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Mitochondrial defects and oxidative stress in Alzheimer disease and Parkinson disease

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Abstract

Alzheimer disease (AD) and Parkinson disease (PD) are the two most common age-related neurodegenerative diseases characterized by prominent neurodegeneration in selective neural systems. Although a small fraction of AD and PD cases exhibit evidence of heritability, among which many genes have been identified, the majority are sporadic without known causes. Molecular mechanisms underlying neurodegeneration and pathogenesis of these diseases remain elusive. Convincing evidence demonstrates oxidative stress as a prominent feature in AD and PD and links oxidative stress to the development of neuronal death and neural dysfunction, which suggests a key pathogenic role for oxidative stress in both AD and PD. Notably, mitochondrial dysfunction is also a prominent feature in these diseases, which is likely to be of critical importance in the genesis and amplification of reactive oxygen species and the pathophysiology of these diseases. In this review, we focus on changes in mitochondrial DNA and mitochondrial dynamics, two aspects critical to the maintenance of mitochondrial homeostasis and function, in relationship with oxidative stress in the pathogenesis of AD and PD.

Keywords

Alzheimer disease; Parkinson disease; Mitochondrial DNA; Mitochondrial dynamics; Mitochondrial dysfunction; Oxidative stress; Free radicals

Introduction

Free radicals are made continuously in eukaryotic cells and must be balanced by antioxidant defense to maintain the redox homeostasis. Imbalance between harmful reactive oxygen species (ROS)[1] and antioxidant defenses causes oxidative stress, which results in oxidative damage. In the brain, when redox balance is lost, oxidative stress causes serious damage that leads to neuronal loss, in congruence with neurodegenerative diseases. ROS, for example, can cause nucleic acid breakage, enzyme inactivation, polysaccharide depolymerization, lipid peroxidation, and a host of other destructive processes. In general, ROS damage all biomolecules, ultimately leading to cell death if in overabundance.

Among all the organelles and enzymes that can generate ROS within the cell, mitochondria are the major sites responsible for more than 90% of the ROS generation. This ROS production can occur when electrons leak out of the electron transport chain (ETC) and react with dioxygen (O_2). Indeed, between 1 and 5% of all O_2 used in complexes I and III of the

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ETC escapes as superoxide. In response, superoxide dismutases (SOD) in the mitochondria (Mn-SOD or SOD2) and cytosol (Cu-Zn-SOD or SOD1) catalyze a reaction changing superoxide to diatomic oxygen and hydrogen peroxide. Glutathione peroxidases and catalase, in turn, act as additional antioxidant defenses by converting hydrogen peroxide to water. Hydrogen peroxide, however, is not a radical; thus it can cross membranes and rapidly propagate throughout the cell. Nevertheless, it can react with Fe^{2+} and other transition metal ions to form the highly dangerous hydroxyl radical, which is the most reactive species and is capable of initiating autocatalytic radical chain reactions [1].

As the sources of the majority of energy production and endogenous ROS production, mitochondria play a key role in the functioning and survival of neurons in the brain, the most energy-intensive organ in the human body. Notably, the long-lived, energy-demanding neurons have very limited glycolysis, thus making them highly dependent on aerobic OXPHOS for energy [2]. Additionally, as postmitotic cells with polyunsaturated fatty acid enriched in their membranes, neurons are sensitive to ROS buildup. Likewise, normal mitochondrial dynamics is important for maintaining polarity in highly polarized neurons [3]. Consequently, dysfunction in mitochondria seems to promote oxidative stress, aging, and neurodegeneration [4,5]. In fact, mitochondrial dysfunction and oxidative stress constitute the most prominent features found in Alzheimer disease (AD) and Parkinson disease (PD) [6–9]. Whereas defects in almost all aspects of mitochondrial function have been implicated in these neurodegenerative diseases, in this review, we focus on changes in mitochondrial DNA (mtDNA) and mitochondrial dynamics, two aspects critical to the maintenance of mitochondrial homeostasis and function, in relationship with oxidative stress in the pathogenesis of AD and PD.

Mitochondrial DNA and oxidative stress

Reflecting the ancient symbiotic eubacteria origin, mitochondria contain multiple copies of their own DNA, which is a circular double-stranded molecule critical to the maintenance of a functionally competent organelle. Human mtDNA contains genes encoding 12 S and 16 S rRNAs and 22 tRNAs necessary for mitochondrial protein synthesis and 13 polypeptide components of the ETC [10]. mtDNA can be replicated independent of the cell cycle, although loss of mtDNA inhibits G1- to S-phase progression by activating an established checkpoint kinase [11]. mtDNA molecules exist in multiple copies within each cell, which creates the possibility of coexistence of mutant and wild-type copies, a condition called heteroplasmy. It is suggested that a minimum critical load of mutant mtDNA must be met before cell dysfunction or clinical signs become apparent and this pathogenic threshold can be lower in tissues that are highly dependent on oxidative metabolism than in those that can rely on glycolysis [10].

It is worth noting that mtDNA has a relatively short half-life [12] and genes coded by mtDNA have few to no noncoding sequences between one another. Coupled with constant ROS exposure, lack of protection by histone, and limited DNA repair mechanisms, however, these unique features make mtDNA particularly vulnerable to oxidative damage, which could lead to harmful and influential mutations including point mutations and large-scale sporadic mtDNA rearrangements. The main products of mtDNA base damage are thymine glycol among pyrimidines [13], which has low mutagenicity, and 7,8-dihydro-8-oxo-2′-deoxyguanosine among purines [14–16], which can cause characteristic G→T transversions upon replication [13]. Large-scale sporadic mtDNA rearrangements are predominantly deletions up to 9 kb in size with one particular 5-kb deletion being the most common form (i.e., common deletion). Although the actual mechanisms remain elusive, oxidative damage-associated single-or double-strand breaks might be involved in the formation of mtDNA deletions. Indeed, numerous studies demonstrated that somatic mutations in mtDNA

progressively accumulate with age in a variety of tissues in humans, and importantly, terminally differentiated tissues with active oxidative metabolism such as the brain accumulate relatively higher levels of mutant mtDNA during the aging process, starting from the mid-30s in humans [17,18].

As a result, these gradually accumulated mtDNA mutations could potentially cause decreases in the efficiency of the ETC, spurring decreased ATP production and increased ROS production. In return, the increase in ROS could cause subsequent accumulation of more mtDNA mutations and create a positive feedback loop of increasing mutations and ROS production, followed by eventual cell death. In conjunction with this hypothesis, numerous studies have shown good correlations between aging, accumulation of mtDNA mutations, mitochondrial function decline, and increased oxidative stress during aging in humans and animals [19,20]. The causal relationship between mtDNA mutations and ROS production is best demonstrated in the affected tissues of patients with mitochondrial diseases when the mutant load of mtDNA mutations reaches a threshold [21–23]. For example, the A8344G mutation in the $tRNA_{Lys}$ gene of mtDNA is the most common mutation associated with MERRF (myoclonic epilepsy with red ragged fibers) syndrome. Cytoplasmic hybrids (cybrids) harboring the A8344G mutation exhibit decreased efficiency of ATP synthesis in mitochondria and become more sensitive to extrinsic oxidative stress such as hydrogen peroxide and UV irradiation [24–26] and the skin fibroblasts from MERRF patients demonstrate higher intracellular hydrogen peroxide levels and increased oxidative damage to the mitochondrial proteins containing iron–sulfur along with imbalance in the gene expression of antioxidant enzymes [27]. Human MELAS (mitochondrial encephalomyopathy and lactic acidosis with stroke-like episodes) patients carrying the A3243G mutation of mtDNA demonstrated increased oxidative stress systemically [28]. Leber's hereditary optic neuropathy (LHON) results from one of three point mutations in mtDNA coding for complex I components and LHON cybrids have increased superoxide production compared to wild-type cells [29]. Nevertheless, this notion is challenged by the observation in mtDNA mutator mice, which harbor homozygous genetic defects in the proofreading exonuclease activity of mtDNA polymerase γ: despite the rapidly accumulated mtDNA mutations in these mice, ROS generation is not significantly increased [30]. Kujoth et al. [31] also failed to find a significant increase in oxidative stress markers in 9-month-old mtDNA mutator mice, although there was a trend toward elevated mitochondrial protein carbonyls. However, recent studies demonstrated that *N*-acetyl-L-cysteine treatment rescued both neural and hematopoietic abnormalities in this mouse model, suggesting that subtle ROS/redox changes induced by mtDNA mutagenesis are involved in the modulation of somatic stem cell function in these mice [32]. Moreover, another group found that cardiac mitochondrial protein carbonyls were increased in this mouse model at 13–14 months of age, and more importantly, over-expression of mitochondria-targeted catalase significantly reduces mitochondrial protein carbonyl content and attenuates cardiomyopathy in the older mouse hearts, indicating that mtDNA mutations must cause cardiomyopathy at least partially through increased mtROS [33]. Therefore, it is likely that oxidative stress also plays a role in the mtDNA mutator mice, at least in the nondividing cells. Overall, these studies demonstrate not only that mtDNA is a target of ROS, but also that its defect contributes to increased ROS generation.

Mitochondrial dynamics and oxidative stress

On a related note, mitochondria are dynamic organelles that constantly undergo fission (or splitting) and fusion (or combining), which is critical to the maintenance of mitochondrial homeostasis and function. Specifically, mitochondrial fusion permits the exchange of mitochondrial contents, such as lipid membrane and mtDNA, such that the percentage of mitochondria containing defective components remains at a minimum [34,35]. Fusion is

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orchestrated by three large GTPases that tether neighboring mitochondria together and merge their inner and outer membranes. These proteins are mitofusin 1 (Mfn1), mitofusin 2 (Mfn2), and optic atrophy protein 1 (OPA-1) [36–38]. The mitofusins are transmembrane proteins that span the outer mitochondrial membrane; they form homo- or heterodimers upon fusion initiation and utilize their GTPase activity to fuse the membranes together [39,40]. As an inner membrane protein, OPA-1 faces the intermembrane space and corresponds with Mfn to enable inner-membrane fusion [39,41]. Mitochondrial fission, conversely, enables the sequestration and elimination of irreversibly damaged mitochondria and mitochondrial content [42]. Mitochondrial fission also involves a large GTPase, dynamin-like protein 1 (DLP1, aka Drp1), that inhabits the cytoplasm until it is recruited to the mitochondrial outer membrane for fission. Fission thus occurs when DLP1 oligomerizes into large ring-like complexes circling the future fission site along the mitochondrial outer surface to physically pinch a mitochondrion into two daughter mitochondria [38,43]. GTPase activity, mitochondrial recruitment, and stability of DLP1 are regulated by posttranslational modifications such as phosphorylation, S-nitrosylation, sumoylation, and ubiquitination [44–48]. Fis1, an OMM protein, was initially suggested to recruit DLP1 to the OMM. However, most recent studies suggest that Fis1 may not be a core component of the mitochondrial fission machinery, but rather plays a regulatory role. Instead, mitochondrial fission factor, also an OMM protein, directly binds to DLP1 and is necessary and sufficient for mitochondrial recruitment of DLP1 during mitochondrial fission [49]. Additional OMM proteins that physically or functionally interact with DLP1 have also been identified, which probably play regulatory roles that probably create more layers for the delicate regulation of this extremely important process [50].

The balance of mitochondrial fission and fusion is very sensitive to the physiological and pathophysiological conditions within the cell: cellular ion homeostasis, changes in metabolism, oxidative stress conditions, and genetic integrity affect mitochondrial fission and fusion to a considerable extent. Low levels of hydrogen peroxide, for example, have been demonstrated to elicit reversible mitochondrial swelling and fragmentation and alterations in the fine structure through modulation of fission/fusion proteins [51]. Mitochondrial depolarization, which may occur via sustained cytosolic Ca^{2+} increases, also causes significant mitochondrial fragmentation, presumably due to phosphorylation of DLP1 [52,53].

Mitochondrial dynamics is critical for mitochondrial integrity in eukaryotic cells and changes in mitochondrial dynamics have a significant impact on almost all aspects of mitochondrial function including energy metabolism, calcium buffering, ROS generation, and apoptosis regulation [39,54–63]. In particular, it seems that excessive mitochondrial fragmentation causes increased ROS production. For example, mitochondrial fragmentation mediated by an excessive fission process is a necessary component for high-glucose-induced respiration increase and ROS overproduction [63]. Extended exposure to high-glucose conditions provoked a periodic and prolonged increase in ROS production, which could be prevented by inhibition of mitochondrial fission [63]. Although the detailed mechanisms underlying mitochondrial dynamics-mediated ROS overproduction are not clear, defects in both mitochondrial ultrastructure and function are probably involved. For example, either fission- or fusion-deficient mitochondria can lead to ultrastructural deficits, which may have deleterious effects on mitochondrial membrane potential [35,64]. Defects in mitochondrial dynamics may also lead to accumulation of damaged mitochondrial components due to inefficient removal through mitophagy coupled with fission [42]. A direct deleterious effect on the function of critical mitochondrial protein complexes is also implicated because mitochondrial fission may also play an important role in the proper assembly of mitochondrial ETC complexes [65]. Therefore, the balance of mitochondrial fission/fusion can be tipped by oxidative stress and its abnormality could further enhance ROS generation.

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Mitochondrial DNA alterations in Alzheimer disease

As oxidative stress has become a key feature in the pathophysiology of AD, the oxidative stress-related mitochondrial role in AD pathogenesis has become highly scrutinized. As mentioned previously, mitochondria contain multiple copies of mtDNA molecules and there are abundant mitochondria in each cell, potentially dampening the effects of some somatic mutations. Through propagation of mtDNA mutations by clonal expansion [66,67], somatic mtDNA mutations can become very influential nonetheless. Additionally, gradual accumulation of disperse heteroplasmic somatic mtDNA mutations may gain momentous deleterious effects, thus explaining why age is considered the greatest risk factor for AD and other neurodegenerative diseases. Studies analyzing mtDNA found that the mtDNA of cortical neurons in AD patients younger than 75 years of age has 15 times more of the common 5-kb mtDNA deletion mutations than age-matched controls [68]. The elevated levels of 5-kb mtDNA deletion mutations in large vulnerable neurons of the hippocampus and neocortex in AD brains were later confirmed by in situ hybridization [69]. A high incidence of mtDNA base changes was also found in Down syndrome patients that progress to an AD-like dementia [70]. Coskun et al. [71] determined that there were many more sporadic mutations in the mtDNA control region in AD patients compared with control cases and that several mutations in the mtDNA control region (e.g., T414G, T414C, and T477C) were unique to AD. These mutations occurred at sites of known mtDNA transcription and replication regulatory elements; therefore, they are associated with reduced transcript levels of and deleterious functional consequences for mitochondrial homeostasis (e.g., COX activity) once they reach a critical mass in postmitotic cells in the brain. To explore the origins of this increase in mutations, Mecocci et al. measured the levels of oxidized nucleoside, 8-hydroxy-2′-deoxyguanosine, in the mtDNA in the cerebral cortex and cerebellum of AD patients and age-matched controls [72]. They found that the mtDNA in AD patients underwent an average threefold increase in oxidative damage, probably the cause of the increase in mutations. In fact, it appears that increased somatic mtDNA mutations are not brain specific because mtDNA control region mutation levels were increased in both blood and brain samples from the same AD patients compared to age-matched controls and in lymphoblastoid cell lines derived from AD blood samples [73,74]. This is consistent with the observation that mitochondrial dysfunction and oxidative stress are also systemic in AD patients.

In addition to somatic mtDNA mutations, ancient accumulated polymorphisms and pathogenic mutations in mtDNA have also been reported to be linked to AD. Specifically, a statistically significant, high increase in a point mutation at position 4336, of A→G, in a tRNA (Gln) gene was found in AD and PD patients compared to controls [75]. Another case–control study concurred in suggesting that the mutation probably leads to an increased risk for AD [76]. Multiple other corroborating studies have found that mtDNA single-nucleotide polymorphisms (SNPs) and mtDNA haplogroups (groups of similar haplotypes) play a role in AD. For example, one study found that males with mtDNA haplogroup U had a greater risk for AD than did males with the most common haplogroup, H [77]. Similarly, a significantly higher proportion of patients with AD were found to have mtDNA haplogroup UK in comparison with controls [78]. Alternatively, mtDNA haplogroups have also been related to apolipoprotein E type 4 (ApoE4) in sporadic AD cases [79]. ApoE4 has been found to be a very important risk factor for both late-onset familial and sporadic AD [80,81]. Specifically, the study analyzed mtDNA variants in AD patients and found statistically significant differences in the frequency distributions of mtDNA haplogroups between ApoE4 carriers and noncarriers. This relationship, however, was found only in AD patients, as the study included the same experimental setup with healthy subjects and found ApoE4 and mtDNA to be independent of one another for these healthy subjects; the study, thus, highlights mtDNA variants as possible risk factors. Moreover, this could suggest that

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sporadic AD results from a combination of risk factors, with oxidative stress being a key propellant. In fact, ApoE has been discovered to affect amyloid-β (Aβ) degradation, perhaps through a complex system of increased Aβ trafficking to lysosomes by regulating cholesterol levels and Rab7 (a protein involved in the vesicular transport of the late endocytotic pathway) recycling [82], and extensive research has found important relationships between Aβ and mitochondria. In contrast, it is also probable that certain mtDNA haplogroups may confer protective effects correlating with a decreased risk of AD, as demonstrated by lower-than-control levels of mtDNA haplogroup *T* in AD patients [83]. Because mtDNA is maternally inherited, it is interesting that fairly recent data have shown AD onset to be related to maternal history of AD [84]. Mutations in mtDNA might be the lurking variable underlying this relationship.

Despite supportive evidence from epidemiological genetic studies, the idea of mtDNA being important to AD pathogenesis is under debate because of seemingly inconsistent findings. In fact, the same study that found an increased risk for AD in males carrying mtDNA haplogroup U also suggested a decreased risk for females with mtDNA haplogroup U [77]. Moreover, a recent large-scale epidemiological study failed to find any conclusive evidence of an association between mtDNA variants and AD [85]. After failing to uncover evidence constituting mtDNA variants as a key etiological factor for AD, the authors of another study concluded that mtDNA mutations may, perhaps, not be a widespread causative agent for AD [86]. However, these and other contradictory findings may be possibly explained by insufficiently large sample sizes, population heterogeneity, and the multifactorial, intricate nature of AD. In AD, numerous factors including the ApoE4 isoform; mutations in amyloid-β protein precursor (APP), presenilin 1 (PS1), PS2, and clusterin; and even diabetes have all been identified as risk factors. The myriad of possible causative factors in AD seem to imply that the pathogenesis of AD may involve multiple, possibly combinable pathways, as well typified by the above-mentioned study connecting ApoE4 and mitochondrial haplogroups in some AD patients [79]. Furthermore, the mtDNA mutations themselves are widely varying and can be categorized under the following categories: ancient accumulated polymorphisms that gave rise to haplotypes followed by haplogroups, pathogenic mutations, and somatic mutations accrued over time. Notably, the mutations themselves, regardless of categories, are not mutually exclusive; thus an accumulated somatic mutation may be the same as that of a pathogenic mutation, for instance. Overall, these factors may have masked the importance of mtDNA in the contrary data of these studies.

In further emphasizing the importance of mtDNA, biochemical studies have provided more convincing evidence that mtDNA alterations in AD enhance ROS generation and influence AD pathogenesis. To combat the confounding results present in many epidemiological studies, Swerdlow and colleagues [87,88] transferred mtDNA from AD patients into cell lines devoid of mtDNA, which resulted in increased ROS levels and free radical-scavenging enzyme activity along with a biochemical defect in COX activity and defects in calcium handling that matched neurons observed in AD patients. In essence, these studies effectively implied that AD pathogenesis, at the least, partially involves mtDNA alterations. On the animal model level, C57BL/6 congenic mouse lines with specific mtDNA polymorphisms (derived from inbred FVB/N, AKR/J, and NOD/LtJ strains) experienced altered cellular metabolism and Aβ accumulation/degradation, revealing these effects to be present in vivo as well [89]. Hirai et al. [69] also found that neurons with elevated mtDNA mutations demonstrated increased nitrotyrosine immunoreactivity and mitochondrial structural damage in AD brain. As a non-crosslinking-related oxidative modification, protein nitration indicates more recent active modification, suggesting that mtDNA mutations probably elicit increased ROS production in AD. Therefore, mutations in mtDNA probably directly account for certain AD pathophysiological features including oxidative stress in AD brain.

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Abnormal mitochondrial dynamics and Alzheimer disease

Earlier ultrastructural morphometric studies on biopsied brain tissues from AD patients revealed significant structural damage to mitochondria as evidenced by broken cristae or sometimes near total loss of the inner structure in the vulnerable pyramidal neurons in AD brain, which probably contributes to mitochondrial dysfunction and increased oxidative stress in AD brain [69]. The slightly, but significantly, increased mitochondrial size and decreased mitochondrial number in AD neurons implicate a potential involvement of abnormal mitochondrial dynamics in AD brain [69]. However, the nature of the impairment in mitochondrial dynamics is unclear because increased mitochondrial size does not necessarily translate into enhanced mitochondrial fusion as suggested by the presence of similarly looking swollen mitochondria observed in fusion-deficient Mfn2 mouse brain [35,64]. Nevertheless, the notion that mitochondrial dynamics is disturbed in AD brain is supported by the studies demonstrating significant changes in mitochondrial fusion (i.e., decreased Mfn1, Mfn2, and OPA1) and fission proteins (i.e., decreased DLP1 and increased Fis1) in AD brain [90–93]. Despite decreased total levels of DLP1, mitochondrial DLP1, the fraction critical for mitochondrial fission, and DLP1 phosphorylated at Ser616, a posttranslational modification that facilitates mitochondrial translocation of DLP1, are increased in AD brain [90]. Increased S-nitrosylation of DLP1, which activates GTP activity of DLP1 and thus facilitates mitochondrial fission, is also reported in AD brain [46]. Together with the decreased fusion proteins and increased Fis1 in AD brain, these data suggest that it is likely to be mitochondrial fragmentation that occurs in AD brain. Moreover, DLP1 interacts with Aβ monomers and oligomers in AD brain, and these abnormal interactions are increased with disease progression [92], although it is not clear how such interaction affects DLP1 function and the balance of mitochondrial fission/fusion. Abnormal changes in mitochondrial morphology are also noted in fibroblasts from sporadic AD patients [94]. However, in contrast to what is found in AD brain, mitochondria become significantly elongated and form a highly connected network in AD fibroblasts, which is distinctively different from age-matched normal human fibroblasts in which mitochondria are predominantly sausage shaped. These morphological differences may be due to the different pattern in the expression of fission/fusion proteins because decreased DLP1 but unchanged OPA1 were found in AD fibroblasts [94]. More recent studies also confirmed that DLP1 is significantly decreased, whereas Fis1 is increased, in peripheral blood lymphocytes from AD and mild cognitive impairment patients [95], thus confirming that deficits in mitochondrial dynamics are systemic. It is of interest to note that mitochondrial dysfunction and increased oxidative stress are also reported in these peripheral cells from AD patients.

Excessive mitochondrial fission and its deleterious effects are more unequivocally demonstrated in in vitro AD models: APP overexpression, via Aβ production, induced mitochondrial fragmentation and dysfunction including heightened ROS production, reduced ATP generation, and lower MMP, as well as increased number of mitochondria with damaged structure [90,96–98]. As expected, such mitochondrial deficits became more severe in M17 cells expressing the familial AD-causing Swedish APP mutation [96]. Indeed, by using a mitochondria-targeted photoactivatable fluorescence protein, it was demonstrated that mitochondrial fusion became impaired. It was further demonstrated that APP affects mitochondrial dynamics directly through the differential modulation of mitochondrial fission and fusion proteins that cause an impaired balance of mitochondrial fission/fusion, and indeed OPA1 overexpression restored the mitochondrial morphology and mitochondrial functional parameter [96]. Therefore, this study demonstrated that mitochondrial fragmentation mediates mitochondrial dysfunction and structural damage induced by AD-related insults in neuronal cells. Calkins et al. [97] also found fragmented mitochondria and an altered expression of mitochondrial fission/fusion proteins in primary neurons isolated

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from Tg2576 transgenic mice expressing the human APP Swedish mutation compared to control neurons and increased interaction between DLP1 and Aβ in the brain tissues of this transgenic model. The involvement of Aβ in the deficits of mitochondrial dynamics is directly demonstrated by the treatment of primary hippocampal neurons with Aβ-derived diffusible ligands (ADDLs), which causes significantly shortened mitochondria in neurites compared to those treated with control peptide [90]. In fact, both mitochondrial fission and fusion processes were impaired in ADDL-treated primary neurons [90]. Increased S-nitrosylation of DLP1 due to nitric oxide produced in response to Aβ is probably involved [46]. Consistent with the in vitro studies, Aβ-induced changes in mitochondrial dynamics and distribution are early events in vivo in *Drosophila* models [99,100]. Abnormal mitochondrial distribution and round, swollen, and damaged mitochondria are also documented, coinciding with the loss of mitochondrial oxidative activity, which preceded the onset of amyloid plaque formation and memory phenotype in the brain of Tg2576 APP transgenic mice and APP/PS1 mice [98]. However, no changes in the expression of any fission/fusion proteins are identified in the brain tissue of these mice [98]. Although a tipped balance toward more fusion in these AD mouse models is implicated by this study [98], because mitochondrial fission/fusion deficiency may lead to mitochondria with heterogeneous size [35,64], it can be very tricky or sometimes misleading to determine whether mitochondrial fission/fusion becomes impaired in vivo based only on measurement of mitochondrial length at a static point. Ideally, the conclusion should be strengthened by the genetic manipulation of mitochondrial dynamics. Overall, these studies demonstrated that mitochondrial dynamic changes mediate the toxic effects of APP mutation and/or Aβ including oxidative stress both in vitro and in vivo.

In a related matter, it has been known for a while that tau alterations affect axonal transport, including that of mitochondria [101]. Increasing evidence demonstrated that, in addition to aberrant phosphorylation, caspase cleavage of tau plays a critical role in the oligomerization and formation of pathological tau species in AD [102]. Okadaic acid (OA) treatment of neuronal cells was used as an in vitro model to study tau phosphorylation. OA-treated primary cortical neurons demonstrated mitochondrial fragmentation accompanied by decreased total DLP1 and increased phosphorylated DLP1 along with increased ROS production [103]. Quintanilla et al. [104] found that expression of tau truncated at Asp421 mimicking caspase cleavage induces mitochondrial fragmentation along with increased ROS production in neuronal cells. They later demonstrated that Asp421-cleaved tau exacerbates mitochondrial fragmentation and oxidative stress induced by sublethal levels of Aβ, suggesting that tau and Aβ cooperate to impair mitochondria [105]. Interestingly, DLP1 is demonstrated to interact with phosphorylated tau in vivo [93]. However, most recently, Duboff et al. [106] found in *Drosophila* that tau overexpression caused mitochondrial elongation, which could be rescued by Mfn2 knockdown and DLP1 overexpression, thus suggesting that tau overexpression probably enhances mitochondrial fusion or inhibits fission in *Drosophila*. Their further genetic manipulations demonstrated that actin stabilization impairs mitochondrial translocation of DLP1, which results in elongation. However, this observation seems contradictory to a prior finding that disruption of actin filaments attenuated fission and recruitment of DLP1 to mitochondria [107]. Overall, although further studies are still needed to understand detailed mechanisms in the mammalian system, and it remains to be determined how tau alterations, especially phosphorylation and caspase cleavage, may influence mitochondrial dynamics in animal models, it is clear that abnormal mitochondrial dynamics also mediates tau toxicity.

Mitochondrial DNA alterations and Parkinson disease

PD is commonly characterized by its clinical symptoms of tremor, bradykinesia, rigidity, and postural instability. In studying the etiology of PD, scientists have learned, quite

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incredibly, not only that the mitochondrion plays a role in the PD pathogenesis but also that its role in PD is quite similar to its role in other neurodegenerative diseases. For one, mtDNA, yet again, seems to be involved in affecting PD onset. In terms of mtDNA haplogroups, immoderate mutations of mtDNA-encoded complex I genes in mtDNA cluster JTWIX were strongly connected to increased risk for PD [108]. These mutations probably modified complex I and OXPHOS efficiency, contributing to the mitochondrial dysfunction and oxidative stress found in PD. Likewise, mtDNA cluster TJ in linkage with the mtDNA 4216C polymorphism seemed to be accompanied by raised risks of PD [109]. Conversely, additional studies have found haplogroup J and the UJKT haplogroup cluster to be associated with notable decreased risks of PD [110,111].

Because dopaminergic neurons in the substantia nigra have high levels of pro-oxidant iron (transition metals can promote ROS production by reducing oxygen) and low levels of glutathione (a crucial antioxidant), they are particularly vulnerable to oxidative stress and oxidative stress-induced somatic mtDNA mutations. Indeed, high levels of somatic mtDNA mutations have been observed in substantia nigra neurons with OXPHOS enzyme defects in aged human and PD patients [112,113], suggesting that somatic mtDNA deletions are important in the selective neuronal loss observed in brain aging and in PD. More specifically, heteroplasmic somatic mtDNA mutations of the ND5 gene (which encodes a complex I subunit) were detected only in PD patients, not in controls [114]. The lack of control patients with ND5 gene mutations suggests its vital importance to normal neuronal vitality, mutations of it causing a significant increase in risk for PD. To further analyze the relationship between accumulated mtDNA damage and PD, a clever experiment studied the effects of transgenically modified mice expressing mito-Pstl (mitochondria-targeted restriction enzyme that induces double-strand breaks in the mtDNA, leading to an OXPHOS deficiency, mostly due to mtDNA depletion) while utilizing dopamine transporter promoter-driven transactivator protein (to localize the expression only in dopaminergic neurons) [115]. The study found that the transgenic mice experienced the PD clinical features of motor function defects, dopaminergic neuron loss, and a paucity of dopamine in the striatum, lending credibility to the proposed role of accumulated mtDNA damage in PD pathogenesis. As might therefore be expected, the motor function defects could be alleviated by levodopa (a dopamine precursor that is commonly used in PD therapy) treatment. Interestingly, human patients with mtDNA polymerase γ mutations that could potentially accelerate the accumulation of mtDNA mutations can present with parkinsonism or idiopathic PD [116–119], thus supporting a more causative role of mtDNA alterations in the pathogenesis of PD.

Just as in AD, however, studies on mtDNA in relation to PD have remained controversial and inconsistent. The mtDNA 10398 G SNP, for instance, was measured at lower levels for PD patients than in normal populations and was thought to have a protective effect [110]; however, another study found no significant difference in frequency of the 10398 G SNP for PD patients [120]. In a comparable manner, one study found that PD patients did not have significantly different overall levels of somatic mtDNA mutations in comparison with age-matched controls [121]. Later, the same group found that early PD and incidental Lewy body disease (considered to be a good model for presymptomatic PD) patients did have significantly raised mtDNA mutation levels [122]. The authors themselves explain the inconsistency as being due to mitochondria with overly mutated mtDNA inducing neuron death and degeneration, thus preventing them from being measured in late-stage tissue. Also, specific, crucial mtDNA mutations may be more important than overall mtDNA mutation levels. As in some of the AD studies, these inconsistencies might be explained by the complex, multifactorial nature of PD. In PD, a multitude of factors such as mutations in genes such as ubiquitin carboxy-terminal hydrolase L1, PTEN-induced putative kinase (PINK1 or PARK 6), leucine-rich repeat kinase 2 (LRRK2 or PARK8), β-

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glucocerebrosidase, ATP13A2, and Nur-related protein 1 [123,124] and neurotoxins including 1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine (MPTP) and rotenone have all been associated with PD pathogenesis. As a result, PD pathogenesis may vary among cases and involve intersections of multiple risk factors, while not including others. One study that investigated the effects of silencing PINK1 expression in SH-SY5Y cell lines (dopaminergic neuroblastoma cells) found that the silencing caused reductions in mtDNA levels and mtDNA synthesis, concurrently triggering mitochondrial dysfunction, inhibited normal cellular respiration, augmented oxidative stress, and increased cell death typical of PD pathophysiology [125]. This may represent one such possible intersection of risk factors in causing PD.

Abnormal mitochondrial dynamics and Parkinson disease

Ample studies suggest that both environmental factors and genetic factors play important roles in PD pathogenesis. MPTP and certain pesticides that inhibit complex I activity in the mitochondria are known to cause human parkinsonia [126]. Specific genetic defects are linked to familial forms of PD that resemble idiopathic PD [127–135]. Interestingly, subsequent studies have connected these mutations with mitochondria and oxidative stress. In particular, increased PD risk has been linked to mutations in α-synuclein, parkin, PINK1, DJ-1, and LRRK2, all of which have been related to mitochondria [136]. Recent studies demonstrated that both PD neurotoxins and PD genes affect mitochondrial dynamics, which may be of pathogenic significance.

Neurotoxins

MPTP causes parkinsonism in humans and nonhuman primates. As such, both MPTP and its active metabolite, MPP^+, have been extensively used in a variety of in vivo mammalian species and in vitro paradigms as experimental models of PD, respectively [137]. As a complex I inhibitor, MPP^+ inhibits ATP production and stimulates superoxide and peroxynitrite formation that damages proteins by oxidation and nitration [138]. Complex I-independent mechanisms appear to also contribute to the neurotoxic effects of MPP^+ [139]. Recent studies demonstrated that MPP^+ induces a DLP1-dependent biphasic increase in mitochondrial fragmentation concurrent with the decrease in ATP levels in both SH-SY5Y neuroblastoma cells and primary rat dopaminergic midbrain neurons [140]. More detailed analysis found that the initial drop in ATP levels is likely to be a direct effect of MPP^+ but that MPP^+-induced excessive mitochondrial fragmentation leads to further ATP decline, especially the second wave of ATP decline. In fact, excessive mitochondrial fragmentation exacerbates MPP^+-induced bioenergetic impairments and mediates the toxic effects of MPP^+ on mitochondrial membrane potential, calcium handling, ROS generation, and mitophagy as well as eventual cell death [140]. Indeed, attenuation of mitochondrial fragmentation by DLP1 knockdown reduces these downstream events induced by MPP^+. Increases in ROS also contribute to MPP^+-induced mitochondrial fragmentation, suggesting the presence of a complex cross talk between mitochondrial fragmentation and ROS production, which probably leads to a vicious downward spiral that augments the adverse effects of MPP^+ [140]. Earlier studies also found that rotenone and 6-OHDA induce a rapid DLP1-dependent mitochondrial fragmentation before cell death in various cells [107,141,142].

α-Synuclein

Point mutations in α-synuclein such as A53T and E46K cause autosomal dominant PD. Transgenic mice lacking α-synuclein show increased resistance to the toxicity of MPTP, whereas mice overexpressing α-synuclein were found to have dysfunctional mitochondria and increased oxidative stress [143]. Furthermore, transgenic mice overexpressing the

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pathogenic A35T α-synuclein mutation had dysfunctional, degenerating mitochondria that contained α-synuclein [144], thus prompting some to speculate that α-synuclein may directly cause mitochondrial damage [145]. Indeed, a fraction of both monomeric and oligomeric α-synuclein is found in mitochondria [146] with the levels of mitochondrial-localized α-synuclein increasing in the brains of PD patients, probably in the inner mitochondrial membrane, where it may interact and selectively inhibit complex I [147]. Most recent studies demonstrated that α-synuclein may have a general protective role preventing spontaneous membrane fusion, and its overexpression causes mitochondrial fragmentation independent of mitochondrial fission/fusion machinery [148]. Interestingly, α-synuclein-induced mitochondrial fragmentation could be partially rescued by parkin, PINK1, or DJ-1 overexpression. A later study confirmed the DLP1-independent fragmentation induced by α-synuclein overexpression [149]. However, the finding that α-synuclein caused fragmentation only of mitochondria and not endoplasmic reticulum or Golgi [149] raised questions about a general inhibitory role of α-synuclein in membrane fusion. Another study demonstrated that A53T α-synuclein overexpression causes mitochondrial fragmentation in vivo in an age-dependent manner in affected brain regions in transgenic mice expressing both mito-CFP and A53T α-synuclein in neurons [150]. It also reported concurrent significant changes in the expression of DLP1/Mfn1/Mfn2 in this mouse model, suggesting the potential involvement of the mitochondrial fission/fusion machinery. Regardless of the exact mechanism, it is clear that α-synuclein can influence mitochondrial function through modulation of mitochondrial dynamics.

PINK1 and parkin

Mutations in both PINK1 and parkin cause a syndrome known as autosomal recessive juvenile parkinsonism. PINK1 is a serine/threonine protein kinase located to the mitochondrial outer membrane with the kinase domain facing the cytoplasm [151]. Parkin is translocated to mitochondria upon phosphorylation by PINK1 [152]. In fact, PINK1-deficient *Drosophil*a and parkin-deficient *Drosophila* demonstrated similar prominent mitochondrial abnormalities including fragmented cristae and hollow-appearing mitochondria or mitochondrial enlargement and disintegration [153–155]. Importantly, PINK1-deficiency-induced abnormalities can be rescued by parkin overexpression [153–155]. These findings suggest that PINK1 and parkin converge within a single pathway that regulates mitochondrial homeostasis and quality control with parkin functioning downstream of PINK1. Subsequent detailed genetic studies demonstrated that the PINK1/parkin pathway promotes mitochondrial fission and/or inhibits mitochondrial fusion in *Drosophila* because PINK1 or parkin deficiency-induced deficits could be suppressed by increasing the levels of DLP1 or Fis1 and/or decreasing the levels of Mfn or OPA1 and exacerbated by decreasing the levels of DLP1 [156–159]. However, various effects, sometimes even opposite to what is observed in *Drosophila*, were noted in mammalian systems. Consistent with the *Drosophila* study, cultured fibroblasts from patients carrying parkin mutations contained more branched mitochondria [160]. PINK1 knockdown in COS-7 cells leads to elongated mitochondria, which can be inhibited by DLP1 or Fis1 overexpression [159]. Recently, Yu and colleagues [202] found that expression of PINK1 and parkin in primary neurons resulted in decreased mitochondrial size, whereas silencing leads to elongated mitochondria. It was further demonstrated in both *Drosophila* and a mammalian system that parkin-mediated ubiquitination and subsequent degradation of Mfn2 probably underlie repressed mitochondrial fusion. However, in contrast, several groups demonstrated that PINK1 or parkin silencing using siRNA in HeLa cells or neuroblastoma cells leads to mitochondrial fragmentation, which could be exacerbated by DLP1 overexpression and rescued by expression of a dominant negative DLP1 mutant [158,161–163]. Primary fibroblasts from PD patients carrying PINK1 mutations also demonstrated a fragmented mitochondria network in a noticeable minority of cells [162,164]. It was also

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demonstrated that parkin effectively promotes the ubiquitination and proteasome-dependent degradation of Drp1, thus promoting mitochondrial elongation in various mammalian cells [165]. Overall, these studies suggest that PINK1/parkin can directly influence mitochondrial dynamics, although more studies are needed to resolve the discrepancy in the mammalian system.

PINK1 and parkin are also involved in selective degradation of damaged mitochondria through mitophagy, a process coupled with mitochondrial fission. Mitochondrial fission is always followed by subsequent fusion [42]. However, mitochondria with a depolarized membrane potential showed a decreased probability of fusion and were often targeted for degradation through mitophagy. In healthy mitochondria, PINK1 levels are kept low through membrane potential-dependent import and constitutive cleavage by the mitochondrial rhomboid protease PARL in the inner membrane followed by subsequent degradation by an MG132-sensitive protease [166,167]. Depolarization, signaling damaged mitochondria, blocks PINK1 proteolysis and leads to PINK1 accumulation, which triggers mitochondrial translocation and activation of parkin [168]. Subsequently, parkin mediates ubiquitination of multiple substrates and promotes autophagosome recruitment to parkin-labeled mitochondria to facilitate the clearance of mitochondria by lysosomes. Increased oxidative stress impairs the E3 ligase activity of parkin, leading to reduced mitochondrial turnover and decreased mitochondrial function [169]. Interestingly, parkin is also involved in mitochondrial biogenesis that may have an impact on mitochondrial dynamics. For example, parkin overexpression boosts mtDNA transcription and replication probably through the association with mitochondrial transcription factor A [170]. More recent studies suggested that parkin can regulate mitochondrial biogenesis through regulation of the levels of PARIS [171], a zinc finger-containing protein functioning as a major transcription repressor of PGC-1 α, the master regulator of mitochondrial biogenesis.

DJ-1

Pathogenic mutations in DJ-1 lead to autosomal recessive early onset parkinsonism [172]. DJ-1 is a small 20-kDa protein that is highly conserved across diverse species [173,174]. Despite its multifunctional features, the most striking and consistent finding about DJ-1 is its involvement in the response to oxidative stress [175]. DJ-1 can become oxidized at its cysteine residues upon oxidative stress and thus function as a scavenger of ROS [176]. DJ-1 also stabilizes the antioxidant transcriptional master regulator Nrf2 to boost antioxidant response [177]. Overexpression of the wild-type DJ-1 protects cells from cytotoxicity caused by oxidative stress, whereas DJ-1 deficiency causes increased cellular vulnerability to oxidative insults [178–180]. Interestingly, oxidative stress induces rapid relocalization of DJ-1 to mitochondria [181,182], suggesting that mitochondria could be a site of neuroprotective action for DJ-1. In relation to mitochondrial dynamics, fragmented mitochondria were identified in human fibroblasts from DJ-1 E64D PD patients or lymphoblasts isolated from DJ-1 L166P or deletion mutation-caused PD patients [183,184]. Indeed, overexpression of various pathogenic DJ-1 mutants causes significant mitochondrial fragmentation and ultrastructural deficits in M17 neuronal cells and primary cortical neurons [185]. In association with these mitochondrial morphological defects, mitochondria had impaired bioenergetics and increased vulnerability to H_2O_2 and MPP^+ [185]. Consistent with the notion that pathogenic mutations result in loss of function, DJ-1 deficiency also produces a fragmented mitochondrial phenotype [183,184,186]. On the other hand, neurons overexpressing wild-type DJ-1 had significantly elongated mitochondria, which probably mediate their enhanced resistance to H_2O_2 and MPP^+ [185].

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Leucine-rich repeat kinase 2

Mutations in LRRK2 are the most common cause of both familial and idiopathic PD [187]. LRRK2 codes for a large, multi-domain protein that contains, among others, a kinase domain and a ROC (Ras of complex proteins) domain with GTP binding and GTPase capabilities [188]. Most of the PD-associated mutations including the R1441C and G2019S mutations increase kinase activity, and both the kinase and the GTPase activities of LRRK2 are required for inducing cell death, suggesting a critical role of the enzymatic activities of LRRK2 in the pathogenesis of PD [189,190]. Interestingly, several lines of evidence suggest the presence of LRRK2 in mitochondria [191–193], predominantly in the outer membrane, indicating a possible mitochondria-centered mechanism of LRRK2 action. Indeed, recent evidence suggests that LRRK2 plays an important role in modulating the response to mitochondrial inhibition [194]. Moreover, a genetic interaction between LRRK2 and PINK1/parkin is identified in *Drosophila* [195,196], and PINK1 deficiency-induced mitochondrial morphological abnormalities can be prevented by lrk-1 (*Caenorhabditis elegans* LRRK2 homolog) deficiency [197]. That LRRK2 may influence mitochondrial dynamics was first implicated in primary human fibroblasts derived from PD patients carrying the LRRK2 G2019S mutant in which increased mitochondrial elongation and interconnectivity along with mitochondrial dysfunction were identified [198]. Most recent studies demonstrated that over-expression of wild-type LRRK2 causes mitochondrial fragmentation and ultrastructural damage along with mitochondrial dysfunction including increased ROS, which is further exacerbated by expression of PD-associated mutants (R1441C or G2019S) in both SH-SY5Y and differentiated primary cortical neurons [199]. These changes are ascertained to be due to the kinase-dependent interaction between LRRK2 and DLP1, which facilitates DLP1 translocation to mitochondria and subsequent mitochondrial fission [199]. Furthermore, the plausibility of the suggested importance of the LRRK2–DLP1 interaction to PD pathogenesis is strengthened by additional evidence that revealed all of the detrimental effects from mutated LRRK2 being abrogated by expression of dominant negative DLP1 mutants, hence preventing DLP1-induced mitochondrial fragmentation and dysfunction [199]. Adding further validation to this proposed mechanism, a later study involving primary neurons from E14.5 mice and LRRK2 variants also reported similar findings [200].

Conclusion

With the average life expectancy rising, the incidence of neurodegenerative diseases is doomed to rise. Although many of the pathophysiological features of AD, PD, and other neurodegenerative diseases are quite distinct and varying, oxidative stress has become an important characteristic among them. Therapies to remedy oxidative stress in AD and PD patients such as vitamin E, a natural antioxidant, supplementation have shown limited success in humans [201]. In analyzing the role of oxidative stress in these diseases, many studies have illustrated mitochondria to be important sources of ROS, points of interaction with ROS, and targets for oxidative stress. Consistent with this notion, abnormal mtDNA alterations and mitochondrial dynamics are induced by oxidative stress and also amplify ROS generation, probably contributing to the increased oxidative stress in AD and PD in a vicious downward spiral manner. Therefore, new treatments with the therapeutic target of improving mitochondrial function may prove to be promising. Ideally, combinational therapies targeting enhancing mitochondrial function and blocking ROS generation may provide the greatest benefits to patients.

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Abbreviations

AD	Alzheimer disease
Aβ	amyloid-β
APP	amyloid-β protein precursor
ADDL	Aβ-derived diffusible ligand
ApoE4	apolipoprotein E
COX	cytochrome *c* oxidase
DLP1	aka Drp1, dynamin-like protein 1
ETC	electron transport chain
LHON	Leber's hereditary optic neuropathy
LRRK2 or PARK8	leucine-rich repeat kinase 2
MMP	mitochondrial membrane potential
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyradine
mtDNA	mitochondrial DNA
Mfn	mitofusin
MERRF	myoclonic epilepsy with red ragged fibers syndrome
OPA-1	optic atrophy protein 1
OMM	outer mitochondrial membrane
OXPHOS	oxidative phosphorylation
PD	Parkinson disease
PS	presenilin
PINK1 or PARK6	PTEN-induced putative kinase
ROS	reactive oxygen species
SNP	single-nucleotide polymorphism
SOD	superoxide dismutase

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