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REVIEW ARTICLE

Mitochondrial turnover and homeostasis in ageing and neurodegeneration

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Ageing is driven by the inexorable and stochastic accumulation of damage in biomolecules vital for proper cellular function. Although this process is fundamentally haphazard and uncontrollable, genetic and extrinsic factors influence senescent decline and ageing. Numerous gene mutations and treatments have been shown to extend the lifespan of organisms ranging from the unicellular *Saccharomyces cerevisiae* to primates. Most such interventions ultimately interface with cellular stress response mechanisms, suggesting that longevity is intimately related to the ability of the organism to counter both intrinsic stress and extrinsic stress. Mitochondria, the main energy hub of the cell, are highly dynamic organelles, playing essential roles in cell physiology. Mitochondrial function impinges on several signalling pathways modulating cellular metabolism, survival and healthspan. Maintenance of mitochondrial function and energy homeostasis requires both generation of new healthy mitochondria and elimination of the dysfunctional ones. Here, we survey the mechanisms regulating mitochondrial number in cells, with particular emphasis on neurons. We, further, discuss recent findings implicating perturbation of mitochondrial homeostasis in cellular senescence and organismal ageing as well as in age-associated neurodegenerative diseases.

Keywords: ageing; energy homeostasis; human disease; mitochondria; mitochondrial turnover; mitophagy; necrosis; neurodegeneration; neurons

Ageing is associated with the progressive accumulation of damage in molecules and cells that eventually leads to functional decline and increased vulnerability to disease. Over the past 30 years, studies in model organisms have culminated in the identification of evolutionarily conserved genes and signalling cascades that influence the ageing process. Such studies have revealed that several pathways modulating ageing are coordinated by stress or nutrient and metabolic sensors [1]. Despite this progress, the cellular and molecular events that transpire during ageing are not yet fully understood. The nervous system is particularly

Abbreviations
AD, Alzheimer's disease; AMPK, adenosine monophosphate-activated protein kinase; BNIP3, BCL2/adenovirus E1B 19 kDa-interacting protein 3; BNIP3L, BNIP3-like; DCT-1, DAF-16/FOXO-controlled germline-tumour affecting-1; GADPH, glyceraldehyde-3-phosphate dehydrogenase; HD, Huntington's disease; IGF-1, insulin-like growth factor 1; IGF-1R, insulin-like growth factor type 1 receptor; IR, insulin receptor; Mfn1/2, mitofusin 1 and mitofusin 2; MPP, mitochondrial processing peptidase; mt-Keima, mitochondrial-targeted Keima; NDP52, nuclear dot protein 52 kDa; NIX, NIP3-like protein X; NRF1, NRF2, nuclear respiratory factors 1 and 2; OMM, outer mitochondrial membrane; OPTN, optineurin; OXPHOS, oxidative phosphorylation; PARL, presenilin-associated rhomboid-like; PD, Parkinson's disease; PDR-1, Parkinson's disease-related-1; PGC-1, peroxisome proliferator-activated receptor coactivator-1; PINK1, PTEN-induced putative kinase protein 1; TFAM, mitochondrial transcription factor A; TOR, target of rapamycin; VCP, valosin-containing protein; VDAC1, voltage-dependent anion channel 1.

susceptible to age-inflicted deterioration [2]. Since age-related decay of the nervous system is a universal phenomenon, elucidation of the mechanisms that are responsible for the detrimental effects of ageing on neuronal function is of particular importance.

A growing body of evidence supports a crucial role for mitochondria in ageing and age-associated diseases. In fact, several studies have reported that mitochondrial integrity and function decline with age both in model organisms and in humans. These abnormalities, which are subsequently amplified by defective quality control mechanisms, have been indicated as important contributors to the ageing process [3]. It is worth to note that postmitotic cells such as neurons, which need to survive throughout an organism's life, suffer more from mitochondrial dysfunction than other cell types. However, the mechanisms underlying mitochondrial failure in ageing and disease are still being understood. In this review, we survey recent advances towards establishing a link between mitochondrial turnover regulatory mechanisms and signalling pathways that influence ageing and neurodegeneration.

Main signalling pathways modulating ageing

It was first shown that downregulation of the insulin/insulin-like growth factor 1 (IGF-1) pathway extends lifespan in a variety of organisms [1]. Indeed, mutations in the gene encoding the insulin/IGF-1-like receptor significantly increase lifespan in a cell nonautonomous manner in diverse organisms, such as yeast, worms, flies and mice [4–6]. Likewise, mutations in the gene that encodes the phosphoinositide-3 kinase AGEing alteration 1 extend lifespan in *Caenorhabditis elegans*. The lifespan-prolonging effects of these mutations require the activity of DAF-16, a Forkhead FoxO transcription factor [1]. DAF-16 controls the expression of a wide variety of stress-responsive genes, among others, thereby enhancing stress resistance and promoting longevity. Similarly, mutations in both the insulin-like receptor and the insulin-receptor substrate (*chico*) extend lifespan in *Drosophila melanogaster*, with evidence indicating that longevity is directly dependent on dFOXO activity [7–9]. In mice, genetic alterations in the insulin receptor (IR), the IGF-1 receptor (IGF-1R) and mutations in genes that regulate insulin, IGF-1 or growth hormone levels increase lifespan [10–12]. Interestingly, mutations in several genes encoding components of the insulin/IGF-1 pathway have also been associated with human longevity [13,14].

The target of rapamycin (TOR) pathway plays a central role in the regulation of ageing in yeast, *C. elegans*, *Drosophila* and mammals. Its central node is the evolutionarily conserved serine/threonine kinase TOR that regulates cell growth and proliferation, development, metabolism and ageing [15]. Notably, postdevelopmental inhibition of TOR extends adult lifespan and promotes healthspan in organisms ranging from *C. elegans* to primates. These beneficial effects on longevity rely mainly on the ability of TOR to modulate protein synthesis and autophagy [16].

Alongside, the AMP-activated protein kinase (AMPK) is a key player of an elegant system that enables eukaryotic cells to sense energetic stress manifested as decreased ATP-to-AMP ratio and reprogram metabolism accordingly so as to meet their energy needs. To achieve this goal, AMPK phosphorylates key proteins involved in TOR signalling, glycolysis and lipid biosynthesis, as well as enzymes that contribute to mitochondrial homeostasis, among others. Besides, once activated, AMPK also redirects cellular metabolism towards catabolic processes by modulating the activity of various transcription factors (TFs), including members of the FOXO family, transcription factor EB and nuclear hormone receptor-49 [17]. As such, AMPK links energetics to several cellular signalling mechanisms that influence longevity and health in an evolutionarily conserved manner.

Neuronal energy homeostasis during ageing

The effectiveness of cellular maintenance, repair and turnover pathways declines with age. Moreover, it is well established that longevity is linked to the ability of an organism to maintain cellular energy homeostasis which greatly depends on neuronal cell contribution [18]. In this regard, the central nervous system (CNS) has received much attention in recent years and several studies have revealed a crucial role for hypothalamus in determining the balance between food intake and energy expenditure in mammals. Indeed, the mammalian melanocortin system of the hypothalamus is one of the most thoroughly characterised neuronal pathways involved in neuroendocrine control of energy homeostasis [19]. In particular, the proopiomelanocortin and neuropeptide-Y–agouti-related-protein neurons within the arcuate nucleus were found to be activated *via* distinct signalling pathways linked to mitochondrial dynamics [20]. Besides CNS, peripheral sensory neurons such as chemosensory,

olfactory and gustatory neurons have been shown to influence the metabolic physiology of worms, flies and mice [18].

Mitochondria cannot simply be viewed as the energy-producing organelles in eukaryotic cells but also as dynamic structures involved in various cellular processes, including apoptosis, regulation of calcium (Ca^{2+}) signalling and innate immunity [3,21]. It is now clear that mitochondrial content, distribution and function vary in different cell types depending on their specific energy needs. In addition, mitochondrial transport along cytoskeletal filaments is critical for coordinating mitochondrial localization with energy demands in polarized cells such as neurons, which display different metabolic requirements in their distinct domains (i.e. the cell body, the axon and dendrites) [22]. On the other hand, mitochondria are almost immotile in muscle cells. At the organismal level, the energetic demands of various tissues are coordinated in order to facilitate metabolic adaptation to extrinsic and intrinsic cues. Therefore, it is important for individual cells to maintain a healthy mitochondrial population to subserve their function while preserving organismal energy homeostasis. The rate at which a mitochondrial pool is refreshed is determined by turnover, the balance between mitochondrial biogenesis and recycling through fusion and fission processes or degradation through mitophagy. In fact, mitochondrial biogenesis provides new healthy organelles and selective autophagy removes superfluous or damaged organelles. Hence, mitophagy regulates mitochondrial number so as to meet the metabolic requirements of the cell in response to physiological changes in energy levels and also mediates the removal of damaged organelles. Accumulating evidence suggests that mitochondrial fission followed by selective fusion is a prerequisite for the degradation of dysfunctional mitochondria *via* autophagy [23,24]. Further elaborating on the contribution of mitochondrial fission to mitophagy, a recent study reported that fission protects healthy mitochondrial domains from elimination by promoting selective degradation of subdomains harbouring misfolded protein aggregates [25]. Defects in mitochondrial turnover have been observed during ageing and in age-related diseases such as obesity, diabetes, cancer, and neurodegenerative disorders [26]. Determining the contribution of defective mitochondrial turnover to neurodegeneration is of particular importance given the crucial role of mitochondria in preserving neuronal function and survival and the essential role of neurons in maintaining whole-body energy homeostasis.

Mitochondrial biogenesis in ageing and neurodegeneration

One of the hallmarks of ageing is mitochondrial dysfunction [27]. The age-related decline in mitochondrial function might affect the integrity and activity of various tissues and organs, increasing vulnerability to degeneration in diverse organisms, including humans [27–29]. Stimulation of mitochondrial biogenesis, in coordination with other adaptive processes, could improve mitochondrial function and attenuate the adverse effects of ageing on various organs such as the brain, heart and skeletal muscle. At the transcriptional level, generation of new functional mitochondria is controlled by several TFs, for instance, the nuclear respiratory factors 1 and 2 (NRF1 and NRF2) that directly regulate the expression of nuclear-encoded mitochondrial genes, mitochondrial transcription factor A (TFAM), which is a mitochondrial matrix protein essential for the replication and transcription of mitochondrial DNA (mtDNA), cAMP response element-binding protein 1, estrogen-related receptor alpha and peroxisome proliferator-activated receptors α, δ. These TFs are coordinately regulated by peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) in mammals [30–32]. To date, no clear PGC-1α homologue has been identified in yeast, worms and flies.

Generation of new healthy mitochondria to replace dysfunctional organelles is fundamental for the metabolic adaptation of cells to various intrinsic and extrinsic stimuli. This is particularly important for postmitotic cells with high energetic requirements such as cardiomyocytes, skeletal muscles and neurons. Impaired mitochondrial biogenesis, at the whole-body level, can disrupt metabolic homeostasis, thereby contributing to ageing and the development of various diseases such as metabolic syndromes, cancer and neurodegenerative disorders. Indeed, evidence suggesting a causative role for defective mitochondrial biogenesis in disease comes from the MitoPark mouse model [33] of Parkinson's disease (PD), the second most common neurodegenerative disorder [34]. Loss of dopaminergic neurons in the substantia nigra, which causes dopamine deficiency in the dorsal striatum pars compacta, and intracellular inclusions composed of α-synuclein aggregates are the neuropathological features of the disease [35,36]. MitoPark mice, which are conditional knockout mice with a disrupted Tfam specifically in dopaminergic neurons, exhibit key PD features, suggesting that impaired mitochondrial biogenesis is implicated in PD pathogenesis [33,37]. Along similar lines, Tfam and PGC-1α are reduced in mouse

models of Huntington's disease (HD) [38]. Specifically, mutant huntingtin (mHtt) has been shown to interfere with PGC-1α transcription in human HD brain and in an HD knock-in mouse model. Accordingly, lentiviral-mediated administration of PGC-1α into the striatum of R6/2 transgenic HD model confers neuroprotection against mHtt [39].

There is increasing evidence that stimulation of mitochondrial biogenesis might be an efficient strategy to treat many primary or secondary mitochondrial disorders [31,40]. Hence, agents that enhance mitochondrial biogenesis appear to have beneficial effects on mouse models deficient for oxidative phosphorylation (OXPHOS). Specifically, it has been shown that activation of the AMPK/PGC-1α axis can restore OXPHOS defects in three models of cytochrome oxidase deficiency [41]. Focusing on neurodegenerative diseases, interventions that increase mitochondrial biogenesis by enhancing the activity of PGC1α and NRF2 or of AMPK have proved neuroprotective in mouse models of PD, Alzheimer's disease (AD) and HD [42]. In summary, several strategies aimed to restore mitochondrial dysfunction in a range of pathologies through the induction of mitochondrial biogenesis are emerging [31,40].

Focusing on mitophagy

Recent detailed analyses have provided critical insights into the molecular mechanisms that mediate mitophagy and the signalling pathways that modulate mitophagic activity. The pathway governed by PTEN-induced putative kinase protein 1 (PINK1) and the E3 ubiquitin (Ub) ligase parkin (PINK1/Parkin) is the best studied mitophagy pathway in higher eukaryotes (no homologues have been found in yeast) [43]. Briefly, under physiological conditions, PINK1 is constitutively degraded *via* a multistep process that involves import into the mitochondrial matrix, cleavage by the mitochondrial processing peptidase (MPP) and the presenilin-associated rhomboid-like (PARL) protease and then retranslocation into the cytosol where PINK1 is degraded through the N-end rule pathway [44]. In depolarized mitochondria, however, PINK1 is stabilized on the outer mitochondrial membrane (OMM) and, upon autophosphorylation, phosphorylates Parkin, thus activating its E3 Ub ligase activity and promoting its recruitment to damaged mitochondria. Activated Parkin, in turn, ubiquitinates mitochondrial substrates, including mitofusin 1 and mitofusin 2 (Mfn1/2) [45], voltage-dependent anion channel 1 (VDAC1) [46], PARIS [47] and Miro [48]. Ubiquitinated mitochondria are subsequently recognised by selective autophagy receptors such as p62, optineurin (OPTN) and nuclear dot protein 52 kDa (NDP52), which mediate their engulfment by a phagophore, the autophagosome precursor, through binding to microtubule-associated protein 1 light chain 3 (MAP1LC3; also known as LC3) (Fig. 1). Engulfed mitochondria are ultimately degraded into lysosomes. In humans, mutations in PINK1 or Parkin are associated with autosomal recessive forms of PD [49].

Besides PINK1/Parkin-mediated mitophagy, alternative mitophagy pathways that might compensate for the loss of Pink1/Parkin, contributing to the maintenance of mitochondrial integrity and function, have been discovered. For instance, damaged mitochondria can be selectively removed with the aid of mitochondrial receptors such as BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3), NIP3-like protein X [NIX; also known as BNIP3-like (BNIP3L)], FUN14 domain-containing protein 1 and activating molecule in Beclin 1-regulated autophagy. These receptors can bind directly to LC3 *via* their LC3-interacting region under mitophagy-inducing conditions. Readers are encouraged to consult recent reviews that dissect in detail the PINK1/Parkin pathway and describe different mitophagy-specific factors and additional mechanisms identified to date [43,49–56]. In the following section, we will focus on the role of mitophagy in normal ageing and age-related neurodegeneration.

Mitophagy in ageing and neurodegeneration

Mitophagy serves a mitochondrial quality control function enabling the selective elimination of dysfunctional or superfluous mitochondria and thus ensures the preservation of a healthy mitochondrial population and the maintenance of energy homeostasis. This fine-tuned mechanism is proposed to protect organisms from a decline in mitochondrial function and/or mitochondrial dysfunction that commonly occurs in ageing cells such as neurons, ultimately affecting whole-body energy homeostasis [57].

Indeed, a relationship between mitophagy and ageing has been reported in *D. melanogaster*. Neuron-specific overexpression of Parkin in the adult stage increases fly lifespan without reducing fertility, physical activity or food consumption. Interestingly, long-lived Parkin-overexpressing flies display reduced levels of ubiquitinated proteins, indicating that upregulation of Parkin prevents proteostasis collapse during ageing. It is worth to note that the levels of mitochondrial fusion-promoting factor *Drosophila* Mitofusin, which is a known Parkin substrate, increase with age. Accordingly, Parkin overexpression reduces *Drosophila*

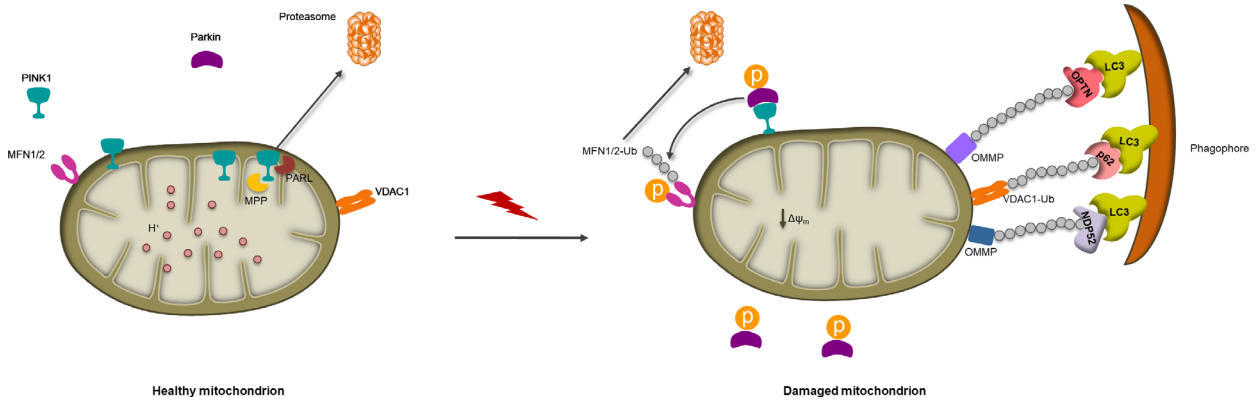

Fig. 1. PINK1/Parkin-mediated mitophagy. In healthy mitochondria, PINK1 is imported into the mitochondria, cleaved by the MPP and the PARL protein and ultimately degraded by the proteasome in the cytosol. In depolarized mitochondria, however, PINK1 is stabilized on the OMM and activated by autophosphorylation. Then, it recruits and activates Parkin, which in turn ubiquitinates several mitochondrial surface proteins, including VDAC1 and MFN1/2. Ubiquitinated mitochondria are recognised by selective autophagy receptors such as p62, OPTN and NDP52, which, upon binding to LC3, mediate their degradation in the lysosome. $\Delta\psi_m$: mitochondrial membrane potential; OMMP: OMM proteins.

Mitofusin levels and increases mitochondrial activity in aged flies. More importantly, neuronal overexpression of Parkin is sufficient to enhance whole organism healthspan and lifespan by regulating mitochondrial metabolism in the ageing *Drosophila* brain [58]. The age-dependent decline in mitophagy has been challenged by emerging observations indicating that mitophagy occurs in *Drosophila* flight muscle and dopaminergic neurons *in vivo* even under physiological conditions and that mitophagy increases during ageing. This age-related increase in mitophagy is abrogated when PINK1 or parkin is depleted. Furthermore, the mitophagy defect of parkin-deficient flies is largely rescued by knockdown of the *Drosophila* homologues of the deubiquitinases USP15 and USP30. Taken together, these findings indicate that PINK1 and Parkin are crucial components of the age-dependent mitophagy in *Drosophila in vivo* [59]. The above-mentioned studies provide insight into the molecular pathways that mediate age-associated degeneration of the brain, with important consequences for longevity.

In *C. elegans*, mitophagy interfaces with mitochondrial biogenesis through a feedback loop that enables cells to adjust their mitochondrial content to meet changes in physiological needs and respond to intrinsic or extrinsic stressors. At the heart of this pathway is the mitophagy receptor DAF-16/FOXO-controlled germline-tumour affecting-1 (DCT-1), a putative homologue to the mammalian NIX/BNIP3L and BNIP3. Knockdown of either *dct-1* or *pdr-1* (PD-related-1 gene encoding the nematode Parkin orthologue) does not affect the lifespan of otherwise wild-type animals. By contrast, knockdown of *dct-1*, *pdr-1* or *pink-1* decreases the lifespan of the long-lived insulin signalling-defective *daf-2(e1370)* mutants and the calorie-restricted *eat-2* mutant animals. These findings establish a role for mitophagy in various longevity pathways. Moreover, mitophagy deficiency leads to mitochondrial dysfunction and increased susceptibility to stress. These adverse effects trigger mitochondrial retrograde signalling through the SKiNhead-1, the nematode homologue of nuclear factor erythroid 2-related factor 2, transcription factor that regulates both mitochondrial biogenesis genes and mitophagy by enhancing *dct-1* expression. Uncoupling of these two processes during ageing contributes to the accumulation of damaged mitochondria and a marked decrease of cellular function, eventually affecting the whole organism [60].

Recent findings indicated that mitophagy is reduced by ~ 70% in the dentate gyrus region of the brain of old mitochondrial-targeted Keima (mt-Keima) reporter mice compared to young animals. Moreover, a mouse model of HD, which expresses the human Huntingtin's transgene along with the mt-Keima reporter, displayed significantly decreased mitophagy levels compared to control. This finding supports a protective role for mitophagy against HD, which has been consistently associated with mitochondrial dysfunction, at least partially, due to altered mitochondrial calcium homeostasis [57]. In agreement with the aforementioned literature, mHtt has been linked to defective mitophagy in a *Drosophila* model of HD. In this context, neuronal expression of mHtt affects mitochondrial morphology leading to the formation of mitochondrial spheroids in photoreceptor neurons. Interestingly,

PINK1 overexpression reduces the formation of abnormal ring-shaped mitochondria, ameliorates mitochondrial function, restores neuronal integrity and enhances adult fly survival. The neuroprotective effects of PINK1 against mHtt are dependent on Parkin and require mitofusin and VDAC1. Consistent with the *Drosophila* data, PINK1 overexpression, at least partially, rescues mitophagy defects in HD striatal cells derived from knock-in HdhQ111 mice carrying 111 CAG in the mouse *htt* gene [61]. Along similar lines, a specific mitophagy mechanism, which relies on glyceraldehyde-3-phosphate dehydrogenase (GADPH) to mediate clearance of damaged mitochondria, has been associated with HD pathology. In this case, abnormal interaction of mitochondrial GADPH with mHtt containing expanded polyglutamine repeats impairs GADPH-driven mitophagy leading to accumulation of damaged mitochondria and eventually cell death in both cell culture models and the HD transgenic mice R6/2. Conversely, overexpression of inactive GADPH rescues defective mitophagy and recovers mitochondrial function, thus promoting cell survival [62]. Providing further insight into the mechanisms underlying HD pathology, a proteomic analysis has identified a valosin-containing protein (VCP) as a molecule that binds mHtt on mitochondria in various cell culture and mouse HD models. Mitochondria-accumulated VCP induces excessive mitophagy, leading to neuronal death. Accordingly, blocking VCP translocation to mitochondria by the HV-3 peptide rescues mitophagy defects and suppresses mitochondrial and neuronal damage, thus ameliorating HD-associated neuropathology in HD models [63]. In line with previous work, a recent study has delineated the routes by which mHtt impairs neuronal mitophagy in differentiated striatal neurons derived from a knock-in mouse HD model. It has been shown that mHtt affects the initiation of mitophagy by interfering with the formation of the autophagy initiation complex. In addition, it prevents the recruitment of mitophagy receptors and their subsequent interaction with LC3II which is crucial for the elongation of the autophagosome membrane around mitochondria. Such perturbations result in accumulation of damaged mitochondria, enhanced production of reactive oxygen species and increased oxidative stress [64].

Accumulating evidence also supports a causative link between AD and mitophagy deficiency. AD is driven by the formation of amyloid beta (Aβ) peptide plaques and intraneuronal tangles of hyperphosphorylated forms of microtubule-associated protein tau [65]. Cells in the brain of AD patients exhibit compromised mitochondrial function and decreased mitochondrial bioenergetics that lead to synaptic dysfunction and neuronal death [66,67]. Indeed, emerging observations suggest that oligomers of the most toxic form of Aβ peptide, $A\beta_{1–42}$, perturb cellular calcium homeostasis and induce AMPK activation in a calcium/calmodulin-dependent protein kinase kinase 2-dependent manner, leading to synaptic deficits and cognitive decline [68]. Furthermore, $A\beta_{1–42}$ and p-tau inhibit axonal motility of mitochondria and the neurotrophin receptor tropomyosin receptor kinase A, both of which have critical roles in neuronal function [69]. Defective mitochondrial transport in AD neurons affects axonal and synaptic homeostasis, leading to neurodegeneration. Interestingly, partial or complete tau reduction prevents Aβ-induced axonal transport defects and the accompanying cognitive deficits in AD mouse models [69,70]. A recent study elucidates the role of defective mitophagy in mitochondrial homeostasis collapse that occurs in AD brains. In fact, mitophagy deficits have been documented in postmortem hippocampal samples of AD patients, in induced pluripotent stem cell-derived human AD neurons and in mouse and nematode AD models. Moreover, the restoration of mitophagy through supplementation of NAD^+, urolithin A and actinonin has been shown to mitigate cognitive decline associated with AD pathology in nematode and mouse models of the disease by enhancing removal of Aβ plaques and inhibiting tau hyperphosphorylation (p-tau). In *C. elegans*, the amelioration of memory relies on the PINK-1, PDR-1 or DCT-1 pathways. Together, these findings support the notion that impaired mitophagy results in accumulation of dysfunctional mitochondria and compromised mitochondrial homeostasis, thereby promoting AD pathology and cognitive decline [71]. It is therefore plausible to assume that strategies or agents targeting mitophagy in an effort to subvert, at least partially, the aetiology of AD and other age-related pathologies, might have far-reaching beneficial effects towards enhanced healthspan.

Mitochondrial dysfunction is a key event that transpires during dopaminergic neuron loss in PD [49]. Indeed, perturbations in mitochondrial function that arise from bioenergetic deficits, mutations in mtDNA, mutations in nuclear genes encoding mitochondrial proteins, impairment of transcription, alterations in mitochondrial dynamics, changes in mitochondrial size and morphology and defects in mitochondrial transport have been associated with PD pathogenesis [72,73]. As previously mentioned, mutations in either PINK1 or Parkin lead to early-onset PD, suggesting that impaired mitophagy may in part account for dopaminergic neuron loss. Moreover, mutations in the

leucine-rich repeat kinase 2 gene, which are also associated with familiar PD, inhibit the degradation of the OMM protein Miro that anchors mitochondria to microtubule motors. Retention of Miro on damaged mitochondria prolongs their active transport and delays their degradation through mitophagy. Such defects lead to increased susceptibility to oxidative damage and neuronal deterioration, as observed in neurons derived from induced pluripotent stem cells from patients with inherited or sporadic PD. Taken together, these findings provide further support to the notion that insufficient mitophagy has a pathological role in PD onset and progression [74].

Conclusions

Impaired mitochondrial function and excessive mitochondrial content are major characteristics of ageing and several human pathophysiological conditions, highlighting the pivotal role of the coordination between mitochondrial biogenesis and mitophagy (Fig. 2). A homeostatic feedback loop allows cells to

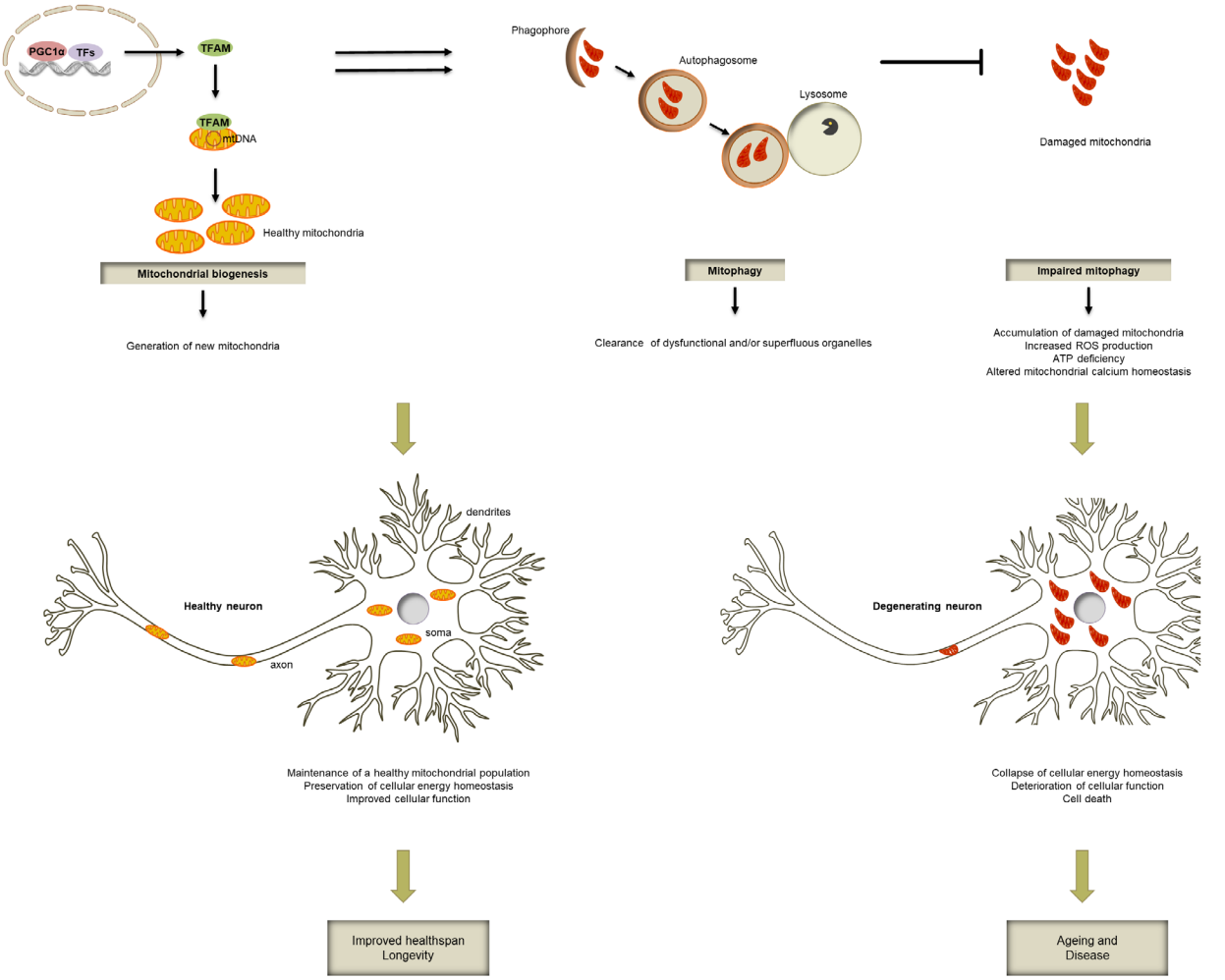

Fig. 2. Balanced mitochondrial biogenesis and mitophagy regulate energy homeostasis and ageing. Mitochondrial biogenesis and mitophagy are two essential processes, responsible for maintaining a healthy mitochondrial population in every cell. In response to various intrinsic and extrinsic stimuli, PGC-1α is upregulated to orchestrate an intricate transcriptional programme that controls the expression of several mitochondrial-related proteins, including the TFAM. TFAM is, in turn, imported into mitochondria where it binds mtDNA to initiate its replication and transcription, promoting the generation of new organelles. By contrast, mitophagy ensures the selective clearance of damaged and/or superfluous mitochondria. Tight coordination between the opposing processes of mitochondrial biogenesis and mitophagy is crucial to preserving energy homeostasis, particularly in postmitotic cells such as neurons. Accordingly, impaired mitophagy causes accumulation of dysfunctional mitochondria, disrupts energy homeostasis and leads to cell and tissue damage, eventually affecting organismal healthspan and lifespan. (see text for details).

adjust their mitochondrial population in response to environmental and intracellular cues. Age-dependent decline of mitophagy both inhibits removal of dysfunctional or superfluous mitochondria and impairs mitochondrial biogenesis, resulting in progressive mitochondrial accretion and consequent deterioration of cell function. A better understanding of the dynamics and reciprocal interplay between stress responses and ageing is critical for the development of novel therapeutic strategies that exploit endogenous stress-combat pathways against age-associated pathologies.

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