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Rapamycin prevents Parkinson's in mouse model of incurable neurodegenerative disease

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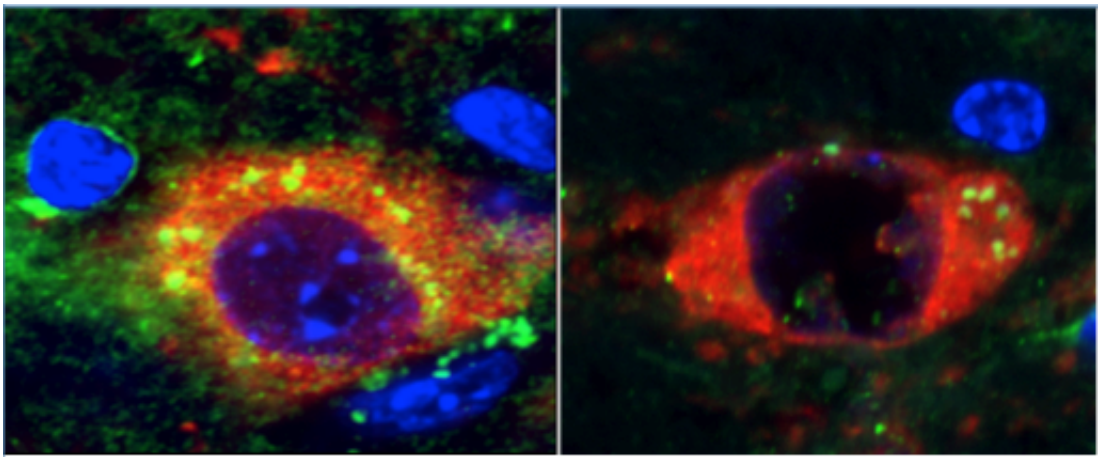

The image on the left shows dysfunctional lysomes clustered outside the nucleus in a mouse model of Parkinson's. The image on the right shows a dramatic reduction of the dysfunctional organelles following treatment with rapamycin. Credit: Shankar Chinta, Ph.D., staff scientist, Buck Institute

Rapamycin, an FDA-approved drug that extends lifespan in several species, prevented Parkinson's disease (PD) in middle-age mice that were genetically fated to develop the incurable neurodegenerative motor disease that affects as many as one million Americans. While the rapamycin did great things for the mice, scientists in the Andersen lab at the Buck Institute also got an unexpected plus from the research - a new understanding of the role parkin plays in cellular dynamics, one that challenges the current dogma in PD research and presents new

opportunities for drug discovery. The study is currently online in the *Journal of Neuroscience*.

"Given its side effects as an immunosuppressant, there are issues with long-term use of rapamycin, but the results of our study suggest that use of derivatives of rapamycin or other agents with similar biological properties may constitute novel therapeutics for the disorder," said senior scientist and Buck faculty Julie Andersen, PhD. "Our discoveries regarding parkin may provide an even more important therapeutic target for PD."

Parkin is a protein encoded by the PARK2 gene in humans. Mutations in PARK2 are most commonly linked to both sporadic and familial forms of PD; they diminish the cell's ability to recycle its internal garbage. PD is characterized by the accumulation of damaged proteins and mitochondria in the area of the brain where the neurotransmitter dopamine is produced.

Rapamycin prevented PD symptoms from occurring in middle-aged mice who had a human mutation in the PARK2 gene. Researchers in the Andersen lab expected this benefit to come via the accepted role of parkin - they thought rapamycin would boost the mutated protein's ability to label certain types of cellular garbage for recycling. Instead they discovered that parkin plays a much broader role in the actual recycling of garbage and the manufacturing of new mitochondria.

"This is a completely new, unrecognized, function for parkin," said Andersen. "Our work shows that parkin plays a much broader role than was originally thought in getting rid of damaged mitochondria and proteins. It's very exciting because it gives us new ways to look at potential therapeutics to boost cellular clean up."

Working in both neuronal stem cell models and mouse tissue, scientists

found that rapamycin not only boosted the mutated protein's ability to label cellular garbage, but also affected the process of recycling the garbage itself via up-regulation of a protein known as TFEB which increased the degradation and purging of both damaged proteins and mitochondria via a process known as lysosomal autophagy. Apart from rapamycin's effects, Andersen's team also discovered that parkin is involved in mitochondrial biogenesis - via up-regulation of PGC1alpha, a protein which drives increased mitochondrial synthesis.

"Problems with autophagy, which result in the accumulation of damaged proteins and organelles, have long been linked to PD," said Ana Maria Cuervo, MD, PhD, professor and recipient of the Robert and Renée Belfer Chair for the Study of Neurodegenerative Diseases at Albert Einstein College of Medicine in New York City. "This novel role of parkin in the regulation of the overall process of autophagy gives us new ways to address its dysfunction in PD."

"Researchers are already very interested in parkin as it relates to PD," said Andersen. "I'm hoping that uncovering this novel role for the protein will bring it center stage as an extremely important therapeutic target for the disorder."

More information: *Journal of Neuroscience*: Mitochondrial Quality Control via the PGC1alpha-TFEB Signaling Pathway is Compromised by Parkin Q311X Mutation but Independently Restored by Rapamycin (2015).

Provided by Buck Institute for Research on Aging