Parkinson's treatments being developed could benefit most people with the disease

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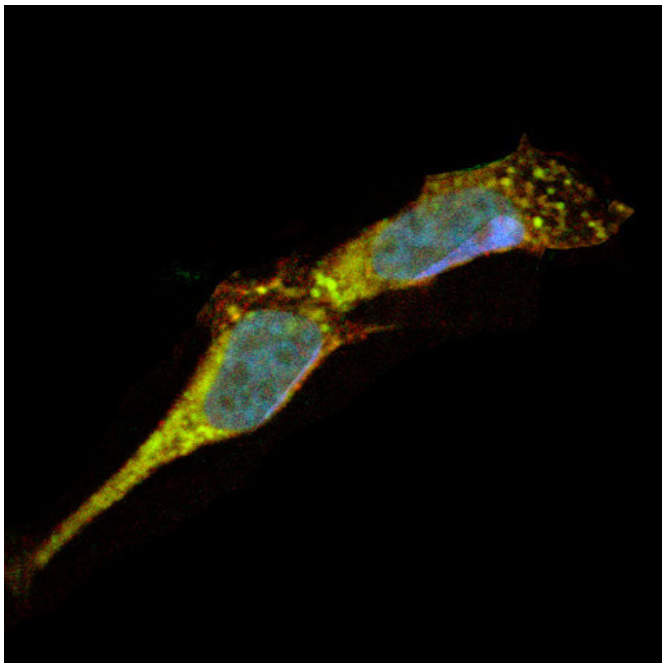

A fluorescent sensor for LRRK2 activity reveals the protein may be involved in many cases of Parkinson's disease. Credit: the Greenamyre lab

A gene linked to 3 to 4 percent of people with Parkinson's disease could play an important role in most, if not all, people with the disease, according to new study findings from the University of Pittsburgh School of Medicine and UPMC. The gene, called LLRK2, was previously thought to only cause disease when mutated, but researchers have found that it may be just as significant in the non-hereditary form of the disease, according to the study published today in the journal *Science Translational Medicine*.

"This discovery is extremely consequential for Parkinson's disease because it suggests that therapies currently being developed for a small group of patients may benefit everybody with the disease," said senior author J. Timothy Greenamyre, M.D., Ph.D., Love Family Professor of Neurology in Pitt's School of Medicine, chief of the Movement Disorders Division at UPMC and director of the Pittsburgh Institute for Neurodegenerative Diseases (PIND).

Parkinson's affects one million people in the U.S. and as many as 10 million worldwide and has no known cause, but is thought to involve both genetic and environmental factors. In 2004, researchers discovered that mutations in the LRRK2 gene (commonly pronounced as "Lark2"), overactivated the protein and caused Parkinson's in a small group of people, often in a hereditary fashion. However, the LRRK2 protein is difficult to study because it is present in extremely small amounts in nerve cells that are affected in Parkinson's.

To overcome this problem, Greenamyre and his team engineered a molecular 'beacon' that attached to LRRK2 and glowed red under a microscope only if the protein was active. This allowed them to also reveal the nerve cells in which LRRK2 was active in the brain.

The researchers applied the test to postmortem brain tissue donated to science by Parkinson's patients, none of whom had mutations in LRRK2, and healthy individuals of approximately the same age.

Remarkably, the test indicated that in 'dopamine neurons,' which are the brain cells most commonly affected in Parkinson's, LRRK2 was highly active in individuals affected by the disease, but not in the healthy individuals. This suggests that LRRK2 overactivity may be important in all people with Parkinson's, not just those who have a mutation in the gene.

A second major finding of the study was that it connected two proteins that have separately been recognized as important players in causing Parkinson's—LRRK2 and alpha-synuclein.

Accumulation of alpha-synuclein leads to the formation of structures called 'Lewy bodies,' a hallmark of Parkinson's.

While enormous efforts have been focused on alpha-synuclein, the cause of its accumulation is still poorly understood. Using a rodent model of Parkinson's induced by an environmental toxin, Greenamyre and his team discovered that activation of LRRK2 blocked the mechanisms that cells use to clear excess alpha-synuclein, leading directly to its accumulation. The researchers then treated the animals with a drug currently being developed to treat familial Parkinson's patients by blocking LRRK2 activity. The drug prevented the accumulation of alpha-synuclein and formation of Lewy bodies.

"LRRK2 ties together both genetic and environmental causes of Parkinson's, as we were able to show that external factors like oxidative stress or toxins can activate LRRK2, which can in turn cause Lewy bodies to form in the brain," noted lead author Roberto Di Maio, Ph.D., an assistant professor in Greenamyre's lab and a researcher at the Ri.MED Foundation.

In the future, Greenamyre expects to build on these findings to discover how neurodegeneration caused by LRRK2 overactivation can be prevented, and identify how oxidative stress and environmental toxins cause LRRK2 activation.

More information: Di Maio el al., "LRRK2 activation in idiopathic Parkinson's disease," *Science Translational Medicine* (2018). stm.sciencemag.org/lookup/doi/ … scitranslmed.aar5429

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