Tracing Parkinson's lethal mechanism

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In the vast majority of Parkinson's disease (PD) patients, the disorder arises not because of a genetic defect, but because some external insult triggers the death of dopamine-producing neurons. Now, researchers have reported progress in understanding the mechanism underlying that death, which they say suggests a new treatment pathway.

In both mice and human patients, the researchers have found evidence that neurons die because of a crippling of a particular protective enzyme that eliminates potentially damaging "reactive oxygen species" normally generated in the cell's power plants, called mitochondria.

David Park, of the Ottawa Health Research Institute, and colleagues published their findings in the July 5, 2007 issue of the journal *Neuron*, published by Cell Press.

The researchers studied the mechanism of PD using a mouse model of the disease, in which a mitochondria-affecting toxin called MPTP is used to produce Parkinson's-like brain pathology. In earlier studies, they had found that MPTP activates protein-snipping enzymes called calpains in mitochondria. They also found evidence that calpains, in turn, activate a cellular switch called Cdk5. The question, however, was how this abnormal activation ultimately kills neurons.

In their new studies, the researchers analyzed neurons to determine that Cdk5 regulates yet another enzyme called Prx2. This enzyme is known as a peroxidase and acts to render harmless the chemically active reactive oxygen species that are produced inside mitochondria in the process of generating energy for the cell.

Specifically, the researchers found that treating neurons with MPTP activates Cdk5 to switch off Prx2. What's more, they found that activating Prx2 in MPTP-treated mice prevented the loss of dopamine-producing neurons. And they experimentally demonstrated that the action of Cdk5 on Prx2 "plays a pivotal role" in the neuronal damage from MPTP.

Importantly, the researchers discovered evidence that the loss of Prx2 activity also plays a role in human PD. They found reduced Prx2 activity in brain tissue from PD patients.

"These findings provide a mechanistic link of how a mitochondrial damaging agent, through calpain-mediated Cdk5 activation and downregulation of an important antioxidant enzyme, can increase oxidative load, leading ultimately to death," concluded the scientists.

"Taken together, our findings suggest that strategies to modulate Prx2 activity serve as beneficial targets for treatment of PD," they concluded. "This is of particular importance since Cdk5 is thought to have normal beneficial roles in neurons and modulating a relevant downstream target rather than Cdk5 directly may be a better therapeutic strategy with regard to this pathway."

Source: Cell Press