CHAPTER 16

MITOCHONDRIAL IMPORTANCE IN ALZHEIMER'S, HUNTINGTON'S AND PARKINSON'S DISEASES

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EDITOR'S NOTE

Sadly, Dr. Mark A. Smith passed away during the production of this book. Please read the full "in memoriam" located on page xxxi in the front of the book. His innovative thinking and contributions to the scientific community will be greatly missed.

Abstract: Mitochondria have been long known as "gatekeepers of life and death". Indeed, these dynamic organelles are the master coordinators of energy metabolism, being responsible for the generation of the majority of cellular ATP. Notably, mitochondria are also one of the primary producers of intracellular reactive oxygen species which are the main inducer of oxidative damage. Neurons, as metabolically active cells with high energy demands, are predominantly dependent on mitochondrial function, as reflected by the observation that mitochondrial defects are key features of chronic neurodegenerative diseases. Indeed, morphologic, biochemical and molecular genetic studies posit that mitochondria constitute a convergence point for neurodegeneration. Moreover, recent findings convey that neurons are particularly reliant on the dynamic properties of mitochondria, further emphasizing the critical role of mitochondria in neuronal functions. This chapter highlights how mitochondrial pathobiology might contribute to neurodegeneration in Alzheimer's, Parkinson's and Huntington's diseases.

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INTRODUCTION

The prevalence of neurodegenerative diseases is rising dramatically due to the increase in life expectancy and demographic changes in the population, representing one of the major health problems. The etiology of most neurodegenerative disorders is complex and multifactorial, involving genetic predisposition, environmental and endogenous factors.[1-3] Nevertheless, mitochondria have emerged as a pivotal "convergence point" for neurodegeneration.[4,5]

Mitochondria are ubiquitous and dynamic organelles involved in many crucial cellular processes in eukaryotic organisms and are considered "gatekeepers of life and death". These organelles have as major functions, the production of over 90% of cellular ATP through the tricarboxylic acid cycle (TCA) cycle and oxidative phosphorylation, regulation of intracellular calcium (Ca^{2+}) and redox signaling and the arbitration of apoptosis.[6-8] Hence, mitochondria possess a notorious significance for neuronal function and survival, since neurons are cells with extremely high energy demands, mitochondrial oxidative phosphorylation being essential for neurons to meet their high energy requirements. That said, neurons are very vulnerable to bioenergetic crisis if there is dysfunction of mitochondrial machinery.[9,10] Dysfunctional mitochondrial energy metabolism culminates in ATP production and Ca^{2+} buffering impairment and exacerbated generation of reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), hydroxyl radical ($^{\cdot}OH$) and superoxide anion ($O_2^{\cdot-}$).[7] ROS, in turn, cause cell membrane damage via lipid peroxidation and accelerates the high mutation rate of mitochondrial DNA (mtDNA).[11] Additionally, accumulation of mtDNA mutations enhances oxidative damage, induces energy crisis and exacerbates ROS generation, in a vicious cycle.[11] Additionally, the brain is especially prone to oxidative stress-induced damage as a consequence of its high levels of polyunsaturated fatty acids, high oxygen consumption, high content in transition metals and poor antioxidant defenses.[12]

Perturbations in dynamic properties of mitochondria, which include fission, fusion, motility and turnover, can lead to distinctive defects in neurons and are recognized as playing a critical role in neurodegeneration.[13] As a matter of fact, mitochondrial dynamics orchestrate a variety of vital functions required for accurate neuronal function, including maintenance of mitochondrial DNA,[14,15] involvement in apoptosis,[16] formation and function of synapses and dendritic spines and proper distribution of mitochondria.[17-21]

Since mitochondria play a critical role in the regulation of both cell survival and death, mitochondrial dysfunction has been posited to take a center stage in age related-neurodegenerative diseases. Herein, we summarize the current knowledge pertaining to the involvement of mitochondrial malfunction in the onset and progression of neurodegenerative diseases, namely Alzheimer's disease (AD), Parkinson's disease (PD) and Huntington's disease (HD). The insights from in vitro, in vivo and human studies could help to unveil the pathogenic mechanisms underlying mitochondrial dysfunction and to develop new and more effective therapeutic strategies to prevent and/or treat neurodegenerative diseases.

MITOCHONDRIAL DYSFUNCTION IN THE LIMELIGHT OF NEURODEGENERATIVE DISEASES

Alzheimer's Disease

AD is the most common form of dementia among people age 65 and older, affecting more than 35 million people worldwide.[22] Clinically, AD is characterized by a progressive

cognitive deterioration, together with impairments in behavior, language and visuospatial skills, culminating in the premature death of the subject.[22] Neuropathologically, AD has as main hallmarks selective neuronal and synaptic loss, deposition of extracellular senile plaques mainly composed of amyloid-β (Aβ) peptide and the presence of intracellular neurofibrillary tangles containing hyperphosphorylated tau protein.[9,23-25]

Since the etiology of AD is complex and multifactorial, several hypotheses have been proposed over the last decades to answer one of the most intriguing questions of the actuality: What is the "culprit" of AD development? With the purpose of explaining many of the biochemical, genetic and pathological features of sporadic AD, Swerdlow and Khan presented the "mitochondrial cascade hypothesis".[26] According to this hypothesis: (1) inheritance determines mitochondrial baseline function and durability; (2) mitochondrial durability influences how mitochondria change with age; and (3) when mitochondrial alterations reach a threshold, AD histopathology and symptoms ensue.[27] Thus, mitochondrial-dependent pathogenic mechanisms are drawing increasing attention for their significant involvement on AD etiopathogenesis.

Energy Hypometabolism, Oxidative Stress and Mitochondrial Dysfunction

It is conceivable that mitochondrial abnormalities that occur in AD result from the complex nature and genesis of oxidative damage in the disease. Indeed, AD patients present reduced metabolic activity, which is believed to be a consequence of oxidative damage to vital mitochondrial components.[28-31] Positron emission tomography imaging studies revealed impaired brain glucose in AD patients, which precedes neuropsychological impairment and atrophy.[32-34] Cerebral glucose utilization is reduced by 45% and cerebral blood flow (CBF) by approximately 20%, in the early stages of AD. However, in the later stages of the disease, metabolic and physiological abnormalities aggravate, resulting in 55-65% reductions in CBF.[35] This decrease in the cerebral glucose metabolism is correlated with the altered expression and decreased activity of mitochondrial energy related proteins, including pyruvate dehydrogenase (PDH), isocitrate dehydrogenase and α-ketoglutarate dehydrogenase, also documented in postmortem AD brain and fibroblasts from AD patients.[36,37] Furthermore, Bubber and collaborators[37] found that all changes in TCA cycle activities (specifically that of PDH complex) correlated with the clinical state, suggesting a coordinated mitochondrial alteration. Moreover, these enzymes are known to be highly susceptible to oxidative modification and are altered by exposure to a range of pro-oxidants.[38]

Accumulating data from in vitro, in vivo and human studies argue that mitochondrial dysfunction and bioenergetics failure are early events implicated in AD pathogenesis. Indeed, impairment in the respiratory chain complexes I, III and IV activities was found in platelets and lymphocytes from AD patients and postmortem AD brain tissue.[39-42] In vitro studies performed in pheochromocytoma cells (PC12) also demonstrated that exposure to $A\beta_{1-40}$ and $A\beta_{25-35}$ potentiated mitochondrial dysfunction characterized by the inhibition of complexes I, III and IV of the mitochondrial respiratory chain.[43] More recently, Fattoretti and collaborators,[44] in order to establish a link between AD and mitochondrial dysfunction, investigated succinic dehydrogenase (SDH) (mitochondrial respiratory complex II) activity in mitochondria of hippocampal CA1 pyramidal neurons obtained from 3xTg-AD mice. The authors observed a decreased density (number of mitochondria/μm^3 of cytoplasm) of SDH-positive mitochondria in 3xTg-AD mice. Data from our laboratory also revealed that AD fibroblasts present high levels of oxidative stress and apoptotic markers when

compared with young and age-matched controls.[45] Moreover, AD-type changes could be generated in control fibroblasts using N-methylprotoporphyrin to inhibit cytochrome c oxidase (COX) assembly, which indicates that the observed oxidative damage was associated with mitochondrial dysfunction.[45] Additionally, the effects promoted by the N-methylprotoporphyrine were reversed or attenuated by lipoic acid and *N*-acetyl cysteine.[45] Accordingly, de la Monte and Wands[46] examined postmortem brain tissue from AD patients with different degrees of severity and found that the severity of AD was related to impairments in mitochondrial gene expression, namely in complex IV, increased levels of p53 and molecular indexes of oxidative stress, including NOS and NADPH-oxidase. Thus, mitochondrial malfunction exacerbates oxidative stress and oxidative damage marked by high levels of lipid, protein and nucleic acid oxidation is increased in vulnerable neurons in AD.[47-51] Overall, these findings suggest that mitochondria are important in oxidative damage that occurs in AD and that antioxidant therapies may be promising.

Mitochondrial DNA Mutations

mtDNA mutations have also been implicated in mitochondrial dysfunction in the pathogenesis of AD. For instance, 20 point mutations in the mitochondrial-encoded cytochrome c oxidase subunits I, II and III genes have been detected in AD patients.[52] Qiu and collaborators[53] also identified two missense mutations in the mtDNA of COX in a patient with AD. Further, a high aggregate burden of somatic mtDNA mutations was observed in postmortem brain tissue from AD patients.[54,55]

Mitochondria, Amyloid-β Protein Precursor and Aβ Peptide

Mitochondria were found to be the target both for amyloid-β protein precursor (AβPP) that accumulates in the mitochondrial import channels and for Aβ that interacts with several proteins inside mitochondria and leads to mitochondrial dysfunction. For instance, Aβ was found to impair cellular respiration, energy production and mitochondrial electron chain complexes activity in human neuroblastoma cells.[56] Moreover, cultured neurons isolated from transgenic mice that overexpress a mutant form of AβPP and Aβ-binding alcohol dehydrogenase (ABAD) (Tg mAβPP/ABAD) display spontaneous generation of H_2O_2 and $O_2^{\cdot-}$, decreased ATP, release of cytochrome c and induction of caspase 3-like activity followed by DNA fragmentation and loss of cell viability.[57] A prominent role for mitochondrial $O_2^{\cdot-}$ in mediating the effects of Aβ on neuronal function was reported by Massaad and collaborators.[58] In fact, it was previously reported that Aβ enters into mitochondria, compromising their integrity through the inactivation of the manganese superoxide dismutase 2 (SOD-2) and, consequently by increasing mitochondrial superoxide anion levels.[59] Moreover, some studies demonstrate that genetic reduction of SOD-2 in AD model mice can intensify AD symptoms and lead to increased plaque deposition.[60-62] Conversely, the overexpression of SOD-2 reduces hippocampal $O_2^{\cdot-}$ and prevents memory deficits in Tg2576 mouse model of AD.[58] Recently, strong evidence for a direct link between free radicals of specific mitochondrial origin and AD-associated vascular and neuronal pathology has been reported.[63] Since SOD-2 is the main $O_2^{\cdot-}$ scavenger in mitochondria, these authors showed that its overexpression culminates in the reduction of mitochondrial superoxide and amelioration of CBF deficits and axonal transport deficits typically exhibited by Tg2576 mice.[63] The reduction of mitochondrial superoxide also resulted in a concomitant reduction of phosphorylation of endothelial

nitric oxide synthase at serine 1177, as well as phosphorylation of tau at serine 262.[63] Thus, one conclusion from this study is that mitochondrial superoxide is a key player in AD-related vascular and neuronal dysfunction, working as a downstream effector of Aβ, possibly affecting Aβ processing.[63]

Furthermore, generation of ROS is associated with dysfunction at the level of COX[57] (Fig. 1). Similarly, Crouch and colleagues[64] also found that $A\beta_{1-42}$ can disrupt mitochondrial COX activity in a sequence- and conformation-dependent manner. In an in vitro study, designed to explore the effect of the AβPP Swedish double mutation (K670M/N671L) on oxidative stress-induced cell death mechanisms in PC12 cells, increased activity of caspase 3 due to an enhanced activation of both intrinsic and extrinsic apoptotic pathways, including activation of JNK pathway was observed.[65] Moreover, apoptosis was attenuated by SP600125, a JNK inhibitor, through protection of mitochondrial dysfunction and reduction of caspase 9 activity.[65] These findings corroborate the hypothesis that the massive neurodegeneration that develops at an early age in familial AD patients could be a result of an increased vulnerability of neurons through the activation of different apoptotic pathways as a consequence of elevated levels of oxidative stress.

In addition, mitochondrial dysfunction was also linked to the accumulation of full-length and carboxy-terminally truncated AβPP across mitochondrial import channels in brain tissue from AD patients.[66] The authors observed that this accumulation of AβPP inhibited the entrance of nuclear-encoded COX subunits IV and Vb proteins, which was associated with decreased cytochrome *c* oxidase activity and increased H_2O_2 levels.[66] Similarly, Anandatheerthavarada et al reported an accumulation of full-length AβPP in the mitochondrial compartment in a transmembrane-arrested form that impaired mitochondrial functionality and energy metabolism.[67] Also, a progressive accumulation of Aβ monomers and oligomers was detected within the mitochondria of both transgenic mice overexpressing mutant AβPP and postmortem brains from AD patients.[64,66,68,69] More recently, Pavlov and coworkers[70] demonstrated that AβPP is a substrate for the mitochondrial γ-secretase and that AβPP intracellular domain (AICD) is produced inside mitochondria, providing a mechanistic view of the mitochondria-associated AβPP metabolism where AICD, P3 peptide and potentially Aβ are produced locally and may contribute to mitochondrial dysfunction in AD. Additionally, Iijima-Ando et al[71] reported that mislocalization of mitochondria underlies the pathogenic effects of $A\beta_{1-42}$ in a transgenic Drosophila model. Indeed, the authors found that in this $A\beta_{1-42}$ model, brain mitochondria were reduced in axons and dendrites and accumulated in the soma without severe mitochondrial damage or neurodegeneration.[71] Notably, perturbations in mitochondrial transport in neurons were sufficient to disrupt protein kinase A (PKA) signaling and induce late-onset behavioral deficits, suggesting a mechanism whereby mitochondrial mislocalization contributes to $A\beta_{1-42}$-induced neuronal dysfunction.[71] A direct link between Aβ-induced toxicity and mitochondrial dysfunction in AD pathology has been suggested by the interaction between mitochondrial Aβ and ABAD.[72,73] Moreover, this interaction was found to induce mitochondrial failure via changes in mitochondrial membrane permeability and a reduction in the activities of enzymes involved in mitochondrial respiration.[73] More recently, Hansson-Petersen et al[74] showed that Aβ peptide is imported into mitochondria via the translocase of the outer membrane import machinery and localized to mitochondrial cristae. Thus, it has been proposed that Aβ species transport to mitochondria cause mitochondrial dysfunction and oxidative damage and consequently damage neurons both structurally and functionally.[64,66,68,69,74] Previous studies from our laboratory also reported an increased susceptibility to mitochondrial permeability transition pore (mPTP) induction

promoted by Aβ peptides.[75,76] In accordance, it provided a plausible mechanism underlying Aβ-induced mitochondrial dysfunction, in which Aβ interacts with cyclophilin D, a critical molecule involved in mPTP formation and cell death.[77] Du et al[77] further showed that the interaction of cyclophilin D with mitochondrial Aβ potentiates mitochondrial, neuronal and synaptic stress. Conversely, cyclophilin D ablation protects neurons from Aβ-induced mPTP formation and the resultant mitochondrial and cellular stresses. Along those same lines, cyclophilin D deficiency substantially improves learning and memory and synaptic function in an AD mouse model and alleviates Aβ-mediated reduction of long-term potentiation.[77] Another study reported that the presequence protease (PreP) is responsible for the degradation of the accumulated Aβ in mitochondria, further supporting the association of Aβ with mitochondria and mitochondrial dysfunction in AD.[78]

However, another key role of mitochondria in AD pathogenesis and the close interrelationship of this organelle and the two main pathological features of the disease were recently highlighted. Rhein et al[79] demonstrated that Aβ and tau synergistically impair mitochondrial function and energy homeostasis in 3xTg-AD mice. Accordingly, a previous study demonstrated that transgenic mice overexpressing the P301L mutant human tau protein present alterations of metabolism-related proteins including mitochondrial respiratory chain complexes, antioxidant enzymes and synaptic proteins that are associated with increased oxidative stress.[80] Moreover, mitochondria prepared from these transgenic mice displayed increased vulnerability toward Aβ insult, which reinforce a possible synergistic action of tau and Aβ pathology on the mitochondria.[80] The authors also suggest that tau pathology involves a mitochondrial and oxidative stress disorder possibly distinct from that caused by Aβ.[80]

Omi/HtrA2, a mitochondrial serine protease with chaperone activity, has also been suggested to participate in AD-associated mitochondrial dysfunction. The first evidence for the involvement of Omi/Htr2 in AD was provided by Gray et al[81] that indentified Omi/HtrA2 as a presenilin-1 (PS1)-interacting factor in a yeast two-hybrid screen. Consistently, a following study demonstrated that the C-terminus of PS1 peptide interacts with Omi/HtrA2 and stimulates Omi/HtrA2 protease activity.[82] Additionally, it was observed that Aβ also interacts with Omi/HtrA2, which results in delayed aggregation of the $A\beta_{1\text{-}42}$ peptide, indicating that besides its protease activity, Omi/HtrA2 also performs a chaperone function role in the metabolism of intracellular Aβ in AD.[83,84] Mitochondrial AβPP was shown to be a direct cleavage target of Omi/HtrA2,[85] proposing that the regulation of Omi/HtrA2 protease activity may be a therapeutic target in AD by preventing mitochondrial dysfunction caused by AβPP accumulation. More recently, it was also reported that Omi/HtrA2 interacts with PS in active γ-secretase complexes located to mitochondria.[86] Moreover, the authors found reduced AICD production in mitochondria isolated from Omi/HtrA2 knockout mouse embryonic fibroblasts, indicating a significant role of Omi/HtrA2 on γ-secretase activity.[86] Overall, these findings suggest the interactions between mitochondrial Omi/HtrA2 and Aβ, PS, or AβPP are possible links to Omi/HtrA2 in AD. These findings may contribute to a better understanding of the biochemical pathways underlying mitochondrial dysfunction in AD and may help the development of novel mitochondrial-targeted therapeutic strategies.

Mitochondrial Dynamics in Alzheimer's Disease

Ultrastructural alterations in mitochondrial morphology such as reduced size and broken internal membrane cristae were also documented in brains from AD patients.[30,87]

One reasonable explanation for these observations could be the increased mitochondrial autophagy found in AD.[88,89] Another consequence of Aβ on mitochondria is the induction of dynamic changes, including mitochondrial fission/fusion perturbations. Wang and collaborators[90] reported abnormal mitochondrial fission and fusion in fibroblasts from sporadic AD patients, marked by lower levels of dynamin-related protein 1 (Drp1), a key regulator of mitochondrial fission. The authors also observed that AD fibroblasts display elongated mitochondria which form collapsed perinuclear networks.[90,91] Accordingly, AβPP overexpression in M17 neuroblastoma cells resulted in predominantly fragmented mitochondria, decreased Drp1 and optic atrophy protein 1 (OPA1) levels and a defect in neuronal differentiation.[92] Moreover, reduced expression levels of Drp1, OPA1, mitofusin (Mfn)1 and 2 and increased mitochondria fission protein 1 (Fis1) levels were found in hippocampal tissues from AD patients compared with age-matched controls.[93] These results suggest that AD is characterized by mitochondrial fission/fusion imbalance and consequently mitochondrial fragmentation and abnormal distribution, which potentiates mitochondrial and neuronal dysfunction in this neurodegenerative disease.

Synaptic Defects in Mitochondria in Alzheimer's Disease

Synaptic defects and disruption of axonal transport have also been documented in AD pathobiology.[94-97] Indeed, a previous study reported that a brief exposure of cultured hippocampal neurons to soluble Aβ molecules resulted in rapid and severe impairment of mitochondrial transport, independent of cell death and other drastic alterations of cellular structures.[98] Similarly, it was reported that soluble oligomers of Aβ are responsible for an abnormal axonal transport of mitochondria in primary hippocampal neurons, most likely contributing to an abnormal mitochondrial distribution.[99] More recently, it was proposed that mitochondrial localization to dendritic spines may be important for the trafficking of the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs), major ionotropic glutamate receptors involved in excitatory synaptic transmission, and Aβ disruption of mitochondrial trafficking could contribute to AMPAR removal and trafficking defects leading to synaptic inhibition.[100]

Parkinson's Disease

PD, the most frequent movement disorder, affects approximately 2% of individuals over 65 years of age and is clinically characterized by three phenotypic aspects: resting tremor, bradykinesia and rigidity. PD is caused by a progressive and massive loss of the dopaminergic neurons within the substantia nigra pars compacta (SNc) and the consequent depletion of the neurotransmitter dopamine (DA) in the striatum, which is required for normal motor function. One of the pathological hallmarks of PD and related synucleinopathies is the presence of intracellular inclusions called Lewy bodies, which are constituted of aggregates of the presynaptic soluble protein called α-synuclein.[101-105] The majority of PD cases are sporadic with unknown cause; however, mutations in several genes have been linked to familial form of PD.[104] Nonetheless, mitochondrial dysfunction is emerging as a key mechanism underlying the pathogenesis of both sporadic and familial forms of PD.[106,107]

In early 1990s, it was reported for the first time that there is reduced activity of the mitochondrial respiratory complex I (NADH-quinone oxidoreductase) in the SNc of PD patients.[108] In accordance, subsequent studies also reported an impairment of

mitochondrial complex I activity in the substantia nigra,[109] platelets,[110-113] lymphocytes,[114,115] and skeletal muscle tissue[116,117] from PD patients. More recently, in highly purified mitochondria, there is a PD-specific complex I deficit in the frontal cortex.[118] Meanwhile, SNc appears to be more susceptible to complex I activity impairment than other brain regions, possibly due to the exacerbated ROS generated within dopaminergic neurons as a result of DA metabolism and iron content.[119] Consistently, cybrids containing mtDNA from PD patients present a significant impairment in complex I activity associated with increased oxidative stress levels,[120] suggesting mtDNA encoded defects in PD. Moreover, Lewy bodies within these cybrids also react positively with cytochrome c antibodies, suggesting a mitochondrial origin.[121] The use of specific complex I inhibitors, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydrodropyridine (MPTP), rotenone and 6-hydroxydopamine (6-OHDA) which causes degeneration of the nigral dopaminergic neurons and PD symptoms in in vivo models, further emphasizes the involvement of mitochondria in the etiology of PD.[122-124] Furthermore, a proteomic analysis of mitochondria-enriched fractions from postmortem PD SNc revealed differential expression of multiple mitochondrial proteins in PD brain as compared to control, including complex I subunits.[125] Moreover, in vitro incubation of isolated rat brain mitochondria with recombinant human α-synuclein was shown to potentiate a dose-dependent loss of mitochondrial transmembrane potential ($\Delta\Psi m$) and phosphorylation capacity[126] (Fig. 1). However, α-synuclein did not affect the activities of respiratory chain complexes, suggesting that the former may impair mitochondrial bioenergetics by direct effect on mitochondrial membranes.[126] Finally, mortalin, a mitochondrial stress protein, is substantially decreased in PD brains and cellular models of PD,[125] being shown that the manipulation of mortalin levels in dopaminergic neurons resulted in significant alteration in sensitivity to PD phenotypes via pathways involving mitochondrial and proteasomal function as well as oxidative stress.[125]

Evidence from the literature also posits a role for mutations in genes encoding both mitochondrially targeted proteins and proteins involved in mitochondrial function and/or oxidative stress responses in PD.[127] Indeed, mitochondrial DNA haplotype analysis revealed that certain haplogroups reduced the risk for PD, which indicated that mtDNA may contribute to PD etiology.[128] Moreover, Swerdlow and collaborators[129] reported maternally inherited mutations in mtDNA in one family with PD. Using a novel single-molecule PCR approach to quantify the total burden of mtDNA molecules with deletions, it was also shown that a high proportion of individual pigmented neurons in the aged human SNc contain very high levels of mtDNA deletions.[130] The fraction of mtDNA deletions is significantly higher in COX-deficient neurons than in COX-positive neurons, suggesting that mtDNA deletions may be directly responsible for impaired cellular respiration.[130] More recently, Ekstrand and collaborators[131] created conditional knockout "MitoPark" mice, which have a disrupted mitochondrial transcription factor A (Tfam) gene in dopaminergic neurons. These knockout mice have reduced mtDNA expression and respiratory chain deficiency in midbrain dopaminergic neurons, which lead to a Parkinsonism phenotype with adult onset and characterized by slowly progressive impairment of motor function accompanied by the formation of intraneuronal inclusions and dopamine nerve cell death.[131]

Familial forms of PD are associated with mutations in leucine-rich repeat kinase 2 (LRRK2), α-synuclein, parkin, DJ1 and PTEN-induced putative kinase 1 (PINK1), these proteins being associated with the mitochondrial outer membrane and involved in ROS production or defense[132] (Fig. 1). HtrA2 is another protein that is mutated

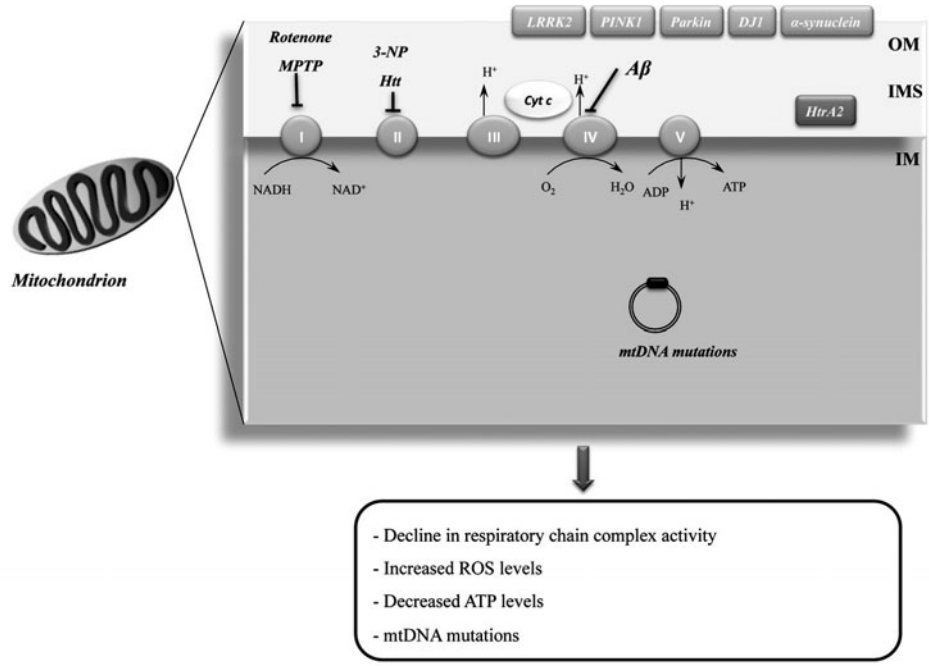

Figure 1. Involvement of mitochondrial abnormalities in Alzheimer's (AD), Parkinson's (PD) and Huntington's (HD) diseases. Impairment of the activity of respiratory chain complex IV by amyloid-β peptide (Aβ), leading to the exacerbation of reactive oxygen species (ROS) generation and ATP levels depletion, is one prominent feature of AD. Mitochondrial DNA (mtDNA) mutations also play a role in the pathogenesis of AD. Concerning PD, there is an extensively documented impairment of mitochondrial complex I activity. Indeed, the use of pharmacological inhibitors of complex I, including rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causes degeneration of the nigral dopaminergic neurons and PD symptoms in in vivo models. In addition, the familial forms of PD are associated with mutations in leucine-rich repeat kinase 2 (LRRK2), α-synuclein, parkin, DJ1 and PTEN-induced putative kinase 1 (PINK1), these proteins being associated with the mitochondrial outer membrane (OM) and involved in ROS production or defense. Also, HtrA2, which is localized in the intermembrane space (IMS) of mitochondria is mutated in familial PD. In HD, mutant huntingtin (Htt) induces a decline of mitochondrial respiration, particularly affecting mitochondrial respiratory complex II activity and ATP synthesis. The use of 3-nitropropionic acid (3-NP), a selective inhibitor of succinate dehydrogenase and complex II, was shown to recapitulate HD-like symptoms in several vertebrate models. Furthermore, mutant Htt is a causative factor of mtDNA damage in HD, suggesting that mtDNA damage is an early biomarker for HD-associated neurodegeneration. ADP- adenosine diphosphate; Cyt c- cytochrome c; IM- inner membrane; NAD^+- oxidized nicotinamide adenine dinucleotide; NADH- reduced nicotinamide adenine dinucleotide; H^+- proton.

in familial PD and localizes in the intermembrane space of mitochondria.[132] In vitro cell culture studies showed that mutant PINK1 or PINK1 knock-down induce mitochondrial respiration, ATP synthesis and proteasome function impairment and increased α-synuclein aggregation.[133] Additionally, it was reported that HtrA2 loss results in transcriptional upregulation of nuclear genes characteristic of the integrated stress response, including the transcription factor C/EBP homologous protein (CHOP), selectively in the brain.[134] HtrA2 loss also induces accumulation of unfolded proteins in the mitochondria, defective mitochondrial respiration and enhanced ROS production,

which contribute to the induction of CHOP expression and neuronal cell death.[134] Previous studies also showed that the overexpression of α-synuclein in cell culture and in transgenic mice impairs mitochondrial function and increases the susceptibility to mPTP induction.[135,136] In contrast, α-synuclein-null mice are resistant to respiratory chain inhibitors implicating an involvement of mitochondria in α-synuclein-mediated toxicity.[137,138] Recently, compelling evidence demonstrated that both PINK1 and Parkin mediate the degradation of damaged mitochondria via selective autophagy (mitophagy),[139-142] the voltage-dependent anion channel 1 emerging as a target of PINK1/Parkin-mediated mitophagy.[143] Indeed, it was suggested that Parkin, together with PINK1, modulates mitochondrial trafficking, especially to the perinuclear region, a subcellular area associated with autophagy. In this way, mutations in either Parkin or PINK1 could culminate in altering mitochondrial turnover which, in turn, may cause the accumulation of defective mitochondria and, ultimately, neurodegeneration. In fact, Geisler and collaborators[144] demonstrated that PINK1 mutations compromise the selective degradation of depolarized mitochondria, mainly due to the decreased physical binding activity of PD-linked PINK1 mutations to Parkin. Thus, PINK1 mutations abrogate autophagy of impaired mitochondria upstream of Parkin. In addition to compromised PINK1 kinase activity, reduced binding of PINK1 to Parkin leads to failure in Parkin mitochondrial translocation, resulting in the accumulation of damaged mitochondria, contributing to the pathogenesis of PD.[144]

Moreover, the PINK1/Parkin pathway also regulates the mitochondrial integrity and morphology via the fission/fusion machinery. Genetic studies in *Drosophila* also demonstrated that the PINK1/Parkin pathway promotes mitochondrial fission and that the loss of mitochondrial and tissue integrity in PINK1 and parkin mutants derives from reduced mitochondrial fission.[145] Accordingly, the PINK1/parkin pathway promotes mitochondrial fission and/or inhibits fusion by negatively regulating Mfn and OPA1 function and/or positively regulating drp1 in *Drosophila*.[146] Moreover, Lutz and collaborators[147] demonstrated that Parkin- or PINK1-deficient SH-SY5Y cells showed a significant increase in the percentage of cells with truncated or fragmented mitochondria along with a decrease in cellular ATP production. The mitochondrial phenotype could morphologically and functionally be prevented by the enhanced expression of Mfn2, OPA1, or dominant negative Drp1, suggesting that a decrease in mitochondrial fusion or an increase in fission is associated with a loss of parkin or PINK1 function.[147] Notably, genetic manipulations and treatment with the small molecule mitochondrial division inhibitor (mdivi-1), which inhibits Drp1, both structural and functional mitochondrial defects induced by mutant PINK1 were attenuated, highlighting a potential therapeutic strategy for PD.[148]

Huntington's Disease

HD is an autosomal dominant neurological disorder caused by an abnormal polyglutamine (polyQ) expansion within a single gene, huntingtin (Htt), leading to the progressive loss of striatal and cortical neurons and consequent decline of cognitive and motor functions.[149] Several lines of evidence indicate that the expression of mutant Htt is associated with mitochondrial dysfunction, in both HD patients and mouse transgenic HD models[150] (Fig. 1). A pronounced decrease in glucose metabolism and a corresponding increase in lactate were documented in affected brain regions of

HD patients, which suggest a bioenergetic defect.[151] In addition, impaired activity of mitochondrial respiratory complexes II, III and IV was found in postmortem brain of HD patients.[152] Similarly, striatal cells from mtHtt mice exhibit impairment of mitochondrial respiration and ATP synthesis.[153] Conversely, it was observed that the expression of complex II subunits in striatal neurons expressing mutant Htt exon 1 restores complex II respiratory activity and protects against cell death.[151] Panov and collaborators[154] also observed that mitochondria isolated from lymphocytes of HD patients have lowered buffering capacity and their $\Delta\Psi m$ depolarizes earlier at lower Ca^{2+} concentrations, proposing that mitochondrial Ca^{2+} abnormalities occur early in HD pathogenesis and may be a direct effect of mutant Htt on the organelle. To further emphasize the role of mitochondrial respiratory chain inhibition in HD pathogenesis, it has been shown that the use of 3-nitropropionic acid (3-NP), a selective inhibitor of SDH and complex II, recapitulates the loss of medium spiny neurons in the substantia nigra and HD-like symptoms in several vertebrate models.[155,156] Additionally, humans exposed to 3-NP also exhibit similar motor dysfunction to that found in HD patients.[156-158] Evidence from the literature also demonstrated that HD patients had higher frequencies of mtDNA deletions in lymphocytes in comparison to the controls, which suggest that CAG repeats instability and mutant Htt are causative factors in mtDNA damage.[159] More recently, Acevedo-Torres and coworkers[160] suggested that mtDNA damage is an early biomarker for HD-associated neurodegeneration, supporting the hypothesis that mtDNA lesions might contribute to HD pathogenesis.

Ultrastructral changes in mitochondria were also reported in HD, raising the possibility for interplay between HD and mitochondrial dynamics.[161] In fact, in rat cortical neurons it was demonstrated that 3-NP exposure leads to fragmentation and condensation of mitochondria, which can be prevented by antioxidant treatment.[162] Accordingly, Wang and collaborators[163] found that mitochondria in HeLa cells over-expressing a mutant Htt with a 74 glutamine repeat (Htt74Q) show fragmentation of mitochondria, reduced mitochondrial fusion, reduced ATP and increased cell death. On the other hand, expression of either dominant-negative Drp1 or Mfn2 restores ATP levels and attenuates cell death.[163] Additionally, mutant Htt was shown to promote a mitochondrial morphologic alteration from an elongated to a round phenotype, which correlates with a blockage in mitochondrial movement.[164,165]

Overall, mitochondrial impairment plays a key role in HD pathogenesis, such that expression of mtHtt culminates in abnormal mitochondrial ultrastructure, impaired Ca^{2+} buffering, bioenergetic defects and mtDNA deletions and damage.

CONCLUSION

Altogether, we highlighted here the clear role of mitochondrial abnormalities, including disturbances in mitochondrial machinery, dynamics and turnover in the onset and/or progression of neurodegenerative diseases, including AD, PD and HD. Mitochondrial disturbances provide a common target for combating the various abnormalities caused by the specific protein substrates of the genetic mutations, the resulting energy imbalance and the increased ROS. That said, it will be important to dissect all the key mitochondrial-dependent pathogenic mechanisms underlying neurodegeneration, which can be useful to develop new therapeutic interventions to prevent and/or mitigate age-related neurodegenerative diseases.

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