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Review

Mitochondria, autophagy and age-associated neurodegenerative diseases: New insights into a complex interplay☆

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ABSTRACT

Mitochondria represent the major bioenergetic hub coordinating cellular and organismal homeostasis. The underlying causes of many pathologies tormenting humans converge on impaired mitochondrial maintenance. Mitochondria-specific autophagy (mitophagy), a cellular catabolic process targeting mitochondria, holds a prominent role in mitochondrial quality control. In addition to core autophagic machinery components, mitophagy exploits a variety of molecules that identify damaged or superfluous mitochondria and mediate their elimination. Signaling pathways integrating environmental and genetic stimuli interact with key mitophagy effectors to activate cellular stress response mechanisms, ultimately modulating health and lifespan. Here, we review the signaling cascades and molecular mechanisms that govern the process of mitophagy and discuss their involvement in ageing and neurodegeneration. This article is part of a Special Issue entitled: Mitochondrial Dysfunction in Aging.

1. Introduction

Mitochondria, the energy-generating organelles in eukaryotic cells, play essential roles in fundamental cellular processes, such as the supply of metabolic intermediates supporting biosynthetic and bioenergetic needs of the cell [1], apoptosis [2], calcium (Ca^{2+}) homeostasis [3,4] and cell signaling [5], among others. Accumulating evidence indicates that mitochondria can signal between cells so as perturbations in mitochondrial function in one tissue can be sensed over considerable distances by other tissues. It is not surprising, therefore, that mitochondria can impinge on cellular stress response pathways, modulating metabolism, cell survival and organismal healthspan.

Research in the field of ageing, in the past few years, has culminated in the identification of an intriguing link between autophagy and mitochondrial function with wide-ranging implications in health and disease [6,7]. A selective form of autophagy, known as mitophagy, that specifically targets damaged or superfluous mitochondria for autophagic degradation [8,9], has been repeatedly shown to participate in the maintenance of a healthy mitochondrial population. Defects in mitophagy have been associated with decreased neuronal function and increased susceptibility to neurodegeneration, during ageing [8,10]. Here, we review the recent advances on the intricate connections between mitochondria and autophagy, focusing on the molecular mechanisms that mediate mitophagy. Furthermore, we discuss how compromised mitophagy affects neuronal function, contributing to the onset and progression of several neurodegenerative diseases during ageing.

2. Mitochondria: The basics

Mitochondria, like their bacterial ancestors, are bounded by two functionally distinct membranes, an outer (OM) and an inner membrane (IM) that is highly folded into cristae. These two membranes give rise to two separate aqueous compartments, the intermembrane space and the internal matrix space. Mitochondria contain their own circular genome of alpha-proteobacterial origin, the mitochondrial DNA (mtDNA) organized into nucleoids in the matrix (Fig. 1). High resolution electron micrographs of mouse and human nucleoids revealed that most of them are located inside mitochondrial tubes. One part of nucleoids is linked to inner membranes of cristae, while the other part is bound to the complexes that cross cut both mitochondrial membranes [11]. Individual cells have a varying copy number of mtDNA depending on cell type and interestingly, they can carry both normal and mutant mtDNA populations, a condition known as heteroplasmy [12].

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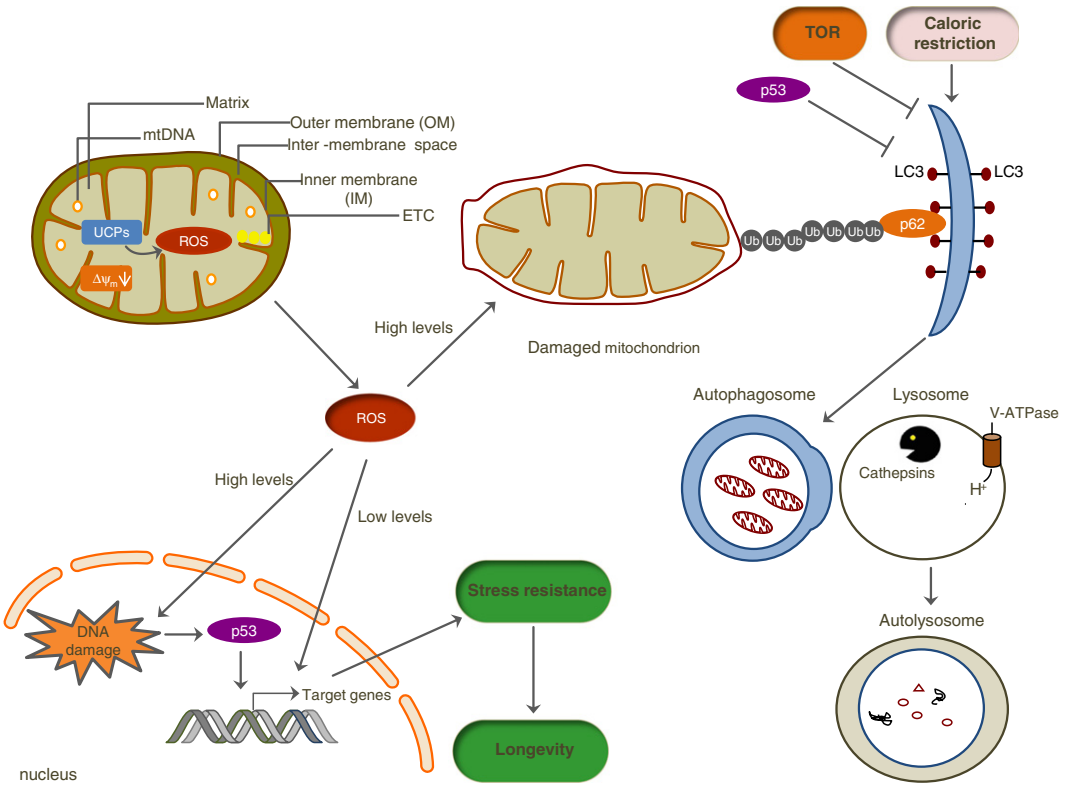

Fig. 1. Linking signal transduction cascades that influence ageing with mitochondrial regulatory mechanisms. Mitochondrial ROS levels are tightly controlled by several mechanisms. For example, UCPs prevent the reduction of molecular oxygen to superoxide by lowering the mitochondrial membrane potential (ΔΨm). Generation of low levels of mitochondrial ROS participate in the regulation of cellular signaling pathways that mediate stress resistance, thereby enhancing longevity. On the contrary, excessive ROS production leads to mitochondrial damage. Damaged mitochondria can be degraded by autophagy, which is induced by caloric restriction, among others. Mitophagy, selective degradation of dysfunctional mitochondria, depends on specific cargo receptors, such as p62. ROS production can also activate the tumour suppressor protein p53, which in turn, may induce autophagy through its transcriptional activity. On the other hand, cytoplasmic p53 suppresses autophagy. ROS cause damage to DNA, proteins and lipids. Arrows indicate stimulatory inputs. Bars indicate inhibitory interactions. For clarity, some of the signaling connections are not shown. ROS, reactive oxygen species; TOR, target of rapamycin; Ub, ubiquitin; UCPs, uncoupling proteins; V-ATPase, vacuolar H^+-ATPase.

Mammalian mtDNA encodes 13 mitochondrial proteins, synthesized by a separate translation machinery, as well as two mitochondrial ribosome-coding RNAs and 22 transfer RNAs. Mitochondrial-encoded proteins play essential roles in regulation of cellular bioenergetics. In addition to mitochondrial-encoded proteins, the organelle activities rely on over 1000 nuclear-encoded proteins, including gene products required for mtDNA replication, transcription and DNA repair. These proteins translocate from the cytosol into the inner mitochondrial membrane and the matrix [13]. Five import pathways cooperate with each other and synergize with other proteins that function in the respiratory chain, mitochondrial membrane organization, protein quality control and endoplasmic reticulum-mitochondria junctions so as to form an interconnected network of machineries harnessed for various mitochondrial functions [14]. mtDNA is maternally inherited as paternal mtDNA and the sperm-derived mitochondria disappear during early embryogenesis in many eukaryotes. Recent studies have demonstrated that elimination of paternal mitochondria, immediately after fertilization, is mediated by the recruitment of autophagosomes around sperm mitochondria, leading to their lysosomal degradation in both the nematode *Caenorhabditis elegans* and in the mouse [15,16]. Later work has indicated that a network of multi-vesicular body-like structures related to the endocytic and autophagic pathways is responsible for the destruction of paternal mitochondria in *Drosophila melanogaster* [17].

It is well established that ageing is associated with progressive accumulation of mutations/deletions in nuclear and mitochondrial genomes and is becoming increasingly clear that increased mtDNA mutagenesis can lead to premature ageing [18]. Indeed, homozygous knock-in mtDNA mutator mice expressing a defective nuclear-encoded mitochondrial DNA polymerase have reduced lifespan and develop various premature ageing phenotypes [19].

3. Mitochondria as determinants of cellular and organismal energetics

Mitochondria are the sites of adenosine triphosphate (ATP) production via oxidative phosphorylation (OXPHOS) taking place in the electron transport chain (ETC). ETC consists of multi-subunit protein complexes embedded in the inner membrane. Electrons are transferred through complexes I–IV to the final electron acceptor oxygen. In the final step, the terminal enzyme of the respiratory chain, cytochrome c oxidase (complex IV) catalyzes the complete reduction of molecular O_2 to water. In 1961, Peter Mitchell proposed the mechanism of coupling electron transport to ATP production, the so called chemiosmotic theory of oxidative phosphorylation, for which he was awarded the Nobel Prize in chemistry in 1978 [20]. Accordingly, the energy derived from the transfer of electrons across complexes I, III and IV of the ETC is coupled to a proton gradient established across the inner mitochondrial membrane through pumping of protons from the matrix to the intermembrane space. As the proton gradient becomes large enough, protons tend to return to the matrix via the ATP synthase (complex V), which consists of two structurally distinct rotary motors, F_0 and F_1. The F_0 subunit is embedded in the membrane and provides a channel through which protons can flow back from the intermembrane space to the matrix. The F_1 subunit uses the energetically favorable proton flow through the F_0 for the phosphorylation of ADP to ATP [21,22]. It is worth noting that, two decades later, the Nobel Prize in chemistry was again awarded for ground-breaking work regarding the elucidation of

the mechanism underlying ATP formation (Paul D. Boyer and John E. Walker) and the discovery of the enzyme sodium, potassium-stimulated adenosine triphosphatase (Jens C. Skou) [23–26].

Besides ATP, mitochondria also produce intermediate metabolites and reducing agents, such as nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FADH2), via the tricarboxylic acid cycle (TCA) in the matrix [27]. Given that TCA cycle and ETC require NAD and NADH respectively, an optimal NAD/NADH ratio is necessary for the mitochondrion to function properly [28,29]. Interestingly, emerging findings suggest that the mitochondrial NAD pool *per se* is essential for maintaining optimal mitochondrial function in different tissues [30]. Moreover, the metabolites generated in the TCA cycle are used in important biosynthetic reactions, such as nucleotide biosynthesis, lipid biosynthesis, amino acid biosynthesis, among others. Mitochondria also play a crucial role in ketone body production, urea cycle, heme biosynthesis and fatty acids β-oxidation. Apart from their important biosynthetic functions, mitochondria are well known for their contribution in reactive oxygen species (ROS) generation through respiration and other enzyme- or metal-catalyzed reactions [31–33]. A wealth of reports in the literature have established that excessive ROS attack macromolecules (nucleic acids, proteins and lipids), and therefore the balance between oxidant species and anti-oxidant defense determines the consequences of oxidative damage for the cell and the organism. ROS generation is believed to be influenced by the mitochondrial membrane potential and oxygen availability [34]. Studies in both invertebrate and vertebrate model systems have shown that mitochondrial ROS are overproduced and mtDNA damage increases with age [35]. Excessive ROS generation has been implicated in ageing and a variety of diseases, such as metabolic syndromes, obesity, diabetes, cardiomyopathies, cancer as well as in various neurodegenerative diseases [36–38].

4. Mitochondrial quality control mechanisms integrate with signal transduction cascades that influence health and lifespan

Recent studies in model organisms led to the intriguing concept that mitochondrial ROS function as signaling molecules to modulate distinct cellular processes, including stem cell proliferation, differentiation and senescence, autophagy, innate immune responses and epigenetics [39–41]. Subsequently, accumulating evidence has questioned the free radical theory of ageing according to which intracellular oxidants, generated mainly by mitochondria in the course of normal metabolism, play a key role in the ageing process [34,42–45]. Thus, it has been assumed that various lifespan-prolonging interventions, such as caloric restriction (CR), glucose restriction and physical exercise are linked, at least in part, with an increase in mitochondrial ROS production. Accordingly, it was reported that low levels of ROS can improve cellular defense mechanisms and activate stress response pathways (a strategy known as mitohormesis) [46] that ultimately enhance the cellular and organismal fitness and promote longevity in yeast, *C. elegans* and mice [47–49].

Impaired mitochondrial function caused by mutations or reduced function of nuclear-encoded ETC components, among others, has also been reported to activate the mitochondrial unfolded protein response (UPR^{mt}). This is a signaling cascade that increases, among others, the expression of nuclear-encoded mitochondrial proteins, such as chaperones and proteases, in order to restore mitochondrial function. The UPR^{mt} responds to cell-autonomous and cell-non-autonomous cues. Notably, neuronal specific knockdown of the nuclear-encoded cytochrome c oxidase-1 subunit Vb/COX4 (*cco-1*) was able to upregulate UPR^{mt} in the intestine, leading to lifespan extension in nematodes [50]. However, the molecular mediators of systemic signaling are yet to be defined.

Recent evidence has indicated that the activation of UPR^{mt} depends on the activating transcription factor associated with stress-1, ATSF-1 in *C. elegans*. Notably, ATSF-1 has both a nuclear localization signal (NLS) and a mitochondrial targeting sequence (MTS). In the absence of stress, ATSF-1 is imported into mitochondria and degraded. However, mitochondrial stress promotes the accumulation of ATSF-1 in the nucleus, where it mediates gene expression changes producing beneficial effects on longevity [51]. Research in flies and mice further suggest that UPR^{mt} is a hitherto unrecognized evolutionarily conserved defense mechanism that regulates whole organism longevity following mitochondrial perturbation [52,53]. These studies support the evolving role of mitochondria as signaling organelles that communicate with the rest of the cell under both physiological and pathophysiological conditions, thereby influencing cellular and organismal homeostasis.

In apparent contrast to the above mentioned lifespan extension conferred by mild mitochondrial dysfunction, severe mitochondrial damage has been repeatedly linked to the ageing process and the development of various diseases. It is not surprising, therefore, that numerous studies have focused on elucidating the mechanisms that contribute to maintenance or restoration of mitochondrial function.

5. Uncoupling proteins (UCPs) in the regulation of mitochondrial function

Accumulating findings in recent years argue for mitochondrial production of ROS being tightly controlled. Uncoupling proteins (UCPs) 1–3, which are mitochondrial anion carriers, appear to play an essential role in preventing the reduction of molecular oxygen to superoxide by lowering the mitochondrial membrane potential (Fig. 1). However, the molecular mechanisms by which UCPs regulate ROS levels in mitochondria remain elusive. Current evidence suggests that ROS and ROS derivatives activate UCPs, which, in turn, induce a mitochondrial proton leak from the intermembrane space to the matrix, thereby providing a negative feedback mechanism that mitigates ROS production. UCP2 and UCP3, in particular, seem to be controlled by reversible S-glutathionylation in response to changes in ROS production and in mitochondrial membrane potential [54]. Together, these findings provide new mechanistic insight into the regulation of mitochondrial ROS emission, placing emphasis on the role of UCPs. Interestingly, UCP2 might be considered as neuroprotective due to its ability to block the release of apoptogenic factors, when activated. Specifically, it has been shown that the overexpression of human UCP2 in mice reduces brain damage induced by experimental stroke and enhances neurological recovery. In addition, UCP2 prevents the activation of caspase-3 under conditions of oxygen and glucose deprivation in cultured cortical neurons [55]. On the other hand, UCP1 reportedly plays an essential role in thermogenesis in brown adipose tissue (BAT) and in white adipose tissue (WAT) in response to cold. To this end, UCP1 stimulates ETC activity, resulting in oxidation of available substrates and consequently in heat generation [56]. A latest study reports that Zfp516 acts as a transcriptional activator of both UCP1 and the proliferator-activated receptor gamma, coactivator 1 alpha (PGC1a). Upon exposure to cold, Zfp516 binds to the proximal region of UCP1 promoter, thus activating a BAT program that is crucial for survival in cold environments. Moreover, Zfp516 overexpression in adipose tissue leads to browning of WAT even at ambient temperature and importantly prevents diet-linked obesity [57]. The emerging role of mitochondria in WAT homeostasis, and their involvement in whole organism homeostasis thereof has recently attracted considerable attention.

6. Mitochondria: Autophagy and more

As briefly mentioned above, several recent studies have revealed an intriguing link between mitochondria and autophagy. Macroautophagy (hereafter, autophagy) is a major catabolic pathway by which eukaryotic cells degrade long-lived proteins, damaged or excess organelles or portions of the cytoplasm. During autophagy, cargoes to be degraded are engulfed in double-membrane vesicles, the autophagosomes. This is followed by fusion of autophagosomes with lysosomes to form autolysosomes, in which the sequestered material is degraded and

recycled back to the cytosol for reuse [58]. Endoplasmic reticulum (ER), the Golgi apparatus, the plasma membrane and mitochondria have all been shown to contribute to autophagosome biogenesis [59].

Autophagy serves housekeeping functions under normal conditions being maintained at basal levels. As such, it is essential for survival, development and homeostasis at both the cellular and whole organism level. However, autophagy is activated under stress, such as nutrient and growth factor deprivation, oxidative damage, hypoxia or anoxia, ER stress, invasion of pathogens, to serve predominantly cytoprotective functions. Several studies in the last few years have revealed the existence of strong connections between autophagy and the cellular energy balance [60–62]. In this regard, mitochondria appear to play a key role in starvation-induced autophagy, supplying membranes for the formation of autophagosomes [63]. Furthermore, autophagosome biogenesis in response to starvation depends on the tethering activity of mitofusin 2 (MFN2), a core component of the mitochondrial fusion machinery. In addition to its role in mitochondrial fusion, MFN2 has also been shown to mediate tethering of mitochondria to ER. MFN2 depletion prevents the activation of autophagy in human cancer cell lines during starvation [64].

Although autophagy is generally considered to be a non-selective process that mediates the bulk degradation of cytoplasmic components, accumulating evidence has clearly shown that it can also specifically target damaged or superfluous organelles, such as mitochondria (mitophagy) [65], peroxisomes (pexophagy) [66], ER (ER-phagy) [67], lipid droplets (lipophagy) [68] or invading bacteria (xenophagy), among others [69] for degradation. Selective autophagy requires receptors that link specific cargoes to the microtubule associated protein 1 light chain-3 (LC3)/GABARAP/GATE-16 proteins, homologous to the *Saccharomyces cerevisiae* Atg8 [70,71]. LC3 localizes to membranous structures appearing during formation of the autophagosome [72]. Mitophagy has received much attention for its role as a mitochondrial quality control mechanism that eliminates defective mitochondria to maintain a healthy mitochondrial network, thus contributing to cell viability and whole organism healthspan. A recent study has revealed a role for cardiolipin, a phospholipid unique to the mitochondrial IM, in a mitochondrial "eat me" signaling process that leads to autophagosome recruitment around damaged mitochondria for degradation. Specifically, externalization of cardiolipin to the outer mitochondrial membrane in response to extrinsic stimuli such as rotenone, staurosporine and 6-hydroxydopamine known to cause serious damage to mitochondria, facilitates the recognition of defective mitochondria by the autophagy pathway in primary cortical neurons and SH-SY5Y cells. Interestingly, the LC3 protein contains cardiolipin-binding sites. These sites are required for autophagy activation [73]. In this regard, it should be noted that autophagy is particularly essential for maintaining cellular homeostasis in terminally differentiated cells such as cardiomyocytes and neurons. Compelling evidence from studies in yeast suggests that general autophagy and mitophagy are regulated independently for one another [8,74,75].

6.1. Mitochondrial ROS and autophagy

Accumulating evidence suggests an interesting link between ROS production and autophagy regulation [76,77]. Remarkably, HeLa cells deficient in ETC function (HeLa ρ° cells) as well as Hela cells overexpressing manganese superoxide dismutase 2 (SOD2) fail to increase superoxide (O_2^-) production under starvation. Moreover, these cells are not able to activate 5′ adenosine monophosphate-activated protein kinase (AMPK) and thereof starvation-induced autophagy [78]. Taken together, these observations support the idea that ROS play an essential role in the regulation of autophagy during starvation.

Along similar lines, recent studies have revealed other molecular players involved in the complex interplay between ROS and autophagy. For example, oxidative stress, among others, can activate the tumour suppressor protein p53 that is able to trigger autophagy through its transcriptional activity, while it has been shown to inhibit autophagy through its cytoplasmic, not nuclear functions. As a transcription factor, p53 transactivates genes that activate autophagy, such as damage-regulated autophagy modulator (DRAM), sestrins-1 and -2 and unc-51-like kinase 1 (ULK1), among others. In turn, autophagy induction leads to ROS suppression [79]. In contrast to the above mentioned p53 targets that activate autophagy, the p53 inducible protein TIGAR, which functions as a fructose-2,6 biphosphatase, contributes to suppression of intracellular ROS and inhibits autophagy. Therefore, TIGAR seems to affect autophagy through ROS regulation [80]. On the other hand, cytoplasmic p53 suppresses autophagy by inhibiting AMPK, a positive regulator of autophagy, which in turn, activates mammalian target of rapamycin (mTOR), thereby inhibiting autophagy (Fig. 1) [81,82]. However, the precise mechanism through which cytoplasmic p53 exerts its inhibitory effects on autophagy still remains elusive.

Although our understanding of the complex crosstalk between autophagy and ROS is rapidly expanding, one of the main questions in the area is how ROS regulate the autophagic activity. Increasing evidence supports the idea that ROS can reversibly oxidize and reduce specific amino acids, most frequently reactive Cys residues, but also Met residues, thereby activating or inactivating their targets proteins. As a consequence, ROS can modulate various intracellular pathways, including autophagy. In particular, the essential autophagy protein ATG4 seems to be one of the Cys-dependent proteases targeted by mitochondrial ROS under nutrient deprivation conditions. Indeed, starvation induces autophagy and reportedly increases H_2O_2 in mitochondria. The link between mitochondrial ROS production and autophagy requires, at least in part, the redox-dependent inactivation of ATG4, which inhibits delipidation of the microtubule-associated light chain 3(LC3), thus increasing autophagosome formation [83]. Interestingly, a similar requirement has been recently reported for peroxisome-derived ROS, which are able to repress mammalian target of rapamycin complex 1 (mTORC1) and induce autophagy [84].

Collectively, ROS can induce autophagy, which in turn dampens oxidative damage, serving a cytoprotective function [83,85]. Readers are referred to recent comprehensive reviews focusing on the role of ROS in the regulation of autophagy and further discussing the complex crosstalk between autophagy and oxidative stress [37,85,86].

7. Mitochondrial dynamics and autophagy: An intricate crosstalk

Mitochondria are dynamic organelles that divide, fuse, migrate and undergo turnover. All these processes are tightly regulated so as to modulate mitochondrial function in response to physiological or stressful stimuli [87], thereby meeting the energy demands at cellular and organismal levels. Accumulating findings indicate that mitochondrial fusion and fission play a crucial role in regulating mitochondrial function. Indeed, mutations in MFN2 and OPA1 (optic atrophy gene 1) dynamin-related GTPases that mediate mitochondrial outer membrane and inner membrane fusion respectively, are associated with diseases affecting several tissues beyond the optic and peripheral nerves. Like inhibition of mitochondrial fusion, fission inhibition can negatively impact mitochondrial function by preventing equal segregation of mitochondria into daughter cells during cell division or more importantly by interfering with autophagy and consequently preventing the elimination of damaged mitochondria [87]. A subsequent study has revealed that mitochondria elongate under nutrient deprivation. Under these conditions of increased energy requirement, elongated mitochondria escape from autophagic degradation and maintain ATP production, thereby promoting cell survival [88].

Consistent with the idea that mitochondrial dynamics interface with mitophagy, a deficiency in fission-mediated proteins such as the dynamin-like protein DRP1 or FIS1 blocks mitochondrial autophagy leading to accumulation of oxidized mitochondrial proteins that compromise the respiratory chain activity and impair insulin secretion in insulin secreting INS-1 cells. Similarly, OPA1-overexpression increases

mitochondrial fusion while blocking mitophagy [89,90]. These findings point at an intriguing interplay between autophagy and mitochondria with important implications for ageing and mitochondria-linked diseases [32,91–95].

7.1. The PINK1/Parkin pathway

The PINK1/Parkin pathway is the most well-studied pathway mediating selective autophagy of damaged mitochondria. This pathway acts as a hub for coordinated regulation of several processes that promote efficient mitochondrial removal, like mitochondrial dynamics, trafficking and recruitment of components of the autophagic machinery. Mechanistic insights into the regulation of the core players of this pathway have emerged in the literature and are described below.

Parkin is a RING In Between RING (RBR) E3 ligase. Structurally, it consists of an N-terminal Ubiquitin-like domain (UblD), three RING-finger domains, RING0, RING1 and RING2, and a Cysteine-rich In Between RING domain (IBR) lying between RING1 and RING2 (Fig. 2A). Under physiological conditions, Parkin exists in the cytoplasm in an autoinhibited state [96,97]. Parkin mitochondrial recruitment depends on the stabilization of Phosphatase and tensin homolog (PTEN)-induced putative kinase 1 (PINK1) on the outer membrane of depolarized mitochondria, both in mammals and in *D. melanogaster* [98–101]. In healthy mitochondria, the serine/threonine kinase PINK1 is continually imported into the inner mitochondrial membrane, in a potential-dependent manner (Fig. 2B). It is processed into a 60 kDa form by the Mitochondrial Processing Peptidase (MPP) [102] and then cleaved between alanine-103 and phenylalanine-104 residues giving rise to an unstable 52 kDa fragment. The cleavage is mediated by the inner membrane rhomboid protease presenilin-associated rhomboid-like protein (PARL) [103,104] and other proteases [102]. The 52 kDa proteolytic fragment is rapidly degraded in a proteasome-dependent manner [99,103].

On depolarized mitochondria, PINK1 can no longer be imported and accumulates in its unprocessed form (63 kDa) on the outer mitochondrial membrane (Fig. 2B) [98,99,103]. On the outer membrane PINK1 is assembled in a 700 kDa complex that includes also core components of the Translocase of the Outer membrane (TOM) complex but not Parkin [105]. However, TOM complex is not required for PINK1 targeting to mitochondria and subsequent Parkin recruitment and activation as artificial targeting of PINK1 in other compartments that lack TOM complex, like lysosomes or peroxisomes, is able to induce Parkin recruitment, organelle ubiquitination and clearance by autophagy [105]. Parkin artificially recruited on mitochondria without PINK1 can neither ubiquitinate mitochondrial proteins nor induce autophagic clearance of mitochondria, advocating for a role of mitochondrial PINK1 in activation of E3 ligase activity of Parkin. Alternatively, PINK1 can be stabilized on the outer membrane of healthy mitochondria when there is excessive unfolded protein load into the matrix. This signal is enhanced when Lon protease is depleted and triggers PINK1-Parkin dependent-mitophagy [106,107].

How is Parkin E3 ligase activity stimulated by PINK1? It was shown that PINK1 becomes activated upon membrane depolarization by autophosphorylation at several sites [108,109]. In turn, activated PINK1 phosphorylates Parkin on conserved Serine-65 of the UblD. Although this phosphorylation event is not sufficient for mitochondrial translocation of Parkin, it is proposed to release the auto-inhibition of Parkin leading to activation of its E3 ligase activity [108,110–112]. RING1 domain of Parkin is important for the physical interaction of Parkin with PINK1 [110], while RING2 is critical for ubiquitin-thiolester transfer through the formation of an ubiquitin-thioester intermediate on Cysteine-431 [113,114]. Under basal conditions, RING0 occludes the ubiquitin-acceptor site Cysteine-431, ensuring autoinhibition of E3 ligase activity [97]. Moreover, Parkin was shown to self-associate in a PINK1-dependent manner, through its IBR domain. This self-association is critical for activation of Parkin E3 activity upstream of its mitochondrial translocation [114]. Interestingly, it was shown that translocation of Parkin onto damaged mitochondria is stabilized by physical interaction with its substrates, namely Voltage Dependent Anion Channel (VDAC) and guanosine triphosphate MFN2 [115,116]. Recruitment of Parkin to mitochondria induces rupture of the outer mitochondrial membrane in a proteasome-dependent manner. However, the latter is not required for mitophagy [117].

Recent landmark studies report that ubiquitin itself is phosphorylated by PINK1 on Serine-65, similar to the UblD of Parkin [118–121]. Initially this phosphorylation was proposed to activate the E3 ligase activity of Parkin. Lately, a different model was proposed, in which phosphorylation of poly-ubiquitin follows ubiquitin conjugation onto Parkin substrates [122,123]. Parkin catalyzes the formation of K6, K11, K27, K48 and K63-linked ubiquitin chains on its substrates [122,124]. The role of each of these different poly-ubiquitin structures in substrate degradation and subsequent mitochondrial fate determination remains

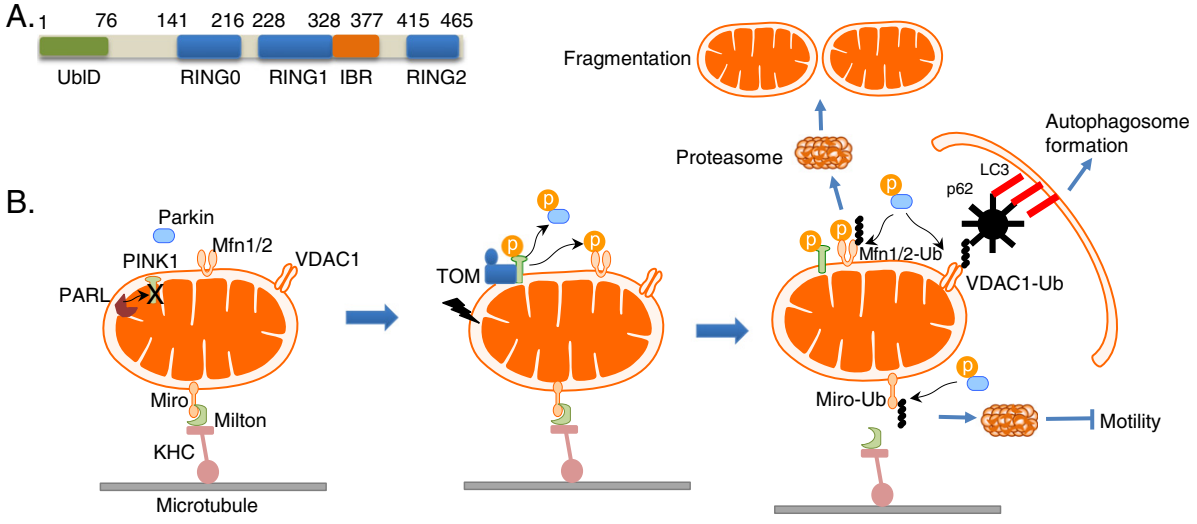

Fig. 2. The PINK1/Parkin pathway at a glance. A. Schematic diagram of Parkin indicating functional domains. Numbers represent amino-acid position. B. The PINK1/Parkin pathway acts as a hub for coordinated mitochondrial maintenance. In healthy mitochondria, PINK1 is imported into the inner membrane, processed by PARL and subsequently degraded. Upon mitochondrial membrane depolarization, PINK1 is stabilized on the outer mitochondrial membrane, activated by autophosphorylation, and then recruits and activates Parkin. Activated Parkin adds ubiquitin chains on several mitochondria-surface molecules simultaneously coordinating mitochondrial motility, dynamics and recruitment of autophagic machinery components. PARL, Presenilin-associated rhomboid-like protein; PINK1, Phosphatase and tensin homolog (PTEN)-induced putative kinase 1.

poorly understood. In a different level of regulation, deubiquitinases come to modulate Parkin's activity by removing ubiquitin chains from Parkin itself and from injured mitochondria [125–127].

7.2. Mitochondrial substrates of Parkin

Parkin has a variety of cellular targets through which it regulates many fundamental cellular pathways involved in cell cycle and survival, protein aggregation, vesicle trafficking, and cytoskeleton. During mitophagy, Parkin, following its activation, ubiquitinates mitochondrial surface proteins usually triggering their degradation by the proteasome. Interestingly, upon mitophagy induction proteasomes are clustered onto damaged mitochondria in the perinuclear region [117]. Nevertheless, Parkin-dependent ubiquitination doesn't always lead to degradation. It is widely accepted that ubiquitinated substrates on mitochondrial surface tag mitochondria for mitophagy through recruitment of components of the autophagic machinery.

Mitofusins (MFN1/2) are the best characterized example of ubiquitinated Parkin substrate. MFN1/2 are large GTPases that mediate mitochondrial fusion. Parkin-dependent ubiquitination of MFN1/2 primes them for degradation by the proteasome in a p97 AAA+ ATPase-dependent manner [101,115,128–130]. It is proposed that selective degradation of MFN1/2 leads to fragmentation of damaged mitochondria, which stands as a prerequisite for their engulfment by autophagosomes. Other outer membrane mitochondrial proteins targeted for proteasomal degradation by Parkin are components of the Translocase of the Outer Mitochondrial Membrane (TOM) complex, such as Tom40, Tom20 and Tom70 as well as Omp25. Proteasomal degradation of those is not a prerequisite for mitophagy [117].

Miro is a Rho GTPase found on the outer mitochondrial membrane. Together with its partners, Milton and Kinesin 1 Heavy Chain (KHC) it serves as an anchor of mitochondria to microtubules, allowing for rapid mitochondrial translocation. Upon mitophagy, phosphorylation of Miro by PINK1 leads to its Parkin-dependent proteasomal degradation rendering impaired mitochondria unable to move [131–133]. This is particularly relevant in neuronal cells where mitochondria need to travel long distances along the neuronal axis. Unhooked mitochondrial are locally removed by autophagy in a PINK1 and Parkin-dependent manner [134]. This focal response along neuronal axis provides rapid neuroprotection against mitochondrial stress.

Parkin-dependent ubiquitinylated VDACs are shown to attract the autophagy scaffold p62/sequestosome 1 (p62/SQSTM1). p62/SQSTM1 contains a K63-ubiquitin binding domain as well as an LC3 bonding motif through which it targets ubiquitinylated proteins to autophagosomes [135]. p62/SQSTM1 was proposed to play a role in PINK1 and Parkin-mediated mitophagy both in mammalian cell lines and in *D. melanogaster* [124,136,137], although this model has been questioned by other studies showing that p62 is crucial for mitochondrial perinuclear aggregation rather than mitophagy [138,139].

7.3. Mitochondria-specific autophagy receptors

Mitochondrial proteins that recruit components of the autophagic machinery are considered as mitophagy receptors. Functional homologs of mitophagy receptors exist from yeast to mammals (Table 1). Two independent screens for mitophagy-deficient mutants in the budding yeast revealed Atg32 as a protein essential for respiratory growth-induced mitophagy in post-log phase cells [140,141]. Atg32 is a mitochondria-anchor protein with an N-terminal cytoplasmic domain, a single transmembrane domain and a C-terminal domain facing mitochondrial intermembrane space. The cytoplasmic domain of Atg32 contains a tetrapeptide sequence, W/F/YxxL/I, (Atg8-family Interacting Motif—AIM) which mediates interaction with Atg8. Atg32 acts as a receptor for the recruitment of Atg8, and it physically interacts with Atg11, the scaffold protein involved in selective types of autophagy [142]. This interaction is required for mitochondrial degradation although it precedes and is independent of isolation membrane and autophagosome formation. The C-terminal domain of Atg32 is processed by i-AAA (ATPases associated with diverse cellular activities) protease of the inner mitochondrial membrane, Yme1 [143]. Although dispensable for mitophagy, the exact role of Atg32 C-terminal domain and the reason for its removal are currently unknown [143]. Atg32 gets phosphorylated at serine-114 and serine-119 by Casein Kinase 2 (CK2) [144,145] and thus it is activated for interaction with Atg11 and mitophagy induction.

Although mitophagy is a conserved process, Atg32 homologs have been found so far only in yeast species [146]. The mammalian functional homologs of Atg32 are also single-spanning transmembrane proteins on the outer mitochondrial membrane which encompass the classic tetrapeptide motif, W/F/YxxL/I, mediating interaction with LC3. BCL2 and adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) and its homolog NIX/BNIP3L are atypical BH3-only molecules initially characterized as pro-apoptotic agents with ability to bind Bcl2 and adenovirus E1B protein [147]. Apart from their role in cell death both proteins have been shown to mediate mitophagy by attracting LC3/GABARAP proteins onto mitochondria. NIX/BNIP3L is required for mitochondrial removal during mitochondrial stress and reticulocyte maturation. Specifically, it serves as a mitochondrial receptor for the LIR-dependent recruitment of LC3/GABARAP proteins to initiate mitophagy [148]. Although NIX is critical for mitophagy during reticulocyte maturation, mitophagy can be partly induced even without NIX and also without core autophagic components like Atg5/Atg7 [149,150] arguing for the operation of

Table 1
The function of mitophagy-related genes is highly conserved across different taxa.

Model organism				Function	Reference
Saccharomyces cerevisiae	*Caenorhabditis elegans*	*Drosophila melanogaster*	*Mus musculus*		
ATG32	–	–	–	Mitophagy receptor; interacts with Atg8 and recruits autophagic machinery	[74,140,143]
–	*dct-1*	–	*Nix/Bnip3*	Mitophagy receptor; interacts with LC3/GABARAP and recruits autophagic machinery	[148]
–	*pink1*	*pink1*	*PINK1*	Protein kinase; phosphorylates Ub and recruits Parkin to mitochondria	[184,204,205]
–	*pdr-1*	*parkin*	*Parkin*	E3 ubiquitin ligase; ubiquitinates outer membrane mitochondrial proteins	[184,204,205]
–	*fundc-1 (T06D8.7)*	*CG5676*	*FUNDC1*	Mitophagy receptor; interacts with LC3/GABARAP and recruits autophagic machinery upon hypoxia	[154]
–	*sqst-1 (T12G3.1)*	*ref(2)P*	*SQST-1/p62*	Adaptor protein; interacts with ubiquitinated proteins to recruit autophagic machinery	[124,135,138,139, 158,206,207]
FZO1	*fzo-1*	*fzo, dmfn*	*MFN-1/2*	Fusion machinery; ubiquitinated by Parkin, MFN1/2 degradation triggers mitophagy	[115,128,208,209]
–	*usp30 (Y67D2.2)*	*usp30*	*USP30*	Deubiquitinating enzyme; reverse Parkin-dependent ubiquitination in mitochondrial proteins	[125]

other redundant pathways. Moreover, BNIP3 is also reported to interact with LC3 mediating mitophagy induction [151,152]. A link between the function of BNIP3L/NIX and the Parkin has emerged in *D. melanogaster* [153]. Specifically, BNIP3L is found ubiquitinated by PARK2 (the *D. melanogaster* Parkin homolog), a post-translational modification that seems to attract the selective autophagy adaptor protein NBR1 (Neighbor of BRCA1 gene 1-similar to p62/SQSTM1) to promote mitophagy. BNIP3L together with PARK2 are degraded upon mitochondrial depolarization in a lysosomal-dependent manner [153].

A different type of mitophagy receptor was identified in mammalian cells. FUNDC1 is highly conserved from *D. melanogaster* to humans. It comprises three putative transmembrane domains near the C-terminus which faces the intermembrane space. Human FUNDC1 is localized exclusively on the outer mitochondrial membrane and it interacts with LC3 in a LIR-dependent manner, during hypoxia-induced mitophagy [154]. FUNDC1 interaction with LC3 is controlled by phosphorylation and dephosphorylation events. Specifically, phosphorylation of serine-17 by ULK1 as well as dephosphorylation of Serine-13 by PGAM5 phosphatase enhances LC3-binding capacity of FUNDC1 upon hypoxia, which is reversed by CK2-mediated phosphorylation [155,156]. Finally, expression of mitophagy receptors FUNDC1 and NIX is regulated by hypoxia-responsive microRNA-137 [157]. miR-137 attenuates expression of FUNDC1 and NIX and thus hypoxia-induced mitophagy. The reason behind this seemingly contradictory role is not understood.

Recently, a new mechanism of p62/SQSTM1 attraction onto damaged mitochondria was proposed through direct interaction of p62/SQSTM1 with choline dehydrogenase (CHDH). CHDC is a mitochondrial enzyme residing on both the outer and inner mitochondrial membranes [158]. CHDH was not found ubiquitinated upon membrane potential disruption. Nevertheless, it was reported to accumulate on the outer mitochondrial membrane of depolarized mitochondria, independently of Parkin, and to form a ternary complex with p62/SQSTM1 and LC3 to drive mitophagy [158].

8. Mitophagy in neurons and age-associated neurodegeneration

Neurons contain increased mitochondrial population, since high ATP levels are demanded to carry out their functions and preserve neuronal homeostasis [159]. Because of the unique neuronal architecture, which is characterized by relative small cell body, long axons and multiple dendritic branches, neurons are equipped with specialized mechanisms for efficient distribution of mitochondria to distal regions, such as presynaptic endings, postsynaptic densities, axonal branches and growth cones, where high energy is required to sustain neuronal activity [160].

Post-mitotic neuronal cells must survive during the lifetime of the organism and they are more vulnerable to the process of ageing due to their intensive metabolism and increased ROS generation. Therefore, neuronal activity and survival depend on mitochondrial homeostasis. Dysfunctional mitochondria not only produce less ATP but also display impaired buffering of cytosolic calcium. Furthermore, elevated ROS production can trigger neuronal stress and lead to neurodegeneration [159]. Thus, aged or damaged mitochondria need either to be repaired through mitochondrial quality control mechanisms, such as proteasome system, mitochondrial proteases and fission–fusion machinery, or eliminated by mitophagy.

Neuronal mitochondrial degradation is a challenging cellular event since the majority of mitochondrial mass is located at the distal neuronal processes, far away from the cell body of the neuron, where mature acidic lysosomes mainly exist [161–163]. Despite the spatial limitations, rapid elimination of dysfunctional mitochondria is essential for neuronal protection against cell death. Indeed, basal autophagy is critical for the maintenance of axons and dendrites since insufficient or excessive autophagy causes neuritic degeneration [164–166]. Autophagy deficiency could also lead to protein aggregation, a hallmark of several neurological disorders such as Parkinson's disease, Alzheimer's disease and Huntington's disease. Conversely, autophagy stimulation has a protective effect against proteinopathies through effective clearance of misfolded and aggregated proteins. Additionally, defective autophagic elimination of damaged mitochondria may contribute to oxidative stress and initiate apoptotic or necrotic cell death in neurons [167–170].

Depolarized mitochondria are characterized by altered motility since they present reduced anterograde and relatively enhanced retrograde transport. Thus, healthy mitochondrial population remains in the distal parts of the neuron and damaged mitochondria are transferred and eliminated in the neuronal cell body (Fig. 3) [171–173]. This model is consistent with the findings of several studies showing that Miro, a mitochondrial adaptor protein anchoring the kinesin motor complex to mitochondria, is degraded in a PINK1/Parkin-dependent manner upon mitochondrial depolarization [132,174–179]. In turn, mitochondria are transported to the soma of the neuron or are immobilized at neuronal axons and dendrites for mitophagy. The fact that autophagosomal maturation requires acidic lysosomes indicates that damaged mitochondria are engulfed locally by autophagosomes and then retrieved to the soma for destruction [175,176,180]. In addition to the autophagosome formation in the axons, the retrograde movement of mitoautophagosomes, which are autophagosomes containing dysfunctional or aged mitochondria, has been reported [175]. A recent study has revealed an additional cell non-autonomous mechanism for distal mitochondrial degradation named as transcellular mitophagy or transmitophagy (Fig. 3). A mitochondrial population of the retinal ganglion cell monitored to be diminished by the optic nerve head astrocytes [181]. The elucidation of transmitophagy opens new avenues in the field of neuronal mitochondrial autophagy underlining the importance of investigating whether other neurons with long-projecting processes adapt transcellular mitophagy as the main quality control mechanism of mitochondrial elimination under physiological or pathological conditions.

Accumulating evidence signifies the maintenance of mitochondrial homeostasis since mitochondrial dysfunction, altered dynamics, defective transport and impaired mitochondrial degradation are associated with the onset and the progression of several age-associated neurodegenerative diseases such as Parkinson's disease, Alzheimer's disease and Huntington's disease [32,87,182,183].

8.1. Parkinson's disease

Loss of dopaminergic neurons in the substantia nigra, a region essential for motor control and coordination, is the major hallmark of Parkinson's disease. *PINK1* and *PARK2* genes have been linked with the hereditary forms of parkinsonism. Interestingly, the function of both genes is involved in the maintenance of healthy mitochondrial population. Several studies unravel the role of the PINK1/Parkin pathway in the elimination of dysfunctional mitochondria through the process of mitophagy [184]. Additionally, Parkinson's disease patients contain mtDNA mutations and/or deletions more frequent compared to aged-matched individuals. Such mutations of mtDNA accumulate during ageing in the neuronal cells of substantia nigra and cause mitochondrial damage [185,186]. Consistently, there is a correlation between dopaminergic neuronal loss and accumulation of mitochondrial damage in the development and progression of Parkinson's disease. Hence, environmental toxins, mtDNA defects and impairment of mitophagy could lead to excessive mitochondrial stress and might also contribute to the pathogenesis of Parkinson's disease [187]. However, it is still unclear whether the PINK1/Parkin pathway orchestrates mitophagy and preserves mitochondrial homeostasis in neurons under steady-state conditions. Mitophagy process has been delineated in non-neuronal cells, with Parkin function remaining controversial and obscure in neurons. A few studies report that mitochondrial impairment does not trigger Parkin translocation [188,189]. On the contrary, other studies show that depolarized mitochondria are engulfed by autophagosomes in PINK1/Parkin-dependent manner [132,171,190]. Furthermore,

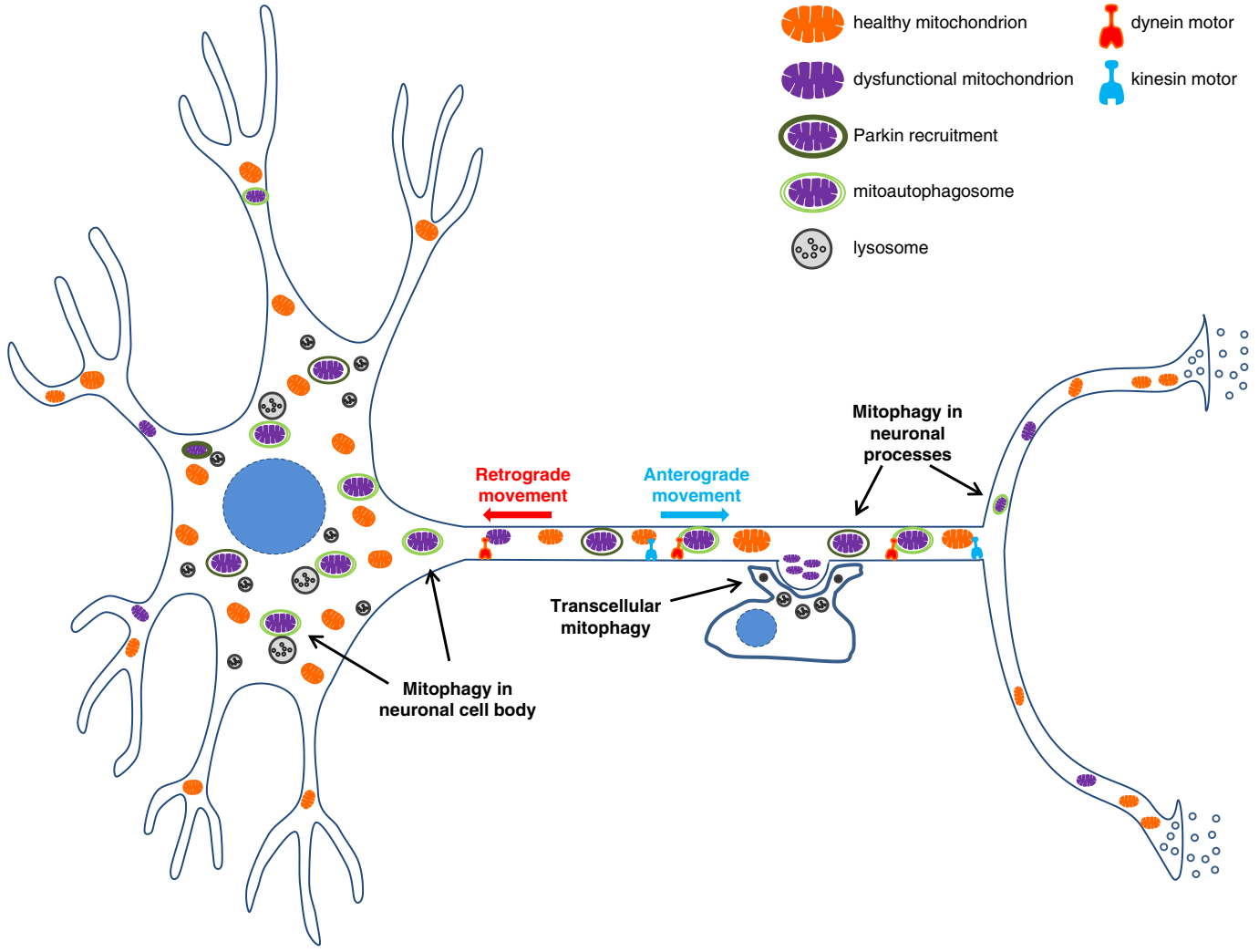

Fig. 3. The mechanisms of neuronal mitophagy. Dysfunctional mitochondria trigger PINK1/Parkin-dependent mitophagy. PINK1 accumulation on outer mitochondrial membrane recruits the cytosolic E3 ubiquitin ligase Parkin. Parkin-targeted mitochondria are engulfed by autophagosomes. Damaged mitochondria or mitoautophagosomes are transported from the distal regions to the soma of the neuron, where acidic lysosomes are mainly located. Therefore, dysfunctional mitochondria display altered motility with reduced anterograde and enhanced retrograde movement. Kinesin and dynein motor proteins promote anterograde and retrograde movement respectively. Additionally, axonal mitochondria could be removed by neighboring astrocytes through the process of trans-cellular mitophagy.

Parkin-deficient mice display shortening of lifespan and decreased neuroprotection during ageing [191]. Recently, it is found that deubiquitinating enzymes, such as USP15 and USP30 oppose and reverse the function of Parkin on mitochondrial proteins [125,126]. Inhibition of deubiquitinases enhances mitophagy in healthy neurons. Additionally, USP30 depletion results in increased survival, decreased dopamine loss and behavioral defects [125]. These findings indicate that impairing the balance between ubiquitination and deubiquitination events either on mitochondrial substrates [125] or on Parkin protein *per se* [127], might lead to elevated mitochondrial dysfunction and subsequently loss of dopaminergic neurons. Thus, further work is needed to clarify the role of PINK1/Parkin pathway *in vivo* in neurons, especially in pathological conditions or during ageing.

8.2. Alzheimer's disease

Alzheimer's disease is the most common age-related neurodegenerative disorder. Death of neurons in the cerebral cortex results in cognitive dysfunction and loss of memory, two hallmarks of Alzheimer's disease pathogenesis. Although the mechanisms that lead to the development and progression of Alzheimer's disease remain unclear, the primary hypothesis is that accumulation of beta-amyloids (Aβ) derived from amyloid precursor protein (APP) causes cellular defects and toxicity. Emerging evidence implicates mitochondrial dysfunction and defective mitophagy in Alzheimer's disease pathogenesis [192]. Elevated ROS production upon mitochondrial damage affects the function of several mitochondrial components including membrane lipids, electron transport chain complex proteins and mtDNA. Deficiency of mitochondrial complexes I and IV is associated with enhanced tau toxicity and Aβ accumulation [193]. Furthermore, the existence of autophagic vacuoles in neurons of Alzheimer's disease patients indicates the implication of non-selective and/or selective autophagy in disease development [194]. Concluding, elimination of impaired mitochondria through mitophagy might be beneficial for maintenance of mitochondrial homeostasis and defense against Alzheimer's disease.

8.3. Huntington's disease

Huntington's disease is an autosomal dominant neurodegenerative disorder. The aberrant expansion of cytosine, adenosine and guanine (CAG) repeats within the huntingtin gene is the main cause of disease pathology. The number of CAG repeats correlates with the severity of the disease. Cytoplasmic and nuclear aggregates of mutant huntingtin protein are the major pathological hallmark of Huntington's disease

[195]. Toxic mutant huntingtin affect multiple cellular processes leading to neuronal disability and death. Impaired mitochondrial function and oxidative stress have been associated with the accumulation of mutant huntingtin. Altered mitochondrial morphology, motility, energy depletion, insufficient cytoplasmic calcium buffering capacity and impairment of membrane potential are some of the reported mitochondrial defects in Huntington's disease patients [196–198]. Notably, stimulation of peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α), which orchestrates the process of mitochondrial biogenesis, alleviates neuronal dysfunction by promoting the activation of transcription factor EB (TFEB) and preventing oxidative stress [199–201]. TFEB is the master regulator of lysosomal and autophagy genes [202]. Therefore, mitophagy induction and degradation of damaged mitochondria might be beneficial and protective against the neuronal loss in Huntington's disease. Indeed, enhancing mitophagy by overexpressing PINK1 promotes neuroprotection against mutant huntingtin toxicity. PINK1 overexpression rescues the abnormal mitochondrial morphology, ATP levels and enhances survival of flies expressing mutant huntingtin in neurons [203]. Furthermore, mutant huntingtin does not affect the recruitment of Parkin on damaged mitochondria but diminishes the engulfment of mitochondria by autophagosomes [203]. These findings are consistent with a previous study showing that autophagic cargo recognition is defective in Huntington's disease and leads to accumulation of dysfunctional mitochondria in the cytoplasm [183]. Thus, enhancing mitophagy could sustain mitochondrial function and lead to neuroprotection in Huntington's disease.

9. Concluding remarks

The maintenance of a healthy mitochondrial population is crucial for cellular and organismal homeostasis. Post-mitotic neuronal cells are more susceptible to mitochondrial damage due to their increased metabolic demands. Therefore, effective mitochondrial quality control is pivotal for neuronal functionality. Despite the fact that molecular mechanisms of mitochondrial selective autophagy have been extensively studied, several controversial questions remain to be answered about neuronal mitophagy. The stimulus and the molecular mechanisms, which regulate autophagosomal formation in axons, cargo recognition and sequestration, transport to the soma, fusion with lysosomes and degradation are still unclear. Moreover, the mechanisms that regulate the interplay between autophagy, apoptosis and necrotic cell death in axonal and dendrite degeneration remain unknown. Unraveling potent mitophagy-inducing compounds and understanding how mitophagy protects against neuronal death would be essential for the development of novel and context-specific pharmacological interventions against neurodegenerative disorders.

Transparency document

The Transparency document associated with this article can be found, in the online version.

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