BBA - Molecular Basis of Disease 1871 (2025) 167547

Contents lists available at ScienceDirect

BBA - Molecular Basis of Disease

journal homepage: www.elsevier.com/locate/bbadis

Review

Mitostasis in age-associated neurodegeneration

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ARTICLE INFO

Keywords:
Age-associated neurodegenerative disorders
Metabolism
Mitochondria
Mitostasis
Neurodegeneration
Neurodegenerative diseases

ABSTRACT

Mitochondria are essential organelles that play crucial roles in various metabolic and signalling pathways. Proper neuronal function is highly dependent on the health of these organelles. Of note, the intricate structure of neurons poses a critical challenge for the transport and distribution of mitochondria to specific energy-intensive domains, such as synapses and dendritic appendages. When faced with chronic metabolic challenges and bioenergetic deficits, neurons undergo degeneration. Unsurprisingly, disruption of mitostasis, the process of maintaining cellular mitochondrial content and function within physiological limits, has been implicated in the pathogenesis of several age-associated neurodegenerative disorders. Indeed, compromised integrity and metabolic activity of mitochondria is a principal hallmark of neurodegeneration. In this review, we survey recent findings elucidating the role of impaired mitochondrial homeostasis and metabolism in the onset and progression of age-related neurodegenerative disorders. We also discuss the importance of neuronal mitostasis, with an emphasis on the major mitochondrial homeostatic and metabolic pathways that contribute to the proper functioning of neurons. A comprehensive delineation of these pathways is crucial for the development of early diagnostic and intervention approaches against neurodegeneration.

1. Introduction

That "Mitochondria are the powerhouse of the cell" was mentioned colloquially by Philip Siekevitz, in a 1957 issue of Scientific American, a phrase that has garnered global acceptance considering that it is being used frequently in the contemporary scientific literature to describe mitochondria across different biomedical research subfields [1].

Although mitochondria are frequently described as endosymbionts, having a bean-like morphology, they often form complex tubular networks within the eukaryotic cytoplasm that exhibit dynamic restructuring [2]. Mitochondria are semi-autonomously replicating cellular organelles surrounded by a double-membrane system. The mitochondrial matrix (MM) is enclosed within the inner membrane (IM), which is separated from the outer membrane (OM) by the intermembrane space (IMS). The IM folds into cristae that provide a larger surface. These dynamic membrane invaginations are enriched with electron transport chain (ETC) protein complexes [3]. The IM is almost impermeable to generic cytoplasmic solutes, thereby aiding the creation of an electrochemical gradient. This gradient is necessary to establish the mitochondrial membrane potential (MMP) which enables the generation of ATP via chemiosmosis. By contrast, the OM incorporates several voltage-dependent anion channels (VDACs) and is permeable to solutes of up to 5000 Da. Overall, the mitochondrial OM, IMS, IM, and MM are characterized by highly distinctive protein compositions [4–6].

Mitochondria play multifaceted roles in coordinating various metabolic processes, such as ATP production, amino acid and phospholipid synthesis and transport, iron-sulfur cluster formation and metabolite compartmentalization, which are essential for maintaining cellular homeostasis [7–9]. Additionally, mitochondria regulate major signalling pathways by acting as both initiators and transducers. This includes fundamental cellular processes such as apoptosis, calcium signalling, growth factor signalling, hypoxic stress response and inflammatory responses, among others [10–12]. Through oxidative phosphorylation (OXPHOS), mitochondria generate reactive oxygen species (ROS) and reactive nitrogen species (RNS), which contribute to cellular oxidative and nitrosative stress. Accumulated ROS and RNS impact the mitochondrial proteome, genome, and lipidome, thereby, damaging the structural and functional integrity of mitochondria, which can release their contents into the cytosol. This, in turn, triggers a further increase in cellular oxidative and nitrosative stress. When coupled with an

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https://doi.org/10.1016/j.bbadis.2024.167547
Received 6 April 2024; Received in revised form 6 October 2024; Accepted 15 October 2024
Available online 20 October 2024

exaggerated inflammatory response, this may lead to the induction of cell death, owing to severe perturbation of metabolism and cellular signalling mechanisms [13–15].

Failure to maintain mitochondrial integrity has been implicated in the manifestation of various pathophysiological abnormalities, associated with ageing and age-related neurodegenerative disorders [16,17]. Indeed, accumulating evidence links impaired mitochondrial function and neurodegeneration. Metabolic alterations such as reduced expression of mitochondrial enzymes and disruption of mitochondrial function are responsible for the onset and progression of neurodegenerative diseases [18–20]. Conversely, neurodegenerative insults, such as formation of amyloid plaques and neurofibrillary tangles of hyperphosphorylated tau protein, impair mitochondrial integrity, leading to collapse of mitostasis. These bidirectional processes are closely linked and iteratively influence each other. Clinical investigations in patients with neurodegenerative disorders have validated the role of mitochondrial dyshomeostasis and perturbed energy metabolism in the manifestation and modulation of disease-associated phenotypes [21,22].

2. Mitostasis

The term mitostasis collectively refers to the multifaceted homeostatic mechanisms that fine-tune and maintain overall mitochondrial quantity and quality under defined physiological conditions [23]. Importantly, impairment of the biogenesis, distribution or turnover of mitochondria contributes directly to ageing [24] and the pathogenesis of debilitating human disorders such as muscular atrophy [25] and neurodegeneration [23].

Generally, the abundance and activity of mitochondria are dynamically calibrated to match the demand and supply of energy and metabolites in different tissues [26]. When energy demands are high in tissues and organs such as the brain, heart, kidneys, liver and skeletal muscle, the content and function of mitochondria are adjusted accordingly to meet elevated cellular activity. By contrast, oxidative stress, caused by oxygen unavailability (hypoxia) or increased ROS levels, triggers mitochondrial clearance via specific cellular pathways [27].

Replenishing the mitochondrial pool upon damage or dysfunction of mitochondria is essential for mitostasis. Mitochondrial damage can be caused either by exposure to environmental factors (such as occupational chemicals, pollutants, mutagens, and pharmaceutical drugs) or by genetic abnormalities (in both nuclear and mitochondrial DNA). Certain pharmaceutical drugs such as acetaminophen, antibiotics (ampicillin, azithromycin, clindamycin, tigecycline), aspirin, AZT (azidothymidine), cocaine, indomethacin, methamphetamine, L-DOPA (L-3,4-dihydroxyphenylalanine), NSAIDs (nonsteroidal anti-inflammatory drugs) and statins can cause mitochondrial damage [28,29]. Given that most of these drugs are widely prescribed, it is important to consider the impact of these side-effects on human health. Notably, it is disconcerting that antibiotics such as ampicillin not only cause cellular oxidative stress, but also damage mtDNA.

Impairment of ETC, dissipation of MMP, compromised transport of critical metabolites, and genetic lesions are some of the causes of mitochondrial dysfunction. Mitostasis counteracts damage caused by these factors by replacing defective with new, functional mitochondria. Nevertheless, persisting environmental and genetic insults may eventually compromise cellular mitostasis mechanisms, thereby contributing to pathology [28]. Sustaining mitostasis involves the coordination of several cellular processes, including mitochondrial biogenesis, transport, anchoring, fission, fusion, and turnover/clearance (Fig. 1). These interlinked, essential components of mitostasis safeguard the overall genomic and proteomic integrity of mitochondria (Fig. 2) [30,31].

2.1. Mitochondrial biogenesis

New mitochondria arise from pre-existing organelles through a dynamic interplay between fusion and fission events. mtDNA only encodes a small fraction of the proteins (13 polypeptides), required for mitochondrial biogenesis. Most of the mitochondrial proteome (~99 %) is encoded by nuclear DNA and is synthesized by cytosolic ribosomes [32]. These proteins are further processed and transported into their specific mitochondrial compartments through dedicated packaging, import, and assembly mechanisms. Mitochondria then undergo fission, giving rise to new organelles [33].

Specific transcription factors and coactivators control the expression of genes encoding mitochondrial proteins. The proliferator-activated receptor gamma coactivator 1 (PGC1α and PGC1β), the transcription factor A (TFAM), and the nuclear respiratory factors (NRF1 and NRF2), are key regulators of mitochondrial biogenesis [34]. Typically, mRNA transcripts encode pre-proteins, with amino-terminal presequences, which traverse the OM, IMS, and IM in an unfolded conformation. This

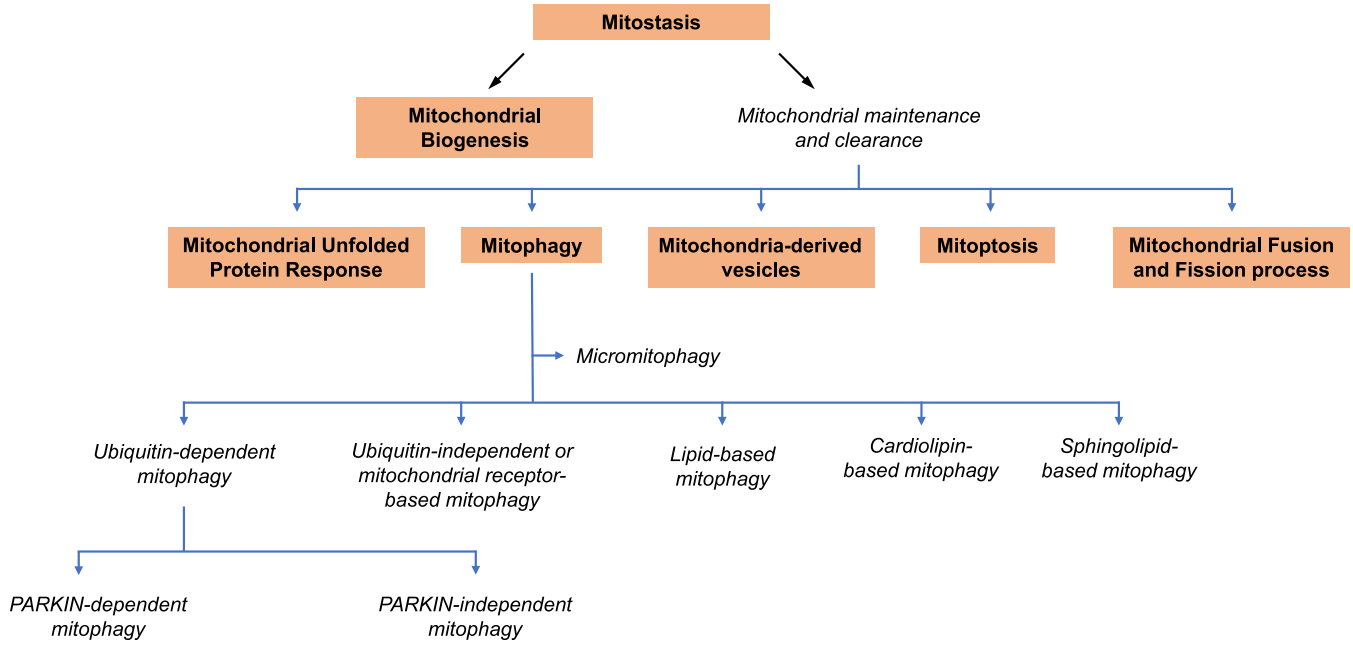

Fig. 1. Classification of mitostasis mechanisms. Schematic classification system for different cellular mitostasis mechanisms.

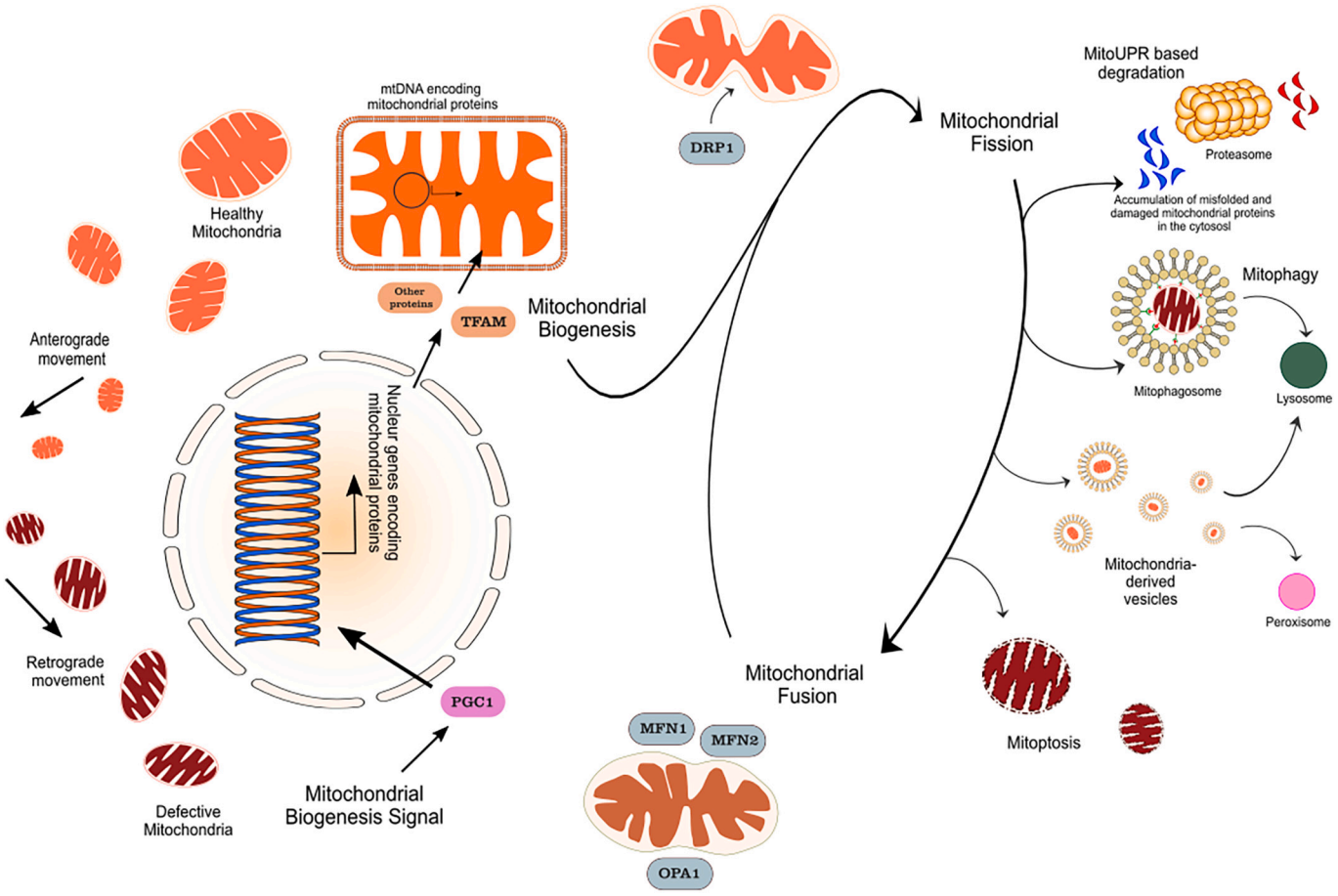

Fig. 2. Mitostasis mechanisms. Various cellular and molecular mechanisms contribute to mitostasis, including the generation of new mitochondria (mitochondrial biogenesis), maintenance of a healthy mitochondrial pool (mitochondrial fusion, mitochondrial fission, mitoUPR, and generation of MDVs), and clearance of superfluous or defective mitochondria (mitophagy and mitoptosis).

ATP- and MMP-dependent process is mediated by specific protein translocase complexes and also requires Hsp70. After entry, the presequence is cleaved by matrix proteases and mitochondrial proteins are then folded with the assistance of molecular chaperones. Mitochondrial pre-proteins devoid of amino-terminal presequences utilize specialized protein-import pathways to enter specific mitochondrial compartments [32].

The PGC-1 family of transcription regulators (PGC-1α, PGC-1β, and PGC-1-related coactivator PRC) [35], together with NRF-1, NRF-2, Estrogen-related receptor α (ERRα) and TFAM coordinate the expression of genes encoding mitochondrial proteins, in response to intrinsic and extrinsic signals [26,36]. In addition, several mitochondrial mRNA translation factors [37,38] and the translational activator of cytochrome *c* oxidase 1 (TACO1) [39], which are encoded by nuclear DNA, bind mitochondrial mRNAs and regulate the expression of mitochondrial DNA-encoded proteins.

2.2. Mitochondrial maintenance and clearance

Maintaining a functional pool of mitochondria is vital for proper cellular function and survival. Mitochondria are generally susceptible to damage inflicted by various extrinsic and intrinsic stimuli. Elaborate cellular quality control mechanisms monitor mitochondrial health and mediate the clearance of damaged or superfluous mitochondria. These mechanisms include the mitochondrial unfolded protein response (mitoUPR), mitophagy, the generation of mitochondria-derived vesicles and mitoptosis.

2.2.1. Mitochondrial unfolded protein response

mitoUPR is an orchestrated stress response pathway that contributes to reestablish mitostasis by transcriptionally activating mitochondrial chaperone proteins and mitoproteases [40]. mitoUPR is triggered by the disruption of mitochondria-associated protein synthesis, translation and folding, uncoupling of OXPHOS, anomalies in mitochondrial DNA, accumulation of excessive ROS, and mitochondrial protein degradation defects [41]. Under physiological conditions, chaperones such as the heat shock proteins Hsp9, Hsp10, Hsp60 and Hsp70 facilitate the folding of translocated, nuclear DNA-encoded mitochondrial proteins or the refolding of misfolded proteins. Defects in the function of these mitochondrial chaperones result in the accumulation of misfolded and damaged proteins, which are degraded via the mitoUPR pathway.

Different mitoUPR axes are activated upon mitochondrial protein misfolding or aggregation [42]. The canonical response leads to the nuclear localization and activation of specific transcription factors that induce the expression of chaperones and proteases to increase mitochondrial protein-folding capacity. Alternatively, SIRT3 can be activated, resulting in the nuclear translocation of FOXO3A, which induces the expression of antioxidant enzymes, such as SOD2 and catalase. When protein misfolding occurs in the mitochondrial intermembrane space, NRF1 is activated via AKT- and ROS-dependent phosphorylation of ERα, thereby increasing protease levels and enhancing proteasome activity. An additional mitoUPR axis initiates a localized response to unfolded proteins in the MM, by pausing pre-mRNA processing, to decrease the overall load on the mitochondrial folding machinery. In conclusion, mitoUPR is a paradigm of how cells implement sophisticated and spatially defined mechanisms to maintain mitostasis in response to

locally induced stress.

2.2.2. Mitophagy

Mitophagy is a cargo-selective autophagic process, targeting damaged or superfluous mitochondria. During mitophagy, mitochondria become sequestered in autophagosomes and are subsequently delivered to lysosomes for degradation. Therefore, by removing aberrant mitochondria, mitophagy contributes to mitostasis. Impairment of mitophagy exacerbates inflammation and neurodegeneration [43,44].

Diverse intracellular and extracellular cues may induce mitophagy. These include mtDNA damage, mitochondrial membrane depolarization, increased ROS production, perturbation of mitochondrial fission-fusion dynamics and oxidative stress, among others. In addition, mitophagy is activated physiologically during erythrocyte maturation, cardiomyocyte maturation, paternal mitochondria removal, and somatic cell reprogramming [45]. Initiation of mitophagy entails the recruitment and activation of specific mitophagy receptors and/or ubiquitin-autophagy adaptors, on the surface of mitochondria, which drive the selective autophagic sequestration and subsequent degradation of targeted mitochondria. Several such receptor/adaptor proteins have been identified, including E2F3d, NLRX1, NIPSNAP1/2, BCL2L13, AMBRA1, MCL1, PHB2, BNIP3/Nix, FUNDC1 and the IMM phospholipid cardiolipin, which externalizes in response to mitochondrial damage to signal mitophagy [46].These molecules bear specific motifs, which interact with corresponding docking sites on core autophagy proteins (ATG8 and FIP200) [47,48]. One such motif is the LC3-interacting region (LIR), which mediates the interaction of autophagy receptors with the LC3/ATG8 family of proteins anchored to the phagophore membrane [49]. This interaction is followed by the recruitment of core autophagy initiation complexes at the omegasome, such as ULK1 and PI3KC3, to generate and expand the phagophore isolation membrane that enwraps mitochondria destined for degradation. These mitochondria-enclosing structures, known as mitophagosomes, fuse with lysosomes, with the aid of specific tethering factors, such as the HOPS complex, PLEKHM1 and SNARE proteins. The SNARE protein Syntaxin17 localizes to the outer membrane of completed autophagosomes and interacts with SNAP29 and VAMP8 (lysosomal SNAREs) to complete the autophagosome–lysosome fusion process [50,51]. Finally, lysosomal acidic hydrolyses degrade mitochondria and their associated content [52,53]. Autophagic machinery components are also released back to the cytoplasm [54].

Based on the specific mitophagy receptor involved, distinct types of mitophagy have been identified [55]. These include ubiquitin-dependent (PARKIN-dependent [56,57] or PARKIN-independent [58–61]), receptor-mediated ubiquitin-independent [62–65], lipid- or cardiolipin-mediated [66], sphingolipid-mediated mitophagy [67,68], and micromitophagy [69].

Clearance of mitochondria via mitophagy has been implicated in several fundamental biological processes, including cellular differentiation, embryonic development, inflammation, and neuroprotection. Numerous studies also highlight the important role of mitophagy in cell survival under stress [17,52]. Indeed, mitophagy deficiency has been implicated in diverse pathologies such as cancer, cardiovascular diseases, neurodegenerative disorders and premature ageing [70,71]. Notably, emerging evidence demonstrates the potential therapeutic effects of mitophagy modulation [72–74].

2.2.3. Generation of mitochondria-derived vesicles

Generation of mitochondria-derived vesicles (MDVs) is a mechanism for shuttling mitochondrial cargo to specific intracellular sites or other organelles. Recent studies have provided valuable insights into the vital role of MDVs in mitostasis and immune signalling [75]. Two basic mechanisms mediate the generation of MDVs. The first entails the formation of electron-dense budding structures on mitochondria that are subsequently released into the cytoplasm [76]. The second involves the formation of thin and long membrane protrusions on the mitochondrial network, along cytoskeletal microtubules, followed by scission close to the protrusion [77].

MDVs contribute to mitostasis independently of mitophagy. In fact, MDV formation occurs in fully intact and polarized mitochondria, in contrast to mitophagy, which is typically triggered by IM depolarization or structural damage [78]. On the other hand, MDVs appear to be formed in response to nutrient deprivation, exposure to toxins, cytosolic or mitochondrial oxidative stress, inhibition of lysosomal function, infection and inflammation, among others [79]. It has been postulated that MDVs may play a key role in protecting mitochondria and preventing mitophagy. Indeed, impairment of MDV formation can potentially trigger aberrant induction of mitophagy, which may compromise cell function and survival [80]. Moreover, MDVs also contribute to mitostasis by shuttling mitochondrial cargo to lysosomes for degradation, independent of mitophagy [81].

2.2.4. Mitoptosis

Mitoptosis is a process mediating the programmed degradation of mitochondria in the cytoplasm or the programmed release of mitochondria from cells [82]. It is primarily induced by apoptotic signals, leading to mechanistic uncoupling of OXPHOS and disruption of MMP. This causes a massive release and accumulation of ROS in the cytoplasm, which results in acute oxidative stress. During IM-associated mitoptosis, the IM begins to coalesce, followed by rarefaction of the MM and deterioration of the cristae, while the OM remains intact. In OM-associated mitoptosis, mitochondrial condensation occurs, followed by swelling and fragmentation of cristae, which ultimately results in bursting of the OM, with remnants of cristae enclosed within vesicles released in the cytoplasm [83]. These mitoptotic bodies can become mitophagosomes that can be recycled in lysosomes or completely extruded from the cell, contributing to mitostasis [84].

2.2.5. Mitochondrial fusion and fission

Specific physiological conditions and metabolic demands, can induce adaptive, dynamic fusion or fission of mitochondria to maintain mitostasis. Under stress, mitochondrial fusion helps to mix partially damaged mitochondria with healthy ones. This allows redistribution of components between organelles, effectively compensating for defects.

On the other hand, mitochondrial fission can facilitate the removal of damaged segments of the mitochondrial network via mitophagy [16,85]. Mitochondrial fusion is a multistep process, with OM and IM fusions regulated by separate sets of proteins. Mfn1 and Mfn2 are recruited to the OM where they interact with adjoining mitochondrial fusion proteins [86]. The fusion of IM is regulated by OPA1, another GTPase localized at the IM. In particular, extensively damaged mitochondria with loss of MMP are prevented from fusing with healthy ones through localized degradation of OPA1, which is mediated by the IM protease OMA1 [87].

Mitochondrial fission primarily involves the Drp1 (Yeast Dnm1), Fis1, Mff, MiD49 and MiD51 proteins. Under conditions of excessive mitochondrial stress, Fis1, Mff, MiD49, and MiD51 guide Drp1 recruitment and proper distribution at mitochondrial fission sites. The Drp1 GTPase mediates membrane constriction and terminal division of mitochondria [88–91]. Mitochondrial fission is a prerequisite for mitophagy and is crucial for mitochondrial quality control. Thus, fine-tuning the two opposing processes of mitochondrial fission and fusion helps to maintain mitostasis [92].

3. Mitochondrial metabolism

In addition to producing ATP, mitochondria also function as nodal metabolic hubs, where intermediate metabolites from catabolic processes can be reintroduced into anabolic pathways that mediate the biosynthesis and compartmentalization of new biomolecules, such as amino acids, fatty acids, cholesterol, nucleotides, glucose, and heme [93]. Key mitochondrial energy-generating pathways, such as the Krebs

cycle and OXPHOS, generate most of the energy required for cell function and survival. Mitochondrial metabolism also results in the generation and intracellular accumulation of toxic by-products, such as ROS, thereby, causing oxidative stress. ROS can react with nitric oxide and generate RNS such as peroxynitrite, which irreversibly modifies tyrosine residues on proteins, via tyrosine nitration [94]. Mitochondria are major contributors to cellular oxidative and nitrosative stress, but they are also equipped with crucial oxidative stress response and management mechanisms [95]. Due to their multiple roles in cellular metabolism, the maintenance of mitochondrial homeostasis is critical for cellular and organismal physiology. Accordingly, perturbation of mitostasis can impact cell function, both through imposing bioenergetic deficits and through interfering with metabolic and signalling pathways. Neurons are particularly sensitive to mitostasis defects, which have been linked

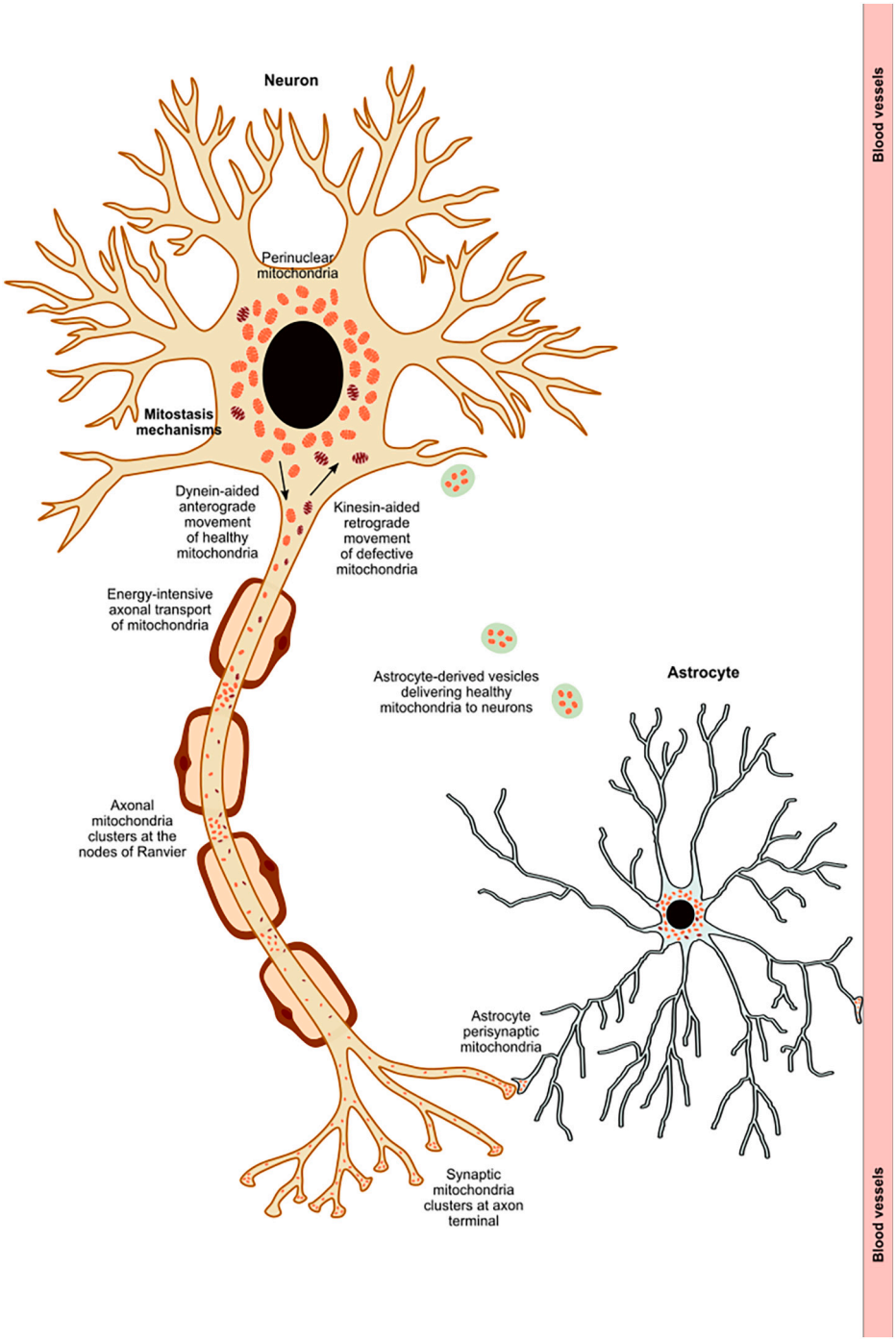

Fig. 3. Mitostasis, distribution and transport of mitochondria in neurons. Nerve cells are typically characterized by an elongated architecture. This makes the energy-intensive distribution and transport of mitochondria throughout their structure a critical challenge. After mitochondrial biogenesis, some mitochondria are retained in the soma, and are mainly localized in the perinuclear space. The remaining mitochondria are trafficked and clustered at high energy-demand sites along axons (axonal mitochondria), such as, the nodes of Ranvier, and near the presynaptic ends (synaptic mitochondria). Anterograde transport of healthy mitochondria and retrograde transport of defective mitochondria occurs with the help of cytoskeletal motor proteins, to maintain a pool of functional mitochondria, throughout neuronal structures. Astrocytes have been shown to assist in neuronal mitostasis by delivering healthy mitochondria through astrocyte-derived vesicles to compensate for energy deficits in specific domains of functional neurons.

to neurodegenerative disorders and age-associated neurodegeneration.

4. Neurodegeneration and neuronal mitostasis

The progressive loss of neurons, and neuron sub structures is referred to as neurodegeneration, and leads to disruption of the overall function of the nervous system, which ultimately manifests as pathology and disease [96]. Neurodegenerative disorders (NDDs) are characterized by a defined set of hallmarks, including aberrant proteostasis, altered energy metabolism, cytoskeletal abnormalities, DNA and RNA defects, inflammation, neuronal cell death, pathological protein aggregation, and synaptic or neuronal network dysfunction [97]. Common NDDs include Alzheimer's Disease (AD), Parkinson's Disease (PD), Huntington's Disease (HD), Amyotrophic Lateral Sclerosis (ALS), Multiple Sclerosis (ALS), Prion Disease, Lewy body Disease, and Spinocerebellar Ataxia (SA), among others.

NDDs affect millions of individuals worldwide. The global status report of the World Health Organization (WHO) on dementia presents an estimated 55 million people affected by dementia in 2019 and forecasts a rise to 139 million cases by 2050 [98]. Ageing is the leading cause of neurodegeneration. Almost all aged brains exhibit characteristic NDD phenotypes including defective mitostasis, genomic instability, protein aggregation, and cellular senescence. Several ageing biomarkers are tightly associated with NDD onset and progression [99]. Environmental and lifestyle factors, along with an individual's genetic predisposition, also contribute to the development of NDDs [100]. Neuronal and neuroglial mitostasis play a critical role towards maintaining overall nervous system health, by alleviating energy deficits and preventing oxidative stress (Fig. 3). Impaired neural mitostasis renders neurons vulnerable to neurodegeneration.

4.1. Mitostasis in neurons

Neurons are typically characterized by an elongated shape with multiple highly differentiated appendages such as axons, dendrites and synapses. This elaborate morphology imposes significant challenges for the distribution and maintenance of mitochondria throughout neuronal structures. In addition, neurons rely almost exclusively on mitochondria for their high and specialized energy requirements to establish membrane excitability and carry out the complex processes of neurotransmission and plasticity. Given that neurons are also long-lived and mitotically quiescent cells, mitostasis is essential for their long-term survival and function. Thus, not surprisingly, defects in neuronal mitostasis contribute to severe NDD pathophysiology [101].

How do neurons achieve mitostasis, despite their unique complexity and elevated bioenergetic requirements? The neuronal soma is the location where mitochondrial biogenesis primarily occurs. Some mitochondria need to be retained in the soma, whereas others need to be trafficked and concentrated at energy-intensive sites along the axons and dendrites, such as the nodes of Ranvier and presynaptic terminals [102,103].

Axonal transport of mitochondria occurs across the microtubule and neurofilament network. Depending on the direction of movement, either kinesin or dynein motor proteins are required (for anterograde or retrograde transport respectively) [104–106]. Members of the MIRO protein family are also involved in modulating axonal transport of mitochondria [107]. Trafficking of mitochondria and other components to distal compartments, across long axons and neuronal appendages, together with the maintenance of plasma membrane potential, are two of the most bioenergetically costly neuronal processes, that mostly depend on ATP generated in mitochondria [108].

4.2. Mitostasis in neuroglia and neuron-glia crosstalk

Neuroglia play essential housekeeping and regulatory roles in the nervous system. Impairment of mitostasis in these cells undermines overall nervous system homeostasis and has been implicated in age-related neurodegeneration and NDDs. The perisynaptic structures of astrocytes, a type of neuroglial cells in the brain, feature a high number of mitochondria, which likely contribute to Ca^{2+} homeostasis and signalling required for neurotransmitter release at these sites [109]. Astrocytic mitochondria have also been found to play an essential role in neuron-glia communication, by providing ATP for the production of adenosine that functions as a neurotransmitter and neuromodulator [110,111].

Notably, recent studies indicate that mitochondria can be horizontally transferred between astrocytes and neurons via astrocyte-derived microvesicles [112,113]. Shuttling mitochondria from astrocytes to neurons may contribute to offset neuronal energy deficits and maintain mitostasis. The molecular mechanisms that govern the intercellular transport of mitochondria are currently being explored as potential therapeutic targets for NDDs [114,115].

5. Mitochondrial metabolism in neurodegeneration

While, in humans, the nervous system constitutes only about 2 % of the overall body weight, it consumes more than 20 % of the total organismal energy output. Most of this energy (70–80 %) is required for the function of neurons, with the remainder used by glial cells [116]. The bulk of the energy consumed by the nervous system is generated by mitochondria through aerobic respiration, rendering neuronal cells particularly sensitive to perturbations of mitochondrial metabolism that can cause oxidative stress.

To counter oxidative stress, neurons engage the hypoxia-inducible factor (HIF) pathway to adjust oxygen consumption by mitochondria, and the HIF-1α-induced, hypoxia up-regulated mitochondrial movement regulator (HUMMR) to regulate mitochondrial transport [117,118]. In addition, mitochondrial calcium (mCa^{2+}) is an important regulator of diverse aspects of mitochondrial physiology and function. In the MM, mCa^{2+} regulates the Krebs cycle by controlling the activity of pyruvate, isocitrate and α-ketoglutarate dehydrogenases, with direct implications for intramitochondrial ATP production [119]. Notably, excess mCa^{2+} impairs mitochondrial metabolism, increases ROS production, and activates the intrinsic cell death pathway [120]. Moreover, disruption of cellular calcium buffering capacity, due to the accumulation of damaged mitochondria during ageing, has been linked to age-associated neurodegeneration [121], as well as, to the onset and progression of NDDs [122].

Several recent studies have revealed the early appearance of mitochondrial bioenergetics defects in asymptomatic stages of NDDs [123,124], suggesting mitochondrial metabolism alterations may underlie the onset of neurodegeneration. Specific therapeutic interventions have established a correlation between sustained mitochondrial function and amelioration of neurodegeneration, further underscoring the importance of mitostasis and proper mitochondrial metabolism for nervous system health [125–127].

Impaired mitostasis, protein aggregation and induction of cell death pathways are common denominators of most NDDs [128]. Accumulating evidence from both clinical studies and animal models of neurodegeneration indicates that aberrant mitochondrial metabolism is central to the pathogenesis of NDDs. Reduced glucose uptake and utilization have been observed in the brains of patients with AD, PD, HD, and ALS using positron emission tomography [129]. Moreover, epidemiological data suggest a link between metabolic disorders, such as diabetes and obesity, and NDDs. This association can be attributed to altered energy metabolism, and the consequent energy deficits in the neurons [130].

6. Mitochondrial dysfunction in age-associated neurodegenerative diseases

Among the various NDDs, AD and PD are the most prevalent,

whereas HD and ALS are comparatively less common. AD patients display impaired mitochondrial biogenesis and turnover, in addition to aberrant morphology and compromised ETC function, in mitochondria of the nervous system [73,131,132]. PD pathology has been linked with mutations in the mitophagy regulators PINK1 and Parkin, and with abnormal ubiquitin^{Ser65} phosphorylation, which interferes with mitochondrial quality control. PD is also associated with a significant decrease in the levels of TFAM and SIRT3, as well as HSP60 and PHB1, which diminishes mitochondrial protein folding capacity [133]. HD is characterized by impaired mitochondrial dynamics, altered OXPHOS

Table 1
Mitochondrial dysfunction in neurodegenerative disorders. The associated pathological features, the specific mitochondrial functions impaired, and the genes and enzymes implicated are referenced.

Neurodegenerative disorder	Associated Pathological features	Mitochondrial dysfunction	Genes implicated	Metabolic enzymes affected	Reference
Alzheimer's Disease	Aggregation of beta-amyloid (Aβ) peptides; Hyperphosphorylation of the Tau (pTau) protein, forming neurofibrillary tangles	Impairment of mitochondrial ETC components; Decreased ATP production; Increased oxidative stress; Defective mitophagy; Compromised mitochondrial integrity; Reduced activity of nutrient transporters; Diminished mitochondrial enzyme activity; Reduced mtDNA copy number; MMP dissipation	APP, PS1, PS2, FoxO3a, Bcl-2, ATG32, PINK1, p-S65-Ub, BNIP3, LC3B-II/I, p62/SQSTM1, GLUT1, GLUT3	Pyruvate dehydrogenase complex, α-ketoglutarate dehydrogenase complex, phosphofructokinase, glucose-6-phosphate isomerase, lactate dehydrogenase, aldolase, phosphoglycerate mutase, cytochrome oxidase	[73,121,139,146,147,195–198]
Parkinson's Disease	Progressive degeneration of dopaminergic neurons; Reduced dopamine levels in the substantia nigra pars compacta (SN); Aggregation of α-synuclein, formation of Lewy neurites	Impairment of mitochondrial ETC components; Decreased ATP production; Increased oxidative imbalance; Defective mitophagy; Dysfunctional mitochondrial protein import pathways; Compromised mitochondrial integrity; Chronic inflammation; Impaired mitochondrial fusion and fission process; Diminished mitochondrial enzyme activity	PARKIN, PINK1, p-S65-Ub, DJ-1, ATP13A2, SNCA, LRRK2, CISD1, HSP60, PHB1, TFAM, SIRT3	Glucose-6-phosphate dehydrogenase, 6-phosphogluconate dehydrogenase, Glucose-6-phosphate isomerase	[133,158,164,198–201]
Huntington's Disease	Aggregation of mutant Huntingtin (mHtt)	Impairment of mitochondrial ETC components; Decreased ATP production; Defective mitophagy; Compromised mitochondrial integrity; Diminished mitochondrial enzyme activity; Impaired mitochondrial fusion and fission process; Decreased mitochondrial biogenesis; Diminished mtDNA copy number; MMP dissipation; Reduced calcium loading capacity	HTT, DRP1, FIS1, MFN1/2, PGC-1α, SLC2A3, GLUT3, SIRT1, SIRT3	Glucose-6-phosphate dehydrogenase, phosphofructokinase	[169,175,176,198,202–204]
Amyotrophic Lateral Sclerosis	Progressive degeneration of nerve cells and astrocyte endfeet in the spinal cord and the brain	Impairment of mitochondrial ETC components; Decreased ATP production; Enhanced ROS; Defective mitophagy; Impaired mitochondrial fusion and fission process; Compromised mitochondrial integrity; Increased mitochondrial swelling; MMP dissipation; Increased calcium accumulation	SOD1, TDP-43, CHCHD10, TBK1, OPTN, SOD1, OPA1, DRP1, Bcl-2	Cytochrome oxidase	[121,169,183,184,186,205]

and defective mitochondrial protein transport [134,135]. Aberrant mitochondrial morphology and functional irregularities have also been observed in ALS models [136]. Fibroblasts derived from frontotemporal lobar degeneration patients show reduced mitochondrial function and p62 accumulation [137]. These findings are consistent with the direct contribution of dysregulated mitostasis and perturbed mitochondrial metabolism in the pathogenesis of neurodegenerative disorders (Table 1).

6.1. Alzheimer's disease (AD)

AD is the most common cause of dementia and is characterized by progressive decline of cognitive function and loss of learning and memory capacity. AD can be generally categorized into early-onset familial AD (FAD) and late-onset sporadic AD. Common AD phenotype includes aggregation of beta-amyloid (Aβ) peptides and hyperphosphorylated tau (pTau) proteins, which form plaques and neurofibrillary tangles, respectively, in the brain [138]. Several studies indicate that these extracellular amyloid plaques and intracellular neurofibrillary tangles disrupt mitochondrial integrity and mitostasis, leading to the accumulation of damaged mitochondria in brain cells [73,139–142]. Consequently, mitochondrial dysfunction induces oxidative and nitrosative stress that exacerbates disease pathology by further increasing the accumulation and aggregation of Aβ and pTau [143]. In AD patient neurons, cytoplasmic levels of FoxO3a are increased and mitophagy genes are downregulated, resulting in accumulation of LC3B-II and p62/SQSTM1. Consequently, mitophagy becomes attenuated, which in turn accelerates disease progression [144,206]. Several studies suggest that Aβ and pTau destabilize MMP by progressive opening of the mitochondrial permeability transition pore [123]. This leads to cytochrome C and pro-apoptotic protein release into the cytoplasm and activation of apoptotic cell death mechanisms [145]. Moreover, the level and activity of proteins involved in mitochondrial quality control are reduced in animal models of AD, and in tissue samples from patients with AD [146]. Finally, mutations in presenilin-1, presenilin-2 and the amyloid precursor protein (APP) that have been linked to early onset FAD, have also been associated with mitochondrial dysfunction and compromised mitostasis [147,207].

Neurovascular dysfunction is an early indicator of AD, as patients show increased blood-brain barrier (BBB) permeability in the early stages of disease manifestation [148]. This may potentially lead to changes in the expression and activity of metabolic enzymes and nutrient transporters. Decreased levels of glucose transporters GLUT1 and GLUT3 have been observed in the brains of patients with AD, consistent with reduced brain glucose uptake and cognitive defects [149]. In mouse AD models, reduced GLUT1 expression aggravates amyloid pathology and cognitive dysfunction [150]. Similarly, the activity of several metabolic enzymes such as the pyruvate dehydrogenase complex, the α-ketoglutarate dehydrogenase complex, phosphofructokinase (PFK), glucose-6-phosphate isomerase, lactate dehydrogenase, aldolase, phosphoglycerate mutase and cytochrome *c* oxidase is reduced in AD models and patients [151–153]. Notably, ketone and nicotinamide riboside supplementation reduces Aβ aggregation and pTau tangles, improving behavioural outcomes and the clinical features of the disease [154–156].

6.2. Parkinson's disease (PD)

Bradykinesia and tremors are the characteristic clinical features of PD, which can be generally categorized into familial PD (FPD) and sporadic PD. Degeneration of dopaminergic neurons in the substantia nigra pars compacta (SN) and reduced dopamine levels are key contributors to PD pathogenesis [157]. In addition, Impaired mitochondrial function, oxidative stress, and chronic inflammation have been associated with PD [158]. Oxidative stress in SN dopaminergic neurons elicits the generation of neurotoxins such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which in turn targets mitochondrial ETC complex I [159]. Another common pathological feature of PD is the formation of Lewy neurites by α-synuclein aggregation [160]. The progressive accumulation of aggregated α-synuclein in the OM of mitochondria interferes with mitochondrial protein import pathways and mitochondrial dynamics [158]. Indeed, α-synuclein accumulation disrupts the mitochondrial fusion process and interferes with mitostasis in neurons [161]. Furthermore, lesions in the mitochondrial quality control proteins such as SCNA and LRRK2 have been linked with autosomal dominant PD, while Parkin, PINK1, and ATP13A2 have been associated with autosomal recessive PD [133]. Recent studies utilizing a *Drosophila* PD model indicate that progressive accumulation of the iron-sulfur cluster protein Cisd during ageing is a key driver of PD pathology. Cisd accumulation hinders mitophagy, while genetic or pharmacological inhibition of Cisd accumulation (e.g., rosiglitazone and NL-1) improves neuronal survival and function. These findings suggest that restoration of mitostasis is a potential therapeutic strategy against PD [162].

Clinical imaging approaches, such as positron imaging tomography and magnetic resonance imaging, have revealed diminished glucose uptake and hypometabolism in the brains of patients with PD [163]. Indeed, the levels and activity of enzymes involved in the phosphate pentose pathway, such as glucose-6-phosphate dehydrogenase (G6PD) and 6-phosphogluconate dehydrogenase are reduced during the early stages of PD [164]. Additionally, glucose-6-phosphate isomerase, a key enzyme involved in glycolysis, has been found to function as key modifier of dopamine metabolism in *C. elegans* and *Drosophila* models of PD [165]. Importantly, interventions that enhance mitochondrial metabolism bring about remarkable improvements, relevant to the neuropathology and motor deficits in animal models of PD [166].

6.3. Huntington's disease (HD)

The pathological symptoms of HD include cognitive defects, involuntary motor movements, progressive dyslexia, and debilitating psychiatric abnormalities. HD is a genetic NDD, caused by trinucleotide (CAG) repeat expansions in the huntingtin gene, resulting in increased expression and subsequent aggregation of the mutant Huntington protein (mHtt) [167]. mHtt interferes with mitophagy by interacting with mitophagy receptors on damaged mitochondria [168]. Moreover, mHtt interferes with mitochondrial fission by binding to DRP1. The mRNA levels of DRP1 and FIS1 progressively increase with the onset of HD, whereas expression of MFN1/2 decreases [169,170]. mHtt can also inhibit PGC-1α, thereby reducing mitochondrial biogenesis [171].

Mitochondrial metabolism in the striatum of HD patients is reduced prior to progressive pathological atrophy, which correlates with glucose hypometabolism [172]. Interestingly, glucose uptake is significantly reduced in the asymptomatic and early stages of HD [173], although the expression of glucose transporters GLUT1 and GLUT3 in the HD caudate is not significantly different from non-HD controls. In contrast, the expression of GLUT1 and GLUT3 has been shown to be significantly reduced in the HD caudate compared to controls at later stages of the disease [174]. Notably, high copy number of GLUT3, also known as SLC2A3 (solute carrier family 2, facilitated glucose transporter member 3), delayed the onset of HD [175]. In fly HD models, overexpression of PFK, G6PD, and GLUT3 protects against HD pathology and increases survival [176]. Likewise, increased expression and activation of NAD + -dependent deacetylases, such as the sirtuins SIRT1 and SIRT3, preserves mitochondrial integrity and prevents striatal neuron degeneration [177–179]. In fact, agents that increase SIRT1 and SIRT3 activity protect neural cells against mHtt-associated toxicity and improve neuron functionality in animal models of HD [179,180].

6.4. Amyotrophic lateral sclerosis (ALS)

Progressive neurodegeneration in the brain and spinal cord is a characteristic phenotype of ALS. Similar to other NDDs, impairment of

mitostasis mechanisms has been linked to the pathogenesis of ALS. Genetic lesions in the TABK-binding kinase 1 (TBK1) moderate the activity of OPTN and consequently reduce mitophagy in neurons of ALS patients [181]. Mutations in the Cu/Zn SOD1 gene have also been implicated in ALS pathogenesis. Expression of mutant SOD in neurons downregulates OPA1 and DRP1, causing erratic mitochondrial fission and impairing mitophagy [182]. Mutant SOD also binds to Bcl-2 and induces conformational changes that disrupt mitochondrial morphology, increase cytochrome *c* release and activate intrinsic apoptosis [183]. Binding of mutant SOD to Bcl-2 also alters the conductivity of VDACs, disrupts calcium homeostasis and reduces ATP production [184]. Mutant SOD-induced MMP disruption and OXPHOS defects lead to increased ROS production and oxidative stress, which contributes to ALS pathogenesis [185].

The clinical hallmarks of ALS include hypercatabolism and elevated static energy expenditure [186]. Patients with ALS show glucose intolerance and insulin resistance [187]. Additionally, degeneration of astrocyte endfeet, coupled with increased permeability of the blood-brain barrier (BBB) and endothelial transporters, cause accumulation of blood proteins in the cerebrospinal fluid and inflammation [188–190]. In mutant SOD mice, BBB breakdown precedes neurodegeneration, indicating that loss of cerebral metabolic homeostasis plays an important role in the onset and progression of ALS [190–193].

7. Concluding remarks

Every year, millions of people worldwide are affected by various age-associated neurodegenerative diseases that have a devastating impact on human health and wellbeing. Recent studies have identified key molecular mechanisms and pathways underlying neurodegeneration. Importantly, an emerging common denominator of these molecular mechanisms and pathways is their extensive crosstalk with mitostasis mechanisms.

Due to their high energy demands, unique architecture and post-mitotic nature, neurons rely heavily on mitochondria for their health and function throughout the lifespan of an organism, as discussed above. Indeed, neurons are highly differentiated and compartmentalized cells that face the challenge of recruiting mitochondria to distant parts of the cell via axonal transport to meet energy demands at these sites. In addition, neurons are non-dividing cells that can survive for the lifetime of an organism and as such are critically dependent on a healthy mitochondrial network for their proper functioning. Faced with diverse metabolic challenges, in response to physiological adaptations and stress conditions developing during ageing, neuronal mitochondria must uphold bioenergetic homeostasis to meet the diverse needs of these cells. Notwithstanding the accumulation of unavoidable damage to mitochondria, neurons engage elaborate quality control mechanisms to maintain a functional mitochondria pool. Studies in different organisms ranging from invertebrates to humans converge to identify failure of mitostasis as a key contributor to neurodegeneration. Conversely, multiple neurodegenerative insults, such as protein aggregation (amyloid plaques, hyperphosphorylated tangles, Lewy neurites, etc.), oxidative stress, and ionic imbalance, directly impinge on mitochondrial function and integrity, causing a breakdown of mitostasis.

Notably, mitostasis is not only influenced by intracellular cues. A recent study investigating the effect of the extracellular matrix (ECM) on mitostasis, revealed that ECM remodelling triggers a TGF-β response that, in turn, induces mitochondrial fission and mitoUPR [194]. This mechanism, which is potentially relevant during neurogenesis, may also play a role in neurodegeneration during ageing. Indeed, while considerable progress has been made towards understanding the causative interlinks between mitostasis and neurodegeneration mechanisms, several questions still remain. Thus, there is ample scope for further investigation of this intimate relationship, which will pave the way for the development of novel and effective therapeutic interventions to tackle the debilitating problem of age-associated NDDs.

CRediT authorship contribution statement

Mrutyunjaya Panda: Writing – review & editing, Writing – original draft, Conceptualization. **Maria Markaki:** Writing – review & editing, Validation, Supervision. **Nektarios Tavernarakis:** Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

We acknowledge the contribution of researchers working to decipher the role of mitochondria in age-associated neurodegeneration and apologize to those colleagues whose work could not be referenced owing to space limitations. Work in the authors' laboratory has been funded by grants from the European Research Council (ERC – GA695190 – MANNA), the Hellenic Foundation for Research and Innovation (H.F.R.I.) under the "1st Call for H.F.R.I. Research Projects to support Faculty members and Researchers and the procurement of high-cost research equipment" (Project Number: HFRI—FM17C3-0869, NeuroMitophagy) and the General Secretariat for Research and Innovation of the Greek Ministry of Development. Mrutyunjaya Panda is supported by TClock4AD within the HORIZON-MSCA-2021-DN-01 call of the European Union, entitled "Targeting Circadian Clock Dysfunction in Alzheimer's Disease" (Grant agreement no. 101072895), on the project entitled "Circadian control of mitochondria-specific autophagy in neuronal degeneration associated with Alzheimer's Disease".

Data availability

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

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