

Mitochondria-mediated damage to dopaminergic neurons in Parkinson's disease (Review)

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Abstract. Mitochondria are important organelles in virtually all eukaryotic cells, and are involved in a wide range of physiological and pathophysiological processes. Besides the generation of cellular energy in the form of adenosine triphosphate, mitochondria are also involved in calcium homeostasis, reactive oxygen species production and the activation of the intrinsic cell death pathway, thus determining cell survival and death. Mitochondrial abnormalities have been implicated in a wide range of disorders, including neurodegenerative disease such as Parkinson's disease (PD), and considered as a primary cause and central event responsible for the progressive loss of dopaminergic neurons in PD. Thus, reversion or attenuation of mitochondrial dysfunction should alleviate the severity or progression of the disease. The present review systematically summarizes the possible mechanisms associated with mitochondria-mediated dopaminergic neuron damage in PD, in an attempt to elucidate the requirement for further studies for the development of effective PD treatments.

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Abbreviations: PD, Parkinson's disease; SNpc, substantia nigra pars compacta; ATP, adenosine triphosphate; ROS, reactive oxygen species; OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; VDAC, voltage-dependent anion channel; ETC, electron transport chain; MCU, mitochondrial Ca^{2+} uniporter; ANT, adenine nucleotide translocator; mPTP, mitochondrial permeability transition pore; HNE, 4-hydroxyl-2-nonenal; SN, substantia nigra; mtDNA, mitochondrial DNA; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; VMAT2, vesicular monoamine transporter 2; OPA1, optic atrophy protein 1

Key words: Parkinson's disease, pathogenesis, mitochondrial dysfunction, reactive oxygen species

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1. Introduction

Parkinson's disease (PD) is a common neurodegenerative disorder, characterized by the progressive degeneration and death of dopaminergic neurons, and by the expression of Lewy bodies in the surviving neurons of the substantia nigra (SN) (1). The exact mechanism of dopaminergic neuron damage remains poorly understood, but several lines of evidence implicate mitochondrial dysfunction as a possible primary cause for the cell death in PD (2-5). Mitochondria are pleiotropic organelles affecting a wide range of molecular and cellular processes. Besides generation of cellular energy in the form of adenosine triphosphate (ATP) by oxidative phosphorylation, they play a crucial role in calcium homeostasis, reactive oxygen species (ROS) production and intrinsic cell death pathway regulation, thus determining cell survival and death (2,5,6). Mitochondria are therefore vital for normal cellular function, including intracellular metabolic activities and signal transduction of various cellular pathways. Mitochondrial dysfunction has been considered as a central event and primary initiator responsible for the progressive loss of dopaminergic neurons in PD (6-8). A better understanding of the molecular mechanisms underlying the pathogenesis will provide potential targets acting as blocking or reversing factors to limit PD progression.

2. Mitochondrial structure and function

Mitochondria are important cytoplasmic organelles with double lipid membranes: The outer mitochondrial membrane (OMM) and the inner mitochondrial membrane (IMM). The elaborate

structures of the mitochondria are required for the maintenance of their normal functions (9). The OMM contains numerous channels formed by the protein, which allow the passage of ions and low molecular-weight substances from the relatively permeable membrane (10). The voltage-dependent anion channel (VDAC) is essential for the exchange of metabolites between the cytosol and intermembrane space bordered by the OMM and the IMM (11). A large hydrophilic pore of the VDAC provides a structural device for the translocation of ions and a variety of metabolites, including ATP and adenosine diphosphate (12). The OMM is involved in mitochondria-mediated cell death via various different pathways through the interaction with a number of regulator proteins. Bcl-2-associated X protein (Bax), for example, translocates from the cytosol into the OMM in response to the apoptotic signals, subsequently oligomerizing at the OMM and promoting the release of apoptotic factors cytochrome *c* and apoptosis-inducing factor, and other pro-apoptotic mediators (13).

The IMM is a convoluted structure formed by a large number of infoldings known as mitochondrial cristae, and is almost impermeable, thus providing an efficient barrier to form an electron gradient and a relatively closed inner matrix for the electron transport chain (ETC), which is required for oxidative phosphorylation in ATP formation (14). The specialized cation transporters and exchangers mediate the cation transmembrane fluxes that are essential for the maintenance of mitochondrial bioactivities. Mitochondrial Ca^{2+} uniporter (MCU) is a specific transport system for Ca^{2+} intake across the IMM, thus playing a role in buffering cytosolic Ca^{2+} . The maintenance of physiologically relevant free Ca^{2+} is required for normal mitochondrial functions, but overload contributes to the opening of the mitochondrial permeability transition pore (mPTP) and matrix swelling, and subsequently cell death (15). The extrusion of mitochondrial Ca^{2+} depends mainly on the Na^{+} -dependent Na^{+} - Ca^{2+} exchanger and the H^{+} - Ca^{2+} exchanger (16,17). The Na^{+} - H^{+} exchanger is a mitochondrial channel that contributes to the maintenance of intracellular pH, which is required for mitochondrial membrane potential formation (14).

The mPTP is a transmembrane channel formed at the contact sites between the OMM and the IMM. Although the components of the mPTP remain controversial, the VDAC, the adenine nucleotide translocator (ANT) and cyclophilin D (CyPD) appear to be implicated (18,19). The mitochondrial matrix protein CyPD mediates direct connection of the IMM protein ANT with the VDAC by binding to a proline residue in ANT (20). The binding results in a conformation of ANT that converts it into a non-specific pore (21). Mitochondrial Ca^{2+} overload and excessive ROS production may be key inducers in the translocation of CyPD from the matrix to IMM, since each plays a crucial role in mPTP opening (13).

The ETC is a multisubunit complex that is required for the production of ATP via oxidative phosphorylation. Synthesis of ETC proteins depends on mitochondrial DNA (mtDNA) and nuclear DNA. mtDNA is double stranded and encodes for 22 transfer RNAs (tRNAs), 2 ribosomal RNAs and 13 polypeptides that are all subunits of respiratory chain complexes (22). Energy production is the most important function for mitochondria, and mitochondrial ATP is generated via oxidative phosphorylation within the IMM (23). Mitochondria are a major source of ROS, which are produced at the sites of the

ETC (24,25). During oxidative phosphorylation, the respiratory chain complexes I and III leak electrons to oxygen, producing primarily superoxide radicals, and subsequently hydrogen peroxide (H_2O_2) and hydroxyl radicals (26,27). Overall, mitochondria participate in energy metabolism, ROS production, calcium homeostasis, the stress response and programmed cell death, thus determining cell survival and death.

3. Mitochondrial ROS production and vulnerability of dopaminergic neurons to oxidative damage

Mitochondria are primary intracellular source of ROS that are generated from the interaction of unpaired electrons with molecular O_2 during oxidative phosphorylation (28,29). Respiratory chain complexes I and III are the major sites of ROS production (26,30,31). The first generated ROS is $\text{O}_2^{\cdot-}$, an amphibolic radical that cannot easily pass through biological membranes and is converted by the mitochondrial matrix enzyme to form H_2O_2 in the mitochondrial intermembrane space and cytosol (32). H_2O_2 is a stable molecule that can diffuse from the mitochondria into the cellular cytosol and nucleus, where it can be detoxified by glutathione peroxidase and catalase into water (33). However, when the balance of H_2O_2 production and antioxidant defense is perturbed, excessive H_2O_2 is accumulated and leads to oxidative stress (34). Particularly in the presence of reduced metals ferrous iron (Fe^{2+}), via the Fenton reaction, H_2O_2 can easily be converted into the highly reactive hydroxyl radical, causing further oxidative damage (35). It is widely accepted that complex I inhibition is a leading cause of increased ROS formation (34). This production of ROS damages in turn the components of the respiratory chain, particularly complex I, leading to its further inhibition and more ROS production. The vicious circle formed between mitochondrial impairment and oxidative stress has been implicated in PD pathogenesis, and may cause the progressive degeneration of dopaminergic neurons by triggering sequential downstream events in neurodegenerative conditions (34,36,37). Nigral dopaminergic neurons are frequently exposed to oxidative stress as they contain high levels of lipids and iron, and exhibit increased dopamine metabolism. Consequently, gradual damage to the dopaminergic neurons occurs due to attack by more ROS (37). Accumulating evidence supports the link of oxidative damage and degeneration of dopaminergic neurons in PD pathogenesis (38-41). Studies in postmortem brains of patients with PD have shown increased levels of lipid oxidation product 4-hydroxyl-2-nonenal (HNE), DNA and RNA oxidation products 8-hydroxy-deoxyguanosine and 8-hydroxy-guanosine, and carbonyl modifications of soluble proteins, supporting the involvement of oxidative stress in dopaminergic neuron damage (37,42). The neurotoxins 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), rotenone and 6-hydroxydopamine are well-known parkinsonism inducers that cause oxidative stress and dopaminergic neuron degeneration in animal models, further supporting the contribution of oxidative stress to PD pathogenesis (43-47). ROS play a major role in causing oxidative stress and damage to all macromolecules, including lipids, proteins and DNA (48).

Lipids participate in membrane fluidity and permeability, and mediate inflammatory processes and apoptotic signals, and

oxidation is the mechanism responsible for the cell damage and death (49). The brain contains high levels of lipids, particular polyunsaturated fatty acids, which are the most prone to lipid peroxidation and responsible for the susceptibility of the organ to oxidative damage (50). The exposure of polyunsaturated fatty acids to free radicals leads to lipid peroxidation which causes the structural damage of membranes, compromising their integrity and consequently cell viability (51). HNE is one of the most important lipid peroxidation products, and has been considered as a inducer responsible for apoptotic cell death via activation of the caspase cascade and induction of DNA fragmentation (52). HNE can also exacerbate oxidative damage by decreasing the levels of glutathione, the major non-enzymatic antioxidant in the central nervous system (53). The elevated levels of lipid peroxidation product HNE have been detected in the SN as well as the cerebrospinal fluid of PD patients, supporting the reinforcement of the hypothesis that peroxidation of polyunsaturated fatty acids leads to dopaminergic neuron damage in oxidative conditions (40,54).

Nigral dopaminergic neurons are particularly exposed to the increased levels of oxidative stress due to increased dopamine metabolism (55). Dopamine is an unstable molecule that can easily undergo oxidative metabolism to form dopamine quinones and free radicals. Normally, the released dopamine is rapidly sequestered into vesicles via vesicular monoamine transporter 2 (VMAT2). A defect in synaptic vesicle formation or function leads to cytoplasmic accumulation of dopamine (56). Inhibition of VMAT2 causes a sustained increase in the formation of dopamine autooxidation products in the cytoplasm, which reinforces the oxidative damage of dopaminergic neurons (56). The levels of dopamine are regulated by monoamine oxidase (MAO)-A and MAO-B, and the latter appears to be a predominant enzyme to metabolize dopamine in neuronal degeneration conditions (57,58). The metabolism of dopamine mediated by MAO-B produces H_2O_2 that diffuses into neighboring dopaminergic neurons where it can react with Fe^{2+} to form hydroxyl radical, leading to further damage to the neurons (59,60). The product of dopamine quinones, aminochrome, can also contribute to neurodegeneration by promoting superoxide generation, α -synuclein fibrillization formation and the neuroinflammatory response (61,62).

Iron can also promote ROS generation and trigger neurotoxicity in neurodegenerative conditions (63,64). As a cofactor for proteins, it is distributed widely in neuronal tissue, particularly the SN (65). However, with aging and degenerative processes such as PD, there is an abnormal, progressive deposition of iron and an increased free iron concentration in the SN pars compacta (SNpc) (66). The increased levels of iron and hydroxyl radicals have been detected in the SN of PD animal models, while total glutathione (glutathione and glutathione disulfide) levels were decreased (67). Administration of the iron chelator desferrioxamine significantly lowers iron levels in the brain and protects against iron and MPTP-induced neurodegeneration in PD mouse models (68). These findings suggest that iron is involved in the process of dopaminergic neuron degeneration in PD. Little is known regarding whether an elevated iron level is a cause or the consequence of neuron damage. However, it is widely accepted that iron-induced toxicity is at least partly responsible for the neuronal cell damage associated with PD (67-69).

Several recent lines of evidence have also implicated reactive nitrogen species in dopaminergic neuronal damage leading to PD pathogenesis (70). Peroxynitrite ($ONOO^-$) is a nitrating agent that acts as a strong oxidant and can damage numerous cellular structures and alter their function, leading to cell death (70). High levels of $ONOO^-$ result in oxidative damage of mitochondrial lipid and protein, inhibition of ETC, Ca^{2+} overload, and subsequent mPTP opening and mitochondria-related pro-apoptotic mediator release (70,71).

Taken together, these results show that dopaminergic neurons in the SNpc are frequently subjected to oxidative damage due to their high levels of lipids and iron, as well as increased dopamine metabolism. Damage to the mitochondrial complexes and the subsequent increase in ROS production are considered to be central causative events responsible for the loss of dopaminergic neurons in PD pathogenesis under neurodegenerative conditions (72,73). Overproduction of ROS causes them to attack macromolecules such as mtDNA and components of the ETC, and causes mtDNA strand breaks, ETC damage and mitochondrial Ca^{2+} overloading, leading to further production of ROS. The vicious circle between ROS production and Ca^{2+} overload favors the sustained opening of mPTP by activation of CyPD (13). Generally, CyPD is a mitochondrial matrix protein that can be translocated to the IMM in response to stimuli. Once located in the IMM, this protein interacts with ANT and changes its conformation, which results in the binding of ANT to VDAC and subsequently mPTP opening (21). Bcl-2 family proteins such as Bax and Bcl-2 homologous killer can also facilitate the opening of the mPTP by translocating and oligomerizing into the OMM as a consequence of oxidative stress (74). The opening of the mPTP causes the collapse of mitochondrial membrane potential and the release of pro-apoptotic mediators from the mitochondria into the cytosol, and subsequently cell death (75) (Fig. 1).

Damage to the ETC and subsequent ROS production form a positive feedback circle that may be a central event driving the progressive loss of dopaminergic neurons under neurodegenerative conditions. Therefore, restoring the function of the ETC and inhibition of ROS production may be a promising method for PD treatment. Coenzyme Q10 (CoQ10), for example, functioning as an endogenous co-enzyme of ETC proteins and an ROS scavenger, plays a crucial role in maintaining the integrity of mitochondrial respiration and the clearance of free radicals (76). *In vitro* and *in vivo* studies have shown that CoQ10 inhibits paraquat-, rotenone- and MPTP-induced mitochondrial dysfunction, and subsequently, ROS production (77-79). As an essential cofactor in the mitochondrial ETC and a ROS scavenger, CoQ10, is currently being investigated in clinical trials of PD.

4. Mitochondria Ca^{2+} -induced cell damage

Ca^{2+} is one of important ions required for the cells to maintain their biological functions, and it is involved in the regulation of not only cell survival, but also cell death, in response to a variety of cellular signals (80,81). Mitochondria are crucial organelles in the regulation of cytoplasmic Ca^{2+} levels and in the maintenance of a Ca^{2+} concentration gradient across their membrane (82). The driving force for the concentration gradient depends on the ETC, which establishes an electrochemical gradient across the IMM

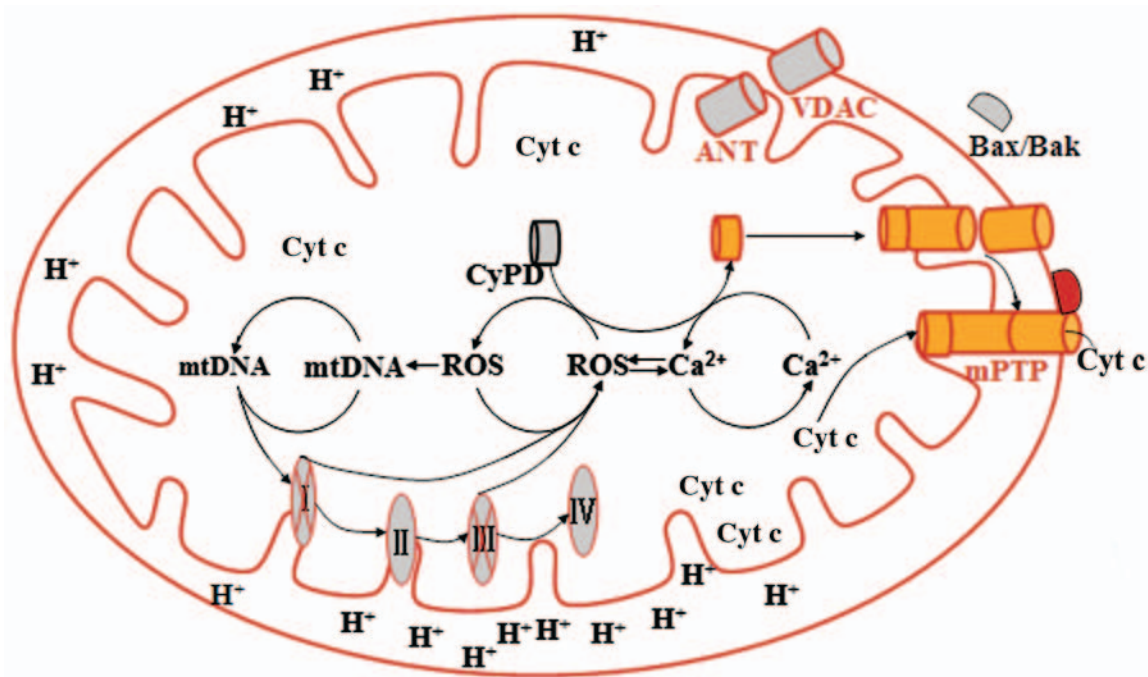


Figure 1. Mitochondrial ROS formation and regulation in apoptosis. Mitochondrial ETC inhibition promotes ROS production. The ROS attack mtDNA and components of the ETC, and cause mtDNA strand breaks, ETC damage and mitochondrial Ca^{2+} overloading, leading to further production of ROS. Mitochondrial ROS and Ca^{2+} can activate CyPD, a mitochondrial matrix protein that can be translocated to the IMM in response to stimuli. Once located in the IMM, this protein interacts with ANT and changes its conformation resulting in the binding of ANT to VDAC and subsequently mPTP opening. Bcl-2 family proteins such as Bax and Bak can also facilitate the opening of mPTP by translocating and oligomerizing into the OMM as a consequence of oxidative stress. The opening of mPTP causes the collapse of mitochondrial membrane potential and the release of pro-apoptotic mediators such as cytochrome *c* from the mitochondria into the cytosol. ROS, reactive oxygen species; mtDNA, mitochondrial DNA; ETC, electron transport chain; CyPD, cyclophilin D; IMM inner mitochondrial membrane; OMM, outer mitochondrial membrane; ANT, adenine nucleotide translocator; VDAC, voltage-dependent anion channel; MCU, mitochondrial Ca^{2+} uniporter; Bax, Bcl-2-associated X protein; Bak, Bcl-2 homologous killer; mPTP, mitochondrial permeability transition pore.

by translocating H^+ ions to the intermembrane space, thereby generating a membrane potential difference for the entry of Ca^{2+} into the mitochondria (83). The transportation of cytosolic Ca^{2+} transports from the OMM into intermembrane space is mediated by the VDAC, which is permeable to Ca^{2+} (84). Ca^{2+} accumulation in the mitochondrial matrix requires the crossing of the relatively impermeable IMM, and the specific transport system, the MCU, is involved (85). The MCU is a two transmembrane domain channel that moves calcium ions across the IMM, and the process is modulated by its regulatory subunits, mitochondrial calcium uptake 1 (MICU1) and MICU2 (86,87). Ca^{2+} plays a crucial role in mitochondrial metabolism through the activation of numerous mitochondrial enzymes (88,89). However, mitochondrial Ca^{2+} overloading may have profound consequences for the cell such as promoting the production of ROS, activating the opening of mPTP and initiating mitochondria-mediated cell death (15). It has been suggested that Ca^{2+} stimulates the activity of nitric oxide synthase to generate NO^* , which results in an inhibition of ETC and subsequent ROS production (90,91). NO^* can react with O_2^- to produce ONOO^- , a highly reactive radical that causes further damage to the ETC and more ROS production, leading to mitochondrial lipid and protein oxidation, mitochondrial membrane rupture, ATP synthesis decrease and the loss of ion homeostasis (13). Impairment of the ETC increases the production of ROS, which in turn damage components of the respiratory chain, thereby triggering a vicious circle between Ca^{2+} overload and oxidative stress, leading to irreversible mPTP opening (92,93). Ca^{2+} overload favors the sustained opening of

the mPTP, which causes the collapse of mitochondrial membrane potential and the swelling of the mitochondria, leading to the release of pro-apoptotic mediators from the mitochondria into the cytosol (94-96) (Fig. 2). Normal neurons are dependent on a calcium signal to regulate diverse processes, including neurotransmitter release, vesicle recycling, axonal transport and neuronal plasticity (97). This is particularly important in dopaminergic neurons that are exposed to frequent influxes of calcium (98). As a central event in mitochondria-mediated intrinsic cell apoptosis, mPTP opening has been reported to be implicated in the pathogenesis of neurodegenerative disorders, including PD (44,99). The mPTP pathway of cell death is mediated by the disruption of the mitochondrial membrane and the release of apoptogenic molecules from the intermembrane space into the cytosol. Cytochrome *c* is one of the important pro-apoptotic factors released by the mitochondria, which triggers the activation of the caspase cascade, leading to the irreversible process toward apoptosis (100,101). Several studies have reported the inhibition of mitochondrial Ca^{2+} overload and mPTP opening, reducing the cell damage in the pathological conditions, including oxidative stress and mitochondrial dysfunction (102). Thus, blockage of mitochondrial Ca^{2+} overload may attenuate the severity of PD that is closely associated with mPTP opening.

5. mtDNA deletions in PD

The most important function of the mitochondria is the generation of ATP through the process of oxidative phosphorylation,

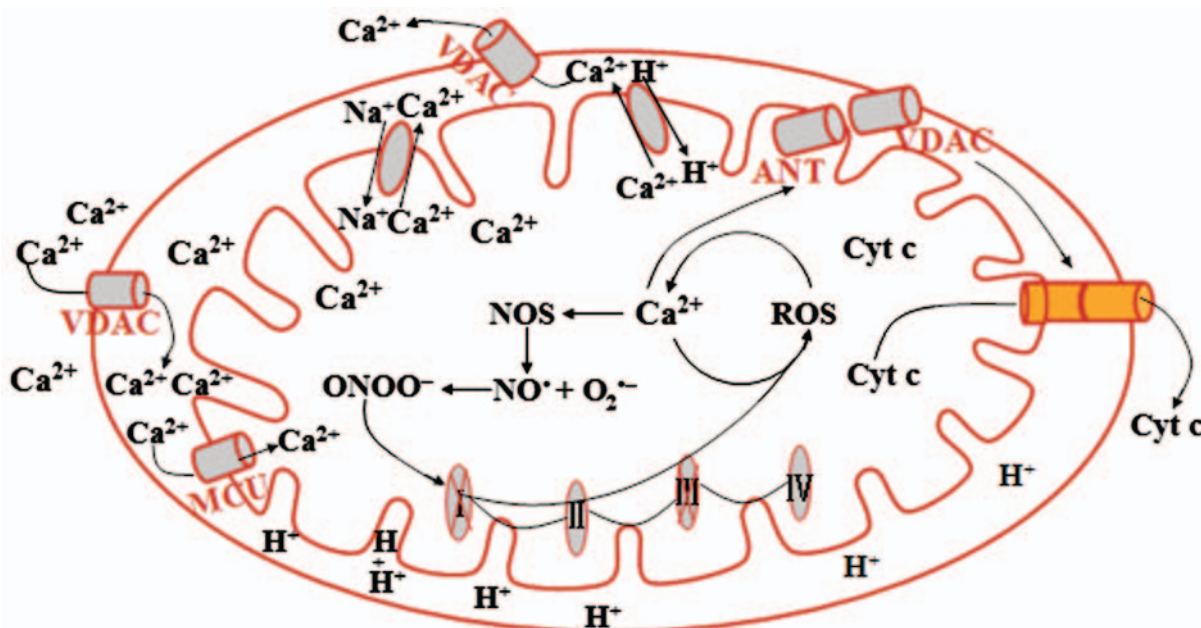


Figure 2. Transporting systems of Ca^{2+} in mitochondria and regulation of mitochondrial Ca^{2+} in apoptosis. The difference membrane potential acrossing the IMM forming by translocating H^+ ions to the intermembrane space drives cytosolic Ca^{2+} from intermembrane space into mitochondria via MCU. The extrusion of mitochondrial Ca^{2+} depends mainly on an Na^+ -dependent Na^+ - Ca^{2+} exchanger and an H^+ - Ca^{2+} exchanger. Ca^{2+} stimulates activity of nitric oxide synthase to generate NO^* and subsequently ONOO^- , which can damage ETC, thus promoting the production of ROS, leading to further Ca^{2+} overloading and ROS production. The overload of mitochondrial Ca^{2+} activates the opening of mPTP, thus initiating mitochondria-mediated cell death. OMM, outer mitochondrial membrane; IMM, inner mitochondrial membrane; VDAC, voltage-dependent anion channel; ONOO^- , peroxynitrite; ETC, electron transport chain; ROS, reactive oxygen species; MCU, mitochondrial Ca^{2+} uniporter.

which depends on mtDNA-encoded proteins. mtDNA encodes 13 proteins that are all ETC complex subunits involved in ATP production, and 2 RNA and 22 tRNAs required for mitochondrial protein synthesis (103). Due to the proximity to the ETC complexes and the source of ROS release, mtDNA is frequently exposed to oxidative stress (104). The lack of histone protein protection results in mtDNA mutation at a high rate relative to nuclear DNA, particularly in cells with high energy demands (105). A number of mitochondria-related diseases could be linked to mutations of the mitochondrial genome (104,106-108). mtDNA deletions that are closely associated with the deficits in normal mitochondrial activity were previously shown to accumulate in nigral dopaminergic neurons of aged individuals and sporadic PD subjects (106-108). Knockout of the mtDNA transcription gene inhibits the expression of mtDNA and the activities in the respiratory chain of dopaminergic neurons, accompanied with progressive parkinsonism in mouse models (109). High levels of mtDNA deletions in the brains of rotenone-induced PD models were observed in the midbrain, but not in the cortex (110). However, somatic mtDNA deletions were shown to be slightly higher in the SN of PD patients compared with age-matched controls (107). These observations demonstrated that mtDNA deletions are specific to nigral neurons, which may increase their susceptibility to oxidative stress and hence contribute to their selective loss in PD. mtDNA is vulnerable to oxidative damage compared with nuclear DNA, since mitochondria are the main sites of ROS production and lack protective histones (103,111). mtDNA damage is associated with the instability of genes and proteins, defect in the ETC and increased ROS production, leading to compromised bioenergetic functions and cell damage. A

number of mitochondria-related diseases could be linked to mutations of the mitochondrial genome (104,106-108).

mtDNA has an autonomously replicating genome encoding a spectrum of mitochondrial respiratory chain proteins (112), and their deletions result in mitochondrial respiratory chain dysfunction (107). The ability to synthesize and repair mitochondrial genomes (mtDNA) is required for the mitochondria to maintain their bioactivities, which rely mainly on mtDNA polymerase. The polymerase γ 1 (POLG1) enzyme is a nuclear-encoded gene product that plays an important role in polymerase synthesis and mtDNA maintenance (113). Mutations in POLG1 have been shown to be associated with severe progressive multisystem disorders, including PD, supporting the involvement of the defective mtDNA in dopaminergic neuron degeneration (114-116). POLG1 mutations contribute to a gradual accumulation of secondary deletions in mtDNA, resulting in dysfunction of the respiratory chain (117). Recently, several studies have shown that selective increased mtDNA damage marker abasic site levels could be detected in the SN in postmortem brains of PD patients. Abasic sites were also shown in brain tissues from mice treated with neuronal toxins rotenone to induce PD-like pathology (118). Abasic sites are segments of DNA that have lost either a purine or a pyrimidine base, resulting in blockage of the polymerase during DNA replication and transcription (119). These studies demonstrated that dopaminergic neuronal injury could be ascribed to mtDNA damage, leading to ETC inhibition and mitochondrial dysfunction in PD pathogenesis. Therefore, the inhibition of this mtDNA damage may be beneficial for PD in neurodegenerative conditions.

6. Abnormalities of mitochondrial fusion and fission in PD

Mitochondria are dynamic organelles with constant changes of morphology that are regulated by mitochondrial fission and fusion. The dynamic balance between fission and fusion is essential for the normal function of the mitochondria and plays a vital role in cellular bioactivities (120,121). Mitochondrial fission serves as a mechanism to facilitate the equal segregation of the mitochondria into daughter cells in mitochondrial division, and to target damaged segments of the mitochondria in the autophagic process. This process is controlled by dynamin-related protein 1 (Drp1), a cytoplasmic dynamin GTPase that translocates to the mitochondria and locates to the OMM in response to mitochondrial dysfunction (122,123). Cytosolic Ca^{2+} is a key mediator in its translocation via the activation of calcineurin and the dephosphorylation of Ser-637 residue in Drp1 (124). Ser-637 of Drp1 can also be phosphorylated by calmodulin kinase I α , leading to its mitochondrial translocation (125). The translocated Drp1 provides a structural device for mechanical force in physical excision of the membrane by formatting a multimeric complex around the OMM (126). Mitochondrial fission 1 protein (Fis1) is another important regulator protein involved in mitochondrial fission. Overexpression of Fis1 has been described to activate the fission process, and results in mitochondrial fragmentation (127). This protein can also trigger autophagy to remove damaged mitochondria, thus contributing to the maintenance of cellular functions (128).

Mitochondrial fusion is another mechanism to maintain mitochondrial bioactivities by mixing the contents of mitochondria, thus enabling its protein complementation, mtDNA repair and equal distribution of metabolites (129). This process depends on three GTPase proteins: Mitofusin 1 (Mfn1), Mfn2 and optic atrophy protein 1 (OPA1) (130,131). Mfn1 and Mfn2 are mitochondrial transmembrane proteins localized to the OMM, and they mediate the outer-membrane connection of neighboring mitochondria by forming homo-oligomeric and hetero-oligomeric complexes via interaction with their coiled-coil domains (132-134). OPA1 is an inner membrane protein mediating IMM fusion. Mitochondrial membrane potential is essential for the connection of the OMM and the IMM, and for maintenance of the mitochondrial tubular network (135,136). Defects in the ETC complexes and damage to the mitochondrial membrane potential contribute to mitochondrial network disintegration, leading to increased fragmentation and cell death (137). Recent studies have suggested that defects in mitochondrial fission and fusion may be one of the underlying mechanisms responsible for mitochondria-mediated neurodegenerative disease (13). Mitochondrial fission and fragmentation can be observed in PD cellular models induced by the neurotoxins rotenone and 1-methyl-4-phenylpyridinium in a rat dopaminergic cell line (138). Depolarization of the mitochondrial membrane causes the loss of OPA1 and the MFNs, leading to the inhibition of fusion and mitochondrial fragmentation (139). The discharge of membrane potential is considered to be a critical factor associated with mitochondrial dysfunction and cell death in neurodegenerative diseases (44,140), indicating its involvement as one of the mechanisms responsible for the degeneration of dopaminergic neurons in PD pathogenesis.

Recent studies have linked Parkin and the PTEN-induced putative kinase 1 (PINK1)/Parkin pathway with the maintenance of mitochondrial dynamics (141,142). PINK1 is a mitochondrial kinase and can be translocated to the OMM where it is cleaved rapidly by presenilin-associated rhomboid-like protease (143). However, when mitochondria are impaired and deplete of membrane potential, the protease activity is inhibited, with the subsequent accumulation of PINK1 on the mitochondrial membrane (143,144). The elevated levels of PINK1 on the OMM trigger the translocation of Parkin to the mitochondria by phosphorylating the protein at Thr-175 in a kinase activity-dependent manner (145,146). PINK1/Parkin mediate mitochondrial fusion and fission dependent on dynamin-like GTPases, including Mfn1, Mfn2, OPA1 and Fis1, and the potential mechanisms of the regulation have been well documented (6). Parkin can facilitate sequestration and elimination of damaged mitochondria via mitophagy, a protective mechanism for maintaining the recycling of proteins and mitochondrial homeostasis to limit cell death (147). Together, the aforementioned studies may provide a molecular target to alleviate the severity of mitochondria-mediated dopaminergic neuron damage in PD pathogenesis.

7. Conclusion

PD is characterized by the progressive degeneration and death of dopaminergic neurons in the SN. The development of molecular and cellular mechanisms associated with dopaminergic neuron damage has implicated the involvement of a range of events in PD pathogenesis, through distinct and divert pathways, to cause progressive neuron damage. Although the precise mechanisms of neuronal damage remain unclear, abnormalities of the mitochondria appear to be a converging point in the cell death processes. Understanding the mechanisms underlying mitochondria-mediated neuron death may provide a promising management solution for PD treatment, however, this requires further elucidation.

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