How a Parkinson's disease-linked protein attacks a cell's powerhouses

August 18 2021, by Charlotte Hsu

Unhealthy mitochondria are marked in a gradient from white to red, with white being the least healthy, in contrast to healthy mitochondria that appear in blue. This still image is from a microscope video showing mitochondria moving in a fruit fly larval neuron expressing elevated levels of the protein alpha-synuclein. Credit: TJ Krzystek and Shermali Gunawardena

Inside cells, organelles called mitochondria carry out a medley of vital tasks. These structures generate energy and help to keep the cells' interior environment in a state of healthy equilibrium, among other functions.

Now, scientists show how a protein associated with Parkinson's disease can damage these cellular powerhouses.

The findings come from experiments in which fruit fly larvae were genetically engineered to produce unusually high amounts of the protein,

called alpha-synuclein.

"When fruit fly larvae expressed alpha-synuclein at elevated levels similar to what is seen in Parkinson's disease, many of the mitochondria we observed became unhealthy, and many became fragmented. Through detailed experiments, we also showed that different parts of the alpha-synuclein protein seem to be responsible for these two problems, and that fragmented mitochondria can actually be healthy. This is a key finding, because before, people thought fragmented mitochondria were unhealthy mitochondria," says Shermali Gunawardena, Ph.D., associate professor of biological sciences in the University at Buffalo College of Arts and Sciences.

The results could be of interest in the context of drug development, as abnormal aggregates of alpha-synuclein in brain cells are a hallmark of Parkinson's disease, and mitochondrial damage has also been observed in patients.

"This research showcases the advantage of using fruit fly larvae as a model organism to study how neurons become damaged during devastating diseases such as Parkinson's disease," says TJ Krzystek, UB Ph.D. candidate in biological sciences. "Through this approach, we pieced together a new understanding for how the Parkinson's disease-related protein alpha-synuclein disrupts the health and movement of mitochondria—the epicenter for energy production in cells. We believe this work emphasizes a promising path that can be explored for potential therapeutics aimed at improving mitochondrial health in Parkinson's disease patients."

The study was published on Aug. 17 in the journal *Cell Death and Disease*.

The co-first authors are Krzystek and Rupkatha Banerjee, Ph.D., a

postdoctoral research associate at Scripps Research who completed her doctorate in biological sciences at UB. Gunawardena is the senior author.

The research was a collaborative effort, with many members of the Gunawardena lab making significant contributions. In addition to Banerjee, Gunawardena and Krzystek, the paper's authors include undergraduates Layne Thurston, JianQiao Huang and Saad Navid Rahman, and Ph.D. student Kelsey Swinter, all in the UB Department of Biological Sciences, and Tomas L. Falzone at the Universidad de Buenos Aires and Instituto de Investigación en Biomedicina de Buenos Aires.

A detailed look at alpha-synuclein and mitochondria

Through tests in fruit fly larvae, the scientists were able to tease out intricate details regarding interactions between alpha-synuclein and mitochondria.

For example, the study not only concludes that different sections of the alpha-synuclein protein are likely responsible for causing mitochondrial fragmentation and damaging mitochondrial health; the research also identifies these sections and describes how other proteins may interact with them to drive these changes. More specifically, the proteins PINK1 and Parkin—both linked to Parkinson's disease—may interact with one end of alpha-synuclein to influence mitochondrial health, while a protein called DRP1 may interact with the other end to break mitochondria, scientists say.

"Mitochondrial impairments have long been linked to the pathogenesis of Parkinson's disease," Banerjee says. "However, the role of alpha-synuclein in mitochondrial quality control so far has not been comprehensively investigated. Our study unravels the intricate molecular mechanisms by which the different regions of alpha-synuclein exert distinct effects on mitochondrial health, bringing into light a potential

pathway that could be targeted for exploring new therapeutic interventions in Parkinson's disease."

"We were able to tease out specific mechanistic functions for alpha synuclein by using imaging tools and a color-tagged marking system to observe the process of what happens to mitochondria when alpha-synuclein is elevated," Gunawardena adds. "This system allowed us to observe the health, size and the movement behaviors of mitochondria at the same time in living neurons in a whole organism."

More information: Thomas J. Krzystek et al, Differential mitochondrial roles for α-synuclein in DRP1-dependent fission and PINK1/Parkin-mediated oxidation, *Cell Death & Disease* (2021). DOI: 10.1038/s41419-021-04046-3

Provided by University at Buffalo