

Mitochondria, oxidative stress and neurodegeneration

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ABSTRACT

Mitochondria are involved in ATP supply to cells through oxidative phosphorylation (OXPHOS), synthesis of key molecules and response to oxidative stress, as well as in apoptosis. They contain many redox enzymes and naturally occurring inefficiencies of oxidative phosphorylation generate reactive oxygen species (ROS). CNS functions depend heavily on efficient mitochondrial function, since brain tissue has a high energy demand. Mutations in mitochondrial DNA (mtDNA), generation and presence of ROS and environmental factors may contribute to energy failure and lead to neurodegenerative diseases. Many rare metabolic disorders have been associated with mitochondrial dysfunction. More than 300 pathogenic mtDNA mutations involve proteins that regulate OXPHOS and mitochondrial structural integrity, and have also been described in neurodegenerative diseases with autosomal inheritance. Mitochondria may have an important role in ageing-related neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). In primary mitochondrial and neurodegenerative disorders, there is strong evidence that mitochondrial dysfunction occurs early and has a primary role in pathogenesis. In the present review, we discuss several mitochondrial diseases as models of neurodegeneration.

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1. Introduction

ATP production by mitochondria is essential for cell function, signalling pathways and overall cell activities. Mitochondria are involved in ATP supply to cells through oxidative phosphorylation (OXPHOS), synthesis of key molecules and response to oxidative stress (Fig. 1). They are also involved in apoptosis and in dynamic movements required for correct respiratory activity and metabolic efficiency through fusion/fission [1]. Mitochondria contain many redox enzymes and naturally occurring inefficiencies of oxidative phosphorylation generate reactive oxygen species (ROS).

CNS functions strongly depend on efficient mitochondrial function, because brain tissue has a high energy demand. Mutations in the mitochondrial genome, defects in mitochondrial dynamics, generation and presence of ROS, protein aggregate-associated dysfunctions and environmental factors may alter energy metabolism and in many cases are associated with neurodegenerative diseases (Fig. 2) [2].

2. Primary mitochondrial disorders and neurodegeneration

Human mitochondrial DNA (mtDNA) is well known as a circular, double-stranded molecule of 16569 base pairs. It contains 37 genes, including 13 protein-encoding genes, 22 transfer RNA genes and

two ribosomal RNA genes. All 13 protein-encoding genes are components of the mitochondrial respiratory chain, which is located in the inner membrane [2].

By the 1980s, many rare metabolic disorders with mitochondrial dysfunctions had been recognized [3]. Since then more than 300 pathogenic mtDNA mutations have been associated with diseases [4]. Mitochondrial dysfunctions have also been described in neurodegenerative diseases with non-maternal inheritance, involving a number of other proteins, which regulate OXPHOS and mitochondrial dynamics, implicated in maintaining mitochondrial structural integrity [5].

Whatever the mechanism, the final common feature of mitochondrial disorders is impaired respiratory chain activity or failure of mitochondrial function, resulting in a wide range of clinical presentations (Table 1). Table 2 shows the genetic classification of neurodegenerative mitochondrial diseases: mutations in mtDNA may be sporadic or maternally transmitted, whereas nuclear gene mutations have Mendelian inheritance. In the present review, we discuss some mitochondrial diseases as models of neurodegeneration (Table 3).

3. Mitochondrial diseases as models of neurodegeneration

Leber's hereditary optic neuropathy (LHON, MIM #535000), the most common cause of maternally inherited blindness, highlights the link between energy production, oxidative stress and neurodegeneration. It is related to mutations in subunits of NADH-dehydrogenase in mtDNA and their impact on mitochondrial OXPHOS has been extensively investigated [17]. Eye pathology in LHON is limited to retinal ganglion cells

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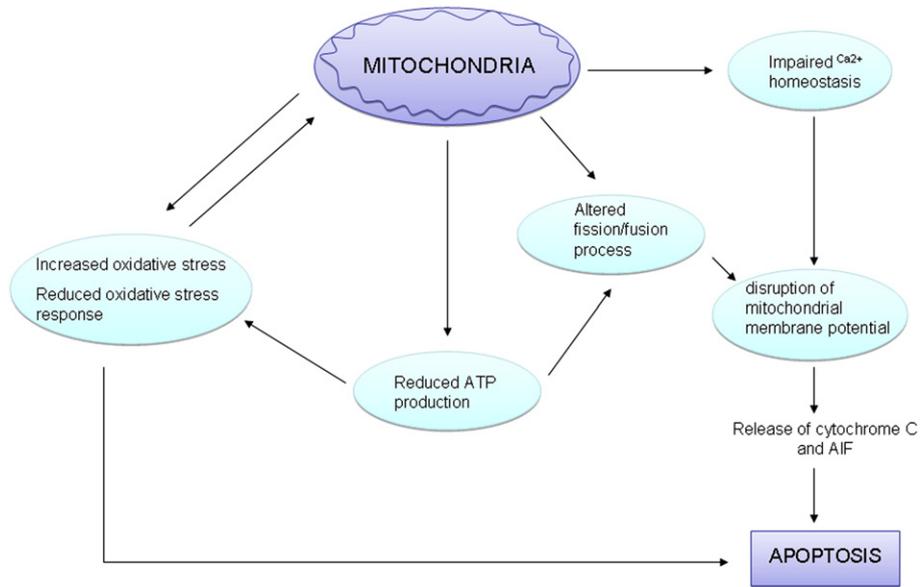


Fig. 1. Main interaction between mitochondria, oxidative stress and apoptosis.

(RGCs), sparing the retinal pigmented epithelium and photoreceptor layer. Pronounced atrophy of cell bodies and axons is associated with demyelination and degeneration from the optic nerve to the lateral geniculate body. Impaired activity of the EAAT1 glutamate transporter and increased mitochondrial reactive oxygen species (ROS) production trigger RGC death by apoptosis [18–20]. Calcium deregulation is another important factor involved in LHON pathogenesis: complex I mutations may shift the voltage threshold for permeability transition pore opening towards resting level, due to Ca²⁺ deregulation and enhanced ROS generation. Impaired axonal distribution of mitochondria in RGC is also thought to contribute to local energy deprivation at sites where most ATP is needed [21]. In fact, it is presumed that this anatomic selectivity is partly a consequence of the high metabolic demand of target tissues, although the mitochondrial defect is not limited to neurons or the nervous system. In addition, incomplete penetrance and male predominance suggest that other genetic and environmental factors contribute to signs and symptoms. Smoking and other environmental factors (including hormones, head trauma, occupational exposure, chemical toxins, drugs or pharmacological substances) are known to trigger LHON,

supporting the notion that excess ROS production may be an important pathogenetic factor [22–25].

Autosomal dominant optic atrophy (ADOA, MIM #165500) is a form of slowly progressive optic neuropathy, usually with onset in the first decade of life. ADOA has mainly been linked to the OPA1 gene, which encodes a mitochondrial dynamin-related GTP protein that plays a role in mitochondrial fusion, crista building, apoptosis and mtDNA maintenance [13]. The pathogenic mechanism of ADOA is not completely understood, but several studies suggest similarities with LHON (Fig. 3). Fibroblasts of ADOA patients carrying OPA1 mutations have shown defects in mitochondrial OXPHOS, mitochondrial membrane potential reduction and mitochondrial DNA instability (mainly in ADOA plus patients) [11,26]. Increased sensitivity to apoptotic signals and altered mitochondrial network, probably a primary consequence of loss of pro-fusion activity of OPA1, have also been reported [27]. The selective degeneration of RGCs in ADOA patients is directly correlated with their sensitivity to cell death. Mitochondrial dysfunction and reduced expression of OPA1 promote degeneration of these cells.

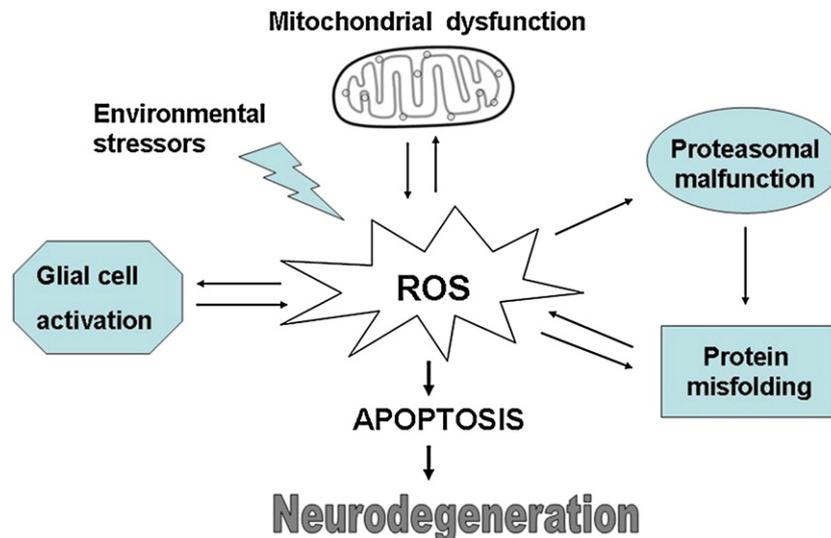


Fig. 2. Different pathogenetic mechanisms leading to neurodegeneration.

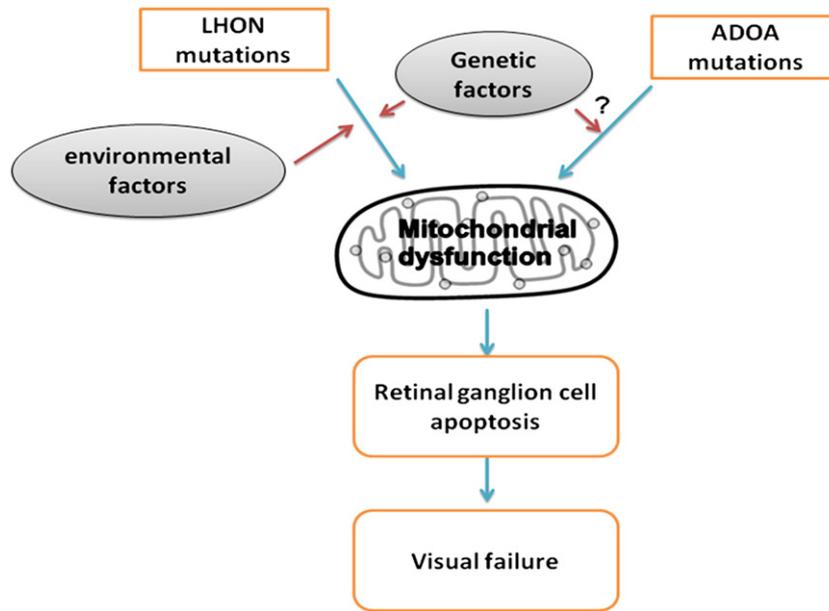


Fig. 3. Mitochondrial dysfunction in LHON and ADOA.

Charcot-Marie-Tooth hereditary neuropathy type 2A (CMT2A, MIM#609260) is an early onset peripheral neuropathy inherited in an autosomal dominant manner. Mutations in the CMT2A locus have been linked to mitofusin 2 (MFN2) genes [28] encoding an outer mitochondrial membrane protein that has an important role in regulating fusion of mitochondria, in cooperation with MFN1 and OPA1 [13]. MFN2 may exert a direct influence on mitochondrial biogenesis by regulating the expression of nuclear-encoded respiratory chain subunits [29]. MFN2 may also be involved in axonal transport of mitochondria by interaction with miro (Miro1/Miro2) and milton (OIP106/GRIF1) proteins, which link mitochondria to kinesin motors [30]. Neuropathological studies of CMT2 patients show degeneration of long peripheral axons and many small axonal mitochondria [31]. In cultured fibroblasts, Rouzier et al. [32] showed mitochondrial fusion deficiency and fragmented mitochondria, leading to respiratory chain and mitochondrial DNA repair defects. In line with this hypothesis, fibroblasts from CMT2A patients show a mitochondrial coupling defect, with impaired membrane potential and reduced OXPHOS capacity [33]. Brain mitochondrial dysfunction similar to that of primary mitochondrial disorders was recently demonstrated in an Italian family with a new MFN2 gene mutation [15].

Myoclonic epilepsy and ragged-red fibres (MERRF, MIM #545000) is usually related to an A to G transition at nucleotide 8344 in the *MT-*

TK gene of mtDNA. Patients with this mutation often show degenerative features in the olivocerebellar pathway, with severe neuronal loss involving inferior olivary complex, Purkinje cells and dentate nucleus. Oversized mitochondria showing inclusions have been described in surviving neurons of the cerebellum [34]. Several biochemical studies show that the 8344 mutation hampers effective synthesis of mitochondrial proteins, leading to electron transport chain malfunction. This impaired activity decreases mitochondrial membrane potential and oxidative production of ATP and modifies calcium homeostasis and ROS production, evolving to increased apoptosis [35]. Wu et al. [36] found functional alterations of antioxidant enzymes in MERRF skin fibroblasts, suggesting that mtDNA mutation-elicited oxidative stress, oxidative damage, and altered gene expression are involved in the pathogenesis and progression of the syndrome.

3.1. Mitochondrial ataxias

Cerebellar or sensory ataxia is a frequent clinical feature of mitochondrial disorders. Purkinje and other cerebellar cells may be selectively vulnerable to mitochondrial respiratory chain dysfunction correlated with varying degrees of cell loss [37]. Many mtDNA mutations cause ataxia [4]. The most frequent and best clinically and genetically characterized are Kearns–Sayre syndrome (KSS), Mitochondrial Encephalopathy, Lactic acidosis and Stroke-like episodes (MELAS), MERRF and Neuropathy, Ataxia and Retinitis pigmentosa (NARP) [38]. Nuclear genes causing mitochondrial ataxia have attracted recent

Table 1

Typical symptoms and signs encountered in mitochondrial disorders.

Peripheral nervous system: myopathy, polineuropathy
Central nervous system: ataxia, retinal degeneration, mental retardation or deterioration, seizures, epilepsy, myoclonus, migraine, stroke-like episodes, dystonia, weakness, dyskinesia, cerebellar signs, psychosis
Sensoryneural deafness
Muscle: weakness, hypotonia, external ophthalmoplegia, exercise intolerance, wasting, fatigue, cramps, myotonia, stiffness, lactic acidosis
Heart: heart block, hypertrophic cardiomyopathy, myocardial thickening
Ear: Hypoacusis, peripheral vertigo
Eye: optic atrophy, retinopathy, glaucoma, cataract
Bowel: dysphagia, vomiting, diarrhoea, anorexia, malabsorption, intestinal pseudo-obstruction
Liver: hepatic failure, transaminase increase
Endocrine glands: infertility, delayed puberty, diabetes, thyroid dysfunction, hypogonadism, short stature, hypoglycaemia, osteoporosis, amenorrhoea
Kidney: renal tubulopathy, renal cysts
Bone marrow: sideroblastic anaemia

Table 2

Genetic classification of neurodegenerative mitochondrialopathies.

- 1) Disorders due to mutations in mtDNA genes encoding for respiratory chain proteins, tRNAs or rRNAs (LHON, MELAS, MERRF, NARP, Leigh syndrome, KSS)
- 2) Disorders due to mutations in nDNA genes encoding for:

- respiratory chain proteins (Leigh syndrome, leukodystrophy, paraganglioma, GRACILE syndrome, leukodystrophy and tubulopathy)
- proteins implicated in mitochondrial metabolism (Leigh syndrome, Alpers syndrome, infant encephalopathy, MNGIE, SANDO, Wolfram syndrome)
- proteins implicated in mitochondrial dynamics (ADOA, CMT type 2A, 4A, and 6)
- proteins correlated to mitochondrial functions (AD, PD, HD, ALS, Friedreich ataxia, Hereditary spastic paraplegia)

Table 3
Mitochondrial diseases as a model of neurodegeneration: gene, protein and disease. Inheritance: AD, autosomal dominant; S, sporadic; M, maternal.

Disease	Gene affected	Inheritance	Protein	Function	Phenotype	Onset	Prevalence	References
Leber's hereditary optic neuropathy	mt-ND1 mt-ND4 mt-ND6 (90% of affected patients)	M, S	ND subunits of Complex I	Respiratory chain Complex I	Bilateral, painless subacute visual failure.	Late adolescence or early adulthood	1:31,000 North of England; 1:39,000 Dutch population; 1:50,000 Finnish population	[6–8]
Autosomal dominant optic atrophy	OPA1 (almost all affected patients)	AD	OPA1	Mitochondrial fusion, cristae structuration, apoptosis and mtDNA maintenance	Variable loss of visual acuity, temporal optic nerve pallor, tritanopia and development of central, paracentral or cocentral scotomas. Additional neurological symptoms: visual failure, optic atrophy, PEO, ataxia, deafness and sensory-motor neuropathy	Childhood	1:35,000 North of England; 1:12,000 Denmark; 1:8,375 south-eastern Sicily, Italy	[7,9–13]
Charcot-Marie-Tooth hereditary neuropathy type 2A	CMT2A (almost all affected patients)	AD	MFN2	Mitochondrial fusion	Sensory-motor axonal polyneuropathy. Additional symptoms: optic atrophy, sensorineural hearing loss, spastic paraparesis	Childhood	Unknown	[14,15]
Myoclonic epilepsy with ragged red fibres	mt-TK (80% of affected patients)	M, S	tRNA lysine (tRNA ^{Lys})	Transfer RNA	Myoclonic epilepsy with photosensitive general tonic-clonic seizures, myopathy with ptosis and ophthalmoparesis, cerebellar ataxia, dementia and deafness.	Childhood	m.8344A>G 0.25:100,000 northern England; 0–0.25:100,000 western Sweden	[8,16]

interest, particularly the group of genes encoding factors affecting mitochondrial DNA maintenance, including the major locus for mitochondrial disease, the *POLG1* gene. This gene encodes the catalytic subunit of human mtDNA polymerase gamma and is subject to various mutations associated with heterogeneous phenotypes having ataxia as the main symptom [39]. Likewise, combination of Sensory Ataxic Neuropathy, Dysarthria and Ophthalmoparesis (SANDO) [40] has been associated with *POLG1* mutations [41], as well as Mitochondrial Recessive Ataxia Syndrome (MIRAS) and Spinocerebellar Ataxia-Epilepsy Syndrome (SCAE).

3.2. Ataxia and coenzyme Q10 deficiency

Coenzyme Q10 (CoQ10) is an essential electron carrier in the mitochondrial respiratory chain and also acts as an antioxidant in various cell membranes. The most common neurological signs associated with CoQ10 deficiency are cerebellar ataxia, mild muscle involvement, mental retardation and hypogonadism (adults) with onset in childhood or adulthood [42]. It was suggested that oxidative phosphorylation dysfunction may occur in CoQ10 deficiency syndrome and *in vitro* studies showed that CoQ10 deficiency has different biochemical consequences leading to cell death [43]. Although there is no evidence of a specific gene directly involved in CoQ10 deficiency associated with ataxia, several mutations in different genes involved in the CoQ10 biosynthetic pathway have recently been reported [38].

3.3. Neurodegenerative *POLG1*-related disorders with extrapyramidal involvement

Mutations in the *POLG1* gene result in aberrant replication and impaired maintenance of mtDNA, leading to a significant decrease in mtDNA copy number, or multiple deletions in mtDNA, which translate into mitochondrial dysfunction. These mutations have been associated with heterogeneous dominant or recessive phenotypes. A significant association of variants of the *POLG1* CAG repeat, encoding a polyglutamine tract (poly-Q) with idiopathic sporadic PD, has been demonstrated in the Finnish [44], in the North American Caucasian [45] and in the Swedish [46] population. However, since controversial reports exist, further genetic studies in cohorts from other geographical regions as well as functional studies of *POLG1* poly-Q variants are needed. In addition, Mancuso et al. [47] reported co-existence of parkinsonism and *POLG1* mutations with mtDNA multiple deletions in several families, suggesting a possible role of *POLG1* in inherited parkinsonism. The role of *POLG1* gene mutations as cause of mitochondrial parkinsonism is discussed more extensively in a recent review [48]. *POLG1* mutations were recently reported in a patient with multiple system atrophy of the cerebellar subtype (MSA-C) [49].

4. Secondary mitochondrial dysfunctions in neurodegenerative diseases

There is much evidence that increased oxidative stress and altered apoptosis are linked to the pathogenesis of several ageing-related neurodegenerative diseases. Many studies have considered the role of mitochondria in the pathogenesis of neurodegenerative diseases, however it is unclear whether mitochondrial impairment and oxidative stress are actually involved in the onset and progression of neurodegenerative disorders like Parkinson's disease (PD), Alzheimer's disease (AD), Huntington's disease (HD) and Amyotrophic Lateral Sclerosis (ALS), or are consequences of neurodegeneration (Fig. 4). Finally, mitochondria interact with an impressive number of specific proteins implicated in genetic forms of neurodegenerative disease (Table 4).

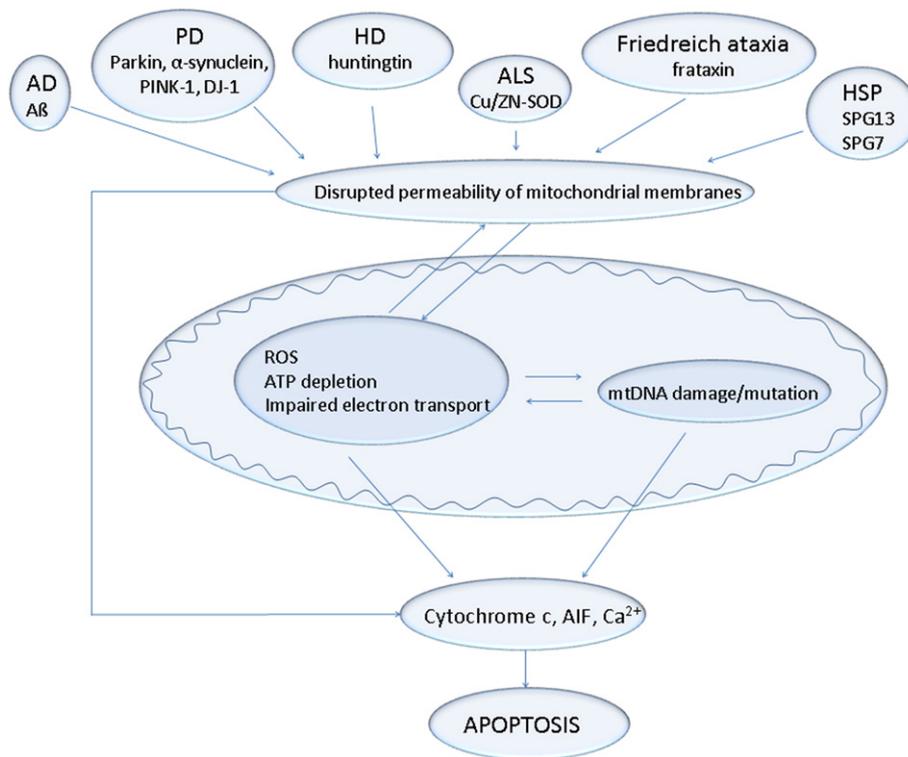


Fig. 4. Role of mitochondria in neurodegenerative disease.

4.1. Mitochondria and Parkinson's disease

Several observations suggest that mitochondrial dysfunction is involved in the pathogenesis of PD and the degeneration of dopaminergic neurons [50]. The substantia nigra of PD patients shows reduced activity of mitochondrial respiratory electron transport chain NADPH dehydrogenase (complex I) and complex I inhibitors such as rotenone, MPTP and pesticides cause neurological changes similar to PD [51]. Point mutations and deletions accumulate in mtDNA of neurons in the brains of PD patients [52] and several mtDNA polymorphisms and haplotypes are associated with the risk of PD [53]. Mutations in mtDNA or nuclear genes involved in mitochondrial

function, such as POLG, cause PD-like symptoms [54]. On the other hand, many genes associated with familial forms of PD are involved in mitochondrial function [51] (Fig. 5).

Recent studies reveal that α-synuclein contains an amino-terminal mitochondrial targeting sequence and can associate with the inner mitochondrial membrane, interacting with mitochondrial complex I function [55]. In transgenic mice, overexpression of α-synuclein impairs mitochondrial function, increases oxidative stress and enhances nigral pathology induced by MPTP [56]. It has also been suggested that mutant A53T α-synuclein might damage mitochondria directly [57]. Finally, wt alpha-synuclein and its mutant forms are reported to induce changes reminiscent of mammalian cell apoptosis [58].

Table 4
Proteins implicated in major neurodegenerative disease with mitochondrial involvement.

Protein	Description	Disease
APP	Precursor of Aβ	Alzheimer's disease
Aβ	Major component of senile plaque	" "
PS1 and PS2	Component of γ-secretase	" "
α-synuclein	Component of Lewy bodies	Parkinson's disease
Parkin	A ubiquitin E3 ligase	" "
DJ-1	DJ-1 acts as a potential ROS scavenger/sensor	" "
PINK1	PINK1 has protective effects against cell death	" "
LRRK2	Kinase	" "
HTRA2	Proapoptotic factor	" "
SOD1	Cu/Zn superoxide dismutase	ALS
Huntingtin	Mutation are associated with expanded polyglutamine repeats	Huntington's disease
Frataxin	Mitochondrial iron chaperone involved in the biogenesis of iron-containing enzymes and iron detoxification	Friedreich's ataxia
SPG7	Mitochondrial membrane metalloprotease	Hereditary spastic paraplegia
SPG13	Mitochondrial chaperone	" " "
SOD1	Cu/Zn superoxide dismutase	ALS
Huntingtin	Mutation are associated with expanded polyglutamine repeats	Huntington's disease
Frataxin	Mitochondrial iron chaperone involved in the biogenesis of iron-containing enzymes and iron detoxification	Friedreich's ataxia
SPG7	Mitochondrial membrane metalloprotease	Hereditary spastic paraplegia
SPG13	Mitochondrial chaperone	" " "

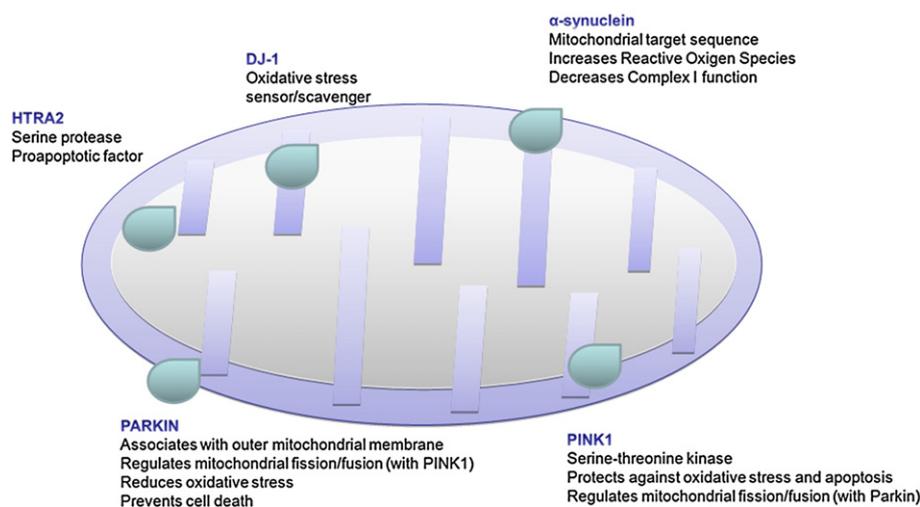


Fig. 5. Interaction between genes associated with familial forms of PD and mitochondrial function.

Our group studied PBLs from two siblings with PD associated with A53T α -synuclein mutation. We demonstrated a higher rate of apoptosis, which suggests that α -synuclein plays an important role in regulation of the mitochondrial apoptotic pathway [59].

The protein parkin is associated with the outer mitochondrial membrane and prevents cell death by inhibiting mitochondrial swelling, cytochrome c release and caspase activation [60]. Parkin deficiency causes oxidative stress and mitochondrial impairment, as demonstrated in leukocytes from patients with parkin mutations showing selective impairment in complex I activity [61]. Muscle alterations with severe depletion of subsarcolemmal and intermyofibrillar mitochondria have been found in a patient with parkin-related parkinsonism without mtDNA mutation [62].

Phosphatase and tensin homologue (PTEN)-induced kinase 1 (PINK1) is a mitochondrial kinase that seems to have protective effects against cell death by suppressing release of cytochrome c by mitochondria [63]. PINK1 deficiency causes a decrease in complex I activity and alters synaptic function in *Drosophila* neurons [64]. There is evidence that PINK1 and parkin may play a role in the same pathway, probably affecting the balance between mitochondrial fission and fusion [65].

DJ-1 is a negative regulator of PTEN tumour-suppressor protein, which promotes apoptosis by phosphorylating phosphatidylinositol-3,4,5-triphosphate, necessary for activation of the Akt pathway [66]. DJ-1 acts as a potential ROS scavenger/sensor and *DJ-1* mutations are associated with increased oxidative stress and apoptosis [67].

HTRA2 is a mitochondrial quality control agent which behaves as a proapoptotic factor when released into the cytosol [68]. Mutations in HTRA2 determine mitochondrial swelling and lower mitochondrial membrane potential [69].

Finally, although the exact role of leucine-rich-repeat kinase 2 (LRRK2) mutations in mitochondrial dysfunction still needs to be elucidated, association of about 10% of LRRK2 with mitochondria suggests that this protein has a role in mediating mitochondrial function [68].

A rare autosomal recessive juvenile parkinsonism, Kufor-Rakeb syndrome, was recently linked to mutations in *ATP13A2*, that encodes a lysosomal transmembrane protein of the P-type ATPase superfamily. Although no direct relation between *ATP13A2* and mitochondrial function has been demonstrated, our group showed high sensitivity to oxidative stress and an evident increase in apoptotic cell death in lymphocytes from patients with c.G2629A mutation in *ATP13A2* [70].

4.2. Mitochondria and Alzheimer's disease (AD)

Several evidences suggest that mitochondrial dysfunction and oxidative damage have a role in the pathogenesis of AD. In transfected

cells and transgenic mice overexpressing precursor amyloid protein (APP), this protein clogged the mitochondrial protein import machinery, causing mitochondrial dysfunction and impaired energy metabolism [71]. In brains of AD patients and transgenic mouse models, β -amyloid protein ($A\beta$) interacts with binding alcohol dehydrogenase protein (ABAD), a mitochondrial-matrix protein, causing mitochondrial oxidative damage and impaired activity of respiratory complexes [72]. $A\beta$ also interacts with HtrA2/Omi, a proapoptotic serine protease released into the cytoplasm by mitochondria on apoptotic stimulation [73]. $A\beta$ inhibits ketoglutarate dehydrogenase complex, and reduced cytochrome-c-oxidase (COX) activity has persistently been found in brain and other tissue of AD patients [74]. Reduced cell energy due to complex I and COX inhibition promotes tau phosphorylation [75], suggesting that mitochondrial damage could play a role in the formation of tangles and neurodegeneration. Presenilin and other components of the γ -secretase complex have also been localized to mitochondria [76].

mtDNA haplogroups seem to influence the risk of AD, and in most cases, the demented parent of an AD patient is the mother [77]. Moreover, when AD mtDNA is transferred to cell lines devoid of mtDNA, a respiratory enzyme deficiency similar to that seen in AD tissues is found, suggesting that the deficit is carried at least in part by mtDNA abnormalities [78]. However, no causative mtDNA changes have been reported in AD patients [79].

An important role of $A\beta$ in modulating proteins involved in mitochondrial fission/fusion processes was recently suggested. In hippocampal tissues of AD patients, reduced levels of Drp-1, OPA1, Mfn1, Mfn2 and increased levels of Fis1 have been shown, suggesting impaired mitochondrial dynamics in favour of fission. Moreover, in hippocampal neurons overexpressing APP, mitochondria accumulated in the perinuclear area suggesting that $A\beta$ can impair mitochondrial transport and consequently contribute to synaptic dysfunction [80].

Impairment of mtDNA base excision repair (BER), the primary nuclear and mtDNA repair pathway for small base modifications, may also play a role in AD pathogenesis. A significant BER deficiency was found in affected and unaffected AD brain regions and has been correlated with severity in patients with MCI [81].

4.3. Mitochondrial and Huntington's disease (HD)

HD is an autosomal dominant disorder due to the expansion of a CAG trinucleotide repeat in the *huntingtin* (*HTT*) gene: repeat numbers greater than 40 are associated with onset of the disease. Mutant *HTT* might cause mitochondrial dysfunction by interacting directly with the organelle, modulating respiration, membrane potential and

Ca²⁺ buffering [82]. Respiratory transport chain activity, in particular complex II activity, is reduced in HD brains [83]. The complex-II inhibitor, 3-nitropropionic acid, induces striatal degeneration and movement disorders resembling those of HD in rodents and primates [82], while overexpression of complex-II subunits restores complex II activity and reduces cell death in striatal neurons expressing mutant HTT [84]. HTT is associated with the outer mitochondrial membrane and mutant HTT increases mitochondrial sensitivity to calcium-induced mitochondria permeabilization and cytochrome *c* release [68].

HTT may alter mitochondrial function by directly affecting transcription of nuclear-encoded proteins: mutant HTT may in fact translocate to the nucleus where it binds to p53, which in turn activates the pro-apoptotic Bcl-2 family proteins, BAX and PUMA [82]. Mice knockout for PGC-1 α , a key transcriptional co-regulator of mitochondrial metabolic pathways, shows impaired mitochondrial function, hyperkinetic movements and striatal degeneration similar to HD [85].

Recent studies suggest that alterations in mitochondrial dynamics may be involved in the pathogenesis of HD: it is likely that normal HTT may regulate mitochondrial fission and fusion complexes and mutant HTT may alter the assembly and function of these complexes, which may in turn cause bioenergy failure, HD-linked neuronal dysfunction and cell death [82]. Finally, degeneration of medium spiny neurons, which are particularly affected in HD, may be due to selective impairment of mitochondrial Ca²⁺ buffering, increased expression of cell death mediators and increased vulnerability of this cell type to trafficking and mitochondrial fission/fusion defects [86].

4.4. Mitochondria in amyotrophic lateral sclerosis (ALS)

Approximately 10% of cases of ALS type 1, a fatal neurodegenerative disorder, are familial and about 20% of Mendelian cases are caused by mutations in the copper-zinc superoxide dismutase type 1 (SOD1) gene [87]. Postmortem and biopsy samples of ALS patients show impaired mitochondrial respiratory chain complex activity, while overexpression of mutant SOD1 in transgenic mice causes impaired electron transport chain activity, decreased mitochondrial calcium-loading capacity and aberrant ROS production [68]. Several studies have demonstrated that SOD1 and its mutant form localize to mitochondria in affected tissues [88]. SOD1 aggregates on the outer mitochondrial membrane may block protein importation and promote aberrant ROS production with consequent oxidative damage to mitochondrial proteins and lipids [89]. Mutant SOD1 mitochondrial aggregates may contribute to apoptotic cell death by causing release of cytochrome *c* [90] and sequestering the anti-apoptotic protein Bcl-2 [91].

4.5. Other common neurodegenerative diseases

Friedreich ataxia is the most common hereditary ataxia, characterized by reduced levels of a mitochondrial protein called frataxin [92]. Frataxin deficiency is associated with abnormalities in iron metabolism leading to accumulation of iron in mitochondria and depletion in the cytosol [93]. Respiratory chain dysfunction enhances oxidative stress by increasing leakage of electrons and superoxide formation [92]. *In vitro* studies have demonstrated that frataxin deficient cells not only generate more free radicals, but also have a reduced capacity to mobilize antioxidant defences [94].

Hereditary spastic paraplegias belong to a genetically heterogeneous group of neurological disorders characterized by progressive weakness and spasticity of the lower extremities. Mitochondrial defects have been directly implicated in two forms of hereditary spastic paraplegias linked to mutations in the genes SPG13 and SPG7 [95]. SPG13 encodes the mitochondrial matrix chaperonin Hsp60, which plays a role in folding imported mitochondrial proteins. SPG7 encodes paraplegin, a subunit of mitochondrial metalloproteinase that localizes to the inner mitochondrial membrane and is implicated in the

turnover of misfolded respiratory chain peptides [96]. Patients with paraplegin mutations show mitochondrial respiratory chain dysfunction, impaired complex I activity and increased sensitivity to oxidative stress [97].

5. Conclusion

Numerous evidences present in literature rise the possibility that mitochondria and oxidative stress play a crucial role in neurodegeneration, opening new perspectives for therapy. The investigation of mitochondrial diseases as a model of neurodegenerative disease, is useful for defining the role of these organelles in normal and pathological conditions.

Conflict of interest

None.

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