FEBS Letters

FEBS PRESS science publishing by scientists

REVIEW ARTICLE

Role of mitochondrial ROS in the brain: from physiology to neurodegeneration

Plamena R. Angelova and Andrey Y. Abramov

Department of Molecular Neuroscience, UCL Institute of Neurology, London, UK

Correspondence
P. R. Angelova or A. Y. Abramov, Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London WC1N 3BG, UK
Fax/Tel: +44 2034484062
E-mail: p.stroh@ucl.ac.uk or a.abramov@ucl.ac.uk

(Received 22 November 2017, revised 17 December 2017, accepted 21 December 2017, available online 18 January 2018)

doi:10.1002/1873-3468.12964

Edited by Wilhelm Just

Mitochondria are key cell organelles in that they are responsible for energy production and control many processes from signalling to cell death. The function of the mitochondrial electron transport chain is coupled with the production of reactive oxygen species (ROS) in the form of superoxide anion or hydrogen peroxide. As a result of the constant production of ROS, mitochondria are protected by highly efficient antioxidant systems. The rapidly changing levels of ROS in mitochondria, coupled with multiple essential cellular functions, make ROS apt for physiological signalling. Thus, mutations, environmental toxins and chronic ischaemic conditions could affect the mitochondrial redox balance and lead to the development of pathology. In long-living and non-mitotic cells such as neurons, oxidative stress induced by overproduction of mitochondrial ROS or impairment of the antioxidant defence results in a dysfunction of mitochondria and initiation of the cell death cascade. Mitochondrial ROS overproduction and changes in mitochondrial redox homeostasis have been shown to be involved in both a number of neurological conditions and a majority of neurodegenerative diseases. Here, we summarise the involvement of mitochondrial ROS in the mechanism of neuronal loss of major neurodegenerative disorders.

Keywords: astrocytes; mitochondria; neurodegeneration; neuron; reactive oxygen species

Mitochondria are organelles that play multiple important functions in the cell. Despite their versatile duties, the main function of mitochondria is the production of energy in the form of ATP and almost all other processes inside mitochondria are connected or dependent on bioenergetics. ATP synthesis by oxidative phosphorylation is coupled with mitochondrial respiration. Respiration is the generation of mitochondrial transmembrane potential by pumping the protons via mitochondrial complexes I, III and IV of the electron transport chain (ETC). Mitochondrial membrane potential ($\Delta\psi m$) is a cross-linked element in mitochondrial function and is used as a proton motive force for ATP synthesis, helping to maintain the shape of this organelle and mitochondrial pro-apoptotic proteins, which are released into cytosol in the case of $\Delta\psi m$ collapse.

The distribution of mitochondrial in the cells from diverse tissues is dependent on energy demands. However, despite the density of mitochondria in myocytes being higher than in neurons, the brain consumes almost ten times more oxygen and glucose compared

Abbreviations
AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; DJ-1, Parkinson protein-1; ETC, electron transport chain; FRDA, Friedrich's ataxia; GSH, glutathione; MAO, monoamine oxidase; MPP+, 1-methyl-4-phenylpyridinium; NBIA, neurodegeneration with brain iron accumulation; PANK2, pantothenate kinase; PD, Parkinson's disease; PSP, progressive supranuclear palsy; PTP, permeability transition pore; ROS, reactive oxygen species; SOD, superoxide dismutase; TCA, tricarboxylic acid; UCP-2, uncoupling protein-2.

to other tissues. Considering the high energy demand and high rate of ATP production and consumption in the brain, most of mitochondrial mutations or mitochondrial toxins damage brain function and lead to neurological pathology [1].

Mitochondria produce free radicals, which are mostly reactive oxygen species (ROS) as a result of the high accessibility of oxygen in this organelle. Although mitochondria produce ROS in number of enzymes, the vast majority of the free radicals termed 'mitochondrial ROS' in the literature are produced in the ETC. The rate of ROS production, mitochondrial membrane potential ($\Delta\psi m$) and the activity of the complexes of the ETC are highly interdependent [2]. Therefore, on the one hand, dissipation of the mitochondrial membrane potential could lead to an increase in ROS generation when respiration is inhibited. On the other hand, if the drop in $\Delta\psi m$ is stimulated by uncoupling, this could lead to a reduced rate of free radical production. Similarly, hyperpolarisation of mitochondria could lead to an increase of ROS production. Thus, the production of ROS in the ETC is dependent on the release of electrons out of the electron transport chain followed by the formation of free radicals. The process of the release of electrons could be induced by the reverse flux of electrons and the activity of complexes I and II as donors of electrons and partial inhibition of the complexes by hyperpolarisation of mitochondrial membrane, ischaemic conditions or chemical compounds [3,4] (Fig. 1). Although hydrogen peroxide was the first ROS shown to be produced in mitochondria [5–7], electron escape from the ETC generates free radicals predominantly in the form of super oxide radical $O_2^{\cdot-}$ which later converts to H_2O_2.

Despite the fact that respiratory chain is a major ROS producer in mitochondria under resting conditions, several matrix proteins and complexes, including enzymes of the tricarboxylic acid (TCA) cycle (e.g. aconitase, pyruvate dehydrogenase and α-ketoglutarate dehydrogenase), could produce $O_2^{\cdot-}$ [8,9]. Some inner

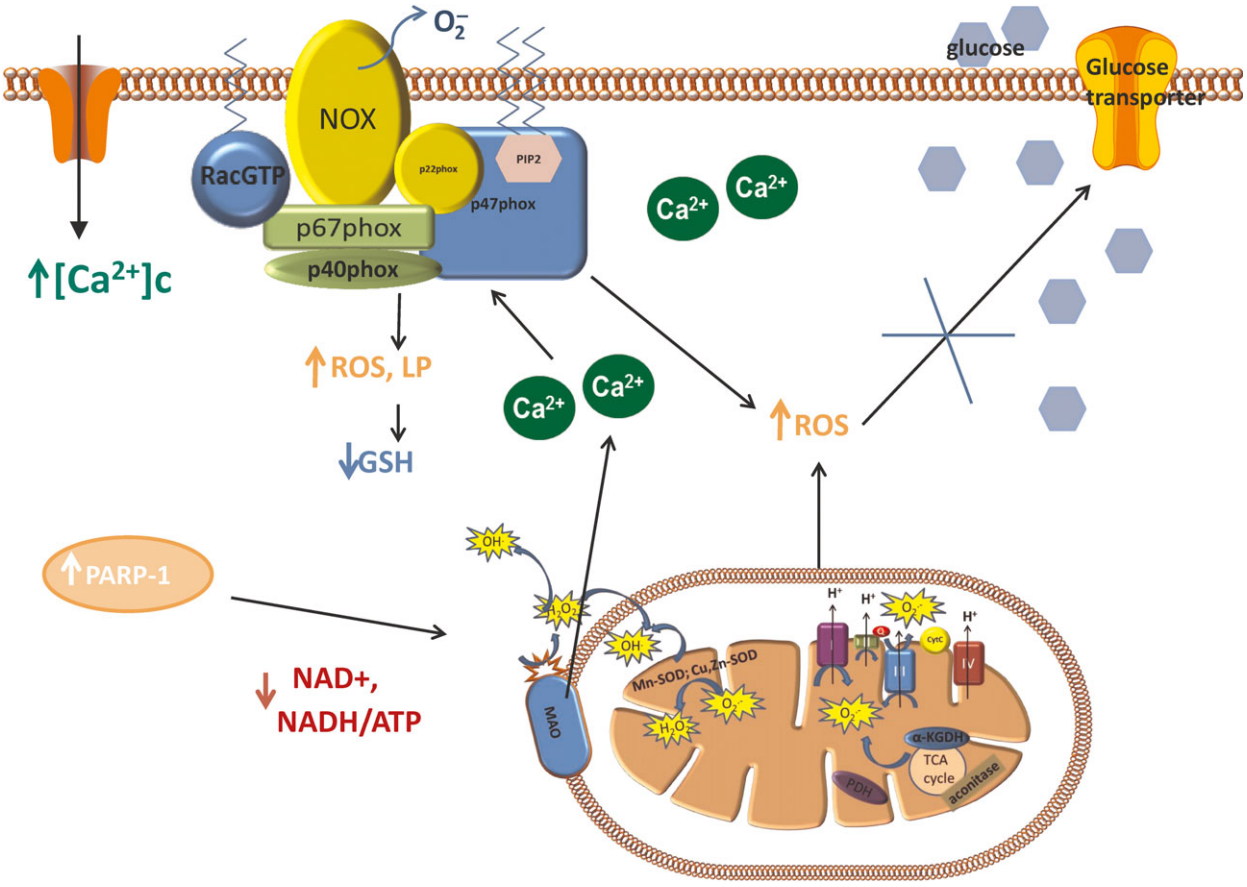

Fig. 1. Mitochondria is a producer and target of ROS. Mitochondria generating ROS in the ETC, TCA cycle enzymes and MAO. Production of hydrogens peroxide in MAO, or superoxide in ETC, can stimulate lipid peroxidation and the inositol trisphosphate-dependent calcium signal. Overproduction of ROS in NADPH oxidase in PS or AD activates PARP, which consumes NAD and reduces NADH for complex I. Mitochondrial ROS production can inhibit glucose transporter and induce the limitation of mitochondrial substrates for mitochondria.

mitochondrial membrane proteins (various cytochrome P450 enzymes, glycerol-3-phosphate dehydrogenase) for which activity is partially dependent on $\Delta\psi m$ can produce ROS. Located on the outer membrane of the mitochondria, enzyme monoamine oxidase (MAO) utilizes monoamines producing aldehydes and hydrogen peroxide. Another outer membrane protein, cytochrome b5 reductase, can also produce ROS (Fig. 1).

Redox balance in the mitochondrial matrix is maintained by an effective antioxidant system. The lifetime of the superoxide anion is 1 ns and it can rapidly dismutate spontaneously or enzymatically, with the help of manganese superoxide dismutase (SOD) in the mitochondrial matrix or by Cu,Zn-SOD in the intermembrane space, to hydrogen peroxide. Major endogenous antioxidant glutathione (GSH) is distributed throughout the mitochondria and the rest of the cell and isolates major peptides from oxidation by $O_2^{\cdot-}$ or other forms of ROS. The permeable H_2O_2 participates in signalling cascades and is degraded by the enzymes catalase, glutathione peroxidase and peroxiredoxin 3 [10,11].

One of the major initial forms of ROS in the mitochondria is superoxide anion radical $O_2^{\cdot-}$. Considering the very short lifetime of this free radical (approximately 1×10^{-9} s), it is very unlikely that superoxide can play role in physiology, although it can possibly induce oxidative damage in the neighbouring area. SOD1 is more likely to be a signalling rather than antioxidative enzyme because it convert $O_2^{\cdot-}$ to the more stable hydrogen peroxide, which can be transported as a signalling molecule (Fig. 1). However, H_2O_2 is dangerous for cells when it produces the most toxic form of ROS: hydroxyl anion in the Fenton reaction [12].

Mitochondria possess a number of 'tools' to produce ROS in response to extracellular (e.g. decrease of the oxygen level, toxins, increase of glucose uptake), cellular (hormones, transmitters) or intramitochondrial (availability of substrates) triggers. Mitochondrially generated ROS (from MAO) can stimulate lipid peroxidation, which activates phospholipase C and the inositol trisphosphate-triggered calcium signal [13–15] (Fig. 1). An increase in mitochondrial ROS in response to hypoxia stimulates the calcium signal in astrocytes [16] and actives respiration [17]. Mitochondrial calcium uptake is redox sensitive and can be regulated by ROS [18]. A more prolonged elevation of ROS in mitochondria was shown to be involved in a number of cell processes, including cell proliferation [19]. However, any well balanced system, even that of mitochondria, could be disrupted, resulting in pathology. Overproduction of ROS or dysregulation of the antioxidant system leads to a number of pathologies. In the brain, it leads to cell death and neurodegeneration.

Neurodegenerative diseases are progressive, devastating and incurable, and are becoming increasingly prevalent in our aging populations. An aging population worldwide means that neurodegenerative diseases are one of the top medical and social problems. There are two major neurodegenerative disorders, namely Alzheimer's disease (AD) and Parkinson's disease (PD), affecting 5% (AD) and 1% (PD) of individuals aged $\geq$ 65 years [20,21]. The annual cost of nursing home care for major neurodegenerative disorders in European countries is estimated to be hundreds of millions of Euros [22].

Neurodegenerative diseases, including AD, PD, motor neuron disease and Huntington's disease, all share several common features, such as an accumulation of abnormally aggregated proteins termed pathological inclusions, the involvement of oxidative damage and mitochondrial dysfunction in pathogenesis. Many of the genes associated with PD, amyotrophic lateral sclerosis (ALS) or ataxias are linked to mitochondria. All aggregated misfolded proteins that are involved in neurodegenerative disorders (β-amyloid, tau, α-synuclein and huntingtin) inhibit mitochondrial function and induce oxidative stress [23,24]. Importantly, mutations in mitochondrial DNA result not only in mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes, or myoclonic epilepsy with ragged red fibres, but also PD. The involvement of oxidative stress in the mechanism neuronal loss is demonstrated for the majority of neurodegenerative disorders [1]. However, antioxidant therapy approaches have failed as a treatment at the clinical level for most of these diseases.

Although mitochondria produce far less ROS compared to NADPH oxidase, in long-lived neurons, where active mitochondria function must be maintained for an entire lifetime, the implication of mitochondrial ROS in physiology and pathology may be crucial. Here, we review the role of mitochondrial ROS in the pathology of neurodegeneration.

Alzheimer's disease

Alzheimer's disease is a most common neurodegenerative disorder affecting the aged population. The pathology of AD is characterised by senile plagues (predominantly consisting of aggregated β-amyloid) and intracellular neurofibrillary tangles (formed by tau aggregates). The involvement of mitochondria in the mechanism of AD pathology is not so direct compared

to other neurodegenerative disorders, although the role of oxidative stress and mitochondrial dysfunction is shown for diverse models of AD [24]. Thus, a reduction in complex IV activity has been demonstrated in mitochondria from the hippocampus and platelets of AD patients and in AD cybrid cells [1,25,26]. Aggregation of βA leads to oxidative stress, mitochondrial dysfunction and energy failure prior to the development of plaque pathology [27].

Aggregated βA can reduce mitochondrial respiration in neurons and astrocytes via the inhibition of complexes I and IV [28,29]. Inhibition of ETC potentially can induce ROS production, although a direct increase in mitochondrial ROS production was shown in some studies [30,31]. However, superoxide production from mitochondria, but not from NADPH oxidase, was shown to be associated with blocked long-term potentiation in a Tg2576 mouse model of AD [32]. The importance of mitochondrial ROS was also confirmed by the results obtained with mitochondrially located antioxidant MitoQ, which prevented cognitive decline, Aβ accumulation, astrogliosis and synaptic loss in a triple transgenic mouse model of AD [33]. MitoQ extends lifespan and improves health in a transgenic *Caenorhabditis elegans* model of AD [34]. The role of oxidative damage in sporadic AD is confirmed in experiments where the inhibition of lipid peroxidation as a result of a deuterium-reinforced polyunsaturated fatty acids diet improves cognition and memory in aldehyde dehydrogenase 2 null mice, which is an established model of oxidative stress-related cognitive impairment that exhibits AD-like pathologies [35]. Olfactory bulbectomy leads to a strong AD phenotype in mice. In mice, neurodegeneration caused by olfactory bulbectomy is accompanied by energy metabolism disturbances and oxidative stress in the brain mitochondriam, similar to those occurring in transgenic animals, familial AD models and patients with sporadic AD [36].

Many cases of autosomal dominant early onset AD result from mutations in the genes encoding presenilins 1 or 2. Mitochondrial ROS was shown to be important for triggering the mitochondrial permeability transition pore (PTP) and activation of the process of cell death in presenilin 1 cells [37].

Mitochondrial ROS production in AD models is much smaller compared to the effects with respect to the production of ROS in NADPH oxidase [38,39]. However, the production of ROS in NADPH oxidase leads to mitochondrial depolarisation because of a lack of substrates as a result of activation of the DNA-repairing enzyme PARP [40–42]. Combination of calcium and ROS production under β-amyloid stimulation induces the opening of mitochondrial PTP and cell death [38,43,44]. Prevention of PTP opening by inducing cyclophilin D deficiency (molecular blocker of PTP opening) also improved mitochondrial function and learning/memory in an aging AD mouse model [45].

Oxidative stress is one of the major triggers for pathology in AD [1], although mitochondria are shown to be a target for oxidative damage rather than a source of ROS production.

The familial form of frontotemporal dementia is induced by a mutation in the MAPT gene, encoding tau. The function of mitochondria is altered in the neurons of these patients. This results in a higher mitochondrial membrane potential, with overproduction of ROS in mitochondria, which in turn causes oxidative stress and cell death. Mitochondrial ROS overproduction in these cells is a major trigger for neuronal cell death and can be prevented by mitochondrial antioxidants [46].

Vascular diseases causing dementia

Vascular dementia is the cognitive decline resulting from cerebral vasculature hypoperfusion. A chronic hypoperfusion or blockade of a brain blood vessel could lead to a damage of the surrounding brain tissue and a build-up of toxic waste substances and this could result in various conditions (e.g. cerebral small vessel disease induced by hypercholesterolemia, cerebral amyloid angiopathy, stroke and ischaemia reperfusion injury, etc.). Very often, vascular dementia is a prerequisite for the development of AD when a defect clearance of β- amyloid is present. Undeniably, all of these conditions have the same output phenotype: impairment of mitochondrial function and increased oxidative stress as a result of chronic hypoxia and substrate deprivation. Oxidative stress and mitochondrial dysfunction are linked to the development of dementia in a majority of cases [47]. Supplementation with last generation antioxidant resveratrol in the form of solid lipid nanoparticles or edaravone has been very promising. This type of treatment could activate the Nrf-2/HO-1 pathway and mitigate mitochondrial ROS production, consequent lipid peroxidation, formation of protein carbonyls and improve MnSOD activity in a permanent bilateral common carotid artery occlusion rodent model of vascular dementia [48,49].

Parkinson's disease

There is much evidence that oxidative stress occurs in and contributes to the pathogenesis of PD. Post

mortem studies of the brains of patients with PD reveal increased levels of lipid peroxidation markers (malondialdehyde and 4-hydroxynonenal) and the presence of protein oxidative damage in the form of protein carbonyls [50]. It has been reported that there is an increase in mtDNA common deletions in the surviving dopaminergic neurons in the substantia nigra of patients with PD. These deletions are caused by oxidative stress [51]. Both the toxin and genetic models of PD also demonstrate increased oxidative stress, which is connected with mitochondrial function. Inhibitors of mitochondrial complex I, rotenone or 1-methyl-4-phenylpyridinium (MPP+) produce superoxide anions in submitochondrial particles, and the neurotoxic effects of MPP+ and rotenone are probably caused by oxidative stress rather than metabolic changes because they can effectively be prevented by treatment with antioxidants [52]. Importantly, mutations in mitochondrial complex I lead to neurodegeneration. In neurons derived from stem cell cybrids that contain such mtDNA mutations, the major trigger for cell death is overproduction of superoxide in the matrix of mitochondria, but not energy deprivation [53]. Mild uncoupling of mitochondria with mitochondrial uncoupling protein-2 (UCP-2) overexpression reduces ROS production in a toxic (MPP+, rotenone) mouse model of PD. UCP-2 deficiency also increases the sensitivity of dopamine neurons to MPTP, whereas UCP-2 overexpression decreases MPTP-induced nigral dopamine cell loss [54]. Mutations in Parkinson protein-1 (DJ-1) cause a rare autosomal-recessive form of PD. Loss of function of DJ-1 results in oxidative stress, with DJ-1 exerting neuroprotection via its antioxidant mechanism in mitochondria [55,56]. DJ-1 knockout mice demonstrate increased mitochondrial oxidant stress and downregulation of mitochondrial uncoupling proteins [57].

Mutations in PINK1 cause a recessive form of PD. PINK1 is a mitochondrial kinase and it has been demonstrated previously that PINK1 deficiency results in impaired respiration with inhibition of complex I, as well as rotenone-like increased production of ROS in mitochondria [58,59]. Fibroblasts from patients with PINK1-associated PD exhibit impaired oxidative phosphorylation and oxidative stress [60,61]. Excessive ROS production in the mitochondria of PINK1 knockout neurons can be an inductor of the inhibition of mitochondrial Na^{2+}/Ca^{2+} exchanger or glucose transporter and is rescued by antioxidants [58,62,63] (Fig. 1). Activation of Nrf2 by pharmacological activators restores mitochondrial metabolism in PINK1 deficient cells [64]. Additional ROS production by MAO via the application of dopamine induces the opening of mitochondrial PTP and cell death in PINK1 deficient neurons [65].

Mitochondrial ROS play an important role not only in the pathology of PINK1 (mutation or deficiency), but also in the physiology of PINK1/Parkin related mitophagy. Mitochondrial ROS production has been shown to be important for the induction of mitochondrial recruitment of Parkin and the initiation of mitophagy [66].

Excessive ROS production in mitochondria of the familial and sporadic form of PD damage DNA that activates DNA repairing enzyme PARP which induce energy deprivation in neurons due to NAD consumption [67,68] (Fig. 1). Both familial and sporadic forms of PD are characterised by the formation of Lewy bodies, which consist of aggregated α-synuclein. Although monomeric α-synuclein plays a physiological role in synaptic transduction and mitochondrial bioenergetics [69,70], the oligomeric peptide becomes toxic for cells [23]. Oligomeric α-synuclein is detected in mitochondria [71] where it inhibits complex I [72,73]. Despite the fact that α-synuclein-induced oxidative stress can be quenched by application of coenzyme Q10 [74], the effect of any form of α-synuclein on mitochondrial ROS production was not identified [75]. Oligomeric α-synuclein produces ROS independently of the known enzymatic pathways that affect mitochondrial function and induce lipid peroxidation [75,76].

Progressive supranuclear palsy (PSP)

Progressive supranuclear palsy is a form of atypical Parkinsonism that is characterised by the accumulation of 4R tau inclusions and is classified as tauopathy. The MAPT H1 haplotype is the major genetic risk factor associated with PSP but, recently, many genes encoding proteins important in mitochondrial function or oxidative stress management (e.g. debrisoquine 4-hydroxylase, paraoxonases 1 and 2, *N*-acetyltransferases 1 and 2, and SOD1 and SOD2) have also been implicated [77]. This links to mitochondrial dysfunction and excess mitochondrial ROS production, as well as early lipid peroxidation as occurs in mesenchymal stem cells from patients with the sporadic form of PSP, indicating the essential contribution of cellular pathology. Importantly, even in the early developmental state, the mesenchymal stem cells exhibit metabolically dysfunctional mitochondria and this negatively influences their differentiation capacity [78], thus diminishing the possibility of the autologous transplantation of mitochondria as a possible therapeutic direction for this disease.

Amyotrophic lateral sclerosis (ALS)

The role of mitochondrially driven oxidative stress is linked to the familial form of ALS with a mutation in mitochondrial SOD1. ALS is a devastating neurodegenerative disease in which the loss of spinal cord and cortical motor neurons leads to progressive paralysis and premature death [79,80]. Mitochondrial oxidative damage has been demonstrated in patients affected by sporadic ALS [81,82] and also in transgenic mice expressing a familial ALS-linked mutant Cu,Zn-SOD1 [83]. Importantly, reduction of the mitochondrial ROS in neurons with a SOD1 mutant mouse model by generating a double transgenic model with UCP-2 did not recover mitochondrial function and accelerated disease progression [84]. Mutations in RNA transactivation response DNA-binding protein 43, FUS/TLS and p62 are also associated with ALS and cells with these mutations also show increased mitochondrial ROS and oxidative stress [85,86].

Neurodegeneration with brain iron accumulation (NBIA)

Neurodegeneration with brain iron accumulation comprises a heterogeneous group of diseases characterised by the accumulation of iron in the basal ganglia and a mutation in pantothenate kinase (PANK2). The PANK2 mutation leads to a deficiency in CoA, which in turn impairs energy metabolism in mitochondria. Acetyl CoA plays a role in the synthesis and oxidation of fatty acids and the oxidation of pyruvate in TCA. Animal models of the disease have failed so far because the rodent PANK$^{-/-}$ phenotype is not the typical neurodegenerative phenotype with brain iron accumulation and defective movements unless it is subjected to a ketogenic diet [87]. This is probably because the localisation of the murine PANK2 homolog is cytosolic, in contrast to that of human PANK2, which has been attributed to the mitochondria. Induced pluripotent stem cells derived from PANK2 patient fibroblasts were recently used in an attempt to model the disease. These neurons have been shown to exhibit reduced glutathione levels and increased cytosolic and mitochondrial ROS production. Moreover, supplementation with CoA was reported to be protective [88]. Similarly, our PANK2-induced pluripotent stem cell-based model demonstrated defective function of mitochondrial complexes I and II, increased ROS production and lower levels of cellular GSH, which further resulted in increased lipid peroxidation [89]. Application in conjunction with the iron chelator desferal further increased ROS production and exacerbated the PANK2 phenotype.

However, mutations in several genes have been known to cause neurodegeneration with brain iron accumulation (e.g. PLA2G6, C19orf12, COASY, FA2H, ATP13A2, FTL/FTL1, etc.) [90] and, importantly, most of them are connected to oxidative stress.

PLA2G6 mutation

The PLA2G6 mutation is an autosomal recessive mutation in the gene encoding the calcium-independent phospholipase A2 located on chromosome 22q12-q13, which leads to infantile neuroaxonal dystrophy. Recently, it was found that the PLA2G6 mutation also lead to NBIA [91]. The PLA2G6 mutation leads to the development of early onset Parkinsonism [92]. Previously, a discovery linking the pathology of NBIA phospholipid metabolism with the disruption of brain iron homeostasis was reported [91,92]. Mitochondrial dysfunction, increased mitochondrial ROS generation and lipid peroxidation in fibroblasts from patients with PLA2G6 mutation were noted. Importantly, feeding *Drosophila* iPLA2-VIA$^{-/-}$ flies with deuterated polyunsaturated fatty acids reduced the rates of lipid peroxidation to basal levels and also partially rescued their locomotor deficits [93].

Friedrich's ataxia (FRDA)

Cerebellar ataxia is caused by a mutation in the FXN gene, leading to a GAA repeat expansion and a lower availability of the protein frataxin, which is a key component for the formation of the Fe-S clusters of mitochondrial complexes I, II and III from the ETC.

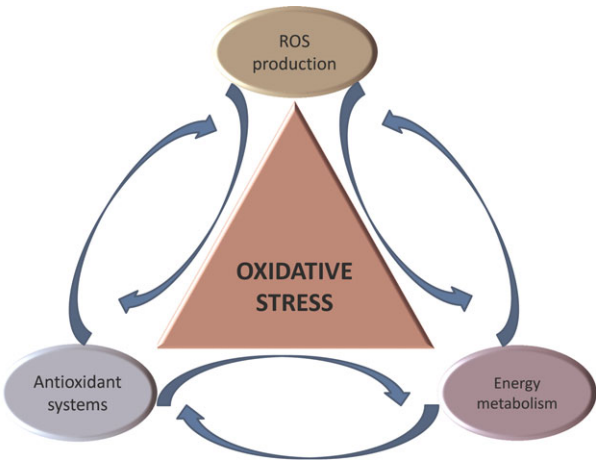

Fig. 2. Balance and interrelation between ROS production, energy metabolism and antioxidant homeostasis. Any changes in this balance lead to oxidative damage.

Increased levels of mitochondrial (and cytosolic) ROS production and the level of lipid peroxidation from cerebellar granule cells from FRDA granule cells [94] are a result of inhibition of mitochondrial respiration complex I and an abnormal accumulation of iron in the mitochondria. In fibroblasts from two FRDA mouse models (YG8R and KIKO), inhibition of lipid peroxidation with deuterated polyunsaturated fatty acids and Nrf-2 activators (TBE31 and sulforaphane) prevented lipid peroxidation damage and consequent cell death in these cells [95].

Huntington's disease

Huntington's disease, an autosomal dominant mutation of the mhtt gene, arises as a result of a CAG repeat expansion of the gene coding the protein huntingtin. Similar to many other neurodegenerative diseases, oxidative stress and inflammation are heavily implicated. Characteristic of HD brain samples are increased levels of SOD (Zn/Cu-SOD and mitochondrial MnSOD), glutathione peroxidase and catalase, although there are no canonical antioxidant response element gene products (NQO1, GCLM, GCLC, HMOX1/HO-1) [96]. However, neither overexpression of cytosolic Zn/Cu-SOD or mitochondrial MnSOD, nor nutritional supplementation with α-tocopherol and coenzyme Q10, has led to prolongation of the lifespan of *Drosophila* HD model flies. By contrast, activation of the Nrf2 pathway by SIRT2 inhibition and induction of NQO1 appears to be very promising and effective with respect to protecting oxidative damage in rodent and human HD models [97].

Conclusions

Mitochondria extensively generate ROS or/and are targeted by free radicals in the aetiopathology of the major neurodegenerative diseases. In most of these diseases, the overproduction of ROS or a loss of function of antioxidant pathways leads to oxidative damage of biological molecules. This in turn leads to deregulation of the function for which they are responsible or, ultimately, the initiation of cell death. Thus, even a small increase in ROS production over the basal rates requires elevated antioxidant activity. Maintenance of the major antioxidant systems (predominantly GSH in the brain) is a highly energy consuming process and any increased activity of antioxidant production may lead to a limitation of substrates required for the normal functioning of mitochondria (Fig. 2).

Mitochondrial redox balance and the physiological role of mitochondrial ROS are very important for neuronal housekeeping. Despite the vast number of studies confirming the damaging role of mitochondrial ROS in neurodegeneration, mitochondrially targeted antioxidants are not effective in the treatment of neurodegenerative diseases at a patient level for various reasons, including a quenching effect on the physiological signalling function of ROS. Antioxidant therapy has been confirmed to be effective for a number of neurodegenerative disorders in experiments conducted at a cellular level, although most of the clinical trials have failed to demonstrate neuroprotection or efficacy in patients. This failure to translate the positive effects of antioxidants is usually attributed to difficulties with respect to the delivery of antioxidants to cells in the brain or the chemical instability of antioxidants. We propose that oxidative damage in neurodegeneration should be prevented or restricted via the direct inhibition of ROS production from specific sources, rather than via the use of scavengers. Furthermore, identifying ways of quenching the production of free radicals in these cells specifically, either via direct inhibition of an enzyme, or by increasing the endogenous antioxidants or increasing energy production, represents one of the most promising future directions for the development of therapeutic strategies.

References

1 Gandhi S and Abramov AY (2012) Mechanism of oxidative stress in neurodegeneration. *Oxid Med Cell Longev* **2012**, 428010.
2 Votyakova TV and Reynolds IJ (2001) DeltaPsi(m)-Dependent and -independent production of reactive oxygen species by rat brain mitochondria. *J Neurochem* **79**, 266–277.
3 Vinogradov AD and Grivennikova VG (2016) Oxidation of NADH and ROS production by respiratory complex I. *Biochim Biophys Acta* **1857**, 863–871.
4 Kovac S, Angelova PR, Holmstrom KM, Zhang Y, Dinkova-Kostova AT and Abramov AY (2015) Nrf2 regulates ROS production by mitochondria and NADPH oxidase. *Biochim Biophys Acta* **1850**, 794–801.
5 Loschen G, Flohe L and Chance B (1971) Respiratory chain linked H(2)O(2) production in pigeon heart mitochondria. *FEBS Lett* **18**, 261–264.
6 Boveris A, Oshino N and Chance B (1972) The cellular production of hydrogen peroxide. *Biochem J* **128**, 617–630.
7 Loschen G, Azzi A, Richter C and Flohe L (1974) Superoxide radicals as precursors of mitochondrial hydrogen peroxide. *FEBS Lett* **42**, 68–72.
8 Gibson GE, Blass JP, Beal MF and Bunik V (2005) The alpha-ketoglutarate-dehydrogenase complex: a

mediator between mitochondria and oxidative stress in neurodegeneration. *Mol Neurobiol* **31**, 43–63.
9 Starkov AA, Fiskum G, Chinopoulos C, Lorenzo BJ, Browne SE, Patel MS and Beal MF (2004) Mitochondrial alpha-ketoglutarate dehydrogenase complex generates reactive oxygen species. *J Neurosci* **24**, 7779–7788.
10 Forman HJ, Maiorino M and Ursini F (2010) Signaling functions of reactive oxygen species. *Biochemistry* **49**, 835–842.
11 Mukherjee SP and Mukherjee C (1982) Similar activities of nerve growth factor and its homologue proinsulin in intracellular hydrogen peroxide production and metabolism in adipocytes. Transmembrane signalling relative to insulin-mimicking cellular effects. *Biochem Pharmacol* **31**, 3163–3172.
12 Wardman P and Candeias LP (1996) Fenton chemistry: an introduction. *Radiat Res* **145**, 523–531.
13 Vaarmann A, Gandhi S and Abramov AY (2010) Dopamine induces Ca2+ signaling in astrocytes through reactive oxygen species generated by monoamine oxidase. *J Biol Chem* **285**, 25018–25023.
14 Domijan AM, Kovac S and Abramov AY (2014) Lipid peroxidation is essential for phospholipase C activity and the inositol-trisphosphate-related Ca(2)(+) signal. *J Cell Sci* **127**, 21–26.
15 Angelova PR and Abramov AY (2016) Functional role of mitochondrial reactive oxygen species in physiology. *Free Radic Biol Med* **100**, 81–85.
16 Abramov AY, Scorziello A and Duchen MR (2007) Three distinct mechanisms generate oxygen free radicals in neurons and contribute to cell death during anoxia and reoxygenation. *J Neurosci* **27**, 1129–1138.
17 Angelova PR, Kasymov V, Christie I, Sheikhbahaei S, Turovsky E, Marina N, Korsak A, Zwicker J, Teschemacher AG, Ackland GL *et al.* (2015) Functional Oxygen Sensitivity of Astrocytes. *J Neurosci* **35**, 10460–10473.
18 Dong Z, Shanmughapriya S, Tomar D, Siddiqui N, Lynch S, Nemani N, Breves SL, Zhang X, Tripathi A, Palaniappan P *et al.* (2017) Mitochondrial Ca2+ Uniporter Is a Mitochondrial Luminal Redox Sensor that Augments MCU Channel Activity. *Mol Cell* **65**, 1014–1028.
19 Diebold L and Chandel NS (2016) Mitochondrial ROS regulation of proliferating cells. *Free Radic Biol Med* **100**, 86–93.
20 Bras J, Singleton A, Cookson MR and Hardy J (2008) Emerging pathways in genetic Parkinson's disease: Potential role of ceramide metabolism in Lewy body disease. *FEBS J* **275**, 5767–5773.
21 Hardy J (2017) The discovery of Alzheimer-causing mutations in the APP gene and the formulation of the "amyloid cascade hypothesis". *FEBS J* **284**, 1040–1044.
22 Vossius C, Nilsen OB and Larsen JP (2009) Parkinson's disease and nursing home placement: the economic impact of the need for care. *Eur J Neurol* **16**, 194–200.
23 Angelova PR and Abramov AY (2017) Alpha-synuclein and beta-amyloid - different targets, same players: calcium, free radicals and mitochondria in the mechanism of neurodegeneration. *Biochem Biophys Res Commun* **483**, 1110–1115.
24 Abramov AY, Berezhnov AV, Fedotova EI, Zinchenko VP and Dolgacheva LP (2017) Interaction of misfolded proteins and mitochondria in neurodegenerative disorders. *Biochem Soc Trans* pii: BST20170024.
25 Sheehan JP, Swerdlow RH, Miller SW, Davis RE, Parks JK, Parker WD and Tuttle JB (1997) Calcium homeostasis and reactive oxygen species production in cells transformed by mitochondria from individuals with sporadic Alzheimer's disease. *J Neurosci* **17**, 4612–4622.
26 Du H, Guo L, Yan S, Sosunov AA, McKhann GM and Yan SS (2010) Early deficits in synaptic mitochondria in an Alzheimer's disease mouse model. *Proc Natl Acad Sci USA* **107**, 18670–18675.
27 Caspersen C, Wang N, Yao J, Sosunov A, Chen X, Lustbader JW, Xu HW, Stern D, McKhann G and Yan SD (2005) Mitochondrial Abeta: a potential focal point for neuronal metabolic dysfunction in Alzheimer's disease. *FASEB J* **19**, 2040–2041.
28 Casley CS, Canevari L, Land JM, Clark JB and Sharpe MA (2002) Beta-amyloid inhibits integrated mitochondrial respiration and key enzyme activities. *J Neurochem* **80**, 91–100.
29 Canevari L, Clark JB and Bates TE (1999) beta-Amyloid fragment 25–35 selectively decreases complex IV activity in isolated mitochondria. *FEBS Lett* **457**, 131–134.
30 Yu F, Gong P, Hu Z, Qiu Y, Cui Y, Gao X, Chen H and Li J (2015) Cu(II) enhances the effect of Alzheimer's amyloid-beta peptide on microglial activation. *J Neuroinflammation* **12**, 122.
31 Aminzadeh M, Roghani M, Sarfallah A and Riazi GH (2017) TRPM2 dependence of ROS-induced NLRP3 activation in Alzheimer's disease. *Int Immunopharmacol* **54**, 78–85.
32 Ma T, Hoeffer CA, Wong H, Massaad CA, Zhou P, Iadecola C, Murphy MP, Pautler RG and Klann E (2011) Amyloid beta-induced impairments in hippocampal synaptic plasticity are rescued by decreasing mitochondrial superoxide. *J Neurosci* **31**, 5589–5595.
33 McManus MJ, Murphy MP and Franklin JL (2011) The mitochondria-targeted antioxidant MitoQ prevents loss of spatial memory retention and early neuropathology in a transgenic mouse model of Alzheimer's disease. *J Neurosci* **31**, 15703–15715.

34 Ng LF, Gruber J, Cheah IK, Goo CK, Cheong WF, Shui G, Sit KP, Wenk MR and Halliwell B (2014) The mitochondria-targeted antioxidant MitoQ extends lifespan and improves healthspan of a transgenic Caenorhabditis elegans model of Alzheimer disease. *Free Radic Biol Med* **71**, 390–401.
35 Elharram A, Czegledy NM, Golod M, Milne GL, Pollock E, Bennett BM and Shchepinov MS (2017) Deuterium-reinforced polyunsaturated fatty acids improve cognition in a mouse model of sporadic Alzheimer's disease. *FEBS J* **284**, 4083–4095.
36 Avetisyan AV, Samokhin AN, Alexandrova IY, Zinovkin RA, Simonyan RA and Bobkova NV (2016) Mitochondrial Dysfunction in Neocortex and Hippocampus of Olfactory Bulbectomized Mice, a Model of Alzheimer's Disease. *Biochemistry (Mosc)* **81**, 615–623.
37 Keller JN, Guo Q, Holtsberg FW, Bruce-Keller AJ and Mattson MP (1998) Increased sensitivity to mitochondrial toxin-induced apoptosis in neural cells expressing mutant presenilin-1 is linked to perturbed calcium homeostasis and enhanced oxyradical production. *J Neurosci* **18**, 4439–4450.
38 Abramov AY and Duchen MR (2005) The role of an astrocytic NADPH oxidase in the neurotoxicity of amyloid beta peptides. *Philos. Trans R Soc Lond B Biol Sci* **360**, 2309–2314.
39 Hashimoto Y, Kaneko Y, Tsukamoto E, Frankowski H, Kouyama K, Kita Y, Niikura T, Aiso S, Bredesen DE, Matsuoka M *et al.* (2004) Molecular characterization of neurohybrid cell death induced by Alzheimer's amyloid-beta peptides via p75NTR/PLAIDD. *J Neurochem* **90**, 549–558.
40 Abramov AY, Canevari L and Duchen MR (2004) Beta-amyloid peptides induce mitochondrial dysfunction and oxidative stress in astrocytes and death of neurons through activation of NADPH oxidase. *J Neurosci* **24**, 565–575.
41 Abeti R, Abramov AY and Duchen MR (2011) Beta-amyloid activates PARP causing astrocytic metabolic failure and neuronal death. *Brain* **134**, 1658–1672.
42 Narayan P, Holmstrom KM, Kim DH, Whitcomb DJ, Wilson MR, St George-Hyslop P, Wood NW, Dobson CM, Cho K, Abramov AY *et al.* (2014) Rare individual amyloid-beta oligomers act on astrocytes to initiate neuronal damage. *Biochemistry* **53**, 2442–2453.
43 Abramov AY, Canevari L and Duchen MR (2004) Calcium signals induced by amyloid beta peptide and their consequences in neurons and astrocytes in culture. *Biochim Biophys Acta* **1742**, 81–87.
44 Shevtsova EF, Vinogradova DV, Neganova ME, Avila-Rodriguez M, Ashraf GM, Barreto GE, Bachurin SO and Aliev G (2017) Mitochondrial Permeability Transition Pore as a Suitable Targ e t for Neuroprotective Agents Against Alzheimer's Disease. *CNS Neurol Disord Drug Targets* **16**, 677–685.
45 Du H, Guo L, Fang F, Chen D, Sosunov AA, McKhann GM, Yan Y, Wang C, Zhang H, Molkentin JD *et al.* (2008) Cyclophilin D deficiency attenuates mitochondrial and neuronal perturbation and ameliorates learning and memory in Alzheimer's disease. *Nat Med* **14**, 1097–1105.
46 Esteras N, Rohrer JD, Hardy J, Wray S and Abramov AY (2017) Mitochondrial hyperpolarization in iPSC-derived neurons from patients of FTDP-17 with 10+16 MAPT mutation leads to oxidative stress and neurodegeneration. *Redox Biol* **12**, 410–422.
47 Liu H and Zhang J (2012) Cerebral hypoperfusion and cognitive impairment: the pathogenic role of vascular oxidative stress. *Int J Neurosci* **122**, 494–499.
48 Yadav A, Sunkaria A, Singhal N and Sandhir R (2018) Resveratrol loaded solid lipid nanoparticles attenuate mitochondrial oxidative stress in vascular dementia by activating Nrf2/HO-1 pathway. *Neurochem Int* **112**, 239–254.
49 Zhang N, Komine-Kobayashi M, Tanaka R, Liu M, Mizuno Y and Urabe T (2005) Edaravone reduces early accumulation of oxidative products and sequential inflammatory responses after transient focal ischemia in mice brain. *Stroke* **36**, 2220–2225.
50 Beal MF (2002) Oxidatively modified proteins in aging and disease. *Free Radic Biol Med* **32**, 797–803.
51 Bender A, Krishnan KJ, Morris CM, Taylor GA, Reeve AK, Perry RH, Jaros E, Hersheson JS, Betts J, Klopstock T *et al.* (2006) High levels of mitochondrial DNA deletions in substantia nigra neurons in aging and Parkinson disease. *Nat Genet* **38**, 515–517.
52 Gonzalez-Polo RA, Soler G, Rodriguezmartin A, Moran JM and Fuentes JM (2004) Protection against MPP+ neurotoxicity in cerebellar granule cells by antioxidants. *Cell Biol Int* **28**, 373–380.
53 Abramov AY, Smulders-Srinivasan TK, Kirby DM, Acin-Perez R, Enriquez JA, Lightowlers RN, Duchen MR and Turnbull DM (2010) Mechanism of neurodegeneration of neurons with mitochondrial DNA mutations. *Brain* **133**, 797–807.
54 Andrews ZB, Horvath B, Barnstable CJ, Elsworth J, Yang L, Beal MF, Roth RH, Matthews RT and Horvath TL (2005) Uncoupling protein-2 is critical for nigral dopamine cell survival in a mouse model of Parkinson's disease. *J Neurosci* **25**, 184–191.
55 Lev N, Ickowicz D, Barhum Y, Melamed E and Offen D (2009) DJ-1 changes in G93A-SOD1 transgenic mice: implications for oxidative stress in ALS. *J Mol Neurosci* **38**, 94–102.
56 Li HM, Niki T, Taira T, Iguchi-Ariga SM and Ariga H (2005) Association of DJ-1 with chaperones and enhanced association and colocalization with

mitochondrial Hsp70 by oxidative stress. *Free Radic Res* **39**, 1091–1099.
57 Guzman JN, Sanchez-Padilla J, Wokosin D, Kondapalli J, Ilijic E, Schumacker PT and Surmeier DJ (2010) Oxidant stress evoked by pacemaking in dopaminergic neurons is attenuated by DJ-1. *Nature* **468**, 696–700.
58 Gandhi S, Wood-Kaczmar A, Yao Z, Plun-Favreau H, Deas E, Klupsch K, Downward J, Latchman DS, Tabrizi SJ, Wood NW *et al*. (2009) PINK1-associated Parkinson's disease is caused by neuronal vulnerability to calcium-induced cell death. *Mol Cell* **33**, 627–638.
59 Piccoli C, Sardanelli A, Scrima R, Ripoli M, Quarato G, D'Aprile A, Bellomo F, Scacco S, De MG, Filla A *et al*. (2008) Mitochondrial respiratory dysfunction in familiar parkinsonism associated with PINK1 mutation. *Neurochem Res* **33**, 2565–2574.
60 Abramov AY, Gegg M, Grunewald A, Wood NW, Klein C and Schapira AH (2011) Bioenergetic consequences of PINK1 mutations in Parkinson disease. *PLoS One* **6**, e25622.
61 Hoepken HH, Gispert S, Morales B, Wingerter O, Del TD, Mulsch A, Nussbaum RL, Muller K, Drose S, Brandt U *et al*. (2007) Mitochondrial dysfunction, peroxidation damage and changes in glutathione metabolism in PARK6. *Neurobiol Dis* **25**, 401–411.
62 Kostic M, Ludtmann MH, Bading H, Hershfinkel M, Steer E, Chu CT, Abramov AY and Sekler I (2015) PKA Phosphorylation of NCLX Reverses Mitochondrial Calcium Overload and Depolarization, Promoting Survival of PINK1-Deficient Dopaminergic Neurons. *Cell Rep* **13**, 376–386.
63 Deas E, Piipari K, Machhada A, Li A, Gutierrez-del-Arroyo A, Withers DJ, Wood NW and Abramov AY (2014) PINK1 deficiency in beta-cells increases basal insulin secretion and improves glucose tolerance in mice. *Open Biol* **4**, 140051.
64 Dinkova-Kostova AT, Baird L, Holmstrom KM, Meyer CJ and Abramov AY (2015) The spatiotemporal regulation of the Keap1-Nrf2 pathway and its importance in cellular bioenergetics. *Biochem Soc Trans* **43**, 602–610.
65 Gandhi S, Vaarmann A, Yao Z, Duchen MR, Wood NW and Abramov AY (2012) Dopamine induced neurodegeneration in a PINK1 model of Parkinson's disease. *PLoS One* **7**, e37564.
66 Xiao B, Goh JY, Xiao L, Xian H, Lim KL and Liou YC (2017) Reactive oxygen species trigger Parkin/PINK1 pathway-dependent mitophagy by inducing mitochondrial recruitment of Parkin. *J Biol Chem* **292**, 16697–16708.
67 Berger NA, Besson VC, Boulares AH, Burkle A, Chiarugi A, Clark RS, Curtin NJ, Cuzzocrea S, Dawson TM, Dawson VL *et al*. (2018) Opportunities for the repurposing of PARP inhibitors for the therapy of non-oncological diseases. *Br J Pharmacol* **175**, 192–222.
68 Delgado-Camprubi M, Esteras N, Soutar MP, Plun-Favreau H and Abramov AY (2017) Deficiency of Parkinson's disease-related gene Fbxo7 is associated with impaired mitochondrial metabolism by PARP activation. *Cell Death Differ* **24**, 120–131.
69 Ludtmann MH, Angelova PR, Ninkina NN, Gandhi S, Buchman VL and Abramov AY (2016) Monomeric Alpha-Synuclein Exerts a Physiological Role on Brain ATP Synthase. *J Neurosci* **36**, 10510–10521.
70 Burre J, Vivona S, Diao J, Sharma M, Brunger AT and Sudhof TC (2013) Properties of native brain alpha-synuclein. *Nature* **498**, E4–E6.
71 Nakamura K, Nemani VM, Wallender EK, Kaehlcke K, Ott M and Edwards RH (2008) Optical reporters for the conformation of alpha-synuclein reveal a specific interaction with mitochondria. *J Neurosci* **28**, 12305–12317.
72 Reeve AK, Ludtmann MH, Angelova PR, Simcox EM, Horrocks MH, Klenerman D, Gandhi S, Turnbull DM and Abramov AY (2015) Aggregated alpha-synuclein and complex I deficiency: exploration of their relationship in differentiated neurons. *Cell Death Dis* **6**, e1820.
73 Luth ES, Stavrovskaya IG, Bartels T, Kristal BS and Selkoe DJ (2014) Soluble, prefibrillar alpha-synuclein oligomers promote complex I-dependent, Ca2+-induced mitochondrial dysfunction. *J Biol Chem* **289**, 21490–21507.
74 Esteves AR, Arduino DM, Swerdlow RH, Oliveira CR and Cardoso SM (2009) Oxidative stress involvement in alpha-synuclein oligomerization in Parkinson's disease cybrids. *Antioxid Redox Signal* **11**, 439–448.
75 Deas E, Cremades N, Angelova PR, Ludtmann MH, Yao Z, Chen S, Horrocks MH, Banushi B, Little D, Devine MJ *et al*. (2016) Alpha-Synuclein Oligomers Interact with Metal Ions to Induce Oxidative Stress and Neuronal Death in Parkinson's Disease. *Antioxid Redox Signal* **24**, 376–391.
76 Angelova PR, Horrocks MH, Klenerman D, Gandhi S, Abramov AY and Shchepinov MS (2015) Lipid peroxidation is essential for alpha-synuclein-induced cell death. *J Neurochem* **133**, 582–589.
77 Litvan I, Campbell G, Mangone CA, Verny M, McKee A, Chaudhuri KR, Jellinger K, Pearce RK and D'Olhaberriague L (1997) Which clinical features differentiate progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome) from related disorders? A clinicopathological study *Brain* **120** (Pt 1), 65–74.
78 Angelova PR, Barilani M, Lovejoy C, Dossena M, Vigano M, Seresini A, Piga D, Gandhi S, Pezzoli G, Abramov AY *et al*. (2018) Mitochondrial dysfunction in Parkinsonian mesenchymal stem cells impairs differentiation. *Redox Biol* **14**, 474–484.

79 Cozzolino M, Pesaresi MG, Gerbino V, Grosskreutz J and Carri MT (2012) Amyotrophic lateral sclerosis: new insights into underlying molecular mechanisms and opportunities for therapeutic intervention. *Antioxid Redox Signal* **17**, 1277–1330.
80 Cozzolino M and Carri MT (2012) Mitochondrial dysfunction in ALS. *Prog Neurobiol* **97**, 54–66.
81 Shaw IC, Fitzmaurice PS, Mitchell JD and Lynch PG (1995) Studies on cellular free radical protection mechanisms in the anterior horn from patients with amyotrophic lateral sclerosis. *Neurodegeneration* **4**, 391–396.
82 Shibata N, Nagai R, Uchida K, Horiuchi S, Yamada S, Hirano A, Kawaguchi M, Yamamoto T, Sasaki S and Kobayashi M (2001) Morphological evidence for lipid peroxidation and protein glycoxidation in spinal cords from sporadic amyotrophic lateral sclerosis patients. *Brain Res* **917**, 97–104.
83 Shibata N (2001) Transgenic mouse model for familial amyotrophic lateral sclerosis with superoxide dismutase-1 mutation. *Neuropathology* **21**, 82–92.
84 Peixoto PM, Kim HJ, Sider B, Starkov A, Horvath TL and Manfredi G (2013) UCP2 overexpression worsens mitochondrial dysfunction and accelerates disease progression in a mouse model of amyotrophic lateral sclerosis. *Mol Cell Neurosci* **57**, 104–110.
85 Onesto E, Colombrita C, Gumina V, Borghi MO, Dusi S, Doretti A, Fagiolari G, Invernizzi F, Moggio M, Tiranti V *et al*. (2016) Gene-specific mitochondria dysfunctions in human TARDBP and C9ORF72 fibroblasts. *Acta Neuropathol Commun* **4**, 47.
86 Bartolome F, Esteras N, Martin-Requero A, Boutoleau-Bretonniere C, Vercelletto M, Gabelle A, Le Ber I, Honda T, Dinkova-Kostova AT, Hardy J *et al*. (2017) Pathogenic p62/SQSTM1 mutations impair energy metabolism through limitation of mitochondrial substrates. *Sci Rep*, **7**, 1666.
87 Brunetti D, Dusi S, Morbin M, Uggetti A, Moda F, D'Amato I, Giordano C, d'Amati G, Cozzi A, Levi S *et al*. (2012) Pantothenate kinase-associated neurodegeneration: altered mitochondria membrane potential and defective respiration in Pank2 knock-out mouse model. *Hum Mol Genet* **21**, 5294–5305.
88 Orellana DI, Santambrogio P, Rubio A, Yekhlef L, Cancellieri C, Dusi S, Giannelli SG, Venco P, Mazzara PG, Cozzi A *et al*. (2016) Coenzyme A corrects pathological defects in human neurons of PANK2-associated neurodegeneration. *EMBO Mol Med* **8**, 1197–1211.
89 Arber C, Angelova PR, Wiethoff S, Tsuchiya Y, Mazzacuva F, Preza E, Bhatia KP, Mills K, Gout I, Abramov AY *et al*. (2017) iPSC-derived neuronal models of PANK2-associated neurodegeneration reveal mitochondrial dysfunction contributing to early disease. *PLoS One* **12**, e0184104.
90 Wiethoff S and Houlden H (2017) Neurodegeneration with brain iron accumulation. *Handb Clin Neurol* **145**, 157–166.
91 Morgan NV, Westaway SK, Morton JE, Gregory A, Gissen P, Sonek S, Cangul H, Coryell J, Canham N, Nardocci N *et al*. (2006) PLA2G6, encoding a phospholipase A2, is mutated in neurodegenerative disorders with high brain iron. *Nat Genet* **38**, 752–754.
92 Giri A, Guven G, Hanagasi H, Hauser AK, Erginul-Unaltuna N, Bilgic B, Gurvit H, Heutink P, Gasser T, Lohmann E *et al*. (2016) PLA2G6 mutations related to distinct phenotypes: a new case with early-onset parkinsonism. *Tremor Other Hyperkinet Mov (NY)* **6**, 363.
93 Kinghorn KJ, Castillo-Quan JI, Bartolome F, Angelova PR, Li L, Pope S, Cocheme HM, Khan S, Asghari S, Bhatia KP *et al*. (2015) Loss of PLA2G6 leads to elevated mitochondrial lipid peroxidation and mitochondrial dysfunction. *Brain* **138**, 1801–1816.
94 Abeti R, Parkinson MH, Hargreaves IP, Angelova PR, Sandi C, Pook MA, Giunti P and Abramov AY (2016) Mitochondrial energy imbalance and lipid peroxidation cause cell death in Friedreich's ataxia. *Cell Death Dis* **7**, e2237.
95 Abeti R, Uzun E, Renganathan I, Honda T, Pook MA and Giunti P (2015) Targeting lipid peroxidation and mitochondrial imbalance in Friedreich's ataxia. *Pharmacol Res* **99**, 344–350.
96 Quinti L, Dayalan NS, Trager U, Chen X, Kegel-Gleason K, Lleres D, Connolly C, Chopra V, Low C, Moniot S *et al*. (2017) KEAP1-modifying small molecule reveals muted NRF2 signaling responses in neural stem cells from Huntington's disease patients. *Proc Natl Acad Sci USA* **114**, E4676–E4685.
97 Quinti L, Casale M, Moniot S, Pais TF, Van Kanegan MJ, Kaltenbach LS, Pallos J, Lim RG, Naidu SD, Runne H *et al*. (2016) SIRT2- and NRF2-targeting thiazole-containing compound with therapeutic activity in Huntington's disease models. *Cell Chem Biol* **23**, 849–861.