MedicalXpress

Study finds promising clue to mechanism behind gene mutation that causes Parkinson's disease

March 25 2011

Researchers at Mount Sinai School of Medicine have discovered a way that mutations in a gene called LRRK2 may cause the most common inherited form of Parkinson's disease. The study, published online this month in the journal Public Library of Science, shows that upon specific modification called phosphorylation, LRRK2 protein binds to a family of proteins called 14-3-3, which has a regulatory function inside cells. When there is a mutation in LRRK2, 14-3-3 is impaired, leading to Parkinson's. This finding explains how mutations lead to the development of Parkinson's, providing a new diagnostic and drug target for the disease.

Using one-of-a-kind mouse models developed at Mount Sinai School of Medicine, Zhenyu Yue, PhD, Associate Professor of Neurology and Neuroscience, and his colleagues, found that several common Parkinson's disease mutations -- including one called G2019S -- disturb the specific phosphorylation of LRRK2.This impairs 14-3-3 binding with varying degrees, depending on the type of mutation.

"We knew that the LRRK2 mutation triggers a cellular response resulting in Parkinson's disease, but we did not know what processes the mutation disrupted," said Dr. Yue. "Now that we know that phosphorylation is disturbed, causing 14-3-3 binding to be impaired, we have a new idea for diagnostic analysis and a new target for drug development."

Dr. Yue's team also identified a potential enzyme called protein kinase A (PKA), responsible for the phosphorylation of LRRK2. Although the exact cellular functions disrupted by these changes are unclear, their study provides a starting point for understanding brain signaling that contributes to the disease. Recent studies have shown that 14-3-3 binds to other proteins implicated in inherited Parkinson's disease and has a neuroprotective function, and when the binding is impaired due to these mutations, the protection may be lost. The findings also demonstrate additional insight into the functional relevance of the LRRK2 and 14-3-3 interaction.

The presence of 14-3-3 in spinal fluid is already used as a biomarker for the presence of neurodegenerative diseases. Further applications of these findings could point to the use of 14-3-3 as a biomarker in testing for Parkinson's disease.

Provided by The Mount Sinai Hospital