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New insight into dementia pathophysiology

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New research unravels a key molecular pathway underlying a neurodegenerative disorder that causes a devastating type of dementia. The study, published by Cell Press in the November 18 issue of the journal *Neuron*, sheds light on the pathological processing of Progranulin, a protein that normally promotes the survival of brain cells but is reduced in some neurodegenerative diseases.

Frontotemporal lobar degeneration (FTLD) refers to a group of disorders associated with degeneration of the frontal and temporal lobes of the brain. Symptoms include dementia, aphasia, and semantic disorders. Mutation of the gene for PGRN is associated with the most common form of FTLD, which is also characterized by inclusions of TDP-43 protein in the brain. Abnormal accumulation of TDP-43 has also been linked with amyotrophic lateral sclerosis (ALS).

While it is clear that a reduction in PGRN is causative for FTLD-TDP, the underlying mechanism is unknown. "Elucidation of PGRN action and the control of PGRN levels may have broad relevance for both FTLD and ALS," explains senior study author, Dr. Stephen M. Strittmatter from Yale University School of Medicine. "In order to advance the understanding of PGRN biology, we searched for cell surface binding sites that interact with PGRN."

Dr. Strittmatter and colleagues identified Sortilin as a key PGRN binding site on the surface of cortical neurons. In the stressed nervous system, PGRN was not expressed in neurons, but in nearby glial cells. Sortilin rapidly transferred PGRN inside of the neurons and delivered it

to lysosomes, cellular structures that degrade proteins. Mice that did not express Sortilin exhibited high levels of extracellular PGRN. Importantly, mice with a PGRN deficiency similar to that seen in FLTD-TDP, were fully normalized with regards to PGRN levels when Sortilin was deleted.

Taken together, the findings implicate Sortilin-mediated PGRN endocytosis in FTLD-TDP pathophysiology and identify Sortilin binding as a potential therapeutic site to alter PGRN pathology. However, the authors are careful to caution that additional studies elucidating the connection between PGRN, Sortilin, and TDP-43 are needed. "Future functional studies of Sortilin in PGRN biology will require development of robust rodent models for PGRN-dependent neurodegeneration," says Dr. Strittmatter. "Nevertheless, our work implicates Sortilin-mediated PGRN endocytosis as a key pathway for further study in FTLD, and possible ALS, pathophysiology."

Provided by Cell Press