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Mitochondrial DNA Damage and Repair in Neurodegenerative Disorders

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Abstract

By producing ATP and regulating intracellular calcium levels, mitochondria are vital for the function and survival of neurons. Oxidative stress and damage to mitochondrial DNA during the aging process can impair mitochondrial energy metabolism and ion homeostasis in neurons, thereby rendering them vulnerable to degeneration. Mitochondrial abnormalities have been documented in all of the major neurodegenerative disorders - Alzheimer's, Parkinson's and Huntington's diseases, and amyotrophic lateral sclerosis. Mitochondrial DNA damage and dysfunction may be downstream of primary disease processes such as accumulation of pathogenic proteins. However, recent experimental evidence demonstrates that mitochondrial DNA damage responses play important roles in aging and in the pathogenesis of neurodegenerative diseases. Therapeutic interventions that target mitochondrial regulatory systems have been shown effective in cell culture and animal models, but their efficacy in humans remains to be established.

Introduction

DNA damage is a well-established trigger of apoptotic cell death in mitotic cells as well as in terminally differentiated cells such as neurons [1,2]. However, cells typically employ a battery of DNA repair enzymes to prevent the accumulation of amounts of DNA damage sufficient to trigger apoptosis [3,4]. Considerable insight into the molecular mechanisms of damage and repair of nuclear DNA (nDNA) has been obtained, particularly in the field of cancer research where DNA mutations can result in cell transformation, and treatments for cancer have focused mainly on DNA-damaging drugs and radiation [5,6]. On the other hand, mechanisms of mitochondrial DNA (mtDNA) damage and repair are poorly understood, despite the fact that mtDNA is subjected to higher levels of oxidative stress than is nuclear DNA [7,8]. mtDNA is believed to be particularly sensitive to oxidative agents due to its proximity to the inner mitochondrial membrane, where oxidants are formed, and to the lack of protective histones [9]. Interestingly, oxidative damage to mtDNA in the heart and brain is inversely related to maximum life span of mammals [10], suggesting that accumulation of mtDNA damage plays a causative role in the various disorders that are associated with aging, cancer and neurodegeneration.

The superoxide anion radical ($O_2^{-\cdot}$) is produced during oxidative phosphorylation and is therefore present in high amounts in mitochondria. The O_2^- can damage mtDNA, but is normally detoxified by conversion to hydrogen peroxide (H_2O_2) in an enzymatic reaction catalyzed by superoxide dismutases (SODs) which include mitochondrial manganese SOD and

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cytoplasmic copper/zinc SOD. However, interaction of H_2O_2 with Fe^{2+} and Cu^{+} generates the hydroxyl radical (OH.) which is highly damaging to mtDNA [11]. In addition to a direct attack on DNA bases, OH is a potent inducer of membrane lipid peroxidation which results in the production of the 4-hydroxynonenal, a toxic aldehyde implicated in brain aging and neurodegenerative disorders [12,13]. Lipid peroxidation products such as 4-hydroxynonenal have been shown to cause DNA damage by forming adducts with DNA bases [14]. In addition, peroxynitrite, which is formed by the interaction of nitric oxide with $O_2^{-}\cdot$ may contribute to mitochondrial DNA damage in neurons during normal aging and neurodegenerative disorders [15].

The identification of mutations in mtDNA in diseases characterized by neurological dysfunction suggests that neurons are particularly sensitive to mitochondrial dysfunction [16]. Neurons in both the peripheral and central nervous systems are adversely affected by mitochondrial mutations. Examples of mitochondrial disease with neurological manifestations include: Alpers-Huttenlocher disease, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; Leber's hereditary optic neuropathy; Leigh syndrome; myoclonic epilepsy and ragged red fibers; Kearns-Sayre syndrome; myoneurogenic gastrointestinal encephalopathy; neuropathy, ataxia, and retinitis pigmentosa; and progressive external ophthalmoplegia (Table 1) [17,18]. The fact that many of these rare inherited mitochondrial diseases share similar neuropathological features with more common neurodegenerative disorders suggests a possible role for mitochondrial dysfunction in the pathogenesis of the neurodegenerative disorders.

Another line of evidence supporting a pivotal role for mitochondrial dysfunction in brain aging and neurodegenerative disorders comes from the observation that compared to other cell types, neurons exhibit a hypersensitivity to mitochondrial toxins. For example, 3-nitropropionic acid (a mold toxin that is a potent inhibitor of succinate dehydrogenase) selectively kills striatal neurons causing Huntington's disease (HD)-like pathology in rodents and monkeys [19]. Two different environmental toxins that selectively inhibit mitochondrial complex I, rotenone and MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine), cause degeneration of dopaminergic neurons in rodents and primates, and are therefore often used to study Parkinson's disease (PD) [20]. The cause of the selective vulnerability of striatal medium spiny neurons and substantia nigra dopaminergic neurons to mitochondrial toxins has yet to be found. Understanding the molecular basis of this selective neuronal vulnerability may lead to novel therapeutic interventions for PD and HD [21].

Base Excision Repair

Base excision repair (BER) is the primary nuclear and mitochondrial DNA repair pathway for small base modifications such as alkylation, deamination and oxidation, and is thought to play a critical role during development and maintenance of the central nervous system (CNS) [22] [23]. The first step of BER is the removal of the damaged base by a substrate-specific DNA glycosylase, generating an abasic (AP) site, which is cleaved by an AP lyase or AP endonuclease (*i.e.*, APE1 in human cells). In the most common BER sub-pathway, known as short patch BER, the resulting one base gap is filled in by a DNA polymerase and ligated by a DNA ligase. If the 5′-termini possess blocking groups that cannot be readily removed the DNA polymerase can add between 2 to 8 nucleotides, with consequent strand displacement, flap processing and finally ligation. This pathway is known as long-patch BER.

Several DNA glysosylases have been identified which have both nuclear and mitochondrial forms, including as uracil-DNA glycosylase (UDG) [24] and adenine-DNA-glycosylases [25]. The human endonuclease III homologue, NTH1, has a putative mitochondrial targeting sequence [26] and its mitochondrial presence has been established by several studies from ours

and other groups [27] [28]. The oxoguanine DNA glycosylase (OGG1) is the primary enzyme for the repair of 8-oxoguanine (8-oxoG) in both the nuclear and mitochondrial DNA [29,30]. In addition, we reported that NEIL1, a recently-identified DNA glycosylase, is found in mouse liver mitochondria [31]. APE1, which removes the AP-site generated after the removal of the damaged base has been localized to the nucleus, the cytoplasm [32–35] and the mitochondria, despite the lack of a classical mitochondrial targeting sequence [36,37]. The gap generated by the cleavage of the abasic site in mtDNA is filled-in by DNA polymerase γ, the only DNA polymerase identified so far in vertebrate mitochondria and it functions both as the replicative and the repair polymerase [38]. Finally, ligation of the nick left behind by the DNA polymerase is believed to be accomplished in mitochondria by ligase III which also encodes for a mitochondrial variant [39,40].

Emerging findings suggest that mtDNA repair may be compromised during normal aging and may also contribute to the pathogenesis of neurodegenerative disorders [3,4,8]. Levels of mtDNA polymerase were decreased prior to motor neuron degeneration in a mouse model of amyotrophic lateral sclerosis (ALS) [41]. Folic acid deficiency, and a resulting elevation of homocysteine levels, occur in aging and have been reported to impair DNA repair, thereby rendering neurons vulnerable to apoptosis [42]. OGG1, a key enzyme in mtDNA repair, is critical for preventing neuronal death under conditions of increased oxidative and metabolic stress [43]. The remainder of this article reviews evidence for the involvement of mtDNA damage and impaired DNA repair in age-related neurodegenerative disorders.

mtDNA damage and neurodegeneration

Each mitochondrion contains 4–10 DNA molecules, and each mammalian cell contains 1,000 – 10,000 copies of approximately 16.5 kb of circular mtDNA encoding 13 proteins of the respiratory chain, 2 ribosomal RNAs, and 22 transfer RNAs [44]. A wide spectrum of neurodegenerative disorders have been associated with mtDNA damage [45]. The most common types of mtDNA damage are point mutations, nucleic acid modification and large-scale deletions, all of which can lead to mitochondrial dysfunction and apoptosis [46,47]. The role of mtDNA damage in relation to apoptosis is not yet understood [48,49]. Mitochondrial oxidative stress and DNA damage trigger the formation of pores in the mitochondrial membrane resulting in the release of cytochrome c and apoptosis inducing factor (AIF) from the intermembrane matrix into the cytosol. Cytochrome c forms a complex with Apaf-1 and caspase 9, resulting in the activation of caspase 3. Caspase-3 cleaves several major protein substrates that execute the cell death process. AIF translocates to the nucleus where it induces chromatin condensation and fragmentation. Other proteins that play important roles in neuronal apoptosis triggered by DNA damage include p53 and pro-apoptotic members of the Bcl-2 family including Bax and Bad [50,51]. On the other hand, neurons also express a range of proteins that protect against DNA damage-induced apoptosis, including Bcl2, Bcl-xL, antioxidant enzymes and heat-shock proteins [51,52].

Alzheimer's disease

AD, the most common form of age-associated dementia, is a progressive and always fatal disorder characterized clinically by memory loss and behavioral abnormalities, and histopathologically by deposition of amyloid β-peptide (Aβ), cytoskeletal pathology, degeneration of synapses and neuronal death [53]. While the vast majority of AD cases are sporadic with an age of onset over 65 years, some cases of AD are inherited with an early age of onset (typically 40–60 years of age). Mutations in three different genes have been shown to cause early-onset familial AD – the β-amyloid precursor protein (APP), presenilin-1 and presenilin-2. The risk of sporadic AD may be affected by several factors including apolipoprotein E alleles, head trauma, hypertension, diabetes and dietary factors[53]. Oxidative

stress and perturbed cellular calcium homeostasis are believed to play key roles in the dysfunction and death of neurons in AD [53,54]. The aging process and accumulation of Aβ are apparently major factors that promote oxidative stress and calcium dysregulation in AD.

Several studies have shown that oxidative modification to both nDNA mtDNA are increased in AD brains [55–57]. An increased levels of 8-hydroxy-2-deoxyguanosine (8-OHdG) was observed in mtDNA isolated from cortical brain regions of AD patients [56]. The study of de la Monte et al. demonstrated that brain cells from AD patients exhibit increased fragmentation of both nDNA and mtDNA, reduced mtDNA content and mass, a reduced level of the COX protein, and evidence of apoptosis [58]. The levels of oxidative DNA damage, including oxidized purine, oxidized pyrimidine and single-stranded breaks, were elevated in leukocytes of subjects with AD and mild cognitive impairment compared to control subjects [59]. Studies of non-neuronal cells from AD patients found defective nDNA repair and accumulation of DNA damage, e.g.[60,61].

We recently found a significant BER dysfunction in brains of AD patients, resulting from reduced UDG, OGG1 and pol β activities [62]. BER deficiencies were present in both affected and non-affected brain regions of AD patients, suggesting that impairment of BER is a general feature of AD brains. We also showed that BER activities in patients with amnestic mild cognitive impairment (MCI), a syndrome associated with a high risk for the development of dementia and AD [63], inversely correlated with the severity of disease. The combined effect of increased oxidative DNA damage and a significant deficiency in DNA repair could potentially lead to neuronal loss. This may also explain why although BER deficiency was detected in both affected and non-affected regions of AD brains, neuronal loss is limited to areas where Aβ plaques and NFT are present.

A 4977 base-pair (bp) deletion of mtDNA ($mtDNA^{4977}$) is commonly observed in a normal aging brain, and an even higher level of accumulation of $mtDNA^{4977}$ is present in mitochondria isolated from brain tissue specimens of AD patients [64]. The elevated mtDNA deletion could diminish enzyme activities of oxidative phosphorylation causing mitochondrial dysfunction. Swerdlow et al. employed a cytoplasmic cell hybrid technique to demonstrate that mtDNA from AD patients exhibit elevated production of ROS and activities of free radical scavenging enzymes [65]. The latter findings suggest that a vicious biochemical cycle occurs in cells in AD in which mtDNA damage fosters increased ROS production which, in turn, causes more mtDNA damage.

Aβ may indirectly cause damage to mitochondria in neurons by inducing oxidative stress and cellular calcium overload [11–13,52,53,66]. However, recent findings suggest that Aβ may directly interact with mitochondria in ways that adversely affect their function (Fig. 1). For example, it was reported that Aβ accumulates in mitochondria, and is associated with decreased oxygen consumption and enzymatic activities of complex III and IV as early as 4 months of age in a mouse model of AD [67]. The study of Manczak et al. showed that Aβ oligomers can exist in mitochondria, where they are mainly associated with the inner membrane [68]. Age-related increases in levels of soluble Aβ positively correlated with the level of hydrogen peroxide (H_2O_2) in the brains of APP mutant transgenic mice, and these changes were associated with decreased activity of cytochrome c oxidase [68] These results suggest that soluble mitochondrial Aβ may promote production of H_2O_2 and mitochondrial function in AD, a possibility consistent with previous evidence that Aβ causes membrane-associated oxidative stress [69,70].

Parkinson's Disease

Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, affecting approximately 2% of individuals after the age of 65 years [71]. PD is clinically characterized

by resting tremor, postural instability, gait disturbance, bradykinesia and rigidity. The pathological hallmark of PD is the massive loss of dopaminergic neurons in the substantia nigra (SN), which is typically associated with the presence of cytoplasmic inclusions called Lewy bodies that contain large amounts of aggregated α-synuclein [72]. Genetic analyses of families with inherited PD lead to the identification of several mutated genes including α-synuclein, Parkin, PTEN-induced putative kinase 1 (PINK1), DJ-1, leucine-rich repeat kinase 2 (LRRK2), ATP13A2, ubiquitin carboxyl terminal hydrolase L1 (UCH-L1) [73,74]. Expression of the mutant human genes in cultured neural cells and transgenic mice provided evidence that several of the PD-linked proteins (DJ-1, PINK1, LRRK2, Parkin and α-synuclein) could aversely affect mitochondria [75–79].

Increasing evidence suggest that oxidative damage to DNA, both nuclear and mitochondrial, contributes to the degeneration of dopaminergic neurons in PD [80,81]. Using a cybrid cell culture model, Swerdlow et al. demonstrated that mitochondria from PD patients exhibit increased production of ROS, decreased activity of complex I and increased DNA damage compared with mitochondria from normal subjects [82]. Treatment of mice and monkeys with -MPTP causes PD-like dopaminergic pathology, and is therefore widely used as a model of PD [83]. MPTP is converted into 1-methyl-4-phenylpyridine (MPP^+) by monoamine oxidase; MPP^+ is then selectively transported into dopaminergic neurons via the activity of the dopamine transporter. MPP^+ damages dopaminergic neurons by inhibiting complex I in the electron transport system. Analyses of brain tissue samples from MPTP-treated and control mice demonstrated larger amounts of damaged nDNA and mtDNA in the SN [84]. MPTP was found to activate PARP in vulnerable dopaminergic neurons of the substantia nigra in mice [85], and mice lacking the PARP gene were rescued from MPTP neurotoxicity [86], suggesting a role for DNA damage in MPTP-induced neuronal death. Chronic exposure of neuroblastoma cells to rotenone, another mitochondrial complex I inhibitor, resulted in increased levels of SDS-insoluble α-synuclein and a significant increase in 8-oxoG immunoreactivity [87]. Increased 8-oxoG was also detected in the mitochondria of the substantia nigra of PD patients [88]. Additionally, higher levels of β-OGG1 were selectively detected in the substantia nigra of PD patients [89].

Point mutations were found to accumulate in mtDNA of both glial cells and neurons in post-mortem human SN tissue samples from PD patients compared to control subjects [90]. In addition, high levels of mtDNA deletions were observed in the SN in aging and PD, and were associated with decreased cytochrome c oxidase (COX) activity [91,92]. Oxidative DNA damage can cause DNA deletion [93,94], yet the specific mechanism of mtDNA deletions in PD is unclear. Transgenic mice that overexpressed the human A53T α-synuclein mutation exhibited DNA double-strand break lesions in neurons of the brainstem, neocortex and spinal cord ventral horn, as well as mtDNA damage in motor neurons [95]. A recent study reported that some PD patients carry a A8344G mutation in the mitochondrial $tRNA^{Lys}$ gene that is responsible for their phenotypic spectrum [96]. These results suggest that mtDNA mutations and deletions occur in PD as a consequence of oxidative damage, and that the mtDNA lesions may contribute to the dysfunction and death of dopaminergic neurons in PD.

Several lines of evidence are consistent with the hypothesis that nDNA and/or mtDNA damage may trigger apoptosis of dopaminergic neurons in PD. The apoptotic markers cleaved caspase-3 and p53 were increased in cells of the brainstem, neocortex and spinal cord of A53T α-synuclein mutant transgenic mice [77]. Accumulation of oxidative DNA damage in nucleus and mitochondria were also present in brain cells of the α-synuclein mutant mice, suggesting a role for mtDNA damage in neuronal apoptosis triggered by α-synuclein mutations.

PINK1 is a protein kinase localized to mitochondrial membranes, and is ubiquitously expressed in neurons in the human brain [97]. A recent study showed that PINK1 can protect cells against

oxidative stress-induced apoptosis by suppressing cytochrome c release from mitochondria, and this protective effect depends on PINK1-mediated phosphorylation of the TNF receptor-associated protein 1 (TRAP1) [98]. TRAP1, also called heat shock protein 75, is a mitochondrial molecular chaperone that may protect against mtDNA damage. PD-linked PINK1 G309D, L247P and W437X mutations are defective in their ability to phosphorylate TRAP1 and to prevent cellular apoptosis [98]. Other studies also demonstrated that overexpressing TRAP1 decreases the levels of ROS, caveolin-1, glutathione peroxidase, manganese superoxide dismutase and senescence-associated –galactosidase activity, whereas silencing TRAP1 or decreasing TRAP1 levels causes accumulation of ROS [99,100]. Altogether, the available data point to a pivotal role for mitochondrial dysfunction and DNA damage in the pathogenesis of PD.

Huntington's Disease

Huntington's disease (HD) is a dominantly inherited neurodegenerative disorder caused by expanded CAG trinucleotide repeats in the amino-terminal (N-terminal) coding region of the huntingtin (Htt) gene. HD is characterized by selective loss of GABAergic neurons in the striatum and cortex, leading to chorea, psychiatric disturbances and cognitive impairment [101]. In a normal individual, the CAG repeat number is typically 34 or less, adult-onset HD patients generally have 38 – 55 CAG repeats, and juvenile-onset HD patients have more than 70 CAG repeats [102]. The severity and age of disease onset in HD depend on the number of CAG repeat. The molecular mechanism responsible for expansion of CAG trinucleotide repeats in HD is as yet unknown.

Increased 8-OHdG has been found in the brains of HD transgenic mice at 12 to 14 weeks of age, and was also detected in the urine, plasma and striatal microdialysates [103]. In the postmortem HD caudate, the level of 8-OHdG in nDNA was increased compared with samples from age-matched control subjects [104]. Interestingly, there is evidence of elevated 8-oxoG levels in mtDNA in parietal cortex of HD patients, but not in frontal cortex or cerebellum [105], suggesting that region-specific damage to mtDNA may play a causative role in the mitochondrial dysfunction observed in HD. It was suggested that expansion of the CAG trinucleotide repeats in HD requires DNA break repair and involves several DNA repair enzymes including flap endonuclease 1 (FEN1), which processes Okazaki fragments during DNA replication and participates in long-patch BER [106–108]. It was also proposed that faulty processing of strand breaks by FEN-1 initiates CAG repeat instability in mammalian cells [109]. It was recently showed that the accumulation of oxidative DNA lesions in brains and livers of R6/1 HD mice, including 8-oxoG, 5-hydroxyuracil (5-OHU), 5-hydroxycytosine (5-OHC), and formamidopyrimidine (FAPY), were correlated with the degree of trinucleotide expansion [110]. Importantly, the latter study provided evidence that initiation of CAG repeats may occur during removal of oxidative DNA lesions, and could be specifically associated with OGG1 activity..

Cell lines stably expressing Htt-GFP fusion proteins containing 43 polyglutamine repeats exhibit high amounts of activated ataxia telangiectasia mutated kinase (ATM) and Rad3-related kinase (ATR), as did fibroblasts from HD patients [111]. Because ATM and ATR are double-strand DNA break response proteins, the latter results suggest that double-strand and/or single-strand DNA breaks are triggered by polyglutamine repeats. The hypothesis that mtDNA may be particularly vulnerable in HD is supported by the high levels of the mtDNA^{4977} deletion found in temporal and frontal lobes of HD patients compared with age-matched control subjects [112].

Normal Htt has been reported to protect neurons against apoptosis by blocking caspase 9 processing and interfering with the activity of the apoptosome complex downstream of

cytochrome c release from mitochondria [113]. Because activated caspase 9 and caspase 3 are observed in vulnerable neuronal populations in the brains of HD patients and huntingtin mutant mice [114], it is possible that the Htt mutations compromise the anti-apoptotic activity of normal Htt. Polyglutamine expansions may also cause a gain of a toxic activity of Htt that damages mitochondria. For example, N-terminal polyglutamine repeats in Htt have been shown to directly interact with neuronal mitochondrial membranes resulting in an altered mitochondrial Ca^{2+} retention and mitochondrial membrane depolarization [115]. Decreased Ca^{2+} retention capacity increases the sensitivity of mitochondria to Ca^{2+} -mediated excitotoxicity. Another potential mechanism whereby mutant Htt may cause increased mitochondrial membrane permeability is by binding to p53 and increasing the levels of nuclear p53 and p53 transcriptional activity, resulting in production of the pro-apoptotic protein Bax [116].

Amyotrophic Lateral Sclerosis

Amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disease, is characterized by selective degeneration and death of lower motor neurons in the spinal cord and brainstem and, to a lesser extent, upper motor neurons in the cerebral cortex [117]. Patients develop progressive muscle weakness, muscular atrophy, spasticity, and eventually paralysis. ALS patients usually die within 3–5 years after the onset of the disease. Approximately 90% of ALS cases are sporadic (SALS) and the rest are inherited (familial) (FALS). Approximately 20% of FALS is caused by mutations in Cu,Zn-superoxide dismutase (SOD1). SOD1 is a prominent antioxidant enzyme that catalyzes the conversion of superoxide to hydrogen peroxide. Mutations in a protein called ALS2 are responsible for rare cases of recessively inherited juvenile and infantile ALS; experimental data suggest that ALS2 has a neuroprotective role against oxidative stress and excitotoxicity [118,119].

Impaired mitochondrial respiratory chain function has been detected in muscle and spinal cord cells of SALS patients, and they exhibit significantly higher levels of point mutations in spinal cord mtDNA [120,121]. Elevated levels of 8-oxoG have been found in the cortex, spinal cord, plasma and urine of ALS patients [122–124], as well as in nDNA and mtDNA from spinal cord motor neurons of presymptomatic transgenic mice harboring a mutated SOD1 gene [125, 126]. In G93A SOD1 mutant mice, single-strand breaks of nDNA and mtDNA were evident in motor neurons of 6-week old mice, and double-strand breaks appeared by 9 weeks of age and progressively increase thereafter [127]. The death of motor neurons in G93A mice involves mitochondrial swelling. Another study showed that nuclear OGG1 levels were increased, while mitochondrial OGG1 remained unchanged, and DNA pol was downregulated in spinal cord motor neurons of SOD1 mutant mice [41]. The latter results suggest that defective mtDNA repair may precede neuronal degeneration in ALS.

Expression of several different FALS SOD1 mutations in cultured neuroblastoma cells resulted in increased levels of mitochondrial superoxide production, which was counteracted by overexpression of manganese SOD (SOD2) [128]. Swerdlow et al. suggested that mtDNA from ALS subjects is damaged and results in impaired electron transport, increased ROS production and perturbed mitochondrial calcium homeostasis [129]. The mutant SOD1 may directly damage mitochondria, as suggested by the finding that SOD1 aggregates accumulate in mitochondria and are associated with severely damaged cristae in spinal cord motor neurons [130]. Aggregates of mutant SOD1 have been detected at the outer mitochondrial membrane and matrix [131,132], and the mutant SOD1 may interact with Bcl-2 and compromise its cell survival-promoting function [133]. Oligomers of mutant SOD1 may associate with, and impair the function of, the mitochondrial electron transport chain complex [134]. Increased levels of the pro-apoptotic proteins Bax, Bid and Bcl-x_S, and decreased levels of the anti-apoptotic proteins Bcl-2 and Bcl-x_L were found in spinal cord tissue samples from ALS patients [135–

138]. Interestingly, motor neurons in mice expressing mutant SOD1 on a Bax null background survive, but are dysfunctional [139]. Collectively, the available data suggest that mtDNA damage and mitochondrial dysfunction occur in motor neurons in ALS and may contribute to both the dysfunction and death of the motor neurons.

Conclusions

MtDNA damage is found in affected neurons in every major neurodegenerative disorders, and is associated with increased ROS production, mitochondrial dysfunction, and dysregulation of cellular calcium homeostasis. Oxidative stress, caused by disease-specific processes such as the accumulation of pathogenic proteins, as well as the aging process itself, contribute to mitochondrial dysfunction. The pathogenic proteins may interact directly with mitochondrial membranes and proteins, resulting in impaired electron transport. Accumulation of nDNA and mtDNA base modifications has been identified as a major factor contributing to genomic instability and mitochondrial dysfunctions in neurodegenerative diseases. DNA repair mechanisms are essential for the proper maintenance of the mammalian CNS. Therefore, deficiency in DNA repair, particularly in BER, is increasingly recognized as a major contributor to neuronal loss. Moreover, at least in the case of HD-associated polyglutamine expansions, DNA repair processes may directly contribute to disease pathogenesis. A better understanding of the molecular mechanisms underying mtDNA damage and repair, as well as mitochondrial dysfunction in neurodegenerative disorders may reveal novel targets for the development of therapeutic interventions.

Acknowledgements

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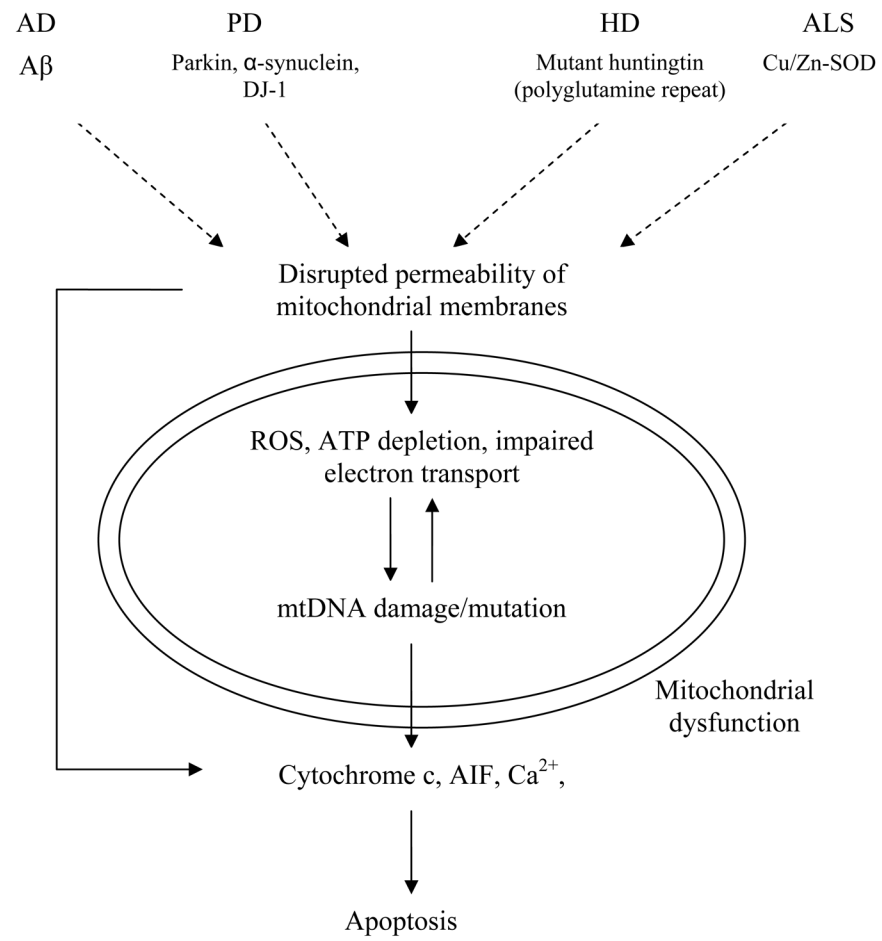

Figure 1.

The pathogenic proteins of Alzheimer' disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS) directly and/or indirectly cause mitochondrial dysfunction and apoptosis. Amyloid β-peptide (Aβ), a pathogenic protein in AD, can induce membrane lipid peroxidaton and the production of the toxic aldehyde 4-hydroxynonenal, resulting in perturbed cellular calcium homeostasis and energy metabolism. Aβ may accumulate in mitochondria and impair the function of electron transport enzymes. Pathogenic proteins of PD include α-synuclein, Parkin, DJ-1, and PTEN-induced putative kinas 1(PINK1) may indirectly promote mitochondrial DNA damage and dysfunction by impairing proteasome function and increasing ROS production. Aggregated α-synuclein increases oxidized lipids that may, in turn, disrupt membrane functions and increase neuronal vulnerability to excitotoxicity. Parkin associates with the mitochondrial outer membrane and may prevent release of cytochrome *c*, a neuroprotective function compromised by Parkin mutations. PINK1 is a mitochondrial kinase that may protect against oxidative stress-induced apoptosis. Mutant huntingtin (htt), with N-terminal polyglutamine repeats, directly interacts with mitochondrial membranes resulting in an altered mitochondrial Ca^{2+} retention and membrane depolarization. Decreased Ca^{2+} retention capacity increases the sensitivity of neurons to Ca^{2+}-mediated excitotoxicity. Mutant htt may cause increased mitochondrial membrane permeability by binding to p53 and increasing the levels of nuclear p53 and p53 transcriptional activity, resulting in production of the pro-apoptotic protein Bax. Mutant Cu/Zn-superoxide dismutase (SOD1) which causes many cases of familial ALS, may directly damage mitochondria; aggregates of mutant SOD1 have been detected at the outer

mitochondrial membrane and matrix, and mutant SOD1 may interact with Bcl-2 and compromise its cell survival-promoting function. Thus, in each of the major age-related neurodegenerative disorders pathogenic proteins may directly and/or directly damage mitochondrial DNA, alter mitochondrial membrane permeability and impair electron transport chain function. The damaged mitochondria may trigger apoptosis by releasing cytochrome *c*, the apoptosis-inducing factor (AIF) and Ca^{2+}.

Table 1

Disease	Pathogenesis	Genetic factors	DNA damage
Alzheimer's disease (AD)	β-amyloid, hyperphosporylated tau	APP, Tau, PS1, PS2, APOE4	DSB, SSB, oxidized purine and pyrimidine mtDNA deletion, mtDNA point mutation
Parkinson's disease (PD)	γ-synuclein	Parkin, DJ-1, PINK1, LRRK2, HTRA2	oxidized purine and pyrimidine, mtDNA deletion, mtDNA point mutation oxidized purine and pyrimidine, mtDNA deletion
Huntington's disease (HD)	N-terminal polyglutamine	Htt	
Amyotrophic lateral sclerosis (ALS)	Cu/Zn-SOD	SOD1	SSB, oxidized purine and pyrimidine, mtDNA point mutation
Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)	$tRNA^{Leu}$, $tRNA^{Lys}$, $tRNA^{Phe}$, $tRNA^{Val}$, RNA^{His}, $tRNA^{Cys}$, COX III, Cyt b	MT-TL1, MT-ND-1, MT-ND3	mtDNA point mutation mtDNA deletion
Alpers-Huttenlocher disease	DNA polymerase γ	*POLG-A*	DNA repair gene mutation.
Leber's hereditary optic neuropathy (LHON)	Complex I of respiratory chain	MT-ND1, MT-ND4, MT-ND6	mtDNA point mutation
Leigh syndrome (LS)	Complex I, complex IV, complex V of respiratory chain, ATP synthase F0 subunit 6	MT-ATP6, MT-TL1, MT-TK, MT-ND1, MT- ND3, MT-ND4, MT- ND5, MT-ND6, MT- CO3, MT-TW, MT-TV	mtDNA point mutation, mtDNA deletion
Myoclonic epilepsy and ragged red fibers (MERRF)	$tRNA^{Lys}$, $tRNA^{Phe}$		mtDNA point mutation mtDNA deletion
Kearns-Sayre syndrome (KSS)	$tRNA^{Leu}$		mtDNA point mutation, mtDNA deletion
Myoneurogenic gastrointestinal encephalopathy (MNGIE)			mtDNA point mutation, mtDNA deletion
Neuropathy, ataxia, and retinitis pigmentosa (NARP)	ATP synthase F0 subunit 6	MT-ATP6	mtDNA point mutation
Progressive external ophthalmoplegia (PEO)	$tRNA^{Leu}$, $tRNA^{Ile}$, $tRNA^{Asn}$,		mtDNA point mutation, mtDNA deletion