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Media Contact: Aline McKenzie
214-648-3404
aline.mckenzie@utsouthwestern.edu

Enzyme fights mutated protein in inherited Parkinson's disease, UT Southwestern researchers find

DALLAS – June 24, 2009 – An enzyme that naturally occurs in the brain helps destroy the mutated protein that is the most common cause of inherited Parkinson's disease, researchers at UT Southwestern Medical Center have found.

Their study, using human cells, provides a focus for further research into halting the action of the mutated protein. One of the most famous carriers of the mutation is Google co-founder Sergey Brin, who wrote about it on his blog in 2008.

"There are currently enormous efforts to identify potential therapies based on inhibiting this mutated protein," said Dr. Matthew Goldberg, assistant professor of neurology and psychiatry and senior author of the paper, which appears online in the journal *Public Library of Science.*

"Our paper is a major advance because we identify a protein that binds to the mutated protein and promotes its breakdown," he said.

The particular mutation that they studied affects a protein whose function is not well understood. In its normal form, it appears to have multiple sites where other molecules can attach themselves, like a space station with many docking areas.

Several mutations can affect the protein, which is named LRRK2. Some of the mutations cause Parkinson's disease.

The current theory is that the mutation leads to increased function of LRRK2 and to the formation of abnormal clumps of proteins inside brain nerve cells. The cells eventually die from these effects.

In the current study, the researchers used cultured human kidney cells and found that LRRK2 and a protein called CHIP "robustly" associated with each other.

Further testing showed that CHIP and LRRK2 could bind to each other in two different ways, either directly or indirectly by a third molecule that acted as a bridge.

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When CHIP bound to either the normal or mutant form of LRRK2, levels of LRRK2 in the cell decreased, the researchers found. This occurred because the cells increased the rate at which they destroyed LRRK2.

"CHIP may be a useful therapeutic target for treatments to break down LRRK2 in people with Parkinson's," Dr. Goldberg said.

"Our next step is to identify cellular mechanisms that signal LRRK2 to be degraded by CHIP or by other mechanisms," he said. "Because LRRK2 mutations are believed to cause Parkinsonism by increasing the activity of LRRK2, enhancing the normal mechanisms that target LRRK2 for degradation by CHIP may be therapeutically beneficial."

Lead author Xiaodong Ding, senior research associate in neurology at UT Southwestern, also contributed to the study.

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