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GLADSTONE RESEARCHERS FIND CLUE TO ALZHEIMER'S DISEASE RISK FACTOR

For years, scientists have recognized a protein called apoE4 as a major risk factor for developing Alzheimer's disease. Researchers at the Gladstone Institute of Neurological Disease are now finding that the protein may influence the structure of the cell's inner skeleton, which is important for the survival and function of nerve cells.

Published in the July 17 issue of the *Proceedings of the National Academy of Sciences USA*, the finding could explain how apoE4 contributes to the memory loss and other symptoms of Alzheimer's.

The researchers studied neurofibrillary tangles, one of the two major pathological hallmarks of Alzheimer's. The tangles are presumed to contribute to the degeneration of neurons in this disease. Previous studies of Alzheimer brains had detected apoE4 in the tangles raising the question whether apoE4 plays a role in their formation.

The study now shows that apoE4 is broken up into fragments that induce tangle-like fibers in nerve cells. These findings suggest that apoE4 may contribute to brain cell damage by contorting the scaffold system that supports the structure and function of these cells.

"This is a significant step that suggests how apoE4 might disrupt the ability of brain cells to interact and interconnect," said senior co-author Robert W. Mahley, MD, PhD, president of the J. David Gladstone Institutes and UCSF professor of medicine and pathology. "Cleaving apoE4 somehow activates it to interact with proteins in nerve cells to form neurofibrillary-tangle-like structures."

Identifying the enzyme that might be responsible for the cleavage of apoE4 could lead to the development of an Alzheimer's treatment, said lead author Yadong Huang, MD, PhD, Gladstone staff research investigator and UCSF assistant professor of pathology.

"If we can find the enzyme that cleaves apoE4, we can design an inhibitor to block its action, and this could prevent or delay Alzheimer's disease in the many people carrying one or more apoE4 genes," he said.

The researchers first examined the brains of deceased Alzheimer's patients and found that the neurofibrillary tangles contained cleaved versions of apoE4, along with the structural proteins. The next piece of evidence came from studies of different cells grown in culture

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dishes. Expression of cleaved versions of apoE4 induced neurofibrillary tangle-like structures only in nerve cells but not in cells from peripheral organs. This increases the relevance of the findings to Alzheimer's primarily affects the brain. A variant of apoE that is not a risk factor for Alzheimer's, apoE3, was cleaved less and did not induce tangles as much as apoE4.

The researchers don't know exactly why apoE4 is so much more susceptible to being cleaved than apoE3 but Huang and Mahley speculated that the reason could lie in the three-dimensional structure of the proteins.

Co-investigators of this study include Xiao Qin Liu, MD, research associate, Walter J. Brecht, senior research associate, and David A. Sanan, PhD, staff research scientist, all of the Gladstone Institute for Cardiovascular Disease; and Tony Wyss-Coray, PhD, staff research investigator at the Gladstone Institute of Neurological Disease and UCSF assistant professor of neurology.

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The Gladstone Institute of Neurological Disease is one of three research institutes that compose The J. David Gladstone Institutes, a private biomedical research institution affiliated with UCSF. The institution is named for a prominent real estate developer who died in 1971. His will created a testamentary trust that reflects his long-standing personal interest in medical education and research.

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