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REVIEW

A central role for PINK1 in governing local mitochondrial biogenesis and degradation in neurons

Marlena Helms[1,2] · Angelika B. Harbauer[2,3,4]

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Abstract
Neurons have adapted the transport and positioning of mitochondria to fit their extended shape and high energy needs. To sustain mitochondrial function, neurons developed systems that allow local biogenesis and adaption to locally regulate mitochondrial form and function. Likewise, fine-tuned degradative systems are required to protect the neurons from mitochondrial dysfunction. Throughout both domains of mitostasis, the local synthesis of the mitochondrial damage-induced kinase PINK1 emerges as a central player. Along with other nuclear encoded mitochondrial proteins, its mRNA associates with mitochondria to sustain mitochondrial function locally. It also regulates mitochondrial degradation, via regulation of proteases, the generation of mitochondria-derived vesicles and mitophagy. In this review, we provide a general overview of the mechanisms governing mitochondrial health in neurons, with a special focus on the role of PINK1 in this endeavor.

Keywords Mitophagy · mRNA transport · Local translation · Mitochondrial proteases

Mitochondrial dynamics in neurons

Mitochondria arose from an ancestral bacterium that was retained after engulfment by the precursor of eukaryotic cells, creating an endosymbiotic relationship that enabled the development of metazoans [1]. Reminiscent of their evolutionary origin, mitochondria resemble rod-like bacteria, especially in the axon of neurons where they mostly occur as solitary, roughly 1 µm long organelles [2]. In dendrites however, they can display a more elongated, fused morphology. Interestingly, even though mitochondrial density is high in dendrites, they form stable compartments that are isolated from each other as seen by the spread of a photoconvertible matrix protein [3]. Finally, in the soma of neurons, mitochondria form a reticular network [4]. How the different shapes of mitochondria in the neuronal sub-compartments are created or maintained is still incompletely understood.

Mitochondrial fission is regulated by recruitment of the cytosolic GTPase dynamin-related protein 1 (DRP1) to the mitochondrial outer membrane by various adaptor proteins, including mitochondrial fission factor (MFF) [5]. Fusion on the other hand relies on the two GTPases optic atrophy 1 (OPA1) in the inner mitochondrial membrane (IMM, [6]) and Mitofusin1/2 (MFN1/2) in the outer mitochondrial membrane (OMM, [7]). Unsurprisingly, depletion of MFF increases mitochondrial length, which is especially evident in axonal mitochondria, yet does not alter the mitochondrial mass within axons [8]. This suggests that the transport of mitochondria and their distribution throughout the axon follows some still undetermined rules that ensure proper occupancy. One study suggests that spacing of axonal mitochondria is determined by the local ATP supply, as removal of one mitochondrion by light-triggered activation of the phototoxic protein KillerRed targeted to mitochondria (mitoKillerRed) elicited a decrease in motility of nearby mitochondria, essentially enhancing their arrest at the site of depletion [9]. This aligns with the observation that mitochondria are stationed at sites of high energy demand, including the presynapse, nodes of Ranvier or

✉ Angelika B. Harbauer
angelika.harbauer@bi.mpg.de

1 TUM Graduate Center for Medicine and Health, Technical University of Munich, Munich, Germany

2 Max Planck Institute for Biological Intelligence, Martinsried, Germany

3 School of Medicine and Health, Institute of Neuronal Cell Biology, Technical University of Munich, Munich, Germany

4 Munich Cluster for Systems Neurology, Munich, Germany

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axonal growth cones [10–12]. However, while neurons rely mostly on mitochondrially-derived ATP as a whole [13], not all synapses contain resident mitochondria, and glycolysis or diffusion may be sufficient to provide ATP at these sites [14, 15]. Nevertheless, mitochondria also fundamentally alter the synaptic release probability due to their Ca^{2+} buffering activity [16, 17]. However, the factors that promote mitochondrial arrest at some synapses but not others remain elusive.

Mitochondrial positioning has also been linked to the extension of axon branches [18], which is also negatively affected by MFF knockdown [8]. This may be due to the role that mitochondrially-derived ATP plays in supporting local translation in both axons and dendrites [3, 19], as local translation of cytoskeletal elements may be necessary for branch formation as well as for spine outgrowth. Vice versa, formation of actin cages around mitochondria serves to arrest mitochondria after their long-range transport on microtubules. Pharmacological depolymerization of Actin destabilizes the dendritic mitochondrial compartments [3] and mobilizes previously stationary mitochondria in the axon [20]. In addition, several mechanisms exist that regulate transport and arrest of mitochondrial transport along microtubules (reviewed by Pekkurnaz & Wang [21]). These often target the mitochondrial motor adaptor complex, consisting of the OMM protein RHOT1/2 (Miro1/2) and TRAK1/2 (Milton) [22–24], which connect mitochondria to kinesin and dynein, or the anchoring protein Syntaphilin [25], (Fig. 1A). Mitochondria move at a speed of approx. 0.5 µm/s in neurons with frequent pauses, and at any given time only a small fraction of mitochondria is observed in motion [26]. Their motility as well as their shape changes during development and aging, with motility decreasing as more and more mitochondria reach their final destination. As protein synthesis in neurons occurs primarily in the somato-dendritic area [27], this might lead to an aging population of mitochondria in distal axons over time. Indeed, a gradient of younger to older mitochondria along neurites is observed by the use of a mitochondrially-targeted fluorescent protein whose maturation from a protein emitting green fluorescence to red fluorescence has been engineered to occur only after approximately 24 h (mitoTimer), allowing a ratiometric readout of its relative age [28]. This probe however does not replicate the intricate relationship some mRNAs encoding mitochondrial proteins have with their encoded protein's target organelle (see next chapter), and thus is not fully representative of the age of mitochondria.

Proper balance of mitochondrial dynamics is crucial for neuronal development and health. Following early differentiation, neurons undergo a switch in their metabolism from generating most of their energy via glycolysis in the beginning, to heavily relying on oxidative phosphorylation, and therefore mitochondria, for their energy production as mature neurons [13, 29, 30]. This metabolic switch is accompanied by changes in mitochondrial dynamics, involving both fusion and fission [31, 32], and also impacts neuronal size and complexity [33]. Neuron-specific knock outs of Drp1 in mice led to smaller forebrains, and primary cultures derived from these mice displayed less neurites, lower expression of synapse markers and disturbed mitochondrial distribution [32]. Loss of fusion on the other hand also impairs neuronal function. Purkinje cells in Mfn2-deficient mice decrease in size and display a decreased number of branches and spines. This was accompanied by a reduction in OXPHOS activity, in line with mitochondrial fusion being a prerequisite for maintenance of mtDNA [34]. Furthermore, mutations in Mfn2 have been linked to the Charcot-Marie-Tooth type 2A (CMT2A) disease [35, 36]. One study suggested that Mfn2 can interact with Miro and Milton, and that an impaired Mfn2 could thus result in impaired axonal mitochondrial transport, possibly contributing to axonal degeneration in CMT [37]. Mitochondrial dynamics thus set the stage for proper mitochondrial distribution and function in the nervous system.

Biogenesis of mitochondrial proteins in neurons is sustained by mitochondrial mRNA association

Mammalian mitochondria contain around 1500 proteins, of which more than 99% are encoded in the nucleus ([38–40]). In order to sort the nuclear encoded mitochondrial (NEM) proteins to the correct compartment after their synthesis on cytosolic ribosomes, specialized import pathways have evolved to accommodate the various topologies of proteins across the two mitochondrial membranes, the inter membrane space and the innermost matrix [41]. The translocase of the OMM (TOM complex) hereby serves as the main entry gate into the organelle and is equipped with receptors that recognize either a N-terminal amphipathic helix, the classical mitochondrial targeting sequence (MTS) recognized by Tom22/Tom20 [42], or internal sequences of mitochondrial protein precursors, that are guided by chaperones and recognized by Tom70 [43]. Chaperones are also crucial for mitochondrial protein import to prevent premature folding of mitochondrial precursors, as import needs to occur in an unfolded state to allow threading through the narrow tunnels of the translocases [44].

While most protein import into mitochondria can occur post-translationally, co-translational targeting has been observed, although it had been viewed as the exception, and can be enhanced by localizing translation close to the mitochondrial surface [45, 46]. Analysis of isolated

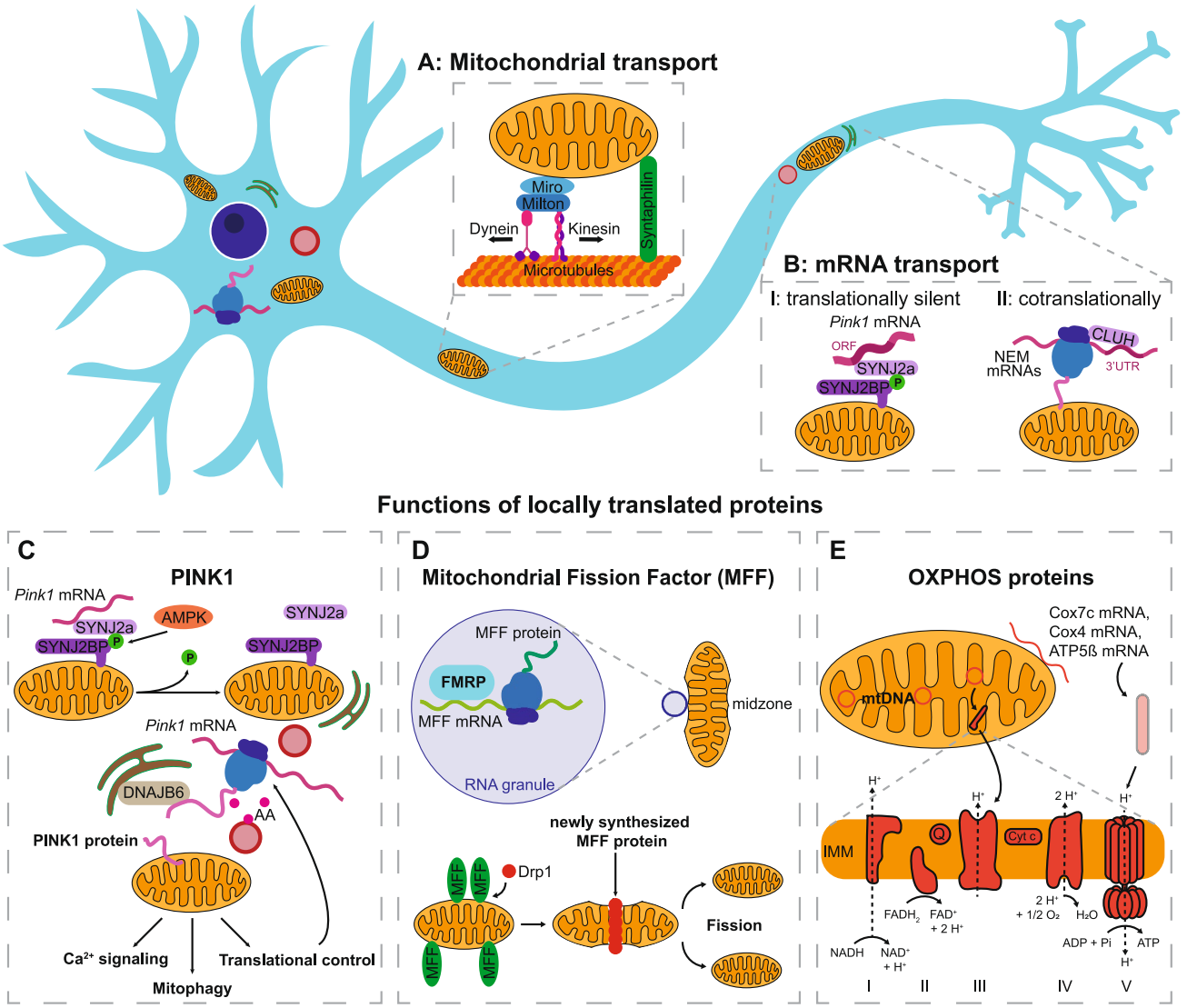

Fig. 1 Biogenesis of mitochondrial proteins. **A** Mitochondrial transport along microtubules is facilitated by kinesin (anterograde transport) or dynein (retrograde transport) binding to Milton and Miro on the outer mitochondrial membrane, whereas Syntaphilin serves as a mitochondrial anchor. **B** Nuclear-encoded mitochondrial (NEM) mRNA can be transported along with mitochondria either translationally silent (I) or co-translationally (II). I: *Pink1* mRNA, following an initial translation step, is bound by SYNJ2a within a region of its open reading frame, preventing complete translation until the *Pink1* mRNA is eventually untethered. II: CLUH is able to bind NEM mRNAs through their 3'UTR, facilitating interaction with ribosomal subunits and co-translational transport of the mRNAs followed by import of the newly synthesized proteins into mitochondria. **C** The short-lived PINK1 protein is locally translated, following hitchhiking of its mRNA along with mitochondria via a complex consisting of SYNJ2a and its binding protein SYNJ2BP, an interaction that is enabled via SYNJ2BP phosphorylation by AMPK. Following local translation near endolysosomes, the PINK1 precursor is guided by the ER resident chaperon DNAJB6 towards mitochondria (ER-SURF pathway). Functions of the PINK1 protein include calcium signaling, mitophagy, or translational control. **D** The mRNA for MFF, on the other hand, colocalizes to mitochondria in the presence of FMRP within RNA granules, which are enriched at the midzone of mitochondria. MFF recruits Drp1 to the midzone of mitochondria and is thereby able to initiate mitochondrial fission. **E** For OXPHOS complexes, proteins from two different sources must be united: some of them are encoded within the mtDNA, allowing for local transcription as well as local translation. Others like Cox7c, Cox4 and ATP5ß are encoded in the nucleus and require transport of their mRNA along with mitochondria which allows them to be translated locally

mitochondria and proximity biotinylation approaches have identified a great wealth of mRNAs associated with mitochondria in a translation- dependent manner in various settings, ranging from yeast and plants to Drosophila and cultured human cell lines [47–49]. It has been reasoned that in fast growing organisms such as yeast, the speed of import may have to exceed the speed of protein translation at the ribosome in order to double the mitochondrial mass within one cell cycle, making co-translational import evolutionary unfavorable [50]. This may however not be as critical in

slower dividing mammalian cells, and even less problematic in mature, postmitotic neurons. Indeed, two recent studies employed ribosome profiling on HEK293T cells and found that almost 20% of their identified mitochondrial proteins were co-translationally imported. Interestingly, the authors also observed that specifically proteins with a large size and complex topology relied on co-translational import [51, 52], with the interaction of the nascent chain with the import complexes likely being the driving force for the association of the mRNA. Interestingly, another observation included a second class of shorter proteins (under 200 amino acids) that were preferentially co-translationally imported which was due to their mRNAs being tethered to the OMM by interaction of the RNA-binding protein La ribonucleoprotein domain family member 4 (LARP4) with A-kinase anchoring protein 1 (AKAP1) on the mitochondrial surface [52, 53]. Such association of the mRNA enables the hitchhiking of the transcripts along with mitochondrial trafficking. In neurons this mode of mRNA transport coupled to local translation is emerging as a fundamental mechanism to allow local repair and adaption of mitochondria in the distal parts of a neuron.

Generally, mitochondrial mRNA association is enhanced by RNA-binding proteins that interact either with ribosomal subunits, or directly with NEM encoding mRNAs [46, 54]. One of these proteins is clustered mitochondria homolog (CLUH), whose role in the stability and mitochondrial targeting of NEM mRNAs is conserved from yeast to human neurons [47, 55–58]. CLUH not only binds to the 3'UTR of many NEM mRNAs, but it also interacts with factors that enhance the re-initiation of translation at the same mRNA [55] (Fig. 1B-II). Loss of CLUH in neurons depletes the axonal pool of NEM transcripts, yet without affecting the movement of the remaining RNA particles [55]. Two scenarios may explain this observation: (i) CLUH has been shown to affect the stability of its clients, thus the lower abundance in axons may simply be a consequence of the reduced half-life of NEM mRNAs. This matches data from global mRNA abundance measurements in cultured neurons, that find a relationship between the mRNA stability and the likelihood of its axonal localization [59]. (ii) As CLUH is necessary to localize ribosome recycling factors to the axon, it ensures the continued reassociation of the ribosomes to the same mRNA after completion of the first round of translation. This allows continued translation of the same NEM transcript and thus exposure of an MTS in close proximity to a potentially moving mitochondrion, and a continued interaction between the TOM complex and the MTS/ribosome/mRNA complex. In line with this idea, overexpression of the ribosome recycling factor ABCE1 rescues mRNA abundance and growth deficits in CLUH knockout motoneurons [55].

The mitochondrial hitch-hiking of mRNAs was experimentally shown to be the case for the *Pink1* mRNA [60], as well as for the *Cox7c* mRNA [61], using live cell imaging of mRNAs labelled by the MS2-tagging approach in cultured neurons. However, hitch-hiking of NEM encoding mRNAs is not restricted to mitochondria. In recent years, mRNAs which are important for mitochondrial functions have been shown to also depend on the transport of endosomes and endolysosomes for their axonal localization [62, 63]. Also other organelles, such as early endosomes, have been shown to associate with NEM encoding mRNAs [64]. Interestingly, several of these hitch-hiking events can be prevented by destabilization of the ribosome by treatment with Puromycin, suggesting that the nascent polypeptides may be involved in the targeting to the organelle. In the case of mitochondria, this can be mediated by an N-terminal MTS, as was shown both for *Pink1* and *Cox7c* [60, 61]. How the translation-dependent targeting would allow an association of NEM nascent proteins to organelles of the endolysosomal system remains to be determined, as the nascent chains of NEM proteins would not find suitable receptors on these types of membranes. In addition to organellar hitch-hiking, some NEM mRNAs without a classical MTS have been shown to be transported within an mRNA granule, containing the RNA binding protein SFPQ, and to be locally translated within the vicinity of mitochondria [65]. Likewise, RNA granules marked by the RNA binding protein FMRP colocalize with the mRNA for MFF [66], allowing its local translation.

Local translation is especially relevant for short-lived proteins like PINK1, as the time to travel to the distal parts of the neurons exceed its life-time [67–69]. Local translation of PINK1 therefore ensures its availability for the detection of dysfunctional mitochondrial also in distal parts of axons, as will be outlined in the mitophagy chapter. Fittingly, the association of the *Pink1* mRNA with mitochondria is not observed in fibroblasts unless its anchoring complex is overexpressed [60], as smaller ("shorter") cells may not need to add this additional layer of regulation. Unlike *Cox7c*, *Pink1* mRNA association is not only driven by translation. After an initial, translation and MTS-dependent targeting to the OMM, the *Pink1* mRNA becomes tethered to the OMM by binding to Synaptojanin 2a (SYNJ2a) and its binding protein SYNJ2BP [70, 71] (Fig. 1B-I). SYNJ2a acts as the RNA binding protein in this complex, and interestingly binds within the coding region of the PINK1 open reading frame [60]. This suggests that unlike most NEM transcripts, the *Pink1* mRNA may be transported in a translationally silent state and needs to be untethered from its mitochondrial association to allow access of the ribosome to the part of the ORF that is otherwise bound by SYNJ2a.

Local translation of mitochondrial proteins occurs at organellar contact sites

Organellar hitch-hiking not only plays an important role in the transport of mRNAs into the axon, but also may be responsible for the localization of ribosomes within the axon. Ribosomes in axons, while rare and mostly translating as monosomes [72], seem to preferentially associate with endomembranes, including the ER [73] or early endosomes via the FERRY complex [64]. Removal of the ER from axons by heterodimer-induced forced association of retrogradely moving motor proteins overall reduced axonal protein synthesis. A similar effect was observed for the knock down of p180/RRBP1, a ribosomal receptor on the ER [73]. Unlike the other ribosomal receptor on the ER, Sec61, RRBP1 is not directly associated with the ER translocon, which allows ER-associated protein synthesis to exist uncoupled from import of the nascent chain into or across the ER membrane [74]. This would allow the synthesis of not only secretory proteins targeted to the ER, but also ER-associated synthesis of cytosolic or even mitochondrial proteins. Whether the ER-associated ribosomes are actively transported into the axon along with ER tubule dynamics or whether they arrive in the axonal compartment by lateral diffusion or other means of transport has not been addressed experimentally. In contrast, association of ribosomes to early endosomes has been shown to depend on components of the FERRY complex [64]. This suggests that hitch-hiking on early endosome during their transport into the axon may provide an active localization mechanism for axonal ribosomes.

Fittingly, it was shown that local hotspots of translation form at contact sites between mitochondria and endolysosomes, including translation of the OMM protein VDAC2 [62]. This is also the case for the local translation of MFF [66], where ribosomes at these contact sites were also visualized by CryoET. In the case of PINK1, local translation at mitochondria endolysosome contact sites was not only observed in axons but also in the soma [75]. Interestingly, the translation of PINK1 at these sites is regulated by metabolic signaling as association of the *Pink1* mRNA to mitochondria depends on phosphorylation of SYNJ2BP by AMP-activated kinase (AMPK), which stabilizes the interaction between the RNA-binding protein SYNJ2a and the OMM protein SYNJ2BP [76]. Interestingly, this association limits the translation and subsequent functionality of PINK1. Inhibition of AMPK, as it occurs downstream of insulin signaling due to inhibitory phosphorylation of AMPK by AKT, leads to the dissociation of the *Pink1* mRNA and its subsequent localization near endolysosomes (Fig. 1C) [76]. However, as a mitochondrial protein, the newly synthesized PINK1 precursor needs to find its way back to mitochondria. Using correlative light and electron microscopy in combination with a PINK1 translation reporter, we now suggest that the gap between endolysosomes and mitochondria may be filled by the ER [75] (Fig. 1C). This enables the transport of the precursor of this transmembrane protein along the ER surface in order to reach mitochondria in association with ER-bound chaperones like DNAJB6 [75], as was shown for other mitochondrial transmembrane proteins in yeast [77]. This fits well with the above described role for ER-associated ribosomes in local protein synthesis.

On the other hand, the role of the endolysosomes in local PINK1 protein synthesis is less clear. While early endosomes may bring in the required ribosomes for PINK1 synthesis via the FERRY, the PINK1 protein translation sensor rather colocalized with markers of late endosomes or lysosomes [75]. Maturation of FERRY-positive endosomes into late endolysosomes may underlie this observation, but this hypothesis needs to be tested. Additionally, the lysosomal surface serves as a signaling hub for both mTORC1 and AMPK signaling, and thus formation of mitochondria lysosome contacts may elicit the untethering of the *Pink1* mRNA from SYNJ2BP on mitochondria. However, inhibition of mTORC1 does not prevent the untethering of the *Pink1* mRNA [76], indicating that while activation of mTORC1 may contribute to the increased biogenesis of PINK1 upon activation of insulin signaling due to its effect on general translation initiation factors, it is not necessary for the initial untethering event. Finally, lysosomes will produce a local supply of amino acids depending on their degradative capacity. While this has not yet been shown to matter for local translation in neurons, a preprint observes a similar effect of lysosomes on translation at three-way junctions of ER in cultured cell lines [78]. Thus, lysosomes may serve as amid acid reservoirs across cell types.

Functions of locally translated mitochondrial proteins

Mitophagy, Ca2+ homeostasis and translational control exerted by PINK1

The best-known function of PINK1 is the detection of damaged mitochondria and their demarcation for mitophagy, as will be described in the next chapter. Local translation of PINK1 therefore ensures the continued supply of this protein also to distal mitochondria in both axons and dendrites [60].

Beyond mitophagy, activation of PINK1 in response to mitochondrial damage has been described to repair rather

than remove damaged mitochondria. It was shown in Drosophila neurons as well as in HeLa cells that PINK1 overexpression, but not expression of a Parkinson's disease (PD)-linked mutant, leads to stimulation of localized translation of mRNAs encoding subunits of the respiratory chain [79]. This is achieved via phosphorylation and subsequent proteasomal degradation of translational repressors, including Pumilio and Glorund/hnRNP-F [79]. Thus, the local translation of PINK1 at endolysosome-mitochondria contact sites will lead to a de-repression of translation and favor the local translation of also other mitochondrially-associated transcripts in a positive feedback loop (Fig. 1C). However, in Drosophila oocytes, PINK1 activation also prevents the transmission of deleterious mtDNA mutations through the germline by limiting the local production of factors necessary for mtDNA replication [80]. To achieve this, PINK1 activation on dysfunctional mitochondria leads to the phosphorylation of the RNA binding protein Larp, which is bound to the OMM protein MDI and normally mediates the localized translation of NEM mRNAs at the OMM [80, 81]. This in turn dampens translation of mitochondrially-associated mRNAs [80]. Thus, PINK1 activation can have opposite effects on localized translation near the OMM depending on the model system used. In mammalian cells, the Larp homologue LARP4 also binds nuclear-encoded mitochondrial transcripts [82], as does the MDI homologue AKAP1 [53], yet whether PINK1 plays a more direct role in coordinating localized translation in mammalian neurons remains to be determined.

Another role of PINK1 includes effects on local Ca^{2+} uptake and release from mitochondria, either directly via phosphorylation of LETM1, a putative Ca^{2+}/H^{+} antiporter in the IMM [83], or indirectly via inhibition of PKA-mediated phosphorylation of mitochondrial Na^{+}/Ca^{2+} exchanger, NCLX [84]. Indeed, the major phenotype of PINK1 loss in neurons is not the accumulation of damaged mitochondria, but an increase in the cytoplasmic Ca^{2+} concentration that leads to cell death [85]. How local translation of PINK1 affects the ability of individual mitochondria to modulate the local Ca^{2+} flux will be an interesting field of study. Whether any of the other regulators of mitochondrial Ca^{2+} flux are locally translated has not been studied. However, given the idea that modulation of Ca^{2+} flux may be the main function of mitochondria in the axon, this would be a powerful way to further tune synaptic signaling through local protein translation.

Mitochondrial fission induced by FMRP mediates local translation of MFF

The RNA binding protein FMRP was recently shown to localize to sites of mitochondrial fission in neurons [66]. These fission events were characterized by their symmetrical nature, which is attributed to MFF-mediated recruitment of DRP1 [86]. Indeed, FMRP-granules colocalized with MFF mRNA and local translation of MFF could be observed at mitochondria-endolysosomal contact sites ([66], Fig. 1D), in agreement with the notion that these organellar contact sites serve as translational hotspots in neurons [62]. This may also explain the previous observation that endolysosomes mark fission events in neurons [87]. The presence of ribosomes at these contacts was corroborated by Cryo-electron microscopy, along with ER tubules marking the fission site [66]. This association of fission events with FMRP granules was not a frequent observation in non-neuronal cells, indicating that this mechanism may represent a unique adaption to the specific needs of neurons. In line with this, loss of FMRP leads to a reduction in MFF mRNA presence in axons, reduced association of the MFF transcript with mitochondria, and a reduction of mitochondrial fission in axons [66], suggesting that it impairs both the transport and the translation of the MFF transcript.

Local translation of OXPHOS components and the question of mtDNA-encoded subunits

On a more global scale, quantitative mass spectrometry and in vitro stimulation of isolated mouse synapses revealed that the synthesis of mitochondrial proteins is upregulated in response to NMDA administration [88]. Many of these newly synthesized proteins comigrated with complexes of the respiratory chain in Blue Native PAGE, suggesting that they are assembled into functional complexes [88]. This fits with the mitochondrial hitch-hiking of the mRNA encoding Cox7c as a subunit of complex IV of the respiratory chain [61]. Additionally, there is evidence that other mRNAs encoding further subunits of complex IV and V also co-localize with mitochondria in neurons [60, 76, 89, 90]. While it has not been directly shown, this suggests that also the ability to perform OXPHOS may be altered by local translation of mitochondrial OXPHOS components (Fig. 1E). In favor of this hypothesis, addition of a protein translation inhibitor to the axonal compartment of neurons, cultured in compartmentalized chambers, decreases the membrane potential across the inner mitochondria membrane [91], which is generated by the respiratory chain complexes I, III and IV. However, it is unclear whether this represents exchange of e.g. short-lived peripheral subunits [92], or a concerted de novo biogenesis of completely new complexes. Recently, the turnover of OXPHOS complexes was measured by feeding mice a pulse of the stable nitrogen isotope ^{15}N followed by mass spectrometric analysis of mitochondria of different tissues, including whole brain [93]. This revealed that some mitochondrial proteins in

brain mitochondria, including many subunits of the respiratory chain complexes, display exceptionally long half-lives of up to several months. On average, complex III and V are more long lived than complexes I, II, and IV, and membrane-embedded subunits have higher stability than matrix-exposed subunits e.g. within complex I [93]. While this suggests that the matrix-exposed subunits may benefit from replacement via local translation of their encoding mRNA in the long run, it remains doubtful whether this would be measurable in the short timeframe stimulation with NMDA or the inhibition of axonal translation. This leaves the possibility that de novo biogenesis of OXPHOS complexes may occur locally.

However, de novo biogenesis of most respiratory chain complexes also requires the incorporation of one or more proteins that are encoded within the mitochondrial genome (mtDNA, Fig. 1E). The coordination between cytoplasmic translation with the translation of mtDNA to generate stochiometric amounts of proteins is an ongoing area of research even in non-neuronal cells [94]. To complicate the matter, it has been suggested that some, if not most, axonal mitochondria lack mtDNA [95], questioning the idea that de novo synthesis of complete respiratory chain complexes can occur in axons. Indeed, the majority of electron transport chain complexes seemed to be downregulated in synaptic mitochondria [96]. This is in line with results from a recent preprint, where the authors performed proteomics on mitochondria isolated from MitoTag mice and found that axonal mitochondria possessed reduced mtDNA expression levels. In addition, compared to their somato-dendritic counterparts, axonal mitochondria showed decreased levels of proteins involved in translation and oxidative phosphorylation, and instead seemed to favor fatty acid oxidation [97].

There is however evidence that local translation of mitochondrially encoded proteins actually happens in axons: Using clickable non-canonical amino acids in the presence of inhibitors of the cytoplasmic ribosome, mitochondrial translation was detected in both axons and dendrites of neurons in culture [98]. Additionally, local translation of mitochondrial initiation factor 3 (mtIF3) has been reported in axons in response to brain-derived neurotrophic factor (BDNF) signaling [99]. This is one of only two translation initiation factors in mitochondria, and fittingly, its local translation boosts formation of the mitoribosome in axons [99]. Two possible solutions could reconciliate the absence of mtDNA with continued translation of mitochondrially encoded mRNAs. Firstly, mitochondria that enter the axon lacking mtDNA may still carry enough mRNA to sustain a limited amount of de novo biogenesis of OXPHOS complexes in the periphery. As also the mRNA associated to the outside of mitochondria cannot be replenished, this scenario seems reasonable, yet also places a "best before" date on an individual mitochondrion, unless it is resupplied by fusing with a younger mitochondrion or replaced altogether. How frequently mitochondria are replaced in the periphery is a matter of debate, as with increasing age and maturity of neurons, less and less mitochondrial transport is observed in cortical axons in vivo [100]. However, this may also vary by the cell type, as a similar reduction has not been observed in axons of retinal ganglion cells even in aged mice [101]. How different cell types manage their mitochondrial biogenesis and whether they all rely to the same extent on mitochondrial transport and local translation of mRNAs encoding mitochondrial proteins remains an active area of research.

The second solution takes advantage of the fact that not all mitochondria entering the axon lack mtDNA. Even in the most extreme examples, around 10% of axonal mitochondria still carried mtDNA [95]. It may be exactly these mitochondria that serve as a local center of OXPHOS biogenesis. This is in line with the idea that translational hotspots occur not at all mitochondria equally, but may be allocated to mitochondria in specific positions, such as at axonal branch sites or in direct contact with an endolysosome. However, it remains an open question how this localized de novo biogenesis of OXPHOS complexes would benefit mitochondria outside of these specialized positions. Mixing of mitochondrial content may occur over time through fission and fusion, which are however restricted in axons due to the high number of stationary mitochondria [26]. Nevertheless, mtDNA replication also occurs in axons [102] and is associated with MFF driven fission [66], which could increase the number of "seeds" for de novo OXPHOS complexes. Replication of mtDNA depends on the translation-elongation factor eEF1A1 of cytoplasmatic translation, suggesting coordination between cytoplasmic translation and the replication of mtDNA [102] that may also occur at the translational hotspots within the axon.

Degradation of mitochondrial proteins in neurons

In order to ensure mitochondrial quality control, different approaches can be taken by the cell. First, mitochondria possess their own set of proteases and chaperones, aiding in the processing and proper folding of mitochondrial proteins [103, 104]. Secondly, damaged mitochondria can be removed via a mitochondria-specific form of autophagy – mitophagy [105]. In recent years, mitochondria-derived vesicles (MDVs) have also been investigated as a mitochondrial quality control mechanism [106] (Fig. 2).

Proteases

The electron transport chain residing in the IMM is a major source of reactive oxygen species within the cell [107], which easily oxidize proteins within mitochondria, often resulting in their inactivation [108]. This is counteracted by a system of proteases within mitochondria (Fig. 2A) that not only keep mitochondrial homeostasis by removing misfolded or oxidized proteins, but also play important regulatory functions during protein import and complex assembly (reviewed by Deshwal et al. [107]).

All inner-mitochondrial compartments contain dedicated proteases for mitochondrial protein quality control: Lon and CLpXP (caseinolytic peptidase P) proteases are located within the matrix [109–111], while two proteases of the ATPases Associated with various cellular activities (AAA) family surveil the inner membrane with one facing the matrix (*m*-AAA) and the other facing the intermembrane space (IMS, *i*-AAA) [112–114]. Additionally, the IMS is also guarded by the HTRA2 (high temperature requirement A2)/Omi protease [115]. As they are located within mitochondria, it is assumed that they will be present in all neuronal subcompartments, but experimental evidence for this is still lacking. However, their importance in neurons is evident due to the link between genetic mutations in some protease subunits and neurodegenerative disorders. For example, HTRA2 mutations are linked to PD [116, 117] and deletions as well as mutations of Paraplegin, an *m*-AAA subunit, have been associated with hereditary spastic paraplegia (HSP) [118, 119], an upper motor neuron disease. Thus, mitochondrial proteases form the first layer of defense against mitochondrial dysfunction in neurons.

In the matrix, an oxidized form of the TCA cycle enzyme aconitase is degraded preferentially by the Lon protease [120]. In line with this, downregulation of Lon leads to the accumulation of damaged aconitase [120], as well as to reduced OXPHOS assembly and even cell death [121]. Lon also binds to mitochondrial DNA directly and associates with Twinkle, the helicase for mtDNA [122, 123]. Lon is therefore not only an important part of the degradative system of mitochondria, but may also regulate mitochondrial protein biogenesis through its processing of proteins responsible for mtDNA replication or transcription [123]. In neurons, Lon protease was investigated in the context of the PD model of treatment with the toxin MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridin), which selectively damages dopaminergic neurons due to its conversion into the neurotoxin MPP^+ [124, 125]. This leads to an accumulation of oxidized and carbonylated proteins, including aconitase and OXPHOS proteins, consistent with a loss of Lon function [125]. Although human post-mortem tissue of PD tissue revealed increased expression levels of Lon, the protease remained inactive, possibly contributing to the accumulation of damaged proteins [125]. How MPP^+ causes Lon dysfunction remains unclear, yet this study demonstrates the tight link between mitochondrial quality control and PD beyond the genetic linkages mentioned above. Enhancing protease function in PD might therefore be an interesting avenue for future research.

Similarily, Clp protease can counteract PD-associated phenotypes [126]. In eukaryotes, the protease named ClpXP is made up of two components: the AAA+ATPase ClpX, which unfolds protein targets, and the peptidase ClpP, which is responsible for the protein degradation [127]. Decrease of ClpP in dopaminergic SH-SY5Y cells is triggered by accumulation of the PD-associated protein aggregate alpha-synuclein and leads to the increased production of reactive oxygen species [128]. Conversely, enhancing ClpP levels in alpha-synuclein A53T mice, a PD model carrying a missense alpha-synuclein mutant, reduces the pathological phosphorylation of alpha-Synuclein at serine 129 [126].

Moving from the matrix to the mitochondrial inner membrane, the *m*-AAA consists of a complex containing paraplegin and AFG3L2, but AFG3L2 is also able to form a homo-oligomeric complex [129–131]. In the brain, Afg1l1 is another, less abundant, complex component of the *m*-AAA [131]. Targets of the *m*-AAA include cytochrome c peroxidase (CCp1), and the ribosomal mitochondrial protein MrpL32 [131]. Failure to process the latter protein has been associated with impaired mitochondrial protein synthesis [132], again linking degradative function to protein biogenesis in mitochondria. Paraplegin-deficient mice were also characterized by neurobiologically defects such as impaired axonal transport, visually affected mitochondria (e.g. abnormal cristae), and progressive axonal degeneration [119].

HTRA2/Omi is another protease shown to localize to the IMM under normal conditions, but is able to catalytically process itself before it translocates to the cytosol. There it is able to interact with its targets, including the X-linked inhibitor of apoptosis proteins (XIAP), which is inhibited by this interaction [133–135]. Downstream, this interaction has been shown to result in cell death [133]. However, HTRA2/Omi appears to serve a neuroprotective role as knockdown of the protease in mice resulted in abnormal neurological behavior, neuron loss and early lethality [134], fitting to its association with PD [136]. Recently, DELE1, a sensor for unfolded proteins within the mitochondrial matrix (UPR_{mt}) [137, 138], has been reported to be another substrate of HTRA2/Omi [139]. Cleaved DELE1 binds and stimulates HRI [137], which in turn phosphorylates eIF2alpha and initiates the integrated stress response (ISR) [140]. Activation of the ISR attenuates cytoplasmic translation, but enables the specific translation of the transcription factor ATF4

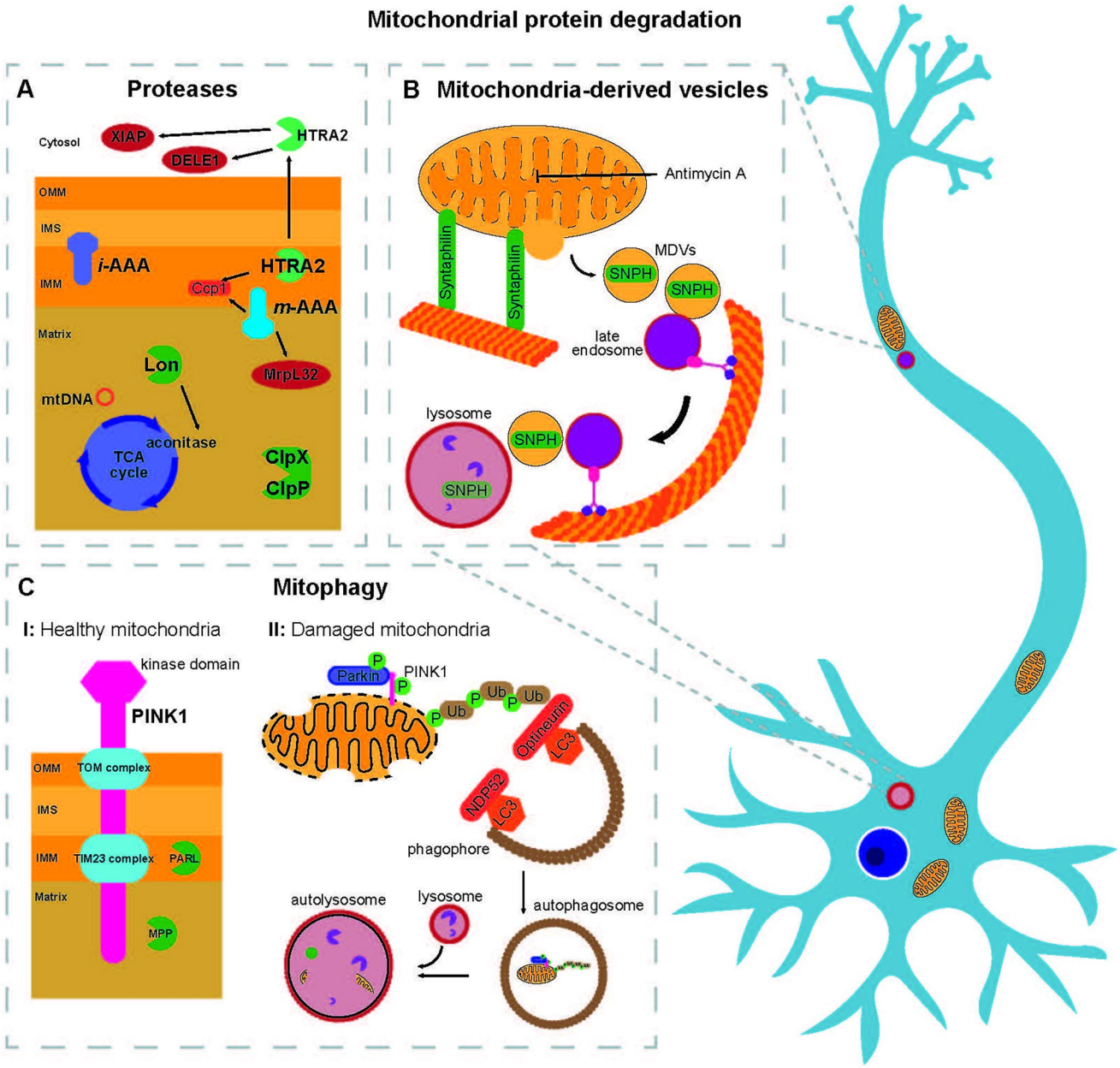

Fig. 2 Mitochondrial protein degradation. **A** Mitochondrial proteases can be divided based on their localization: ClpPX and Lon make up the proteases surveilling the mitochondrial matrix, with Lon targeting both mitochondrial DNA as well as aconitase, an enzyme of the TCA cycle. The inner mitochondrial membrane (IMM) contains the *i*-AAA, *m*-AAA (targeting the cytochrome c peroxidase (Ccp1) as well as the ribosomal protein MrpL32), and HTRA2. HTRA2 is able to process itself and subsequently translocates to the cytosol where it processes its targets XIAP and DELE1. **B** In healthy mitochondria, PINK1 is quickly imported and processed by the proteases PARL and MPP (I). In contrast, when mitochondria are damaged and their membrane potential is depolarized (II), PINK1 stabilizes on the mitochondrial surface where it then phosphorylates target proteins, resulting in the recruitment of Parkin to mitochondria, which in turn ubiquitinylates phosphorylated proteins. This results in a positive feedback loop leading to the formation of phospho-ubiquitin chains, which can be recognized by NDP52 or Optineurin, and subsequently LC3, triggering the formation of a phagophore membrane around the tagged mitochondria. Upon fusion with lysosomes, autolysosomes are formed and digest the damaged mitochondria. **C** Mitochondria-derived vesicles (MDV) can form upon mitochondrial damage, for example triggered by treatment with Antimycin A, and package specific cargo, e.g. Syntaphilin (SNPH). SNPH-containing MDVs can then be transported along with late endosomes towards the soma of neurons where they are degraded by lysosomes. Additionally, treatment with Antimycin A can result in the formation of MDVs in a Parkin/PINK1-dependent manner that results in lysosomal degradation of these MDVs independently of mitophagy as described in B.

[141]. This may also occur in the periphery of neurons, as also the mRNA of ATF4 is locally available [142] and, like other locally synthesized nuclear proteins [143], its retrograde transport will enable transcriptional changes triggered by the ISR. However, whether the transcriptional response, including the upregulation of mitochondrial proteases and chaperons, can in any way be targeted to the source or if all mitochondria will benefit from the change is unknown. Depending on the cell line, DELE1 can also be cleaved by another mitochondrial protease, OMA1 [144]. In fact, loss of HTRA2 was linked to increased instead of decreased induction of CHOP [145], an ATF4 target, suggesting that OMA1 may compensate for the loss of HTRA2 and mediate DELE1 cleavage. However, the absence of HTRA2 still increased levels of ROS and caused an excess of unfolded proteins in mitochondria [145], supporting its role in ameliorating UPR_{mt}.

Interestingly, HTRA2/Omi itself seems to be phosphorylated by PINK1 upon mitochondrial stress, likely resulting in its enhanced activity. Subsequently, PD patients carrying PINK1 mutations show decreased HTRA2 phosphorylation levels in brain tissue [136]. It would be tempting to speculate that the stress response enhancing HTRA2 phosphorylation by PINK1 is also linked to mitophagy or an altered UPR_{mt}, but so far, the involvement of HTRA2 in the PINK1/Parkin pathway of mitophagy has been disputed [146, 147].

Mitophagy

Mitochondria can be subjected to a special form of autophagy, called mitophagy [105]. Selective, distinct pathways cull mitochondria upon different cues, such as during the elimination of mitochondria during erythrocyte development, during hypoxia or upon mitochondrial damage [148]. Some basal turnover of mitochondria is required in neurons to balance mitochondrial biogenesis to maintain mitochondrial numbers [26]. Overall, mitophagic flux in neurons is rather low [149], which may be due to a high expression of negative regulators of autophagy [150], which restricts also the degradation of mitochondria by general, non-selective autophagy. Interestingly, mitochondrially-derived proteins, especially those associated with mtDNA, still make up a major factor of the autophagosomal content in the brain [151], arguing that also targeted mechanisms to remove mitochondria or mitochondrial content contribute to the turnover of mitochondria in the brain. Some autophagosomes form at the tip of axons and mature on their way to the soma [152], while other studies suggest that mitochondria first move retrogradely before they are captured by the autophagosomal machinery [153, 154] or are exclusively degraded in the soma [155]. To reunite all these different models, it will be imperative to understand which pathways trigger basal mitophagy in neurons. Selective basal mitophagy has been hypothesized to be independent of the damage-induced PINK1-Parkin pathway (see below) [149] and instead to be mediated by receptors such as the Bcl-2 interacting protein 3 (BNIP3L). BNIP3L has been shown to be responsible for mitophagic flux during neuronal development [156], but also partially appears to be able to compensate for PINK1 deficiency in more mature neurons [157]. The mechanisms of BNIP3L-mediated mitophagy are reviewed elsewhere [158]. It is likely that both redundant mechanisms for basal mitophagy in different subcellular compartments as well as dedicated mechanisms to detect damaged mitochondria coexist, and that neuronal cell type diversity is reflected in their reliance on one pathway over the other.

Most work in neurons has focused on the damage-induced PINK1-Parkin pathway of mitophagy (Fig. 2B), given its association to PD [159, 160]. As a mitochondrial protein, PINK1 resides on mitochondria, orienting its C-terminal kinase domain towards the cytoplasm [161]. In healthy cells with an intact mitochondrial membrane potential, PINK1 is quickly imported into mitochondria via TOM and TIM23 [162, 163] before it is primarily cleaved by PARL and MPP, but also by *m*-AAA and ClpXP [164, 165], and protein remains undergo proteasomal degradation [166].

However, when the mitochondrial membrane potential is disrupted, PINK1 no longer gets imported into mitochondria and instead stabilizes on the OMM [167, 168], where it subsequently undergoes autophosphorylation [169] and phosphorylates target proteins such as ubiquitin [170–172]. Another one of these target proteins is Miro, resulting in its degradation and subsequently halting mitochondrial movement [173].

Additionally, phosphorylation of ubiquitin in the vicinity of the OMM leads to the recruitment of the E3 ubiquitin ligase Parkin to mitochondria [169, 170, 174, 175]. Parkin continues to ubiquitinate phosphorylated OMM proteins [176], and these ubiquitin chains are then further phosphorylated by PINK1 [177]. PINK1 also phosphorylates Parkin at Serin 65, further enhancing its activity [171]. These reactions of phosphorylation and subsequent ubiquitination result in the formation of phospho-ubiquitin chains on the damaged mitochondria [177]. The first reaction to the phosphorylation of OMM proteins is in most cases their selective removal from the OMM and degradation via the proteasome [176]. This is the case for Miro [173] as well as the Mitofusins [178]. This results in mitochondrial fragmentation, preventing the fusion of damaged with healthy mitochondria, and thereby promoting mitophagy [179]. Recruitment of the AAA+ATPase, p97/VCP, to mitochondria helps with the extraction of the OMM proteins from the membrane and

the release of mitochondria from ER contacts mediated by those OMM proteins [180].

Extensively phospho-ubiquitinated mitochondria can be recognized by autophagy receptors, including NDP52 and optineurin [181]. Proteins on phagophores, such as the microtubule-associated protein light chain 3B (LC3B) are also recruited, resulting in the formation of autophagosomes around the labelled mitochondria [182]. Fusion with lysosomes and the formation of autolysosomes is followed by the acidic degradation of the damaged mitochondria [182]. Interestingly, a recent pre-print suggests that while PINK1-Parkin activation can take place throughout the axon and its terminals, phagophore formation seemed to be spatially restricted to boutons, placing this step of mitophagy in the necessary lipid-rich environment. While this may be beneficial for facilitating mitophagy, it also appears to make pre-synapses more vulnerable to mitophagy-defects, again highlighting the importance of this pathway especially in neurons [157].

Mitochondria-derived vesicles (MDVs)

While mitophagy clears whole mitochondria, the enrichment of some but not all mitochondrial proteins in autophagosomes in the brain suggests that piecemeal forms of autophagy must exist in the brain [151]. Also other pathways, including mitochondria-derived vesicles, could deliver selected cargo to lysosomes. Only the size of 60–150 nm, MDVs originate from mitochondria mostly independently of DRP1, and selectively choose their cargo [183, 184], before its delivery to lysosomes or peroxisomes ([185], reviewed by Sugiura et al. [104]. MDV transport can be initiated e.g. by oxidative stress, which increases their loading with oxidized subunits of complexes II, III and IV, and may contain both OMM and IMM membranes [184]. Knockdown of Parkin also resulted in less formation of an MDV-subtype upon Antimycin A treatment, a process that was also dependent on the presence of PINK1 [186] (Fig. 2C, upper part). Interestingly, this elimination of damaged proteins via MDVs could act as a mitochondrial quality control mechanism, preceding loss of the mitochondrial membrane potential and subsequent mitophagy [186].

In neurons treated with Antimycin A, Lin et al. [182] observed a reduction in Syntaphilin in axonal mitochondria. Immuno-electron microscopy revealed that Syntaphilin was indeed redistributed within stressed mitochondria and eventually shed via MDVs. However, these MDVs do not remain in the vicinity of mitochondria but instead hitch a ride with late endosomes towards the soma, where they are then lysosomally degraded (Fig. 2C lower part). The absence of Syntaphilin at mitochondria should then allow for damaged mitochondria to be moved out of the axons. Testing their observation in PD and ALS mouse models, the authors were able to observe the same decrease in Syntaphilin levels [187].

Mitostasis in neurons

Taken together, the previous chapters highlight the neuron-specific adaptions mitochondrial biogenesis and degradation have to undergo to support the extended morphology in neurons. While mitostasis is essential for all cell types, neurons are especially dependent on healthy mitochondria. Neurons are post-mitotic and, once fully developed, are limited in their numbers as neurogenesis in adults takes place scarcely [188, 189], facing them with the challenge to either function properly or be subjected to cell death. Reduced mitochondrial quality control, ranging from mitochondrial proteases to MDVs and mitophagy, will impact neurons more than most other cell types. Similarly, failure to transport mitochondria, and the mRNAs associated with them, will over time lead to the accumulation of dysfunctional organelles in the periphery [26]. Some mitochondrial damage may be repaired locally, e.g. through local translation of mitochondrial components, including PINK1 with its multifaceted downstream targets that further enhance local translation [79], activate the UPR_{mt} via phosphorylation of HTRA2 [136], and by initiating the removal of dysfunctional proteins via MDVs [186]. Only in the most extreme cases, PINK1 may actually activate mitophagy, as under basal conditions the amount of PINK1-dependent mitophagy in neurons is negligible [149]. This is all sustained by the transport of its mRNA via mitochondrial mRNA hitchhiking [60] and its local translation, again showing the importance of local translation for mitostasis in neurons. Several questions remain to be solved, for example how communication with the nucleus is orchestrated in neurons. Retrograde transport of locally-synthesized transcription factors such as ATF4 upon activation of the UPR_{mt}/ISR can mediate this communication, but mitochondria also have been reported to form direct contact sites with the nucleus that sustain pro-survival signaling [190]. Do retrogradely travelling mitochondria serve as sentinels that bring news from the periphery? And is a directed transport of replacement mitochondria into affected areas possible or will all transcriptional measures remain a global response? Only future research will be able to answer these questions.

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