PARKINSON DISEASE

PINK1 targets dysfunctional mitochondria for autophagy in Parkinson disease

A report published in *PLoS Biology* provides evidence that PTEN-induced putative kinase 1 (PINK1) is involved in selective autophagy of dysfunctional mitochondria. Recessive mutations in the *PINK1* gene are associated with cases of familial Parkinson disease (PD), so this research provides further support for a mitochondrial involvement in this condition.

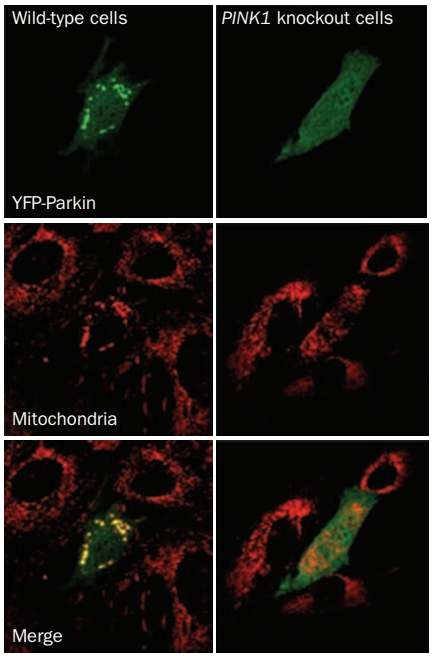
PD is a chronic neurodegenerative disease characterized by motor and postural symptoms such as bradykinesia, rigidity and tremor. A wealth of data indicates that degeneration of dopaminergic neurons in the substantia nigra is the underlying cause of the motor symptoms, but little is known about why these neurons degenerate, and no disease-modifying treatments are yet available.

Mutations in the genes encoding the E3 ligase Parkin and the mitochondrial kinase PINK1 are known to be associated with familial forms of PD, and research also suggests a link between mutant forms of these enzymes and mitochondrial dysfunction. Furthermore, several lines of evidence suggest that mitochondrial dysfunction could be partially responsible for sporadic cases of PD. Understanding how dysregulation of mitochondrial function is related to degeneration of dopaminergic neurons could, therefore, aid the development of therapies for this condition.

Richard Youle at the NIH and his colleagues have already shown that Parkin translocates from the cytosol to the surface of damaged mitochondria. "We also found that Parkin translocation to mitochondria will activate elimination of damaged mitochondria by autophagy, suggesting that Parkin mediates quality control of mitochondria by selectively removing the damaged ones," Youle explains. The means by which Parkin induced autophagy of dysfunctional mitochondria was unclear, although PINK1 is known to localize on the surface of mitochondria, and studies in *Drosophila* have shown that PINK1 functions upstream of Parkin. Both PINK1 and Parkin might, therefore, be integral components in the autophagic degradation of defective mitochondria.

To test this hypothesis, Youle's team conducted standard laboratory tests—including immunocytochemistry and reverse transcriptase PCR—in cultured cells, and assessed the affects of *PINK1* and *Parkin* mutations on mitochondrial autophagy. "We uncovered evidence for a novel mechanism by which PINK1 identifies damaged mitochondria," reports Youle. "PINK1 is constitutively produced and sent to all mitochondria where it is rapidly degraded. When mitochondria are damaged, PINK1 degradation halts and PINK1 levels rapidly rise specifically on damaged mitochondria to activate Parkin recruitment."

The mechanisms underlying selective proteolysis of PINK1 on polarized mitochondria and selective stabilization of PINK1on the membrane of dysfunctional mitochondria—which are chronically depolarized—are not fully understood. However, by conducting *in vitro* studies, Youle *et al.* determined that PINK1 expression on the outer mitochondrial membrane is not only required for Parkin translocation from the cytosol to the damaged mitochondria, but is also sufficient to elicit translocation of Parkin to the defective organelles. Furthermore, PINK1 is required for the Parkin-mediated elimination of damaged mitochondria. Disease-causing *Parkin* mutations were shown to markedly disrupt Parkin recruitment and Parkin-mediated autophagy, and *PINK1* mutations were shown to profoundly disrupt Parkin recruitment. These latter findings indicate that PINK1 and Parkin might interact on the mitochondrial surface, although the exact nature of this interaction remains to be established.



In wild-type cells Parkin tagged with yellow florescent protein (YFP-Parkin) (shown in green) translocates to mitochondria (shown in red). In PINK1 knockout cells Parkin does not translocate to mitochondria. Image provided by Dr Richard Youle.

Clearly, further research is needed before we fully understand how this PINK1–Parkin pathway controls mitochondrial degradation, and to what extent mutations in *PINK1* and *Parkin* influence the development of sporadic PD. To achieve this goal, "it will be important to corroborate our model that PINK1 and Parkin mediate a mitochondrial quality control pathway in animal models of PD," states Youle. Both PINK1 and Parkin are widely expressed in a variety of cell types, so future experiments should also address why dopaminergic neurons are more susceptible to PINK1 and Parkin loss-of-function mutations than other cell types.

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Original article Narendra, D. P. *et al.* PINK1 is selectively stabilized on impaired mitochondria to activate Parkin. *PLoS Biol.* **8**, e1000298 (2010)