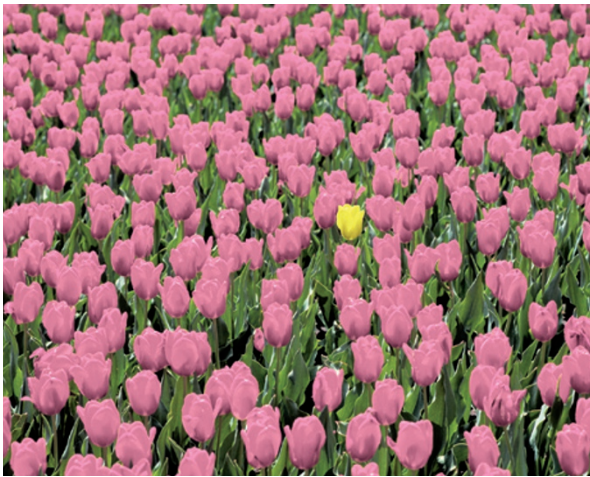


NEURODEGENERATIVE DISEASE

In the PINK



Parkinson's disease (PD) has been associated with mitochondrial dysfunction and, in some cases, with mutations in specific genes, such as *parkin* and PTEN-induced kinase 1 (*PINK1*). Flies with mutations in *parkin* or *Pink1* show mitochondrial dysfunction, but how the genes contribute to mitochondrial integrity is unknown. Two new studies published in *PNAS* shed light on the mechanisms by which *PINK1* and *parkin* influence mitochondrial function, by showing their role in fission and protection against mitochondrial toxins.

Haque *et al.* tested the role of *PINK1* in the neuron loss that is caused by exposure to MPTP and its metabolite MPP⁺ (a mitochondrial toxin), both of which are used to generate animal models of PD. The authors used small interfering RNA to downregulate *Pink1* expression in mouse primary neurons, and showed that this reduced neuronal survival in the presence of MPP⁺. Conversely, *Pink1* overexpression had a protective

effect. This required *PINK1*'s kinase activity, as a mutant *PINK1* in which the kinase activity was abolished was not protective. Interestingly, a *PINK1* mutant lacking the putative mitochondrial targeting motif also protected neurons from MPP⁺ toxicity, indicating that targeting to the mitochondria is not required for the protective effect.

PINK1 had similar actions *in vivo*: overexpression of wild-type *Pink1* in the substantia nigra protected dopamine neurons against the neurotoxic effects of MPTP injections. Again, this required *PINK1*'s kinase activity but not the mitochondrial targeting motif, indicating that *PINK1* might act in the cytoplasm.

How *PINK1* protects neurons against mitochondrial toxins is unknown; however, a second study provides clues about its role in maintaining mitochondrial morphology. In this paper, Poole *et al.* explored whether *PINK1* and *parkin*, which acts downstream from *PINK1*, have a role in mitochondrial fission and fusion in *Drosophila melanogaster*. Dynamic regulation of these opposing processes is required to maintain the morphological integrity of mitochondria. The authors examined the effect of manipulating *Mfn2* and *Opa1*, which promote mitochondrial fusion, and *Drp1*, which promotes mitochondrial fission, in *parkin*- or *Pink1*-mutant flies.

Flies with mutations in *parkin* or *Pink1* have a phenotype that is characterized by thoracic indentations and impaired climbing and flying owing to muscle degeneration. Overexpression of *Drp1* in *Pink1* mutants normalized this phenotype,

as did loss-of-function mutations in *Opa1* or deletion of *Mfn2* in *Pink1* and *parkin* mutants. Moreover, reducing the activity of *Drp1* or of *Mfn2* or *Opa1* suppressed and exacerbated, respectively, the eye-structure abnormalities that result from *Pink1* overexpression.

These findings suggest that the phenotype of *Pink1* and *parkin* mutants is caused by disturbed mitochondrial fission. Indeed, the severe defects in mitochondrial morphology in *Pink1*- and *parkin*-mutant flight muscles were normalized by increasing *Drp1* gene dosage or reducing *Opa1* gene dosage. Similarly, inactivation of both *Pink1* and *parkin* in a *D. melanogaster* cell line by RNA interference caused changes in the structure of the cells' mitochondria, and these changes were reversed by inactivation of *Mfn2* or *Opa1*. Together, these data show that the *PINK1*/*parkin* pathway promotes mitochondrial fission.

It is unclear whether the findings of the two studies are linked — specifically, whether impaired cytoplasmic function of *PINK1* might result in defects in mitochondrial fission with consequent mitochondrial dysfunction. Nevertheless, these data provide evidence for two ways in which mutations in *PINK1* and *parkin* might lead to mitochondrial dysfunction and, possibly, PD.

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ORIGINAL RESEARCH PAPERS Poole, A. C. *et al.* The *PINK1*/*Parkin* pathway regulates mitochondrial morphology. *Proc. Natl Acad. Sci. USA.* **105**, 1638–1643 (2008) | Haque, M. E. *et al.* Cytoplasmic *Pink1* activity protects neurons from dopaminergic neurotoxin MPTP. *Proc. Natl Acad. Sci. USA.* **105**, 1716–1721 (2008)