intracellular routes are overwhelmed or defective, MDVs can be released into the extracellular space within exosomes or other small extracellular vesicles (sEVs). Therefore, the process of MDV formation and release serves as an alternative pathway to wholesale mitophagy, acting as an early checkpoint in mitochondrial quality control (MQC) (Todkar et al., 2021).

The study of MDVs has increased enormously over the past decade as investigators have also recognized their potential role as mediators at the intersection of mitochondrial dysfunction and sterile inflammation in health and disease (Ferrucci et al., 2024). In aging-related conditions such as physical frailty and sarcopenia (PF&S) and neurodegenerative diseases such as Parkinson's disease (PD), systemic inflammation

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coexists with mitochondrial dysfunction and deranged MQC (Picca et al., 2020a, 2020b).

Data from recent studies provide a framework to understand how aging and altered intracellular trafficking differentially shape MDV biology. Herein, we discuss how MDV dynamics may change with age and/or specific conditions under perturbations of MQC machinery and vesicle trafficking.

2. Mitochondria and neuronal quality

2.1. Integration of mitochondrial quality control systems for cell quality

A hierarchically organized surveillance network integrates mitochondrial proteostasis, genome integrity, and bioenergetic organelle competence to achieve mitochondrial homeostasis.

At the protein level, intra-mitochondrial proteases, including the ATP-dependent LonP1 and ClpXP proteases of the matrix, and the i-AAA and m-AAA proteases YME1L and AFG3L2 of the inner membrane, degrade oxidatively modified and/or misfolded organelle proteins. On the other hand, molecular chaperones such as mitochondrial heat shock protein 70 (mtHSP70), HSP60, and HSP10 assist in protein refolding and import across the translocase of the inner membrane/translocase of the outer membrane complexes (Song et al., 2021). When proteostatic stress exceeds local repair capacity, mitochondria activate the mitochondrial unfolded protein response (UPR_{mt}), a retrograde signaling pathway mediated by a set of transcription factors including activating transcription factor 4 (ATF4), ATF5, and CCAAT-enhancer-binding protein homologous protein (CHOP) (Fiorese et al., 2016; Melber and Haynes, 2018; Shpilka and Haynes, 2018; Song et al., 2021). Such factors coordinate nuclear upregulation of chaperones, proteases, and antioxidant enzymes to restore homeostasis (Fiorese et al., 2016; Melber and Haynes, 2018; Shpilka and Haynes, 2018; Song et al., 2021).

At the organelle level, mitochondrial dynamics balance fusion and fission to maintain a healthy mitochondrial network. Fusion is driven by the GTPases mitofusin-1 and -2 (MFN1/2) on the outer mitochondrial membrane and optic atrophy 1 (OPA1) on the inner membrane, enabling complementation of mtDNA copies and mixing of metabolites and proteins. Fission, regulated by dynamin-related protein 1 (DRP1) and its adaptors mitochondrial fission factor (MFF), fission protein 1 (FIS1), and mitochondrial dynamics protein (MID) 49/51, partitions damaged mitochondrial segments for subsequent clearance (Losón et al., 2013; Youle and Van Der Bliek, 2012). These events are also spatiotemporally coordinated by endoplasmic reticulum (ER) contact sites and actin cytoskeleton remodeling (Korobova et al., 2013). ER–mitochondria contacts spatially define mitochondrial division sites by promoting actin-dependent pre-constriction and recruitment of DRP1. Local Ca^{2+} signaling and lipid exchange at these interfaces further regulate membrane remodeling and coordinate fission with fusion processes to maintain mitochondrial network integrity.

When mitochondria face irreversible damage, mitophagy is activated to selectively remove entire organelles and/or portions. In the canonical PTEN-induced kinase 1 (PINK1)/Parkin pathway, mitochondrial membrane depolarization stabilizes PINK1 on the outer membrane, leading to phosphorylation and recruitment of the E3 ubiquitin ligase Parkin, which ubiquitinates voltage-dependent anion channel 1 (VDAC1) and MFN1/2 outer-membrane proteins. Ubiquitin-binding adaptor proteins such as optineurin, nuclear dot protein 52 kDa (NDP52), and p62/sequestosome 1, recruit the autophagy machinery by binding light chain 3 (LC3) protein on the phagophore, enabling autophagosome formation around damaged mitochondria (Kane et al., 2014; Koyano et al., 2014). In parallel, receptor-mediated mitophagy operates independently of PINK1/Parkin, where outer membrane proteins such as Bcl-2/adenovirus E1B 19-kDa-interacting protein 3 (BNIP3), NIX (BNIP3L), and FUN14 domain-containing protein 1 (FUNDC1) interact directly with LC3 via their LIR (LC3-interacting region) motifs, particularly under hypoxia or during erythroid differentiation (Liu et al., 2012; Novak et al., 2010; Sandoval et al., 2008; Zhu et al., 2013).

Beyond degradation, mitochondrial biogenesis replenishes the mitochondrial population through peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α)-dependent transcriptional programs that co-activate nuclear respiratory factor (NRF) 1/2 and mitochondrial transcription factor A (TFAM) to promote mtDNA replication and expression of oxidative phosphorylation components (Lazarou et al., 2015; Scarpulla, 2008). mtDNA maintenance involves base-excision repair enzymes such as 8-oxoguanine DNA glycosylase (OGG1), DNA polymerase subunit gamma, and the mitochondrial ligase, while the mitochondrial antioxidant system, including superoxide dismutase 2 (SOD2), peroxiredoxins, and the glutathione (GSH–GSSG) cycle, limits reactive oxygen species (ROS) accumulation (Baker et al., 2011; Youle and Van Der Bliek, 2012). Collectively, these intertwined mechanisms form an adaptive network that continuously remodels the mitochondrial network to preserve cellular energy homeostasis and viability (Fig. 1).

2.2. Mitochondrial quality control in neuronal metabolism and viability

Neurons are highly specialized and metabolically demanding cells that require a constant and finely regulated energy supply to sustain synaptic signaling, maintenance of the membrane potential, axon–dendrite transport, and ionic homeostasis. Neurites display complex and variable morphologies, characterized by long axons and dendritic tree branched at different levels, which requires diversified energy supply and rapid local adaptation of mitochondrial function (Li et al., 2004; MacAskill et al., 2010). To this aim, as in other cellular context, mitochondria play a central role not only as "powerhouses" responsible for ATP production through oxidative phosphorylation, but also as regulators of other processes such as calcium homeostasis, fatty acid and lipid metabolism, ROS production, and cell death signaling (Shen et al., 2022). Under high neuronal metabolic demands and compromised antioxidants defence, oxidative stress can be installed and promote neuronal damage and ultimately degeneration. An efficient and integrated MQC system can, at least partly, help maintain mitochondrial integrity, distribution, and renewal to support neuronal and brain homeostasis.

2.2.1. Mitophagy in neurons

Mitophagy is essential for the proper functioning of neurites: it limits ROS production, prevents the accumulation of mtDNA mutations, preserves mitochondrial respiratory efficiency by removing dysfunctional organelles, thereby helping maintain ATP production, and suppresses both apoptotic signaling and inflammasome activation (Han et al., 2021).

With the support of the cytoskeleton, mitochondria can be trafficked between the various neuronal compartments. Two main forms of transport can be distinguished: 1) anterograde, from the cell body toward the distal axons; and 2) retrograde, from the distal axons back to the soma (Mandal et al., 2021; Zhou et al., 2016). While mitochondria are predominantly distributed within neuronal processes, lysosomes tend to remain close to the nucleus. During mitophagy, a reduction in anterograde transport and an increase in retrograde transport are observed, directing damaged mitochondria toward the soma, rich in lysosomes (Mandal et al., 2021; Tseng et al., 2013; Zheng et al., 2019). Anterograde transport is mediated mainly by the motor protein kinesin-1 (Pilling et al., 2006) via trafficking kinesin proteins (Brickley and Stephenson, 2011) and Miro (Fransson et al., 2003), or syntabulin (Cai et al., 2005). Retrograde transport, instead, depends primarily on dynein and dynactin (Pilling et al., 2006; Schroer, 2004). Although dynein can bind directly to mitochondria (Schwarzer et al., 2002), Miro also contributes to this process (Russo et al., 2009). These movements stop in regions with high ATP demand (Li et al., 2020; Mironov, 2007) and intense Ca^{2+} regulation, such as synapses (Wang and Schwarz, 2009).

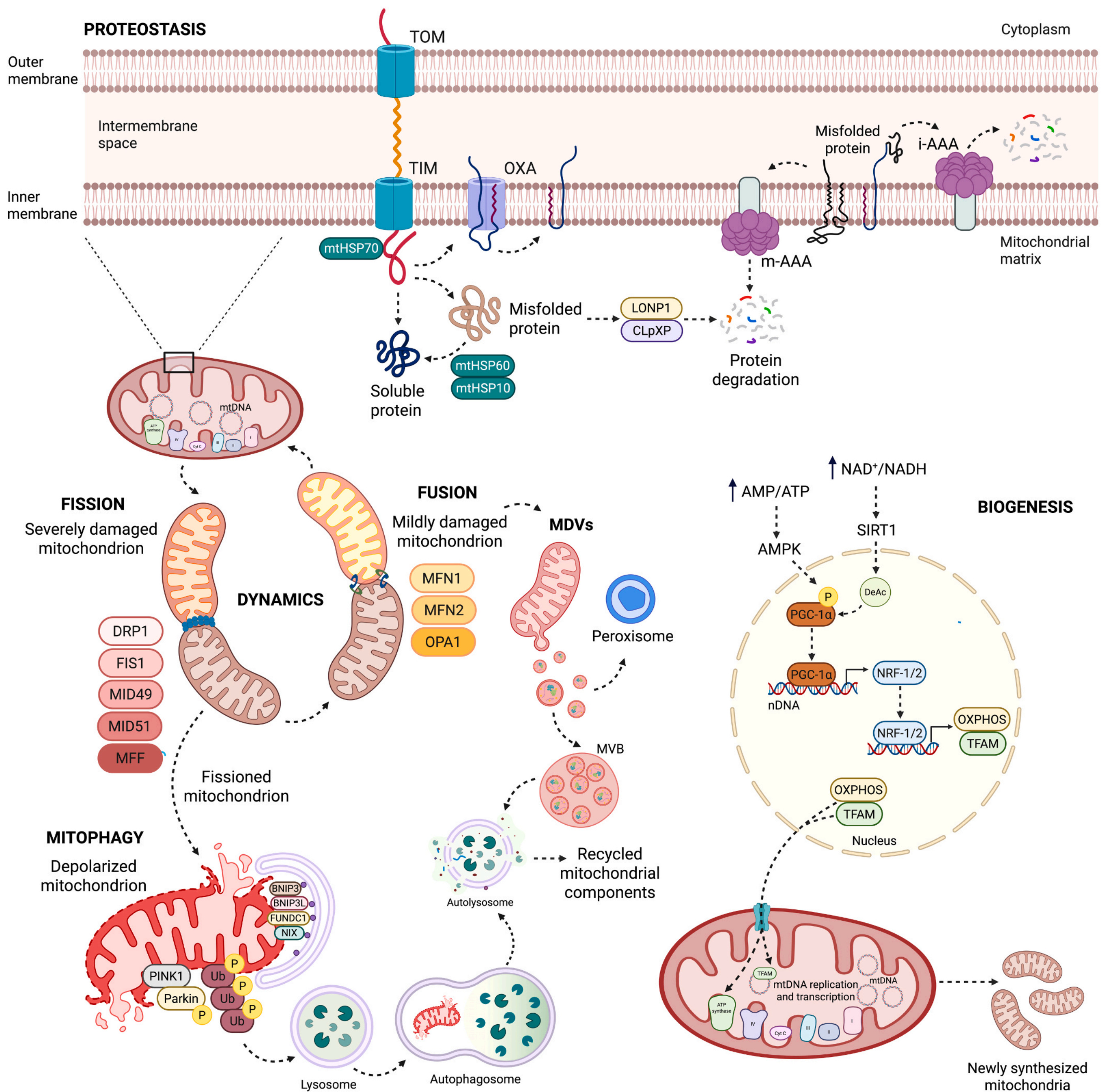

Fig. 1. Schematic representation of mitochondrial quality control (MQC) modules and their points of integration. MQC depends on multiple, coordinated surveillance systems, including proteostasis, fusion–fission dynamics, mitochondria-derived vesicles (MDVs), mitophagy, and biogenesis, that cooperate to maintain mitochondrial function under basal and stress conditions. *Proteostasis*: Misfolded or unstable proteins in the matrix and intermembrane space are refolded by chaperones (e.g., mtHSP70, HSP60, HSP10) or degraded by ATP-dependent proteases such as LONP1 and ClpXP. AAA$^+$ proteases (m-AAA and i-AAA) further remove oxidized or misassembled proteins, fine-tuning activity during stress. *Fusion–fission dynamics*: Mitochondrial remodeling balances network connectivity and quality segregation. Fusion is mediated by MFN1/MFN2 and OPA1, whereas fission is driven by DRP1 recruited by FIS1, MFF, and MiD49/51. *MDVs*: These vesicles selectively transport mitochondrial cargo to endolysosomes or peroxisomes, providing a rapid, localized quality-control mechanism that complements mitophagy. *Mitophagy*: When repair fails, damaged mitochondria are eliminated via the PINK1–Parkin pathway or LC3-interacting receptor–mediated routes (e.g., BNIP3, FUNDC1), ensuring selective organelle turnover. *Biogenesis*: Recovery and renewal of mitochondrial mass are driven by PGC-1α–dependent transcriptional programs linking AMPK/SIRT1 signalling to NRF1/NRF2 and TFAM activation, thereby restoring mitochondrial number and function. Abbreviations: AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; BNIP3, BCL2/adenovirus E1B 19-kDa protein-interacting protein 3; BNIP3L, BNIP3 like; CLPXP, ClpXP protease complex; DeAc, deacetylase; DRP1, dynamin-related protein-1; FIS1, mitochondrial fission 1 protein; FUNDC1, FUN14 domain-containing 1; HSP, heat shock protein; LONP1, LON peptidase 1; MDV, mitochondria-derived vesicle; MFF, mitochondrial fission factor; MFN1/2, mitofusin-1/2; MiD49/51, mitochondrial dynamics proteins 49 and 51 kDa; mtHSP70, mitochondrial heat shock protein 70; mtDNA, mitochondrial DNA; MVB, multivesicular body; NAD+ , nicotinamide adenine dinucleotide; NIX, Nip3-like protein X; NRF1/2, nuclear respiratory factor 1/2; OPA1, optic atrophy protein 1; OXA, oxidase assembly translocase; OXPHOS, oxidative phosphorylation; P, Phosphate residue; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; PINK1, PTEN-induced kinase-1; SIRT1, sirtuin-1; TFAM, mitochondrial transcription factor A; TIM, translocase of the inner membrane; TOM, translocase of the outer membrane; Ub, ubiquitin. Created with BioRender.com.

Mitophagy can occur via three main mechanisms: non-receptor-mediated mitophagy, receptor-mediated mitophagy, and transcellular mitophagy (Fig. 2). The first and best characterized mechanism is the non-receptor-mediated mitophagy which follows the PINK1/Parkin signaling pathway. This pathway isolates damaged mitochondrial portions and initiates autophagy through adaptor proteins such as microtubule-associated protein 1 A/1B light chain 3 (LC3) and GABA type A receptor-associated protein (GABARAP) (Narendra et al., 2012).

Neurodegenerative diseases, like Parkinson's (PD), Alzheimer's (AD), and Huntington's disease (HD), show profound alterations in mitophagy (Li et al., 2023). In early-onset PD, mutations in *Park2*, *Pink1*, and *DJ-1* genes impair crucial mitochondrial proteins, disrupting energy

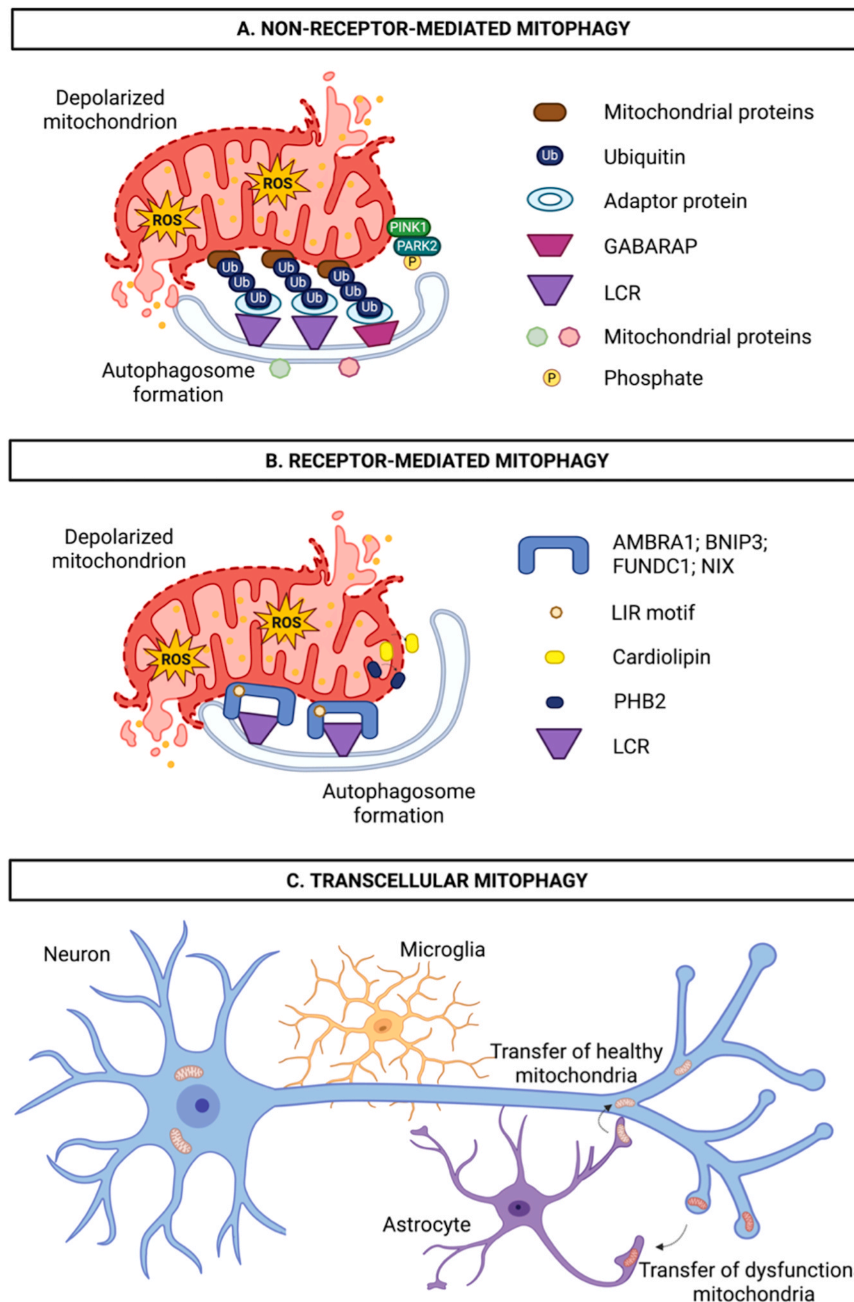

Fig. 2. Schematic representation of the three main mechanisms regulating mitophagy in neurons. A) Non-receptor-mediated mitophagy. Damaged mitochondria accumulate PTEN-induced kinase 1 (PINK1) on the outer mitochondrial membrane (OMM), where it associates with and activates parkin (PARK2) through phosphorylation of its serine 65 (S65) residue. This signaling cascade subsequently triggers the ubiquitination of several mitochondrial proteins located in the OMM. Through the ubiquitin-binding adaptor proteins, parkin-ubiquitinated mitochondrial substrates interact with microtubule-associated protein 1 A/1B-light chain 3 (LC3) and GABAA receptor-associated protein type A (GABARAP) on the autophagosome, ultimately leading to autophagic degradation of mitochondrial components. Degradation products generated in autolysosomes are recycled and reused for cellular metabolism and mitochondrial biogenesis. B) Receptor-dependent mitophagy is activated through mitochondrial receptors containing LC3-interacting region (LIR) motifs. These include OMM proteins such as beclin-regulated autophagy activator molecule (AMBRA1), BCL2-interacting protein 3 (BNIP3), FUN14 domain containing 1 (FUNDC1), and Nip3-like X protein (NIX), as well as components of the inner mitochondrial membrane (IMM), including cardiolipin and PHB2 (prohibitin 2). These mitophagy receptors subsequently bind to the autophagosomal protein LC3 to promote mitochondrial clearance. C) Transcellular mitophagy. At the synapse, damaged mitochondria can be expelled via exocytosis, after which the extracellular organelles are eliminated by nearby glial cells via endocytosis or phagocytosis. A reverse transfer of mitochondria from glial cells to neurons has also been described. Created with BioRender.com.

metabolism and increasing neuronal vulnerability to oxidative stress (Klein and Westenberger, 2012). Alpha-synuclein exacerbates defects in PINK1–Parkin mitophagy by promoting mitochondrial fragmentation through direct interactions with or increased DRP1 activity (Klein and Westenberger, 2012; Martinez et al., 2018; Nakamura et al., 2011). In mouse models of AD, even early increases in mitochondrial respiratory activity and associated ROS signaling, which can trigger MQC and turnover, do not compensate for energy deficits but instead exacerbate synaptic loss due to impaired mitophagy (Han et al., 2021). Conversely, enhanced lysosomal activity restores metabolic function by promoting the removal of damaged mitochondria and protecting synapses (Han et al., 2021). Reduced Parkin levels and abnormal accumulation of PINK1 in AD impair PINK1–Parkin complex formation and mitophagy initiation (Bellot et al., 2009; Martín-Maestro et al., 2019). Parkin overexpression restores the process (Martín-Maestro et al., 2019). As the disease progresses, cytosolic Parkin levels decrease and its recruitment to mitochondria becomes destabilized, likely via protein- or tau-mediated sequestration (Ye et al., 2015). Reduced sirtuin 3 in amyloid precursor protein/presenilin transgenic mice models has also been shown to contribute to mitophagy defects (Yang et al., 2015), whereas alterations in Unc-51 like autophagy activating kinase 1 (ULK1) and TANK-binding kinase 1 interfere with the initiation of mitophagy (Fang et al., 2019). Sirtuin 3-mediated mitophagy is also a target of the petroleum ether extract active fraction of *Polyrhachis vicina* Roger (AFPR), that has been reported to reduce neurological damage and infarct volume in cerebral ischemia–reperfusion in rat models by promoting angiogenesis in the damaged area (Pang et al., 2024). Recent studies in ischemia–reperfusion injury and chemotherapy-related tissue damage indicate that perturbation of complex I subunits (e.g., NDUFS4) and post-translational regulators such as sirtuin 5 and dual-specificity phosphatase 1 can jointly remodel MQC, coordinating mtUPR signaling, mitochondrial dynamics, and downstream inflammatory outputs (Pu et al., 2025a, 2025b; Shi et al., 2012).

In HD, CAG expansion in the huntingtin gene leads to the formation of mutant poly(Q) huntingtin aggregates that hinder the recruitment of mitophagy receptors and the interaction between damaged mitochondria and autophagosomes (Franco-Iborra et al., 2021). Because huntingtin interacts with ULK1, its dysfunction results in the accumulation of defective mitochondria and oxidative stress, especially in striatal neurons (Franco-Iborra et al., 2021; Guedes-Dias et al., 2015).

Receptor-mediated mitophagy relies on mitochondrial proteins containing LIR motifs (Wong and Holzbaur, 2014). Via interactions with autophagy-related protein (ATG) 8 family members, these receptors enable the recognition and incorporation of damaged mitochondria into the expanding phagophore (Johansen and Lamark, 2020). Among the best-studied receptors are the activating molecules in Beclin-1-regulated autophagy (AMBRA1), BNIP3, FUNDC1, and NIX, along with inner mitochondrial membrane components such as cardiolipin and prohibitin 2 (Liu et al., 2012; Novak et al., 2010; Sandoval et al., 2008; Wu et al., 2014; Zhang and Ney, 2008). Activation of this form of mitophagy occurs in specific contexts. For example, chronic glucocorticoid exposure profoundly alters mitochondrial morphology, trafficking, and mitophagy, reducing biogenesis and causing energy deficits, especially at synapses (Choi and Han, 2021). Stress-related glucocorticoids reduce NIX, causing synaptic deficits as observed in mouse hippocampal neurons and SH-SY5Y cells; this occurs through interactions between the glucocorticoid receptor and PGC-1α, which limits its nuclear entry and suppresses NIX-mediated mitophagy (Choi et al., 2021). Conversely, FUNDC1 activation exerts neuroprotective effects during ischemia–reperfusion injury (Cai et al., 2021), participating in both mitochondrial dynamics and mitophagy (Liu et al., 2022). The nuclear receptor subfamily 4 group A member 1 (NR4A1) has been shown to regulate mitochondrial dynamics in ischemia–reperfusion injury by promoting mitochondrial fission through mitochondrial fission factor (MFF) and modulating FUNDC1-mediated mitophagy (Wang et al., 2024). NR4A1 expression increases following ischemia–reperfusion injury, driving MFF-dependent mitochondrial fragmentation and altering mitophagy responses. In contrast, NR4A1-knockout mice exhibit resistance to ischemia–reperfusion injury, reduced pathological mitochondrial fission, and enhanced mitophagy activation compared with wild-type littermates (Wang et al., 2024). AMBRA1 can act as an autonomous receptor in the absence of Parkin (Strappazzon et al., 2015), while BNIP3L can promote mitophagy independent of the PINK1–Parkin system, offering a potential compensatory mechanism in PD (Gao et al., 2015; Koentjoro et al., 2017).

Transcellular mitophagy represents another mitophagy strategy based on the release of mitochondria from neurons and their subsequent phagocytosis by glial cells (Davis et al., 2014; Narendra et al., 2012). A reverse transfer from glia to neurons has also been observed as a form of cellular communication (Babenko et al., 2015; Davis et al., 2014). Under stress conditions, such as oxygen–glucose deprivation followed by reoxygenation, cells can exchange mitochondria through tunnelling nanotubes (Nasoni et al., 2021). In stroke models, glia-to-neuron transfer mediated by $CD38^+$ cells have a protective effect, whereas its inhibition worsens outcomes (Hayakawa et al., 2016). Impaired astrocytic mitochondrial transfer has been observed in hPSC models carrying glial fibrillary acidic protein mutations (Gao et al., 2019). However, several studies using mitochondria-specific fluorescent markers have detected no transfer between neurons (Misgeld et al., 2007; Plucińska et al., 2012), suggesting that this is a rare event limited to pathological conditions. Even when present, the number of mitochondria transferred is minimal and insufficient to meet neuronal energy demands.

Additional mechanisms contributing to mitophagy exist but are still only partially understood and include: 1) the role of the mitochondrial E3 ligase MUL1, which ubiquitinates MFN2 and SUMOylates DRP1, modulating morphology and ER–mitochondria contacts (Puri et al., 2019); 2) involvement of Rab9 in a form of an "alternative mitophagy" pathway involving trans-Golgi membranes (Saito et al., 2019); 3) regulation of basal mitophagy by cyclin G-associated kinase and protein kinase C delta (Munson et al., 2021); and 4) the action of Spata18, which in response to mtDNA damage promotes MQC by inducing the formation of acidic, lysosome-like vacuoles that facilitate degradation of damaged mitochondrial components (Dan et al., 2020; Miyamoto et al., 2011).

Mitochondrial clearance can also occur through additional pathways such as MDV formation, which will be discussed later. Another fascinating mechanism is the production of "exospheres", large vesicles containing mitochondria and protein aggregates targeted for elimination via phagocytosis by surrounding cells (Melentijevic et al., 2017).

Although mitophagy is a degradative process, MQC is not always intended for degradation: it also includes the biogenesis of new mitochondria and the regulation of mitochondrial dynamics through fusion and fission. Thanks to the balance between removal of damaged mitochondria and production of new ones, the mitochondrial network preserves high membrane potential, robust respiratory capacity, efficient ATP production, and proper redox balance, all essential elements for neuronal metabolism.

2.2.2. *Mitochondrial biogenesis in neurons*

Neurons, highly specialized and extraordinarily long-living postmitotic cells, tend to accumulate damage in their mitochondria. Signals from energetic stress, such as changes in AMP/ATP or NAD^+/NADH ratios and increases in intracellular calcium, can activate transcriptional nuclear programs that promote the formation of new mitochondria. PGC-1α is the main coordinator of mitochondrial biogenesis and, in neurons, regulates mitochondrial density in axons through the activity of sirtuin 1 (Sirt1) (Wareski et al., 2009). In zebrafish, biogenesis is supported by retrograde transport of mitochondria from the axon to the soma, a process that activates mtDNA replication and transcription via estrogen-related receptors. These receptors link metabolic and transcriptional regulation via modulation of PGC-1α and Sirt1 (Lang et al., 2025). PGC-1α is also activated by neuronal depolarization through AMPK, which increases the expression of NRF-1 and TFAM, thereby

enhancing mitochondrial content and ATP production (Yu and Yang, 2010). This highlights the strong connection between mitochondrial biogenesis and synaptic activity. When PGC-1α is inhibited, dendritic mitochondria decrease, leading to a reduction in synapse number (Cheng et al., 2012) and a deficit in filopodia formation and axonal branch maturation (Spillane et al., 2013). Synaptic plasticity induced by the brain-derived neurotrophic factor (BDNF) also requires PGC-1α (Wrann et al., 2013). BDNF activates cAMP response element-binding protein (CREB), which in turn increases the expression of PGC-1α, NRF-1, and TFAM to enhance mitochondrial biogenesis and function. Consistently, protein levels of PGC-1α, NRF-1, and TFAM are reduced in HD, PD, and AD (Ferreira et al., 2020; Jang et al., 2018; Koo and Cho, 2017; Sheng et al., 2012; Taherzadeh-Fard et al., 2011).

The location of mitochondrial biogenesis in neurons has long been debated. Since the mitochondrial proteome consists of over a thousand proteins, only 13 of which are encoded by mtDNA (Rath et al., 2021), and most originate from the nucleus, it has been proposed that biogenesis occurs primarily in the soma. However, mtDNA duplication has been shown to occur also in distal axonal regions (Amiri and Hollenbeck, 2008; Van Laar et al., 2018). Two hypotheses therefore coexist: 1) mitochondria are produced in the soma and then transported to distal compartments; 2) mitochondrial replication occurs directly on-site in far-distal regions of the cell body (Fedorovich et al., 2017; Misgeld and Schwarz, 2017). In the first model, the soma generates new mitochondria intended for synapses, whereas damaged ones return to the cell body for degradation. This view aligns with the fact that mtDNA encodes exclusively OXPHOS proteins, while the factors required for replication reside in the nucleus and require activation of PGC-1α- and NRF-1/2–dependent programs. If biogenesis occurred far from the soma, a mechanism independent of PGC-1α would be needed, an unlikely scenario given the central role of this coactivator in synapse formation and in the pathogenesis of neurodegenerative diseases. In neurons, about 30% of mitochondria are in motion, although the mobile fraction fluctuates over time: stationary mitochondria can resume movement, whereas motile ones tend to anchor in areas rich in Ca^{2+} or with high energy demand (Chen and Sheng, 2013; Kang et al., 2008). This dynamic suggests that mitochondria produced in the soma can "sense" their appropriate destination. However, this model has limitations: mitochondria move at approximately 0.5 μm/s (Bros et al., 2015), a speed like that observed in motoneurons (Miller et al., 2016). This implies that a newly formed mitochondrion would take days to reach the axon terminal, an interval incompatible with the immediate needs of regions with high energy demand, such as synaptic terminals, growth cones, and Ranvier nodes (Bristow et al., 2002; Fabricius et al., 1993; Kageyama and Wong-Riley, 1982; Rowland et al., 2000). Furthermore, during neuronal maturation the percentage of mobile mitochondria drops below 10% (Lewis et al., 2016), a finding confirmed also in vivo (Misgeld et al., 2007; Smit-Rigter et al., 2016). Considering the extreme length of human axons, which can reach one meter, it is unlikely that the soma is the sole site of renewal, suggesting that biogenesis may also occurs in distal regions. Indeed, mtDNA replication can occur far from the soma (Amiri and Hollenbeck, 2008; Van Laar et al., 2018). The problem remains: biogenesis requires nuclear transcription factors such as PGC-1α and NRF-1/2, which act exclusively in the nucleus. A plausible solution may be provided by mRNAs and ribosomes localized in axons (Aschrafi et al., 2016; Shigeoka et al., 2016), which allow local translation of both mtDNA- (Kuzniewska et al., 2020) and nuclear-encoded proteins (Cioni et al., 2019; Cosker et al., 2016; Yoon et al., 2012). This mechanism obviates the need of continuous mitochondrial transport from the soma and enables rapid, efficient replenishment. In fact, inhibition of local protein synthesis compromises mitochondrial function in axons (Cioni et al., 2019; Hillefors et al., 2007).

Neuronal activity enhances local RNA translation, essential for plasticity and memory, suggesting that synaptic stimuli may activate distal biogenesis (Kuzniewska et al., 2020; Yoon et al., 2012). At the molecular level, Ca^{2+} influx can activate calcium/calmodulin-stimulated protein kinase II (CaMKII), which phosphorylates cytoplasmic polyadenylation element-binding protein (Atkins et al., 2004), promoting polyadenylation and mRNA translation. CaMKII can also activate eukaryotic translation initiation factor 4E (eIF4E) and stimulate synaptic protein synthesis (Mockett et al., 2011). A similar mechanism involves the mammalian target of rapamycin complex 1 (mTORC1), which activates eIF4E and promotes local translation (Takei et al., 2004), whereas AMPK can antagonize mTORC1 and thus inhibit distal biogenesis (Ishizuka et al., 2013).

Activation of N-methyl-D-aspartate receptors in mouse synaptosomes has also been shown to stimulate local production of mitochondrial proteins and to enhance biogenesis (Kuzniewska et al., 2020) through Ca^{2+} influx that activates extracellular signal-regulated kinase (ERK) 1/2 kinase (Hardingham et al., 2001), a key node of the mitogen-activated protein kinase (MAPK) pathway (Iroegbu et al., 2021). Alterations in ERK1/2 can damage mitochondria and promote apoptosis, although the mechanisms of this process remain unclear (de Oliveira et al., 2017). Studies on physically isolated axons from the soma show an autonomous increase in mitochondrial density and mtDNA replication (Van Laar et al., 2018). In spinal ganglia, both the translation of nuclear-encoded mitochondrial proteins and mtDNA synthesis occur directly in axons (Amiri and Hollenbeck, 2008). In motoneurons, nuclear mRNA for cytochrome C oxidase subunit 7 C travels along axons in mitochondrial-associated ribonucleoprotein complexes (Cohen et al., 2022). Once reached the neural distant site, this is translated locally, thus contributing to mtDNA replication and functional renewal of mitochondria (Qin et al., 2021). For neurons with very long axons, transporting mRNA is more efficient than transporting entire organelles, also because many mitochondrial proteins have half-lives too short to reach synapses solely via organelle transport (Kuzniewska et al., 2020). Local translation therefore enables not only repair of mitochondria on-site but also the generation of new organelles directly within axons (Kuzniewska et al., 2020).

Alterations in biogenesis can impair neurite survival and contribute to neurological diseases. In AD, altered mitochondrial function is observed (Zhu et al., 2006), and hyperphosphorylated tau seems to impair complex I activity, leading to high ROS and reduced ATP production in preclinical models (Stojakovic et al., 2021). AD models also show reduced protein levels of PGC-1α, NRF-1/2, and TFAM (Gong et al., 2013; Sheng et al., 2012). Aβ interferes with the SIRT1/PGC-1α interaction, altering the nuclear–cytoplasmic balance and disturbing mitochondrial dynamics (Panes et al., 2020).

The activation of the PGC-1α–NRF1/2–TFAM pathway in AD model mice has been shown to promote mitochondrial biogenesis and improve spatial learning and memory, reduce Aβ burden, enhance cell viability, and decrease ROS production, ultimately preserving mitochondrial structure and function (Liu et al., 2021; Pang et al., 2024). These findings underscore the importance of mitochondrial biogenesis not only in neurons but also in the whole neurovascular unit in AD. Indeed, mitochondrial dysfunction in cerebrovascular endothelial cells has been indicated as a target for interventions (Pang et al., 2024). Oxidative stress can damage vascular endothelial cells, compromising blood–brain barrier integrity and vascular function (Aliev et al., 2009). ROS signaling reduces nitric oxide (NO) bioavailability, impairing vasodilation while promoting endothelin-1-mediated vasoconstriction, thereby contributing to chronic cerebral hypoperfusion and disease progression. Moreover, oxidative stress and mitochondrial depletion in AD neurons can exacerbate vascular injury, a process further intensified by Aβ deposition around cerebral blood vessels (Aliev et al., 2009).

In PD, variations in the levels and mutations of mtDNA (Dölle et al., 2016), PGC-1α, and its downstream targets have been described (Zheng et al., 2010; Guerra et al., 2019). Of note, such changes are interrelated. Indeed, α-Synuclein can modify Parkin, promoting the accumulation of PARIS (Wilkaniec et al., 2021), a repressor of PGC-1α that induces mitochondrial depolarization, ATP deficits, ROS increases, and

dopaminergic neurodegeneration (Pirooznia et al., 2022; Shin et al., 2011; Stevens et al., 2015). Although PARIS is degraded by PINK1 and Parkin, its accumulation is evident also in sporadic PD (Lee et al., 2017; Shin et al., 2011). Reducing PARIS restores PGC-1α activity and alleviates damage (Lin et al., 2021). Activation of PGC-1α through resveratrol, instead, reduces α-synuclein and apoptosis (ur Rasheed et al., 2016). Loss of PGC-1α results in degeneration of dopaminergic neurons and dopamine deficits (Jiang et al., 2016), thus confirming its protective role. Similarly, loss of TFAM in dopaminergic neurons induces mtDNA reduction and respiratory defects, leading to neurodegeneration and motor symptoms (Ekstrand et al., 2007).

In HD, mutant huntingtin binds to the PGC-1α promoter and inhibits its transcription (Cui et al., 2006), inducing reduced expression in the striatum while its restoration prevents neuronal loss in mouse models (Cui et al., 2006). PGC-1α knockout mice also show striatal lesions and HD-like phenotypes (Ma et al., 2010). PGC-1α-mediated dysregulation of mitochondrial biogenesis at the neuromuscular junction has been reported (Arnold et al., 2014) and linked to morphological and functional remodelling occurring in pathological conditions like amyotrophic lateral sclerosis (ALS). Experimental transgenic models of ALS show respiratory defects, biogenesis alterations, and abnormalities in muscle acetylcholine receptors (Eschbach et al., 2013; Mehta et al., 2021). Overexpression of PGC-1α in superoxide dismutase 1 G93A models improves mitochondrial function, reduces dyskinesia, and delays motor neuron death (Zhao et al., 2011). More recently, 7,8-dihydroxyflavone was shown to activate the AMPK/PGC-1α/NRF1/TFAM pathway, to improve biogenesis and to slow down symptom progression (Xia et al., 2021).

Understanding the molecular mechanisms regulating mitochondrial biogenesis in neurons in different settings may open new perspectives on how to preserve mitochondrial number and function at synapses.

2.2.3. Mitochondrial dynamics in neurons

The rapid morphological changes of mitochondria through dynamics shape their structure to support several cellular features, including bioenergetic activity and overall quality (Mishra and Chan, 2016). Mitochondrial dynamics is regulated by coordinated cycles of fission and fusion, processes that influence not only morphology and distribution but also mitochondrial transport and selective degradation (Mishra and Chan, 2016). Fission can increase the number of organelles or selectively eliminate damaged portions, depending on the division site (Kleele et al., 2021), while fusion promotes the exchange of components, synchronizes the mitochondriome, and enhances energy production (Yao et al., 2019), generating elongated mitochondria (Picard et al., 2013). These dynamic processes are essential for neuronal development and functionality (Reddy et al., 2012). Fission is orchestrated by the GTPase DRP1, which is recruited to the outer mitochondrial membrane through interactions with the endoplasmic reticulum and proteins such as MFF or FIS1 (Friedman et al., 2011; Lewis et al., 2018). In neurons, MFF-dependent fission is fundamental for maintaining mitochondria of appropriate size for axonal transport and synaptic transmission; its reduction alters presynaptic calcium levels and exocytosis without affecting ATP or membrane potential (Lewis et al., 2018), and compromises axonal branching (Catalano and Shatz, 1998; Gomez et al., 2001; Gu et al., 1994). Defects in fission prevent the elimination of damaged mitochondria, promoting apoptosis. Outer mitochondrial membrane fusion, mediated by MFN1 and MFN2, plays distinct roles in membrane fusion and the formation of MAM complexes (de Brito and Scorrano, 2008; Ishihara et al., 2004). Their activity is modulated by redox signals (Mattie et al., 2018) and shows tissue specificity, with higher expression of MFN2 in the brain (Eura et al., 2003; Ishihara et al., 2004). Loss of MFN2 after placentation causes severe cerebellar defects (Chen et al., 2007). Inner membrane fusion is regulated by OPA1 via cooperation of the L-OPA1 and S-OPA1 isoforms, whose balance prevents uncontrolled fragmentation (Ban et al., 2017; Song et al., 2007). This process also allows protein exchange, DNA repair, and proper metabolite distribution (Chen et al., 2003; Twig et al., 2008). During periods of high energy demand, elongated mitochondria optimize oxidative phosphorylation, significantly increase ATP production, and facilitate movement toward cellular regions with greater energy needs (Gomes et al., 2011). Fusion deficits cause mitochondrial swelling and neuritic degeneration (Chen et al., 2007), and mutations in MFN2, OPA1, or DRP1 lead to severe defects in neuronal development (Chen et al., 2007; Fang et al., 2016). During neuronal development, mitochondria adopt different morphologies: elongated in neural stem cells and fragmented in progenitor cells (Beckervordersandforth et al., 2017; Khacho et al., 2016). They accumulate in growth cones to sustain high metabolic demand (Morris and Hollenbeck, 1993) and regulate Ca^{2+} dynamics (Gomez and Zheng, 2006). Mitochondrial dynamics also contribute to mitochondrial genome stability and compensation of mutations (Ono et al., 2001).

In neurodegenerative diseases, the balance between fusion and fission is consistently impaired, leading to inefficient ATP distribution and inadequate mitophagy, contributing to neuronal degeneration and cognitive decline (Burté et al., 2015).

In AD, reduced mitochondrial energy production is a hallmark of the disease; decreases in electron transport chain complex activity have been reported in peripheral cells and post-mortem brain samples (Bosetti et al., 2002; Kish et al., 1992). The pro-apoptotic protein appoptosin, induced by amyloid-beta (Aβ), promotes mitochondrial fragmentation by interfering with MFN1 and MFN2 (Zhang et al., 2016b; Zhang et al., 2012), and together with MFN2 may have a pro-apoptotic role (Guo et al., 2007; Papanicolaou et al., 2011; Shen et al., 2007; Zhang et al., 2016a). DRP1 is also aberrantly expressed in AD brains (Manczak et al., 2018). Aβ accumulation increases DRP1 and reduces MFN1/2 and OPA1, along with a decrease in PGC-1α, indicating reduced biogenesis (Kandimalla et al., 2016; Manczak et al., 2018). In APOE4 models, an early compensatory increase in MFN1 is observed as an adaptive response to synaptic pathology (Li et al., 2016; Simonovitch et al., 2019). Later, in advanced disease stages a shift toward fission with elevated DRP1 and reduced MFN2 protein levels, influenced by age, sex, and brain region is observed (Djordjevic et al., 2020). Interactions among DRP1, Aβ, and tau amplify fission and impair mitochondrial function (de la Fuente-Muñoz et al., 2020; Manczak et al., 2011; Manczak and Reddy, 2012), while DRP1 inhibition reduces fragmentation, mitophagy, and synaptic dysfunction (Baek et al., 2017; Kandimalla et al., 2016; Wang et al., 2017). In advanced AD stages, giant mitochondria appear, possibly resulting from incomplete fission and attempts to avoid mitophagy (Zhang et al., 2016a). Differential local brain responses of PGC-1α, MFN2, and DRP1 to amyloid have been observed in preclinical models of AD (Baranich et al., 2024; de la Cueva et al., 2022), while collapsin response mediator protein 2 links neurite growth to mitochondrial alterations via DRP1 (Brustovetsky et al., 2021). Analyses in human tissues confirm morphological abnormalities in synaptic and somatic mitochondria, associated with synaptic vesicle deficits and impaired neuronal transmission (Wang et al., 2023).

In familial PD, mutations in PINK1 and Parkin impair mitochondrial dynamics. PINK1-dependent phosphorylation of DRP1 enhances mitochondrial fission, whereas Parkin-mediated ubiquitination promotes DRP1 degradation. A decline of Parkin-mediated ubiquitination is more commonly observed in the context of familial PD that leads to the accumulation of DRP1, excessive mitochondrial fragmentation, and impaired mitochondrial homeostasis (Han et al., 2020; Wang et al., 2011). PGC-1α, instead, has a neuroprotective role, reducing oxidative damage and supporting mitochondrial function (Mudò et al., 2012). Other PD-associated genes, such as LRRK2 and DJ-1, influence fusion and fission, altering neurite growth and mitochondrial morphology (Ottolini et al., 2013; Stafa et al., 2014). Similar abnormalities have been found in idiopathic PD and synucleinopathy models (Portz and Lee, 2021).

Early evidence in HD, indicate that CAG expansion in HTT is associated with bioenergetic deficits, reduced brain mitochondria, and

impaired OXPHOS (Brennan et al., 1985; Gu et al., 1996). Subsequent studies have confirmed such findings and highlighted the necessity of assessing mitochondrial bioenergetics and function in the context of cellular environment (Oliveira et al., 2007). Finally, mutant HTT interfere with mitochondrial network and quality and predisposed to mtDNA mutations (Neueder et al., 2024)

Several proteins associated with both familial and sporadic ALS, including FUS, TDP-43, SOD1, and C9ORF72, are linked to mitochondrial dynamics (Kodavati et al., 2020). Mouse models of TDP-43 pathology display alterations in mitochondrial shape and aggregation (Hong et al., 2012). Overexpression of TDP-43, both wild-type and mutant, disrupts mitochondrial structure and movement while co-expression of MFN2, which interacts with TDP-43, can counteract these defects (Wang et al., 2013). At the same time, it was observed that TDP-43 determines a fission/fusion imbalance associated with mitochondrial fragmentation and a decrease in the expression of mitochondrial complex I and II subunits, mitochondrial membrane potential, cellular respiration, and cytochrome C oxidase activity (Petito et al., 2025). TDP-43 expression in the cortex and hippocampus of 4-month-old mice increases DRP1 phosphorylation at S637 while reducing fission, thus indicating a role in regulating mitochondrial dynamics (Davis et al., 2018). Overexpression of TDP-43 also affects ER–mitochondria contact sites and activates glycogen synthase kinase 3 beta, which influences Ca^{2+} homeostasis and may trigger motor neuron death (Stoica et al., 2014). Multiple studies show that also FUS alters mitochondrial dynamics. Ultrastructural analysis of the spinal cord in ALS-FUS reveals disorganization of mitochondria and ER associated with the P525L mutation (Huang et al., 2010). Expression of FUS mutants R521G or R521H causes shortened mitochondria in motor neurons (Tradewell et al., 2012), while iPSC-derived motor neurons from patients with mutant FUS show defects in axonal transport and reduced ER–mitochondria membranes, which can be rescued by inhibiting or silencing histone deacetylase 6 (Guo et al., 2017). Increased FUS within mitochondria leads to elevated FIS1, fragmentation, loss of membrane potential, increased ROS, and deficits in axonal transport (Deng et al., 2018). Cortical and motor neurons from transgenic mice with ALS linked to SOD1 G93A mutation show reduced anterograde mitochondrial transport (De vos et al., 2007). Reductions in MFN1 and OPA1 protein levels have also been observed, while DRP1 and FIS1 are unchanged, disrupting the fusion–fission balance (Liu et al., 2013). Fibroblasts from patients with C9ORF72 mutations show fusion–fission imbalance, elevated MFN1, and morphological mitochondrial abnormalities (Onesto et al., 2016). These fibroblasts exhibit increased mitochondrial membrane potential and mtDNA content, along with fragmentation, deformities, and loss of cristae (Lopez-Gonzalez et al., 2016). Cristae abnormalities and stress granule formation have also been identified in iPSC-derived motor neurons from patients with C9ORF72 mutations (Dafinca et al., 2016; Onesto et al., 2016).

Altogether, these findings indicate that the balance between fusion and fission is crucial for neuronal health. Its disruption leads to energy deficits, cellular stress, and synaptic dysfunction and underly neurodegeneration. Clarification of the molecular mechanisms underlying these processes are warranted and may open new perspectives for developing early therapeutic strategies aimed at restoring mitochondrial function.

3. MDV signaling in aging and neurodegeneration

Advancing age is characterized by progressive alterations across physiological, biological, and metabolic domains. Mitochondrial dysfunction and low-grade sterile inflammation are prominent features of aging and associated conditions. Among these are the declining muscle mass, strength, and power combined with reduced physiological reserve and vulnerability to stressors referred to PF&S.

MDVs have been proposed as key mediators in linking age-related mitochondrial dysfunction and inflammation because of their role in shuttling damaged mitochondrial components to degradative compartments that, if secreted, may act as damage-associated molecular patterns (DAMPs) that activate immune responses (Todkar et al., 2021).

Purification of circulating sEVs from sera of older adults with PF&S allowed quantification of canonical exosomal tetraspanins (CD9, CD63, and CD81) and mitochondrial proteins consisting in multiple subunits of respiratory chain complexes (i.e., nicotinamide adenine dinucleotide reduced form:ubiquinone oxidoreductase subunit S3 (NDUFS3) for complex I, succinate dehydrogenase subunit B (SDHB) for complex II, and ATP synthase F1 subunit alpha (ATP5A) for complex V) (Picca et al., 2020a). This analysis revealed that individuals with PF&S had higher levels of circulating sEVs relative to controls, but mitochondrial markers ATP5A, NDUFS3, and SDHB were lower in sEVs from PF&S participants. Moreover, CD9 and CD63 were lower in PF&S, while CD81 was not different between groups (Picca et al., 2020a). Reduced levels of the exosomal tetraspanins CD9 and CD63 may reflect alterations in endosomal–lysosomal trafficking and EV biogenesis, potentially affecting cargo sorting, vesicle targeting, and intercellular communication. Therefore, these results indicate that, despite an increased release of sEVs, the mitochondrial component of those vesicles is depleted in PF&S. Of note, subsequent analysis of EVs in larger multimarker study involving metabolic and inflammatory characterization of people with PF&S included MDV-derived NDUFS3 among the best predictors for discriminating older adults with and without PF&S (Marzetti et al., 2020).

Altogether these results suggest that aging muscle may be shedding more vesicles but exporting fewer mitochondrial proteins per vesicle. This is in contrast with the expectation that increased mitochondrial damage would drive increased mitochondrial cargo in MDVs. Several mechanisms could explain this paradox. First, MDV biogenesis may decline with age. Moreover, PINK1/Parkin signaling and dynamin-related GTPases orchestrate MDV formation in response to mild mitochondrial stress. Aging downregulates these pathways, reducing the efficiency of mitochondrial cargo sorting even as vesicle numbers rise. Second, MDV formation is energy-intensive and depends on lipid remodeling at mitochondrial–endosomal contact sites. Aging mitochondria produce less ATP and likely have altered membrane composition, thereby limiting the packaging of mitochondrial proteins. Third, lysosomes in aged cells exhibit reduced acidification and protease activity. A backlog of undegraded cargo may signal upstream to restraint on MDV biogenesis or cargo loading. Finally, cells may preferentially eliminate damaged mitochondria by mitophagy or apoptosis rather than by MDVs in late life. Taken together, PF&S represents an age-associated conditions in which quantitative upregulation EVs occurs but qualitative mitochondria recycling via MDV-related vesicles seems to be reduced.

AD, the most common cause of dementia in late life, also implicates mitochondrial dysfunction and MDV biology in its pathogenesis. Neuronal mitochondrial dysfunction is an early hallmark of AD, and recent studies have identified a distinct class of MDVs termed mitovesicles, which carry respiratory chain proteins and other mitochondrial constituents and are altered in neurodegenerative conditions such as AD and Down syndrome models of dementia (D'Acunzo et al., 2021). The concept that MDV and mitovesicle pathways contribute to mitochondrial quality control and intercellular signaling in neurodegeneration has been increasingly recognized. Mitovesicles isolated from brains with mitochondrial dysfunction were recently shown to impair hippocampal long-term potentiation through mechanisms involving altered mitochondrial enzyme content and monoamine oxidases type B–dependent signaling, demonstrating that aberrant mitochondrial vesicle release can exert pathogenic effects on synaptic plasticity (D'Acunzo et al., 2024). Complementing these CNS findings, analyses of plasma-derived extracellular vesicles from individuals with AD reveal pronounced reductions and dysfunction of mitochondrial electron transport chain proteins, including complexes I, III, IV, and V, which correlate with clinical disease severity and reflect systemic bioenergetic compromise (Yao et al., 2021). Additional work indicates that circulating EVs in AD contain

elevated and qualitatively altered mitochondrial RNAs, suggesting disrupted mitochondrial turnover and export pathways, and raising the possibility that mitochondrial nucleic acids act as peripheral biomarkers or DAMP-like signals capable of amplifying neuroinflammatory processes (Kim et al., 2020). Beyond these mitochondrial alterations, neuron-derived EV (nEV) studies further support the diagnostic and pathogenic relevance of vesicle-based biomarkers in AD. nEV cargo, particularly phosphorylated tau, Aβ species, and insulin-signaling markers, has been shown to predict AD years before clinical onset in longitudinal cohorts (Kapogiannis et al., 2019), and to track ongoing cognitive decline through dynamic changes in synaptic proteins and amyloid-related cargo (Eren et al., 2022). Additional analyses demonstrate that nEVs and astrocyte-derived EVs capture mitochondrial and metabolic signatures relevant to neurodegeneration, providing a peripheral window into CNS bioenergetics (Nogueras-Ortiz et al., 2020). Moreover, intervention studies show that EV-associated neuroprotective factors such as BDNF, proBDNF, and humanin respond to behavioral modulation, including exercise, in individuals with AD, indicating that vesicle cargo is not only reflective of pathology but also sensitive to physiological remodeling (Delgado-Peraza et al., 2023). Finally, a recent plasma profiling study showed that neuron-, astrocyte-, and oligodendrocyte-derived MDVs are significantly decreased in AD patients compared with controls, pointing to compromised MDV release or trafficking in AD and highlighting their promise as noninvasive biomarkers of CNS mitochondrial dysfunction (Liu et al., 2025). Collectively, age-associated alterations in MDV/mitovesicle biology may underlie mitochondrial quality control failure, promote chronic inflammation via mitochondrial DAMPs, and contribute to AD pathophysiology.

PD, the second most common neurodegenerative disorder, shares pathophysiologic features with age-related conditions like PF&S, including mitochondrial dysfunction and systemic inflammation. In the EXosomes in PArkiNon Disease (EXPAND) study, circulating sEVs from older adults with PD and matched controls were analyzed. PD participants had a greater amount of circulating sEVs than controls (Picca et al., 2020b). Levels of CD9 and CD63 proteins were lower, while CD81 was unvaried. Protein analyses of MDVs indicated that ATP5A, NDUFS3, and SDHB were reduced in sEVs from PD participants (Picca et al., 2020b). A combined model of sEV and serum inflammatory biomarkers correctly classified 94% of PD participants, identifying CD9, NDUFS3, C-reactive protein (CRP), fibroblast growth factor 21 (FGF21), interleukin (IL)-9, macrophage inflammatory protein (MIP)-1β, and tumor necrosis factor-α (TNF-α) as discriminant markers (Picca et al., 2020b). These data mirror findings in PF&S in which higher vesicle secretion and reduced mitochondrial cargo per vesicle were identified. They also reveal a distinct inflammatory signature, consistent with the idea that mitochondrial-derived components in EVs can act as DAMPs that may prime systemic inflammation.

Finally, CMT2B, a rare inherited neuropathy caused by missense mutations in *Rab7A*, a small GTPase that regulates late endosome–lysosome trafficking, also shows EV disarrangements. Clinically, CMT2B features distal sensory loss, weakness, and ulcer-mutilating neuropathy. RAB7A also participates in mitophagy and MDV trafficking (Gagliardi et al., 2024). In a case–control study including five CMT2B patients (four with p.V162M, one with p.K126R) and four healthy controls, circulating cell-free mtDNA (ccf-mtDNA), mitochondrial proteins from MDVs, and panels of inflammatory and metabolic markers were quantified (Girolimetti et al., 2025). No significant differences were observed in total ccf-mtDNA levels between groups but differences in MDV content between CMT2B and controls were found (Girolimetti et al., 2025). CMT2B participants showed elevated asymmetric dimethylarginine (ADMA) and increased IL-1β, IL-8, IL-9, IL-13, eotaxin, and most fatty acids; some amino acids were decreased (Girolimetti et al., 2025).

Mechanistically, RAB7 controls the fusion of MDVs with late endosomes for degradation and contributes to antigen presentation from mitochondrial cargo in immune cells. Mutations in RAB7A impair this fusion, leading to accumulation of MDVs in the cytosol and extracellular release. This enhances exposure of mitochondrial DAMPs (e.g., oxidized mtDNA, cardiolipin) to immune receptors and drives chronic neuroinflammation and metabolic alterations. Unlike aging, where MDV biogenesis itself may be blunted, CMT2B represents a state of misdirected MDVs: the biogenesis may be intact or even upregulated, but trafficking is defective, leading to extracellular accumulation of MDVs enriched in mitochondrial components.

Trafficking and fate of MDVs also depend on cytoskeletal transport and membrane remodeling. Microtubule dynamics influence organelle positioning, vesicular transport and stress signaling; accordingly, microtubule dysregulation has been linked to cardiovascular pathology and is being explored therapeutically (Wu et al., 2024). Given that MDVs must be transported to endosomes/lysosomes or peroxisomes, microtubule-dependent trafficking is likely a conserved determinant of MDV delivery efficiency and, therefore, of phenotype severity when mitochondrial stress is chronic. Finally, multiple disease-relevant cell death and stress phenotypes are mechanistically coupled to mitochondrial quality pathways that may be upstream or downstream of MDV formation. Hyperglycemia-induced DNA damage signaling can drive YAP1 activation and ferroptosis (Wang et al., 2025), while targeted mitochondrial metabolic perturbation can induce mitophagy programs that suppress necroptosis (Chang et al., 2024). These examples support a model in which MDVs act as an early "triage" arm of MQC: when successful, selective MDV disposal may prevent propagation to ferroptosis, necroptosis, or inflammatory cascades; when overwhelmed, cells transition to broader degradative or lethal pathways. Integrating these mitochondrial targets and phenotypic mechanisms also strengthens the translational rationale for therapeutically tuning MDV biogenesis/cargo selection through redox and MQC modulators, which is an active area across multiple disease contexts (Chang et al., 2025; Wu et al., 2024; Yang et al., 2024).

4. Conclusions

MQC is increasingly recognized as a dynamic and modular system in which mitochondrial repair operates alongside organelle elimination. Within this framework, MDVs have emerged as a potentially critical, yet still incompletely understood, layer of selective mitochondrial surveillance. By enabling the targeted removal of damaged mitochondrial components under conditions of mild or localized stress, MDVs may contribute to cellular homeostasis while delaying or modulating the engagement of mitophagy. However, many fundamental aspects of MDV biology remain unresolved, particularly in the context of aging and neurodegeneration. A major open question concerns the molecular logic governing MDV cargo selection and routing. While oxidative damage, protein misfolding, and mitochondrial dynamics have been implicated, it remains unclear how cells determine whether mitochondrial material is degraded locally via MDVs, incorporated into whole organelle mitophagy, or released through extracellular vesicle pathways. Age-associated alterations in endolysosomal function and vesicle trafficking are likely to shift this balance, but direct experimental evidence linking these changes to MDV fate is still limited. Another key challenge lies in defining the physiological versus pathological consequences of mitochondrial cargo appearing in EVs. Whether this process represents a protective overflow mechanism, a means of intercellular communication, or a contributor to sterile inflammation may depend on cellular context, disease stage, and tissue environment. Disentangling these possibilities will require standardized approaches to vesicle isolation, specific markers that can distinguish MDVs from other mitochondrial vesicle populations, and in vivo models that allow temporal tracking of vesicle biogenesis and fate.

Advances in MDV research may hold important translational implications. Because MDV cargo reflects early mitochondrial stress and trafficking defects, mitochondrial components in circulating vesicles

may serve as minimally invasive biomarkers of mitochondrial dysfunction, biological aging, and neurodegenerative disease progression. Targeting MDV biogenesis, cargo selection, or vesicle trafficking may also represent a therapeutic strategy to preserve mitochondrial integrity, limit mitochondrial release of DAMPs, and mitigate chronic inflammation, potentially complementing approaches that enhance mitophagy or mitochondrial biogenesis. However, evidence gaps limit clinical feasibility. No consensus has been reached on markers reliably distinguishing MDVs from other mitochondrial vesicle populations, and the molecular determinants of cargo selectivity remain poorly defined. Longitudinal human studies linking MDV signatures with disease onset, progression, and treatment response are scarce, and tools for in vivo tracking of MDV dynamics are limited. Variability in vesicle isolation methods and nomenclature further complicates cross-study comparisons, and the protective versus pro-inflammatory roles of MDVs appear context-dependent. Moreover, causal relationships between altered MDV signaling and neurodegeneration remain to be established. Addressing these challenges will require coordinated efforts across cell biology, systems neuroscience, biomarker discovery, and clinical research. Clarifying MDV biology may ultimately position these vesicles as both mechanistic links and translational tools connecting mitochondrial dysfunction, aging biology, and neurodegenerative disease.

CRediT authorship contribution statement

Anna Picca: Writing – original draft, Conceptualization. **Cecilia Bucci:** Supervision, Funding acquisition. **Flora Guerra:** Writing – review & editing. **Vito Pesce:** Writing – review & editing. **Francesco Landi:** Writing – review & editing. **Coelho-Junior Helio Jose:** Writing – review & editing. **D'Argento Ettore:** Writing – review & editing. **Rosa Di Lorenzo:** Writing – original draft, Conceptualization. **Riccardo Calvani:** Writing – review & editing. **Emanuele Marzetti:** Writing – review & editing, Supervision, Funding acquisition.

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Declaration of Competing Interest

None to declare.

Data availability

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

References

Aliev, G., Palacios, H.H., Walrafen, B., Lipsitt, A.E., Obrenovich, M.E., Morales, L., 2009. Brain mitochondria as a primary target in the development of treatment strategies for Alzheimer disease. Int. J. Biochem. Cell Biol. 41, 1989–2004. https://doi.org/10.1016/j.biocel.2009.03.015.

Amiri, M., Hollenbeck, P.J., 2008. Mitochondrial biogenesis in the axons of vertebrate peripheral neurons. Dev. Neurobiol. 68, 1348–1361. https://doi.org/10.1002/DNEU.20668.

Arnold, A.S., Gill, J., Christe, M., Ruiz, R., McGuirk, S., St-Pierre, J., Tabares, L., Handschin, C., 2014. Morphological and functional remodelling of the neuromuscular junction by skeletal muscle PGC-1α. Nat. Commun. 5, 3569. https://doi.org/10.1038/NCOMMS4569.

Aschrafi, A., Kar, A.N., Gale, J.R., Elkahloun, A.G., Vargas, J.N.S., Sales, N., Wilson, G., Tompkins, M., Gioio, A.E., Kaplan, B.B., 2016. A heterogeneous population of nuclear-encoded mitochondrial mRNAs is present in the axons of primary sympathetic neurons. Mitochondrion 30, 18–23. https://doi.org/10.1016/j.mito.2016.06.002.

Atkins, C.M., Nozaki, N., Shigeri, Y., Soderling, T.R., 2004. Cytoplasmic polyadenylation element binding protein-dependent protein synthesis is regulated by calcium/calmodulin-dependent protein kinase II. J. Neurosci. 24, 5193–5201. https://doi.org/10.1523/JNEUROSCI.0854-04.2004.

Babenko, V.A., Silachev, D.N., Zorova, L.D., Pevzner, I.B., Khutornenko, A.A., Plotnikov, E.Y., Sukhikh, G.T., Zorov, D.B., 2015. Improving the post-stroke therapeutic potency of mesenchymal multipotent stromal cells by cocultivation with cortical neurons: The role of crosstalk between cells. Stem Cells Transl. Med. 4, 1011–1020. https://doi.org/10.5966/SCTM.2015-0010.

Baek, S.H., Park, S.J., Jeong, J.I., Kim, S.H., Han, J., Kyung, J.W., Baik, S.H., Choi, Y., Choi, B.Y., Park, J.S., Bahn, G., Shin, J.H., Jo, D.S., Lee, J.Y., Jang, C.G., Arumugam, T.V., Kim, J., Han, J.W., Koh, J.Y., Cho, D.H., Jo, D.G., 2017. Inhibition of Drp1 ameliorates synaptic depression, Aβ deposition, and cognitive impairment in an Alzheimer's disease model. J. Neurosci. 37, 5099–5110. https://doi.org/10.1523/JNEUROSCI.2385-16.2017.

Baker, M.J., Tatsuta, T., Langer, T., 2011. Quality control of mitochondrial proteostasis. Cold Spring Harb. Perspect. Biol. 3, 1–19. https://doi.org/10.1101/CSHPERSPECT.A007559.

Ban, T., Ishihara, T., Kohno, H., Saita, S., Ichimura, A., Maenaka, K., Oka, T., Mihara, K., Ishihara, N., 2017. Molecular basis of selective mitochondrial fusion by heterotypic action between OPA1 and cardiolipin. Nat. Cell Biol. 19, 856–863. https://doi.org/10.1038/NCB3560.

Baranich, T.I., Skvortsova, K.A., Voronkov, D.N., Egorova, A.V., Averchuk, A.S., Ryazanova, M.V., Stavrovskaya, A.V., Glinkina, V.V., Salmina, A.B., Sukhorukov, V. S., 2024. Immunohistochemical analysis of mitochondrial dynamics in different zones of the hippocampus during experimental modeling of Alzheimer's disease. Bull. Exp. Biol. Med. 176, 523–527. https://doi.org/10.1007/S10517-024-06060-9.

Beckervordersandforth, R., Ebert, B., Schäffner, I., Moss, J., Fiebig, C., Shin, J., Moore, D. L., Ghosh, L., Trinchero, M.F., Stockburger, C., Friedland, K., Steib, K., von Wittgenstein, J., Keiner, S., Redecker, C., Hölter, S.M., Xiang, W., Wurst, W., Jagasia, R., Schinder, A.F., Ming, G. li, Toni, N., Jessberger, S., Song, H., Lie, D.C., 2017. Role of mitochondrial metabolism in the control of early lineage progression and aging phenotypes in adult hippocampal neurogenesis. Neuron 93, 560–573.e6. https://doi.org/10.1016/j.neuron.2016.12.017.

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

Bosetti, F., Brizzi, F., Barogi, S., Mancuso, M., Siciliano, G., Tendi, E.A., Murri, L., Rapoport, S.I., Solaini, G., 2002. Cytochrome c oxidase and mitochondrial F1F0-ATPase (ATP synthase) activities in platelets and brain from patients with Alzheimer's disease. Neurobiol. Aging 23, 371–376. https://doi.org/10.1016/S0197-4580(01)00314-1.

Brennan, W.A., Bird, E.D., Aprille, J.R., 1985. Regional mitochondrial respiratory activity in Huntington's disease brain. J. Neurochem. 44, 1948–1950. https://doi.org/10.1111/J.1471-4159.1985.TB07192.X.

Brickley, K., Stephenson, F.A., 2011. Trafficking kinesin protein (TRAK)-mediated transport of mitochondria in axons of hippocampal neurons. J. Biol. Chem. 286, 18079–18092. https://doi.org/10.1074/jbc.M111.236018.

Bristow, E.A., Griffiths, P.G., Andrews, R.M., Johnson, M.A., Turnbull, D.M., 2002. The distribution of mitochondrial activity in relation to optic nerve structure. Arch. Ophthalmol. 120, 791–796. https://doi.org/10.1001/ARCHOPHT.120.6.791.

Bros, H., Hauser, A., Paul, F., Niesner, R., Infante-Duarte, C., 2015. Assessing mitochondrial movement within neurons: manual versus automated tracking methods. Traffic 16, 906–917. https://doi.org/10.1111/TRA.12291.

Brustovetsky, T., Khanna, R., Brustovetsky, N., 2021. CRMP2 is involved in regulation of mitochondrial morphology and motility in neurons. Cells 10, 2781. https://doi.org/10.3390/CELLS10102781.

Burté, F., Carelli, V., Chinnery, P.F., Yu-Wai-Man, P., 2015. Disturbed mitochondrial dynamics and neurodegenerative disorders. Nat. Rev. Neurol. 11, 11–24. https://doi.org/10.1038/NRNEUROL.2014.228.

Cai, Q., Gerwin, C., Sheng, Z.H., 2005. Syntabulin-mediated anterograde transport of mitochondria along neuronal processes. J. Cell Biol. 170, 959–969. https://doi.org/10.1083/JCB.200506042.

Cai, Y., Yang, E., Yao, X., Zhang, X., Wang, Q., Wang, Y., Liu, J., Fan, W., Yi, K., Kang, C., Wu, J., 2021. FUNDC1-dependent mitophagy induced by tPA protects neurons against cerebral ischemia-reperfusion injury. Redox Biol. 38, 101792. https://doi.org/10.1016/j.redox.2020.101792.

Catalano, S.M., Shatz, C.J., 1998. Activity-dependent cortical target selection by thalamic axons. Science 281, 559–562. https://doi.org/10.1126/SCIENCE.281.5376.559.

Chang, X., Zhou, H., Hu, J., Ge, T., He, K., Chen, Y., Zou, R., Fan, X., 2024. Targeting mitochondria by lipid-selenium conjugate drug results in malate/fumarate exhaustion and induces mitophagy-mediated necroptosis suppression. Int. J. Biol. Sci. 20, 5793–5811. https://doi.org/10.7150/ijbs.102424.

Chang, X., Zhou, S., Yan, Z., Zhang, Q., Liu, J., Wang, Y., Guan, X., Wu, Q., Liu, R., 2025. Potential candidates of natural antioxidants from herbs for treating lung disorders: Focus on redox balance and natural products. Phytother. Res. 39, 3353–3385. https://doi.org/10.1002/ptr.70008.

Chen, H., Detmer, S.A., Ewald, A.J., Griffin, E.E., Fraser, S.E., Chan, D.C., 2003. Mitofusins Mfn1 and Mfn2 coordinately regulate mitochondrial fusion and are essential for embryonic development. J. Cell Biol. 160, 189–200. https://doi.org/10.1083/JCB.200211046.

Chen, H., McCaffery, J.M., Chan, D.C., 2007. Mitochondrial fusion protects against neurodegeneration in the cerebellum. Cell 130, 548–562. https://doi.org/10.1016/j.cell.2007.06.026.

Chen, Y., Sheng, Z.H., 2013. Kinesin-1-syntaphilin coupling mediates activity-dependent regulation of axonal mitochondrial transport. J. Cell Biol. 202, 351–364. https://doi.org/10.1083/JCB.201302040.

Cheng, A., Wan, R., Yang, J.L., Kamimura, N., Son, T.G., Ouyang, X., Luo, Y., Okun, E., Mattson, M.P., 2012. Involvement of PGC-1α in the formation and maintenance of neuronal dendritic spines. Nat. Commun. 3, 1250. https://doi.org/10.1038/NCOMMS2238.

Choi, G.E., Han, H.J., 2021. Glucocorticoid impairs mitochondrial quality control in neurons. Neurobiol. Dis. 152, 105301. https://doi.org/10.1016/j.nbd.2021.105301.

Choi, G.E., Lee, H.J., Chae, C.W., Cho, J.H., Jung, Y.H., Kim, J.S., Kim, S.Y., Lim, J.R., Han, H.J., 2021. BNIP3L/NIX-mediated mitophagy protects against glucocorticoid-induced synapse defects. Nat. Commun. 12, 487. https://doi.org/10.1038/S41467-020-20679-Y.

Cioni, J.M., Lin, J.Q., Holtermann, A.V., Koppers, M., Jakobs, M.A.H., Azizi, A., Turner-Bridger, B., Shigeoka, T., Franze, K., Harris, W.A., Holt, C.E., 2019. Late endosomes act as mRNA translation platforms and sustain mitochondria in axons. Cell 176, 56–72.e15. https://doi.org/10.1016/j.cell.2018.11.030.

Cohen, B., Altman, T., Golani-Armon, A., Savulescu, A.F., Ibraheem, A., Mhlanga, M.M., Perlson, E., Arava, Y.S., 2022. Co-transport of the nuclear-encoded Cox7c mRNA with mitochondria along axons occurs through a coding-region-dependent mechanism. J. Cell Sci. 135, jcs259436. https://doi.org/10.1242/JCS.259436.

Cosker, K.E., Fenstermacher, S.J., Pazyra-Murphy, M.F., Elliott, H.L., Segal, R.A., 2016. The RNA-binding protein SFPQ orchestrates an RNA regulon to promote axon viability. Nat. Neurosci. 19, 690–696. https://doi.org/10.1038/NN.4280.

Cui, L., Jeong, H., Borovecki, F., Parkhurst, C.N., Tanese, N., Krainc, D., 2006. Transcriptional repression of PGC-1α by mutant huntingtin leads to mitochondrial dysfunction and neurodegeneration. Cell 127, 59–69. https://doi.org/10.1016/j.cell.2006.09.015.

D'Acunzo, P., Argyrousi, E.K., Ungania, J.M., Kim, Y., DeRosa, S., Pawlik, M., Goulbourne, C.N., Arancio, O., Levy, E., 2024. Mitovesicles secreted into the extracellular space of brains with mitochondrial dysfunction impair synaptic plasticity. Mol. Neurodegener. 19, 34. https://doi.org/10.1186/S13024-024-00721-Z.

D'Acunzo, P., Pérez-González, R., Kim, Y., Hargash, T., Miller, C., Alldred, M.J., Erdjument-Bromage, H., Penikalapati, S.C., Pawlik, M., Saito, Mitsuo, Saito, Mariko, Ginsberg, S.D., Neubert, T.A., Goulbourne, C.N., Levy, E., 2021. Mitovesicles are a novel population of extracellular vesicles of mitochondrial origin altered in Down syndrome. Sci. Adv. 7, eabe5085. https://doi.org/10.1126/sciadv.abe5085.

Dafinca, R., Scaber, J., Ababneh, N., Lalic, T., Weir, G., Christian, H., Vowles, J., Douglas, A.G.L., Fletcher-Jones, A., Browne, C., Nakanishi, M., Turner, M.R., Wade-Martins, R., Cowley, S.A., Talbot, K., 2016. C9orf72 hexanucleotide expansions are associated with altered endoplasmic reticulum calcium homeostasis and stress granule formation in induced pluripotent stem cell-derived neurons from patients with amyotrophic lateral sclerosis and frontotemporal dementia. Stem Cells 34, 2063–2078. https://doi.org/10.1002/STEM.2388.

Dan, X., Babbar, M., Moore, A., Wechter, N., Tian, J., Mohanty, J.G., Croteau, D.L., Bohr, V.A., 2020. DNA damage invokes mitophagy through a pathway involving Spata18. Nucleic Acids Res. 48, 6611–6623. https://doi.org/10.1093/NAR/GKAA393.

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

Davis, C.H.O., Kim, K.Y., Bushong, E.A., Mills, E.A., Boassa, D., Shih, T., Kinebuchi, M., Phan, S., Zhou, Y., Bihlmeyer, N.A., Nguyen, J.V., Jin, Y., Ellisman, M.H., Marsh-Armstrong, N., 2014. Transcellular degradation of axonal mitochondria. Proc. Natl. Acad. Sci. USA 111, 9633–9638. https://doi.org/10.1073/PNAS.1404651111/-/DCSUPPLEMENTAL/PNAS.201404651SI.PDF.

de Brito, O.M., Scorrano, L., 2008. Mitofusin 2 tethers endoplasmic reticulum to mitochondria. Nature 456, 605–610. https://doi.org/10.1038/nature07534.

de la Cueva, M., Antequera, D., Ordoñez-Gutierrez, L., Wandosell, F., Camins, A., Carro, E., Bartolome, F., 2022. Amyloid-β impairs mitochondrial dynamics and autophagy in Alzheimer's disease experimental models. Sci. Rep. 12, 10092. https://doi.org/10.1038/S41598-022-13683-3.

de la Fuente-Muñoz, C.E., Rosas-Lemus, M., Moreno-Castilla, P., Bermúdez-Rattoni, F., Uribe-Carvajal, S., Arias, C., 2020. Age-dependent decline in synaptic mitochondrial function is exacerbated in vulnerable brain regions of female 3xTg-AD mice. Int. J. Mol. Sci. 21, 1–13. https://doi.org/10.3390/IJMS21228727.

de Oliveira, M.R., Peres, A., Gama, C.S., Bosco, S.M.D., 2017. Pinocembrin provides mitochondrial protection by the activation of the Erk1/2-Nrf2 signaling pathway in SH-SY5Y neuroblastoma cells exposed to paraquat. Mol. Neurobiol. 54, 6018–6031. https://doi.org/10.1007/S12035-016-0135-5.

De vos, K.J., Chapman, A.L., Tennant, M.E., Manser, C., Tudor, E.L., Lau, K.F., Brownlees, J., Ackerley, S., Shaw, P.J., Mcloughlin, D.M., Shaw, C.E., Leigh, P.N., Miller, C.C.J., Grierson, A.J., 2007. Familial amyotrophic lateral sclerosis-linked SOD1 mutants perturb fast axonal transport to reduce axonal mitochondria content. Hum. Mol. Genet 16, 2720–2728. https://doi.org/10.1093/HMG/DDM226.

Delgado-Peraza, F., Nogueras-Ortiz, C., Simonsen, A.H., Knight, D.D.A., Yao, P.J., Goetzl, E.J., Jensen, C.S., Høgh, P., Gottrup, H., Vestergaard, K., Hasselbalch, S.G., Kapogiannis, D., 2023. Neuron-derived extracellular vesicles in blood reveal effects of exercise in Alzheimer's disease. Alzheimers Res. Ther. 15, 156. https://doi.org/10.1186/S13195-023-01303-9.

Deng, J., Wang, P., Chen, X., Cheng, H., Liu, J., Fushimi, K., Zhu, L., Wu, J.Y., 2018. FUS interacts with ATP synthase beta subunit and induces mitochondrial unfolded protein response in cellular and animal models. Proc. Natl. Acad. Sci. USA 115, E9678–E9686. https://doi.org/10.1073/PNAS.1806655115/-/DCSUPPLEMENTAL.

Djordjevic, J., Roy Chowdhury, S., Snow, W.M., Perez, C., Cadonic, C., Fernyhough, P., Albensi, B.C., 2020. Early onset of sex-dependent mitochondrial deficits in the cortex of 3xTg Alzheimer's mice. Cells 9, 1541. https://doi.org/10.3390/CELLS9061541.

Dölle, C., Flønes, I., Nido, G.S., Miletic, H., Osuagwu, N., Kristoffersen, S., Lilleng, P.K., Larsen, J.P., Tysnes, O.-B., Haugarvoll, K., Bindoff, L.A., Tzoulis, C., 2016. Defective mitochondrial DNA homeostasis in the substantia nigra in Parkinson disease. Nat. Commun. 7, 13548. https://doi.org/10.1038/ncomms13548.

Ekstrand, M.I., Terzioglu, M., Galter, D., Zhu, S., Hofstetter, C., Lindqvist, E., Thams, S., Bergstrand, A., Hansson, F.S., Trifunovic, A., Hoffer, B., Cullheim, S., Mohammed, A. H., Olson, L., Larsson, N.G., 2007. Progressive parkinsonism in mice with respiratory-chain-deficient dopamine neurons. Proc. Natl. Acad. Sci. USA 104, 1325–1330. https://doi.org/10.1073/PNAS.0605208103.

Eren, E., Leoutsakos, J.M., Troncoso, J., Lyketsos, C.G., Oh, E.S., Kapogiannis, D., 2022. Neuronal-derived EV biomarkers track cognitive decline in Alzheimer's disease. Cells 11, 436. https://doi.org/10.3390/CELLS11030436.

Eschbach, J., Schwalenstö cker, B., Soyal, S.M., Bayer, H., Wiesner, D., Akimoto, C., Nilsson, A.C., Birve, A., Meyer, T., Dupuis, L., Danzer, K.M., Andersen, P.M., Witting, A., Ludolph, A.C., Patsch, W., Weydt, P., 2013. PGC-1α is a male-specific disease modifier of human and experimental amyotrophic lateral sclerosis. Hum. Mol. Genet 22, 3477–3484. https://doi.org/10.1093/HMG/DDT202.

Eura, Y., Ishihara, N., Yokota, S., Mihara, K., 2003. Two mitofusin proteins, mammalian homologues of FZO, with distinct functions are both required for mitochondrial fusion. J. Biochem. 134, 333–344. https://doi.org/10.1093/JB/MVG150.

Fabricius, C., Berthold, C.H., Rydmark, M., 1993. Axoplasmic organelles at nodes of Ranvier. II. Occurrence and distribution in large myelinated spinal cord axons of the adult cat. J. Neurocytol. 22, 941–954. https://doi.org/10.1007/BF01218352.

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., Rocktäschel, P., Croteau, D.L., Akbari, M., Greig, N.H., Fladby, T., Nilsen, H., Cader, M.Z., Mattson, M.P., Tavernarakis, N., Bohr, V.A., 2019. Mitophagy inhibits amyloid-β and tau pathology and reverses cognitive deficits in models of Alzheimer's disease. Nat. Neurosci. 22, 401–412. https://doi.org/10.1038/s41593-018-0332-9.

Fang, D., Yan, S., Yu, Q., Chen, D., Yan, S.S., 2016. Mfn2 is required for mitochondrial development and synapse formation in human induced pluripotent stem cells/hiPSC derived cortical neurons. Sci. Rep. 6, 31462. https://doi.org/10.1038/SREP31462.

Fedorovich, S.V., Waseem, T.V., Puchkova, L.V., 2017. Biogenetic and morphofunctional heterogeneity of mitochondria: the case of synaptic mitochondria. Rev. Neurosci. 28, 363–373. https://doi.org/10.1515/REVNEURO-2016-0077.

Ferreira, A.F.F., Binda, K.H., Singulani, M.P., Pereira, C.P.M., Ferrari, G.D., Alberici, L.C., Real, C.C., Britto, L.R., 2020. Physical exercise protects against mitochondria alterations in the 6-hidroxydopamine rat model of Parkinson's disease. Behav. Brain Res. 387, 112607. https://doi.org/10.1016/j.bbr.2020.112607.

Ferrucci, L., Guerra, F., Bucci, C., Marzetti, E., Picca, A., 2024. Mitochondria break free: Mitochondria-derived vesicles in aging and associated conditions. Ageing Res. Rev. 102, 102549. https://doi.org/10.1016/J.ARR.2024.102549.

Fiorese, C.J., Schulz, A.M., Lin, Y.F., Rosin, N., Pellegrino, M.W., Haynes, C.M., 2016. The transcription factor ATF5 mediates a mammalian mitochondrial UPR. Curr. Biol. 26, 2037–2043. https://doi.org/10.1016/j.cub.2016.06.002.

Franco-Iborra, S., Plaza-Zabala, A., Montpeyo, M., Sebastian, D., Vila, M., Martinez-Vicente, M., 2021. Mutant HTT (huntingtin) impairs mitophagy in a cellular model of Huntington disease. Autophagy 17, 672–689. https://doi.org/10.1080/15548627.2020.1728096.

Fransson, Å., Ruusala, A., Aspenström, P., 2003. Atypical Rho GTPases have roles in mitochondrial homeostasis and apoptosis. J. Biol. Chem. 278, 6495–6502. https://doi.org/10.1074/jbc.M208609200.

Friedman, J.R., Lackner, L.L., West, M., DiBenedetto, J.R., Nunnari, J., Voeltz, G.K., 2011. ER tubules mark sites of mitochondrial division. Science 334, 358–362. https://doi.org/10.1126/science.1207385.

Gagliardi, S., Mitruccio, M., Di Corato, R., Romano, R., Aloisi, A., Rinaldi, R., Alifano, P., Guerra, F., Bucci, C., 2024. Defects of mitochondria-lysosomes communication induce secretion of mitochondria-derived vesicles and drive chemoresistance in ovarian cancer cells. Cell Commun. Signal 22, 165. https://doi.org/10.1186/s12964-024-01507-y.

Gao, F., Chen, D., Si, J., Hu, Q., Qin, Z., Fang, M., Wang, G., 2015. The mitochondrial protein BNIP3L is the substrate of PARK2 and mediates mitophagy in PINK1/PARK2 pathway. Hum. Mol. Genet 24, 2528–2538. https://doi.org/10.1093/HMG/DDV017.

Gao, L., Zhang, Z., Lu, J., Pei, G., 2019. Mitochondria are dynamically transferring between human neural cells and Alexander disease-associated GFAP mutations impair the astrocytic transfer. Front Cell Neurosci. 13, 316. https://doi.org/10.3389/FNCEL.2019.00316.

Girolimetti, G., Marini, F., Calvani, R., Coelho-Júnior, H.J., Gervasoni, J., Santucci, L., Tozza, S., Manganelli, F., Saveri, P., Pareyson, D., Marzetti, E., Bucci, C., Picca, A., Guerra, F., 2025. Circulating mitochondrial components and metabolic and inflammatory markers in Charcot-Marie-Tooth type 2B. Neurobiol. Dis. 214, 107051. https://doi.org/10.1016/J.NBD.2025.107051.

Gomes, L.C., Benedetto, G., Di, Scorrano, L., 2011. During autophagy mitochondria elongate, are spared from degradation and sustain cell viability. Nat. Cell Biol. 13, 589–598. https://doi.org/10.1038/NCB2220.

Gomez, T.M., Robles, E., Poo, M.M., Spitzer, N.C., 2001. Filopodial calcium transients promote substrate-dependent growth cone turning. Science 291, 1983–1987. https://doi.org/10.1126/SCIENCE.1056490.

Gomez, T.M., Zheng, J.Q., 2006. The molecular basis for calcium-dependent axon pathfinding. Nat. Rev. Neurosci. 7, 115–125. https://doi.org/10.1038/NRN1844.

Gong, B., Pan, Y., Vempati, P., Zhao, W., Knable, L., Ho, L., Wang, J., Sastre, M., Ono, K., Sauve, A.A., Pasinetti, G.M., 2013. Nicotinamide riboside restores cognition through an upregulation of proliferator-activated receptor-γ coactivator 1α regulated β-secretase 1 degradation and mitochondrial gene expression in Alzheimer's mouse models. Neurobiol. Aging 34, 1581–1588. https://doi.org/10.1016/j.neurobiolaging.2012.12.005.

Gu, M., Gash, M.T., Mann, V.M., Javoy-Agid, F., Cooper, J.M., Schapira, A.H.V., 1996. Mitochondrial defect in Huntington's disease caudate nucleus. Ann. Neurol. 39, 385–389. https://doi.org/10.1002/ANA.410390317.

Gu, X., Olson, E.C., Spitzer, N.C., 1994. Spontaneous neuronal calcium spikes and waves during early differentiation. J. Neurosci. 14, 6325–6335. https://doi.org/10.1523/JNEUROSCI.14-11-06325.1994.

Guedes-Dias, P., de Proença, J., Soares, T.R., Leitão-Rocha, A., Pinho, B.R., Duchen, M.R., Oliveira, J.M.A., 2015. HDAC6 inhibition induces mitochondrial fusion, autophagic flux and reduces diffuse mutant huntingtin in striatal neurons. Biochim. Biophys. Acta Mol. Basis Dis. 1852, 2484–2493. https://doi.org/10.1016/j.bbadis.2015.08.012.

Guerra, F., Girolimetti, G., Beli, R., Mitruccio, M., Pacelli, C., Ferretta, A., Gasparre, G., Cocco, T., Bucci, C., 2019. Synergistic effect of mitochondrial and lysosomal dysfunction in Parkinson's disease. Cells 8, 452. https://doi.org/10.3390/cells8050452.

Guo, X., Chen, K.H., Guo, Y., Liao, H., Tang, J., Xiao, R.P., 2007. Mitofusin 2 triggers vascular smooth muscle cell apoptosis via mitochondrial death pathway. Circ. Res 101, 1113–1122. https://doi.org/10.1161/CIRCRESAHA.107.157644.

Guo, W., Naujock, M., Fumagalli, L., Vandoorne, T., Baatsen, P., Boon, R., Ordovás, L., Patel, A., Welters, M., Vanwelden, T., Geens, N., Tricot, T., Benoy, V., Steyaert, J., Lefebvre-Omar, C., Boesmans, W., Jarpe, M., Sterneckert, J., Wegner, F., Petri, S., Bohl, D., Vanden Berghe, P., Robberecht, W., Van Damme, P., Verfaillie, C., Van Den Bosch, L., 2017. HDAC6 inhibition reverses axonal transport defects in motor neurons derived from FUS-ALS patients. Nat. Commun. 8, 861. https://doi.org/10.1038/S41467-017-00911-Y.

Han, H., Tan, J., Wang, R., Wan, H., He, Y., Yan, X., Guo, J., Gao, Q., Li, J., Shang, S., Chen, F., Tian, R., Liu, W., Liao, L., Tang, B., Zhang, Z., 2020. PINK1 phosphorylates Drp1S616 to regulate mitophagy-independent mitochondrial dynamics. EMBO Rep. 21, e48686. https://doi.org/10.15252/EMBR.201948686.

Han, S., Zhang, M., Jeong, Y.Y., Margolis, D.J., Cai, Q., 2021. The role of mitophagy in the regulation of mitochondrial energetic status in neurons. Autophagy 17, 4182–4201. https://doi.org/10.1080/15548627.2021.1907167.

Hardingham, G.E., Arnold, F.J.L., Bading, H., 2001. A calcium microdomain near NMDA receptors: on switch for ERK-dependent synapse-to-nucleus communication. Nat. Neurosci. 4, 565–566. https://doi.org/10.1038/88380.

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

Hillefors, M., Gioio, A.E., Mameza, M.G., Kaplan, B.B., 2007. Axon viability and mitochondrial function are dependent on local protein synthesis in sympathetic neurons. Cell Mol. Neurobiol. 27, 701–716. https://doi.org/10.1007/S10571-007-9148-Y.

Hong, K., Li, Y., Duan, W., Guo, Y., Jiang, H., Li, W., Li, C., 2012. Full-length TDP-43 and its C-terminal fragments activate mitophagy in NSC34 cell line. Neurosci. Lett. 530, 144–149. https://doi.org/10.1016/j.neulet.2012.10.003.

Huang, E.J., Zhang, J., Geser, F., Trojanowski, J.Q., Strober, J.B., Dickson, D.W., Brown, R.H., Shapiro, B.E., Lomen-Hoerth, C., 2010. Extensive FUS-immunoreactive pathology in juvenile amyotrophic lateral sclerosis with basophilic inclusions. Brain Pathol. 20, 1069–1076. https://doi.org/10.1111/J.1750-3639.2010.00413.X.

Iroegbu, J.D., Ijomone, O.K., Femi-Akinlosotu, O.M., Ijomone, O.M., 2021. ERK/MAPK signalling in the developing brain: Perturbations and consequences. Neurosci. Biobehav Rev. 131, 792–805. https://doi.org/10.1016/j.neubiorev.2021.10.009.

Ishihara, N., Eura, Y., Mihara, K., 2004. Mitofusin 1 and 2 play distinct roles in mitochondrial fusion reactions via GTPase activity. J. Cell Sci. 117, 6535–6546. https://doi.org/10.1242/JCS.01565.

Ishizuka, Y., Kakiya, N., Witters, L.A., Oshiro, N., Shirao, T., Nawa, H., Takei, N., 2013. AMP-activated protein kinase counteracts brain-derived neurotrophic factor-induced mammalian target of rapamycin complex 1 signaling in neurons. J. Neurochem. 127, 66–77. https://doi.org/10.1111/JNC.12362.

Jang, Y., Kwon, I., Song, W., Cosio-Lima, L.M., Taylor, S., Lee, Y., 2018. Modulation of mitochondrial phenotypes by endurance exercise contributes to neuroprotection against a MPTP-induced animal model of PD. Life Sci. 209, 455–465. https://doi.org/10.1016/j.lfs.2018.08.045.

Jiang, H., Kang, S.U., Zhang, S., Karuppagounder, S., Xu, J., Lee, Y.K., Kang, B.G., Lee, Y., Zhang, J., Pletnikova, O., Troncoso, J.C., Pirooznia, S., Andrabi, S.A., Dawson, V.L., Dawson, T.M., 2016. Adult conditional knockout of PGC-1α leads to loss of dopamine neurons. eNeuro 3. https://doi.org/10.1523/ENEURO.0183-16.2016.

Johansen, T., Lamark, T., 2020. Selective autophagy: ATG8 family proteins, LIR motifs and cargo receptors. J. Mol. Biol. 432, 80–103. https://doi.org/10.1016/j.jmb.2019.07.016.

Kageyama, G.H., Wong-Riley, M.T.T., 1982. Histochemical localization of cytochrome oxidase in the hippocampus: correlation with specific neuronal types and afferent pathways. Neuroscience 7, 2337–2361. https://doi.org/10.1016/0306-4522(82)90199-3.

Kandimalla, R., Manczak, M., Fry, D., Suneetha, Y., Sesaki, H., Reddy, P.H., 2016. Reduced dynamin-related protein 1 protects against phosphorylated Tau-induced mitochondrial dysfunction and synaptic damage in Alzheimer's disease. Hum. Mol. Genet 25, 4881–4897. https://doi.org/10.1093/HMG/DDW312.

Kane, L.A., Lazarou, M., Fogel, A.I., Li, Y., Yamano, K., Sarraf, S.A., Banerjee, S., Youle, R.J., 2014. PINK1 phosphorylates ubiquitin to activate Parkin E3 ubiquitin ligase activity. J. Cell Biol. 205, 143–153. https://doi.org/10.1083/jcb.201402104.

Kang, J.S., Tian, J.H., Pan, P.Y., Zald, P., Li, C., Deng, C., Sheng, Z.H., 2008. Docking of axonal mitochondria by syntaphilin controls their mobility and affects short-term facilitation. Cell 132, 137–148. https://doi.org/10.1016/j.cell.2007.11.024.

Kapogiannis, D., Mustapic, M., Shardell, M.D., Berkowitz, S.T., Diehl, T.C., Spangler, R.D., Tran, J., Lazaropoulos, M.P., Chawla, S., Gulyani, S., Eitan, E., An, Y., Huang, C.W., Oh, E.S., Lyketsos, C.G., Resnick, S.M., Goetzl, E.J., Ferrucci, L., 2019. Association of extracellular vesicle biomarkers with Alzheimer disease in the Baltimore Longitudinal Study of Aging. JAMA Neurol. 76, 1340–1351. https://doi.org/10.1001/jamaneurol.2019.2462.

Khacho, M., Clark, A., Svoboda, D.S., Azzi, J., MacLaurin, J.G., Meghaizel, C., Sesaki, H., Lagace, D.C., Germain, M., Harper, M.E., Park, D.S., Slack, R.S., 2016. Mitochondrial dynamics impacts stem cell identity and fate decisions by regulating a nuclear transcriptional program. Cell Stem Cell 19, 232–247. https://doi.org/10.1016/j.stem.2016.04.015.

Kim, K.M., Meng, Q., Perez de Acha, O., Mustapic, M., Cheng, A., Eren, E., Kundu, G., Piao, Y., Munk, R., Wood, W.H., De, S., Noh, J.H., Delannoy, M., Cheng, L., Abdelmohsen, K., Kapogiannis, D., Gorospe, M., 2020. Mitochondrial RNA in Alzheimer's disease circulating extracellular vesicles. Front Cell Dev. Biol. 8, 581882. https://doi.org/10.3389/FCELL.2020.581882.

Kish, S.J., Bergeron, C., Rajput, A., Dozic, S., Mastrogiacomo, F., Chang, L. -J., Wilson, J.M., DiStefano, L.M., Nobrega, J.N., 1992. Brain cytochrome oxidase in Alzheimer's disease. J. Neurochem. 59, 776–779. https://doi.org/10.1111/J.1471-4159.1992.TB09439.X.

Kleele, T., Rey, T., Winter, J., Zaganelli, S., Mahecic, D., Perreten Lambert, H., Ruberto, F.P., Nemir, M., Wai, T., Pedrazzini, T., Manley, S., 2021. Distinct fission signatures predict mitochondrial degradation or biogenesis. Nature 593, 435–439. https://doi.org/10.1038/S41586-021-03510-6.

Klein, C., Westenberger, A., 2012. Genetics of Parkinson's disease. Cold Spring Harb. Perspect. Med. 2. https://doi.org/10.1101/CSHPERSPECT.A008888.

Kodavati, M., Wang, H., Hegde, M.L., 2020. Altered mitochondrial dynamics in motor neuron disease: an emerging perspective. Cells 9, 1065. https://doi.org/10.3390/CELLS9041065.

Koentjoro, B., Park, J.S., Sue, C.M., 2017. Nix restores mitophagy and mitochondrial function to protect against PINK1/Parkin-related Parkinson's disease. Sci. Rep. 7, 44373. https://doi.org/10.1038/SREP44373.

König, T., McBride, H.M., 2024. Mitochondrial-derived vesicles in metabolism, disease, and aging. Cell Metab. 36, 21–35. https://doi.org/10.1016/J.CMET.2023.11.014.

Koo, J.H., Cho, J.Y., 2017. Treadmill exercise attenuates α-synuclein levels by promoting mitochondrial function and autophagy possibly via SIRT1 in the chronic MPTP/P-induced mouse model of Parkinson's disease. Neurotox. Res 32, 473–486. https://doi.org/10.1007/S12640-017-9770-5.

Korobova, F., Ramabhadran, V., Higgs, H.N., 2013. An actin-dependent step in mitochondrial fission mediated by the ER-associated formin INF2. Science 339, 464–467. https://doi.org/10.1126/SCIENCE.1228360.

Koyano, F., Okatsu, K., Kosako, H., Tamura, Y., Go, E., Kimura, M., Kimura, Y., Tsuchiya, H., Yoshihara, H., Hirokawa, T., Endo, T., Fon, E.A., Trempe, J.-F., Saeki, Y., Tanaka, K., Matsuda, N., 2014. Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature 510, 162–166. https://doi.org/10.1038/nature13392.

Kuzniewska, B., Cysewski, D., Wasilewski, M., Sakowska, P., Milek, J., Kulinski, T.M., Winiarski, M., Kozielewicz, P., Knapska, E., Dadlez, M., Chacinska, A., Dziembowski, A., Dziembowska, M., 2020. Mitochondrial protein biogenesis in the synapse is supported by local translation. EMBO Rep. 21, e48882. https://doi.org/10.15252/EMBR.201948882.

Lang, A.E., Stein, C., Drerup, C.M., 2025. Retrograde mitochondrial transport regulates mitochondrial biogenesis in zebrafish neurons. bioRxiv, 2025.09.29.679307. https://doi.org/10.1101/2025.09.29.679307.

Lazarou, M., Sliter, D.A., Kane, L.A., Sarraf, S.A., Wang, C., Burman, J.L., Sideris, D.P., Fogel, A.I., Youle, R.J., 2015. The ubiquitin kinase PINK1 recruits autophagy receptors to induce mitophagy. Nature 524, 309–314. https://doi.org/10.1038/nature14893.

Lee, Yunjong, Stevens, D.A., Kang, S.U., Jiang, H., Lee, Yun Il, Ko, H.S., Scarffe, L.A., Umanah, G.E., Kang, H., Ham, S., Kam, T.I., Allen, K., Brahmachari, S., Kim, J.W., Neifert, S., Yun, S.P., Fiesel, F.C., Springer, W., Dawson, V.L., Shin, J.H., Dawson, T.M., 2017. PINK1 primes Parkin-mediated ubiquitination of PARIS in dopaminergic neuronal survival. Cell Rep. 18, 918–932. https://doi.org/10.1016/j.celrep.2016.12.090.

Lewis, T.L., Kwon, S.K., Lee, A., Shaw, R., Polleux, F., 2018. MFF-dependent mitochondrial fission regulates presynaptic release and axon branching by limiting axonal mitochondria size. Nat. Commun. 9, 5008. https://doi.org/10.1038/S41467-018-07416-2.

Lewis, T.L., Turi, G.F., Kwon, S.K., Losonczy, A., Polleux, F., 2016. Progressive decrease of mitochondrial motility during maturation of cortical axons in vitro and in vivo. Curr. Biol. 26, 2602–2608. https://doi.org/10.1016/j.cub.2016.07.064.

Li, X.C., Hu, Y., Wang, Z.H., Luo, Y., Zhang, Y., Liu, X.P., Feng, Q., Wang, Q., Ye, K., Liu, G.P., Wang, J.Z., 2016. Human wild-type full-length tau accumulation disrupts mitochondrial dynamics and the functions via increasing mitofusins. Sci. Rep. 6, 24756. https://doi.org/10.1038/SREP24756.

Li, Z., Okamoto, K.I., Hayashi, Y., Sheng, M., 2004. The importance of dendritic mitochondria in the morphogenesis and plasticity of spines and synapses. Cell 119, 873–887. https://doi.org/10.1016/j.cell.2004.11.003.

Li, S., Xiong, G.J., Huang, N., Sheng, Z.H., 2020. The cross-talk of energy sensing and mitochondrial anchoring sustains synaptic efficacy by maintaining presynaptic metabolism. Nat. Metab. 2, 1077–1095. https://doi.org/10.1038/S42255-020-00289-0.

Li, J., Yang, D., Li, Z., Zhao, M., Wang, D., Sun, Z., Wen, P., Dai, Y., Gou, F., Ji, Y., Zhao, D., Yang, L., 2023. PINK1/Parkin-mediated mitophagy in neurodegenerative diseases. Ageing Res. Rev. 84, 101817. https://doi.org/10.1016/j.arr.2022.101817.

Lin, C.Y., Huang, Y.N., Fu, R.H., Liao, Y.H., Kuo, T.Y., Tsai, C.W., 2021. Promotion of mitochondrial biogenesis via the regulation of PARIS and PGC-1α by parkin as a mechanism of neuroprotection by carnosic acid. Phytomedicine 80, 153369. https://doi.org/10.1016/j.phymed.2020.153369.

Liu, Q., Chen, W., Wu, Y., Guo, Z., Chen, J., Tian, C., Wang, P., Zeng, S., Xu, B., Duan, J., Han, S., Xiong, X., Zhang, J., 2025. CNS mitochondria-derived vesicle in blood: potential biomarkers for brain mitochondria dysfunction. Ann. Clin. Transl. Neurol. 12, 1312–1323. https://doi.org/10.1002/ACN3.70060.

Liu, X., Chu, B., Jin, S., Li, M., Xu, Y., Yang, H., Feng, Z., Bi, J., Wang, P., 2021. Vascular endothelial growth factor alleviates mitochondrial dysfunction and suppression of mitochondrial biogenesis in models of Alzheimer's disease. Int. J. Neurosci. 131, 154–162. https://doi.org/10.1080/00207454.2020.1733564.

Liu, L., Feng, D., Chen, G., Chen, M., Zheng, Q., Song, P., Ma, Q., Zhu, C., Wang, R., Qi, W., Huang, L., Xue, P., Li, B., Wang, X., Jin, H., Wang, J., Yang, F., Liu, P., Zhu, Y., Sui, S., Chen, Q., 2012. Mitochondrial outer-membrane protein FUNDC1 mediates hypoxia-induced mitophagy in mammalian cells. Nat. Cell Biol. 14, 177–185. https://doi.org/10.1038/NCB2422.

Liu, W., Yamashita, T., Tian, F., Morimoto, N., Ikeda, Y., Deguchi, K., Abe, K., 2013. Mitochondrial fusion and fission proteins expression dynamically change in a murine model of amyotrophic lateral sclerosis. Curr. Neurovasc Res. 10, 222–230. https://doi.org/10.2174/15672026113109990060.

Liu, H., Zang, C., Yuan, F., Ju, C., Shang, M., Ning, J., Yang, Y., Ma, J., Li, G., Bao, X., Zhang, D., 2022. The role of FUNDC1 in mitophagy, mitochondrial dynamics and human diseases. Biochem. Pharm. 197, 114891. https://doi.org/10.1016/j.bcp.2021.114891.

Lopez-Gonzalez, R., Lu, Y., Gendron, T.F., Karydas, A., Tran, H., Yang, D., Petrucelli, L., Miller, B.L., Almeida, S., Gao, F.B., 2016. Poly(GR) in C9ORF72-related ALS/FTD compromises mitochondrial function and increases oxidative stress and DNA damage in iPSC-derived motor neurons. Neuron 92, 383–391. https://doi.org/10.1016/j.neuron.2016.09.015.

Losón, O.C., Song, Z., Chen, H., Chan, D.C., 2013. Fis1, Mff, MiD49, and MiD51 mediate Drp1 recruitment in mitochondrial fission. Mol. Biol. Cell 24, 659–667. https://doi.org/10.1091/MBC.E12-10-0721.

Ma, D., Li, S., Lucas, E.K., Cowell, R.M., Lin, J.D., 2010. Neuronal inactivation of peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α) protects mice from diet-induced obesity and leads to degenerative lesions. J. Biol. Chem. 285, 39087–39095. https://doi.org/10.1074/jbc.M110.151688.

MacAskill, A.F., Atkin, T.A., Kittler, J.T., 2010. Mitochondrial trafficking and the provision of energy and calcium buffering at excitatory synapses. Eur. J. Neurosci. 32, 231–240. https://doi.org/10.1111/J.1460-9568.2010.07345.X.

Manczak, M., Calkins, M.J., Reddy, P.H., 2011. Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: lications for neuronal damage. Hum. Mol. Genet 20, 2495–2509. https://doi.org/10.1093/HMG/DDR139.

Manczak, M., Kandimalla, R., Yin, X., Reddy, P.H., 2018. 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 27, 1332–1342. https://doi.org/10.1093/HMG/DDY042.

Manczak, M., Reddy, P.H., 2012. Abnormal interaction between the mitochondrial fission protein Drp1 and hyperphosphorylated tau in Alzheimer's disease neurons: implications for mitochondrial dysfunction and neuronal damage. Hum. Mol. Genet 21, 2538–2547. https://doi.org/10.1093/HMG/DDS072.

Mandal, A., Wong, H.T.C., Pinter, K., Mosqueda, N., Beirl, A., Lomash, R.M., Won, S., Kindt, K.S., Drerup, C.M., 2021. Retrograde mitochondrial transport is essential for organelle distribution and health in Zebrafish neurons. J. Neurosci. 41, 1371–1392. https://doi.org/10.1523/JNEUROSCI.1316-20.2020.

Martinez, J.H., Alaimo, A., Gorojod, R.M., Porte Alcon, S., Fuentes, F., Coluccio Leskow, F., Kotler, M.L., 2018. Drp-1 dependent mitochondrial fragmentation and protective autophagy in dopaminergic SH-SY5Y cells overexpressing alpha-synuclein. Mol. Cell Neurosci. 88, 107–117. https://doi.org/10.1016/j.mcn.2018.01.004.

Martín-Maestro, P., Sproul, A., Martinez, H., Paquet, D., Gerges, M., Noggle, S., Starkov, A.A., 2019. Autophagy induction by bexarotene promotes mitophagy in presenilin 1 familial Alzheimer's disease iPSC-derived neural stem cells. Mol. Neurobiol. 56, 8220–8236. https://doi.org/10.1007/S12035-019-01665-Y.

Marzetti, E., Guerra, F., Calvani, R., Marini, F., Biancolillo, A., Gervasoni, J., Primiano, A., Coelho-Júnior, H.J., Landi, F., Bernabei, R., Bucci, C., Picca, A., 2020. Circulating mitochondrial-derived vesicles, inflammatory biomarkers and amino acids in older adults with physical frailty and sarcopenia: a preliminary BIOSPHERE multi-marker study using sequential and orthogonalized covariance selection - linear discriminant analysis. Front Cell Dev. Biol. 8, 564417. https://doi.org/10.3389/fcell.2020.564417.

Mattie, S., Riemer, J., Wideman, J.G., McBride, H.M., 2018. A new mitofusin topology places the redox-regulated C terminus in the mitochondrial intermembrane space. J. Cell Biol. 217, 507–515. https://doi.org/10.1083/JCB.201611194.

Mehta, A.R., Gregory, J.M., Dando, O., Carter, R.N., Burr, K., Nanda, J., Story, D., McDade, K., Smith, C., Morton, N.M., Mahad, D.J., Hardingham, G.E., Chandran, S., Selvaraj, B.T., 2021. Mitochondrial bioenergetic deficits in C9orf72 amyotrophic lateral sclerosis motor neurons cause dysfunctional axonal homeostasis. Acta Neuropathol. 141, 257–279. https://doi.org/10.1007/S00401-020-02252-5.

Melber, A., Haynes, C.M., 2018. UPRmt regulation and output: a stress response mediated by mitochondrial-nuclear communication. Cell Res 28, 281–295. https://doi.org/10.1038/cr.2018.16.

Melentijevic, I., Toth, M.L., Arnold, M.L., Guasp, R.J., Harinath, G., Nguyen, K.C., Taub, D., Parker, J.A., Neri, C., Gabel, C.V., Hall, D.H., Driscoll, M., 2017. C. elegans neurons jettison protein aggregates and mitochondria under neurotoxic stress. Nature 542, 367–371. https://doi.org/10.1038/NATURE21362.

Miller, N., Shi, H., Zelikovich, A.S., Ma, Y.C., 2016. Motor neuron mitochondrial dysfunction in spinal muscular atrophy. Hum. Mol. Genet 25, 3395–3406. https://doi.org/10.1093/HMG/DDW262.

Mironov, S.L., 2007. ADP regulates movements of mitochondria in neurons. Biophys. J. 92, 2944–2952. https://doi.org/10.1529/biophysj.106.092981.

Misgeld, T., Kerschensteiner, M., Bareyre, F.M., Burgess, R.W., Lichtman, J.W., 2007. Imaging axonal transport of mitochondria in vivo. Nat. Methods 4, 559–561. https://doi.org/10.1038/NMETH1055.

Misgeld, T., Schwarz, T.L., 2017. Mitostasis in neurons: maintaining mitochondria in an extended cellular architecture. Neuron 96, 651–666. https://doi.org/10.1016/j.neuron.2017.09.055.

Mishra, P., Chan, D.C., 2016. Metabolic regulation of mitochondrial dynamics. J. Cell Biol. 212, 379–387. https://doi.org/10.1083/jcb.201511036.

Miyamoto, Y., Kitamura, N., Nakamura, Y., Futamura, M., Miyamoto, T., Yoshida, M., Ono, M., Ichinose, S., Arakawa, H., 2011. Possible existence of lysosome-like organella within mitochondria and its role in mitochondrial quality control. PLoS One 6, e16054. https://doi.org/10.1371/journal.pone.0016054.

Mockett, B.G., Guévremont, D., Wutte, M., Hulme, S.R., Williams, J.M., Abraham, W.C., 2011. Calcium/calmodulin-dependent protein kinase II mediates group I metabotropic glutamate receptor-dependent protein synthesis and long-term depression in rat hippocampus. J. Neurosci. 31, 7380–7391. https://doi.org/10.1523/JNEUROSCI.6656-10.2011.

Morris, R.L., Hollenbeck, P.J., 1993. The regulation of bidirectional mitochondrial transport is coordinated with axonal outgrowth. J. Cell Sci. 104, 917–927. https://doi.org/10.1242/JCS.104.3.917.

Mudò, G., Mäkelä, J., Di Liberto, V., Tselykh, T.V., Olivieri, M., Piepponen, P., Eriksson, O., Mälkiä, A., Bonomo, A., Kairisalo, M., Aguirre, J.A., Korhonen, L., Belluardo, N., Lindholm, D., 2012. Transgenic expression and activation of PGC-1α protect dopaminergic neurons in the MPTP mouse model of Parkinson's disease. Cell Mol. Life Sci. 69, 1153–1165. https://doi.org/10.1007/S00018-011-0850-Z.

Munson, M.J., Mathai, B.J., Ng, M.Y.W., Trachsel-Moncho, L., de la Ballina, L.R., Schultz, S.W., Aman, Y., Lystad, A.H., Singh, Sakshi, Singh, Sachin, Wesche, J., Fang, E.F., Simonsen, A., 2021. GAK and PRKCD are positive regulators of PRKN-independent mitophagy. Nat. Commun. 12, 6101. https://doi.org/10.1038/S41467-021-26331-7.

Nakamura, K., Nemani, V.M., Azarbal, F., Skibinski, G., Levy, J.M., Egami, K., Munishkina, L., Zhang, J., Gardner, B., Wakabayashi, J., Sesaki, H., Cheng, Y., Finkbeiner, S., Nussbaum, R.L., Masliah, E., Edwards, R.H., 2011. Direct membrane association drives mitochondrial fission by the Parkinson disease-associated protein α-synuclein. J. Biol. Chem. 286, 20710–20726. https://doi.org/10.1074/jbc.M110.213538.

Narendra, D., Walker, J.E., Youle, R., 2012. Mitochondrial quality control mediated by PINK1 and Parkin: Links to parkinsonism. Cold Spring Harb. Perspect. Biol. 4, a011338. https://doi.org/10.1101/CSHPERSPECT.A011338.

Nasoni, M.G., Carloni, S., Canonico, B., Burattini, S., Cesarini, E., Papa, S., Pagliarini, M., Ambrogini, P., Balduini, W., Luchetti, F., 2021. Melatonin reshapes the mitochondrial network and promotes intercellular mitochondrial transfer via tunneling nanotubes after ischemic-like injury in hippocampal HT22 cells. J. Pineal Res. 71. https://doi.org/10.1111/JPI.12747.

Neueder, A., Kojer, K., Gu, Z., Wang, Y., Hering, T., Tabrizi, S., Taanman, J.W., Orth, M., 2024. Huntington's disease affects mitochondrial network dynamics predisposing to pathogenic mitochondrial DNA mutations. Brain 147, 2009–2022. https://doi.org/10.1093/BRAIN/AWAE007.

Nogueras-Ortiz, C.J., Mahairaki, V., Delgado-Peraza, F., Das, D., Avgerinos, K., Eren, E., Hentschel, M., Goetzl, E.J., Mattson, M.P., Kapogiannis, D., 2020. Astrocyte- and neuron-derived extracellular vesicles from Alzheimer's disease patients effect complement-mediated neurotoxicity. Cells 9, 1618. https://doi.org/10.3390/cells9071618.

Novak, I., Kirkin, V., McEwan, D., Zhang, J., Wild, P., Rozenknop, A., Rogov, V., Löhr, F., Popovic, D., Occhipinti, A., Reichert, A., Terzic, J., Dötsch, V., Ney, P., Dikic, I., 2010. Nix is a selective autophagy receptor for mitochondrial clearance. EMBO Rep. 11, 45–51. https://doi.org/10.1038/EMBOR.2009.256.

Oliveira, J.M.A., Jekabsons, M.B., Chen, S., Lin, A., Rego, A.C., Gonçalves, J., Ellerby, L.M., Nicholls, D.G., 2007. Mitochondrial dysfunction in Huntington's disease: The bioenergetics of isolated and in situ mitochondria from transgenic mice. J. Neurochem. 101, 241–249. https://doi.org/10.1111/J.1471-4159.2006.04361.X.

Onesto, E., Colombrita, C., Gumina, V., Borghi, M.O., Dusi, S., Doretti, A., Fagiolari, G., Invernizzi, F., Moggio, M., Tiranti, V., Silani, V., Ratti, A., 2016. Gene-specific mitochondria dysfunctions in human TARDBP and C9ORF72 fibroblasts. Acta Neuropathol. Commun. 4, 47. https://doi.org/10.1186/S40478-016-0316-5.

Ono, T., Isobe, K., Nakada, K., Hayashi, J.I., 2001. Human cells are protected from mitochondrial dysfunction by complementation of DNA products in fused mitochondria. Nat. Genet 28, 272–275. https://doi.org/10.1038/90116.

Ottolini, D., Calì, T., Negro, A., Brini, M., 2013. The Parkinson disease-related protein DJ-1 counteracts mitochondrial impairment induced by the tumour suppressor protein p53 by enhancing endoplasmic reticulum-mitochondria tethering. Hum. Mol. Genet 22, 2152–2168. https://doi.org/10.1093/HMG/DDT068.

Panes, J.D., Godoy, P.A., Silva-Grecchi, T., Celis, M.T., Ramirez-Molina, O., Gavilan, J., Muñoz-Montecino, C., Castro, P.A., Moraga-Cid, G., Yévenes, G.E., Guzmán, L., Salisbury, J.L., Trushina, E., Fuentealba, J., 2020. Changes in PGC-1α/SIRT1 signaling impact on mitochondrial homeostasis in amyloid-beta peptide toxicity model. Front Pharm. 11, 709. https://doi.org/10.3389/FPHAR.2020.00709.

Pang, B., Dong, G., Pang, T., Sun, X., Liu, X., Nie, Y., Chang, X., 2024. Advances in pathogenesis and treatment of vascular endothelial injury-related diseases mediated by mitochondrial abnormality. Front Pharm. 15, 1422686. https://doi.org/10.3389/fphar.2024.1422686.

Papanicolaou, K.N., Khairallah, R.J., Ngoh, G.A., Chikando, A., Luptak, I., O'Shea, K.M., Riley, D.D., Lugus, J.J., Colucci, W.S., Lederer, W.J., Stanley, W.C., Walsh, K., 2011. Mitofusin-2 maintains mitochondrial structure and contributes to stress-induced permeability transition in cardiac myocytes. Mol. Cell Biol. 31, 1309–1328. https://doi.org/10.1128/MCB.00911-10.

Petito, G., Del Fiore, V.S., Cuomo, A., Cioffi, F., Cobellis, G., Lanni, A., Guerra, F., Bucci, C., Senese, R., Romano, R., 2025. Dysfunctional mitochondria characterize amyotrophic lateral sclerosis patients' cells carrying the p.G376D TARDBP pathogenetic substitution. Antioxidants 14, 401. https://doi.org/10.3390/antiox14040401.

Picard, M., Shirihai, O.S., Gentil, B.J., Burelle, Y., 2013. Mitochondrial morphology transitions and functions: implications for retrograde signaling? Am. J. Physiol. Regul. Integr. Comp. Physiol. 304, 393–406. https://doi.org/10.1152/AJPREGU.00584.2012.

Picca, A., Beli, R., Calvani, R., Coelho-Júnior, H.J., Landi, F., Bernabei, R., Bucci, C., Guerra, F., Marzetti, E., 2020a. Older adults with physical frailty and sarcopenia show increased levels of circulating small extracellular vesicles with a specific mitochondrial signature. Cells 9, 973. https://doi.org/10.3390/cells9040973.

Picca, A., Guerra, F., Calvani, R., Marini, F., Biancolillo, A., Landi, G., Beli, R., Landi, F., Bernabei, R., Bentivoglio, A.R., Lo Monaco, M.R., Bucci, C., Marzetti, E., 2020b. Mitochondrial signatures in circulating extracellular vesicles of older adults with Parkinson's disease: results from the exosomes in PArkiNson's disease (EXPAND) study. J. Clin. Med. 9, 504. https://doi.org/10.3390/JCM9020504.

Pilling, A.D., Horiuchi, D., Lively, C.M., Saxton, W.M., 2006. Kinesin-1 and Dynein are the primary motors for fast transport of mitochondria in Drosophila motor axons. Mol. Biol. Cell 17, 2057–2068. https://doi.org/10.1091/MBC.E05-06-0526.

Pirooznia, S.K., Wang, H., Panicker, N., Kumar, M., Neifert, S., Dar, M.A., Lau, E., Kang, B.G., Redding-Ochoa, J., Troncoso, J.C., Dawson, V.L., Dawson, T.M., 2022. Deubiquitinase CYLD acts as a negative regulator of dopamine neuron survival in Parkinson's disease. Sci. Adv. 8, 1824. https://doi.org/10.1126/SCIADV.ABH1824.

Plucińska, G., Paquet, D., Hruscha, A., Godinho, L., Haass, C., Schmid, B., Misgeld, T., 2012. vivo imaging of disease-related mitochondrial dynamics in a vertebrate model system. J. Neurosci. 32, 16203–16212. https://doi.org/10.1523/JNEUROSCI.1327-12.2012.

Portz, P., Lee, M.K., 2021. Changes in Drp1 function and mitochondrial morphology are associated with the α-synuclein pathology in a transgenic mouse model of Parkinson's disease. Cells 10, 885. https://doi.org/10.3390/CELLS10040885.

Pu, X., Liu, J., Wang, Y., Guan, X., Wu, Q., Zhang, Q., Liu, R., Chang, X., 2025b. Ginsenoside Rb1 attenuates coronary microvascular inflammatory injury via NDUFS4-SIRT5-DUSP1-mediated mitochondrial quality control in a murine ischemia-reperfusion model. J. Ginseng Res. 49, 509–522. https://doi.org/10.1016/j.jgr.2025.04.006.

Pu, X., Wu, Q., Yan, Z., Zhou, S., Zhang, Q., Zhang, X., Cai, Y., Liu, Z., Liu, R., Chang, X., 2025a. Tanshinone IIA modulates Sirt5 and Metll3 interaction to govern mitochondria-endoplasmic reticulum unfolded protein response in coronary microvascular injury. Phytomedicine 145, 156982. https://doi.org/10.1016/j.phymed.2025.156982.

Puri, R., Cheng, X.T., Lin, M.Y., Huang, N., Sheng, Z.H., 2019. Mul1 restrains Parkin-mediated mitophagy in mature neurons by maintaining ER-mitochondrial contacts. Nat. Commun. 10, 3645. https://doi.org/10.1038/S41467-019-11636-5.

Qin, W., Myers, S.A., Carey, D.K., Carr, S.A., Ting, A.Y., 2021. Spatiotemporally-resolved mapping of RNA binding proteins via functional proximity labeling reveals a mitochondrial mRNA anchor promoting stress recovery. Nat. Commun. 12, 4980. https://doi.org/10.1038/S41467-021-25259-2.

Rath, S., Sharma, R., Gupta, R., Ast, T., Chan, C., Durham, T.J., Goodman, R.P., Grabarek, Z., Haas, M.E., Hung, W.H.W., Joshi, P.R., Jourdain, A.A., Kim, S.H., Kotrys, A.V., Lam, S.S., McCoy, J.G., Meisel, J.D., Miranda, M., Panda, A., Patgiri, A., Rogers, R., Sadre, S., Shah, H., Skinner, O.S., To, T.L., Walker, M.A., Wang, H., Ward, P.S., Wengrod, J., Yuan, C.C., Calvo, S.E., Mootha, V.K., 2021. MitoCarta3.0: an updated mitochondrial proteome now with sub-organelle localization and pathway annotations. Nucleic Acids Res. 49, D1541–D1547. https://doi.org/10.1093/NAR/GKAA1011.

Reddy, P.H., Tripathi, R., Troung, Q., Tirumala, K., Reddy, T.P., Anekonda, V., Shirendeb, U.P., Calkins, M.J., Reddy, A.P., Mao, P., Manczak, M., 2012. Abnormal mitochondrial dynamics and synaptic degeneration as early events in Alzheimer's disease: implications to mitochondria-targeted antioxidant therapeutics. Biochim. Biophys. Acta Mol. Basis Dis. 1822, 639–649. https://doi.org/10.1016/j.bbadis.2011.10.011.

Rowland, K.C., Irby, N.K., Spirou, G.A., 2000. Specialized synapse-associated structures within the calyx of Held. J. Neurosci. 20, 9135–9144. https://doi.org/10.1523/JNEUROSCI.20-24-09135.2000.

Russo, G.J., Louie, K., Wellington, A., Macleod, G.T., Hu, F., Panchumarthi, S., Zinsmaier, K.E., 2009. Drosophila Miro is required for both anterograde and retrograde axonal mitochondrial transport. J. Neurosci. 29, 5443–5455. https://doi.org/10.1523/JNEUROSCI.5417-08.2009.

Saito, T., Nah, J., Oka, S. ichi, Mukai, R., Monden, Y., Maejima, Y., Ikeda, Y., Sciarretta, S., Liu, T., Li, H., Baljinnyam, E., Fraidenraich, D., Fritzky, L., Zhai, P., Ichinose, S., Isobe, M., Hsu, C.P., Kundu, M., Sadoshima, J., 2019. An alternative mitophagy pathway mediated by Rab9 protects the heart against ischemia. J. Clin. Invest. 129, 802–819. https://doi.org/10.1172/JCI122035.

Sandoval, H., Thiagarajan, P., Dasgupta, S.K., Schumacher, A., Prchal, J.T., Chen, M., Wang, J., 2008. Essential role for Nix in autophagic maturation of erythroid cells. Nature 454, 232–235. https://doi.org/10.1038/nature07006.

Scarpulla, R.C., 2008. Transcriptional paradigms in mammalian mitochondrial biogenesis and function. Physiol. Rev. 88, 611–638. https://doi.org/10.1152/PHYSREV.00025.2007.

Schroer, T.A., 2004. Dynactin. Annu Rev. Cell Dev. Biol. 20, 759–779. https://doi.org/10.1146/ANNUREV.CELLBIO.20.012103.094623.

Schwarzer, C., Barnikol-Watanabe, S., Thinnes, F.P., Hilschmann, N., 2002. Voltage-dependent anion-selective channel (VDAC) interacts with the dynein light chain Tctex1 and the heat-shock protein PBP74. Int. J. Biochem. Cell Biol. 34, 1059–1070. https://doi.org/10.1016/S1357-2725(02)00026-2.

Shen, K., Pender, C.L., Bar-Ziv, R., Zhang, H., Wickham, K., Willey, E., Durieux, J., Ahmad, Q., Dillin, A., 2022. Mitochondria as cellular and organismal signaling hubs. Annu Rev. Cell Dev. Biol. 38, 179–218. https://doi.org/10.1146/ANNUREV-CELLBIO-120420-015303.

Shen, T., Zheng, M., Cao, C., Chen, C., Tang, J., Zhang, W., Cheng, H., Chen, K.H., Xiao, R.P., 2007. Mitofusin-2 is a major determinant of oxidative stress-mediated heart muscle cell apoptosis. J. Biol. Chem. 282, 23354–23361. https://doi.org/10.1074/jbc.M702657200.

Sheng, B., Wang, X., Su, B., Lee, H.G., Casadesus, G., Perry, G., Zhu, X., 2012. Impaired mitochondrial biogenesis contributes to mitochondrial dysfunction in Alzheimer's disease. J. Neurochem. 120, 419–429. https://doi.org/10.1111/J.1471-4159.2011.07581.X.

Shi, H., Pang, B., Zhang, F., Guo, Z., Xu, W., Zheng, M., You, Y., Liu, G., Nie, Y., Liang, J., Chang, X., 2012. A novel ligustrazine-based nanodelivery system protects against doxorubicin-induced cardiotoxicity by targeting the SIRT5-DUSP1 axis for mitochondrial repair. J. Nanobiotechnology 23, 681. https://doi.org/10.1186/s12951-025-03667-6.

Shigeoka, T., Jung, H., Jung, J., Turner-Bridger, B., Ohk, J., Lin, J.Q., Amieux, P.S., Holt, C.E., 2016. Dynamic axonal translation in developing and mature visual circuits. Cell 166, 181–192. https://doi.org/10.1016/j.cell.2016.05.029.

Shin, J.H., Ko, H.S., Kang, H., Lee, Yunjong, Lee, Yun, Il, Pletinkova, O., Troconso, J.C., Dawson, V.L., Dawson, T.M., 2011. PARIS (ZNF746) repression of PGC-1α contributes to neurodegeneration in Parkinson's disease. Cell 144, 689–702. https://doi.org/10.1016/j.cell.2011.02.010.

Shpilka, T., Haynes, C.M., 2018. The mitochondrial UPR: mechanisms, physiological functions and implications in ageing. Nat. Rev. Mol. Cell Biol. 19, 109–120. https://doi.org/10.1038/nrm.2017.110.

Simonovitch, S., Schmukler, E., Masliah, E., Pinkas-Kramarski, R., Michaelson, D.M., 2019. The effects of APOE4 on mitochondrial dynamics and proteins in vivo. J. Alzheimers Dis. 70, 861–875. https://doi.org/10.3233/JAD-190074.

Smit-Rigter, L., Rajendran, R., Silva, C.A.P., Spierenburg, L., Groeneweg, F., Ruimschotel, E.M., van Versendaal, D., van der Togt, C., Eysel, U.T., Heimel, J.A., Lohmann, C., Levelt, C.N., 2016. Mitochondrial dynamics in visual cortex are limited in vivo and not affected by axonal structural plasticity. Curr. Biol. 26, 2609–2616. https://doi.org/10.1016/j.cub.2016.07.033.

Song, Z., Chen, H., Fiket, M., Alexander, C., Chan, D.C., 2007. OPA1 processing controls mitochondrial fusion and is regulated by mRNA splicing, membrane potential, and Yme1L. J. Cell Biol. 178, 749–755. https://doi.org/10.1083/JCB.200704110.

Song, J., Herrmann, J.M., Becker, T., 2021. Quality control of the mitochondrial proteome. Nat. Rev. Mol. Cell Biol. 22, 54–70. https://doi.org/10.1038/S41580-020-00300-2.

Spillane, M., Ketschek, A., Merianda, T.T., Twiss, J.L., Gallo, G., 2013. Mitochondria coordinate sites of axon branching through localized intra-axonal protein synthesis. Cell Rep. 5, 1564–1575. https://doi.org/10.1016/j.celrep.2013.11.022.

Stafa, K., Tsika, E., Moser, R., Musso, A., Glauser, L., Jones, A., Biskup, S., Xiong, Y., Bandopadhyay, R., Dawson, V.L., Dawson, T.M., Moore, D.J., 2014. Functional interaction of Parkinson's disease-associated LRRK2 with members of the dynamin GTPase superfamily. Hum. Mol. Genet 23, 2055–2077. https://doi.org/10.1093/HMG/DDT600.

Stevens, D.A., Lee, Yunjong, Kang, H.C., Lee, B.D., Lee, Yun, Il, Bower, A., Jiang, H., Kang, S.U., Andrabi, S.A., Dawson, V.L., Shin, J.H., Dawson, T.M., 2015. Parkin loss leads to PARIS-dependent declines in mitochondrial mass and respiration. Proc. Natl. Acad. Sci. USA 112, 11696–11701. https://doi.org/10.1073/PNAS.1500624112.

Stoica, R., De Vos, K.J., Paillusson, S., Mueller, S., Sancho, R.M., Lau, K.F., Vizcay-Barrena, G., Lin, W.L., Xu, Y.F., Lewis, J., Dickson, D.W., Petrucelli, L., Mitchell, J.C., Shaw, C.E., Miller, C.C., 2014. ER-mitochondria associations are regulated by the VAPB-PTPIP51 interaction and are disrupted by ALS/FTD-associated TDP-43. Nat. Commun. 5, 34–41. https://doi.org/10.1038/NCOMMS4996.

Stojakovic, A., Trushin, S., Sheu, A., Khalili, L., Chang, S.Y., Li, X., Christensen, T., Salisbury, J.L., Geroux, R.E., Gateno, B., Flannery, P.J., Dehankar, M., Funk, C.C., Wilkins, J., Stepanova, A., O'Hagan, T., Galkin, A., Nesbitt, J., Zhu, X., Tripathi, U., Macura, S., Tchkonia, T., Pirtskhalava, T., Kirkland, J.L., Kudgus, R.A., Schoon, R.A., Reid, J.M., Yamazaki, Y., Kanekiyo, T., Zhang, S., Nemutlu, E., Dzeja, P., Jaspersen, A., Kwon, Y.I.C., Lee, M.K., Trushina, E., 2021. Partial inhibition of mitochondrial complex I ameliorates Alzheimer's disease pathology and cognition in APP/PS1 female mice. Commun. Biol. 4, 61. https://doi.org/10.1038/S42003-020-01584-Y.

Strappazzon, F., Nazio, F., Corrado, M., Cianfanelli, V., Romagnoli, A., Fimia, G.M., Campello, S., Nardacci, R., Piacentini, M., Campanella, M., Cecconi, F., 2015. AMBRA1 is able to induce mitophagy via LC3 binding, regardless of PARKIN and p62/SQSTM1. Cell Death Differ. 22, 419–432. https://doi.org/10.1038/CDD.2014.139.

Taherzadeh-Fard, E., Saft, C., Akkad, D.A., Wieczorek, S., Haghikia, A., Chan, A., Epplen, J.T., Arning, L., 2011. PGC-1alpha downstream transcription factors NRF-1 and TFAM are genetic modifiers of Huntington disease. Mol. Neurodegener. 6, 32. https://doi.org/10.1186/1750-1326-6-32.

Takei, N., Inamura, N., Kawamura, M., Namba, H., Hara, K., Yonezawa, K., Nawa, H., 2004. Brain-derived neurotrophic factor induces mammalian target of rapamycin-dependent local activation of translation machinery and protein synthesis in neuronal dendrites. J. Neurosci. 24, 9760–9769. https://doi.org/10.1523/JNEUROSCI.1427-04.2004.

Todkar, K., Chikhi, L., Desjardins, V., El-Mortada, F., Pépin, G., Germain, M., 2021. Selective packaging of mitochondrial proteins into extracellular vesicles prevents the release of mitochondrial DAMPs. Nat. Commun. 12, 1971. https://doi.org/10.1038/s41467-021-21984-w.

Tradewell, M.L., Yu, Z., Tibshirani, M., Boulanger, M.C., Durham, H.D., Richard, S., 2012. Arginine methylation by PRMT1 regulates nuclear-cytoplasmic localization and toxicity of FUS/TLS harbouring ALS-linked mutations. Hum. Mol. Genet 21, 136–149. https://doi.org/10.1093/HMG/DDR448.

Tseng, A.H.H., Shieh, S.S., Wang, D.L., 2013. SIRT3 deacetylates FOXO3 to protect mitochondria against oxidative damage. Free Radic. Biol. Med. 63, 222–234. https://doi.org/10.1016/j.freeradbiomed.2013.05.002.

Twig, G., Elorza, A., Molina, A.J.A., Mohamed, H., Wikstrom, J.D., Walzer, G., Stiles, L., Haigh, S.E., Katz, S., Las, G., Alroy, J., Wu, M., Py, B.F., Yuan, J., Deeney, J.T., Corkey, B.E., Shirihai, O.S., 2008. Fission and selective fusion govern mitochondrial segregation and elimination by autophagy. EMBO J. 27, 433–446. https://doi.org/10.1038/sj.emboj.7601963.

ur Rasheed, M.S., Tripathi, M.K., Mishra, A.K., Shukla, S., Singh, M.P., 2016. Resveratrol protects from toxin-induced parkinsonism: Plethora of proofs hitherto petty translational value. Mol. Neurobiol. 53, 2751–2760. https://doi.org/10.1007/S12035-015-9124-3.

Van Laar, V.S., Arnold, B., Howlett, E.H., Calderon, M.J., St. Croix, C.M., Greenamyre, J. T., Sanders, L.H., Berman, S.B., 2018. Evidence for compartmentalized axonal mitochondrial biogenesis: mitochondrial DNA replication increases in distal axons as an early response to Parkinson's disease-relevant stress. J. Neurosci. 38, 7505–7515. https://doi.org/10.1523/JNEUROSCI.0541-18.2018.

Wang, J., Chang, X., Li, C., Gao, J., Guo, Z., Zhuang, H., Wang, L., Huang, Y., Wang, W., Li, C., He, Q., 2025. DNA-PKcs-driven YAP1 phosphorylation and nuclear translocation: a key regulator of ferroptosis in hyperglycemia-induced cardiac dysfunction in type 1 diabetes. Adv. Sci. 12, e2412698. https://doi.org/10.1002/advs.202412698.

Wang, W., Li, L., Lin, W.L., Dickson, D.W., Petrucelli, L., Zhang, T., Wang, X., 2013. The ALS disease-associated mutant TDP-43 impairs mitochondrial dynamics and function in motor neurons. Hum. Mol. Genet 22, 4706–4719. https://doi.org/10.1093/HMG/DDT319.

Wang, X., Schwarz, T.L., 2009. The mechanism of Ca^{2+}-dependent regulation of kinesin-mediated mitochondrial motility. Cell 136, 163–174. https://doi.org/10.1016/j.cell.2008.11.046.

Wang, H., Song, P., Du, L., Tian, W., Yue, W., Liu, M., Li, D., Wang, B., Zhu, Y., Cao, C., Zhou, J., Chen, Q., 2011. Parkin ubiquitinates Drp1 for proteasome-dependent degradation: Implication of dysregulated mitochondrial dynamics in Parkinson disease. J. Biol. Chem. 286, 11649–11658. https://doi.org/10.1074/jbc.M110.144238.

Wang, W., Yin, J., Ma, X., Zhao, F., Siedlak, S.L., Wang, Z., Torres, S., Fujioka, H., Xu, Y., Perry, G., Zhu, X., 2017. Inhibition of mitochondrial fragmentation protects against Alzheimer's disease in rodent model. Hum. Mol. Genet 26, 4118–4131. https://doi.org/10.1093/HMG/DDX299.

Wang, W., Zhao, F., Lu, Y., Siedlak, S.L., Fujioka, H., Feng, H., Perry, G., Zhu, X., 2023. Damaged mitochondria coincide with presynaptic vesicle loss and abnormalities in Alzheimer's disease brain. Acta Neuropathol. Commun. 11, 54. https://doi.org/10.1186/S40478-023-01552-7.

Wang, J., Zhuang, H., Jia, L., He, X., Zheng, S., Ji, K., Xie, K., Ying, T., Zhang, Y., Li, C., Chang, X., 2024. Nuclear receptor subfamily 4 group A member 1 promotes myocardial ischemia/reperfusion injury through inducing mitochondrial fission factor-mediated mitochondrial fragmentation and inhibiting FUN14 domain containing 1-depedent mitophagy. Int. J. Biol. Sci. 20, 4458–4475. https://doi.org/10.7150/ijbs.95853.

Wareski, P., Vaarmann, A., Choubey, V., Safiulina, D., Liiv, J., Kuum, M., Kaasik, A., 2009. PGC-1α and PGC-1β regulate mitochondrial density in neurons. J. Biol. Chem. 284, 21379–21385. https://doi.org/10.1074/jbc.M109.018911.

Wilkaniec, A., Lenkiewicz, A.M., Babiec, L., Murawska, E., Jęśko, H.M., Cieślik, M., Culmsee, C., Adamczyk, A., 2021. Exogenous alpha-synuclein evoked parkin downregulation promotes mitochondrial dysfunction in neuronal cells. Implications for Parkinson's Disease Pathology. Front Aging Neurosci. 13, 591475. https://doi.org/10.3389/FNAGI.2021.591475.

Wong, Y.C., Holzbaur, E.L.F., 2014. Optineurin is an autophagy receptor for damaged mitochondria in parkin-mediated mitophagy that is disrupted by an ALS-linked mutation. Proc. Natl. Acad. Sci. USA 111, E4439–E4448. https://doi.org/10.1073/pnas.1405752111.

Wrann, C.D., White, J.P., Salogiannnis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., Lin, J. D., Greenberg, M.E., Spiegelman, B.M., 2013. Exercise induces hippocampal BDNF through a PGC-1α/FNDC5 pathway. Cell Metab. 18, 649–659. https://doi.org/10.1016/j.cmet.2013.09.008.

Wu, W., Tian, W., Hu, Z., Chen, G., Huang, L., Li, W., Zhang, Xingli, Xue, P., Zhou, C., Liu, L., Zhu, Y., Zhang, Xingliang, Li, L., Zhang, L., Sui, S., Zhao, B., Feng, D., 2014. ULK1 translocates to mitochondria and phosphorylates FUNDC1 to regulate mitophagy. EMBO Rep. 15, 566–575. https://doi.org/10.1002/EMBR.201438501.

Wu, Q., Wang, Y., Liu, J., Guan, X., Chang, X., Liu, Z., Liu, R., 2024. Microtubules and cardiovascular diseases: insights into pathology and therapeutic strategies. Int. J. Biochem. Cell Biol. 175, 106650. https://doi.org/10.1016/j.biocel.2024.106650.

Xia, Q., Mao, M., Zeng, Z., Luo, Z., Zhao, Y., Shi, J., Li, X., 2021. R13 preserves motor performance in SOD1G93A mice by improving mitochondrial function. Theranostics 11, 7450–7470. https://doi.org/10.7150/THNO.56070.

Yang, K., Zhang, P., Li, J., Zhang, G., Chang, X., 2024. Potential of natural drug modulation of endoplasmic reticulum stress in the treatment of myocardial injury. J. Pharm. Anal. 14, 101034. https://doi.org/10.1016/j.jpha.2024.101034.

Yang, W., Zou, Y., Zhang, M., Zhao, N., Tian, Q., Gu, M., Liu, W., Shi, R., Lü, Y., Yu, W., 2015. Mitochondrial Sirt3 expression is decreased in APP/PS1 double transgenic mouse model of Alzheimer's disease. Neurochem. Res. 40, 1576–1582. https://doi.org/10.1007/S11064-015-1630-1.

Yao, P.J., Eren, E., Goetzl, E.J., Kapogiannis, D., 2021. Mitochondrial electron transport chain protein abnormalities detected in plasma extracellular vesicles in Alzheimer's disease. Biomedicines 9, 1587. https://doi.org/10.3390/BIOMEDICINES9111587.

Yao, C.H., Wang, R., Wang, Y., Kung, C.P., Weber, J.D., Patti, G.J., 2019. Mitochondrial fusion supports increased oxidative phosphorylation during cell proliferation. Elife 8, e42351. https://doi.org/10.7554/ELIFE.41351.

Ye, X., Sun, X., Starovoytov, V., Cai, Q., 2015. Parkin-mediated mitophagy in mutant hAPP neurons and Alzheimer's disease patient brains. Hum. Mol. Genet 24, 2938–2951. https://doi.org/10.1093/HMG/DDV056.

Yoon, B.C., Jung, H., Dwivedy, A., O'Hare, C.M., Zivraj, K.H., Holt, C.E., 2012. Local translation of extranuclear lamin B promotes axon maintenance. Cell 148, 752–764. https://doi.org/10.1016/j.cell.2011.11.064.

Youle, R.J., Van Der Bliek, A.M., 2012. Mitochondrial fission, fusion, and stress. Science 337, 1062–1065. https://doi.org/10.1126/SCIENCE.1219855.

Yu, L., Yang, S.J., 2010. AMP-activated protein kinase mediates activity-dependent regulation of peroxisome proliferator-activated receptor γ coactivator-1α and nuclear respiratory factor 1 expression in rat visual cortical neurons. Neuroscience 169, 23–38. https://doi.org/10.1016/j.neuroscience.2010.04.063.

Zhang, J., Ney, P.A., 2008. NIX induces mitochondrial autophagy in reticulocytes. Autophagy 4, 354–356. https://doi.org/10.4161/AUTO.5552.

Zhang, C., Shi, Z., Zhang, L., Zhou, Z., Zheng, X., Liu, G., Bu, G., Fraser, P.E., Xu, H., Zhang, Y.W., 2016b. Appoptosin interacts with mitochondrial outer-membrane fusion proteins and regulates mitochondrial morphology. J. Cell Sci. 129, 994–1002. https://doi.org/10.1242/JCS.176792.

Zhang, L., Trushin, S., Christensen, T.A., Bachmeier, B.V., Gateno, B., Schroeder, A., Yao, J., Itoh, K., Sesaki, H., Poon, W.W., Gylys, K.H., Patterson, E.R., Parisi, J.E., Diaz Brinton, R., Salisbury, J.L., Trushina, E., 2016a. Altered brain energetics induces mitochondrial fission arrest in Alzheimer's Disease. Sci. Rep. 6, 18725. https://doi.org/10.1038/SREP18725.

Zhang, H., Zhang, Y. wu, Chen, Y., Huang, X., Zhou, F., Wang, W., Xian, B., Zhang, X., Masliah, E., Chen, Q., Han, J.D.J., Bu, G., Reed, J.C., Liao, F.F., Chen, Y.G., Xu, H., 2012. Appoptosin is a novel pro-apoptotic protein and mediates cell death in neurodegeneration. J. Neurosci. 32, 15565–15576. https://doi.org/10.1523/JNEUROSCI.3668-12.2012.

Zhao, W., Varghese, M., Yemul, S., Pan, Y., Cheng, A., Marano, P., Hassan, S., Vempati, P., Chen, F., Qian, X., Pasinetti, G., 2011. Peroxisome proliferator activator receptor gamma coactivator-1alpha (PGC-1α) improves motor performance and survival in a mouse model of amyotrophic lateral sclerosis. Mol. Neurodegener. 6, 51. https://doi.org/10.1186/1750-1326-6-51.

Zheng, B., Liao, Z., Locascio, J.J., Lesniak, K.A., Roderick, S.S., Watt, M.L., Eklund, A.C., Zhang-James, Y., Kim, P.D., Hauser, M.A., Grünblatt, E., Moran, L.B., Mandel, S.A., Riederer, P., Miller, R.M., Federoff, H.J., Wüllner, U., Papapetropoulos, S., Youdim, M.B., Cantuti-Castelvetri, I., Young, A.B., Vance, J.M., Davis, R.L., Hedreen, J.C., Adler, C.H., Beach, T.G., Graeber, M.B., Middleton, F.A., Rochet, J.C., Scherzer, C.R., 2010. PGC-1α, a potential therapeutic target for early intervention in Parkinson's disease. Sci. Transl. Med. 2, 52–73. https://doi.org/10.1126/SCITRANSLMED.3001059.

Zheng, Y., Wu, X., Chen, Z., Zhang, X., 2019. Come and eat: mitochondrial transport guides mitophagy in ischemic neuronal axons. Autophagy 15, 1483–1484. https://doi.org/10.1080/15548627.2019.1618099.

Zhou, B., Yu, P., Lin, M.Y., Sun, T., Chen, Y., Sheng, Z.H., 2016. Facilitation of axon regeneration by enhancing mitochondrial transport and rescuing energy deficits. J. Cell Biol. 214, 103–119. https://doi.org/10.1083/JCB.201605101.

Zhu, Y., Massen, S., Terenzio, M., Lang, V., Chen-Lindner, S., Eils, R., Novak, I., Dikic, I., Hamacher-Brady, A., Brady, N.R., 2013. Modulation of serines 17 and 24 in the LC3-interacting region of Bnip3 determines pro-survival mitophagy versus apoptosis. J. Biol. Chem. 288, 1099–1113. https://doi.org/10.1074/jbc.M112.399345.

Zhu, X., Perry, G., Moreira, P.I., Aliev, G., Cash, A.D., Hirai, K., Smith, M.A., 2006. Mitochondrial abnormalities and oxidative imbalance in Alzheimer disease. J. Alzheimers Dis. 9, 147–153. https://doi.org/10.3233/JAD-2006-9207.