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REVIEW

SUBJECT COLLECTION: AUTOPHAGY

Mitophagy and long-term neuronal homeostasis

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ABSTRACT

Neurons are highly polarized, post-mitotic cells that are characterized by unique morphological diversity and complexity. As highly differentiated cells that need to survive throughout organismal lifespan, neurons face exceptional energy challenges in time and space. Therefore, neurons are heavily dependent on a healthy mitochondrial network for their proper function and maintenance under both physiological and stress conditions. Multiple quality control systems have evolved to fine-tune mitochondrial number and quality, thus preserving neuronal energy homeostasis. Here, we review the contribution of mitophagy, a selective form of autophagy that targets dysfunctional or superfluous mitochondria for degradation, in maintaining nervous system homeostasis. In addition, we discuss recent evidence implicating defective or dysregulated mitophagy in the pathogenesis of neurodegenerative diseases.

KEY WORDS: Autophagy, Energy homeostasis, Mitochondria, Mitophagy, Nervous system, Neurodegeneration, Neurodegenerative diseases, Neuron, Non-neuronal cells

Introduction

Life expectancy has increased. Hence, the elderly population is expected to be twice as large as today in upcoming years (United Nations Department of Economic and Social Affairs report on World Population Ageing, 2019; https://www.un.org/development/desa/pd/news/world-population-ageing-2019-0). Older individuals are more susceptible to lifelong accumulation of damage that eventually affects their physical and mental capacities. In particular, the brain, with its post-mitotic cells, is highly vulnerable to injury and deterioration (Mattson and Arumugam, 2018). Population studies of individuals over the age of 50 years who had not been diagnosed with a neurological disease have reported accumulation of aggregation-prone proteins such as amyloid-β (Aβ), α-synuclein and transactive response (TAR) DNA-binding protein 43 (TDP43, also known as TARDBP) in the brain, as well as synaptic abnormalities and neuronal loss (Elobeid et al., 2016; Wyss-Coray, 2016). Accumulating findings support the key role of the nervous system in maintaining whole-body homeostasis and survival in organisms as diverse as the nematode *Caenorhabditis elegans* and humans (Waterson and Horvath, 2015). Therefore, efficient quality control mechanisms are required to preserve nervous system homeostasis. Given the increased metabolic demands of neurons and their central role in modulating energy balance at the organismal level, such quality control mechanisms do necessarily contribute to the maintenance of mitochondrial homeostasis.

Beyond their role in energy production, mitochondria have essential roles in supporting the biosynthetic needs of the cell, including the synthesis of fatty acids, amino acids, nucleotides and cholesterol, as well as the biosynthesis of haem, iron–sulfur cluster biogenesis and the management of metabolic by-products, among others. Mitochondria are also crucial for the maintenance of Ca^{2+} homeostasis, as well as for the regulation of signal transduction cascades and cellular stress responses (Chandel, 2014; Kalkavan and Green, 2018). Owing to these diverse roles, mitochondria have evolved a variety of quality control mechanisms, which often interface with each other to maintain their own homeostasis, eventually promoting cell and organismal homeostasis. One such mechanism is the selective autophagic elimination of damaged or superfluous mitochondria, which is known as mitophagy and is important for the maintenance of the requisite number of healthy mitochondria both under physiological conditions and in response to stress (Evans and Holzbaur, 2020; Held and Houtkooper, 2015; Palikaras and Tavernarakis, 2014; Song et al., 2021). There are different mitophagy pathways, depending on the induction stimuli and the cell type, and these are generally classified as either ubiquitin dependent or ubiquitin independent (Ganley and Simonsen, 2022; Khaminets et al., 2016). Ubiquitin-dependent mitophagy is mainly represented by the phosphatase and tensin homologue (PTEN)-induced putative kinase protein 1 (PINK1)–Parkin (PRKN) pathway, although there are also many reports of Parkin-independent cases (Fu et al., 2013; Lokireddy et al., 2012). Ubiquitin-independent mitophagy is also known as receptor-mediated mitophagy (Frank et al., 2012; Gatica et al., 2018; Jin and Youle, 2013; Onishi et al., 2021; Sandoval et al., 2008).

The rate by which the mitochondrial population is refreshed is determined by turnover – the balance between mitochondrial biogenesis and degradation – with mitochondrial biogenesis providing new mitochondria, and mitochondrial degradation removing the existing and probably damaged or superfluous organelles (Palikaras et al., 2015; Palikaras and Tavernarakis, 2014; Pickles et al., 2018). Accumulating evidence demonstrates that the activity of general and specific degradation pathways, such as the proteasome system, autophagy and mitophagy, declines during post-mitotic ageing (Bakula and Scheibye-Knudsen, 2020; Chen et al., 2020; Tanaka and Matsuda, 2014). This is especially critical for the nervous system, given the pronounced bioenergetic demands and the exceptional longevity of neurons throughout life. Indeed, mitophagy defects have been implicated in neuronal ageing and age-related neurodegenerative pathologies, such as Parkinson's disease (PD), Alzheimer's disease (AD) and Huntington's disease (HD), among others (Jetto et al., 2022; Lou et al., 2020; Martinez-Vicente, 2017; Wang et al., 2019a) (Box 1). Of note, emerging observations suggest that mitophagy also has an important role in maintaining glial morphology and function, and its dysregulation has been linked to ageing and disease (Sukhorukov et al., 2021). Here, we focus on the role of PINK1–Parkin-mediated mitophagy

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Journal of Cell Science (2023) 136, jcs260638. doi:10.1242/jcs.260638

Box 1. Pathophysiology of neurodegenerative diseases

Parkinson's disease

Signs and symptoms: progressive bradykinesia, resting tremor and rigidity (de Lau and Breteler, 2006). Neuropathological symptoms: loss of dopaminergic neurons in the substantia nigra and accumulation of α-synuclein aggregates, which are the major components of Lewy bodies (inclusion bodies) (de Lau and Breteler, 2006).

Alzheimer's disease

Signs and symptoms: memory and cognitive decline (Gatz et al., 2006). Neuropathological symptoms: accumulation of Aβ aggregates in extracellular senile plaques and hyperphosphorylation of Tau, forming intracellular neurofibrillary tangles (De Strooper and Karran, 2016).

Huntington's disease

Signs and symptoms: an autosomal dominant inherited disorder characterized by emotional, motor and cognitive disturbances caused by a mutation in the protein huntingtin (HTT) (Harper, 1991; Mangiarini et al., 1996). Neuropathological symptoms: demyelinating disease and axonal degeneration (Harper, 1991).

and receptor-mediated mitophagy in neurons and non-neuronal cells, highlighting recent discoveries that shed light on the molecular mechanisms underlying the effects of mitophagy on nervous system homeostasis. Moreover, we consider accumulating evidence that implicates impaired or dysregulated mitophagy in neuronal dysfunction and death linked to neurodegenerative diseases. Finally, we discuss open questions and consider forthcoming challenges in the field of neuronal mitophagy.

Mitophagy in nervous system homeostasis – unlocking the underlying mechanisms

Neurons are long-lived cells consisting of a soma (or cell body), an axon and dendrites. As polarized and compartmentalized cells, neurons face unique challenges in supplying energy to distant cellular regions, such as the highly energy-consuming synapses that form the basic unit of communication between neurons (Misgeld and Schwarz, 2017). It is not surprising, therefore, that a pool of healthy and motile mitochondria appropriately distributed according to local energy demands is required to promote neuronal survival and function. Accumulating evidence suggests that mitophagy is a homeostatic mechanism that helps each region of a neuron to maintain a proper mitochondrial population in order to fulfil specific energetic needs, thus contributing to structural and functional neuronal integrity under basal or stress conditions (Borbolis and Palikaras, 2022; McWilliams et al., 2018; Rappe and McWilliams, 2022). Along similar lines, emerging findings indicate that multiple mitophagy pathways may function in parallel to preserve a homeostatic metabolic environment at the neural level (Evans and Holzbaur, 2020).

Basal mitophagy in the brain

The development of genetically encoded fluorescent reporters for detecting mitophagy *in vivo* has provided insight into mitophagy regulation under physiological conditions. For example, mt-Keima is a mitochondrial-targeted fluorescent reporter that has been constructed by fusing Keima (a coral-derived protein characterized by pH-dependent excitation and lysosomal protease resistance) with the mitochondrial targeting sequence of the cytochrome *c* oxidase subunit VIII (COXVIII; Sun et al., 2015). A single copy of the mt-Keima fluorescent reporter has been inserted into the *Hipp11* locus on chromosome 11 to generate a mt-Keima reporter mouse, and integration of the transgene in this specific location has been shown to lead to consistent expression of the transgene in mice, without any adverse consequences (Tasic et al., 2011). Tissue analysis of mt-Keima mice – in which mitophagy can be assessed by overlaying the signal of green fluorescent structures, representing the tubular mitochondria, with red fluorescent round punctate structures that represent the lysosomes – has shown that basal mitophagy occurs in the brain (Sun et al., 2015). Interestingly, assessment of the ratio of red pixels to total pixels has revealed strong basal mitophagy signals in regions of the brain known to be enriched in neural stem cells, such as the dentate gyrus of the hippocampus and the lateral ventricle, whereas the cortex, striatum and substantia nigra display lower levels of mitophagy (Sun et al., 2015). These observations suggest that there is a variability in basal mitophagy levels in heterogenous tissues, such as the brain. Similarly, differential levels of basal mitophagy have also been detected in the vertebrate nervous system by using the *mito*-QC transgenic mouse model, which expresses a tandem mCherry–GFP tag fused to the mitochondrial targeting sequence of the outer mitochondrial membrane (OMM) protein FIS1 (McWilliams et al., 2016). *Mito*-QC mice display an increased number of mitolysosomes, namely lysosomes containing mitochondria (Montava-Garriga et al., 2020), in the somata of Purkinje neurons, suggesting that mitochondria are most likely transported to the cell body for degradation by various proteases (McWilliams et al., 2016). Taken together, these studies confirm that basal mitophagy occurs in neurons.

The PINK1–Parkin pathway

The most well-characterized pathway of neuronal mitophagy is mediated by PINK1 and Parkin (Fig. 1, top left and middle). Under normal conditions, the cytosolic kinase PINK1 enters the mitochondria through the translocase of the outer membrane (TOM) complex and the translocase of the inner membrane (TIM) complex (Jin et al., 2010). At first, PINK1 is cleaved by the mitochondrial processing peptidase (MMP) and the presenilin-associated rhomboid-like protease (PARL), and is finally completely degraded by an MG132-sensitive protease (Deas et al., 2011; Greene et al., 2012; Jin et al., 2010). However, upon mitochondrial depolarization, PINK1 is stabilized on the OMM and activated by autophosphorylation at Thr257, Ser228 and Ser402, leading to recruitment of the cytosolic E3 ubiquitin ligase Parkin and its activation by PINK1-mediated phosphorylation (Kondapalli et al., 2012; Matsuda et al., 2010; Okatsu et al., 2012). Thereafter, Parkin and PINK1 continuously ubiquitylates and phosphorylates, respectively, Ser65 of ubiquitin attached to various OMM proteins, such as mitofusins (MFN1 and MFN2), voltage-dependent anion-selective channel protein 1 (VDAC1) and the mitochondrial Rho GTPase Miro1 (also known as RHOT1) (Geisler et al., 2010; Narendra et al., 2010; Ziviani et al., 2010; Wang et al., 2011). The polyubiquitin chains that are phosphorylated on Ser65 are recognized by autophagy receptors, such as p62 (also known as SQSTM1), optineurin (OPTN), nuclear dot protein 52 (NDP52; also known as CALCOCO2, calcium-binding and coiled-coil domain-containing protein 2), Tax1-binding protein 1 (TAX1BP1) and neighbour of BRCA1 gene 1 (NBR1) (Dikic and Elazar, 2018; Johansen and Lamark, 2011, 2020; Lazarou et al., 2015; Mizushima and Komatsu, 2011).These autophagy receptors bind to the polyubiquitylated cargoes through their ubiquitin-binding domain to engage with proteins of the ATG8 family, such as microtubule-associated protein 1A/1B light chain 3 proteins (hereafter referred to collectively as LC3) (Abdollahzadeh et al., 2017), in the autophagosome membrane for transport and delivery to the lysosomes to be degraded by luminal hydrolases (Stolz et al., 2014; Svenning and Johansen, 2013).

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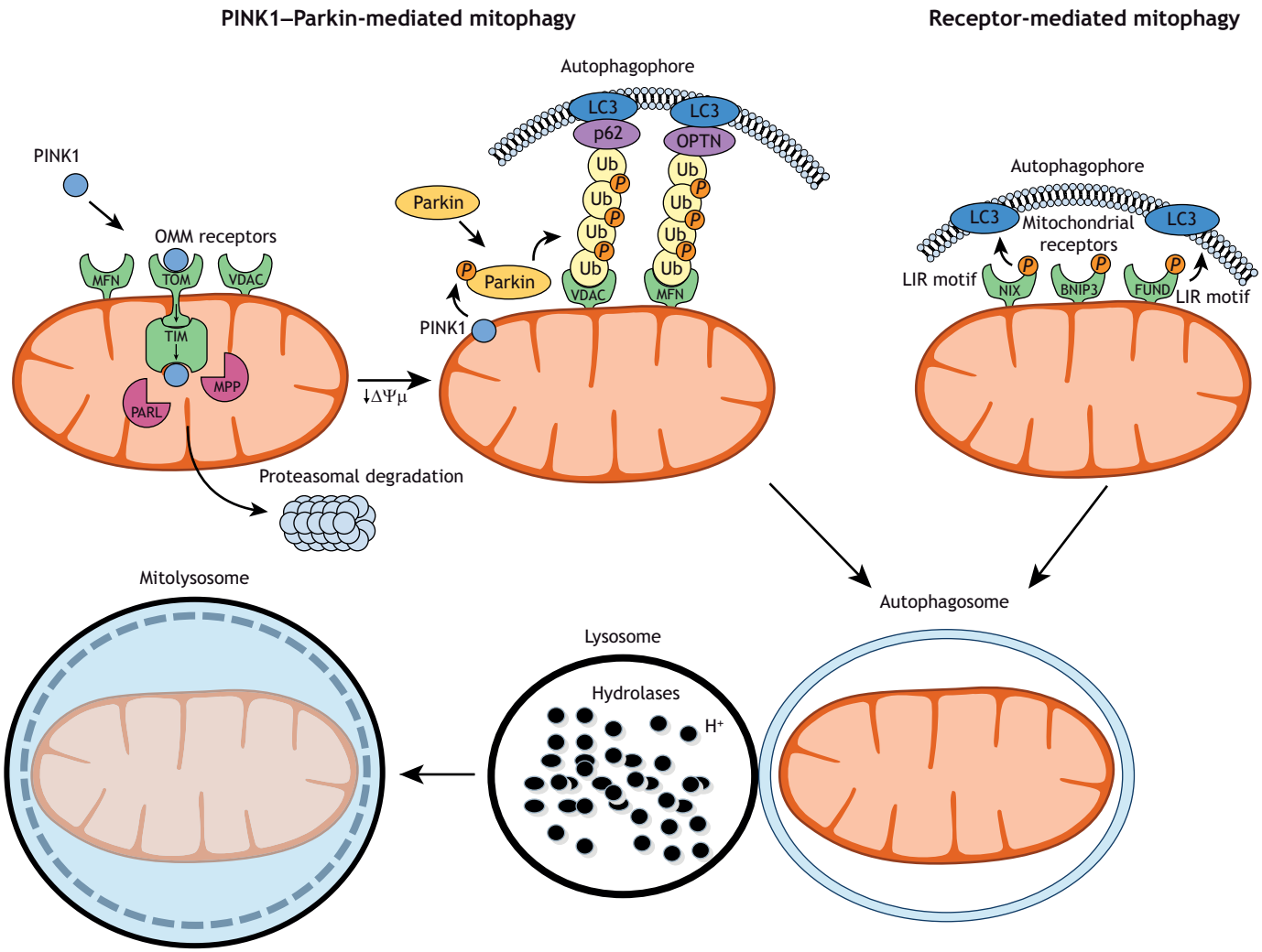

Fig. 1. Pathways of neuronal mitophagy. The PINK1–Parkin pathway mediates mitophagy of depolarized mitochondria. In healthy mitochondria (top left), PINK1 is continuously imported across the TOM and TIM complexes for enzymatic cleavage by MMP and PARL. Once cleaved, PINK1 is retro-translocated into the cytosol and is subsequently degraded by the proteasome. Upon mitochondrial depolarization (top middle; ↓Δψμ, decreased mitochondrial membrane potential), PINK1 is stabilized on the OMM and activated by autophosphorylation to recruit and phosphorylate the cytosolic E3 ubiquitin ligase Parkin, which then ubiquitylates OMM proteins such as mitofusins (MFN1 and MFN2) and VDAC1, and the resulting polyubiquitin chains are phosphorylated by PINK1. The phosphorylated polyubiquitin chains are recognized by adaptor proteins, such as p62 and OPTN, that bind both to ubiquitylated cargo and the autophagosomal membrane proteins LC3 and GABARAP, promoting autophagy. Mitophagy also occurs via the receptor-mediated pathway (top right), wherein OMM receptors, such as FUNDC1, BNIP3 and NIX, are activated by phosphorylation and are able to directly interact with LC3 or GABARAP through N-terminal LIR motifs. In both the PINK1–Parkin pathway and the receptor-mediated pathway, after engulfment of mitochondria by the autophagosomes, the resulting mitophagosomes fuse with lysosomes (to form mitolysosomes), which provide luminal hydrolases that degrade the mitochondria. FUND, FUNDC1; MFN, mitofusins; *P*, phosphorylation; Ub, ubiquitylation; VDAC, VDAC1.

Interestingly, PINK1 and Parkin have been found to interfere with mitochondrial motility in neurons (Wang et al., 2011). Indeed, PINK1 overexpression leads to phosphorylation of Miro1 and its subsequent proteosomal degradation in a Parkin-dependent manner, thereby arresting mitochondrial movement (Wang et al., 2011).

It is thought that the PINK1–Parkin pathway in neurons is activated only under stress conditions, as has been shown by many *in vivo* studies in both mice and *Drosophila* demonstrating that knockout (KO) of PINK1 or Parkin does not affect the basal levels of mitophagy (Devireddy et al., 2015; Lee et al., 2018; McWilliams et al., 2018; Sung et al., 2016). More specifically, a recent study has examined the contribution of PINK1 to basal mitophagy *in vivo* by using wild-type (WT) and PINK1 KO mice expressing the *mito*-QC transgene, revealing high levels of mitophagy in neural cells – including dopaminergic neurons and microglia – and, notably, showing that basal mitophagy proceeds independently of PINK1 in these cell types (McWilliams et al., 2018). In line with these findings, *Pink1* and *parkin* mutant flies expressing mt-Keima or *mito*-QC mitophagy reporters do not show substantial defects in mitophagy under physiological conditions, suggesting that PINK1 and Parkin are dispensable for basal mitophagy (Lee et al., 2018). Finally, a study in *Drosophila* motor neurons has demonstrated that *parkin* mutations result in the formation of an abnormal mitochondrial network in cell bodies (Sung et al., 2016). By contrast, mitochondria in the motor axons of *parkin* mutant flies display normal shape, movement and metabolic state, but are reduced in number compared to those in control flies (Sung et al., 2016). Notably, Parkin-dependent axonal mitophagy occurs in cultured neurons, whereas it is very rare *in vivo* under normal conditions (Sung et al., 2016). Therefore, the role of Parkin in

mediating mitochondrial quality control in the *Drosophila* nervous system *in vivo* is not obviously related to mitophagy. In fact, Parkin appears to modulate mitochondrial dynamics mainly in motor neuron cell bodies and, indirectly, the mitochondrial composition of motor axons (Sung et al., 2016). Therefore, the way in which mitochondrial quality control is distributed and works *in vivo* is significantly different from what is observed *in vitro*. Moreover, PINK1 and Parkin might have different roles in maintaining mitochondrial function in different compartments of neurons. Consistent with this notion, loss of PINK1 in *Drosophila* neurons reduces mitochondrial membrane potential and impairs both anterograde and retrograde axonal transport without affecting mitochondrial turnover or fission-fusion events in axons. (Devireddy et al., 2015). Moreover, loss of PINK1 affects mitochondrial morphology in the cell bodies of motor neurons, but not in motor axons *in vivo*, suggesting that PINK1 is crucial for the maintenance of a normal mitochondrial network in the somatic compartment (Devireddy et al., 2015).

Regulation of PINK1–Parkin-mediated mitophagy in neurons

PINK1–Parkin-mediated mitophagy has been extensively studied in HeLa cells (Gladkova et al., 2018; Narendra et al., 2008; Sauve et al., 2018) but is less well understood in neurons. Neuronal mitophagy is quite distinct compared to mitophagy in other tissues, not only with respect to the kinetics of Parkin, but also the topological regulation of the PINK1–Parkin pathway. In neurons, Parkin is gradually recruited to depolarized mitochondria almost 12 h after treatment with the mitochondrial uncoupler carbonyl cyanide chlorophenylhydrazone (CCCP), whereas CCCP treatment in HeLa cells leads to fast recruitment within 1–2 h (Cai et al., 2012). In contrast, treatment with antimycin A, a milder depolarizer than CCCP, results in a rapid accumulation of Parkin at the mitochondria (Ashrafi et al., 2014). These contradictory results may be attributed to the method of induction, suggesting that stimulation of stress-induced mitophagy leads to slow Parkin recruitment, whereas under mild stress, Parkin is rapidly recruited to depolarized mitochondria. The fact that the Parkin kinetics of PINK1–Parkin-mediated mitophagy in neurons can vary is also supported by a recent study (Li et al., 2021) in which Parkin has been shown to accumulate indirectly and quickly in the mitochondrial matrix following recruitment to the OMM of depolarized mitochondria, but also directly without proceeding through the OMM–Parkin step. Interestingly, this direct Parkin recruitment to the mitochondrial matrix occurs more slowly (∼14 h) and is observed in mitochondria that have a normal pH and subsequently become mildly acidified, but it is not seen in depolarized mitochondria. In this experimental approach, mitochondria could be tracked for up to 21 h by time-lapse imaging, more closely analysing the processes that occur under physiological conditions (Li et al., 2021).

Earlier studies of neuronal mitophagy have presented conflicting findings regarding the topology of mitophagy. PINK1 overexpression induces retrograde movement of depolarized mitochondria to the soma, whereas Parkin translocation or downregulation of either PINK1 or Parkin promotes anterograde mitochondrial motility (Cai et al., 2012; Devireddy et al., 2015; McWilliams et al., 2018). In addition, autophagosomes are formed in the axons but mature as they move retrogradely from the axon to the soma (Maday et al., 2012), while in non-neuronal cells, autophagosomes move bidirectionally (Jahreiss et al., 2008; Yang et al., 2008). Thus, the observed motility of both neuronal autophagosomes and mitochondria suggests that PINK1–Parkin-mediated autophagy of damaged or superfluous mitochondria is initiated in the axons and completed in the soma, where lysosomes are mainly located (Lee et al., 2018), probably to maintain a healthy mitochondrial network in the axons (Fig. 2) (Maday et al., 2012; McWilliams et al., 2018). However, other studies suggest that PINK1–Parkin mitophagy can also occur in the axons (Ashrafi et al., 2014; Harbauer et al., 2022; Zheng et al., 2019). According to these reports, it is more favourable for depolarized mitochondria to be eliminated at the site of injury, rather than moving retrogradely and releasing reactive oxygen species (ROS) throughout the neuron (Fig. 2). Recently, a novel mechanism for axonal mitophagy, which has been difficult to unravel due to the short half-life of PINK1, has been elucidated (Harbauer et al., 2022). Nuclear-encoded mitochondrial transcripts, including *PINK1* mRNA, have previously been found in axons, providing evidence for the occurrence of local translation of mitochondrial mRNAs (Shigeoka et al., 2016; Zivraj et al., 2010). A recent study has now demonstrated that the interaction between two OMM proteins, synaptojanin 2 (SYNJ2) and SYNJ2-binding protein (SYNJ2BP), permits the localization of *PINK1* mRNA transcripts to the mitochondrial surface by a tethering mechanism, facilitating transport to axons and dendrites (Harbauer et al., 2022). Thus, local translation of *PINK1* mRNA that is co-transported with neuronal mitochondria to the axons ensures a continuous supply of PINK1, sustaining mitophagy far from the soma (Fig. 2) (Harbauer et al., 2022). It is therefore plausible that different types of topological regulation exist in neuronal mitophagy, and how and where damaged or superfluous mitochondria will be removed actually depends not only on the type of mitophagy (basal or stress-induced), but also on the site and extent of damage.

The role of PINK1–Parkin-mediated mitophagy in non-neuronal cells

Mitophagy in the brain does not occur solely in neurons, it also occurs in glial cells, including astrocytes, oligodendrocytes and microglia. Interestingly, it has been suggested that the PINK1–Parkin pathway is activated mainly in glial cells, especially astrocytes, rather than in neurons, based on measurements of the immunofluorescence intensity of phosphorylated ubiquitin (pSer65-Ub) in different types of brain cells, both under basal conditions and after treatment with the mild depolarizer valinomycin (Barodia et al., 2019). In general, the importance of PINK1 in astrocytes was first highlighted when its deletion was found to disturb the differentiation of neural stem cells and glial fibrillary acidic protein (GFAP)-positive astrogliogenesis – the biogenesis of astrocytes that express GFAP, which is an intermediate filament protein necessary for neural support and strength (Choi et al., 2012, 2016). The fact that mitophagy is an essential process in astrocytes is not surprising, as their mitochondria are often localized in close proximity to neighbouring neuronal bodies and dendrites, and thus their turnover needs to be tightly regulated by quality control mechanisms to maintain a healthy mitochondrial network (Motori et al., 2013). Surprisingly, it has been shown that upon acute brain injury, mitophagy is the activating mechanism to balance alterations in mitochondrial dynamics, but under steady-state conditions, the level of PINK1–Parkin-mediated astrocytic mitophagy appears to be quite low (Motori et al., 2013; Sukhorukov et al., 2021). Interestingly, the mitochondrial deubiquitylase USP30 has been found to act as a negative regulator of the PINK1–Parkin pathway (Marcassa et al., 2018; Ordureau et al., 2020). This inhibitory role appears to be conserved across cell types, as pharmacological suppression of USP30 increases PINK1–Parkin-dependent mitophagy in both neurons and astrocytes (Niu et al., 2020; Tsefou et al., 2021). Overall, the PINK1–Parkin pathway might have a more crucial role in

Journal of Cell Science (2023) 136, jcs260638. doi:10.1242/jcs.260638

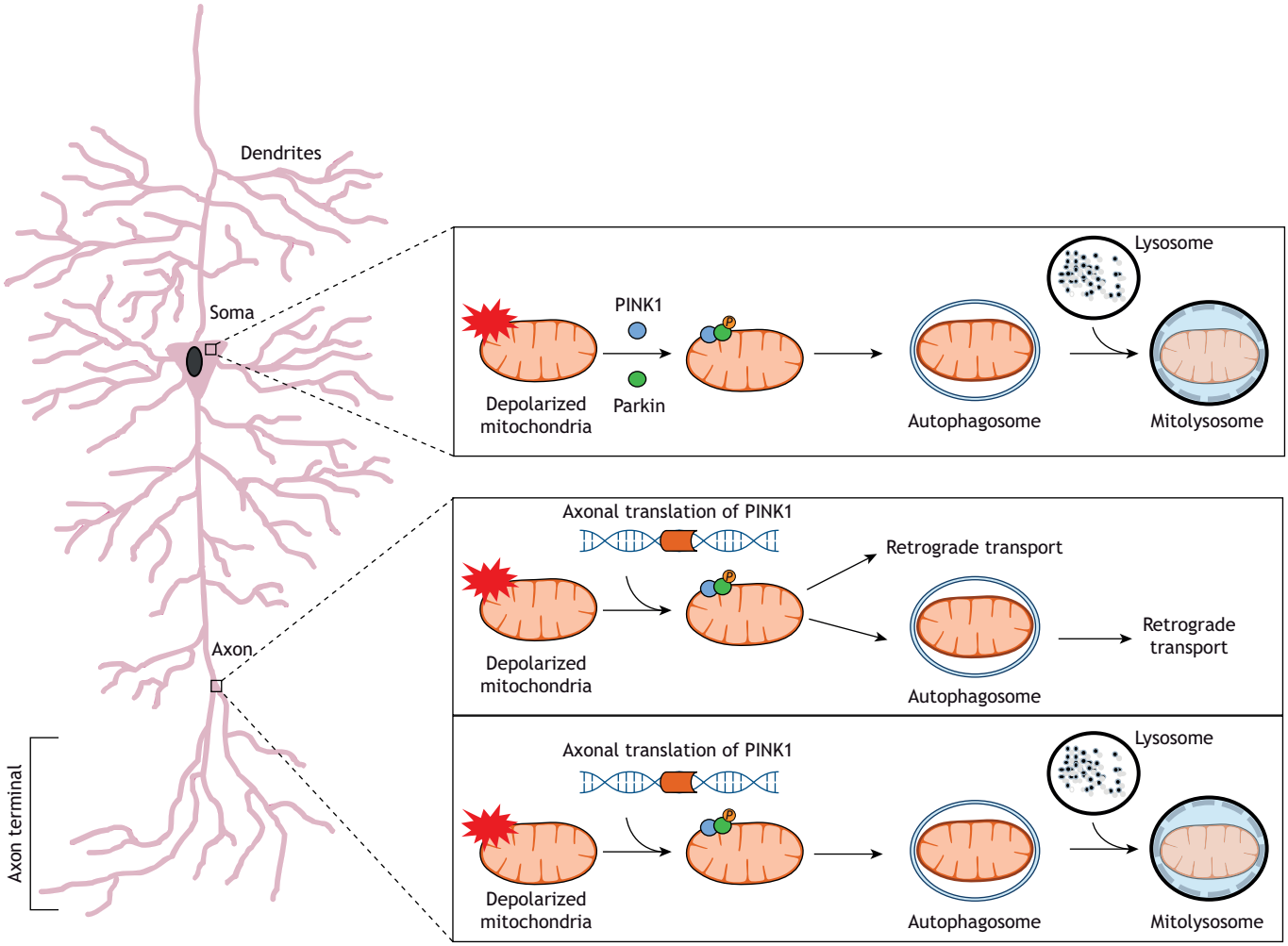

Fig. 2. PINK1–Parkin-mediated mitophagy in neuronal physiology. PINK1–Parkin-mediated mitophagy can occur in both the soma and axons of neurons. In the soma (top), PINK1, which is located on the surface of superfluous or damaged mitochondria, recruits Parkin as an 'eat-me' signal for autophagosome formation. Engulfed mitochondria are then fused with lysosomes in the soma for degradation. *PINK1* mRNA is also present in axons, and thus PINK1 can be locally translated for stabilization on the OMM and subsequent Parkin recruitment. Thereafter, mitochondria are transported retrogradely to the soma for degradation by lysosomes, either by being engulfed by autophagosomes or by fusing with mature autophagosomes along the way (middle). There is also the possibility that mitophagy initiates and concludes in the axons (bottom), because transport of depolarized mitochondria to the soma might spread damage as a result of increased ROS production. *P*, phosphorylation.

astrocytes, as compared with its role in neurons, in which PINK1 and Parkin are sometimes dispensable.

The receptor-mediated pathway

Another pathway that is mainly responsible for basal mitophagy is receptor mediated and acts independently of Parkin (Fig. 1, top right). This pathway involves the direct interaction of mitochondrial receptors that contain a so-called LC3-interacting region (LIR) motif with LC3 or gamma-aminobutyric acid receptor-associated protein (GABARAP) (Ganley and Simonsen, 2022; Lazarou et al., 2015; Palikaras et al., 2018). Some examples of these mitophagy receptors include FUN14 domain-containing protein 1 (FUNDC1) (Liu et al., 2012a) and homologous members of the BCL2/adenovirus E1B 19 kDa protein-interacting protein (BNIP) family, such as BNIP3 and Nip3-like protein X (NIX, also known as BNIP3L) (Novak et al., 2010; Schwarten et al., 2009). These receptors are constitutively localized on the OMM and recruit autophagic components for autophagosome formation and subsequent lysosomal degradation of damaged mitochondria. Recently, novel receptors, such as cyclin G-associated kinase (GAK) and protein kinase C delta (PRKCD), have been identified as positive regulators of Parkin-independent mitophagy *in vivo*, since inhibition of GAK and PRKCD homologues in *C. elegans* and zebrafish, respectively, reduces the basal levels of mitophagy (Munson et al., 2021).

The role of receptor-mediated mitophagy in neurons

Receptor-mediated mitophagy usually involves one of the aforementioned OMM receptors. FUNDC1 is normally phosphorylated by Src kinase at Tyr18 in its LIR motif, which maintains it in a dormant state, but upon dephosphorylation, FUNDC1 colocalizes with and binds to LC3 to activate neuronal mitophagy (Cai et al., 2021). FUNDC1 and NIX-mediated mitophagy in neurons is reported to be induced only after ischaemia–reperfusion injury, a type of brain injury caused by blood flow interruption followed by reperfusion, probably as a compensatory effect to reduce the levels of ROS and protect the neurons (Cai et al., 2021; Yuan et al., 2017). NIX-mediated

mitophagy is also affected by consistent treatment of neurons with glucocorticoids, a type of stress hormone that in the long-term can have negative effects on the hippocampus, such as synaptic dysfunction due to excessive glutamate release (Choi et al., 2021). Interestingly, restoring NIX-mediated mitophagy, but not PINK1–Parkin-mediated mitophagy, has a neuronal protective effect against this stress both *in vitro* and *in vivo*, promoting retrograde transport of depolarized mitochondria for elimination (Choi et al., 2021). Finally, a recent study in *Drosophila* has shown that neuronal overexpression of BNIP3 can induce mitophagy and protect against accumulation of dysfunctional mitochondria in the aged brain (Schmid et al., 2022), ultimately extending healthspan and lifespan. These findings highlight the critical role BNIP3 in modulation of age-associated processes.

The role of receptor-mediated mitophagy in non-neuronal cells

BNIP3-mediated mitophagy is a key regulator of cell differentiation (Aerbajinai et al., 2003; Esteban-Martinez and Boya, 2018; Lampert et al., 2019). Recently, it has been shown that BNIP3-mediated mitophagy is also required for the differentiation of oligodendrocytes in the optic nerve (Yazdankhah et al., 2021). During this differentiation process, both the autophagic flux and mitochondrial fission, which precedes mitophagy, are upregulated, resulting in altered mitochondrial morphology, with mitochondria transitioning from tubular form to a more fragmented shape (Yazdankhah et al., 2021). In addition, BNIP3 is required for the regulation of astrocytic proliferation, as its deletion leads to increased cell proliferation and DNA synthesis compared to that of WT cells. By contrast, BNIP3 overexpression promotes mitophagy and reduces cell growth (Singh et al., 2018). Apart from astrocytes, receptor-mediated mitophagy in other types of glial cells under basal conditions has not been thoroughly investigated. Instead, many studies have explored this type of mitophagy only in the context of neurodegeneration and have reported that downregulation of mitophagy in astrocytes is associated with enhanced neurodegeneration, as has been described in other recent reviews (Sukhorukov et al., 2021; Swerdlow and Wilkins, 2020).

Mitophagy and age-related neurodegeneration

Alterations in mitophagy are associated with ageing and age-related diseases. As studies in *Drosophila* have shown, basal mitophagy increases during ageing, and this increase is abolished in dopaminergic neurons of PINK1- and Parkin-deficient flies (Cornelissen et al., 2018a,b). In addition, defective mitophagy is emerging as a common pathogenic mechanism that is implicated in severe neurodegenerative disorders (Jetto et al., 2022). Here, we will discuss the mechanisms that lead to defects in mitophagy in three common neurodegenerative diseases, namely PD, AD and HD (Box 1).

Mechanisms that lead to impaired mitophagy in PD

Despite the knowledge gained in recent years, the mechanisms underlying PD pathogenesis remain poorly understood. Nevertheless, genetic and epidemiological studies have demonstrated that PD pathology is associated with mitochondrial dysfunction (de Lau and Breteler, 2006). Mutations in the *PINK1* and *Parkin* genes that compromise PINK1–Parkin-mediated mitophagy and lead to accumulation of damaged mitochondria are also causatively linked to familial PD (Geisler et al., 2010). PINK1 KO rat models exhibit progressive dopaminergic neuron loss and significant motor deficits, which are pathophysiological features of PD (Dave et al., 2014). However, using Parkin KO mice as a model to study PD has proven more complicated (Dave et al., 2014; Goldberg et al., 2003; Perez and Palmiter, 2005). Interestingly, Parkin KO mice are viable, have normal brain morphology and do not display pathological characteristics of PD, such as dopaminergic neuron loss, motor deficits and behavioural abnormalities, implying that additional mitophagy pathways contribute to neuronal survival (Dave et al., 2014; Perez and Palmiter, 2005). In one study, Parkin KO mice were found to display behavioural deficits reminiscent of the phenotypes observed in animals with an impaired nigrostriatal pathway and increased extracellular release of dopamine, suggesting that Parkin is crucial for dopamine regulation and nigrostriatal function, but it is not essential for the survival of dopaminergic neurons (Goldberg et al., 2003). Another recent study has shown that Parkin KO mice display dopaminergic neuron loss when crossed with POLG mutator mice that are deficient in DNA polymerase γ – the polymerase responsible for replication and repair of mitochondrial DNA (mtDNA) (Copeland, 2010; Pickrell et al., 2015). These mice lack mtDNA proofreading function and exhibit progressive accumulation of mtDNA mutations, resulting in mitochondrial dysfunction and premature ageing phenotypes (Kujoth et al., 2005; Trifunovic et al., 2004). Taken together, these findings suggest that endogenous Parkin protects dopaminergic neurons from mitochondrial stress (Pickrell et al., 2015).

Apart from PINK1 and Parkin, other proteins that are implicated in PD have recently been shown to affect mitophagy when mutated. For example, mutations in leucine-rich repeat kinase 2 (LRRK2) are responsible for the most common hereditary forms of PD (Steger et al., 2016). Such mutations generally increase the activity of the protein (Di Maio et al., 2018; Gilks et al., 2005); however, the mechanisms that link LRRK2 overactivation with PD remain poorly understood (Singh and Ganley, 2021). The direct effect of LRRK2 on mitophagy impairment has been confirmed by many studies investigating the most common pathogenic LRRK2 mutation, glycine-to-serine substitution at amino acid 2019 (G2019S) (Bonello et al., 2019; Singh and Ganley, 2021; Wauters et al., 2020). G2019S mutant mice display significantly lower levels of basal mitophagy, but not of autophagy, in both neurons and microglia, and pharmacological inhibition of LRRK2 kinase activity increases mitophagy through a canonical autophagy pathway and independently of PINK1 and Parkin (Singh et al., 2021). In line with these findings, experiments in cell lines and primary fibroblasts from PD patients carrying the G2019S mutation have revealed that LRRK2 downregulates mitophagy but not autophagy (Bonello et al., 2019; Wauters et al., 2020). In fact, LRRK2 kinase hyperactivity disrupts the interactions of Parkin and the fission-promoting GTPase dynamin-related protein 1 (DRP1, also known as DNM1L) with other OMM proteins during PINK1–Parkin-mediated mitophagy (Fig. 3) (Bonello et al., 2019). Another study has shown that the pathogenic LRRK2 G2019S mutation impairs mitophagy by delaying degradation of Miro1 and the subsequent arrest of damaged mitochondria (Hsieh et al., 2016). Moreover, mitophagy has been found to be disturbed by *LRRK2* mutations due to unsuccessful recruitment of the autophagy receptor OPTN to depolarized mitochondria (Wauters et al., 2020). Specifically, enhanced LRRK2 kinase activity causes hyperphosphorylation of several GTPase family members, including Ras-related protein RAB10, which interacts with OPTN for efficient recruitment to mitochondria in WT cells (Fig. 3) (Wauters et al., 2020). In this case, impairment of the RAB10–OPTN interaction is responsible for the pathogenic effects of *LRRK2* mutation. Mutations in the F-box domain-containing

Journal of Cell Science (2023) 136, jcs260638. doi:10.1242/jcs.260638

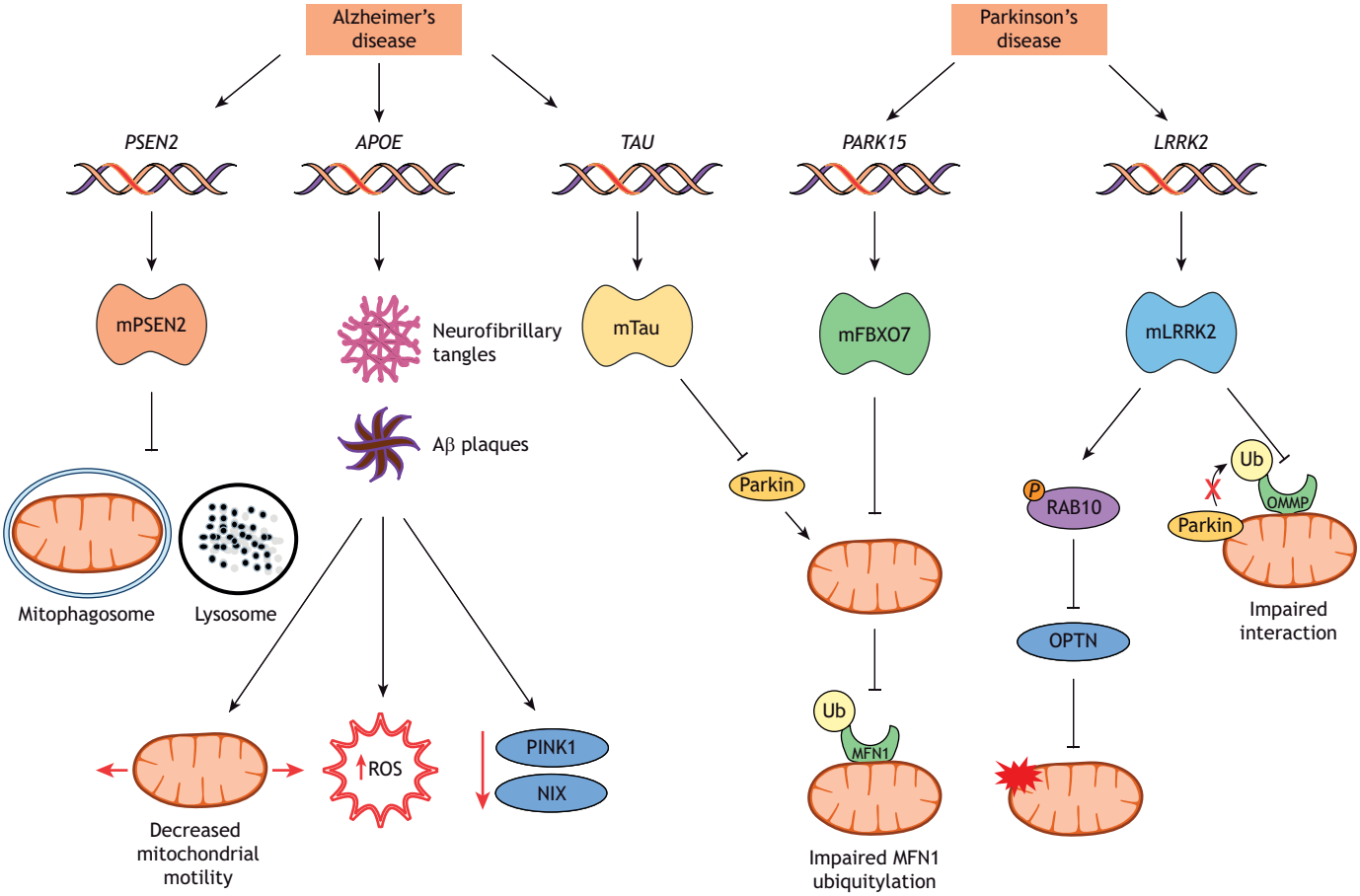

Fig. 3. Mechanisms that lead to impaired mitophagy in AD and PD. Examples of mutations associated with AD affect the *APOE*, *PSEN2* and *TAU* genes. Mutations in *PSEN2* block the fusion of autophagosomes with lysosomes, leading to accumulation of autophagosomes. Mutations in *APOE* are associated with formation of neurofibrillary tangles and Aβ plaques, which disrupt mitophagy by affecting mitochondrial motility, increasing production of ROS and downregulating mitophagy-associated proteins such as NIX and PINK1. Mutated Tau can also inhibit mitophagy directly by blocking Parkin recruitment to depolarized mitochondria. Some examples of mutations associated with PD affect the *LRRK2* and *PARK15* genes. Mutations in the *PARK15* gene encoding the FBXO7 protein restrain the recruitment of Parkin during mitophagy and, thus, the ubiquitylation of the OMM protein MFN1. Finally, mutant LRRK2 can interrupt mitophagy by impairing the interaction of Parkin with OMM proteins or by preventing OPTN recruitment to depolarized mitochondria through hyperphosphorylation of the GTPase RAB10. mFBXO7, mutated FBXO7; mLRRK2, mutated LRRK2; mPSEN2, mutated PSEN2; mTau, mutated Tau; OMMP, OMM protein; *P*, phosphorylation; Ub, ubiquitylation.

protein FBXO7 (encoded by the *PARK15* gene) that cause early onset autosomal recessive PD have also been linked to defective mitophagy (Burchell et al., 2013). FBXO7 has been shown to be required for recruitment of Parkin to damaged mitochondria, ubiquitylation of MFN1, and mitophagy, further supporting the contribution of impaired mitochondrial turnover to PD pathogenesis (Fig. 3) (Burchell et al., 2013). In *Drosophila*, overexpression of human FBXO7 rescues *parkin* mutant phenotypes, such as locomotor defects, dopaminergic neuron loss, muscle degeneration and mitochondrial disruption, indicating that the two proteins function in a common pathway *in vivo* (Burchell et al., 2013). Moreover, α-synuclein aggregates, one of the histopathological hallmarks of PD, have toxic effects on mitochondrial function, but α-synuclein also affects mitophagy directly by binding to the acidic phospholipid cardiolipin in the inner mitochondrial membrane (Rocha et al., 2018). In addition, α-synuclein has been shown to upregulate the protein levels of Miro1, which is important for the PINK1–Parkin pathway, as it acts as a ubiquitylation substrate for Parkin, promoting its stabilization on depolarized mitochondria (Liu et al., 2012b; Shaltouki et al., 2018). Consistent with this, partial reduction of Miro1 protein levels has been found to ameliorate mitophagy defects and neurodegeneration in human neurons and flies, pointing to Miro1 as a promising therapeutic target in PD (Shaltouki et al., 2018).

Mechanisms that lead to impaired mitophagy in AD

Accumulating evidence suggests that mitochondrial dysfunction and defective mitophagy are implicated in AD (Cai and Jeong, 2020; Kerr et al., 2017; Kingwell, 2019). The best-known pathogenic variants associated with AD affect the apolipoprotein E (*APOE*) gene, the amyloid-beta precursor protein (*APP*) gene, as well as the presenilin 1 (*PSEN1*) and presenilin 2 (*PSEN2*) genes, which encode the proteins that form the catalytic core of the γ-secretase complex (Mary et al., 2023). Over the past decade, high-throughput genomic approaches have culminated in the identification of more than 40 AD-associated genes and/or loci (Bellenguez et al., 2020). One such genome-wide association study of late onset AD has identified three rare coding variants in the phospholipase C γ2 (*PLCG2*), ABI gene family member 3 (*ABI3*) and triggering receptor expressed on myeloid cells 2 (*TREM2*) genes. Given that these genes are expressed in microglia, these findings indicate that aberrant microglial activation is not simply a

corollary of neurodegeneration, but rather has a causative role in AD etiology (Sims et al., 2017). Moreover, a recent study has shown that mitophagy in microglia is impaired in APP/PS1 AD mouse models, whereas pharmacological treatment with the mitophagy-inducing agents urolithin A and actinonin enhances the phagocytic activity of microglia and upregulates the pro-inflammatory cytokines interleukin-6 (IL-6) and tumour necrosis factor (TNF) (Fang et al., 2019). Microglial phagocytosis and increased neuroinflammation are probably a mechanism to clear the Aβ plaques, which are found in close proximity to microglia (Bamberger et al., 2003; Venegas et al., 2017). Thus, alterations in mitophagy, not only in neurons but also in microglia, are implicated in AD and might be targeted for therapeutic interventions.

The results of several studies in different model systems converge to indicate that basal mitophagy is downregulated in AD. For example, markedly reduced levels of mitophagy have been determined in induced pluripotent stem cell-derived human AD neurons and post-mortem hippocampal brain samples from AD patients, compared with those in samples from sex- and age-matched cognitive-normal subjects, by assessing levels of proteins related to mitophagy, such as PINK1, FUNDC1 and NIX (Fig. 3) (Fang et al., 2019). Furthermore, stimulation of mitophagy reverses memory deficits in both Aβ and Tau (also known as MAPT) *C. elegans* models of AD, and this memory improvement is mediated by PINK-1-, PDR-1 (Parkinson's disease-related-1; a Parkin orthologue)- or DCT-1 (DAF-16/FOXO controlled germline tumor affecting-1)-dependent pathways (Fang et al., 2019). Alterations in mitophagy are often associated with defects in the core autophagy machinery. Indeed, a study in PSEN2 KO mice has discovered defective clearance of autophagic vacuoles due to impaired autophagosome–lysosome fusion (Fig. 3) (Fedeli et al., 2019). Further supporting a causative relationship between mitophagy and AD pathology, a recent study has shown that overexpression of human WT or mutant Tau (P301L) causes its accumulation, which is a histopathological hallmark of AD. Accumulated Tau directly impairs Parkin recruitment to damaged mitochondria by trapping it in the cytosol, thus preventing initiation of mitophagy in both cell lines and *C. elegans* models of AD (Fig. 3) (Cummins et al., 2019). However, another study has shown that activation of PINK1–Parkin-mediated mitophagy causes mitochondrial deficits at synaptic terminals, a characteristic feature of early tauopathy (Jeong et al., 2022). In addition, Parkin activation accelerates Miro1 turnover and, in turn, reduces mitochondrial anterograde transport to synaptic terminals, eventually preventing mitochondrial supply at synapses in two different tauopathy mouse models expressing mutant forms (P301L and P301S; Santacruz et al., 2005; Yoshiyama et al., 2007) of human Tau (Jeong et al., 2022). Moreover, disrupted in schizophrenia-1 (DISC1), which is downregulated in AD, also influences mitophagy. In fact, DISC1 has been identified as a novel mitophagy receptor, as it can bind to and interact directly with LC3 through its LIR motif, mediating mitophagy (Wang et al., 2019b). DISC1 levels are reduced in the brains of AD patients, in transgenic model mice and in Aβ-treated cultured cells compared to controls, suggesting a link between DISC1 and Aβ accumulation. By contrast, DISC1 overexpression rescues synaptic loss, cognitive deficits and Aβ accumulation in a transgenic mouse model of AD by promoting mitophagy (Wang et al., 2019b).

Mechanisms that lead to impaired mitophagy in HD

Compelling evidence also implicates mitochondrial impairment and defective mitophagy in the pathogenesis of HD. HD is the most common among a number of neurodegenerative diseases that are caused by cytosine–adenine–guanine (CAG) repeat expansion (also known as polyglutamine repeat expansion; Orr, 2001). In HD, a pathogenic mutation produces an expanded polyglutamine tract at the N terminus of the protein HTT. Compromised autophagy is one of the mechanisms that has been proposed to contribute to HD pathogenesis. In fact, experimental data from cellular and mouse models of HD, and lymphoblasts from patients with HD suggest that the autophagosomes formed are unable to recognize cytosolic cargo and cytoplasmic organelles, such as lipid droplets and mitochondria (Martinez-Vicente et al., 2010). Thus, insufficient cargo sequestration and engulfment by autophagosomes, due to interaction of mutant HTT (mHTT) with the autophagic adaptor and substrate p62 (Komatsu et al., 2007), appears to be responsible for the increased levels of protein aggregates, lipid stores and damaged mitochondria in HD (Martinez-Vicente et al., 2010). More recent work has shown that mice expressing mt-Keima along with a mutant human *HTT* gene display reduced levels of mitophagy in the dentate gyrus region compared to those in control animals (Sun et al., 2015). This is in line with the finding that mitophagy is impaired in HD striatal cells derived from HD mice and *Drosophila* with neuronal expression of mHTT, resulting in accumulation of abnormal spheroid mitochondria (Khalil et al., 2015). Specifically, it has been shown that mHTT does not affect recruitment of Parkin or its activity but does affect the interaction of depolarized mitochondria with LC3 for formation of autophagosomes (Khalil et al., 2015). PINK1 overexpression partially restores mitophagy in these cells, ameliorates mitochondrial defects and rescues HD neuronal pathology in HD flies (Khalil et al., 2015). Finally, a recent study investigating the mechanism by which mHTT impairs mitophagy has revealed that mHTT interferes with mitophagy during its initiation, by disturbing interactions between the OPTN, NDP52, p62 and NBR1 receptors and LC3 (Franco-Iborra et al., 2021).

Concluding remarks

The significance of the nervous system in maintaining whole-body homeostasis is increasingly being appreciated. As post-mitotic, long-lived cells with unique architecture, neurons have pronounced bioenergetic needs throughout life and rely heavily on mitochondria to support local energy demands, such as within the distal axon or at synapses.

Maintenance of a healthy mitochondrial pool necessitates tight control over the number and function of these organelles. Toward this end, cells have evolved multiple mitochondrial quality control mechanisms, including mitophagy, to meet their metabolic needs under different physiological conditions and in response to stress. The studies discussed herein focus on the crucial role of mitophagy in maintaining nervous system homeostasis, and consistent with this, defective mitophagy has been implicated in ageing and various pathologies, including neurodegenerative diseases. However, excessive mitophagy may also be detrimental, leading to neuronal dysfunction and necrotic cell death.

Although significant progress has been made in recent years towards delineating the molecular mechanisms that regulate basal mitophagy *in vivo*, multiple aspects of this process remain elusive (Box 2). A better understanding of the dynamics and molecular mechanisms that modulate mitophagy under diverse conditions is critical for the assessment of the therapeutic potential of interventions targeting mitophagy in neurodegenerative diseases. Studies in simple model organisms, where mitophagy pathways can be genetically manipulated, are expected to provide significant

Box 2. Open questions

Basal mitophagy has been suggested to occur rarely in axons and to be largely independent of PINK1 (McWilliams et al., 2018). However, several important open questions remain. Which mitophagy pathways are crucial for promoting mitochondrial integrity and function in neurons under physiological conditions, and how do they interact? What are their relative contributions to neuronal homeostasis in different physiological contexts?

Along similar lines, the roles of non-neuronal cells, such as microglia and astrocytes, in nervous system homeostasis are steadily emerging. How is basal mitophagy regulated in these cells?

Emerging evidence suggests that transcellular mitophagy – namely, the exocytosis and subsequent glial cell-mediated phagocytosis of damaged mitochondria released by neurons – is crucial for nervous system homeostasis. What are the mechanisms responsible for this type of mitophagy?

insights into these issues. Moreover, development of new genetically encoded reporters for monitoring neuronal mitophagy *in vivo*, combined with state-of-the-art optical imaging technologies, will also be valuable. Such insights could contribute towards converting biological knowledge into practical applications. For example, new candidate targets can serve as molecular biomarkers for neurodegenerative diseases, to help early diagnosis. Furthermore, key identified molecular targets are expected to facilitate the design of intervention strategies against disease pathologies, to improve human health and quality of life.

Acknowledgements

We apologize to those colleagues whose work could not be referenced owing to space limitations.

Competing interests

The authors declare no competing or financial interests.

Funding

Work in the authors' laboratory is funded by grants from the European Research Council (ERC–GA695190–MANNA), the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the '1st Call for H.F.R.I. Research Projects to support Faculty members and Researchers and the procurement of high-cost research equipment' (project number HFRI–FM17C3–0869, NeuroMitophagy), and the General Secretariat for Research and Innovation of the Greek Ministry of Development and Investments. D.T. is supported by HealthAge (Horizon 2020 Joint Training and Research Program on Lifespan Regulation Mechanisms in Health and Disease, GA812830).

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