New therapeutic target for Parkinson's disease discovered

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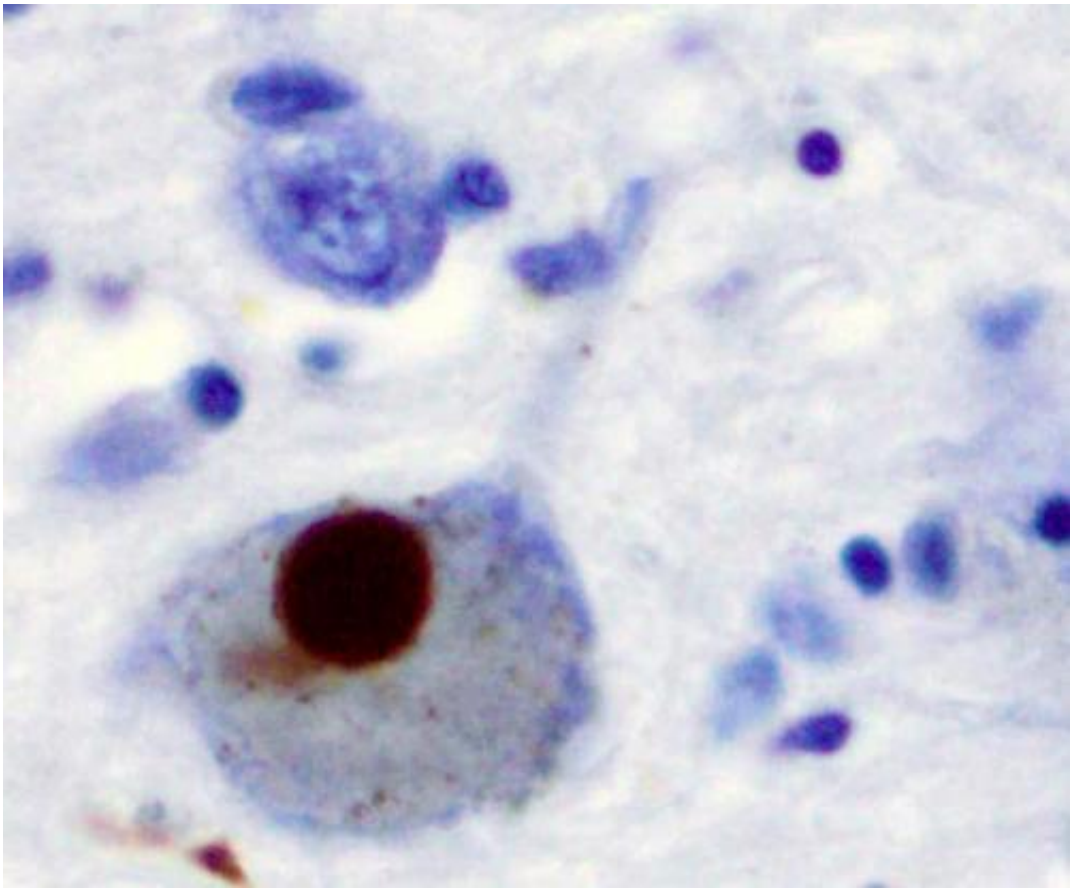

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Northwestern Medicine scientists have uncovered a new mechanism by

which mutations in a gene parkin contribute to familial forms of Parkinson's disease. The discovery opens a new avenue for Parkinson's therapeutics, scientists report in a new study.

The Northwestern scientists discovered that mutations in parkin result in a breakdown of contacts between two key workers in the cell—lysosomes and mitochondria.

Mitochondria are the main producers of energy in cells, and lysosomes recycle cellular debris that accumulates during normal function of our cells. These organelles are especially important in our brains because neurons are highly dependent on energy production by mitochondria, and because of their activity, neurons produce an abundance of cellular debris that must be cleared by lysosomes.

In a prior study, published in *Nature*, Dr. Dimitri Krainc, chair of neurology and director of Simpson Querrey Center for Neurogenetics at Northwestern University Feinberg School of Medicine, and his group discovered that lysosomes and mitochondria form contacts with each other. After the initial discovery, Northwestern scientists tried to understand the function of these contacts in Parkinson's disease.

In the new study published in *Science Advances*, the investigators report that lysosomes help mitochondria by providing key metabolites for their function. Mitochondria must import many of their essential ingredients, but it has not been well known where some of these metabolites come from. On the other hand, lysosomes serve as recycling factories in cells and, therefore, produce many breakdown products that could be used by other organelles such as mitochondria.

In this work, scientists found that lysosomes provide important amino acids that support the function of mitochondria. However, they also found that in some forms of Parkinson's disease, lysosomes cannot serve

as a "helping hand" to mitochondria because the contacts between the two organelles are disrupted. This results in dysfunctional mitochondria and ultimately degeneration of vulnerable neurons in Parkinson's disease.

"Findings from this study suggest that dysregulation of mitochondria-lysosome contacts contributes to the Parkinson's disease pathophysiology," said Krainc, the study's corresponding author. "We propose that restoring such mitochondria-lysosome contacts represents an important new therapeutic opportunity for Parkinson's disease."

From a broader perspective, this study opens a new avenue of research in neurodegenerative disorders, by highlighting the importance of direct communication and collaboration between cellular organelles in the pathogenesis of these disorders.

The first author of the study is Dr. Wesley Peng who recently completed the medical scientist training program (MD-Ph.D.) at Northwestern and currently serves as a neurology resident at Mass General Brigham and Harvard Medical School. Other contributors to the study include Leonie Schroder, Pingping Song and Yvette Wong.

The title of the study is "Parkin regulates amino acid homeostasis at mitochondria-lysosome (M/L) contact sites in Parkinson's disease."

More information: Wesley Peng et al, Parkin regulates amino acid homeostasis at mitochondria-lysosome (M/L) contact sites in Parkinson's disease, *Science Advances* (2023). DOI: 10.1126/sciadv.adh3347. www.science.org/doi/10.1126/sciadv.adh3347

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