Scientists shed new light on two proteins that exacerbate the progression of Parkinson's disease

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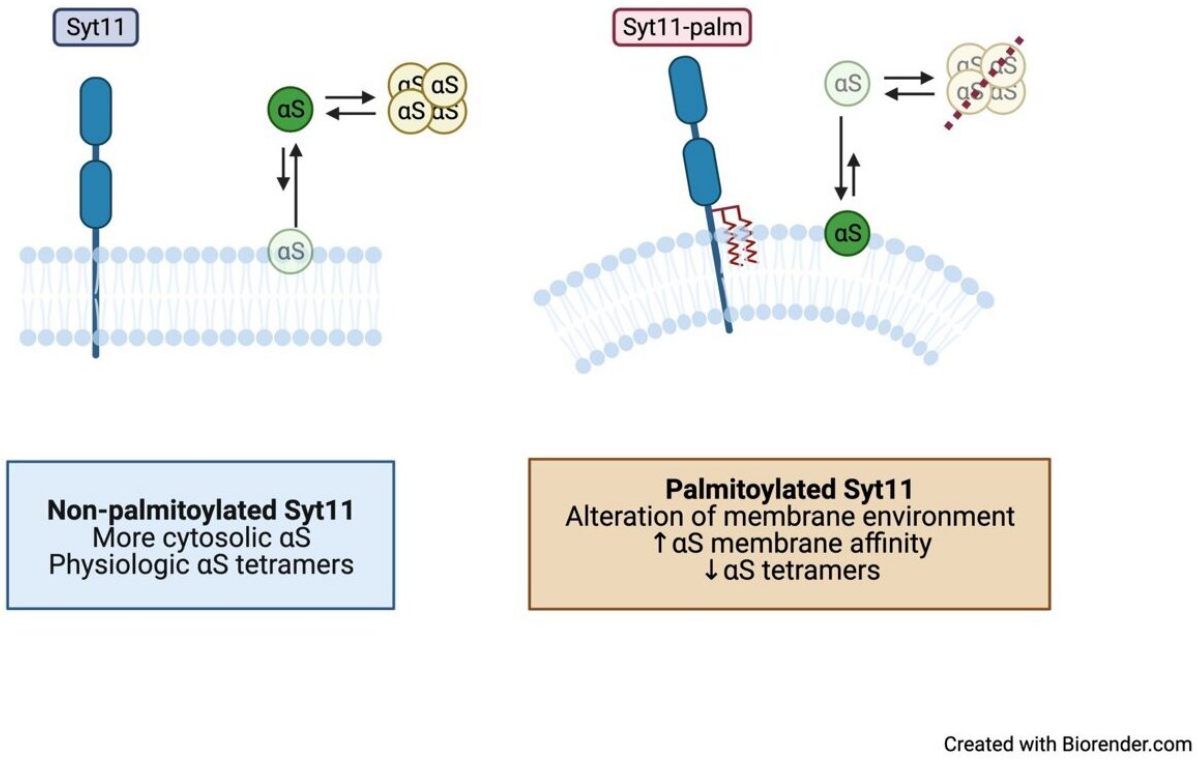

Model. Left: When synaptotagmin-11 (Syt11) is not palmitoylated, alpha-synuclein (αS) is less membrane bound and present in physiologic tetrameric form. Right: Palmitoylated Syt11 alters the local membrane environment, resulting in more membrane-bound αS and decreased physiologic tetramers. Credit: Created with Biorender.com

Two proteins may be intimately linked to the progression of Parkinson's disease, a relentless and disabling neurodegenerative disorder that affects millions of people around the world.

Scientists are racing to find new clues about the condition whose prevalence is increasing alongside the inexorable aging of the global population. Most cases occur after age 60, but an estimated 5% to 10% are early onset forms of the disease occurring before age 50. These cases are frequently—but not exclusively—related to a genetic mutation passed from one generation to the next.

Parkinson's is marked by degeneration of the brain's basal ganglia and a deficiency of the vital neurotransmitter dopamine. Tremor is a characteristic symptom of the disorder as are muscular rigidity and a slow, imprecise gait. As serious as those symptoms are, patients are further impacted by a complex and disparate range of non-motor symptoms that can greatly affect their quality of life.

Depression, anxiety, apathy, hallucinations, constipation, sleep disorders, loss of sense of smell, and a variety of cognitive impairments can complicate patients' ability to cope with the condition, according to the Parkinson's Foundation, a U.S. nonprofit that serves as an information resource for patients and their families.

A new study has zeroed in on critical molecular mechanisms that underlie the disease, illuminating a connection between a pair of proteins that exacerbate the disorder's progression.

Dr. Gary P.H. Ho and colleagues of the Ann Romney Center for Neurologic Diseases at Brigham and Women's Hospital in Boston, have identified those proteins as synaptotagmin-11—Syt11—and alpha-synuclein, more commonly written as α-synuclein. This renegade pairing likely contributes to the hallmark cellular pathology of the disease, Ho

and colleagues found.

The new research demystifies the biochemical connection between α-synuclein—a core driver of Parkinson's disease in the brain—and Syt11 and may explain why Syt11 was previously linked to the condition, but its role remaining stubbornly undefined until now. The new deep dive into Syt11's activity in tandem with α-synuclein has fine-tuned scientific understanding of Syt11.

"We investigated whether the two proteins were connected," writes Ho, lead author of the study reported in the journal *Science Signaling*. "We found that Syt11 was palmitoylated in mouse and human brain tissue and in cultured cortical neurons and that this modification to Syt11 disrupted α-synuclein homeostasis in neurons."

Palmitoylation is the covalent attachment of fatty acids, such as palmitic acid, to cysteine (and less frequently to serine and threonine). In the study, Ho and colleagues found that palmitoylation affected two cysteine residues on Syt11, which caused the protein to move to areas of the intracellular membrane in neurons where it couldn't be degraded. Additional experiments showed that the palmitoylation of Syt11 disrupted the regulation of α-synuclein in neurons and boosted the abundance of the aggregation-prone, disease-linked form of α-synuclein.

"In neurons, palmitoylation of Syt11 increased its abundance and enhanced the binding of α-synuclein to intracellular membranes," Ho added. "As a result, the abundance of the physiologic tetrameric form of α-synuclein was decreased, and that of its aggregation-prone monomeric form was increased."

In the study, Ho and his collaborators studied brain tissue from a Parkinson's animal model as well as from human donors. The effects of

the two deleterious proteins were seen "in primary neurons from mice and in neurons derived from cells from healthy donors and a patient with familial Parkinson's disease," according to data in *Science Signaling*.

While the research opens a new window of understanding into the molecular mechanisms that underlie Parkinson's disease, the cause of the devastating disorder remains elusive and there is no cure. The neurodegenerative condition can have familial roots for a small number of people whose diagnosis is explained by a genetic mutation. For most, there is no obvious reason why the disease manifested, although scientists suggest that exposure to pesticides or herbicides may play a role.

A flurry of studies in recent years has made strides in understanding both the core mechanisms and genetic risk factors for the disorder. For example, genome-wide association studies have linked the gene that encodes Syt11 to a higher risk for Parkinson's disease.

Now, the Boston team, all colleagues in the laboratory of Dr. Dennis Selkoe, has taken the link between Syt11 and α-synuclein a tantalizing step further by demonstrating how the two proteins are interconnected.

More than 10 million people worldwide are living with Parkinson's disease, according to the Parkinson's Foundation, which has headquarters in Miami and New York City. The primary medication for the disorder is levodopa, which treats the motor symptoms of the disease. Neurons process the drug to replenish missing dopamine. Other medications, such as carbidopa, help support the brain amid the progression of a relentless disease.

Ho and colleagues, meanwhile, posit that their research is adding a new dimension to the overall understanding of Parkinson's disease. "This work begins to bring mechanistic clarity to the role of Syt11 in the

disease and provides further evidence that palmitoylation influences multiple pathways in the biology of [α-synuclein]," Ho concluded.

More information: Gary P. H. Ho et al, Palmitoylation of the Parkinson's disease–associated protein synaptotagmin-11 links its turnover to α-synuclein homeostasis, *Science Signaling* (2023). DOI: 10.1126/scisignal.add7220

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