Swelling along brain's axons may be true culprit in Alzheimer's disease

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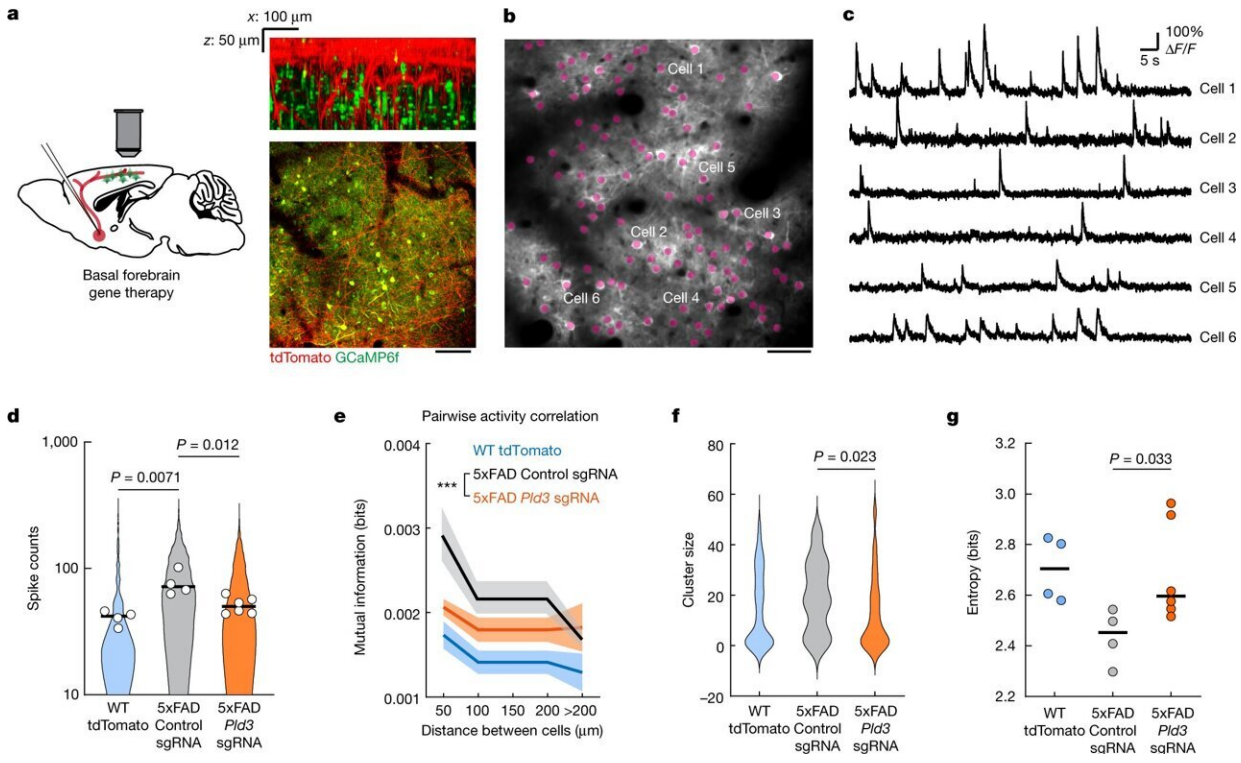

Reduction in axonal spheroids by Pld3 deletion improves neural circuit function. a, Schematics of cholinergic neurons in the basal forebrain projecting to the cortex, infected with AAV viruses encoding either Pld3 or control sgRNAs (left). Right, two-photon images showing intermingled projecting basal forebrain axons (red) from the basal forebrain (red) with GCaMP6f-labeled cortical neurons (green). Scale bar, 100 µm. b, Representative two-photon image of GCaMP6f-labeled cortical neurons (purple dots). Scale bar, 50 µm. c, Example raw calcium traces from individual cortical neurons. d, Single-cell spike counts from individual neurons during a 30 min imaging session. Each dot represents the average spike count from all cells in the same mouse. The violin plots show

distributions of spike counts from all individual neurons. e, Pairwise mutual information grouped by the distances between neurons. Data are mean ± s.e.m. Two-way analysis of variance was used to compare between groups. f, Neuron cluster size distributions classified by activity patterns (Louvain clustering; Methods). g, Quantification of population entropy (a measurement of temporal variance of the firing pattern) from each mouse imaged. For d,e and g, n = 4, n = 4 and n = 6 mice in the WT group, 5xFAD with control sgRNA group and 5xFAD with Pld3 sgRNA group, respectively. For f, n = 67, n = 21 and n = 45 clusters in the WT group, 5xFAD with control sgRNA group and 5xFAD with Pld3 sgRNA group, respectively. For d,f and g, statistical analysis was performed using one-way analysis of variance to compare among groups and the P values indicate a post hoc comparison between the groups, with Sidak's correction for multiple comparisons. For d and g, the bars indicate the group mean. Credit: *Nature* (2022). DOI: 10.1038/s41586-022-05491-6

The formation of amyloid plaques in the brain is a hallmark of Alzheimer's disease. But drugs designed to reduce accumulations of these plaques have so far yielded, at best, mixed results in clinical trials.

Yale researchers have found, however, that swelling caused by a byproduct of these plaques may be the true cause of the disease's debilitating symptoms, they report Nov. 30 in the journal *Nature*. And they identified a biomarker that may help physicians better diagnose Alzheimer's and provide a target for future therapies.

According to their findings, each formation of plaque can cause an accumulation of spheroid-shaped swellings along hundreds of axons—the thin cellular wires that connect the brain's neurons—near amyloid plaque deposits. The swellings are caused by the gradual accumulation of organelles within cells known as lysosomes, which are known to digest cellular waste, researchers found. As the swellings enlarge, researchers say, they can blunt the transmission of normal

electrical signals from one region of the brain to another.

This pileup of lysosomes, the researchers say, causes swelling along axons, which in turn triggers the devasting effects of dementia.

"We have identified a potential signature of Alzheimer's which has functional repercussions on brain circuitry, with each spheroid having the potential to disrupt activity in hundreds of neuronal axons and thousands of interconnected neurons," said Dr. Jaime Grutzendler, the Dr. Harry M. Zimmerman and Dr. Nicholas and Viola Spinelli Professor of Neurology and Neuroscience at the Yale School of Medicine and senior author of the study.

Further, the researchers discovered that a protein in lysosomes called PLD3 caused these organelles to grow and clump together along axons, eventually leading to the swelling of axons and the breakdown of electrical conduction.

When they used gene therapy to remove PLD3 from neurons in mice with a condition resembling Alzheimer's disease, they found that this led to a dramatic reduction of axonal swelling. This, in turn, normalized the electrical conduction of axons and improved the function of neurons in the brain regions linked by these axons.

The researchers say PLD3 may be used as a marker in diagnosing the risk of Alzheimer's disease and provide a target for future therapies.

"It may be possible to eliminate this breakdown of the electrical signals in axons by targeting PLD3 or other molecules that regulate lysosomes, independent of the presence of plaques," Grutzendler said.

More information: Peng Yuan et al, PLD3 affects axonal spheroids and network defects in Alzheimer's disease, *Nature* (2022). DOI:

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