New player in Alzheimer's disease pathogenesis identified

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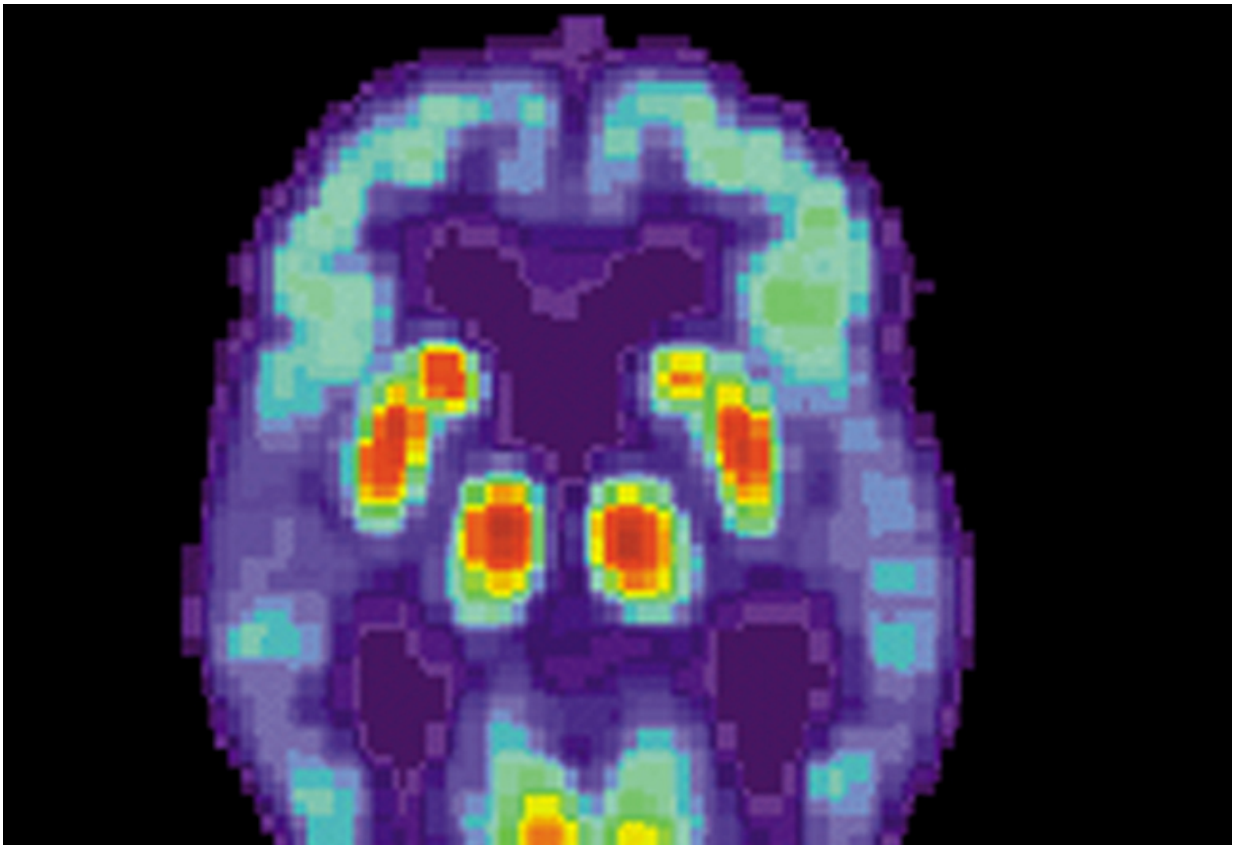

PET scan of a human brain with Alzheimer's disease. Credit: public domain

Scientists at Sanford Burnham Prebys Medical Discovery Institute (SBP) have shown that a protein called membralin is critical for keeping Alzheimer's disease pathology in check. The study, published in *Nature*

Communications, shows that membralin regulates the cell's machinery for producing beta-amyloid (or amyloid beta, Aβ), the protein that causes neurons to die in Alzheimer's disease.

"Our results suggest a new path toward future treatments for Alzheimer's disease," says Huaxi Xu, Ph.D., the Jeanne and Gary Herberger Leadership Chair of SBP's Neuroscience and Aging Research Center. "If we can find molecules that modulate membralin, or identify its role in the cellular protein disposal machinery known as the endoplasmic reticulum-associated degradation (ERAD) system, this may put the brakes on neurodegeneration."

ERAD is the mechanism by which cells get rid of proteins that are folded incorrectly in the ER. It also controls the levels of certain mature, functional proteins. Xu's team found that one of the fully formed, working proteins that ERAD regulates is a component of an enzyme called gamma secretase that generates Aβ.

This discovery helps fill in the picture of how Alzheimer's disease, an incredibly complicated disorder influenced by many genetic and environmental factors. No therapies have yet been demonstrated to slow progression of the disease, which affects around 47 million people worldwide. Until such drugs are developed, patients face a steady, or sometimes rapid, decline in memory and reasoning.

Memory loss in Alzheimer's results from the toxic effects of Aβ, which causes connections between neurons to break down. Aβ is created when gamma secretase cuts the amyloid precursor protein into smaller pieces. While Aβ is made in all human brains as they age, differences in the rate at which it is produced and eliminated from the brain and in how it affects neurons, means that not everyone develops dementia.

"We were interested in membralin because of its genetic association with

Alzheimer's, and in this study we established the connection between membralin and Alzheimer's based on findings from the laboratory of a former colleague at SBP, Professor Dongxian Zhang," Xu explains. "That investigation showed that eliminating the gene for membralin leads to rapid motor neuron degeneration, but its cellular function wasn't clear."

Using proteomics, microscopic analysis, and functional assays, the group provided definitive evidence that membralin functions as part of the ERAD system. Later, they found that membralin-dependent ERAD breaks down a protein that's part of the gamma secretase enzyme complex, and that reducing the amount of membralin in a mouse model of Alzheimer's exacerbates neurodegeneration and memory problems.

"Our findings explain why mutations that decrease membralin expression would increase the risk for Alzheimer's," Xu comments. "This would lead to an accumulation of gamma secretase because its degradation is disabled, and the gamma-secretase complex would then generate more Aβ. Those mutations are rare, but there may be other factors that cause neurons to make less membralin."

Xu and colleagues also observed lower levels of membralin, on average, in the brains of patients with Alzheimer's than in unaffected individuals, demonstrating the relevance of their findings to humans.

"Previous studies have suggested that ERAD contributes to many diseases where cells become overwhelmed by an irregular accumulation of proteins, including Alzheimer's," says Xu. "This study provides conclusive, mechanistic evidence that ERAD plays an important role in restraining Alzheimer's disease pathology. We now plan to search for compounds that enhance production of membralin or the rate of ERAD to test whether they ameliorate pathology and cognitive decline in models of Alzheimer's. That would further support the validity of this

mechanism as a drug target."

More information: Bing Zhu et al, ER-associated degradation regulates Alzheimer's amyloid pathology and memory function by modulating γ-secretase activity, *Nature Communications* (2017). DOI: 10.1038/s41467-017-01799-4

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