Chapter

Mitochondrial Quality Control and Parkinson’s Disease

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Abstract

Parkinson’s disease (PD) is a late-onset and progressive motor disease marked by relatively selective nigrostriatal dopaminergic degeneration. The pathogenesis of PD is not completely understood but environmental and genetics factors are believed to play important roles. In recent years, a great amount of evidence has accumulated focusing on the potential role of mitochondria in PD etiopathogenesis. Mitochondria are highly dynamic organelles continuously undergoing fusion, fission, transport, mitophagy and turnover, which form a complex interacting and dynamic network to determine cellular fate. We call the dynamic properties of mitochondria as mitochondrial quality control, which influence not only mitochondrial morphology, mitochondrial biogenesis, mitochondrial distribution and mitochondrial function within the cell, but also eventually cell bioenergetics, cellular integrity and cell injury or death. Mitochondrial function is directly linked to mitochondrial quality control, and vice versa. In this chapter, we will focus on the main controlling pathways of mitochondrial quality control, which may be helpful to understand some neurodegenerative disease, such as Parkinson’s disease.

Keywords

Mitochondrial Homeostasis; UPS; Mitophagy, Fission/Fusion; Biogenesis; Mobility; Antioxidation; Parkinson’s Disease
Introduction

Parkinson’s disease (PD) is the second most common age-related neurodegenerative disease following Alzheimer’s disease (AD), and is a lethal complex disease of progressive development. Mitochondria are crucial regulators of energy metabolism and are considered essential organelles for life and death of neurons, owing to their high energy demands for their specialized functions, complex morphology and synaptic activity. Thus, in addition to being a source of ATP, mitochondria perform pivotal biochemical functions necessary for arbiter of neuron cell death and survival. Mitochondrial function is associated with mitochondrial quality control. Recent evidence suggests that an imbalance in mitochondrial quality control may contribute to neurodegenerative disease, such as Parkinson’s diseases [1-3]. The aim of this part is to identify all the mechanisms currently understood to be involved in mitochondrial quality control and PD [4]. In addition, We also aim to highlight current understanding of mitochondrial quality control processes as they relate to different aspects of mitochondrial structure and function, as well as focusing on the role of various pathway that are essential for quality control in Parkinson’s disease.

Regulation of Mitochondrial Quality Control

The mechanism to keep mitochondrial quality control is complex and is modulated by too many factors and
at too many levels [3-5]. The major mechanisms of maintaining mitochondrial quality control can be conceptualized into five major points. The first point involves the localized degradation of damaged proteins by ubiquitin-proteasomal degradation, a mitochondrial protein quality control system named as the cytosolic ubiquitin/proteasome system (UPS), and the whole elimination of the dysfunctional mitochondria by a form of autophagy in which defective mitochondria are selectively cleared, named as mitophagy [6,7]. The second pathway is activated by more severe dysfunction and involves fission-based sequestration of damaged segments of mitochondria and fusion-based complementation of a healthy mitochondrion with a damaged mitochondrion, which is called as the fission/fusion machinery [8-10]. The third involves the mitochondrial mobility of its constant shape remodeling and subcellular trafficking to the cellular region of high metabolic requirements dependent on the microtubules network and motor proteins, which designates mitochondrial mobility [8]. The fourth controlling pathway is effective formation of new mitochondrial components to increase their individual mitochondrial masses or copy numbers, which is named as mitochondrial biogenesiss [11,12]. The fifth line involves that mitochondria may keep the cellular free radicals under toxic level to compensate for mitochondrial defects by the function of self-contained antioxidant enzymes and nonprotein antioxidants confronted with oxidative stress, and we call it as an effective of anti-
oxidant defense mechanism [13,14]. Thus the neurons are dependent on the different control pathways mentioned above to effectively integrate cellular responses to achieve mitochondrial homeostasis to maintain cell normal function avoiding neurons injury.

The Axes of Mitochondrial Quality Control

The First Pathway of Ubiquitin-Proteasomal System (UPS) and Mitochondrial Autophagy (Mitophagy)

The inherent structure and function lead to mitochondria susceptible to exogenous and endogenous damages, easily resulting the accumulation of unfolded or misfolded proteins within mitochondria, which of [15] ten eventually prompt critical mitochondrial functions disrupted and mitochondrial integrity loss. Therefore, clearance of misfolded and aggregated proteins is constantly needed to maintain the integrity and function of mitochondria [16]. And increasing evidences implicate the cytosolic ubiquitin/proteasome system (UPS) is a part of the mitochondrial protein quality control system protecting mitochondrial homeostasis [17]. Furthermore, in order to prevent the problem of unsalvageable damaged mitochondria spreading within the cell, there is a mechanism to eliminate the dysfunctional mitochondria by au-
tophagy, called mitophagy [18,19]. In addition to UPS in mitochondrial protein degradation, mitophagy (a selective mitochondrial autophagy) mediates a bulk removal of damaged mitochondria [3]. It is also an important system in promoting mitochondrial homeostasis and maintaining the normal function of cells.

The mechanism of UPS-mediating mitochondrial protein degradation is complicated [17]. Now we summarize the process as follows: First, misfolded or damaged mitochondrial proteins in the cytosol are recruited to the outer mitochondrial membrane (OMM) for proteasomal degradation; Upon reaching the OMM, these proteins are presented to the polyubiquitinated proteasome of K48 by Parkin or other mitochondrial ubiquitin E3 ligases; Then, these polyubiquitinated mitochondrial substrate proteins are retranslocated to the cytoplasm to be degraded by the proteasome [16].

Lots of evidences show that UPS plays essential roles in regulating mitochondrial homeostasis. It is well known that mitochondrial fusion and fission are intimately associated with mitochondrial homeostasis, which will be discussed next. However, Mfn1/2, Fis1 and Drp1, major players in regulating mitochondrial fusion and fission, can be degraded by the proteasome [20-22]. Additionally, mitochondrial fragmentation was decreased with the depletion or inactivation of MITOL (requiring for Drp1-
dependent mitochondrial fission as a mitochondrial E3 ubiquitin ligase) [23]. Moreover, elongated mitochondrial morphology appears with USP30 knockdown (an OMM-localized deubiquitinating enzyme), which indicates there may be a defect in fission [16,24]. In addition, the accumulation of aberrant proteins within mitochondria often disturbs mitochondrial function and threatens cell survival in PD. For example, alpha-synuclein, a protein associated with the development of Parkinson’s disease, can be targeted to the IMM where it binds to the mitochondrial respiratory complex I and impairs its function under stress conditions [25]. Aberrant alpha-synuclein with its unique interaction on the mitochondrial membrane can also disturb the fusion process in mitochondrial dynamics [26]. Therefore, prompt removal of dysfunctional or aberrant proteins with UPS becomes crucially important in maintaining mitochondrial function and integrity [16].

Mitophagy refers to the selective removal of mitochondria by the autophagic machinery, appearing to be a universal route for the degradation of dysfunctional mitochondria [27]. It has been demonstrated that PINK1/Par-kin pathway plays a vital role in the turnover of mitochondrial mitophagy [28-31]. Detrimental stimulus-caused mitochondria damage result in mitochondrial membrane potential depolarization, which inhibits PINK1 cleavage. Full length PINK1 thereby increases in the mitochondria and enhances the phosphorylation of parkin [32]. Then,
Parkin translocates from the cytosol to the mitochondrion in response to a fall in mitochondrial membrane potential [33]. Recent data suggest this action in turn triggers either directly or indirectly VDAC1 and/or MFN to be ubiquitinated in a Parkin-dependent manner [34]. And then, mitochondrial aggregation occurs because of the Parkin-mediated ubiquitination of mitochondrial outer membrane proteins. Finally, both p62 and HDAC6 link polyubiquitinated mitochondria with LC3, initiating mitophagy. In addition, the increased oxidative stress as a result of DJ-1 deficiency has been suggested as a cause to mitophagy. Thereby, DJ-1 may be implicated in mitophagy and may work in a parallel pathway to PINK1 and Parkin [2,35].

It is well known that mitochondria are one of the main sources of reactive oxygen species (ROS), and they are also the immediate targets of ROS damage. However, dysfunctional mitochondria, if they are not degraded effectively and timely, can produce higher amounts of ROS, which is further vicious to neurons. Thus, mitophagy seems to be of special importance in keeping the quality control of mitochondrial homeostasis, which is associated with the PD pathogenesis [5]. If the function of mitophagy is impaired, the defective mitochondria will not be effectively cleared from the cell and a large number of damaged mitochondria accumulate in neurons [5,27]. The aggregation of mitochondria in neurons generates excess superoxide radicals and ultimately leads to neurodegeneration. It has
been described that mitophagy protein expression was re-
duced in PD nigra and amygdale, which may be a reflect
of defects of autophagy existing in PD [5,15].

The Second Pathway of the Mitochondrial
Fission/Fusion Machinery

Mitochondria constantly keep elongating and divid-
ing to form a network that spans the entire area of the
neurons to meet with cellular functional demands. The
dynamic nature of mitochondrial networks is due to fre-
quent cycles of two completely opposing processes, includ-
ing mitochondrial fission (the separation of long, tubular
mitochondria into two or more smaller parts) and fusion
(the combination of two mitochondria into a single orga-
nelle) [8,10,36-39]. The mitochondrial fission/fusion op-
erate concurrently. Repetitive cycles of fusion and fission
in mitochondria are important process to keep mitochon-
drial homeostasis to meet their functional and integral
demands. The two opposing processes not only determine
the structure of the entire mitochondrial population in
the neurons, but also influence nearly every aspect of mi-
tochondrial functions, such as respiration, calcium buff-
ering, and apoptosis [40,41]. Additionally, mitochondrial
fusion, as well as mitochondrial fission has also been ob-
served to be associated with cell death mechanisms apart
from maintaining normal mitochondrial functions and
integrity [40,42].
The normal function of a damaged mitochondria can possibly be complemented and be restored by fusing with a neighboring integral mitochondria, named as mitochondrial fusion [43]. In addition, it has been reported that the transfer of mtDNA or whole mitochondria between cells can occur in vitro and rescue aerobic respiration in cells. Actually, mitochondrial fusion is a complementary route for the proper respiratory activity, the intact mitochondrial membrane components, and the efficient mitochondria metabolism, as well as, for the stabilization and protection of mitochondrial DNA (mtDNA) and proteins [44,45].

Mitochondrial fusion involves the tethering of two adjacent mitochondria of the inner and outer mitochondrial membranes merging respectively. This action facilitates the exchange of contents between these organelles and aids the renovation of defective mitochondria. Neurons with defective fusion of mitochondria display enhanced cell death, mitochondrial membrane potential depolarization and defective respiration. Therefore, efficient mitochondrial fusion is important in maintaining the mitochondrial homeostasis.

The entire mitochondrial fusion process can be summed up with at least three events: docking, fusion of the outer membrane and fusion of the inner membrane. It has been reported that mitofusions(Mfn1 and Mfn2) are engaged in mitochondrial tethering and outer membrane fusion. Because loss of both proteins leads to gross mi-
tochondrial fragmentation due to impaired fusion [46]. While mitofusins are important for the outer mitochondrial membrane fusion, Opa1 is not only involved in the outer membrane fusion step with the inner membrane contacts and also has a direct physical action on the inner membranes fusion [46]. And knockout of this protein suppresses the mitochondrial fusion in cells and results in the disorganization of cristae and widening of cristae junctions [47]. It is suggested that Opa1 plays an important role in maintaining mitochondrial cristae structure, even the mitochondrial homeostasis.

Fission may play a double protect action in maintaining the mitochondrial function and integrity. First, fission facilitates equal segregation of mitochondria into daughter cells during cell division and improves distribution of mitochondria along cytoskeletal tracks. Second, fission may help to isolate damaged segments of dysfunctional mitochondria from the entire mitochondrial web and to sort out mutant mtDNA copies, promoting their clearance by autophagy as above mentioned “mitophagy” [48]. The two aspects of mitochondrial fission are important for the maintenance of healthy mitochondria.

However, the precise mechanism of the two sides of mitochondrial fission in mammals is largely unknown, most insights concerning the mechanisms largely deriving from studies in yeast. It is thought that mitochondrial fission in mammals follows the same procedures as in
Mitochondria are dynamic organelles that have the ability to divide and fuse continuously with each other to keep mitochondrial homeostasis. The dynamic characteristic of mitochondria is especially crucial for polarized cells like neurons, with high energy demands. The critical balance between mitochondrial fission/fusion is greatly dependent on a large group of conserved proteins, the dynamin-related GTPases [10]. Not only Mfn1/2 and Opa1 involved in mitochondrial fusion, but also Drp1, the principal component of mitochondrial fission, all belong to the family of large GTPase proteins. May be this is the common between mitochondrial fusion and fission. However, the detail mechanisms of the two processes largely differ as discussed above.

Mitochondria are now recognized to be dynamic and mobile organelles that constantly undergo membrane re-
modeling through repeated cycles of fusion and fission. In neurons, the mitochondrial fission/fusion machinery has important roles in the modulation of mitochondrial function and integrity. Actually, the full-mitochondrial lifecycle is largely derived from the balance of mitochondrial fusion and fission. Any disruption on their balance can change the normal distribution of mitochondria in neurons. Either inhibition of the fission protein Drp1 expression or overexpression of the fusion protein Mfn1 to disturb the mitochondrial fission or fusion mechanisms, can prevent mitochondria from distributing to synapses, which leads to a loss of mitochondria from dendritic spines and consequently to a reduction of synapse formation [53-56]. On the other hand, counteraction of this process by Drp1 overexpression and to promote its effects on dendritic mitochondria in turn restore synapse formation [53]. In conclusion, mitochondrial fission may help mitochondrial renewal, redistribution, and proliferation into synapses, while mitochondrial fusion may be benefit mitochondrial mobility and distribution across axons into the synapses.

Additionally, mitochondrial fission has been described to be critical to maintain the stability of mtDNA [57], whereas mitochondrial fusion has been directly involved in preventing the accumulation of damaged mtDNA in neurons [58,59]. While the two processes of fission and fusion maybe completely opposite, it seems at least in one point they serve the same purposes along neu-
rons: fission is the final step in mitochondrial duplication, whereas fusion dilutes errors in mtDNA, which are both important processes required to maintain a healthy mitochondrial cellular pool and to protect mitochondrial integrity and function [60,61]. It is well known that neuron function is intimately dependent on mitochondrial homeostasis. Accordingly, there should be no surprise of the strong association between mitochondrial dysfunction and neurodegenerative diseases. One case of neonatal lethality has been attributed to a defect in Drp1. This patient carried a dominant-negative allele that caused perinuclear tangles of elongated, large-diameter mitochondria [62]. Also it has been found that the impaired balance of mitochondrial dynamics between fission and fusion is strongly implicated in the pathogenesis of PD.

**The Third Pathway of Mitochondrial Mobility**

Another aspect of mitochondrial homeostasis beyond above mentioned is the motility of mitochondria, with constant shape remodeling and subcellular trafficking. The process that mitochondria are transported within the cell along cytoskeletal tracks is named as mitochondrial mobility. Neurons are highly polarized cells requiring mitochondria at sites distant from the cell body, which is critically important to maintain the normal function of the neuron. Thus, mitochondria are effectively concentrated and are actively recruited to subcellular regions with high metabolic requirements, such as the axonal and dendritic processes of neurons.
Based upon the particular needs of the cell and characteristics of its microtubular network, mitochondria may be organized into lengthy traveling chains, pack tightly into relatively stable groups, or appear in many other formations. The constant shape remodeling, subcellular trafficking and positioning of mitochondria within neurons largely depend on the microtubules network and the molecular motors, such as kinesins and dyneins [63-65]. Movement of mitochondria towards the axon terminal direction occurs along microtubule tracks and depends mainly on kinesin motors, such as KHC and Kif5b. While movement towards the cell body direction occurs largely along actin tracks and utilizes dynein motors [66]. These movements are also supported by a number of signalling and adaptor molecules such as Miro and Milton. For example, KHC and Kif5b can interact with mitochondria through Miro1 and Miro2, an important calcium sensitive regulator of axonal mitochondrial transport [63,67]. In neurons, when the concentrations of calcium increasing, it acts on Miro to prompt mitochondrial movement stop, and thus keeps mitochondria at sites where ATP production and Ca2+ buffering are needed [68,69].

When the Miro-dependent transport pathway was affected in neurons, it might result in the depletion of mitochondria from dendrites and axons, and the defect of neurotransmission during prolonged stimulation [70,71]. In another way, when Miro was overexpressed, it affect-
ed mitochondrial morphology and led to mitochondrial thread formation and elongated mitochondria (Fransson, Ruusala et al. 2006; Reis, Fransson et al. 2009). Therefore, in mammalian cells, manipulation of Miro can dramatically influence mitochondrial morphology and function [70]. Another reports also showed depression of dynein function sequestered Drp1 in the cytoplasm and resulted in perinuclear, elongated mitochondria [72].

The Fourth Pathway of Mitochondrial Biogenesis

Mitochondria are key regulators in maintaining the normal function of the neurons. However, mitochondria are also particularly susceptible to damage. It has been reported that higher mitochondrial copy number or higher mitochondrial mass is essential to maintain the mitochondrial homeostasis and is protective to the neurons. Therefore, mitochondria require continuous recycling and regeneration throughout the lifespan to keep the normal function of the cell.

However, mitochondria cannot be made de novo. The formation of new mitochondria called as mitochondrial biogenesis, refers the process by which new mitochondria are formed and via which the individual mitochondrial mass are increased. It encompasses all processes involved in maintenance and growth of these organelles, as well as the ones required for their division and segregation during the cell cycle mentioned above as mitochondrial fis-
Mitochondria have their own DNA and are semi-autonomous organelle in the cell. The majority of mitochondrial protein comes from the nuclear genome, while the mitochondrial genome encodes most parts of the electron transport chain along with mitochondrial rRNA and tRNA. Thus, the formation of new mitochondrial is two-fold process. In the regeneration, new mitochondrial are formed from the transcription and translation of genes both in the nuclear genome and in the mitochondrial genome. Mitochondrial biogenesis requires the coordination of the transcription of the large number of mitochondrial genes in the nucleus, as well as of the fewer but essential genes in mitochondria [11].

Mitochondrial biogenesis is regulated by a series of transcription factors, transcription co-activators and signal transduction proteins to balance the mitochondrial number and mass within neurons [74]. PGC-1α is be-
lieved to be the master regulator of mitochondrial biogenesis [11]. It is particularly important and nuclear respiratory factor 1/2 (NRF2/NRF1) are their co-activators. The NRFs, in turn, activate the mitochondrial transcription factor A (TFAM) in a further, which is directly responsible for transcribing nuclear-encoded mitochondrial proteins. This includes both structural mitochondrial proteins as well as those involved in mtDNA transcription, translation and repair.

To maintain the energy production and to prevent the endogenous oxidative stress, effective control of mitochondrial biogenesis becomes critical for the promotion of the normal function of the healthy neurons [11]. Therefore, if mitochondrial biogenesis deceases, the reserve capacity of mitochondrial itself reduces accordingly. And if the function of mitochondrial biogenesis was affected, the balance of mitochondrial homeostasis would be disturbed. There would be influence on the organism, especially the neurons in the central nervous system (CNS). Exposure of neurons to adverse factors is more apt to produce deleterious effects leading to mitochondrial malfunction, which further damages neuron cells. Easily to be understood, it is critical to maintain normal mitochondria biogenesis for balancing mitochondrial function to prevent the accumulation of oxidized lipids, proteins and DNA in neurons. Thus, stimulation of the regulatory factors of mitochondrial biogenesis, mainly through PGC-1α, should play a key role in this prevention [73]. Thus, it is conceivable that
higher activity levels of PGC-1α could sustain neuronal health by maintaining the mitochondrial turnover. Indeed, repression of PGC-1α activity by mutant huntingtin clearly leads to mitochondrial dysfunction and neurodegeneration whereas overexpression of PGC-1α rescues the activity of neurons [75].

**The Fifth Pathway of Antioxidant Defense Mechanism [SH]**

Mitochondria are considered the main source of reactive oxygen species (ROS) production by virtue of their function in oxidative respiration, which generate superoxide anion (a precursor of other forms of free radical) as an inevitable byproduct. However, mitochondrial are particularly vulnerable to ROS-induced damages. The accumulation of ROS can damage the respiratory chain complexes, leading to a progressive decline in mitochondrial function and eventually inducing cell death [76].

To protect against potential ROS-induced lesions in mitochondria, most cells have developed an effective antioxidant defense mechanism that consists of antioxidant enzymes (such as superoxide dismutase [SOD], glutathione peroxidase, and catalase), as well as nonprotein antioxidants (such as glutathione, α-tocopherol, and ascorbic acid) to keep the levels of cellular free radicals under toxic levels [77,78]. It is well known that superoxide anion can not diffuse through the mitochondrial mem-
brane except in the protonated form. There are several pathways for superoxide anion transformation in cell [79]. First, part of the superoxide anion produced by the mitochondrial respiratory chain can be released into the inner membrane space and then be converted to H2O2 with the help of Cu-SOD or Zn-SOD [80]. Second, some of the superoxide anion present in the intermembrane space might be scavenged by cytochrome c or release into the cytosol reliant on the voltage-dependent anion channel (VDAC) [81]. Third, some of superoxide anion in the inner membrane space may also react with NO to form highly reactive ONOO− in the cell to avoid the direct action of superoxide anion toxicity on cells [82]. Fourth, part of superoxide anion are cleared by the glutathione (GSH) and multiple GSH-linked antioxidant enzymes [82]. Among GSH-linked enzymes involved in mitochondrial antioxidant defense are Gpx1 and Gpx4 (Franco, Posser et al. 2009). These enzymes exert an important antioxidant action in catalyzing the reduction of H2O2 and of lipid hydroperoxides. For example, ROS byproducts produced by mitochondrial respiration are rapidly detoxified by SOD 2, which converts superoxide anion to hydrogen peroxide within the mitochondrial matrix. The accumulated hydrogen peroxide can be further metabolized by glutathione peroxidase (Gpx 1) and peroxiredoxin (Prx) III or diffused from the mitochondria into the cytosol to control their basal levels low and nontoxic to cells [83].
The connection of oxidative stress and PD has been extensively studied, lots of results are conclusive. It is also consistent with the implication of oxidative damage to lipids, proteins and DNA in the pathogenesis of PD, as observed in the SNpc of sporadic PD brains of post-mortem studies. The source of this increased oxidative stress is uncertain but may at least include impaired antioxidant pathways and mitochondrial dysfunction.

**Mitochondrial Quality Control in Parkinson’s Disease**

Recent findings from genetic studies suggest that defective mitochondrial quality control may play an important role in the development of PD, a common neurodegenerative disease characterised by the progressive loss of dopaminergic neurons [3-5,84]. The pathologic character of PD is the accumulation-damaged protein aggregates such as α-synuclein (SNCA) and ubiquitin into intracytoplasmic inclusions termed Lewy bodies [15]. The mechanisms underlying the process of Parkinson’s disease are very complex and not fully understood. It has been identified that PD was associated with mutations in at least six genes that are responsible for generating mutations in the following proteins: SNCA, Parkin, PINK1, the protein deglycase DJ1, and leucine-rich repeat kinase 2 (LRRK2) [15]. Interestingly, these genes give rise to proteins that are associated with mitochondria or located within mitochondria, thereby implicating mitochondrial dysfunction.
as an important contributor to the development of Parkinson’s disease [85].

There are lots of evidence of mitochondrial abnormalities in Parkinson’s disease, such as reduced complex I activity, reduced mitochondrial membrane potential, increased ROS production, altered mitochondrial dynamics, impaired mitochondrial trafficking, and increases in mtDNA mutations [27]. For example, it is known that sporadic and familial variants of PD share some common pathways that converge at mitochondria [86]. Moreover, there is increasing evidence that mitochondrial complex I deficiency was also found in the brain, skeletal muscle, and platelets of sporadic PD patients [87]. Additionally, rotenone and paraquat as commonly used pesticides and herbicides that selectively inhibit complex I, also result in Parkinsonism in animal models and possibly in people [88]. It is also has been reported that the activity of complex I was reduced by 33% in the SNc and frontal cortex of PD patients at autopsy [89]. Moreover, complex I in mitochondrial and nuclear genomes were found to be oxidatively injured in mitochondrial preparations derived from PD frontal cortex samples, indicating that oxidative stress may decrease the stability of mitochondrial complex I subunits [89]. These changes in mitochondria further confirmed the association of mitochondria and Parkinsons’ disease from the other side. Additionally, several studies have also reported that some genes associated with Hereditary Parkinson are all involved in the mitochondrial qual-
ity control pathways (at different levels). Impairment of mitochondrial protein quality control processes that leads to mitochondrial dysfunction and accumulation of dysfunctional mitochondria in the neuron. Therefore, it can be concluded that mitochondrial function and fitness are fundamental to Parkinson’s disease and dysfunctions in mitochondrial quality control have also been implicated to contribute to neurodegeneration, especially PD.

As mentioned in the above sections, mitochondria are now appreciated to constitute a population of organelles which require a careful balance and integration of numerous processes, involving with the fission–fusion machinery, the regulation of biogenesis, migration throughout the cell, shape remodeling and autophagy [90]. These dynamic processes prompt mitochondrial recruitment to critical subcellular compartments, content exchange between mitochondria, mitochondrial shape control, mitochondrial communication with the cytosol, so that to regulate mitochondrial function and integrity to maintain mitochondrial quality control [91]. Mitochondrial homeostasis is essential for maintaining neuronal function, such as neuronal signaling, plasticity and transmitter release. The controlling pathways of mitochondrial quality control played an important role in maintaining mitochondrial homeostasis in healthy cells.

To maintain a healthy mitochondrial network, cells must undergo mitophagy or mitochondrial fusion to dispose of damaged and dysfunctional mitochondria and
produce new healthy mitochondria via mitochondrial biogenesis or mitochondrial fission [91]. Dysfunctional mitochondria may arise due to accumulation of mitochondrial DNA mutations and misfolded and oxidatively modified proteins. In PD, it has been well established that mitochondria are targeted and that mitochondrial complex I is downregulated [89]. This further induces mitochondrial reactive oxygen, respiratory chain dysfunction, and mtDNA damage. These events are all thought to contribute to Parkinson’s disease. Multiple lines of evidence indicate that the accumulation of dysfunctional mitochondria in neurodegeneration or Parkinson’s disease, in part, be due to reduced mitochondrial quality control.

UPS system is important in the quality control of mitochondrial proteins, particularly those on the OMM, and studies have found that inadequate proteasomal degradation exists in animal models of Parkinson’s disease [16]. Dysregulation of ubiquitination or even excess proteasomal activity can similarly result in detrimental effects. Ubiquitinated proteins as well as ubiquitin itself are elevated in Parkinson’s disease [16]. Excessive activity of the proteasome is observed in and thought to contribute to Parkinson’s disease [39].

It is known that mitochondrial quality control system maintains normal mitochondrial bioenergetics. Mitophagy through removing injured proteins play an important role in this process. In addition, it has been proposed that the
reduced autophagic response contributes directly to Parkinson’s disease [27] and autophagy slowly weakens when the neuron degeneration occurs. Mitophagy is a complex program which is mainly regulated by two key proteins PINK1 and parkin [16]. In patients with PD, PINK1 and Parkin mutations display impaired mitophagy. If there are mutations and defects in PINK1, Parkin might diminish both the mitochondrial translocation and activation. Then this can result in the failure to segregate dysfunctional mitochondria for mitophagy via fission, and have also been associated with a decrease in phospho-Drp1 levels and an increase in Drp1 GTPase activity. Therefore, it is suggested there is a direct role of PINK1 with Parkin to induce fission. Finally, and not surprisingly as mentioned above, mutations in PINK1 reportedly increase the sensitivity of neuron degeneration. On the other hand, mutations in Parkin, can result in impaired ubiquitination of outer mitochondrial membrane proteins and this process has been shown to associated with autophagosome recognition. Moreover, in Parkin knockout mice, neurons displayed severe mitochondrial damage and decreases in complexes I and IV in the ventral midbrain [92]. As discussed previously, under normal conditions, these damaged mitochondria would be sequestered and undergo mitophagy or degradation. However, in PD, defects in PINK1 and Parkin compromise the ability of the neuron to dispose of proteins or damaged mitochondria, and the accrual of damaged mitochondria would, in all likelihood, ultimately
lead to cell death. Therefore based on the aforementioned discussion, PINK1 and parkin play an important role in modulating mitochondrial quality control. Therefore, it is conceivable that the failure of the control mechanisms would result in the degeneration of dopaminergic neurons observed in PD, which plays a causative role in this disease. Consistent with this notion, PD patients with either PINK1 or Parkin mutations might have a compromised mitochondrial quality control that accelerates the death of dopaminergic neurons. In addition, being the major supplier of energy in mammalian cells, mitochondria are necessary to provide more energy for damage repair and cellular survival during disease processes with excessive oxidative stress [1]. In order to meet the demand for energy supply, signals transmitted to the nucleus may induce mitochondrial proliferation and mtDNA amplification to produce more functional mitochondria. The abundance of mitochondria in a cell is determined by the biogenesis. Genes controlling mitochondrial biogenesis that are expressed in response to peroxisome proliferator-activated receptor γ coactivator-1α (PGC-1α) are under expressed in patients with PD [93]. Conversely, we have proved that overexpression of PGC-1α results in increased mitochondrial function and blocks the dopaminergic neuron loss induced the pesticide rotenone in cellular disease models [94]. It is also been reported that PGC-1α as a potential therapeutic target for early intervention of PD [93]. The results indicate that promotion of mitochondrial biogenesis initiate neuroprotection and neurorescue in PD.
Parkin has also been recently shown to regulate mitochondrial function by promoting mitochondrial biogenesis [95]. It has been reported that accumulated levels of PARIS were observed both in PD patients with Parkin mutations and in sporadic PD patients, it therefore can be concluded that Parkin might promote the ubiquitination of the PGC1α-transcriptional repressor PARIS [96], which is an important transcriptional activator of genes involved in mitochondrial biogenesis. Therefore, it is possible that mitochondrial dysfunction in these patients is linked to defective mitochondrial quality control. Additionally, it has been reported that a genetic variant rs2306604 A-allele in TFAM could be a moderate risk factor for Alzheimer’s disease (AD), which suggests that disturbance of maintenance of mtDNA integrity or mitochondrial function may underlie neurodegenerative disorders [97,98]. Recently, the production of a TFAM knockout mouse model of PD further provided evidence to support this hypothesis.

Concomitantly, the cell not only stimulates mitochondrial biogenesis to maintain the mitochondrial population. It also activates mitochondrial fusion and fission process to divide and segregate damage mitochondria to increase the population of healthy mitochondria [38]. This is a complex process which is controlled by communication between the nucleus and the mitochondria. Therefore, it can be summarized that maintaining mitochondrial quality control is a key process in the contribution of mitochondria to cell division and physiological maintenance.
Antioxidant defense is also a very important element in mitochondrial quality control. In response to increased oxidative stress, mitochondrial abundance, copy number and integrity of mtDNA would be altered under these pathological conditions in dopaminergic neurons. Within its tolerable threshold, ROS may induce expression of specific genes to help these cells cope with risk factors, which is called protective responses. Once beyond this threshold, ROS may cause nociceptive response to damage to mtDNA and other biomolecules of the affected dopaminergic neurons. Ultimately, it can result in induction of mitochondrial membrane permeability transition and release of proapoptotic proteins to elicit an apoptotic cascade, which eventually leads to dopaminergic neuron degeneration in the pars compacta of the midbrain of PD. Moreover, low quality mitochondria can damage remaining healthy mitochondria through the release of ROS and Ca\(^{2+}\) from the organelle. In a conclusion, lot of evidence has been proved that impairment of mitochondrial quality control may be involved in the pathological process culminating in neuronal cell death in PD. Therefore, maintaining the balance of mitochondrial quality control might block the pathological process at an early stage in PD. Understanding the interaction between these different mechanisms maintaining mitochondrial quality control might offer early and novel prospects for therapy in PD. Exploring the mechanism of mitochondrial quality control can further provide strategies to prevent and treat
neurodegeneration in PD, including of rendering neuron more resistant to conditions associated with mitochondrial dysfunction, application of antioxidants to protect the neurons from oxidative damage, maintaining proper mitochondrial biogenesis in the early stage of disease, promoting damaged mitochondria degradation and keeping dynamic balance of mitochondrial fission and fusion to maintaining mitochondrial homestasis in PD.

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