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Review

# Parkin and PINK1 functions in oxidative stress and neurodegeneration

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ABSTRACT

Loss-of-function mutations in the genes encoding Parkin and PINK1 are causally linked to autosomal recessive Parkinson's disease (PD). Parkin, an E3 ubiquitin ligase, and PINK1, a mitochondrial-targeted kinase, function together in a common pathway to remove dysfunctional mitochondria by autophagy. Presumably, deficiency for Parkin or PINK1 impairs mitochondrial autophagy and thereby increases oxidative stress due to the accumulation of dysfunctional mitochondria that release reactive oxygen species. Parkin and PINK1 likely have additional functions that may be relevant to the mechanisms by which mutations in these genes cause neurodegeneration, such as regulating inflammation, apoptosis, or dendritic morphogenesis. Here we briefly review what is known about functions of Parkin and PINK1 related to oxidative stress and neurodegeneration.



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## 1. Introduction

Oxidative stress has been implicated as a likely cause of many neurodegenerative diseases including Parkinson's disease (PD). PD is the most common neurodegenerative movement disorder and affects millions of people worldwide. PD is defined clinically by bradykinesia, resting tremor, rigidity and abnormal gait. It is diagnosed neuropathologically by relatively selective loss of dopaminergic neurons in the substantia nigra and the presence of Lewy body intraneuronal inclusions containing α-synuclein. Current pharmacological therapies treat the symptoms, mostly by enhancing dopaminergic signaling, which is required for normal movement. There are currently no therapies proven to slow down disease progression or to protect against neurodegeneration. Most PD cases are sporadic, but the recent identification of genes with mutations linked to familial forms of PD provides important clues that could help determine the causes of both familial and idiopathic PD, and could lead to the development of more effective therapies (Kumaran and Cookson, 2015). Even prior to the identification of the first genetic mutations linked to PD, mitochondrial dysfunction and oxidative stress were implicated in PD pathogenesis because neurotoxins, such as 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), can induce parkinsonism in

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humans and animal models by inhibiting mitochondrial respiration and increasing production of reactive oxygen species (ROS) (Langston, 1987; Mizuno, et al., 1995; Jenner and Olanow, 1996; Fukae et al., 2007; Zhou et al., 2008; Camilleri and Vassallo, 2014; Gautier et al., 2014; Moon and Paek, 2015). Even under normal physiological conditions, electron leakage from the mitochondrial electron transport chain is a major cellular source of ROS that damage proteins, lipids and DNA (Beal, 2005). Because this damage likely accumulates with age and because age is the greatest PD risk factor, mitochondrial dysfunction and oxidative stress are likely causes of idiopathic PD initiation and progression (Beal, 2003; Shults, 2004). Consistent with this, oxidatively damaged subunits of mitochondrial complex I are increased in PD brains (Keeney et al., 2006) and impaired complex I activity has been observed in multiple tissues and peripheral blood leukocytes from PD patients (Mann et al., 1992; Albers and Beal, 2000; Muftuoglu et al., 2004; Schapira, 2008). Perhaps the most compelling evidence for mitochondrial dysfunction as a direct cause of parkinsonism (rather than a consequence or an age-coupled epiphenomenon) comes from the genetic linkage of loss-of-function mutations in the mitochondrial kinase Phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) to early onset recessive parkinsonism (Valente et al., 2004). PINK1 is a mitochondrial kinase that accumulates on the surface of defective mitochondria and recruits Parkin to promote selective degradation of dysfunctional mitochondria (Narendra et al., 2008; Matsuda et al., 2010). Loss-of-function mutations in Parkin account for about 50% of all cases of early onset PD (Kitada et al., 1998; Lucking et al., 2000). Here, we briefly review the known functions of PINK1 and Parkin with respect to potential mechanisms of PD pathogenesis.

## 2. Mitochondrial dysfunction and oxidative stress in PD

The single greatest risk factor for PD is age, which strongly implicates cumulative oxidative damage as a causative mechanism. There is now overwhelming evidence that oxidative damage plays a key role in idiopathic PD and inherited parkinsonism, as well as neurotoxin-induced PD animal models (Fahn and Cohen, 1992; Cassarino et al., 1997; Beal, 2005). Low-level oxidative stress may promote mitochondrial biogenesis and elimination or repair of damaged mitochondria while high-level oxidative stress beyond the cellular capacity to repair or remove oxidative damage may lead to the accumulation of damaged mitochondria (Lee and Wei, 2005). Of all the proteins with mutations so far linked to parkinsonism, Parkin is one of the most sensitive to oxidation and mounting evidence suggests that Parkin is important for protecting cells from oxidative stress (Hyun et al., 2002; Palacino et al., 2004; Pesah et al., 2004; Greene et al., 2005). Observations that Parkin is sensitive to oxidative damage by nitrosylation supports the idea that oxidative damage to endogenous Parkin may contribute to idiopathic PD (Yao et al., 2004). Dopamine readily oxidizes to form ROS and dopamine quinone, which can covalently modify and inactivate Parkin, providing further evidence that progressive loss of Parkin function in dopaminergic neurons in combination with oxidative stress may contribute to onset or progression of idiopathic PD (LaVoie et al., 2005). Although inherited mutations in Parkin cause only a small fraction of all clinical parkinsonism cases, oxidative damage to Parkin protein is observed in the brains of sporadic PD patients, which supports the hypothesis that inactivation of Parkin in conjunction with oxidative damage could cause idiopathic PD (Chung et al., 2004; Yao et al., 2004).

## 3. Mutations in Parkin and PINK1 causally linked to PD

Mutations in five genes have so far been definitively linked to familial PD. Gain-of-function mutations in α-*synuclein* and *LRRK2* have been linked to dominantly inherited parkinsonism (Polymeropoulos et al., 1997; Paisan-Ruiz et al., 2004; Zimprich et al., 2004), and loss-of-function mutations in *parkin, DJ-1,* and *PINK1* have been linked to recessively inherited parkinsonism (Kitada et al., 1998; Bonifati et al., 2003; Valente et al., 2004).

*Parkin* was the first gene to be identified with mutations linked to recessive parkinsonism (Kitada et al., 1998). Over 100 different *parkin* mutations affecting each of *parkin's* 12 exons have since been identified in parkinsonian patients, including missense point mutations, truncation mutations, large chromosomal deletions and duplications spanning one or more exons, as well as promoter mutations (Hedrich et al., 2004; Lesage et al., 2007). The recessive mode of inheritance and the absence of Parkin protein (or radically truncated protein in some patients) are consistent with a loss-of-function mechanism by which *parkin* gene mutations cause disease (Shimura et al., 1999). Parkin is expressed widely throughout the brain and other tissues, with the highest mRNA abundance in brain, heart and skeletal muscle (Kitada et al., 1998).

Loss-of-function mutations in *parkin* are found in nearly 50% of parkinsonism cases with onset of symptoms before age 45 (Lucking et al., 2000). Other than an earlier average age of onset, the clinical symptoms of patients bearing *parkin* mutations resembles that of typical late-onset idiopathic PD, with good therapeutic response to L-DOPA and slightly slower disease progression (Lucking et al., 2000). There is so much overlap in clinical symptoms between idiopathic PD and *parkin*-linked disease that it is not possible to distinguish patients bearing *parkin* mutations from idiopathic PD based on clinical criteria alone (Lucking et al., 2000). Although *parkin* mutations were first identified in patients with very young age at onset, *parkin* mutations have since been identified in typical late-onset PD patients and *parkin* polymorphisms or heterozygous mutations are suspected of increasing susceptibility to typical late-onset PD (Klein et al., 2000; Schlitter et al., 2006). *Parkin* polymorphisms, in combination with increased environmental exposures to substances suspected of causing idiopathic PD, are associated with earlier onset of symptoms more than either factor alone (Ghione et al., 2007).

The initial neuropathological examinations reported for cases bearing *parkin* mutations led to the assumption that Parkin is required for Lewy body formation because no Lewy bodies were observed in the initial autopsies; however, Lewy bodies have since been observed in cases from 2 independent families bearing *parkin* mutations (Farrer et al., 2001; Pramstaller et al., 2005). All autopsies of *parkin*-linked PD showed profound loss of neuromelanin-containing neurons in the substantia nigra pars compacta as well as prominent loss of locus coeruleus neurons, which is also observed in idiopathic PD. Given that cortical Lewy bodies are commonly observed in neuropathological examinations of aged brains, it is likely that the absence of Lewy bodies in some cases of *parkin*-linked PD reflects the earlier age at onset of these cases and the many years or decades that may be required for insoluble protein aggregates to accumulate to the extent that they can be detected by visible light microscopy in the form of Lewy bodies. We and others have put forward the hypothesis that small protein aggregates are more likely to be mechanistically involved in PD pathogenesis than Lewy bodies or large fibrillar aggregates that can be detected by microscopy (Goldberg and Lansbury, 2000). We speculate that Parkin and PINK1 function, at least in part, to prevent the accumulation of small protein aggregates or oxidized proteins that could be neurotoxic.

Loss-of-function mutations in *PINK1* cause clinical symptoms and neuropathology indistinguishable from PD with young onset (Valente et al., 2004; Samaranch et al., 2010). *PINK1* was first cloned in the course of a search for genes upregulated by the tumor suppressor gene PTEN (Unoki and Nakamura, 2001). Loss-of-function mutations in *PINK1* were subsequently identified as the cause of