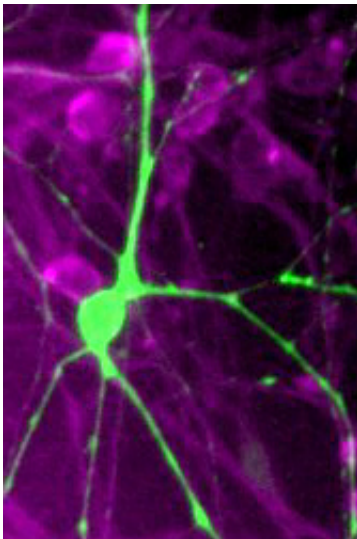


Too much protein may kill brain cells as Parkinson's progresses

April 10 2014



NIH-funded scientists show that the deadly Parkinson's gene LRRK2 can kill nerve cells (green) by tagging the s15 ribosomal protein (purple), a cog in a cell's protein-making machinery. Credit: Dawson lab, JHU Morris K. Udall Center of Excellence for Parkinson's Disease.

Scientists may have discovered how the most common genetic cause of Parkinson's disease destroys brain cells and devastates many patients worldwide. The study was partially funded by the National Institutes of Health's National Institute of Neurological Disorders and Stroke (NINDS); the results may help scientists develop new therapies.

"This may be a major discovery for Parkinson's disease patients," said

Ted Dawson, M.D., Ph.D., director of the Johns Hopkins University (JHU) Morris K. Udall Center of Excellence for Parkinson's Disease, Baltimore, MD. Dr. Dawson and his wife Valina Dawson, Ph.D., director of the JHU Stem Cell and Neurodegeneration Programs at the Institute for Cell Engineering, led the study published in *Cell*.

The investigators found that mutations in a gene called leucine-rich repeat kinase 2 (LRRK2; pronounced "lark two" or "lurk two") may increase the rate at which LRRK2 tags ribosomal proteins, which are key components of protein-making machinery inside cells. This could cause the machinery to manufacture too many proteins, leading to [cell death](#).

"For nearly a decade, scientists have been trying to figure out how mutations in LRRK2 cause Parkinson's disease," said Margaret Sutherland, Ph.D., a program director at NINDS. "This study represents a clear link between LRRK2 and a pathogenic mechanism linked to Parkinson's disease."

Affecting more than half a million people in the United States, Parkinson's disease is a degenerative disorder that attacks nerve cells in many parts of the nervous system, most notably in a brain region called the substantia nigra, which releases dopamine, a chemical messenger important for movement. Initially, Parkinson's disease causes uncontrolled movements; including trembling of the hands, arms, or legs. As the disease gradually worsens, patients lose ability to walk, talk or complete simple tasks.

For the majority of cases of Parkinson's disease, a cause remains unknown. Mutations in the LRRK2 gene are a leading genetic cause. They have been implicated in as many as 10 percent of inherited forms of the disease and in about 4 percent of patients who have no family history. One study showed that the most common LRRK2 mutation, called G2019S, may be the cause of 30-40 percent of all Parkinson's

cases in people of North African Arabic descent.

LRRK2 is a kinase enzyme, a type of protein found in cells that tags molecules with chemicals called phosphate groups. The process of phosphorylation helps regulate basic nerve cell function and health. Previous studies suggest that disease-causing mutations, like the G2019S mutation, increase the rate at which LRRK2 tags molecules. Identifying the molecules that LRRK2 tags provides clues as to how nerve cells may die during Parkinson's disease.

In this study, the researchers used LRRK2 as bait to fish out the proteins that it normally tags. Multiple experiments performed on [human kidney cells](#) suggested that LRRK2 tags ribosomal proteins. These proteins combine with other molecules, called ribonucleic acids, to form ribosomes, which are the cell's protein-making factories.

Further experiments suggested that disease-causing mutations in LRRK2 increase the rate at which it tags two ribosomal proteins, called s11 and s15. Moreover, brain tissue samples from patients with LRRK2 mutations had greater levels of phosphorylated s15 than seen in controls.

Next, the researchers investigated whether phosphorylation could be linked to cell death, by studying nerve cells derived from rats or from human [embryonic stem cells](#). Genetically engineering the cells to have a LRRK2 mutant gene increased the amount of cell death and phosphorylated s15. In contrast, the researchers prevented cell death when they engineered the cells to also make a mutant s15 protein that could not be tagged by LRRK2.

"These results suggest that s15 ribosome protein may play a critical role in the development of Parkinson's disease," said Dr. Dawson.

How might phosphorylation of s15 kill nerve cells? To investigate this,

Dr. Dawson and his colleagues performed experiments on fruit flies.

Previous studies on flies showed that genetically engineering dopamine-releasing [nerve cells](#) to overproduce the LRRK2 mutant protein induced nerve cell damage and movement disorders. Dr. Dawson's team found that the brains of these flies had increased levels of phosphorylated s15 and that engineering the flies so that s15 could not be tagged by LRRK2 prevented cell damage and restored normal movement.

Interestingly, the brains of the LRRK2 mutant flies also had abnormally high levels of all proteins, suggesting that increased s15 tagging caused ribosomes to make too much protein. Treating the flies with low doses of anisomycin, a drug that blocks protein production, prevented [nerve cell damage](#) and restored the flies' movement even though levels of s15 phosphorylation remained high.

"Our results support the idea that changes in the way cells make proteins might be a common cause of Parkinson's disease and possibly other neurodegenerative disorders," said Dr. Dawson.

Dr. Dawson and his colleagues think that blocking the phosphorylation of s15 ribosomal proteins could lead to future therapies as might other strategies which decrease bulk protein synthesis or increase the [cells'](#) ability to cope with increased protein metabolism. They also think that a means to measure s15 phosphorylation could also act as a biomarker of LRRK2 activity in treatment trials of LRRK2 inhibitors.

More information: Martin et al. "Ribosomal protein s15 phosphorylation mediates LRRK2 neurodegeneration in Parkinson's disease," *Cell*, April 10, 2014. [DOI: 10.1016/j.cell.2014.01.064](https://doi.org/10.1016/j.cell.2014.01.064)

Provided by National Institutes of Health

Citation: Too much protein may kill brain cells as Parkinson's progresses (2014, April 10)
retrieved 30 April 2024 from

<https://medicalxpress.com/news/2014-04-protein-brain-cells-parkinson.html>

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.