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Mitochondrial Biology and Neurological Diseases

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Abstract: Mitochondria are extremely active organelles that perform a variety of roles in the cell including energy production, regulation of calcium homeostasis, apoptosis, and population maintenance through fission and fusion. Mitochondrial dysfunction in the form of oxidative stress and mutations can contribute to the pathogenesis of various neurodegenerative diseases such as Parkinson's (PD), Alzheimer's (AD), and Huntington's diseases (HD). Abnormalities of Complex I function in the electron transport chain have been implicated in some neurodegenerative diseases, inhibiting ATP production and generating reactive oxygen species that can cause major damage to mitochondria.

Mutations in both nuclear and mitochondrial DNA can contribute to neurodegenerative disease, although the pathogenesis of these conditions tends to focus on nuclear mutations. In PD, nuclear genome mutations in the PINK1 and parkin genes have been implicated in neurodegeneration [1], while mutations in APP, PSEN1 and PSEN2 have been implicated in a variety of clinical symptoms of AD [5]. Mutant htt protein is known to cause HD [2]. Much progress has been made to determine some causes of these neurodegenerative diseases, though permanent treatments have yet to be developed. In this review, we discuss the roles of mitochondrial dysfunction in the pathogenesis of these diseases.

Keywords: Alzheimer's disease, huntington's disease, mitochondrial dysfunction, neurodegeneration, Parkinson's disease.

1. INTRODUCTION

Mitochondria are dynamic organelles that perform many important roles in the cell. First observed in the 1840s, the mitochondrion, whose name was coined in 1898 by Carl Benda, supplies energy to the cell through a process known as oxidative respiration. The origin of the mitochondria, known as the Endosymbiotic Theory, states that mitochondria were once aerobic bacteria capable of performing oxidative respiration that were subsequently engulfed by anaerobic eukaryotic cells. These eukaryotic cells and aerobic bacteria formed a symbiotic relationship in which the aerobic bacteria generated energy for the cell efficiently through oxidative respiration. Through evolution, these bacteria evolved into the modern mitochondria [3].

The Electron Transport Chain (ETC) is one of the hallmarks of mitochondria, and one of the most vital components of energy production. Since the majority of ATP is produced in the ETC, it is crucial for cells that the chain works properly. The ETC is separated into two processes: electron transfer and formation of the proton gradient across the membrane. Dysfunction at different complexes in the ETC, either by genetic or exogenous factors, can contribute to the neurodegenerative diseases mentioned earlier. For example, the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) inhibits the protein NADH:ubiquinone oxidoreductase (Complex I) from pumping protons across the mitochondrial membrane and thereby prevents the formation of the electrochemical gradient. This blockade hinders ATP production and subsequently induces energetic failure [4]. The pathological effects of the defects in mitochondrial respiration will be discussed later.

Neurodegenerative diseases that have correlations with mitochondrial dysfunction and mtDNA defects are PD, AD, and HD. PD is characterized by loss of pigmented dopaminergic neurons in substantia nigra pars compacta, leading to resting tremor, rigidity, bradykinesia, and postural instability. Cellular pathological characteristics include electron transport chain dysfunction, particularly complex I defects, and increased levels of reactive oxygen species. Nuclear mutations in PARK2, PARK8, and PINK1 have been implicated in Parkinsonian symptoms [1]. AD is another common condition that affects memory, cognition, and behavior. Pathologically, AD is characterized by accumulation of beta-amyloid proteins and neurofibrillary tangles composed of aggregates of hyper-phosphorylated tau protein. Mutations in APP, PSEN1, and PSEN2 were shown in Alzheimer's disease [5]. HD is a neurodegenerative disease that affects muscle coordination and leads to cognitive decline and psychiatric disability. It was shown that changes in the ETC resulting in the overproduction of ROS and alterations in mitochondrial dynamics, specifically disruption of fission-fusion balance, can contribute to neuronal death in HD [2]. These neurodegenerative diseases and their relation to mitochondrial dysfunction will be discussed in detail.

2. THE GENETICS OF NEURODEGENERATIVE DISEASES

In PD, mutations in genes encoding α-synuclein (SNCA), parkin (encoded by PARK2), PINK1, and LRRK2 (encoded

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by PARK8) (see Table **1**) have resulted in protein aggregation and induced mitochondrial dysfunction and oxidative stress that characterize PD [6-8]. Mutations in POLG were also shown to contribute to the pathogenesis of PD. Knockdown of POLG in *Drosophila* led to decreased expression in mitochondrial respiratory chain subunits such as cytochrome c oxidase subunits I and III, and cytochrome b. It was also seen that the lifespan of affected *Drosophila* was significantly decreased in adult flies, showing that knockdown of POLG in adult *Drosophila* flies induced shorter lifespan [9].

In AD, mutations in APP, PSEN1, and PSEN2 have been implicated in disease pathogenesis (Table **1**). APP (human amyloid precursor protein) becomes characteristically unfolded and tangled, forming plaques that become toxic to neurons, directly contributing to neurodegeneration [10]. The presenilin (PSEN1/PSEN2) genes contribute components to the gamma-secretase complex, which cleaves APP. Thus, mutations in the secretase can directly result in the accumulation of aberrantly folded APP tangles [11].

In HD, the aberrant repetition of the CAG trinucleotide sequence in exon 1 of the huntingtin gene has been known to induce symptoms of this disease [12] (Table **1**). The expanded CAG repeat typically characterizes HD, but the length of the repeat was shown to vary between generations. For example, some males have been observed to pass larger repeat lengths to their progeny, and these transmissions could potentially cause early-onset HD at a younger age. Another genetic condition by the name of "Huntington's disease-like 2" was caused by a mutation, which is similar to Huntington's disease. It is a CTG/CAG in the spliced exon following exon 1 of the junctophilin-3 gene, resulting in neurodegeneration. Although this mutation does not directly cause Huntington's disease, it indicates that this type of mutations may lead to characteristics that parallel Huntington symptoms [13].

Mitochondria contain their own genome and, similar to bacteria, replicate through binary fission. They are extremely important organelles, supplying energy to the entire cell and regulating apoptosis. Their DNA is different from that of the nuclear genome in that it is circular. Mitochondrial DNA (mtDNA) is ~16.6kb long, double-stranded, and is comprised of 37 genes, of which 13 encode for the proteins involved in ATP production, while the other 24 encode for proteins involved in mtDNA translation within the

Table 1. Genes associated with neurodegenerative disease pathogenesis.

Neurodegenerative Disease	Gene	Function
Parkinson Disease *adapted from Verstraeten *et al.* 2015 [1]	SNCA (PARK1)	Encodes a-synuclein, the primary component in Lewy bodies [14]
	PARK2	E3 ubiquitin ligase, protein degradation [15]
	PINK1 (PARK6)	Serine/threonine kinase, stress-induced mitochondrial response [15]
	DJ-1 (PARK7)	Antioxidant and oxidative stress sensor [15]
	LRRK2 (PARK8)	Leucine-rich repeat kinase 2, scaffold protein function. Overall function unknown [15]
	ATP13A2 (PARK9)	Lysosomal transmembrane ATPase protein, necessary for lysosomal function [16]
	PLA2G6 (PARK14)	Encodes iPLA2-VI, cell membrane homeostasis [18]
	FBXO7 (PARK15)	F-box-containing protein, protection of neurons and apoptosis inhibitor [17]
	VPS35 (PARK17)	Subunit of retromer complex, involved in Golgi endosomal transport [19]
	EIF4G1 (PARK18)	Eukaryotic translation initiation factor 4-gamma 1, translation initiation [20]
	DNAJC6	Encodes auxilin, synaptic vesicle recycling [21]
	ATP6AP2	(Pro)renin receptor, glucose metabolism [22]
	COQ2	Ubiquinone, mitochondrial electron transport chain [23]
	SYNJ1	Encodes synaptojanin 1, synaptic vesicle recycling [21]
	DNAJC13	Regulation of endosomal clathrin coats [24]
Alzheimer's Disease *adapted from Vilatela *et al.* 2012 [25]	APP	Transmembrane protein, amyloid plaques in AD [26]
	PSEN1	Component of gamma-secretase, cleaves APP [26]
	PSEN2	Component of gamma-secretase, cleaves APP [26]
	APOE	Glycoprotein, cholesterol distribution [26]
Huntington's disease	Huntingtin	Aggregation leads to neurodegeneration [27]

mitochondria. Mutations have been implicated in neurodegenerative diseases such as Parkinson's, Alzheimer's, and Huntington's diseases. However, the existence of multiple versions of mtDNA complicates the potential for somatic mtDNA mutations contributing to disease, since the effects of any deleterious mutations are diminished in a pool of alleles.

Interestingly, mtDNA mutations were seen to accumulate over the course of Parkinson's disease, with the amount of mutations seen to correlate with severity and burden of the disease in a rat model [28]. Selective damage to mtDNA may also serve as a marker of disease in nigral neurons [29]. These somatic mutations in mtDNA may contribute to disease progression due to ETC dysfunction [30]. mtDNA haplotypes have had controversial associations with disease. For example, one study examining a set of families with history of PD sought to determine maternal inheritance within the pedigrees, but did not identify any strong haplotype associations [31]. Large numbers of studies have explored mitochondrial haplotypes within specific populations, identifying specific loci of mtDNA mutations statistically associated with PD. None have been consistently implicated across all studied ethnic populations [32, 33]. However, a recent meta analysis revealed specific 'super-haplogroups' that statistically show higher risk of developing PD [34].

While mtDNA damage can be associated with burden of disease in PD, there is a possibility that mtDNA methylation may serve as a biomarker for diseases such as AD [35]. Additionally, it does not seem likely that the degree of mtDNA damage correlates with severity of AD symptoms [36]. However, studies have looked into specific mitochondrial defects associated with AD. Specific mtDNA mutations have been associated with the disease, resulting in elevated oxidative damage. Specific haplogroups have also been proposed as associated with AD, albeit in specific study groups [37]. One particular excision, mtDNAdelta4977, has been correlated with late-onset AD, although further work needs to be performed to understand the vast heterogeneity of this particular mutation across cell types and brain structures [38]. Other studies have been less optimistic, failing to reproduce statistically significant correlations from previous work [39, 40].

There is conflicting evidence for the association of specific mitochondrial haplogroups with HD [41, 42]. However, over the course of disease in HD, buildup of mitochondrial damage can potentiate some of the symptoms of neurodegeneration [43, 44]. Targeted antioxidant delivery to mtDNA prevents the buildup of damage in HD and can mitigate the severity of disease [45].

Mitochondrial mutations potently affect tissues that require large amounts of ATP to function, such as brain and heart tissue, and thus, cause an array of disease. The aging process has been closely associated with many neurodegenerative diseases and other disorders. Mutations and age exhibit a direct variation, meaning that as age increases, the number of mutations in mtDNA increases, and as these mutations accumulate, the efficiency of ETC decreases, lowering the levels of ATP in cells and causing increased levels of ROS [37]. This creates a vicious cycle because more mutations accumulate as ROS damages the efficiency of the ETC, in turn leading to an increased production of ROS [37]. This can be explained by gradual accumulation of mutations, especially large-scale deletions and point mutations, which can cause a decline in mitochondrial function [46]. It was observed that loss of function mutations in PINK1 are able to potentiate the apoptosis pathway. It was found that PINK1-deficient cells were sensitive to toxin STS, which opens the mitochondrial transition pore and releases cytochrome c, inducing apoptosis [47]. In addition, Bax translocation from cytosol to mitochondria and the cytochrome c release occur significantly earlier in PINK1 deficient cells than in normal cells, leading to increased activation of caspases [47].

2.1. Mitochondrial Dynamics- Fusion, Fission, and Motility

Balance between mitochondrial fusion (the combination of two smaller mitochondria into a single organelle) and fission (division of one large mitochondrion into two smaller fragments) is crucial. Fusion is essential for active cells because it allows enzymes and metabolites to spread efficiently throughout the mitochondrial compartments, slowing down the aging process. Fusion has also been shown to improve the stability of mtDNA. Fission, on the other hand, plays vital roles in the scavenging of damaged organelles by autophagy, as it is easier to select damaged mitochondria if they are smaller in size [48]. Disrupting the fusion-fission balance can result in mitochondrial dysfunction, which leads to subsequent reduction in ATP production.

First observed in *Drosophila melanogaster,* the fuzzy onion (FZO) proteins were shown to regulate mitochondrial fusion during spermatogenesis. FZO is the first member of a group of proteins called mitofusins, which regulate mitochondrial fusion in yeast and humans and are large GTPases [48]. In mammals, fusion is regulated by mitofusins (Mfn), which aredynamin-related GTPases, and optic dominant atrophy 1 (Opa1). Mitofusins (Mfn1 and Mfn2) are located in the outer mitochondrial membrane (OMM) and fuse the OMMs of neighboring tubules through various interactions. In mammals, Opa1, located in the inner mitochondrial membrane (IMM), fuses the inner membranes together, and possibly works with mitofusins to help with the fusion of the OMM and IMM [49]. The MIEF1 protein (mitochondrial elongation factor 1) is a mitochondrial outer membrane protein that plays a role in mitochondrial fission and fusion. MIEF1 interacts with the fission protein Drp1 and induces the translocation of Drp Ifrom cytoplasm to the mitochondria [50]. In mitochondria, the MIEF1 gene, when overexpressed, results in excessive fusion. However, when it is under-expressed, it leads to excessively fragmented mitochondria [50].

Mitochondrial fission is regulated by a GTPase called dynamin-related protein (Drp1). It is known as Fis1in humans. The fission proteins shape into helices through many interactions, but GTP hydrolysis is induced when one of the helices completes a rotation, igniting the enzymatic activity needed to split the mitochondria into two [49].

In neurons and other cells, high levels of ATP are needed for synaptic transmission. Therefore, mitochondria are required to supply the cells with the necessary amount of energy. Mitochondria move along cytoskeletal tracks made up of either microtubules or actin filaments [51]. For short distances, mitochondria usually travel along actin filaments and require myosin motors. However, for longer distances, mitochondria travel along microtubules that require dynein or dynactin for backward movement and kinesin for forward movement [51]. Defects in fusion and fission were shown to hinder mitochondrial movement. Mfn2 most likely plays a role in maintaining microtubule structures, so defects in Mfn2 readily affect mitochondrial motility, since mitochondria move along tracks comprised of microtubules [52]. For example, if the fission-fusion ratio were higher, then the plethora of mitochondria in the cell would hinder efficient movement. In the cell, proteins Miro1and Miro2 play vital roles in mitochondrial motility. If these proteins are damaged or unavailable, the number of mitochondria in neurons could be depleted, resulting in defects in neurotransmission. It was shown that defects in mitochondrial transmission at Miro may contribute to the pathogenesis of Alzheimer's disease. In a study by Iijima-Ando *et al*. 2012, it was shown that cells of *Drosophila* lacking Miroand another mitochondrial protein Milton possess axons lacking mitochondria, which increases tau phosphorylation and induces neuronal death. In the same study, it was also observed that knockdown of Miltonor Miroincreases tau phosphorylation at Ser262 through Par-1, which stimulates separation of tau from microtubules [53]. Therefore, dysfunction in mitochondria motility at Miro or Milton could manifest tau phosphorylation at Ser262, and cause neurodegeneration.

It has also been shown that PINK1 and parkin play major roles in the mitochondrial degradation pathway. When mitochondrial membrane potential is reduced, PINK1 accumulates on the OMM, and then recruits parkin from the cytosol. This recruitment in turn allows for the activation of mitophagy, or the engulfing of damaged mitochondria. In a study by Ashrafi *et al*. 2014, it was shown that mitophagy of damaged mitochondria takes place away from the center of neurons, and also depends on PINK1 and parkin [54]. Mitophagy of depolarized axonal mitochondria occurred due to the recruitment of parkin by PINK1. As shown in the study, mitophagy occurred in depolarized axonal mitochondria, and since mitochondria in axon are few in number and fragmented, mutations in PINK1 and parkin could significantly affect the mitochondrial degradation pathway with subsequent impairment in the clearing of damaged mitochondria [54].

Mutations in PINK1 have been known to alter the fission-fusion machinery and ultimately contribute to pathogenesis of Parkinson's disease. In a study by Y.Yang *et al*. 2008, it was further shown that PINK1 acts through Fis1 and Drp1 to regulate mitochondrial fission [55]. In an experiment conducted by Dadga *et al*. 2009, overexpression of wild-type PINK1 induced mitochondrial fusion as the mitochondria were less fragmented and more elongated. Knockdown of PINK1, however, resulted in increased fragmentation of mitochondria, showing that PINK1 and mutations in PINK1 do play a role in the fission-fusion machinery of mitochondria [56].

In Huntington's disease, the fission-fusion machinery of mitochondria is disrupted. It was shown by Shirendeb *et al*. 2011 that mitochondrial fission was promoted and mitochondrial fusion proteins such as Mfn2 were downregulated at Grades III and IV of HD. Mitofusins are even further downregulated as the severity of HD increased. The increase in fission found in later stages of HD possibly contributed to mitochondrial swelling in cortex and striatum. The increase in fission and downregulation of fusion proteins may also result in increased polyQ (polyglutamine tracts, or a series of glutamine residues) repeats that characterize HD, leading to progressive neurodegeneration [57]. Abnormalities in PINK1, parkin, and alpha-synuclein can also contribute to disruptions of the fission-fusion dynamics in PD [58-60]. Disruptions to mitochondrial homeostasis and dynamics have also been observed in AD, in part due to interaction between key proteins and hyperphosphorylated tau [61-63].

2.2. Apoptosis

Apoptosis, a form of programmed cell death (PCD), is a process in which molecular programs in the cell are activated to cause its own destruction, which is useful in defending against infected or hyper-proliferative cells. The balance between cell death and cell proliferation is vital in order for physiological processes to function properly. Disruption in apoptosis disturbs the proliferation-death balance, and can attribute to some neurodegenerative disorders, such as Parkinson's disease [64], and other diseases regulated and induced by ROS [65]. Apoptosis is regulated by mitochondria and is characterized by condensation and schism of DNA, decrease in size of the cell, and lastly, removal by the phagocyte [65].

Mitochondria contain several molecules, which, when released into the cytosol, activate caspase-dependent or caspase-independent pathways that initiate apoptosis. Several proteins of the Bcl-2 family regulate this process; Bcl-2 and Bcl-xL inhibit apoptosis, whereas Bax and Bak promote cell death. The pro-apoptotic proteins Bax and Bak operate by inserting themselves into mitochondrial membranes, where apoptogenic factors such as cytochrome *c* can be released through the mitochondrial permeability transition pore (PTP) or other channels throughout the membrane. A study conducted by Perier *et al*. 2005 used MPTP-intoxicated mice to initiate uncontrolled apoptosis [66]. Complex I inhibition does not release cytochrome *c* from the mitochondria but merely increases the amount of soluble cytochrome *c* in the intermembrane space, which Bax uses to initiate apoptosis. Elevated levels of soluble cytochrome c can lead to the increased incidence of cell death seen in neurodegeneration [66].

Caspases are a family of proteases that play a role in apoptosis. Caspase-6 is known to cleave mutant htt, which in turn, causes neurodegeneration in Huntington's disease [67]. Active caspase-6 exists in brains of early onset HD patients, where the caspase levels correlate with CAG repeat number. It was observed that when mice expressed resistance to

caspase-6 cleaving the mutant htt, the mice retained normal neuronal function and neurodegeneration did not occur [67]. In Alzheimer's disease, apoptosis plays a major role as well. Protein phosphatases play major roles in the cell including metabolism, cell division, and growth. Knockdown of phosphotyrosyl phosphatase activator (PTPA) was observed in Alzheimer's disease to induce apoptosis [68]. Hyperphosphorylated tau protein aggregates also characterize AD. In the aforementioned study, it was also shown that knockdown of PTPA resulted in the increase of phosphorylation of tyrosine 307 and the decrease of methylation of leucine 309, thereby inducing the phosphorylation of tau protein [68].

Mitochondrial dysfunction also leads to elevated levels of ROS that affects the cell-death signaling pathway. In a study conducted by Maharjan *et al*. 2014, it was shown that inhibition of the ubiquitin-proteasome pathway reduced the mitochondrial membrane potential and produced excess amount of ROS, leading to oxidative damage and cell death [69]. The ubiquitin-proteasome pathway mediates protein death by eliminating damaged or disfigured proteins. Genetic mutations in the ubiquitin-proteasome system lead to an accumulation of misfolded proteins, allowing ROS to be generated through interactions with redox-active ions [69]. The study examined changes in ROS production and redox state following proteasome inhibition. It was found that levels of polyubiquitinated proteins were significantly increased, resulting in cytosolic oxidative state and loss of membrane potential [69]. ROS can be attenuated by the administration of resveratrol [70], and sesamin [71], which increase expression of antioxidant enzymes and minimize the harmful effects of ROS. Although resveratrol did not decrease the accumulation of polyubiquitinated proteins, it did stabilize the oxidative state and improve the cell's overall health [69].

It was observed in a study by Wood-Kaczmar *et al*. 2008 that loss of function mutations in PINK1 can lead to early signals for apoptosis. It was found that PINK1-deficient cells were sensitive to the toxin STS, which opens the mitochondrial transition pore and releases cytochromec, inducing Bax translocation and subsequent apoptosis. Additionally, Bax translocation from cytosol to mitochondria and cytochrome c release occurs significantly earlier than in cells with PINK1, leading to increased activation of caspase, resulting in neurodegeneration [47].

3. MITOCHONDRIAL RESPIRATION DEFECTS

3.1. Electron Transport Chain Dysfunction

Various disorders have been associated with mutations in nuclear genes encoding proteins responsible for the maintenance of mtDNA and ensuring its proper function. These errors possibly contribute to the pathogenesis of various neurodegenerative diseases such as PD, AD, and HD. Mitochondria play major roles in the production of the ATP, most of which is produced through the Electron Transport Chain (ETC). Electrons produced from energy substrates such as NADH and $FADH_2$ are transported through the different protein complexes to molecular oxygen, which is then reduced to water. Simultaneously, protons are pumped by Complexes I, III, and IV, across the inner mitochondrial membrane to generate an electrochemical gradient, which is used by ATP Synthase to produce ATP. However, dysfunction at Complex I can result in a reduction of ATP production and lead to bioenergetic failure. ROS are normal byproducts of cellular metabolism that can have damaging effects on the mitochondria and cell if they are not suppressed properly by cellular antioxidants. With Complex I blockade, the amount of ROS produced increases due to a higher proportion of oxygen being converted into free radicals. Inhibition of Complex I function has been demonstrated to result in parkinsonian-like symptoms. Increased ROS levels in the mitochondria due to Complex I blockade can damage cellular proteins, lipids, and DNA [51].

Interestingly, deficiencies in different complexes of the ETC are associated with various neurodegenerative diseases; Complex I with PD, Complex II with HD, and Complex IV with AD. It is important to note, however, that this complex dysfunction is not absolutely specific for a particular disease. For example, in a study by Cottrell *et al*. 2002, it was shown that regions of central nervous system most affected by neurodegeneration also possessed Complex IV deficiency. It was suggested that in regions with higher chance of oxidative phosphorylation dysfunction, there would be a higher loss of neurons with Complex IV deficiency. It was also shown that Complex IV deficient neurons have a strong presence in AD when compared to normal brains, and this Complex IV deficiency could be caused by increased levels of mutant mtDNA, resulting in oxidative damage [72]. In a study by Tabrizi *et al*. 1999, it was shown that severe deficiencies of Complex II and III have been seen in HD brains. Aconitase inhibition was increased most significantly in presence of nitric oxides, suggesting that with aconitase inhibition comes complex II and complex III inhibition, creating a further cycle of ROS generation [73].

PINK1 deficiency has been observed to cause mitochondrial dysfunction and ROS generation. In an experiment conducted by Wood-Kaczmar *et al*. 2008, PINK1 decreased the mitochondrial membrane potential, reducing the proton gradient needed to produce ATP, thus explaining the decreased ATP levels observed in PINK1 knockout models [47]. Levels of antioxidant glutathione were significantly decreased, supporting the evidence that mitochondria and antioxidants were severely damaged due to oxidative stress. Decreased levels of antioxidants were unable to protect against increased concentrations of ROS, leading to widespread cellular damage and dysfunction [47].

SIRT3, one of the members of the sirtuin family that localizes to the mitochondria, has been associated with extended lifespan in humans and possesses roles in metabolism, antioxidant defenses, and neuroprotection [74]. Sirtuins are NAD+ dependent deacetylases localized to nucleus or mitochondria. An indirect relationship exists between antioxidant defenses and aging; as age increases, the amount of antioxidants in mitochondria decreases significantly. SIRT3 protects against oxidative stress and reduces ROS levels by targeting antioxidant enzymes. In mitochondria, SIRT3 deacetylates manganese superoxide dismutase (MnSod), increasing its antioxidant activity [74].

Thus, neuroprotection mediated by sirtuins may be due to direct protective effects on mitochondria.

4. NEUROLOGICAL DISEASE CORRELATED WITH MITOCHONDRIA

4.1. Parkinson's Disease

Parkinson's disease (PD) is one of the most common neurodegenerative disorders and is correlated with aging and mitochondrial dysfunction. PD is characterized by loss of pigmented dopaminergic neurons in substantia nigra pars compacta, leading to resting tremor, rigidity, bradykinesia, and postural instability. One potential pathogenesis for PD was implicated in defective mitochondrial respiration specifically at Complex I, though in the past few years, it has been found that mutations and other mitochondrial dysfunctions have been able to induce this disease. In Langston *et al*. 1983 [75], dysfunction at Complex I first emerged when it was observed that drug abusers were exposed to a neurotoxin MPTP(1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). MPTP, which is an inhibitor of complex I, results in irreversible parkinsonian syndrome with features similar to PD [75]. Currently, therapeutics attenuate symptoms of PD, but there are no treatments that permanently and completely halt neurodegeneration.

Though environmental toxins and aging had been long thought to induce PD, it has been recently observed that genetic mutations also play major roles in exacerbating parkinsonian symptoms. In PD, the genes PARK2 and PINK1 are associated with autosomal recessive forms, while SNCA is affiliated with autosomal dominant forms of PD [76]. Mutations in SNCA gene induce aberrant versions of α-synucleinprone to aggregation, which were observed to be a component of Lewy bodies [76]. Mutations in α-synuclein and PINK1 were shown to induce sporadic PD. PINK1 is localized to the mitochondria and was shown to protect against neuronal death during cases of acute oxidative stress. In a study conducted by Oliveras-Salvas *et al*. 2014 [77], it was shown that downregulation of PINK1 resulted in accumulation of α-synuclein and a greater number of apoptotic cells. It has also been shown that α-synuclein promotes oxidative damage [77]. In the absence of PINK1, the toxicity of α-synuclein is sufficient to cause neurodegeneration in susbtantia nigra pars compacta and mitochondrial dysfunction. Also, mitochondrial import and accumulation of α-synuclein hamper Complex I processes and induce neurodegeneration in dopaminergic neurons. In a study by Devi *et al*. 2008 [78], it was shown that accumulation of α-synuclein resulted in Complex I dysfunction and an imbalance between ROS production and antioxidant levels. In this study, it was observed that A53T/syn FLAG cells (cells with α-synuclein accumulation) possessed a decrease in complex I activity and elevated ROS levels. These results were substantiated by the observation that α-synuclein accumulated appreciably in mitochondria merely 20 hours after starting the experiment [78].

In PD, the downregulation of PINK1 has effects on the balance between mitochondrial fission and fusion. In an experiment conducted by Rojas-Charry *et al*. 2014, it was shown that fission was favored when PINK1 was absent as indicated by the increased appearance of fragmented mitochondria when compared to cells with PINK1 [60]. In PINK1-absent cells, Drp1 and Mfn2 levels were significantly lower when compared to control cells with PINK1. In contrast, Fis1 expression increased greatly in PINK1-absent cells compared to cells with PINK1. In addition, when PINK1 is downregulated, the number of cells possessing fragmented mitochondria increased in PINK1-absent cells [60]. Fis1 expression is increased due to calcium accumulation and changes in membrane potential, preventing formation of electrochemical gradient and promoting overproduction of ROS. PINK1 also regulates cell death and interacts with Parkin to do so. However, the absence of PINK1 compromises the apoptotic cycle, ultimately leading to neuronal death [56]. Thus, PINK1 is crucial for neurons because its absence induces significant decrease in Mfn2 and an increase in Fis1, promoting fission rather than fusion. Dysfunction in the mitochondrial apoptotic pathway can be caused by aging and mutations in PINK1 [79]. Small amounts of stress contributed to inhibition of PINK1 and downregulation of autophagy proteins such as Beclin and LC3. Astrocytes deficient in PINK1 demonstrated impaired cell growth, potentially due to aberrant apoptosis [79].

The PARK2 gene is affiliated with autosomal recessive PD, and mutations in PARK2 account for almost 10% of the PD patients with onset before 50 years [80]. Parkin, encoded by the PARK2 gene, is an E3 ligase, which regulates the substrate RTP801 and mediates neuronal death in PD. In a study by Romani-Audeles *et al*. 2014 [81], it was proposed that one way to avert neurodegeneration is by preventing the accumulation of RTP801 protein levels. In parkin-knockout mice, a small increase in RTP801 was found, but the data suggests that even this minor accumulation contributed to motor and behavioral impairments and oxidative stress. Loss-of-function mutations in the PARKIN gene have been shown to lead to the accumulation of RTP801, which induces neurodegeneration and PD [81]. Mutations in PARK8 encoding LRRK2 have been observed to contribute to the pathogenesis of PD [82]. For example, the LRRK2 G2019S mutation causes visual degeneration and mitochondrial impairments in retinal dopaminergic neurons, due to increased kinase activity of the enzyme [82]. LRRK2 also plays a major role in protein homeostasis. Loss of LRRK2 leads to accumulation of α-synuclein and increased production of ROS [83].

Damage to mtDNA can also cause oxidative stress, genetic and protein instability, compromised energy production, and cell death. An environmental toxin, rotenone, was shown to cause mitochondrial dysfunction combined with mtDNA damage. Sanders *et al*. 2014 [29] found that mtDNA contained apurinic and apyrimidinic regions, where portions of DNA lost either purine or pyrimidine bases [29]. These base losses (potentially mediated by ROS) render the DNA 'genotoxic' such that mitochondrial DNA polymerase is inhibited from sliding along the DNA during replication and transcription. Polymerase γ, the mtDNA polymerase, pauses at these damaged sites, resulting in cessation of the replication process. This blockage inevitably leads to impaired

respiration and mitochondrial dysfunction. Rotenone is a pesticide that has been observed to cause mitochondrial dysfunction, resulting in oxidative damage. When rats were injected with rotenone, the majority of base loss was found in tyrosine hydroxylase neurons. mtDNA lesions induced by rotenone treatment through oxidative stress appeared to inhibit polymerases from interacting with and replicating DNA [29].

4.2. Alzheimer's Disease

Alzheimer's disease (AD) is another common neurodegenerative disease that affects memory, cognition, and behavior [5]. AD accounts for around 60-80% of dementia cases, and gradually worsens over time. In the early stages of AD, symptoms are mild, with minimal memory loss, but in the late stages, memory loss becomes severe and serious neurodegeneration is evident [5]. Pathologically, AD is characterized by accumulation of beta-amyloid proteins and neurofibrillary tangles composed of aggregates of hyper-phosphorylated tau protein [5].

Mild cognitive impairment (MCI) occurs in the primary predementia stage of Alzheimer's disease. Since patients with MCI typically progress to AD, it can be important therapeutically to determine early on the causes underlying MCI to predict further neurodegeneration. In a study conducted by Gan *et al*. 2014, it was noticed that the fission-fusion balance was disrupted in cybrid (cytoplasmic hybrid) cells, with fusion being favored [84]. Mitochondria from the neurons of MCI patients were combined with neuronal cells originally lacking endogenous mtDNA, using the cybrid model. Cybrid cells are produced by the fusion of a whole cell with a cytoplast, mixing the nuclear genes from one cell with mitochondrial genes of another cell, thereby allowing distinction of mitochondria's role in inducing disease. In this study, mitochondria from MCI or age-matched non-MCI subjects were incorporated into a human neuronal cell line, which is depleted of endogenous mitochondrial DNA. In non-MCI cells, mitochondria were highly distributed and more rod like, suggesting a balance between fusion and fission. In MCI cybrid cells, however, the mitochondria were 1.4-fold longer than those of non-MCI cybrid cells. This data is supported by the fact that Mfn2, which regulates mitochondrial fusion, was increased 1.8-fold in MCI cybrids, with no other regulatory fission/fusion proteins possessing changes. Excessive fusion results in a lower number of mitochondria in the cell, which leads to impaired respiration, a lower production of ATP, and increased oxidative damage [84].

As mentioned earlier, AD can be characterized by the presence of amyloid plaques. These amyloid plaques are comprised of β-amyloid peptides (Aβ proteins), which are formed after the proteolytic cleavage of the transmembrane amyloid precursor protein [85]. Aβ proteins have strong effects on mitochondria, specifically in mitochondrial enzymatic activity and respiratory dysfunction [86]. Aβ proteins also activate signaling pathways, such as the NF-κB pathway, which plays roles in inflammation and regulation of cell death and division [87]. Toxic Aβ proteins inhibit mitochondrial respiration by decreasing the enzymatic activity of complexes III and IV. This leads to increased ROS production, inducing mitochondrial damage and neurodegeneration [86].

Amyloid deposits have been long thought to contribute to the pathogenesis of AD [88]. It has also been observed that neurons in the brains of AD patients possess high concentrations of damaged mitochondria. Additionally, AD is characterized by neurofibrillary tangles (NFTs) created by helical filament structures containing aggregated hyper-phosphorylated tau, another mitochondrial protein involved in microtubule assembly [85]. The oxidative stress significantly increases the Aβ levels, encouraging phosphorylation and polymerization of tau protein and disrupting the redox balance in the ETC. Studies of post-mortem brains of AD patients demonstrated decreased numbers of mitochondria in neurons along with increased presence of mtDNA and mitochondrial proteins in the cytosol [85].

Early onset Alzheimer's disease has also been associated with mutations in the protein called presenilin (PSEN1 and PSEN2). Diagnosis of early onset AD is somewhat difficult because there are many mutations that could cause early neurodegeneration. For example, 185 different mutations of PSEN1 have been recognized due to a variety of clinical symptoms [89]. PSEN1 and PSEN2 comprise the catalytic center of γ-secretase complex, which helps to produce the toxic Aβ species known to cause AD. In a study by Nygaard *et al*. 2014, a novel mutation in PSEN1 was shown to cause increasing cortical atrophy and aggregation of Aβ in the dorsolateral frontal lobes [90]. A PSEN1 deletion of codon 40 in exon 4 was shown to possibly contribute to the frontal lobe dysfunction. In a case examined by Klimkowicz-Mrowiec *et al*. 2014 [89], there were clinical symptoms of early onset Alzheimer's disease as a result of a mutation in exon 12 of the PSEN1 gene. The patient in this case exhibited worsening cognitive impairment, and involuntary movements. Mutations also have been shown to contribute to AD pathogenesis by speeding up the aging process as well as inducing accumulation of Aβ protein deposits. A study by Kukreja *et al*. 2014 sought to see whether inactivating the proofreading function of mtDNA polymerase PolgAD257A caused Aβ protein accumulation and eventual neurodegeneration. PolgA typically prevents mtDNA mutations from occurring, so loss of the proofreading function would lead to accumulation of mtDNA mutations. Interestingly, a specific knockout mutation of PolgA proofreading mechanism led to the accumulation and deposition of Aβ fragments, leading to brain atrophy and early neuronal apoptosis. The cortex and hippocampus exhibited features that indicated apoptosis when the stainings of coronal brain sections were examined. The hematoxylin-stained sections showed clear cytoplasm and swollen nuclei, when compared to cells and genotypes without the mutation. In mice with D257A mutation, caspase-3 was activated, leading to apoptotic death [91].

4.3. Huntington's Disease

Huntington's disease (HD) is another neurodegenerative disease that affects muscle coordination and leads to cognitive decline and psychiatric disability. Characteristics of this disease include chorea, involuntary movements, and

loss of cognitive function. As the disease progresses, motor rigidity and dementia emerge. The projected lifespan of patients with HD is 15-20 years following initial onset of symptoms. Currently, there is no treatment that can cure or even inhibit the progression of this severe neurodegenerative disease [92]. HD is classified into five grades, 0 through IV, where grade IV is the most severe. Grade 0 occurs when there are no visible neuropathological symptoms and abnormalities. In grade I, neuropathological changes could be observed only microscopically. Grades II through IV of Huntington's disease are often characterized by significant loss of neurons, and a tremendous increase in astrocyte composition [93]. Recently, it has been observed that mitochondria play a role in the pathogenesis of HD.

HD is an autosomal dominant disease that is caused by an expanded trinucleotide CAG repeat in exon 1 of the gene encoding the protein huntingtin (Htt) [12]. One hypothesis regarding HD is that mutations in the genes encoding Htt instigate cascades of damaged metabolic and molecular processes. Since neurons require large amounts of ATP to function properly, they are extremely vulnerable to mitochondrial damage and mutations. CAG repeats in exon 1 are translated into a polyglutamine (polyQ) sequence near the N-terminal of Htt. Normal polyQ length is 6-34 repeats, while patients with HD have at least 40 repeats [94]. Individuals when they have at least 36 CAG repeats usually exhibit characteristics of HD, such as motor deficit and cognitive abnormalities [95]. Therefore, the mutations causing a CAG repeat contribute to neuronal death, though the sources of said apoptosis are speculated to stem from mitochondrial dysfunction [96]. Interestingly, some pre-symptomatic patients that carry the mutation show significant atrophy of the caudate and putamen, indicating that neurodegeneration can occur years before symptoms are apparent [92]. In a study conducted by Shirendeb *et al*. 2011, it was shown that mutant htt oligomers possibly could be involved in abnormal mitochondrial dynamics, which possibly contributes to the onset of HD [57]. Using A11 antibody that recognizes oligomeric mutant proteins in neurodegenerative diseases limited to Alzheimer's and Parkinson's diseases, it was found that mutant htt oligomers were present in grades III and IV HD patients, and the htt oligomers increased as the severity of the disease increased. Mutant htt also directly correlated with decreased glucose utilization in the brain, possibly showing how mutant htt interferes with mitochondrial processes [57].

Transcription factor PGC-1α plays a major role in mitochondrial function. PGC-1α expresses the gene required for mitochondrial energy production, and also induces genes used to counter reactive oxygen species generated as byproducts of oxidative respiration. In a study by Tsunemi *et al*. 2012, it was shown that PGC-1α removes htt protein compositions in the brains of HD mice, and mitigates levels of oxidative stress. In this study, it was found that PGC-1αeliminated all the htt aggregates, and could be a potential therapeutic target for HD [97].

Changes in the ETC resulting in the overproduction of ROS and alterations in mitochondrial dynamics, specifically disruption of fission-fusion balance, can contribute to neuronal death in HD. Recently, studies have shown that huntingtin interacts with the regulatory fission protein *Drp1*, resulting in excessive fission. A study conducted by Shirendeb *et al*. 2011, found high levels of fission regulatory genes and low levels of fusion genes in striatum and cortex sections of HD patients, revealed shorter (and greater numbers of) mitochondria in these neurons. Thus, there appears to be an indirect relationship between the expression of fission and fusion regulatory proteins. Levels of Mfn2 were found to be lower in grade IV HD patients as compared to grade III HD patients, suggesting that mitochondrial fusion decreases as HD becomes more and more severe [57]. The opposite is found with regulatory fission proteins such as Fis1. As HD becomes more severe, the expression of Fis1 increases along with mRNA levels in the fission genes [57]. Fis1 levels in grade IV HD patients were significantly higher when compared to levels in Grade III patients, showing clearly that as HD progresses, fission becomes favored and short fragmented mitochondria are ubiquitous. In striatum and cortex, accumulation of mutant htt and oligomers has been found, implying that oligomers are also involved in damaging mitochondria in HD patients.

Glucose is the chief source of energy for the brain, so dysfunction involving glucose metabolism readily leads to metabolic failure and neurodegeneration. In an experiment conducted by Li *et al*. 2012, glucose utilization was reduced in HD neurons when compared to the WT neurons [98]. Rab11 is known to mediate utilization of nutrients in the cell. It was tested whether neurons with virus expressing Rab11S25N (dominant negative) or virus expressing Rab11Q70L (dominant active) would promote either increased or decreased glucose uptake. It was shown that glucose uptake was reduced in cell with virus expressing Rab11 dominant negative and promoted HD symptoms, whereas virus expressing Rab11 dominant active promoted normal glucose uptake in neurons. On the other hand, increased expression of Rab11 activity can normalize glucose uptake in neurons, though Rab11 absence reduces the glucose uptake, disrupting ATP production [98].

It has also been shown that insulin and IGF-1 improve mitochondrial function and reduce the production of ROS in neurons, specifically striatal cells. As mentioned earlier, fission is favored in HD, leading to a higher concentration of fragmented mitochondria in neurons. Insulin and IGF-1 both reduce Drp1 activity, which can help maintain the fusion-fission balance [99]. HD striatal cells demonstrate apoptosis induced by increased caspase-3 activation. However, insulin and IGF-1 decrease the amount of apoptotic nuclei in mutant cells, further preventing ROS generation. Insulin was also able to prevent activation of caspase-3 in cells expressing mutant htt. Insulin and IGF-1 were also shown to increase the membrane potential in HD striatal cells and mutant htt cells respectively. Since decreased membrane potential induces ROS production, it ultimately decreases net production of ROS [99].

5. CONCLUSION

Mitochondria are dynamic organelles that perform various roles such as ATP production, regulation of calcium

homeostasis, apoptosis, and maintain their own population through fission and fusion. Dysfunction of any of these processes can manifest in the form of neurodegenerative disease. In Parkinson's, Alzheimer's, and Huntington's diseases, oxidative stress resulting in an imbalance between antioxidants and ROS can damage organelles and injure the brain, resulting in irreparable neurodegeneration. Genetic mutations for example in PINK1, PARK2, and LRRK2, and in polymerases PolgA and protein Htt have been shown to cause Parkinson's disease, Alzheimer's disease, and Huntington's diseases respectively. Mitochondria play extremely important roles in the cell, though dysfunction is implicated in Parkinson's, Alzheimer's, and Huntington's diseases. Although therapeutics was shown to alleviate symptoms, no permanent treatments have been developed for these diseases. Involvement of mitochondria in the development of neurodegeneration hints at the possibility for new therapeutic interventions aimed at these organelles.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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