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Is there a pathogenic role for mitochondria in Parkinson's disease?

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SUMMARY

Parkinson's disease (PD) is a common neurodegenerative disorder of unknown cause. For decades, a deficit in mitochondrial respiration was thought to be a key factor in PD neurodegeneration. However, excluding a few exceptions where a clinical picture of parkinsonism is associated with a mitochondrial DNA mutation, preclinical and clinical studies have failed to identify any genetic mutations in the genes encoding for the electron transport chain complexes in PD patients. More recently, it has been discovered that mutations in the genes encoding for Parkin, PINK1 and DJ1 are associated with familial forms of PD and with mitochondrial alterations, including morphological abnormalities. These results have led many researchers to revisit the question of mitochondrial biology as a primary mechanism in PD pathogenesis, this time from an angle of perturbation in mitochondrial dynamics and not from the angle of a deficit in respiration.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder of the aging brain after the dementia of Alzheimer [1]. PD's mean age at onset is 55, and its incidence increases with age [2]. The cause of almost all occurrences of PD remains unknown. PD arises essentially as a sporadic condition, i.e. in absence of any apparent genetic linkage, but occasionally, the disease is inherited due to mutations in a variety of genes including *DJ-1*, *PARKIN* and *PINK1* [3–5]. In both sporadic and familial PD, a primary hallmark is the degeneration of the nigrostriatal dopaminergic pathway, which, in depleting the brain of dopamine, leads to the emergence of abnormal motor manifestations such as resting tremor, stiffness, slowness of voluntary movement, and postural instability [1]. At the onset of these manifestations, striatal dopamine is depleted by ~80% and substantia nigra dopaminergic neurons lost by ~60% [1]. However, the neuropathology of PD is far from being restricted to the nigrostriatal pathway, as histological changes can be found in many other dopaminergic and even non-dopaminergic cell groups including locus coeruleus, raphe nuclei, nucleus basalis of Meynert and dorsal motor nucleus of vagus [6]. Because a host of distinct neurological conditions share PD clinical features, a definite diagnosis of PD can only be achieved at autopsy and is customarily based not only on the loss of nigrostriatal dopaminergic neurons, but also on the identification of intraneuronal inclusions called Lewy bodies (LBs) [7]. These inclusions are spherical eosinophilic cytoplasmic aggregates composed of a variety of proteins, such as α-synuclein, parkin, ubiquitin and neurofilaments, and can be found in every affected brain region [7]. Whether identification of LBs should still be considered necessary for the diagnosis of PD is controversial, since cases of inherited PD linked to parkin mutations typically lack LBs and are still regarded as cases of PD.

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2. Why a mitochondrial defect was sought in PD

As mentioned above, the cause of sporadic PD is currently unknown and, over the years, a variety of pathogenic scenarios have been proposed to try to explain the why and the how of neurodegeneration in PD. The idea of mitochondrial dysfunction as a pathogenic mechanism in PD seems to have emanated from the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) story. Indeed, in the early 1980s, some drug users developed a rapidly progressive parkinsonian syndrome almost indistinguishable from PD [8]. In these individuals, even the beneficial response and development of long-term motor complications following the administration of L-DOPA were virtually identical to that seen in PD patients. Thanks to some fine detective work, this cluster of a sudden occurrence of PD-like syndrome was traced to the intravenous use of a street preparation of 1-methyl-4-phenyl-4-propionpiperidine (MPPP), an analogue of the narcotic meperidine (Demerol). MPTP was the responsible neurotoxic contaminant, inadvertently produced during the illicit synthesis of MPPP in a basement laboratory. Subsequently, it was established that 1-methyl-4-phenylpyridinium (MPP^+), the active neurotoxic metabolite of MPTP, accumulates in the mitochondrial matrix where it inhibits oxidative phosphorylation as reviewed in [9]. The use of several MPP^+ analogs and cationic inhibitors has demonstrated that MPP^+ inhibits the oxidation of NAD (nicotinamide adenine dinucleotide)-linked substrates by blocking electron transfer through complex I of the electron transport chain (ETC) [10], somewhere in the proximity of its quinone binding site [11]. Therefore, it is believed that, in response to MPP^+ binding to complex I, the flow of electrons along the respiratory chain is hampered, leading to an energy crisis and oxidative stress and, ultimately, to neuronal death. MPP^+ also inhibits the activity of the α-ketoglutarate dehydrogenase complex, a key enzyme of the tricarboxylic acid cycle, thereby impairing ATP synthesis and inducing an energy deficit *in vitro* [12] and *in vivo* [13]. In combination with 6-hydroxydopamine or dopamine, MPP^+ strongly stimulates Ca^{2+} release from mitochondria and hydrolysis of intramitochondrial pyridine nucleotides [14].

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The phenotypic similarity between PD and MPTP-induced parkinsonism in humans and the fact that MPP^+ is poisonous to the oxidative phosphorylation system prompted many investigators to search for mitochondrial respiratory defects in PD patients. Despite the fact that parkinsonism is hardly associated with genuine mitochondrial diseases, less than a decade later, as discussed in the next section, this idea has gained more than sufficient enthusiasm among PD researchers.

3. Mitochondrial dysfunction In PD

The direct relation between mitochondrial dysfunction and PD came from the post-mortem description of complex I deficiency in the substantia nigra of patients with PD [15]. Subsequently, this deficiency has also been reported in several tissues from PD patients including skeletal muscles and platelets [16–18]. Remarkably, the severity of this defect in complex I activity reported in the substantia nigra of PD patients corresponds to about a 35% reduction compared to control populations. However, the substantia nigra samples used in the aforementioned studies were obtained from autopsies, which typically derive from advanced cases of PD. In these PD samples, we can thus safely assume that most of the neurons of interest, such as the dopaminergic neurons, are gone and the number of glial cells, in contrast, has grown due to neurodegeneration-associated gliosis. Consequently, it is legitimate to posit that it is unlikely that the reported complex I deficit could have emanated from dopaminergic neurons only, since the vast majority of the cells contained in the studied samples are probably non-dopaminergic neurons.

As to how a complex I defect may provoke neurodegeneration, this question remains enigmatic. For instance, in mitochondrial cytopathy where known mitochondrial DNA (mtDNA) mutations cause a documented deficit in complex I and a neurodegenerative phenotype such as in Leber's optic atrophy [19], we still do not know the actual mechanisms responsible for cell death. Preclinical studies, especially with MPTP, have suggested that a blockade of complex I kills cells via a recruitment of the mitochondrial-dependent apoptotic pathway [20,21]. However, in isolated brain mitochondria, complex I dysfunction, caused by either pharmacological or genetic means, fails to directly activate this cell death pathway and to kill cells. Instead, defects of complex I lower the threshold for activation of mitochondrial-dependent apoptosis by Bax, thereby rendering compromised neurons more prone to degeneration [22,23].

4. Mitochondrial DNA in patients with PD

mtDNA encodes 13 structural polypeptides of the oxidative phosphorylation system, including seven of the approximately 46 subunits of complex I. Thus, given the alleged complex I defect in PD brains, mutations in mtDNA are an obvious early target for analysis. The number of mtDNA deletions in individual neurons in the substantia nigra is increased substantially in PD patients older than 65 years [24]. This striking result was associated with decreased cytochrome c oxidase (i.e. complex IV and not complex I) activity, as evidenced by histochemistry.

Aside from the above analyses, sequencing of the mtDNA of patients with PD has generally been done in unselected groups with and without a mitochondrial deficiency [25,26]. Although the results of some reports have suggested increased frequency of specific mtDNA polymorphisms in patients with PD, others have not [27–31]. For instance, certain mtDNA haplotypes influence PD expression, and haplotype J has been associated with both a decreased and an increased risk of developing PD [32]. Some evidence suggests that mtDNA haplotypes might influence cytosolic pH and mitochondrial calcium regulation which could influence neuronal function and integrity over time [33].

Genetic transplantation has been used in two different studies to investigate the potential of mtDNA from patients with PD to determine the origin of the complex I defect. In the first study, platelets from unselected patients with PD were fused and grown in mixed cultures [34]. In the second, patients with PD were selected on the basis of a platelets complex I deficiency [35] and cells from these patients were fused with cells that lack mtDNA (Rho 0) and grown in mixed or clonal cultures. In both instances, the mtDNA that was transferred from the patients with PD caused a complex I defect in the recipient cybrid cells, suggesting that the mtDNA from these patients caused the complex I deficiency through inherited or somatic mutations. However, in PD, the maternal inheritance pattern of mtDNA is rare and may be a mere coincidence [36–38]. Nevertheless, a few case reports are consistent with the idea that mtDNA mutations may contribute to the occurrence of a parkisonism. For instance, a mutation in the mtDNA 12S RNA was found in a patient with maternally inherited, early-onset parkinsonism, deafness, and neuropathy [38], and a deletion in the gene encoding cytochrome b was found in a patient with parkinsonism and encephalomyopathy with lactic acidosis and stroke-like episodes [39]. There is also evidence for the occurrence of parkinsonism in association with the Leber's optic atrophy mitochondrial mutation G11778A [40]. However, in all of the above-cited reports, none of the patients who harbored a mtDNA mutation displayed a picture of pure parkinsonism like that seen in PD.

5. Mitochondrial function and familial PD

As indicated in the introduction, in rare instances, the PD phenotype can be transmitted as a dominant or recessive trait due to mutations in the nuclear DNA and, relevant to the present article, some of these involve *PARKIN*, *PINK1* and *DJ-1*, which are gene products whose role in mitochondrial biology are increasingly recognized.

5.1. The ubiquitin ligase, Parkin

Parkin is transcribed ubiquitously, and ultrastructural studies have shown that it is essentially cytosolic and that a small fraction may be associated with intracellular membranes including mitochondria [41]. The definite biological role of Parkin remains uncertain, but the protein contains several domains for protein–protein interactions and has E3 ligase activity [42]. Relevant to the latter property, several putative substrates for Parkin have been reported [1], but whether any of these are *bona fide* Parkin substrates remains to be established.

Recessive loss-of-function mutations in *PARKIN* were first reported in patients with juvenile-onset parkinsonism [3]. Subsequently *PARKIN* mutations have been shown to be the most common cause of PD in individuals younger than 20 [43]. However, occasionally, *PARKIN* mutations in patients with older-onset PD (i.e. >40 years of age) have also been reported [44]. An increase in striatal extracellular dopamine concentrations, reduced synaptic excitability, and a mild, non-progressive motor deficit at 2–4 months were described in a *Parkin* knockout mouse line [45]. However, no loss of dopaminergic neurons and, like in most patients with *PARKIN* mutations, no inclusion formations were noted in these mice [45]. It has been reported that *Parkin* knockout mice have decreased mitochondrial respiratory chain function in the striatum and reductions in specific respiratory chain and antioxidant proteins [46]. More striking is the fact that *Parkin* knockout *Drosophila* develop muscle pathology, abnormal mitochondrial morphology, and apoptotic cell death [47]. Amazingly, it has been shown that Parkin can be recruited to depolarized mitochondria, promoting their engulfment in autophagosomes and destruction by autophagy [48]. This observation led to the hypothesis that Parkin may be a key player in the turnover of damaged mitochondria by mitophagy [49].

5.2. PINK1 (PTEN-induced putative kinase 1)

The gene encoding PINK1 consists of 8 exons and encodes a ubiquitously expressed, insoluble, 581 amino acid, 63 kDa protein with an amino-terminal, mitochondrial-targeting sequence. There

is some evidence that PINK1 is, at least in part, localized to the inner mitochondrial membrane, while its carboxy-terminus is exposed to the cytoplasm [50]. The serine–threonine kinase domain of PINK1 has substantial homology with the CG4523 protein in *Drosophila* [51]. CG4523 interacts with a protein in the fly that is the orthologue of the mammalian mitochondrial translation-initiating factor 3 (MTIF3), making the latter a possible interactor with PINK1. Interesting, analysis of genetic variants of MTIF3 in patients with PD found an allelic association between the C798T polymorphism and PD [51].

Mutations in *PINK1* are a cause of autosomal recessive PD [4]. Mutations have been reported within and outside of the kinase domain [4,52]; however, the localization of PINK1 to the mitochondria is not affected by these mutations [50]. Patients harboring the causative *PINK1* mutations have features of typical early-onset PD.

Pink1 knockout flies are viable but sterile or hypofertile, have a motor deficit, a shorter life-span, an abnormal flight muscle with impaired function, disorganized mitochondrial morphology, reduced mitochondrial mass, lower concentrations of ATP, and a small reduction in the number of dopaminergic neurons [53,54]. This phenotype is very close to that seen in the *Parkin* knockout flies [47]. Relevant to this fact are the observations that the over-expression of *Parkin* can rescue the mitochondrial abnormalities linked to the loss of Pink1 or its pathogenic mutations [53,54]. These data suggest that *PARKIN* and *PINK1* participate in the same pathogenetic pathway. While more work needs to be done to elucidate the role played by both Pink1 and Parkin in mitochondria, mounting evidence indicate that, at least in insect cells, both proteins modulate mitochondrial dynamics including fusion/fission. Mitochondrial fission is a process controlled by DRP1 (dynamin-related protein 1) and by FIS (mitochondrial fission protein) which involves the separation of mitochondria into two or more smaller parts, whereas mitochondrial fusion, controlled by mitofusin (MFN) and optic atrophy 1 (OPA1), involves the combining of two mitochondria into single organelles. A balance between fission and fusion is crucial to normal mitochondrial function and thus, cell homeostasis. It has been suggested that PINK1 promotes mitochondrial fission and regulates mitochondrial morphology in *Drosophila* and several mammalian models [55–57]. In flies, the overexpression of *Drp1* or the knock-down of *Mfn* and *Opa1* rescues *Pink1* mutant phenotypes such as the degeneration of dopaminergic neurons and muscles [55,56].

5.3. Oncogene DJ-1

Mutations in the gene encoding DJ-1 are also a rare cause of autosomal recessive PD [5]. Patients with mutations in *DJ-1* have young-onset PD, progress slowly, respond well to L-DOPA, and may have dystonia. Interestingly, the DJ-1 L166P mutation has been reported to cause increased mitochondrial localization of DJ-1 [5], although this conclusion has not been confirmed in other studies.

DJ-1 is a 23 kDa protein that is expressed in peripheral tissues and in neurons and glia in parts of the brain including the striatum, the substantia nigra pars compacta and pars reticulata. It is also highly expressed in the cerebellum, the hippocampus, and the olfactory bulbs [58]. Studies on the intracellular distribution of DJ-1 show that it is found in several pools, including in the mitochondria, where it is present, presumably, in the intermembrane space and matrix.

Thus far, studies on DJ-1 function have yielded confusing results and its role played at the mitochondrial level remains unclear. DJ-1 seems to possess several functions, including that of an oncogene, a modulator of androgen-receptor-dependent transcription, and a sensor of oxidative stress [59–61]. Of note, some studies have reported that oxidative stress and PD-associated mutations do not increase the mitochondrial localization of DJ-1, while others showed that DJ-1 might translocate to the outer mitochondrial membrane during oxidative stress [61–63]. The deletion or silencing of DJ-1 has been reported to sensitize cells to oxidative stress, and the overexpression of DJ-1 to protect cells against free radicals [64]. There is evidence that DJ-1 functions as an atypical peroxiredoxin-like-peroxidase and that loss of this function results in impaired mitochondrial reactive oxygen species scavenging [65]. In conjunction with this, some mouse lines lacking DJ-1 [66], but not others [65], were reported to be more susceptible to the dopaminergic neurotoxicity produced by MPTP. It has also been suggested that DJ-1 forms a nuclear complex with RNA-binding proteins and DNA-binding proteins which regulates gene transcription and which can prevent apoptotic cell death by α-synuclein or oxidative stress [67].

6. Conclusion

During the past decades, there has been an enormous amount of work dedicated to the role of mitochondria in neurodegenerative diseases in general and in PD in particular [68]. Despite these huge efforts, we still do not know with certainty whether, unless of dramatic magnitude, a decrease in ATP production, an increase in reactive oxygen species formation, or the release of mitochondrial apoptogenic factors play – alone or in combination – any role in neurodegenerative processes. We also increasingly recognize that the potential role of mitochondrial dysfunction in PD may not be due to a defect in respiration but rather may involve alterations in mitochondrial dynamics. Perhaps, some of the previous observations about the mitochondrial respiratory defect in PD did merely report on non-specific alterations that occur in dying neurons or on alterations that are secondary to perturbations in mitochondrial dynamics. The development of better *in vivo* experimental models of neurodegenerative diseases may provide us with the necessary tools to examine, appropriately, the mechanistic relationship between neurodegeneration and mitochondrial dysfunction and to address, once and for all, many of the pending issues that cloud the field of sporadic *mitochondrial* neurodegenerative diseases.

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Conflict of interests

The authors have nothing to declare.

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