Parkinson's disease: Excess of special protein identified as key to symptoms, possible new target

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Johns Hopkins scientists have discovered that the over-activation of a single protein may shut down the brain-protecting effects of a molecule and facilitate the most common form of Parkinson's disease. The finding of this mechanism could lead to important new targets for drugs already known to inhibit it, thus controlling symptoms of the disorder, which affects about 1 million older Americans.

Previous research demonstrated that a protein called parkin protects brain cells by "tagging" certain toxic elements that are then destroyed naturally. It was also known that mutations in the gene that holds the code for parkin cause rare, familial forms of PD. However, parkin's role remained unclear in sporadic late-onset PD, the prevalence of which is increasing as the population ages.

Results of the new study, published Sept. 7 in the Proceedings of the National Academy of Sciences (*PNAS*) Online Early Edition, indicate that an over-activation of a protein called c-Abl- can shut down the activity of parkin and contribute to a build-up of toxic proteins that kill brain cells and enables the progression of PD.

C-Abl contributes to the regulation of cell death and is implicated in a host of diseases. It has already has proven to be a target for certain types of cancer-killing drugs, such as imatinib (Gleevec), the first drug designed to directly switch off a biochemical signal that directly targets a

protein vital to cancer growth, says Ted Dawson, M.D., Ph.D., Leonard and Madlyn Abramson Professor in Neurodegenerative Diseases and scientific director of the Johns Hopkins Institute for Cell Engineering.

"Our new appreciation of c-Abl's role in sporadic PD suggests that we can give brain-permeable inhibitors of c-Abl to maintain parkin's normal protective function," Dawson says. "The testing of these already approved, well-tolerated drugs for a new use — as a neuro-protective treatment for PD — is a potentially exciting therapeutic arc that should be pursued."

The researchers first used a test called the Western blot to label certain proteins in neuron-like human cells in culture. They could see that c-Abl shut down the activity of parkin by measuring the levels of chemical tags on proteins that, in a healthy system, are marked for destruction. These "garbage" proteins, when overabundant, have been shown previously by Dawson's lab to be selectively toxic to neurons. When c-Abl was active, parkin's ability to tag those proteins was significantly decreased.

The team then incubated these cells with STI-571, a well-known c-Abl inhibitor marketed as imatinib or Gleevec. When compared to cultures not incubated with the compound, the inhibition of parkin's function by c-Abl was wholly prevented.

The c-Abl inhibitor, STI-571 was approved by the Food and Drug Administration in 2001 for the treatment of a cancer of white blood cells and in 2002 for the treatment of a rare form of stomach cancer. It works by blocking the activity of the abnormal c-Abl protein, which is much more active than the normal version. For a c-Abl inhibitor to be an effective treatment for Parkinson's disease, it would need to cross the blood-brain barrier, Dawson says.

Next, using a mouse which had been given drugs that cause Parkinson's-

like traits, the team proved that when c-Abl is activated, parkin's function shuts down and as a result, garbage proteins accumulate and lead to a significant loss of neurons. The team also demonstrated that genetically altered mice in which c-Abl had been knocked out were protected against the same significant loss of neurons. They measured the loss of neurons by counting them: Wild-type (normal) mice lost about 8,000 neurons, while the genetically altered mice with the disabled c-Abl lost only about half that many.

Finally, the scientists turned to human brain tissue to look for evidence that c-Abl is a major regulator of parkin function. By comparing brain tissue of patients who died with Parkinson's disease with those who died of other causes, they established that when c-Abl shuts down Parkin, the "garbage" proteins accumulate and result is the death of neurons.

"With people living longer, lots more people are developing this common, debilitating neurological disorder," Dawson says, citing that one in 100 people are afflicted at the age of 60, and four times that many by the age of 80. "Now that we know the mechanism, it's important that we explore new, effective therapies that can slow or stop its progression."

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