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## Review Article

# Mitochondrial dysfunction and neurodegenerative proteinopathies: mechanisms and prospects for therapeutic intervention

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Neurodegenerative proteinopathies are a group of pathologically similar, progressive disorders of the nervous system, characterised by structural alterations within and toxic misfolding of susceptible proteins. Oligomerisation of Aβ, tau, α-synuclein and TDP-43 leads to a toxin gain- or loss-of-function contributing to the phenotype observed in Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis and frontotemporal dementia. Misfolded proteins can adversely affect mitochondria, and post-mitotic neurones are especially sensitive to metabolic dysfunction. Misfolded proteins impair mitochondrial dynamics (morphology and trafficking), preventing functional mitochondria reaching the synapse, the primary site of ATP utilisation. Furthermore, a direct association of misfolded proteins with mitochondria may precipitate or augment dysfunctional oxidative phosphorylation and mitochondrial quality control, causing redox dyshomeostasis observed in disease. As such, a significant interest lies in understanding mechanisms of mitochondrial toxicity in neurodegenerative disorders and in dissecting these mechanisms with a view of maintaining mitochondrial homeostasis in disease. Recent advances in understanding mitochondrially controlled cell death pathways and elucidating the mitochondrial permeability pore bioarchitecture are beginning to present new avenues to target neurodegeneration. Novel mitochondrial roles of deubiquitinating enzymes are coming to light and present an opportunity for a new class of proteins to target therapeutically with the aim of promoting mitophagy and the ubiquitin–proteasome system. The brain is enormously metabolically active, placing a large emphasis on maintaining ATP supply. Therefore, identifying mechanisms to sustain mitochondrial function may represent a common intervention point across all proteinopathies.

## Introduction

The energetic requirements of neuronal excitability, synaptic activity and plasticity are extensive and are almost exclusively fulfilled by mitochondrial oxidative phosphorylation (OXPHOS) [1]. Mitochondria are often trafficked long distances to meet spatiotemporal adenosine triphosphate (ATP) requirements and dynamic mechanisms determine mitochondrial localisation to best satisfy local demands of the neurone. It is also now clear that, during the lifetime of a neurone, mitochondria can become dysfunctional to the extent they cannot maintain a proton motive force sufficient for ATP generation. Cellular mechanisms engage to remove damaged mitochondria and replenish the mitochondrial pool. These cycles of mitochondrial fusion and fission can become defective in neurodegenerative disorders and consequent accumulation of damaged components within mitochondria can adversely affect mitochondrial function and cellular homeostasis.

# Mitochondrial dysfunction in neurodegenerative proteinopathies

Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) are pathologically similar, progressive neurodegenerative proteinopathies [2] (Figure 1). Proteinopathy refers to a disease-causing conformational change in a protein that normally has other roles in cell biology. Such proteins undergo pathogenic misfolding and oligomerisation into higher-order structures, revealing self-templating conformations, and have an ability to undergo prion-like spreading between cells, together resulting in toxin gain- or loss-of-function [2,3]. Misfolded proteins can adversely affect mitochondria, either through a direct association, damaging mitochondrial DNA, altering trafficking and dynamics, deregulating bioenergetics and quality control pathways or promoting mitochondria-dependent cell death pathways. Mitochondrial dysfunction as a cause or a consequence of neurodegenerative disease pathogenesis is still debated and a self-perpetuating feed-forward toxic cycle may exist (Figure 2).
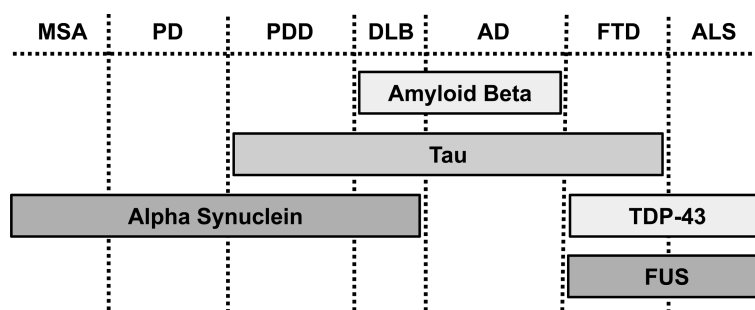


**Figure 1. Pathological overlap of proteinopathies in different neurodegenerative diseases.**
Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DLB, dementia with Lewy bodies; MSA, multiple systems atrophy; PD, Parkinson's disease; PDD, Parkinson's disease dementia; TDP-43, TAR DNA-binding protein 43; FUS, fused in sarcoma.
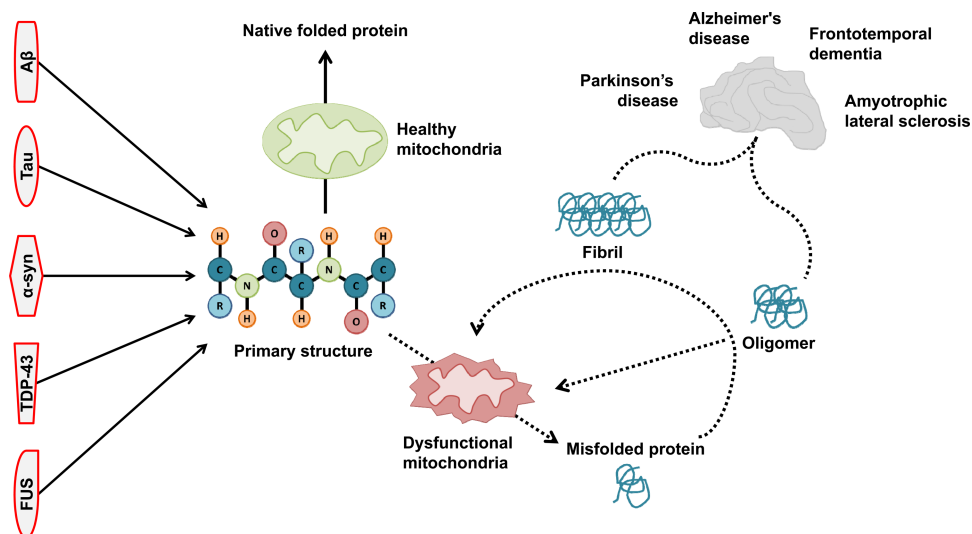


**Figure 2. Reciprocal relationship between mitochondrial function and protein misfolding.**
Mitochondrial function is adversely affected by toxic misfolded proteins. Additionally, mitochondrial function is necessary for correct protein folding and processing in neurodegenerative proteinopathies.

## Mitochondrial relationship with amyloid β and tau

AD is the most prevalent proteinopathy, characterised by accumulation of extracellular plaques containing amyloid β (Aβ) and intracellular tangles of tau. Aβ and tau both have detrimental effects on mitochondria [4]. Disruptions in mitochondrial DNA maintenance, protein import, electron transport chain (ETC) activity and redox balance are all consequences of Aβ-induced toxicity [5–12] (Figure 3 and Table 1). Mitochondrial localisation of Aβ peptide has been observed, albeit the exact sub-mitochondrial topology remains less well defined [13,14] and, indeed, Aβ may be produced at the mitochondrial-associated membrane (MAM) [15], linking mitochondrial–ER contact sites, $Ca^{2+}$ handling and bioenergetics to Aβ toxicity.

Tau is a highly soluble, natively unfolded protein [16]. Tau hyperphosphorylation impairs its ability to bind and stabilise microtubules, and tau aggregation and intraneuronal filaments are common in the pathology of tauopathies (Figure 1). The influence of tau on mitochondrial dynamics and quality control is well documented [17–21] (Figure 3). N-terminal tau fragments are associated with mitochondrial functional changes and defects in mitochondrial quality control, and the accumulation of tau fragments in human mitochondria isolated from synaptosomes correlates with synaptic changes observed in AD [17,22,23]. Changes in mitochondrial dynamics are also observed following tau overexpression in cultured cells or in *in vivo* models of tauopathy [18,24,25] (Table 1).

Some literature suggests that the accumulation of (phospho-)tau and Aβ is a direct consequence of mitochondrial dysfunction [26–30]. Perturbations to mitochondrial proteases and chaperones have demonstrated relationships with AD disease markers. Missense mutations in the mitochondrial matrix peptidase, pitrilysin metalloprotease 1 (PITRM1), are associated with Aβ-positive deposits and a slowly progressing neurodegenerative phenotype [31]. In addition, decreased activity in pre-sequence protease (PreP) has been observed in the temporal lobe region of AD patients [32] and has been linked to Aβ processing [33]. Overexpression of heat
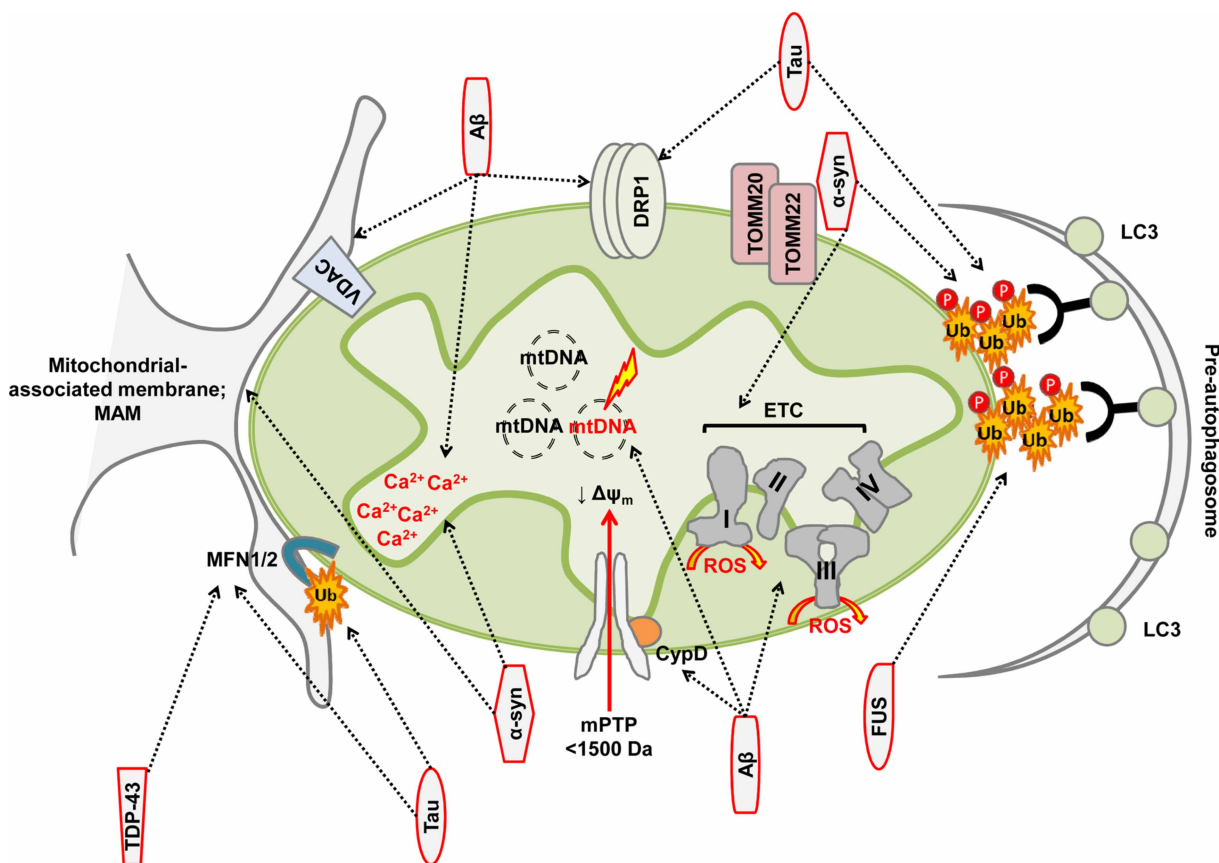


**Figure 3. Mitochondrial toxicity of misfolded proteins.**
Red outline depicts misfolded proteins and arrows indicate mitochondrial directed association or toxicity.

**Table 1 Mitochondrial relationship and toxicities with AD associated pathogenic proteins**

| Pathogenic protein | Mitochondrial toxicity or association | Reference |
|---|---|---|
| Amyloid β | *Mitochondrial association and protein import:*<br>• Localised to mitochondria<br>• Aβ peptide import mediated through the TOMM complex<br>• Disruption of mitochondrial precursor protein import<br>• Interaction with VDAC1 in AD patients, APP and APP/PS1 mice<br>• Interaction/co-localisation with OSCP subunit of $F_1F_0$-ATP synthase<br>• Production at the MAM | [6,13–15,37] |
| | *Mitochondrial DNA maintenance:*<br>• Deregulation of mitochondrially encoded mRNA transcripts (reduced complex I and increased complexes III and IV)<br>• Increased somatic mtDNA mutations in AD brain<br>• Oxidative damage to mtDNA | [5,11,12] |
| | *ETC and bioenergetics:*<br>• Increased complex I content and decreased complex I activity in tripleAD mice at 12 months<br>• Reduced cytochrome *C* oxidase activity (complex IV) in platelet mitochondria of AD patients and APP overexpressing cell models and mice<br>• Reduced ATP, respiratory rate and inner membrane potential | [6–10] |
| | *Oxidative stress and cell death pathways:*<br>• Oxidative stress, $H_2O_2$ production and lipid peroxidation in APP mice<br>• Increased superoxide levels APP/PS2 mice and triple AD mice<br>• Cytochrome *C*-mediated apoptosis<br>• Increased inner membrane localised CypD in mAPP mice | [4,6,8,38] |
| Tau | *Mitochondrial association and protein import:*<br>• Phospho–tau interaction with VDAC1 in AD patients and APP, APP/PS1 and triple AD transgenic mice<br>• N-terminal tau fragment localisation to mitochondria in AD brain<br>• N-terminal tau fragment accumulation in human mitochondria isolated from synaptosomes correlates with synaptic changes in AD | [6,17,22,23] |
| | *Deregulated mitophagy:*<br>• N-terminal tau fragment-mediated net mitochondrial removal and increased mitophagy<br>• N-terminal tau fragment-induced trafficking and/or recruitment of parkin and UCHL-1 to mitochondria<br>• Increased COX-IV and TOMM20 protein and mtDNA (ratio of mt-Atp6/Rpl13) in AD brain<br>• Increased mitochondrial membrane potential (decelerated mitophagy) | [17,19,20] |
| | *Mitochondrial trafficking and dynamics:*<br>• Hyperphosphorylated tau impaired mitochondrial trafficking<br>• Mitochondrial dynamic and trafficking defects following tau overexpression in cultured cells or in *in vivo* models of tauopathy<br>• N-terminal tau fragment-induced mitochondrial redistribution to soma<br>• Mislocalisation of DRP1<br>• Enhanced levels of OPA1 and mitofusins (mfn1/mfn2) following hTau overexpression<br>• Reduced mfn2 ubiquitination in hTau models<br>• N-terminal tau fragment-induced mitochondrial fragmentation and cristae remodelling | [17,18,21,24,25] |

shock chaperone, mortalin, alleviates Aβ-induced toxicity, while pharmacological inhibition or siRNA down-regulation of mortalin induces DRP-1 (dynamin-related protein 1)-mediated mitochondrial fission and potentiates Aβ-induced mitochondrial and cellular toxicity [34,35]. With respect to pathogenic tau, antioxidant treatment of *sod2* nullizygous neonatal mice reverses phospho–tau accumulation, placing mitochondrial

**Table 2 Mitochondrial toxicities associated with synucleinopathies**

| Pathogenic protein | Mitochondrial toxicity or association | Reference |
|---|---|---|
| α-Synuclein | *Mitochondrial association and protein import:*<br>• Disruption of TOMM20 and co-receptor interaction leading to inhibition of mitochondrial protein import<br>• Localised to MAM<br>• Localised to mitochondria in striatum and substantia nigra of PD brain<br>• A53T α-synuclein localised to the mitochondria as both monomers and oligomers | [46,57–59,61] |
| | *Mitochondrial dynamics and morphology:*<br>• α-Synuclein-induced mitochondrial fragmentation via effects on ER–mitochondria contact sites<br>• α-Synuclein-mediated destabilisation of the spectrin cytoskeleton and mislocalisation of DRP1<br>• Mitochondrial fragmentation and disordered cristae following α-synuclein overexpression<br>• Wild-type and A53T α-synuclein outer mitochondrial membrane localisation associated with mitochondrial fragmentation | [58–60,65] |
| | *ETC and bioenergetics:*<br>• Monomeric and oligomeric A53T α-synuclein-induced complex I dysfunction in dopaminergic midbrain neurones<br>• Reduced complex I activity in α-synuclein overexpressing cell lines and PD brain<br>• Reduced complex IV activity in spinal neurones of A53T α-synuclein transgenic mice<br>• Complex I misassembly in PD brains | [46,56,57,66] |
| | *Deregulated mitophagy:*<br>• Enhanced mitophagy in mutant α-synuclein expressing cells following reduced cardiolipin-mediated refolding | |
| | *Oxidative stress and cell death pathways:*<br>• N-terminal α-synuclein regulation of mitochondrial membrane permeability<br>• Association of α-synuclein with the ANT<br>• Increased oxidative stress in α-synuclein overexpressing cell lines<br>• Oxidation of complex I in frontal cortex of PD brain | [55,57,66,67] |

oxidative stress upstream of tau pathology [26]. Finally, mitochondrial dysfunction induced by loss of either prohibitin 2 (PHB2), a mitochondrial membrane scaffold protein, or the *m*-AAA protease subunit, AFG3L2, both results in tau hyperphosphorylation [27,36], potentially linking mitochondrial dysfunction and the cytoskeleton. Taken together, these observations link mitochondrial dynamics, quality control and function to accumulation and toxicity of Aβ and tau.

## Mitochondrial toxicity associated with synucleinopathies

PD is characterised by loss of dopaminergic neurones within the substantia nigra pars compacta and reduced dopamine innovation to the striatum. Mitochondrial dysfunction is a prominent pathological feature of both sporadic and familial diseases [39–45], and many PD-causing genes have overt mitochondrial phenotypes [44–53]. Accumulation of insoluble α-synuclein (α-syn) is a common feature of many clinical phenotypes, known collectively as synucleinopathies [54] (Figure 1).

Mitochondrial localisation of α-syn negatively affects mitochondrial function, morphology and dynamics [46,55–60] (Figure 3 and Table 2). Constitutive import of α-syn to mitochondria is transmembrane potential-dependent and is facilitated through a cryptic mitochondrial targeting sequence within the N-terminal region [57]. α-Syn associates with the mitochondrial inner membrane where a direct interaction and toxicity towards mitochondrial complex I has been observed [46,57]. Oligomeric and dopamine-modified α-syn-dependent reduction in protein import occurs via disruption of the association between translocase of the outer

**Table 3 Mitochondrial toxicities for ALS/FTD associated pathogenic proteins**

| Pathogenic protein | Mitochondrial toxicity or association | Reference |
|---|---|---|
| TDP-43 | *Mitochondrial association and protein import:*<br>• N-terminal (27 kDa) and C-terminal (30 kDa) fragments of TDP-43 are localised to mitochondria in APP/PS1 mice | [74] |
| | *Mitochondrial dynamics and morphology:*<br>• Reduced mfn1 and increased fis1, correlating with increasing TDP-43 expression in brain lysates<br>• Morphological and ultrastructural alterations observed in animal models of TDP-43 pathology<br>• Mitochondrial fragmentation following mutant TDP-43 overexpression | [73,75] |
| | *Mitochondrial trafficking:*<br>• Mitochondria and organelle redistribution and clustering within cytoplasmic inclusions | [72,73] |
| | *Deregulated mitophagy:*<br>• TDP-43 knockdown decreases mitophagy | [74] |
| FUS | *Mitochondrial dynamics and morphology:*<br>• Disorganised ER and mitochondria within cytoplasmic inclusions of spinal motor neurones<br>• Mitochondrial COX-IV-positive aggregates | [70,71] |

mitochondrial membrane (TOMM)-20 and its co-receptor, TOMM22 [61]. As a result, diminished protein import in nigrostriatal neurones impairs mitochondrial function, decreasing respiration and transmembrane potential, and increasing mitochondrial reactive oxygen species (ROS) [61]. Purification of crude mitochondrial preparations has led to the hypothesis that α-syn is, in fact, localised to the MAM [58] and α-syn point mutations reduce mitochondria–ER contacts, causing mitochondrial fragmentation [58]. Finally, α-syn has significant effects on mitochondrial quality control and its accumulation is becoming recognised as a consequence of deficient mitophagy [50,62,63]. α-Syn competes with LC3 for cardiolipin on the outer mitochondrial membrane. Cardiolipin facilitates refolding of α-syn oligomers; however, following prolonged exposure, LC3 is recruited. Mutated α-Syn is less able to compete with LC3, contributing to increased mitophagic flux observed in disease cells [64].

## Mitochondrial toxicity in ALS and FTD-linked proteinopathies

ALS and FTD share pathological and genetic similarities and potentially common neurodegenerative pathways [68]. Aggregated transactive response DNA-binding protein 43 kDa (TDP-43) and fused in sarcoma (FUS) are pathological hallmarks of both ALS and FTD (Figure 1). Both are ribonuclear proteins and contain prion-like domains, rich in glycine molecules, increasing their propensity for aggregation and cell-to-cell transmission. Dysfunction in OXPHOS, $Ca^{2+}$ handling and ROS have all been proposed as key mitochondrially-associated determinants of ALS pathogenesis [69] (Table 3). Furthermore, mitochondrial trafficking defects are responsible for accumulation of defective mitochondria around cell bodies in motor neurones [69].

Ubiquitin-positive aggregates are observed in aged, mutant *FUS*-expressing transgenic animals and correlate with neuronal loss. Aggregates are also positive for mitochondrial cytochrome C oxidase (COX-IV), suggesting that defective mitochondria may be tagged for removal through the mitophagic machinery [70]. Similar pathology has been observed in a single post-mortem analysis of an *FUS* mutation carrier [71]. C- and N-terminal fragments of TDP-43 have been identified within mitochondria in Amyloid precursor protein (APP)/PS1 mice and mitochondrial dynamic changes, including trafficking and quality control defects, organelle redistribution and clustering within cytoplasmic inclusions, as well as morphological and ultrastructural alterations, are observed in animal models of TDP-43 pathology [72–74]. Taken together, these observations suggest a phenotype of dysfunctional, mislocalised and fragmented mitochondria in ALS and FTD (Figure 3).

# Mitochondrially targeted strategies as disease-modifiers in neurodegenerative proteinopathies

Despite evidence of mitochondrial dysfunction in the pathology of proteinopathies and exacerbation of neuro-degenerative disorders, the exact biochemical, neurotoxic mechanisms of misfolded, aggregated proteins remain poorly understood. Protecting mitochondrial function therefore may be one plausible drug discovery strategy for neuroprotective or disease-modifying end-points.

## Inhibition of mitochondrial permeability transition pore opening

Mitochondrial permeability transition pore (mPTP) opening has been implicated as a major cell death pathway in multiple neurodegenerative diseases [76–78]. A shift in the mitochondrial redox balance towards oxidative stress, coupled with $Ca^{2+}$ overload, triggers opening of the mPTP leading to osmotic swelling, uncoupling of electron transport and metabolic collapse [79–86]. The mitochondrial matrix enzyme, cyclophilin D (CypD), is a known positive regulator of mPTP opening [86]. Genetic ablation or pharmacological inhibition of CypD desensitises the pore to $Ca^{2+}$, restricting pore opening [85,86]. Direct binding between Aβ and CypD links amyloid toxicity to mPTP opening in AD [38,87] and CypD deficiency corrects mitochondrial trafficking defects observed in AD models [88]. Previous literature supports a role for the $F_1F_0$-ATP synthase in pore formation [89,90], suggesting that the oligomycin-sensitivity conferring protein (OSCP) serves as a docking site for CypD [90]. Interestingly, OSCP is decreased during AD progression and may directly interact with Aβ [37]. Given the relationship between CypD, OSCP, Aβ and the propensity for mPTP opening, it is plausible that targeting these processes may have clinical benefits. Indeed, recently, phenotypic screening approaches have identified mPTP inhibitors and CypD-binding compounds in a model of Aβ-induced mPTP opening [91–94]. Overexpression of an N-terminal region of α-syn has also been observed to regulate mitochondrial membrane permeability [67], linking mPTP to synucleinopathies. Moreover, following overexpression, α-syn associates
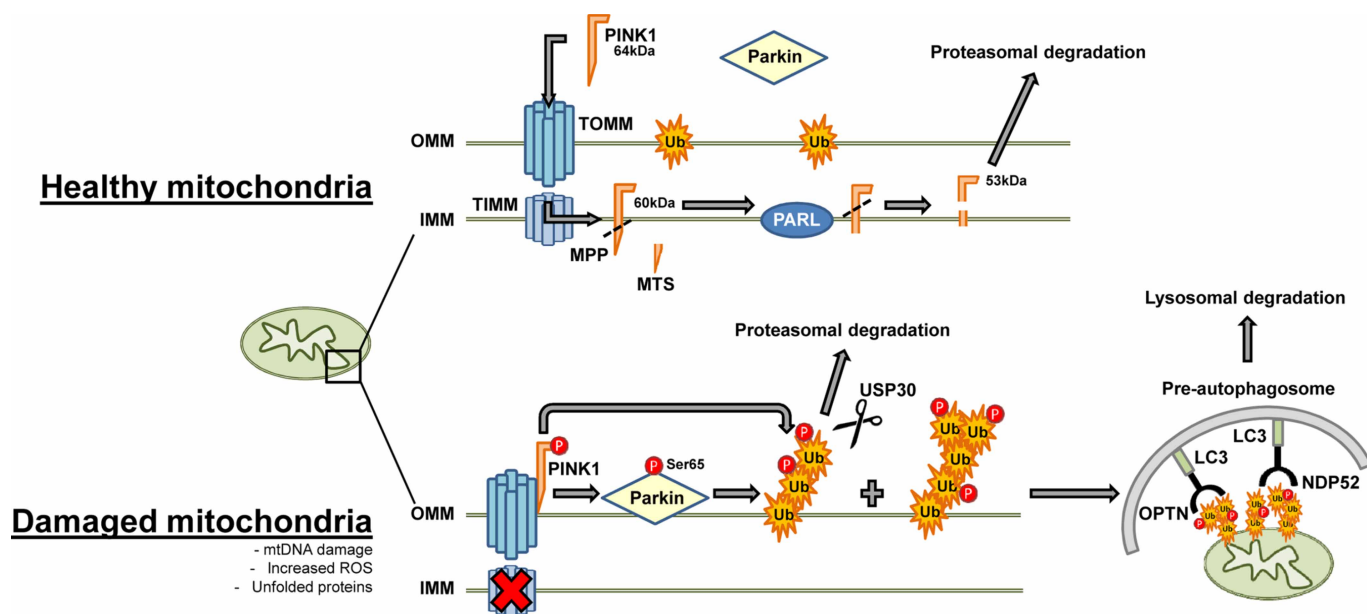


**Figure 4. Defective mitochondria are removed from the cell by mitophagy.**
In healthy mitochondria, mitophagy proceeds at a slow rate due to the low abundance of ubiquitinated mitochondrial proteins, PINK1 import and degradation. PINK1 is stabilised on the OMM following mitochondrial depolarisation and phosphorylates both parkin and ubiquitin. Parkin is activated and translocates to mitochondria. Parkin ubiquitinates outer membrane proteins which then serve as targets for autophagic adaptor proteins and mitochondria are then cleared through the autophagic machinery. Abbreviations: IMM, inner mitochondrial membrane; OMM, outer mitochondrial membrane; TIMM, translocase of the inner mitochondrial membrane; MPP, mitochondrial processing peptidase; MTS, mitochondrial targeting sequence; TOMM, translocase of the outer mitochondrial membrane; Ub, ubiquitin.

with the adenine nucleotide translocase (ANT), another putative pore component [95,96]. Interestingly, pharmacological inhibition of ANT partially reverses the associated α-syn-induced mitochondrial toxicity [97].

Homology within the cyclophilin isoenzyme family makes selective targeting of CypD therapeutically challenging [98]. Moreover, since CypD does not constitute a principal pore component, and effects are indirect, mitochondria remain capable of permeability transition given enough stimuli [86,99]. CypD confers sensitivity to the mPTP inhibitor, cyclosporin A (CsA) [85,100], and number of CsA analogues have been developed [101,102]. CsA and its derivatives are large molecular mass natural products and penetrate the blood–brain barrier poorly, limiting efficacy in neurodegenerative disease. Many groups have developed CypD-independent inhibitors [103–107], but to date, none, as far as we are aware, have been tested in models of neurodegenerative disease.

## Activating mitophagy to improve mitochondrial function in neurodegenerative proteinopathies

Dysfunctional lysosomal and proteasomal degradation pathways have been implicated in neurodegenerative diseases. A selective form of macroautophagy, termed mitophagy, is responsible for the clearance of defective mitochondria from cells [44,45,108–110]. PTEN-induced putative kinase 1 (PINK1) and parkin are regulators of mitophagy and are integral to a mechanism that identifies and tags defective mitochondria for removal [110,111] (Figure 4). The association between mutations in these proteins and dysfunction in the mitophagy pathway has direct implications in both familial and sporadic PD [43,51,112].

PINK1 and parkin function may be necessary for α-syn clearance. Preceding neurodegeneration, α-syn A53T transgenic mice accumulate neuronal inclusions containing mitochondrial remnants and autophagic markers which increase in size and number with PINK1 or parkin knockout [62]. PINK1 loss-of-function potentiates the A53T phenotype, decreasing lifespan and enhancing movement deficits and protein aggregation [63]. Similarly, iPSCs from mutant PINK1/parkin carriers accumulate cytoplasmic inclusions and insoluble α-syn, a phenotype which can be partially corrected following PINK1 re-expression [50]. Interestingly, following mitochondrial uncoupling, autophagic α-syn removal is reduced and the likelihood of aggregate formation in oligodendrocytes is enhanced, suggesting that mitochondrial damage over time may play a role in α-syn accumulation [48]. Finally, a novel mechanism of PINK1 protection in α-syn models has been proposed as being mediated through protein phosphatase 2A activity [113].

Mitophagy has been linked to both Aβ and tau in AD. PINK1 is down-regulated in AD patients and in transgenic AD models [114]. Furthermore, the absence of PINK1 augments the mutant APP phenotype and stereotaxic injection of rAAV2–PINK1 into the hippocampus of mutant APP mice significantly reduced Aβ compared with control, improving synaptic function and memory [114]. An association between deficient mitophagy and abnormal tau accumulation has been found in AD patient brain homogenate and transgenic mice. This deficit can be rescued by up-regulating parkin expression [20]. Exogenous parkin has also been found to decrease Aβ levels *in vitro* and Aβ-induced plaque formation in transgenic mice [115–117].

Parkin activation may be a promising strategy to enhance mitophagy in disease models. Nilotinib, originally discovered as a tyrosine kinase inhibitor, increases parkin abundance and ubiquitination, potentially increasing parkin recycling via the proteasome [118]. Nilotinib-mediated c-ABL inhibition also prevents parkin tyrosine phosphorylation, resulting in release of parkin auto-inhibition and demonstrating protection in PD models [119]. Additionally, nilotinib has been demonstrated to increase the parkin–beclin 1 interaction and increase clearance of Aβ in transgenic APP mice following chronic treatment [120]. Finally, with respect to ALS and FTD, motor and cognitive deficits measured in TDP-43 transgenic mice have also been reversed using nilotinib [121].

## Deubiquitinating (deubiquitinase; DUB) enzymes in neurodegenerative proteinopathies

Down-regulation of the ubiquitin–proteasome system (UPS) is common across neurodegenerative diseases and promoting UPS activity is an emerging strategy for the treatment of proteinopathies. Deubiquitinases (DUBs) hydrolyse isopeptide bonds covalently binding ubiquitin to proteins, regulating degradation, localisation or activity. Multiple DUBs regulate mitochondrial function [122–126]. Ubiquitin-specific protease 15 (USP15) and USP30 both antagonise parkin-mediated mitophagy [122,125]. USP30 is the only DUB exclusively localised to mitochondria [127], tethered to the outer mitochondrial membrane. USP30 deubiquitinates parkin substrates, including TOMM20 and MIRO1 [122], and inhibition has been proposed to enhance parkin-mediated mitophagy [128,129]

(Figure 4). In one study, USP35 was also found to oppose parkin-mediated mitophagy, with both a distinct mechanism to USP30 and lack of influence on the translocation of parkin [124]. USP8 enhances mitophagy by removing lysine-6-linked ubiquitin from parkin, promoting its turnover [126]. However, confusingly, USP8 knockout also limits toxicity in an α-syn model in *Drosophila melanogaster* [130]. Other DUBs localise to mitochondria, albeit not exclusively; Ataxin-3 [131,132] and the X-chromosome-linked deubiquitinase, USP9x [132] have demonstrated mitochondrial localisation under specific conditions. USP9x deubiquitinates α-syn and silencing increases the abundance of mono-ubiquitinated α-syn, enhancing its propensity for aggregation [133].

## Eliminating ROS in neurodegenerative proteinopathies

Mitochondria are a principal source of cellular ROS. ROS are generated as a by-product of OXPHOS and their abundance presents a fine balance between signalling and toxicity. Much interest has focussed around limiting oxidative stress in neurodegenerative disease. Exogenous expression of a mitochondrially targeted catalase decreases monomeric and oligomeric Aβ and Aβ plaques in mice carrying the APP KM670/671NL (Swedish) mutation [134]. Synthetic analogues of mitochondrial coenzyme $Q_{10}$ prevent Aβ oligomer-induced changes in mitochondrial mRNA transcript expression, protecting cells against oligomeric Aβ damage [135]. Although perturbation of ROS in preclinical models has so far proved beneficial, to date translation to human disease has been challenging and yielded multiple clinical failures across multiple neurodegenerative diseases [136]. Interestingly, the antioxidant MitoQ has been assessed in many models of ageing and neurodegenerative disease. MitoQ is a redox active ubiquinone, targeted to mitochondria [137]. MitoQ has demonstrated positive effects in an $SOD1^{G93A}$ ALS mouse model [138], a triple transgenic AD mouse [139] and in models of AD in *Caenorhabditis elegans* [140], together linking mitochondrial ROS and proteinopathy-related neuropathologies. MitoQ is currently in clinical trials testing the efficacy for improving vascular, motor and cognitive function in middle-aged and older adults (NCT02597023).

# Conclusion and prospects

Compelling evidence suggests that mitochondrial dysfunction plays a significant role in neurodegenerative proteinopathies. Neuronal ATP is provided almost exclusively through mitochondrial OXPHOS, and complicated processes controlling mitochondrial dynamics, redox equilibrium, protein import and mitochondrial quality control work in concert to meet spatiotemporal bioenergetic demands. Aberrant misfolded proteins disrupt these processes, triggering mitochondrial dysfunction and having wider effects on cellular homeostasis.

Numerous disease-modifying strategies targeting mitochondria are currently under investigation. Further development of mPTP inhibitors is warranted due to the emerging evidence of the involvement of $Ca^{2+}$ homeostasis, ROS and mPTP opening in multiple neurodegenerative diseases. Accelerating removal of damaged mitochondria has been proposed as a novel disease-modifying strategy not only in PD, but in many proteinopathies. Identification of a mechanism to enhance mitophagy may demand increased understanding of DUB biology and the substrate diversity and selectivity of these enzymes. Clinical trials of mitochondrially targeted antioxidants will provide proof-of-concept concerning ROS manipulation. Taken together, thoroughly understanding the mitochondrial relationship with neurodegenerative proteinopathies is likely to pave the way for the development of targeted therapies, potentially modifying the disease course of these progressive degenerative disorders.

## Abbreviations

AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; ANT, adenine nucleotide translocase; APP, amyloid precursor protein; ATP, adenosine triphosphate; Aβ, amyloid β; COX, cytochrome *C* oxidase; CsA, cyclosporin A; CypD, cyclophilin D; DRP-1, dynamin-related protein 1; DUB, deubiquitinase; ETC, electron transport chain; fis1, mitochondrial fission 1; FTD, frontotemporal dementia; FUS, fused in sarcoma; MAM, mitochondrial-associated membrane; mPTP, mitochondrial permeability transition pore; OPA-1, optic atrophy 1; OSCP, oligomycin-sensitivity conferring protein; OXPHOS, oxidative phosphorylation; PD, Parkinson's disease; PINK1, PTEN-induced putative kinase 1; ROS, reactive oxygen species; TDP-43, transactive response DNA-binding protein 43 kDa; TOMM, translocase of the outer mitochondrial membrane; UPS, ubiquitin–proteasome system; USP, ubiquitin-specific protease; α-syn, α-synuclein.

## Author Contribution

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## Acknowledgements

## Competing Interests

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