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Mitochondrial matters in Parkinson disease: introduction

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Abstract Individuals with Parkinson disease (PD) are encountered frequently and have progressively severe neurologic changes. The central nervous system changes involve dopaminergic neurons in the basal ganglia and substantia nigra. Although usually sporadic, rare forms of PD are familial and the responsible genes have been identified. These genes affect mitochondrial function and can be studied in animals. Brains of affected animals reveal consequences of reactive oxygen species (ROS)—quinones, dopamine oxidation products, tyrosine nitration, lipid peroxidation and amino-aldehyde adducts. The three genes are important for maintaining physical and functional mitochondrial integrity. The cumulative effects of mitochondrial dysfunction, particularly those mediated by ROS, ultimately lead to at least some of the clinical and pathologic changes of PD.

Keywords Mitochondrion · Oxidation · Neurodegeneration · Mutation · Parkinson

Background

In 1817, James Parkinson described the disorder that continues to bear his name. Parkinson Disease (PD) is now recognized as the second most frequent neurodegenerative disorder (after Alzheimer disease). PD affects nearly 1% of Americans but appears to be pan-ethnic and worldwide in distribution. It is characterized by neurologic dysfunction, initially often nonspecific but relentlessly progressing to movement changes including a resting tremor, rigidity and a general reduction in spontaneous movement. By contrast with Alzheimer disease, cognitive changes are infrequent.

Early neuropathologic studies showed degeneration of the basal ganglia and substantia nigra with loss of neurons that use dopamine for neurotransmission. An important breakthrough nearly 40 years ago was the introduction of L-DOPA as an oral agent that could minimize the clinical manifestations, presumably compensating for the contributions from lost neurons. Despite the encouraging initial clinical improvement that may persist for many years, affected individuals gradually lose responsiveness to L-DOPA and their symptoms (often more debilitating) reappear, consistent with underlying progressive neuronal loss only transiently compensated by medication.

The basic pathophysiology of PD remains unclear and likely has multiple contributing factors. However, careful observations have revealed several important features that must be considered in any proposed disease mechanism(s):

1) Relatively late onset—peaking in the 6th decade
2) Relentless neurodegeneration
3) Particular susceptibility of dopaminergic neurons of basal ganglia
4) Intraneuronal accumulation of so-called "Lewy bodies"—containing ubiquitin, α-synuclein and other proteins
5) The "experimental" development of PD-like symptoms in individuals who had injected the drug MPTP (later found to be an inhibitor of complex I of the mitochondrial respiratory chain)
6) Rare but important inherited forms of PD

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Table 1 Genetic mutations in Parkinson disease

OMIM #	Gene	Function	Reference
606324	DJ1	Transcriptional Activator; Mutants can bind to parkin and PINK1.	van Duijn et al. (2001)
605909	PINK 1	Serine/Threonine kinase; regulates mitochondrial $Na+/Ca^{++}$ exchanger. Mutants lead to mitochondrial calcium accumulation and ROS production.	Hatano et al. (2004)
600116	parkin	Ubiquitin-protein ligase; ubiquitinates synphilin-1 which interacts with α-synuclein-coexpression of the 3 proteins leads to Lewy body formation.	Takahashi et al. (1994)

Although most PD appears to be sporadic, affected individuals occasionally show familial transmission. Several single-gene forms are recognized and the responsible genes have been isolated. All are involved with mitochondrial function. They are summarized in Table 1.

The relationships of several pathways to mitochondria are considered in this issue. As background, it is important to recall that mitochondria likely undergo various types of change over time. In particular, the small circular mitochondrial genome appears particularly vulnerable to mutations including nucleotide changes, deletions and reorganizations. These are likely mediated, at least in part, by free radicals generated by electron transport. Such effects may be concentrated in certain cells or regions. Obviously, with their high energy requirements, brain cells may be particularly susceptible to showing aberrant behavior in the presence of mitochondrial dysfunction. The combination of accumulated mitochondrial gene changes with inherited (nuclear genome) factors may thus underlie at least some forms of neuropathologic degeneration.

This minireview series examines potential contributions of mitochondrial physiology to neurodegeneration. The mutations already described in human kindreds are particularly useful tools. It remains important to note, however, that the final picture likely reflects many contributions with cumulative effects.

Brief overview of contributions to this minireview series

Several reports present evidence for aberrant oxidation and the effects of reactive oxygen species (ROS). Hastings (2009) describes detecting reactive quinones and dopamine oxidation. Studies of mitochondrial proteomics by Smith (2009) reveal tyrosine nitration, a combination effect of ROS and NO. Navarro and Boveris (2009) show mitochondrial dysfunction in both the substantia nigra and the frontal cortex with reduced function of complex I. ONOO-, lipid peroxidation and amino-aldehyde adducts were detected.

An interesting report by Marella et al. (2009) showed that providing yeast Ndi1 protein (an NADH dehydrogenase) via a transgene could "bridge" defective complex I activity while still maintaining a proton gradient and generating ATP. Although unlikely to be a direct therapeutic strategy, this approach clarifies both that complex I is a site of at least some defects and that electron transport can be extended to O_2 under experimental conditions.

The observations of Powers (2009) that PET scans in early PD patients showed *increased* oxygen consumption argue against reduced electron transport in early PD. However, O_2 consumption may change later in the course of the disease. In addition, if cell destruction is present, inflammation might contribute to the results.

Clarifying the role(s) of nuclear genes in PD neurodegeneration has been a central goal. Dagda and Chu (2009) review the 3 genes and their products in neuronal cells and other cell lines. They present evidence that these 3 have individual roles in maintaining mitochrondrial intergrity. Whitworth and Pallanck (2009) show that PINK1 functions upstream of parkin in a pathway involved with promoting mitochondrial fission and segregating dysfunctional mitochondria for degradation. Jendrach et al. (2009) note that PINK1 deficiency leads to mitochondrial dysfunction even in peripheral tissues and that this could thus be particularly important for high stress neuronal environments that depend on clearance of damaged mitochondria. In the presence of PINK1 respiratory depression, loss of cytochrome c and increased cellular ROS were found to be associated with homoplasmic ND5 and ND6 mutations in the mitochondrial genome by Papa et al. (2009).

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