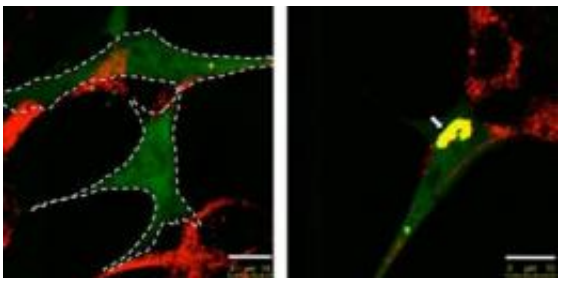
Mutations that cause Parkinson's disease prevent cells from destroying defective mitochondria

May 10 2010



Parkin (green) promotes the turnover of damaged mitochondria (red, left), but defective organelles accumulate near the nucleus if Parkin lacks its ubiquitin ligase activity (right). Credit: Lee, J.-Y., et al. 2010. *J. Cell Biol.* doi:10.1083/jcb.201001039.

Mutations that cause Parkinson's disease prevent cells from destroying defective mitochondria, according to a study published online May 10 in the *Journal of Cell Biology*.

Defects in the ubiquitin ligase Parkin are linked to early-onset cases of this neurodegenerative disorder. The wild-type protein promotes the removal of impaired mitochondria by a specialized version of the autophagy pathway called mitophagy, delivering mitochondria to the lysosomes for degradation. Mitochondria are often dysfunctional in Parkinson's disease, but how Parkin stimulates mitophagy and whether

the pathway goes wrong during pathogenesis is unknown.

A team of researchers led by Tso-Pang Yao (Duke University) found that cells expressing mutant forms of Parkin failed to clear their mitochondria after the organelles were damaged. Different mutations blocked mitophagy at distinct steps: mitochondria accumulated in the perinuclear region of cells expressing Parkin lacking its ubiquitin ligase activity, for example. The researchers found that ubiquitination of defective mitochondria by Parkin normally recruits the autophagy proteins HDAC6 and p62 to clear these mitochondrial aggregates.

Depolymerizing microtubules or inhibiting the dynein motor protein blocked aggregation and prevented mitochondrial turnover. Transport to the perinuclear region was also blocked by a mutation in Parkin, indicating that this stage of mitophagy is also regulated by the protein.

The clearance of defective mitochondria is therefore similar to the removal of damaged proteins, another autophagic process that goes wrong in Parkinson's disease resulting in the accumulation of toxic protein aggregates. Both pathways rely on microtubules, HDAC6, and p62, says Yao, providing a common link between the two main features of the neurodegenerative disorder.

More information: Lee, J.-Y., et al. 2010. J. Cell Biol. doi:10.1083/jcb.201001039

Provided by Rockefeller University