

Review Article

Mitochondrial Contribution to Parkinson's Disease Pathogenesis

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The identification of the etiologies and pathogenesis of Parkinson's disease (PD) should play an important role in enabling the development of novel treatment strategies to prevent or slow the progression of the disease. The last few years have seen enormous progress in this respect. Abnormalities of mitochondrial function and increased free radical mediated damage were described in post mortem PD brain before the first gene mutations causing familial PD were published. Several genetic causes are now known to induce loss of dopaminergic cells and parkinsonism, and study of the mechanisms by which these mutations produce this effect has provided important insights into the pathogenesis of PD and confirmed mitochondrial dysfunction and oxidative stress pathways as central to PD pathogenesis. Abnormalities of protein metabolism including protein mis-folding and aggregation are also crucial to the pathology of PD. Genetic causes of PD have specifically highlighted the importance of mitochondrial dysfunction to PD: PINK1, parkin, DJ-1 and most recently alpha-synuclein proteins have been shown to localise to mitochondria and influence function. The turnover of mitochondria by autophagy (mitophagy) has also become a focus of attention. This review summarises recent discoveries in the contribution of mitochondrial abnormalities to PD etiology and pathogenesis.

1. Introduction

Mitochondria are ubiquitous organelles, critical for cell survival and for correct cellular function [1]. Furthermore, they play an important role in mediating cell death by apoptosis and in determining their own destruction by mitophagy. Mitochondria are recognised to play an important role in neurodegenerative disorders. This may be a consequence of a primary mutation of mitochondrial DNA (mtDNA), for example, the A3243G mutation—a cause of myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS), a mutation of a nuclear gene regulating mtDNA, for example, the mtDNA depletion syndromes, a nuclear gene encoding a mitochondrial protein, for example, frataxin in Friedreich's ataxia, secondary effects of disordered cell metabolism, for example, free radical stress, or environmental toxin exposure [2, 3]. This review will focus on the contribution of mitochondrial pathology to the pathogenesis of Parkinson's disease (PD), and it is notable that the mitochondrial involvement covers the entire etiological spectrum detailed above.

The first report of a mitochondrial defect in PD identified deficiency of complex I activity in substantia nigra compared

to age-matched controls [4] and was followed by reports of mitochondrial defects in skeletal muscle, platelets, and lymphoblasts in a proportion of cases (see [5] for review). The mitochondrial deficiency within the brain appeared to be confined to the nigra [6, 7] although other reports have identified defects in the frontal cortex [8]. These mitochondrial abnormalities, identified in pathologically confirmed, apparently sporadic PD, were seen against a background of increased oxidative stress and elevated brain iron levels—and emphasised the importance of interconnecting pathways even at this early stage [9–14]. It was a fortuitous accident of timing that these observations of abnormal mitochondrial metabolism in PD were being made when important insights were gained into mitochondrial diseases by identification of mutations of mtDNA.

2. Mitochondrial Diseases and Parkinsonism

Primary mutations of mtDNA, as opposed to, for instance mutations secondary to a nuclear housekeeping gene, rarely manifest with parkinsonism [15, 16]. In part this may be a result of regional distribution of the mutation

with a relatively lower level in nigral cells (although this has never been investigated), or alternatively, related to better physiological compensatory mechanisms in the younger patient, that is, those that usually manifest with the encephalomyopathies. In any event, tissue specificity of an ubiquitously expressed mutation remains common in mitochondrial disorders and is poorly explained, but may in part be related to the dependence of a tissue on high energy demands, for example, brain and muscle. Inherited mtDNA-mediated defects of complex I usually manifest with encephalomyopathic features rather than parkinsonism [17, 18], as do other inherited primary specific respiratory chain defects, for example, affecting complex IV [19, 20].

Mutations of mtDNA polymerase gamma (POLG) are a recognised cause of parkinsonism, usually, but not always, preceded by ophthalmoplegia and are often associated with a peripheral neuropathy [21–23]. These cases have multiple deletions of mtDNA, sometimes with mtDNA depletion, and usually exhibit ragged red fibres in muscle biopsies. They have reduced dopamine transporter density by single photon emission tomography scanning, respond well to levodopa, and have Lewy bodies at postmortem. Patients with POLG mutations can also present with other phenotypes including childhood onset liver failure, myopathy, and renal disease [24, 25]. Mutations of POLG in sporadic PD are rare [26, 27].

Mutations of mtDNA may be inherited or somatic. Somatic mutations of mtDNA are known to develop with aging and are thought to represent cumulative damage due to excess exposure to free radicals [28]. The mitochondrial genome resides in the matrix, probably in close proximity to the inner mitochondrial membrane, a site of high superoxide ion production. Initial studies did not demonstrate any increase in deleted mtDNA genomes in pathologically proven PD [29]. However, quantitation of deleted mtDNA molecules in individual nigral neurons showed a significant rise with age [30], and this appeared to be increased in parkinsonian brains [31]. This may be the result of the enhanced oxidative stress in the nigra in these brains. Nevertheless, the neurons with the highest load of deleted mtDNA expressed a mitochondrial defect in the form of cytochrome oxidase deficiency, indicating that the deleted mtDNA population did have a functional effect [31]. Mitochondria have an important role in calcium homeostasis. Prominent calcium influx occurs in nigral dopaminergic neurons via L-type channels and is a phenomenon not shared by neighbouring dopaminergic neuronal populations, which are much less affected in PD [32]. In a *DJ-1* knockout mouse model this created oxidative stress and resulted in increased oxidation of mitochondrial proteins specific to vulnerable nigral dopaminergic neurons [33].

Although the potential contribution of mtDNA to respiratory chain deficiency in PD has received support from cybrid studies [34–37] no abnormality of this genome has been consistently identified in PD patients.

3. PARK Genes and Mitochondria

There remains a debate as to whether the parkinsonism caused by these genes is phenotypically equivalent to

“idiopathic” PD or not. In many respects this is a sterile argument given the phenotypic spectrum in idiopathic PD itself. Furthermore, mutations of several of these genes have been identified in patients who satisfy the Queen Square Brain Bank criteria for PD. The real point is that these gene mutations cause dopaminergic nigrostriatal cell death. The proteins encoded by the *PINK1*, *parkin*, and *DJ-1* genes can translocate to mitochondria and influence function within that organelle, although this does not exclude additional activities in other cell compartments.

3.1. *PINK1*. Recessive mutations in *PINK1* (Park6) were found to be responsible for a familial form of early-onset parkinsonism, previously mapped to chromosome 1p36 [38]. *PINK1* protein has a mitochondrial targeting sequence at its N-terminus and has been shown to have an intramitochondrial location, although in which compartment(s) remains uncertain. Several reports have demonstrated abnormal mitochondrial function in models of *PINK1* knockout and in patients with *PINK1* mutations including defective oxidative phosphorylation, increased free radical damage and reduced mitochondrial levels [39–45].

Several of the reported mutations of *PINK1* are located in the kinase domain [38, 46–48] and altered phosphorylation of target proteins probably represents a key pathogenic mechanism. The phosphorylation of mitochondrial proteins is considered pivotal to the regulation of respiratory activity in the cell and to signalling pathways leading to apoptosis, as well as for other vital mitochondrial processes. The generation of monoclonal antibodies to respiratory chain subunits [49, 50] has enabled the demonstration that a number of the subunits are phosphorylated, including several subunits of complex I [51–54].

3.2. *Parkin*. *Parkin* (Park2) gene mutations were first identified in autosomal recessive juvenile onset parkinsonism (ARJPD) [55]. Pathologically there is dopaminergic cell loss in the substantia nigra pars compacta and locus ceruleus, but Lewy bodies are rarely seen [56–58]. Patients carry deletions or point mutations in various parts of the *parkin* gene [59, 60]. The relevance of *parkin* mutations to idiopathic PD has been highlighted by the identification of *parkin* mutations in apparently sporadic cases of PD and by the description of Lewy bodies in *parkin* positive patients with later onset disease than ARJPD [61, 62].

Parkin protein functions as an E3 ligase, ubiquitinating proteins for destruction by the proteasome [63, 64] or lysosome [65]. *Parkin* knockout mice have decreased striatal mitochondrial respiratory chain function and reduced respiratory chain activity [66]. *Parkin* knockout flies developed muscle pathology, mitochondrial abnormalities, and apoptotic cell death [67]. Overexpression of *parkin* in PC12 cells indicated that it is associated with the mitochondrial outer membrane [68]. *Parkin* mutation positive patients have decreased lymphocyte complex I activity [69]. Fibroblasts from *parkin* mutation positive patients also exhibit decreased complex I activity and complex I-linked ATP production [70, 71].

3.3. *DJ-1*. Mutations of *DJ-1* are a rare cause of familial PD. This protein is located in the cytosol, nucleus, and mitochondria but under conditions of oxidative stress preferentially partitions to the mitochondrial matrix and intermembranous space to mediate a protective effect [72]. This protection may also be an effect of mRNA regulation and increased translation under conditions of oxidative stress [73–75]. *DJ1* knockout mice downregulated uncoupling proteins 4 and 5, impaired calcium-induced uncoupling and increased oxidant damage [76]. *DJ-1* is thought to have a protective role in reducing protein misfolding and aggregation that may be a consequence of oxidative stress and so has been reported to reduce alpha-synuclein aggregation [77].

3.4. *Alpha-Synuclein*. Point mutations in the *alpha-synuclein* (Park1) gene [78, 79] and more recently duplications of the wild-type gene have been described as causes of familial PD. A triplication of the gene was identified in a large autosomal dominant kindred with PD and tremor [80] and duplication of the gene was found in one of 42 familial probands of early onset PD [81]. A further *alpha-synuclein* point mutation (E46K) has been reported in an autosomal dominant family with parkinsonism and Lewy body dementia [82]. Alpha-synuclein is a major component of Lewy bodies in idiopathic, apparently sporadic PD [83].

Alpha-synuclein protein is predominantly cytosolic, but a fraction has been identified in mitochondria [84], appears to interact directly with mitochondrial membranes, including at the neuronal synapse [85], and to inhibit complex I in a dose dependent manner that reflects the brain regional expression of alpha-synuclein [86, 87]. Alpha-synuclein has also been shown to reduce ATP synthesis and mitochondrial membrane potential, although in one study alpha-synuclein did not affect respiratory chain activity or membrane potential [88, 89]. Mitochondrial abnormalities of structure and function have been observed in transgenic mice over-expressing mutant alpha-synuclein [90]. Alpha-synuclein undergoes an important posttranslational modification with phosphorylation at serine 129 [91], and it would be interesting to determine whether this might influence the effect of the protein on mitochondrial function.

4. Mitochondrial Dynamics and Mitophagy

Abnormal mitochondrial morphology and changes in mitochondrial dynamics have been reported for PINK1, parkin, *DJ-1*, and alpha-synuclein in a variety of cell and animal models [70, 89, 92–98]. These events could be due to direct effects on mitochondrial fission and fusion [89, 94, 97, 98], be secondary to deficiencies in oxidative phosphorylation [86], and/or be related to impaired mitochondrial turnover [99].

Recent studies have demonstrated that PINK1 together with parkin play a vital role in the turnover of mitochondria mitophagy [96, 98, 100, 101]. Parkin translocates from the cytosol to the mitochondrion in response to a fall in mitochondrial membrane potential [102]. Recent data suggest

that this is preceded by phosphorylation of parkin by PINK1 [103]. Parkin translocation to depolarised mitochondria is abolished in *PINK1* knockout mouse embryonic fibroblasts (MEFS). Transfection of these MEFS with wild-type *PINK1* restored parkin translocation [104]. However, transfection of kinase-dead PINK1 could not restore mitophagy suggesting that PINK1 recruits parkin to mitochondria by a kinase pathway. Parkin and PINK1 involvement in mitophagy includes the ubiquitination of mitofusin 1 and 2 (mfn 1 and 2) by parkin [105, 106]. Recently *DJ-1* has also been implicated in mitophagy [92, 107]. The increased oxidative stress as a result of *DJ-1* deficiency has been suggested as a cause. Data also suggests that *DJ-1* works in a parallel pathway to PINK1 and parkin [107, 108].

HtrA2 is a mitochondrial protease thought to be involved in the turnover of mitochondrial proteins. The phosphorylation of HtrA2 is dependent on PINK1, probably via a kinase cascade, rather than as a direct substrate [109]. Mutations in the *HtrA2* gene are a possible rare cause of PD [110, 111]. The mitochondrial chaperone TRAP1 has been shown to be a direct substrate of PINK1 [112]. These data suggest that PINK1 might be involved in the regulation of mitochondrial proteins as well as mitochondria as a whole.

Thus, quality control of mitochondria may play an important role in PD pathogenesis if the essential clearance of defective mitochondria is impaired and damaged mitochondria accumulate, utilising substrate and generating excess superoxide radicals. The recent description of reduced autophagy protein expression in PD nigra and amygdala may mirror defects of mitophagy [113]. Defective trafficking of mitochondria between cell compartments may be an additional consequence of impaired fission fusion and in turn may contribute to regional cellular dysfunction such as at the synapse.

5. Conclusion

Since the discovery of mitochondrial dysfunction in PD, a very large body of evidence has accrued to confirm that this organelle plays an important part in pathogenesis. Mitochondrial toxins have been used to induce dopaminergic cell death [114–116] and environmental exposure to toxins can increase the risk for parkinsonism [117]. The familial causes of parkinsonism/PD function in pathways that influence mitochondrial function directly or indirectly. This is not to aver that mitochondrial dysfunction is *the* cause of PD, but rather to suggest that it is a critical feature and one worthy of further investigation, particularly in relation to the development of interventions to modify the course of PD. Indeed, several studies have been performed using agents that influence mitochondrial function [118–120].

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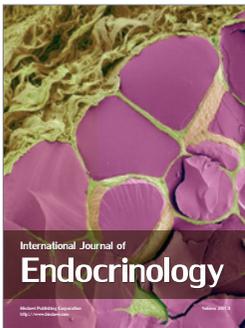
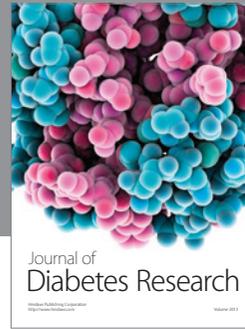
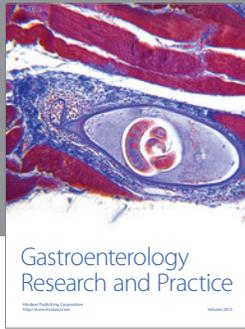
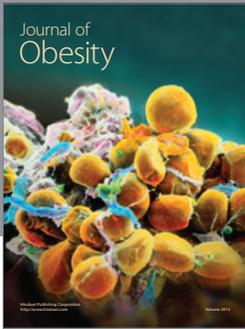
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