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REVIEW

Mitochondria, Cell Death, and Neurodegeneration

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Abstract—Mitochondria, acquired during the evolution of eukaryotic cells, have become essential organelles for cellular life. Beyond their well-established role in energy production, mitochondria are key regulators of intracellular signaling, acting as modulators of Ca^{2+} transport and major sources of reactive oxygen species. Mitochondrial metabolism is also closely linked to the metabolism of signaling molecules, including glutamate and monoamines. Another vital role of mitochondria is their involvement in the regulation of cell death. Disruption of mitochondrial functions contributes to the development of multiple pathological conditions, including neurodegenerative diseases. Here, we discuss how impairments in major mitochondrial processes contribute to neuronal death in neurodegenerative diseases and highlight the principal mitochondrial targets with potential pharmacological relevance.

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INTRODUCTION

Mitochondria are regarded as unique organelles for several reasons, including the presence of their own circular DNA and involvement in a broad range of vital cellular functions. Their fundamental role is the production of energy in a form of adenosine triphosphate (ATP), in a process coupled to oxygen consumption and the generation of the transmembrane mitochondrial potential ($\Delta\Psi m$). The mitochondrial membrane potential serves as the proton-motive force that drives ATP production by ATP synthase; however, it is also required for other mitochondrial processes, including mitochondrial Ca^{2+} signaling, the activity of several transport proteins. and, importantly, the initiation of cell death. Complete loss of $\Delta\Psi m$ associated with the opening of the mitochondrial permeability transition pore (mPTP) leads to mitochondrial swelling and the irreversible release of pro-apoptotic proteins [1]. The involvement of mitochondria in necrosis, as well as in ferroptosis and parthanatos, which have been recognized by some authors as separate forms of cell death, has also been extensively demonstrated [2, 3].

Mitochondrial turnover, including both mitochondrial biogenesis and the selective removal of damaged organelles through mitophagy, also depends on cellular energy demands and oxygen consumption [4].

Neurodegenerative diseases represent a growing challenge for both medicine and society. Despite obvious progress in understanding their underlying mechanisms, these diseases remain incurable. A prominent feature shared by almost all neurodegenerative disorders is the involvement of mitochondria in disease pathogenesis is [5]. Thus, mitochondrial toxins induce Parkinson's disease (PD) in animal models and humans [6, 7], while most of mutations associated with hereditary forms of PD affect genes encoding either mitochondrial proteins or proteins that control mitochondrial function [8]. Mitochondrial dysfunction

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has also been demonstrated in Alzheimer's disease (AD), frontotemporal dementia (FTD), motor neuron diseases, and other disorders [9-11].

Given the high demand of neurons for ATP, it could be assumed that the vulnerability of brain cells to mitochondrial dysfunction is primarily due to energy deficit. However, neurons can compensate for impaired ATP production by oxidative phosphorylation (OXPHOS) through glycolysis and possibly other metabolic pathways. Moreover, the involvement of dysfunctions in a wide range of mitochondrial processes, such as mitophagy, mitochondrial Ca^{2+} transport, and oxidative stress in neurodegenerative diseases suggests an existence of cell death mechanisms extending beyond energy failure. Here, we discuss the contributions of different mitochondrial processes in the mechanisms of cell death during neurodegeneration and seek to identify the key processes, or combinations of these processes, that are characteristic of cell death in specific neurodegenerative disorders.

MITOCHONDRIAL BIOENERGETICS, ATP DEFICIENCY, AND CELL DEATH

Although the brain accounts for only ~2% of body mass, it is among the most metabolically demanding organs, consuming approximately 20% of the body's glucose and oxygen supply [12, 13]. These exceptionally high energy demands reflect the need to maintain ion gradients, support neurotransmitter cycling, sustain intracellular signaling and biosynthetic reactions, and perform other functions essential for neuronal and glial activity [12]. ATP also serves as a phosphate donor for a wide range of phosphorylation reactions that regulate cellular metabolism and signal transduction [14, 15]. Although ATP can be generated through glycolysis and other metabolic pathways, OXPHOS accounts for up to 90% of high-energy phosphate production in brain tissue. Consequently, impaired mitochondrial bioenergetics represents a major driver of energy failure in neural cells [16].

ATP depletion is a common feature of brain injury, neurodegenerative diseases, and physiological ageing. In the B6.Cg-Tg mouse model of AD, ATP levels decline progressively with age compared to wild-type animals [17]. This age-dependent loss of ATP is associated with increased vulnerability of mitochondrial bioenergetics to reduced oxygen and glucose availability [18]. Importantly, these alterations are unlikely to occur uniformly across the brain, as different brain regions have different energy demands and physiological activity [19]. Consistent with this concept, in the TgCRND mouse model of AD associated with caspase-independent regulated cell death, increased expression of apoptosis-inducing factor (AIF) and pronounced age-related cell loss are observed mostly in the cortex [20]. This regional vulnerability may therefore reflect intrinsic differences in energy production and consumption across brain regions [19].

Post-mortem analyses of brain tissue from patients with AD further support a link between energy metabolism, antioxidant capacity, and cell death. ATP levels were associated with the abundance of reduced glutathione (GSH), whose synthesis requires high-energy phosphate consumption, as well as with the susceptibility of cells to ferroptosis [21]. However, although ATP availability can be rate-limiting for GSH synthesis, the relationship between mitochondrial dysfunction and cell death is not necessarily linear, since mitochondria are not only the main source of cellular ATP but also important consumers of antioxidant capacity [21].

Experimental models of PD also illustrate the close relationship between mitochondrial bioenergetic failure and neuronal death. In MPTP models, oxidative deamination of MPTP generates MPP^+, which inhibits complex I of the mitochondrial electron transport chain (ETC), thereby impairing electron transfer and causing a profound ATP deficit that contributes to cell death [22, 23]. ATP depletion is also one of the earliest consequences of exposure to 3-nitropropionic acid, an inhibitor of succinate dehydrogenase, that induces neuronal degeneration [24]. Similarly, overexpression of mitochondria-targeted α-synuclein in human dopaminergic neurons leads to the respiratory chain uncoupling, bioenergetic collapse, and cell death [25].

Changes in ATP levels are also linked to the severity and outcome of acute brain injury. ATP dynamics correlate with other pathological parameters and with both short- and long-term consequences of stroke [26]. Intracellular ATP depletion is associated with profound axonal pathology, including condensation of the axoplasm and synaptic vesicles, disruption of glutamatergic synapse organization, and condensation and aggregation of proteins implicated in neurodegeneration [27]. ATP depletion during secondary ischemia after traumatic brain injury reduces the viability of hippocampal CA1 neurons [28]. In primary rat neuron–glia cultures, exposure to hydrogen peroxide or elevated extracellular Ca^{2+} induces bioenergetic disturbances that correlate with changes in metabolic activity assessed by the MTT assay [29].

Collectively, these findings support the use of ATP content as a useful readout of brain tissue state and pathology progression. This concept has been applied in *in vivo* studies to assess the protective effects of receptor antagonists against excitotoxic injury [30]. However, a central question remains unresolved: does ATP depletion itself act as a direct trigger of cell death, or does neuronal loss result from the failure

of ATP-dependent processes that are required to maintain cellular homeostasis?

Most studies support a positive relationship between enhanced bioenergetic capacity and cell survival, suggesting that ATP availability is tightly linked to neuronal viability. For example, high glucose concentrations can slow cell death and, under some conditions, restore survival to near-control levels, consistent with a greater contribution of OXPHOS-independent energy production [22]. Similarly, upregulation of ATP synthesis by inhibiting pyruvate dehydrogenase kinase with dichloroacetic acid or by supplementing cultures with pyruvate protects brain cells in a pilocarpine model of epilepsy [31].

Restoration of ATP levels has also been associated with structural and proteostatic benefits manifested as improvements in the neuronal structure and proteostasis in disease-relevant neuronal models. In neurons derived from patients with PD and amyotrophic lateral sclerosis (ALS), increased ATP availability was linked to normalization of axoplasmic organization, while in ALS motor neurons, it reduced TDP-43 aggregation [27]. Increasing ATP levels or reducing the consumption of high-energy phosphates may therefore represent a strategy to limit neuronal loss in *in vivo* MPTP models of PD [32]. This concept is particularly relevant to hereditary forms of ALS, in which dysfunction of the ATP/ADP exchanger has been associated with pronounced mitochondrial uncoupling, ATP depletion, and subsequent cell death [33, 34].

Importantly, ATP availability is a major determinant of cell death modality [35, 36], reflecting the dependence of several steps of the apoptotic program, including apoptosome assembly and kinase-dependent signaling, on ATP. For example, JNK-mediated phosphorylation contributes to the inactivation of the anti-apoptotic protein Bcl-2 and to the activation of the pro-apoptotic proteins Bad, Bim, and Bmf [37]. Consistent with this, ATP depletion is generally more pronounced during necrosis and caspase-independent forms of cell death than during apoptosis [38, 39].

The mode of neuronal death also depends on the cellular context. In models of 3-nitropropionic acid toxicity, the presence of supportive glial cells shifts the response towards apoptosis in mixed cultures, whereas neuronal monocultures predominantly undergo necrosis [40]. In cortical neurons exposed to hydrogen peroxide, the extent of ATP loss is concentration-dependent and is associated with distinct death modalities: 100 μM H_2O_2 reduces ATP levels to 40-50% of control and promotes apoptosis, whereas 1 mM H_2O_2 lowers ATP to ~15% of control and favors necrosis [41]. Similarly, in cells treated with 50 μM H_2O_2, additional inhibition of F_1F_O-ATP synthase by oligomycin shifts cell death from apoptosis towards necrosis and PARP1-dependent parthanatos [35]. Conversely, restoration of ATP levels can redirect cell death from necrosis towards apoptosis [38].

Thus, ATP availability not only determines whether a cell survives or dies, it also influences the mode and trajectory of cell death. In addition to the extent of ATP depletion, cell fate depends on the duration of energy stress. A transient 30% reduction in ATP over 3 h promotes apoptosis, whereas more prolonged energy deprivation favors necrosis [37].

The link between ATP availability and cell death modality is further illustrated by studies using caspase inhibition. In cyanide-induced toxicity, treatment with the pan-caspase inhibitor zVAD-fmk promotes a shift away from apoptosis under conditions of ATP depletion, accompanied by increased reactive oxygen species (ROS) production and enhanced PARP1 activity [42]. This response favors alternative, non-apoptotic routes of cell death. Conversely, pretreatment with 3-aminobenzamide, a PARP1 inhibitor, attenuates necrotic cell death and helps preserve intracellular ATP levels [42].

The dependence of apoptosis on ATP may also be relevant for neuroprotection in specific pathological settings. In a model of ischemia–reperfusion induced by transient occlusion of the right middle cerebral artery, the protective effect of the alkaloid oxysophoridine was associated with normalization of high-energy phosphate levels compared to control tissue [43].

Collectively, these findings suggest that impaired mitochondrial ATP production does not inevitably lead to cell death. Under basal conditions, reduced mitochondrial ATP output can be partially compensated by alternative energy-producing pathways. However, this compensation can fail when energy demands rise sharply, as occurs during epileptic activity or glutamate excitotoxicity, thereby converting impairments in mitochondrial bioenergetics into neuronal injury [44-46].

BALANCE BETWEEN MITOCHONDRIAL BIOGENESIS AND MITOPHAGY IN NEURODEGENERATION

Neurons are particularly dependent on mitochondrial integrity because of their high energy demand and complex polarized architecture [47, 48]. Even modest mitochondrial dysfunction can therefore induce energy stress and activate cell death programs. Mitochondrial integrity is maintained by the mitochondrial quality control (mitoQC) network, a coordinated system of pathways that detects and resolves defects within the mitochondrial compartment [49, 50]. These pathways include mitochondrial biogenesis [51], regulation of the dynamic balance between mitochondrial fusion and fission [52], selective

mitophagy [53] and the mitochondrial unfolded protein response (mtUPR) [54].

By preserving organelle function and cellular homeostasis, mitoQC also influences neuronal susceptibility to regulated cell death, including apoptosis, necrosis, and ferroptosis. The predominant mode of cell death depends on the nature and severity of mitochondrial damage, the extent of oxidative stress, and the intrinsic phenotypic properties of the affected neuronal population.

Mitochondrial dynamics is controlled by large dynamin-related GTPases, including Mfn1 (mitofusin 1) and Mfn2, which mediate outer mitochondrial membrane (OMM) fusion; Opa1, which regulates inner mitochondrial membrane (IMM) fusion; and Drp1 (dynamin-related protein 1), which drives mitochondrial fission [55, 56]. Under physiological conditions, this machinery preserves mitochondrial plasticity, supports organelle redistribution in neuronal processes and enables the segregation of damaged mitochondrial segments for subsequent removal. Mitochondrial depolarization can act as a physiological trigger for Drp1-dependent fission, leading to the separation of dysfunctional fragments from the network. However, sustained Drp1 activation or Opa1 deficiency can shift this adaptive response towards excessive fragmentation, which further decreases $\Delta\Psi m$ and upregulates ROS production, establishing a feed-forward cycle of mitochondrial damage [57-59].

Mitochondrial fragmentation is not inherently pathological. In neurons, fission can facilitate organelle transport, local mitochondrial turnover, and the isolation of damaged fragments before mitophagy. Its pathogenic role emerges when the fusion–fission balance is chronically or excessively shifted towards fission.

This imbalance is closely linked to activation of the intrinsic apoptotic pathway. The central event in this pathway is mitochondrial outer membrane permeabilization (MOMP) driven by oligomerization of the pro-apoptotic proteins Bax and Bak [60]. MOMP often occurs alongside mitochondrial fragmentation, with Drp1 being recruited to future fission sites [61]. Several studies suggest that Drp1 can promote Bax oligomerization and increase the likelihood of pore formation in the OMM [62]. Once MOMP occurred, cytochrome *c* is released into the cytosol, where it binds apoptotic protease-activating factor 1 (Apaf-1) and procaspase-9, leading to apoptosome assembly and activation of the effector caspases 3 and 7 [63].

Altered mitochondrial dynamics is a common feature of major neurodegenerative diseases. Early studies in AD models showed that amyloid precursor protein (APP), through its downstream product amyloid-β (Aβ), disrupts the balance between mitochondrial fusion and fission. In M17 cells and primary neurons, APP/Aβ altered the expression and subcellular distribution of mitochondrial dynamics proteins, including Drp1 and Opa1, while increasing expression of the fission-associated protein Fis1. These changes were accompanied by mitochondrial fragmentation and perinuclear clustering [64]. Similar alterations have been detected in AD brain tissue, where reduced levels of Drp1, Opa1, Mfn1, and Mfn2, together with increased Fis1 content, were associated with mitochondrial redistribution from neuronal processes to the soma [65].

Further analyses of post-mortem brain tissue from patients with AD at different disease stages provided additional evidence for a progressive shift towards mitochondrial fission. Expression of the fission-related genes *Drp1* and *Fis1* was increased, whereas *Mfn1*, *Mfn2*, and *Opa1* were downregulated. Oligomeric Aβ was shown to physically interact with Drp1, with the extent of Aβ/Drp1 colocalization increasing in parallel with disease progression [66]. Mechanistically, Aβ can promote Drp1 activation through several post-translational modifications. Aβ-induced S-nitrosylation of Drp1 increases its activity and promotes mitochondrial fragmentation, bioenergetic dysfunction, and synaptic damage in AD models [67]. Aβ also activates cyclin-dependent kinase 5 (Cdk5), which phosphorylates Drp1 at Ser579, thereby promoting excessive mitochondrial fission and neuronal apoptosis [68]. Expression of the phosphorylation-deficient Drp1-S579A mutant prevents Aβ-induced mitochondrial fission, caspase-3 activation, and neuronal apoptosis [69]. Similar effects have been reported for GSK3β-dependent phosphorylation of Drp1 at Ser40/Ser44 [70]. Tau pathology may converge on the same pathway. In HEK293 cells, acetylated tau disrupted mitochondrial dynamics and promoted apoptosis, suggesting that tau-dependent mechanisms can also shift the fusion–fission balance towards a pro-death state [71]. Together, these findings identify Aβ-dependent modification and activation of Drp1 as a key mechanism linking impaired mitochondrial dynamics to the increased susceptibility of neurons to mitochondria-mediated apoptosis in AD.

Disrupted mitochondrial dynamics is also implicated in PD. The loss of functions of the serine/threonine kinase PINK1 or Parkin, an E3 ubiquitin ligase, induces marked mitochondrial fragmentation in SH-SY5Y neuroblastoma cells and primary mouse neurons. This phenotype is rescued by Drp1 knockdown or by overexpression of the fusion-promoting proteins Mfn2 and Opa1, indicating a shift in the fusion–fission balance towards excessive fission [72]. Following mitochondrial damage, PINK1 and Parkin also cooperate to ubiquitinate the Mfn1 and Mfn2, targeting them to proteasomal degradation. Failure of selective autophagy then limits the clearance of

damaged mitochondria and favors their accumulation [73].

α-Synuclein provides another mechanism by which mitochondrial dynamics may become disrupted. It inhibits membrane fusion *in vitro*, whereas its overexpression in cultured cells and *in vivo* promotes mitochondrial fragmentation [74]. These findings support a model in which the loss of PINK1/Parkin function and α-synuclein toxicity disturb the coordinated regulation of mitochondrial fission, fusion, and turnover, thereby increasing the susceptibility of dopaminergic neurons to the Bax/Bak-mediated apoptosis. In an MPTP model of PD, Drp1 activation was associated with mitochondrial accumulation of p53, Bax, and PUMA (p53 upregulated modulator of apoptosis), whereas pharmacological inhibition of Drp1 with the peptide P110 prevented these changes and suppressed apoptosis of dopaminergic neurons [75]. Similarly, mutant α-synuclein activates the p38 MAPK–Drp1 pathway, leading to mitochondrial fragmentation and apoptotic cell death, while Drp1 inhibition exerts neuroprotective effects [76].

However, disruption of mitochondrial dynamics is not invariably sufficient to cause neuronal death. For example, induction of endogenous α-synuclein aggregation by exogenous fibrillar α-synuclein impaired mitochondrial dynamics but did not lead to neuronal loss [77].

In Huntington's disease (HD), mitochondrial dynamics is disrupted largely through direct action of mutant huntingtin (mHtt) on the fusion–fission machinery. mHtt aberrantly interacts with Drp1 in brain tissue from patients with HD and in mouse models, increasing the GTPase activity of Drp1 and inducing mitochondrial fragmentation before the onset of neurological symptoms and protein aggregate formation [78]. Reducing Drp1 activity using the dominant-negative K38A mutant markedly attenuates neuronal damage and cell death, supporting a causal role for excessive fission in HD-associated neurodegeneration [78].

Analyses of cortical tissue from patients with HD further support a disease stage-dependent shift towards mitochondrial division. Expression of the fission-related genes *Drp1* and *Fis1* is increased, whereas expression of the fusion-related genes *Mfn1*, *Mfn2*, and *Opa1* is reduced, with the magnitude of these changes correlating with disease progression [79]. Mechanistically, mHtt can activate Drp1 through calcineurin-dependent signaling, leading to excessive mitochondrial fission, disruption of cristae, and increased susceptibility to apoptosis [80].

Necroptotic mechanisms may also intersect with this pathway. In experimental HD models, inhibition of PGAM5 (phosphoglycerate mutase family member 5), a regulator of Drp1-dependent fission, suppresses activation of the RIPK1–RIPK3–MLKL necroptotic cascade and protects neurons [81]. Thus, mHtt-induced mitochondrial fragmentation may act as a convergence point that increases the vulnerability of striatal neurons to both intrinsic apoptosis and programmed necrosis.

The role of mitochondrial dynamics in ALS has been established largely through studies of mutant superoxide dismutase 1 (SOD1). Mutant SOD1 localized to the mitochondrial intermembrane space, promotes mitochondrial fragmentation in axons and disrupts mitochondrial dynamics in motor neurons [82, 83]. Subsequent studies have shown that defects in mitochondrial dynamics are not restricted to the SOD1-associated ALS, but represent a broader feature shared across several genetic forms of this disease [84].

In spinal motor neurons from mice expressing mutant SOD1-G93A, mitochondria become shorter and accumulate as rounded, fragmented organelles. This fusion–fission imbalance can be corrected by expression of the dominant-negative Drp1 mutant K38A, supporting a causal contribution of excessive fission [85]. Similarly, inhibition of interaction between Drp1 and Fis1 by the peptide P110 improves mitochondrial structure and function in ALS models, suppresses activation of apoptotic pathways, and slows disease progression in SOD1-G93A mice [86]. Thus, mitochondrial fragmentation driven by the mutant SOD1 is closely linked to impaired organelle dynamics and increased susceptibility of motor neurons to apoptotic death.

Collectively, these findings identify disruption of the fusion–fission balance as a recurrent pathogenic mechanism across major neurodegenerative diseases. By promoting mitochondrial fragmentation, bioenergetic failure, and pro-death signaling, impaired mitochondrial dynamics facilitates intrinsic apoptosis and, under specific conditions, may also contribute to necrotic neuronal death.

Mitophagy is a selective form of macroautophagy that maintains mitochondrial quality by recognizing damaged or dysfunctional mitochondria and targeting them for lysosomal degradation [53, 87]. The canonical pathway is controlled by PINK1 and Parkin. Following the loss of $\Delta\Psi m$, PINK1 accumulates on the OMM, where it phosphorylates ubiquitin and the ubiquitin-like domain of Parkin, thereby promoting Parkin recruitment and activation [88]. Activated Parkin ubiquitinates multiple OMM proteins, generating ubiquitin signals that are recognized by autophagy receptors, such as p62/SQSTM1, optineurin (OPTN), NDP52, and TAX1BP1 [89].

These receptors link ubiquitinated mitochondria to the forming autophagosome through LC3-interacting regions, enabling sequestration of the damaged

organelles and their subsequent delivery to lysosomes. Disruption of this cascade at any step, from pathogenic variants of PINK1 or Parkin to impaired receptor function, can reduce mitophagic flux. As a consequence, depolarized mitochondria accumulate, ROS production increases, and neurons become more vulnerable to mitochondrial stress [90, 91].

In AD, defects in mitophagy emerge early and contribute to progressive neuronal loss. Accumulation of Aβ and hyperphosphorylated tau suppresses mitophagic clearance, leading to the persistence of dysfunctional mitochondria and promoting oxidative stress [92]. An increasing attention has also been focused on the link between impaired mitophagy and ferroptotic injury in AD. Liu et al. proposed that defective mitophagy disrupts intracellular redox and iron homeostasis, thereby increasing neuronal susceptibility to ferroptosis [93]. Consistent with this model, impaired mitochondrial clearance may lower the threshold for ferroptotic damage in AD neurons [94].

Mitophagy is also linked to apoptotic signaling. In experimental models, pharmacological activation of the PINK1/Parkin-dependent mitophagy by uric acid or remimazolam attenuated Aβ-induced neuronal injury and apoptosis, whereas PINK1 knockdown abolished these protective effects [95, 96].

Pathogenic variants of PINK1 and Parkin, which cause autosomal-recessive forms of PD, directly impair ubiquitination of mitochondrial proteins and the subsequent clearance of damaged mitochondria. Mitophagy can also influence the dominant cellular response to mitochondrial injury. Ham et al. showed that the pattern of Parkin-dependent VDAC1 (voltage-dependent anion-selective channel protein 1) ubiquitination acts as a switch between mitophagy and apoptosis. Whereas specific ubiquitin signals favor mitochondrial clearance, the PD-associated T415N missense mutation fails to induce VDAC1 monoubiquitination and instead promotes apoptotic death of dopaminergic neurons [97].

Defective mitophagy is increasingly recognized as a contributor to ferroptotic vulnerability in PD. Key et al. showed that loss of PINK1 is accompanied by alterations in iron homeostasis, including changes in the regulation of ferritin family proteins, suggesting a link between impaired mitoQC and iron-dependent neuronal injury [98]. Consistent with this idea, Han et al. demonstrated that activation of Nrf2 (nuclear factor erythroid 2-related factor 2)-mediated mitophagy suppresses ferroptosis in dopaminergic neurons by preserving mitochondrial integrity and reducing lipid peroxidation [99]. Data from 6-OHDA models of PD further indicate that ferritinophagy and ferroptotic mechanisms contribute to dopaminergic neuronal damage [100].

A direct link between defective mitophagy and apoptotic death of motor neurons in ALS has been demonstrated in several studies. ALS- and FTD-associated mutations in TBK1 (TANK-binding kinase 1) differentially impair mitophagy, including optineurin (OPTN)-dependent recognition and clearance of damaged mitochondria [101]. Mutant SOD1 aggregates can also interfere with mitophagy by disabling the mitophagy receptor OPTN, potentially promoting the accumulation of damaged mitochondria and increasing motor neuron vulnerability [102]. Mitophagy defects are also characteristic of C9orf72-associated ALS. In a *Danio rerio* model, accumulation of poly-GP dipeptides, predominantly in motor neurons, impaired mitophagic flux and was accompanied by mitochondrial swelling, caspase-3 activation, and other apoptotic features [103].

The neuroprotective role of mitophagy is supported by evidence that stimulation of this pathway reduces motor neuron loss. The mitophagy receptor FUNDC1 is downregulated in the spinal cord of SOD1G93A mice, whereas its restoration enhances the clearance of damaged mitochondria, reduces motor neuron apoptosis, and extends animal survival [104]. Thus, mitophagy defects caused by mutations in distinct ALS-linked genes converge on increased susceptibility of motor neurons to apoptotic death.

In HD, mitophagy defects are implicated in the activation of multiple cell death programs in striatal neurons. In an experimental HD model, morin hydrate attenuated apoptotic signaling and mitophagy abnormalities through mechanisms involving the mTORC1/IRE-1α/JNK and IP3R/VDAC1 pathways [105]. In addition to apoptosis, ferroptosis is increasingly recognized as a contributor to neuronal loss in HD. Jamal et al. noted that mHtt promotes iron overload, enhances Fenton reactions, and increases production of free radicals, whereas inefficient mitophagy may further facilitate iron-dependent ferroptosis in vulnerable striatal neurons [106]. Mitophagy dysregulation in HD may also involve pathological overactivation: mHtt can drive aberrant recruitment of valosin-containing protein (VCP) to mitochondria, disrupting mitophagic flux and promoting neurodegenerative changes in HD models [107].

Thus, impaired clearance of dysfunctional mitochondria, followed by activation of neuronal death pathways, represents a shared feature of several neurodegenerative diseases, including AD, PD, ALS and HD [108]. Conversely, stimulation of mitophagy can be neuroprotective. In both genetic and toxin-based models of PD, pharmacological or metabolic activation of mitophagy, including transient cytosolic acidification, protects neurons against cell death [109, 110].

Mitochondrial biogenesis is a regulated process that generates new, functionally competent mitochon-

dria and is controlled at the transcriptional level by the co-activator PGC-1α (peroxisome proliferator-activated receptor-γ coactivator 1α) encoded by *PPARGC1A*) [51]. PGC-1α co-activates the transcription factors NRF1 and NRF2 (nuclear respiratory factors 1 and 2), as well as PPARγ (peroxisome proliferator-activated receptor gamma), which together promote the expression of nuclear genes encoding mitochondrial proteins, including TFAM (transcription factor A, mitochondrial), a key regulator of mitochondrial transcription and replication. Impaired mitochondrial biogenesis leads to a progressive decline in the abundance of functional ETC complexes, reduced ATP synthesis, and accumulation of dysfunctional organelles, thereby creating conditions that favor activation of programmed cell death pathways.

In AD, reduced expression of PGC-1α and its transcriptional targets, including NRF1, TFAM, and ERRα (estrogen-related receptor alpha), has been reported in post mortem brain tissue and transgenic models [111, 112]. In N2a neuroblastoma cells, Aβ1-42 oligomers suppress the expression of PGC-1α and BDNF (brain-derived neurotrophic factor), whereas PGC-1α overexpression counteracts Aβ toxicity and prevents apoptotic cell death [113]. Consistent with these findings, interventions that restore mitochondrial biogenesis at different regulatory levels, including PGC-1α overexpression and NRF1 activation, protect neurons from death and reduce apoptosis [114-116]. Thus, Aβ-mediated suppression of PGC-1α and its downstream transcriptional program may impair mitochondrial biogenesis, creating a permissive state for activation of the intrinsic apoptotic pathway and neuronal loss in AD.

In PD, impaired mitochondrial biogenesis is linked to the accumulation of PARIS, a protein that is normally ubiquitinated by Parkin and targeted for proteasomal degradation. The loss of Parkin function promotes PARIS accumulation, which suppresses expression of the transcriptional co-activator PGC-1α and its downstream target NRF1 [117]. Experimental studies have shown that both PARIS knockdown and PGC-1α overexpression restore mitochondrial gene expression and protect dopaminergic neurons in substantia nigra from death [118]. Lin et al. further demonstrated that carnosic acid enhances Parkin-mediated ubiquitination of PARIS, restores PGC-1α expression, stimulates mitochondrial biogenesis, and reduces apoptotic cell death, as well as decreases caspase-3 activation [119]. Thus, the PARIS–PGC-1α axis provides a mechanistic link between Parkin dysfunction, impaired mitochondrial biogenesis, and loss of dopaminergic neurons.

In HD, restoration of PGC-1α expression has also emerged as a promising strategy to reduce neurotoxicity and cell death. The ginsenosides Rg3 and Rf activate the expression of mitochondrial biogenesis genes while suppressing mHtt-induced apoptotic cell death [120].

Overall, reduced expression or activity of PGC-1α represents an important link between mitochondrial dysfunction and neuronal death in neurodegenerative diseases.

MITOCHONDRIAL ROS PRODUCTION AND NEURODEGENERATION

As the primary site of cellular oxygen reduction, mitochondria are a major source of ROS. Mitochondrial ROS (mtROS) are generated primarily through electron leakage in the ETC and by the activity of several enzymes located in the mitochondrial matrix and OMM, including monoamine oxidases [121-123]. Increased mtROS production is also an intrinsic consequence of elevated mitochondrial metabolic activity [124, 125]. Although substantial progress has been made in defining the physiological roles of mtROS in intracellular signaling [125, 126], their contribution to disease pathophysiology remains well established. In neurodegenerative diseases, excessive ROS production, together with insufficient antioxidant capacity, promotes oxidative damage to proteins, lipids, and nucleic acids, resulting in a state commonly referred to as oxidative stress [39, 127, 128].

Increased mtROS generation is a common feature of mitochondrial dysfunction in neurodegenerative disorders [125, 126, 129, 130]. However, a key question remains: where does excessive mtROS production fit within the sequence of events that ultimately lead to neuronal death?

In this context, it is important to note that several forms of cell death are directly linked to a critical imbalance between ROS production and detoxification, with ROS acting as key triggers of pathological metabolic remodeling. Ferroptosis, which results from the accumulation of lipid peroxidation (LPO) products driven by iron-catalyzed ROS generation, has been implicated in the progression of PD, AD, HD, ALS, and multiple sclerosis [131-136]. Ferroptotic signaling has also been observed in models involving disruption of specific components of mitostasis [137] or impairment of antioxidant defense systems [138]. Parthanatos, another form of regulated cell death, is associated with PARP1 hyperactivation following ROS- and reactive nitrogen species-mediated DNA damage and has been described in a wide range of pathological conditions [139-141].

Although ROS have been implicated in individual steps of multiple cell death pathways, as discussed in numerous reviews [142-144], their precise contribution and significance require context-specific evaluation. Experimental interventions that directly

neutralize ROS provide important means of determining whether oxidative stress functions as a causal driver of cell death. In the rotenone mouse model of PD, characterized by reduced expression and activity of short-chain enoyl-CoA hydratase 1 (ECHS1), administration of the mitochondria-targeted antioxidant MitoTEMPO restored mitochondrial function, thus supporting a critical role of mtROS in disease development [145]. Another mitochondria-targeted antioxidant, MitoQ, reduced oxidative stress in an *in vivo* model of neurodegeneration induced by O,O-dimethyl O-2,2-dichlorovinyl phosphate by normalizing mtROS production, increasing MnSOD activity and GSH content, and improving brain cell viability [146]. MitoQ was among the most effective interventions for preventing cell death under conditions of glutathione peroxidase inhibition [138].

Similar evidence comes from cellular models of neurotoxicity. The carotenoid lycopene suppressed Aβ-induced apoptosis in SH-SY5Y neuroblastoma cells by reducing ROS production in both the cytosol and mitochondria [147]. In HT22 hippocampal cells, L-cysteine reduced apoptosis induced by 2,3-dimethoxy-1,4-naphthoquinone in a dose-dependent manner, an effect attributed to its direct ROS-scavenging activity rather than to the increase in endogenous antioxidant capacity [148]. A comparable protective effect was reported by the same research group for L-serine [149]. Studies in primary cortical neurons from transgenic mice, immortalized lymphoblasts from patients with PD, transfected SH-SY5Y and H1299 cells, and genetic knockout animal models further demonstrated a close relationship between DJ-1 dysfunction and mtROS overproduction. Reduction of ROS levels with N-acetylcysteine substantially normalized the mitochondrial phenotype [150].

The natural polyphenol resveratrol, which exhibits pronounced ROS-scavenging properties, has also demonstrated protective effects in neuronal injury models. Resveratrol reduced apoptosis in an *in vitro* hypoxia model induced by the $CoCl_2$-mediated stabilization of HIF1α (hypoxia-inducible factor 1 alpha) [151], as well as in animal and astrocyte culture models of traumatic brain injury [152]. In both settings, restoration of mitochondrial function was associated with a marked reduction in mtROS levels.

Mitochondrial ROS generated by monoamine oxidase during oxidative deamination of catecholamines, such as dopamine and adrenaline, can serve signaling functions in astrocytes. However, when combined with ROS overproduction from additional sources, this pathway may contribute to cell death, as shown in cellular models carrying mutations in *PINK1* [153-155].

Further evidence for a causal role of mtROS comes from studies using mitochondria-targeted compounds that directly enhance ROS production, such as mitoPQ [156]. MitoPQ has been shown to induce a PD-like phenotype in zebrafish larvae and to promote mHtt aggregation in U2OS cells [157].

Mitochondria-targeted antioxidants have also helped define how mtROS can drive pathology beyond the mitochondrial compartment. In tau-dependent FTD, mitochondrial hyperpolarization increases ROS production, resulting in oxidation of proteins involved in glutamate receptor trafficking. This disrupts receptor function and, more broadly, neuronal signaling [9, 158].

Thus, excessive mtROS production can act as a trigger for both cellular dysfunction and cell death. However, its pathological effects are likely shaped by interactions with additional stressors, including critical changes in intracellular and mitochondrial Ca^{2+} homeostasis.

MITOCHONDRIAL CA^{2+} SIGNALING IN NEURODEGENERATION

Calcium (Ca^{2+}) is one of the principal second messengers in mammalian cells. To enable rapid and transient Ca^{2+} influx into the cytosol, cells maintain a steep, 10,000-20,000-fold concentration gradient between the extracellular space and the cytoplasm. The endoplasmic reticulum (ER) is the major intracellular Ca^{2+} store that can accumulate Ca^{2+} at concentrations of up to ~1 mM, corresponding to an approximately 10,000-fold gradient relative to the cytosol. Within the endoplasmic reticulum (ER), however, Ca^{2+} is largely maintained in a bound, or "buffered", state through interactions with Ca^{2+}-binding proteins such as calreticulin and calsequestrin. Upon stimulation, ER-stored Ca^{2+} can be rapidly released into the cytoplasm through the activation of inositol 1,4,5-trisphosphate (IP_3) receptors or ryanodine receptors [159].

In brain cells, both Ca^{2+} influx or release initiate a broad range of physiological processes. In neurons, cytosolic Ca^{2+} increases mainly through the influx from the extracellular space, primarily via voltage-gated Ca^{2+} channels, which account for ~70-80% of Ca^{2+} entry under physiological conditions, as well as through ionotropic NMDA receptors. The principal Ca^{2+}-dependent event in neurons is the fusion of neurotransmitter-containing vesicles with the plasma membrane, resulting in exocytosis, neurotransmitter release, and signals propagation to neighboring cells.

In astrocytes, Ca^{2+} also regulates vesicular and signaling processes, but the major source of cytosolic Ca^{2+} elevation is its release from the ER, which accounts for ~70-80% of the response. By contrast, extracellular Ca^{2+} entry, mediated mainly by store-operated Ca^{2+} entry (SOCE) channels and transient receptor potential (TRP) channels, contributes ~15-25%, whereas

gap junctions, which provide direct intercellular communication, account for ~5-10% of the increase in cytosolic Ca^{2+} through Ca^{2+} diffusion [160].

Under physiological conditions, Ca^{2+} signaling in microglia is mediated predominantly by metabotropic receptor activation and Ca^{2+} release from the ER, supporting intercellular communication. During neuroinflammation, however, this balance is markedly altered: Ca^{2+} enters the cytoplasm predominantly from the extracellular space through ionotropic receptors, including P2X7 and TRPV channels, promoting multiple processes such as phagocytosis and migration.

Upon elevation in cytosolic Ca^{2+}, Ca^{2+} efflux and re-sequestration are rapidly activated through Ca^{2+}-ATPases in the plasma membrane and ER (PMCA and SERCA, respectively), as well as the plasma membrane Na^+/Ca^{2+} exchanger (NCX). At the same time, a fraction of cytosolic Ca^{2+} is taken up by mitochondria, which are now recognized not only as bioenergetic organelles but also as central components of Ca^{2+} signaling [130]. Ca^{2+} enters the mitochondrial matrix through the mitochondrial calcium uniporter (MCU), whereas its efflux is mediated by the mitochondrial Na^+/Ca^{2+} exchanger or, in some cell types, by the Ca^{2+}/H^+ exchange.

Within the mitochondrial matrix, a fraction of accumulated Ca^{2+} can form calcium phosphate precipitates, thereby transiently entering a buffered state. However, during mitochondrial dysfunction, when $\Delta\Psi m$ and matrix pH decline, Ca^{2+} is released from these precipitates and act as an early signal during hypoxia [161]. Under physiological conditions, mitochondrial Ca^{2+} release may also occur through transient openings of the mitochondrial permeability transition pore (mPTP) (Fig. 1) [162].

Mitochondrial Ca^{2+} uptake activates several Ca^{2+}-dependent matrix enzymes, thereby enhancing oxidative metabolism and ATP synthesis. This response supports the energy demand required to restore Ca^{2+} homeostasis and sustains cellular processes triggered by the Ca^{2+} entry. In parallel, mitochondria act as transient Ca^{2+} buffers, limiting elevation in the cytosolic Ca^{2+} and attenuating the impact of rapid, high-amplitude Ca^{2+} signals. Disruption of these processes can lead to mitochondrial Ca^{2+} overload, increased ROS production, mPTP opening, and activation of cell death pathways [163].

Thus, mitochondrial Ca^{2+} uptake is an essential mechanism that couples Ca^{2+} signaling to bioenergetic adaptation and supports normal cellular physiology. However, the pathological consequences of either insufficient or excessive Ca^{2+} entry into mitochondria, as well as abnormal prolongation or shortening of mitochondrial Ca^{2+} retention, can be detrimental.

MCU and neurodegeneration. The molecular identity of MCU had remained unresolved for decades and was discovered in 2011 in two parallel studies that identified MCU as the pore-forming subunit of the IMM responsible for electrophoretic Ca^{2+} uptake driven by $\Delta\Psi m$ of approximately −180 mV [164, 165]. The regulatory protein MICU1 (mitochondrial calcium uptake 1) identified in 2010 [165], contains EF-hand domains and acts as a Ca^{2+}-dependent gatekeeper. At low cytosolic Ca^{2+} concentrations. MICU1 limits pore opening, whereas Ca^{2+} levels above a threshold of ~0.5-3 μM (depending on cell type) induce conformational changes that permit channel activation.

Subsequent studies identified functionally divergent MICU1 paralogues. MICU2 increases the activation threshold and exerts an inhibitory effect on MCU activity [166, 167], whereas MICU3 is preferentially expressed in neurons and skeletal muscle and shifts uniporter sensitivity towards lower Ca^{2+} concentrations [168]. EMRE (essential MCU regulator) is another critical regulatory component of the MCU complex, linking the pore-forming MCU tetramer to MICU regulatory subunits [169]. EMRE is a small IMM protein of ~10 kDa that contains a single transmembrane domain positioned at an angle of ~45° relative to the transmembrane domain 1 (TM1) of MCU, the N-terminal PKP motif that strengthens MCU binding, and a conserved C-terminal polyaspartate tail exposed to the mitochondrial matrix.

EMRE has a dual role: it enables MCU channel activity, as Ca^{2+} transport does not occur in its absence even when MCU is expressed and oligomerized, and it acts as a molecular bridge between MCU and MICU1/MICU2, thus supporting Ca^{2+}-dependent gating of the channel in response to changes in cytosolic Ca^{2+} [170-172].

Dysfunction of the MCU complex in neurodegeneration can arise through distinct molecular scenarios, including pathological enhancement of Ca^{2+} entry, loss of regulatory control over uniporter gating, and impaired function of individual complex components. Despite the mechanistic differences, these alterations converge on a common outcome: mitochondrial Ca^{2+} overload and bioenergetic collapse. In AD, Aβ oligomers pathologically enhance MCU-dependent Ca^{2+} uptake. Elevated mitochondrial Ca^{2+} levels have been detected in the living brains of transgenic mice and correlate closely with the plaque formation and neuronal death [173]. Conversely, MCU knockdown in hippocampal neurons of APP/PS1/tau mice restores synaptic structure and improves spatial memory [174].

In PD, disease-associated factors, including α-synuclein, disruption of mitochondria–ER contact sites (MERCSs) and exposure to paraquat, increase MCU expression and destabilize the MCU/MCUb balance. This promotes progressive Ca^{2+} overload in dopaminergic neurons and subsequent cell death through impairment of the Opa1-dependent mitochondrial

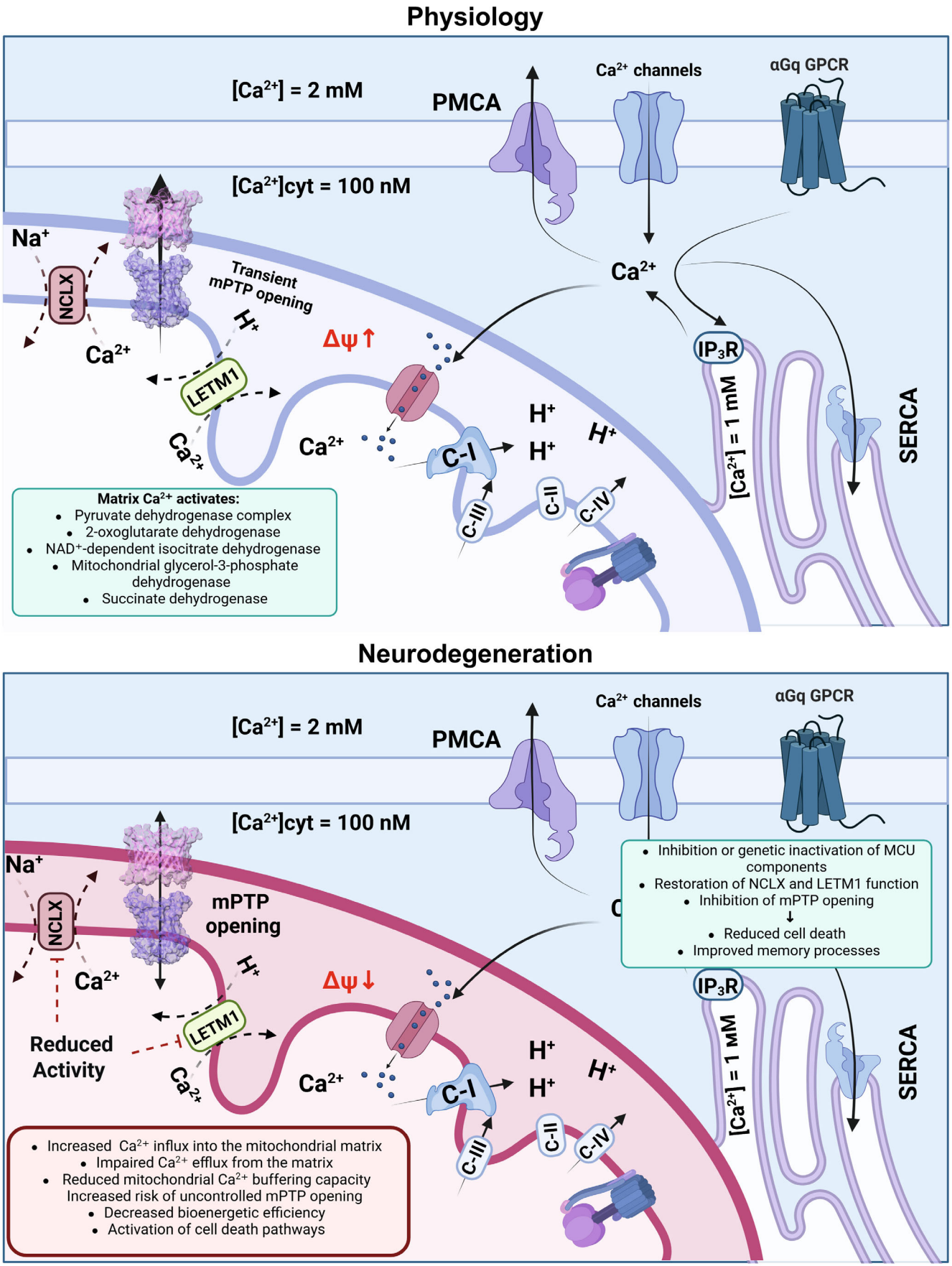

Fig. 1. Role of mitochondrial Ca^{2+} in neurodegenerative processes.

fusion [174, 175]. In HD, mHtt sensitizes IP_3 receptors and NMDA receptors, thereby increasing Ca^{2+} uptake to mitochondria and overloading the uniporter complex. In ALS, disease-associated proteins TDP-43, SOD1, and C9orf72 physically interact with mitochondria and disrupt normal MCU-dependent Ca^{2+} uptake. In both cases, these disturbances are associated with the loss of ΔΨm, increased ROS production, and mPTP formation [176].

MICU1 is also essential for controlling mitochondrial Ca^{2+} transport. In humans, MICU1 loss of function causes a progressive extrapyramidal movement disorder, myopathy, and cognitive impairment, accompanied by fragmentation of the mitochondrial network and dysregulated Ca^{2+} entry at low cytosolic Ca^{2+} concentrations [177]. In neuronal models, MICU1 knockout recapitulates a neurodegenerative phenotype that can be rescued by limiting MCU activity [173].

Finally, direct genetic experiments have provided compelling evidence for a causal role of MCU dysregulation in neuronal degeneration. Increased neuronal MCU expression *in vitro* and *in vivo* is sufficient to induce Ca^{2+}-dependent neuronal death [178, 179]. Conversely, partial inhibition of MCU activity normalizes elevated basal mitochondrial Ca^{2+} levels and protects neurons from degeneration in models of PD, AD and HD, as well as in ischemic stroke and acute carbon monoxide poisoning [180-182].

Mitochondrial Ca^{2+} efflux and neurodegenerative pathology. Mitochondrial Ca^{2+} efflux is mediated primarily by two exchangers: NCLX (mitochondrial $Na^+/Li^+/Ca^{2+}$ exchanger) and LETM1 (H^+/Ca^{2+} exchanger).

NCLX is a mitochondrial cation/Ca^{2+} exchanger encoded by *SLC8B1*. It is the only member of the NCX family located in the IMM and represents the principal route for Ca^{2+} efflux from the matrix in neurons and many other cell types [183, 184]. Cryo-electron microscopy revealed a canonical Calcium/Cation Antiporter (CaCA) superfamily architecture comprising ten transmembrane helices, a central ion-binding domain, and mobile helices that mediate alternating access to the matrix and the intermembrane space. NCLX operates as a cation/Ca^{2+} antiporter, extruding Ca^{2+} from the mitochondrial matrix in exchange for Na^+, Li^+, and possibly other cations.

Recent evidence suggests that NCLX is not a strictly Na^+-dependent exchanger, but rather a broader cation/Ca^{2+} transporter that can also use protons as countertransported ions. This expands the regulatory framework of NCLX activity, implying that this exchanger may be directly influenced by matrix and intermembrane space pH and thereby more tightly integrated with mitochondrial metabolism and stress responses than previously appreciated [185]. Under physiological conditions, NCLX dissipates mitochondrial Ca^{2+} gradients after cellular stimulation, thereby balancing Ca^{2+}-dependent stimulation of oxidative metabolism with the need to prevent mitochondrial Ca^{2+} overload, excessive ROS production, and cell death driven by prolonged mPTP opening.

Reduced NCLX activity converts physiological Ca^{2+} signals into a source of mitochondrial stress. Impaired Ca^{2+} efflux promotes mitochondrial Ca^{2+} overload, leading to the loss of ΔΨm, increased ROS generation, and greater susceptibility to mPTP opening. Regardless of the initiating trigger – genetic deletion, pathological protein accumulation, or dysregulated exchanger control – the downstream effects converge on a common pathway: $[Ca^{2+}] \uparrow \rightarrow$ ROS $\uparrow \rightarrow$ ΔΨm $\downarrow \rightarrow$ mPTP $\rightarrow$ cell death.

Defects in NCLX-dependent mitochondrial Ca^{2+} efflux have been described across a broad spectrum of neurodegenerative diseases. The underlying mechanisms vary, ranging from reduced protein expression to functional inhibition through interactions with disease-associated proteins. In AD, remodeling of mitochondrial Ca^{2+} handling in the prefrontal cortex is accompanied by reduced NCLX efflux capacity. In the 3xTg-AD model, impaired mitochondrial Ca^{2+} extrusion precedes the development of overt neuropathology, whereas neuron-specific deletion of NCLX accelerates cognitive impairment and amyloidosis. Conversely, genetic restoration of NCLX in the same models is sufficient to slow disease progression [174]. Reduced NCLX levels alone can also reproduce an age-dependent AD-like phenotype, including impaired long-term potentiation and synaptic degeneration, in the absence of additional genetic manipulations [186].

In PD, reduced NCLX function has been observed in models carrying mutations in PINK1 or LRRK2 (leucine-rich repeat kinase 2), as well as under conditions of increased expression of α-synuclein or tau [187-191]. In each case, impaired Ca^{2+} efflux resulted in chronic mitochondrial Ca^{2+} overload, highlighting a shared pathogenic feature of PD. Notably, restoration of NCLX function through the protein kinase A (PKA)-dependent phosphorylation at Ser258 or expression of the active phosphomimetic mutant NCLX(S258D) fully restored mitochondrial Ca^{2+} efflux and prevented the death of PINK1-deficient neurons [189], as well as neurons with LRRK2 deletion or mutations [190].

NCLX dysfunction has also been implicated in Friedreich ataxia. Frataxin deficiency reduces NCLX protein expression in dorsal root ganglion neurons and cardiomyocytes, leading to neurodegeneration and apoptosis. Notably, these effects can be reversed by calcitriol-mediated restoration of NCLX [192]. The causal role of NCLX in neurodegenerative pathology is further supported by genetic studies. Patients carrying the homozygous recessive *SLC8B1* variant that impairs NCLX activity, present with severe intellectual disability [193]. Genetic inactivation of NCLX in mice

caused mitochondrial Ca^{2+} overload and depolarization, together with reduced amplitude and kinetics of mitochondrial Ca^{2+} uptake and release. NCLX deficiency also markedly diminished presynaptic Ca^{2+} transients, thereby decreasing neurotransmitter release probability, weakening synaptic transmission, and abolishing long-term potentiation. Thus, the loss of NCLX function is sufficient to reproduce key features of a neurodegenerative phenotype [193].

LETM1 as a second route for mitochondrial Ca^{2+} efflux. LETM1 (leucine zipper-EF-hand-containing transmembrane protein 1) is a nuclear-encoded IMM protein that had been initially identified as a product of a gene deleted in the Wolf–Hirschhorn syndrome (WHS) and later characterized as a mitochondrial Ca^{2+}/H^+ antiporter [194, 195]. Unlike NCLX, LETM1 mediates electroneutral antiport, exporting one Ca^{2+} ion from the matrix in exchange for two protons. Consequently, its activity is directly linked to the mitochondrial pH gradient and, therefore, to the intensity of oxidative metabolism.

LETM1 contains a single transmembrane domain and a matrix-facing EF-hand domain that binds Ca^{2+} with an affinity of ~25 μM. LETM1 forms hexameric complexes with a central cavity and can adopt distinct conformational states in response to changes in pH. The lack of sensitivity of LETM1-dependent Ca^{2+} transport to ruthenium red and CGP-37157 suggests that this flux is not mediated by MCU or NCLX, respectively.

Under physiological conditions, LETM1 acts alongside NCLX to support Ca^{2+} extrusion from the matrix after mitochondrial Ca^{2+} loading. However, its quantitative contribution to the overall mitochondrial Ca^{2+} efflux remains controversial. Some studies identify LETM1 as a major H^+-dependent efflux mechanism at low matrix Ca^{2+} concentrations, whereas others suggest that LETM1 regulates Ca^{2+} release indirectly by controlling Na^+/K^+ homeostasis in the matrix and thereby modulating NCLX activity. Notably, partial reduction of LETM1 expression, unlike its complete deletion, does not necessarily disrupt mitochondrial homeostasis but may prolong Ca^{2+} retention in the matrix within a physiological range.

The link between LETM1 and neurodegenerative pathologies is most clearly illustrated by the PINK1–LETM1 axis [196]. PINK1 directly interacts with LETM1 and phosphorylates it at Thr192. Phosphorylated LETM1 or its phosphomimetic LETM1(T192E) mutant enhance Ca^{2+} efflux in artificial liposomes and intact mitochondria. Expression of LETM1(T192E), but not wild-type LETM1, fully restores mitochondrial Ca^{2+} handling in PINK1-deficient neurons. Thus, in PINK1-associated PD, pathological mitochondrial Ca^{2+} overload results not only from impaired NCLX regulation but also from defective LETM1-dependent Ca^{2+} export, indicating that the two mitochondrial Ca^{2+} efflux pathways act in a complementary manner in parkinsonian pathology.

The importance of LETM1 in neuronal homeostasis is further supported by clinical evidence. Biallelic pathogenic variants of LETM1 cause an early-onset neurodegenerative syndrome with multisystem involvement, characterized by psychomotor delay, cerebellar ataxia, optic atrophy, sensorineural hearing loss, and lactic acidosis. Functional studies in patient-derived cells revealed disrupted cation homeostasis, mitochondrial matrix swelling, and deficiency of OXPHOS components [197]. Heterozygous LETM1 haploinsufficiency, as observed in Wolf–Hirschhorn syndrome, also impairs mitochondrial glucose metabolism and neuronal bioenergetics, which is clinically manifested as seizures and cognitive deficits and can be recapitulated in neuron-specific *Letm1* heterozygous mice [198].

Together, the studies of NCLX and LETM1 support a key concept: mitochondrial Ca^{2+} efflux constitutes an important a regulatory mechanism that is as important as MCU-mediated Ca^{2+} uptake. Disruption of either major efflux pathway, whether independently or in combination, is sufficient to promote mitochondrial Ca^{2+} overload and reproduce the features of a neurodegenerative phenotype.

Although chronic mitochondrial Ca^{2+} overload is widely recognized as a driver of neurodegeneration, accumulating evidence supports a more nuanced view. Controlled prolongation of mitochondrial Ca^{2+} elevation, achieved by reducing the activity of NCLX or LETM1, may enhance bioenergetic output, cognitive performance, and adaptation to hypoxia without reaching the threshold for toxic Ca^{2+} overload. Direct experimental support for this concept comes from a study showing that genetic reduction of LETM1 prolonged mitochondrial Ca^{2+} signaling and increased ATP production in hippocampal neurons. This effect was sufficient to enable long-term memory formation after a single training session, whereas control animals required repeated training to fulfill the same task [199].

A related mechanism was described by Hernansanz-Agustín et al., who showed that NCLX-mediated Na^+ entry into the mitochondrial matrix at the onset of hypoxia is required for complex III-dependent ROS generation and subsequent HIF-dependent transcriptional adaptation [161]. In this context, a moderate reduction in the mitochondrial Ca^{2+} efflux could preserve Ca^{2+}-dependent metabolic stimulation, while limiting pathological Na^+ influx. However, whether this mechanism operates in neural cells, and whether it contributes to the adaptation or injury during central nervous system ischemia, requires direct experimental validation.

Finally, Bhosale et al. showed that NCLX inhibition can exert neuroprotective effects in models of neurodegeneration induced by the combined toxicity of α-synuclein and rotenone [200]. Collectively, these findings support the concept of an optimal mitochondrial matrix Ca^{2+} window, in which mitochondrial function depends not solely on maintaining low Ca^{2+} levels, but on precisely tuning the duration of Ca^{2+} retention within a physiological range. Excessively rapid Ca^{2+} extrusion may deprive mitochondria of both metabolic stimulation and signaling capacity.

CONCLUSION

Together, the evidence reviewed here indicates that mitochondrial dysfunction is not merely an accompanying feature of neurodegenerative diseases, but an active driver of their pathogenesis. Its damaging effects are mediated through interconnected disturbances in bioenergetics, Ca^{2+} homeostasis, redox balance, and mitostasis. Importantly, none of these abnormalities acts in isolation. A decline in ΔΨm destabilizes MCU-dependent Ca^{2+} uptake and promotes electron leakage from the ETC; excessive ROS production drives oxidative modification of respiratory complexes and sensitizes mPTP into opening; impaired mitophagy or mitochondrial biogenesis allow damaged organelles to accumulate and serve as persistent sources of pathological signaling.

It is therefore the convergence of these processes, rather than any single defect alone, that determines the transition from reversible neuronal dysfunction to irreversible cell death. The modality of cell death – whether apoptosis, necrosis, ferroptosis or parthanatos – is shaped by the bioenergetic state of the cell, the extent of oxidative damage, and the kinetics of the pathological cascade. This integrated view provides a conceptual framework for pharmacological intervention. Accumulating mechanistic evidence suggests that the most effective neuroprotective strategies are unlikely to target isolated components of mitochondrial pathology, but rather the nodal points at which bioenergetic failure, Ca^{2+} dysregulation, oxidative stress, and impaired mitoQC converge.

Abbreviations

ΔΨm	transmembrane mitochondrial potential
Aβ	amyloid-β
AD	Alzheimer's disease
ALS	amyotrophic lateral sclerosis
ETC	electron transport chain
FTD	frontotemporal dementia
HD	Huntington's disease
IMM	inner mitochondrial membrane
LETM1	leucine zipper and EF-hand containing transmembrane protein 1, H^+/Ca^{2+} exchanger
MCU	mitochondrial calcium uniporter
mHtt	mutant huntingtin
mitoQC	mitochondrial quality control
mtROS	mitochondrial reactive oxygen species
mPTP	mitochondrial permeability transition pore
NCLX	mitochondrial $Na^+/Li^+/Ca^{2+}$ exchanger
OMM	outer mitochondrial membrane
OXPHOS	oxidative phosphorylation
PD	Parkinson's disease
ROS	reactive oxygen species

Contributions

A.Yu.A. developed the concept and supervised the project. A.Yu.V., A.Yu.B., E.V.P., and A.Yu.A. wrote and edited the manuscript.

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Ethics approval and consent to participate

This work does not contain any studies involving human or animal subjects.

Conflict of interest

The authors of this work declare that they have no conflicts of interest.

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