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Small molecules found to protect cells in multiple models of Parkinson's disease

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Several structurally similar small molecules appear capable of protecting cells from alpha-synuclein toxicity in multiple models of Parkinson's disease, according to Whitehead Institute researchers. Misfolded copies of the alpha-synuclein protein in brain cells are a hallmark of Parkinson's disease.

"In this research, we used yeast as a Parkinson's disease model system to identify the compounds that really work in two higher order model systems of Parkinson's," says Julie Su, a first co-author on the paper describing the research and a former postdoctoral researcher in Whitehead Member Susan Lindquist's lab. "And that shows that those compounds' targets are highly conserved over a billion years of evolution."

Parkinson's disease is a neurodegenerative disorder characterized by tremors, muscle rigidity, and slowed movements. In the neurons of Parkinson's patients' brains, researchers have noted Lewy bodies, abnormal spheres composed of the protein alpha-synuclein. There is currently no cure for the disease, and current Parkinson's therapies only address disease symptoms, not the disease's cellular cause.

In their article in Disease Models and Mechanisms (DMM), Lindquist scientists report that four related small molecules prevented the development of several cellular traits associated with Parkinson's disease, including the accumulation of alpha-synuclein deposits in the cell, improper protein trafficking from one organelle to another, and

damage inflicted on the cells' engines, the mitochondria.

The research is based on a type of brewer's yeast modified to produce too much of the alpha-synuclein protein in its cells. The resulting cells manifest adverse effects similar to those experienced in brain cells from Parkinson's patients.

Using this yeast strain, the Lindquist team screened 115,000 small compounds to see which ones alleviate the Parkinson's-like traits. During a screen, a compound is added to a small amount of yeast. Researchers can then easily and efficiently detect if that compound changes the yeast's growth rate, compared to a control. The technique takes advantage of the yeast's normally fast growth, which allows researchers to quickly test thousands of compounds, a process that is not possible in other frequently-used Parkinson's disease models.

Four compounds were found to restore the alpha-synuclein yeast cells' growth to 50% of normal yeast cells. Yeast cells that were not treated with the compounds died. The four compounds have similar chemical structures, a finding that indicates they may be acting on the same target or targets. The researchers also identified two commercially available compounds with similar chemical structures and used those in further tests.

To determine if the six compounds would work in animal models of Parkinson's, the scientists tested the compounds in the round worm Caenorhabditis elegans and in rat neurons. In both of these disease models, cells overproduce alpha-synuclein resulting in the same deleterious effects as in the yeast model. During testing, the first four compounds were able to rescue the round worms, while in the rat neurons, three of the four original compounds and one of the commercial compounds improved the nerve cells' growth.

In all of the models, the compounds improved protein trafficking and decreased mitochondrial damage.

"Those two things are obviously related," says Pavan Auluck, first co-author and a visiting scientist in the Lindquist lab. "We're trying to figure out what the connections are between them. And there are a number of ways they can be related."

Lindquist agrees: "There are very deeply rooted processes that connect protein trafficking and mitochondrial viability," says Lindquist, who is also a Howard Hughes Medical Institute investigator and a professor of biology at MIT. "That emphasizes that the underlying problem caused by alpha-synuclein is a general cellular defect that is part of the machinery of all eukaryotic cells. The specific problems in Parkinson's are due to the neurons being particularly sensitive to that process going awry."

As for the future of the specific compounds identified in this study, Daniel Tardiff, a Lindquist postdoctoral researcher, remains optimistic.

"Theoretically if a compound is having a beneficial effect on yeast cells, and in a worm, and in primary neurons, then possibly through years and years of work, it might actually be a potential therapeutic avenue or drug," says Tardiff. "Though we started in yeast, one of those compounds could actually have some potential for human health in Parkinson's disease. That's always a lofty goal."

More information: Compounds from an unbiased chemical screen reverse both ER-to-Golgi trafficking defects and mitochondrial dysfunction in Parkinson disease models," *Disease Models and Mechanisms*, published online December 28, 2009