Protein-linked sugars are crucial for the uptake of proteins linked to Parkinson's disease

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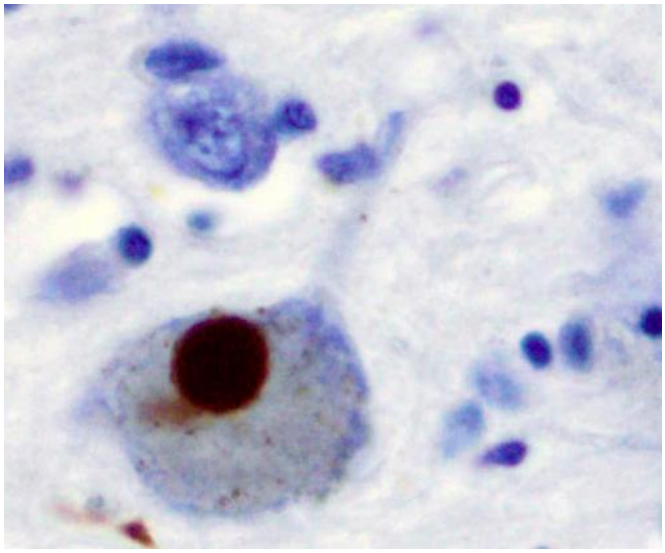

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

Parkinson's disease, a neurodegenerative disorder that affects more than 6 million people worldwide, is caused by the buildup of alpha-synuclein proteins in the brain. The biological function of alpha-synuclein is still not well understood, but because of its role in neurodegenerative diseases, researchers are actively studying this protein to understand the mechanisms of the disease and to look for new treatment strategies.

A new study from Elizabeth Rhoades and postdoc Melissa Birol found that when alpha-synuclein binds to extracellular glycoproteins, proteins with added sugar molecules, it can be taken up by neurons more easily. The paper also identified a specific presynaptic protein, neurexin 1?, as a key regulator in this process and a potential therapeutic target. Their findings were published in the journal *PLOS Biology*.

In one possible model for the pathology of Parkinson's disease, bundles of alpha-synuclein proteins, known as aggregates, form inside a neuron. This then leads to cell death and the release of alpha-synuclein protein clusters that are taken up by other neurons. Since neurodegenerative diseases have typical progression patterns, knowing how alpha-synuclein moves between neurons in the brain helps researchers understand disease propagation.

Previous work from the Rhoades lab implicated the presence of a glycan binding site on alpha-synuclein. This finding, combined with Birol's experience in analyzing protein-membrane interactions, led to this study of how alpha-synuclein interacts with cell membranes.

Birol was able to enzymatically remove specific glycans from the cell surface to see how their presence or absence would change how alpha-synuclein was taken up by neurons. The study found that when glycans were removed, the amount of alpha-synuclein clusters taken up by cells was greatly reduced.

And by analyzing giant plasma membrane vesicles, synthetic membranes derived from components of real cells that have the same protein and lipid composition, Birol was also able to see the detailed physical interactions between alpha-synuclein and glycans. "There's a structural basis for the alpha-synuclein binding to the glycan, and when the glycans are removed, it changes the nature of the interaction of alpha-synuclein with the cell membrane," explains Rhoades.

This research focused on the acetylated form of

alpha-synuclein proteins, which is present in both healthy and diseased neurons and is less frequently studied. They found that the acetylated form was more effective at forming clusters of proteins inside neurons and was required for interactions with glycans. "No one's really stressed the importance of these acetylated versions," Birol says. "Generally, we need take a step back in trying to understand how this protein may be propagating between cells, and I think glycans could be an aspect."

Rhoades and Birol say that the most unexpected finding was the discovery of neurexin 1? as a potential partner in how alpha-synuclein is taken up by neurons. They hope that future research on this presynaptic protein could provide insights into new treatment strategies for Parkinson's and other neurodegenerative diseases.

In the near term, Rhoades and her group hope to obtain higher-resolution structural information of alpha-synuclein proteins bound to glycans. They also hope that this study will inspire future research on alpha-synuclein acetylation and the role of glycans in the progression of the disease and will provide an impetus to look at previously unstudied protein modifications that might be connected to Parkinson's disease.

"Some cells spontaneously internalize these [alpha-synuclein] proteins and some do not. It has generally been assumed that there are alpha-synuclein specific receptors on the cells that do internalize aggregates. That may or may not be true, but [our study] suggests that it's not just the protein receptors but the glycans that are also important," says Rhoades.

More information: Melissa Birol et al, Identification of N-linked glycans as specific mediators of neuronal uptake of acetylated ?-Synuclein, *PLOS Biology* (2019). DOI: 10.1371/journal.pbio.3000318

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