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## GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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### GLADSTONE STUDY LINKS ALZHEIMER'S WITH TOXIC PROTEIN FRAGMENTS

New research from the Gladstone Institute of Neurological Disease details exactly how a mutant form of the protein apolipoprotein E, also known as apoE, is a causative factor for Alzheimer's disease.

It pinpoints mitochondria, the organelles within cells designed to turn glucose into energy, as a key site that specific fragments of a particular form of apoE attack, leading to the neuronal death characteristic of Alzheimer's disease (AD).

The findings are published online by the *Proceedings of the National Academy of Science*, in advance of publication in the December 20, 2005, issue of *PNAS*.

According to Gladstone Assistant Investigator Yadong Huang, MD, PhD, who headed the study, it has been known for several years that a correlation exists between lowered glucose metabolism and the presence in the brain of a mutant form of a protein that transports cholesterol.

Scientists have been unable to determine if this mutant protein actually interferes with the ability of neurons to make use of glucose in the brain, but they have theorized that such an inability to access glucose might kill off crucial brain cells, causing AD symptoms.

The devastating effects of AD are well known: progressive and inexorable loss of cognitive function that erases memories, extinguishes personality, and robs people of their ability to think, reason and carry out the activities of everyday life. Despite intensive efforts to identify the underlying causes, and considerable progress in unraveling the web of contributing factors, the pathogenesis of AD remains tantalizingly elusive, and a cure is still out of reach, says Huang.

Seeking answers to a fundamental question in AD research on what actually causes brain cells to die in affected patients, Huang and his scientific team pursued a particularly promising avenue of research over the last few years. Their efforts focused on apoE, a protein comprised of 299 amino acids whose apoE4 isoform has been known for the last decade to be the most significant genetic risk factor for AD.

"Several years ago, we found that apoE is subject to cleavage that results in fragments that are toxic to neurons," says Huang, who also is assistant professor of pathology and neurology at UC San Francisco. "This study shows which parts of apoE are toxic and gives hints as to the site of its action."

The research team investigated the cellular and molecular mechanisms of the neurotoxicity caused by apoE4 fragments, performing a series of studies in cultured mouse neuronal cells. The cells expressed apoE fragments of various lengths and with mutations designed to enable the investigators to determine precisely which portions of the fragment—that is, which of apoE4's 299 amino acids—are responsible for its detrimental effects.

Research findings showed that fragments containing both the lipid- and receptor-binding regions, but lacking the C-terminal 27 amino acids (273-299), were found to be neurotoxic. The toxic fragments appear in the mitochondria, where they impaired membrane integrity and mitochondrial function.

(more)

“Blocking interaction of apoE4 fragments with the mitochondria is a potential new strategy for inhibiting the detrimental effects of apoE4 in AD and other neurological diseases,” Huang explains.

“Alzheimer’s disease is a complex condition,” says co-author Robert W. Mahley, MD, PhD, president of the Gladstone Institutes and UCSF professor of pathology and medicine. “Many factors seem to be involved, and all need to be explored to help us find a way to combat this terrible disease. We are very excited about these particular results because they point to a new and potentially valuable therapeutic strategy.”

The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution founded in 1979. Much of the pioneering work on apoE has been done at the Gladstone Institutes over the last 26 years.

Gladstone scientists began by studying apoE and its involvement in cholesterol metabolism and cardiovascular disease. Their seminal research on the structure and function of the apoE isomers laid the groundwork for current research on apoE4 in AD. In the 1980s, Gladstone scientists discovered that apoE is synthesized in the brain and that it is the major lipid transport vehicle in the cerebrospinal fluid. They showed that apoE plays a critical role in neuronal repair and remodeling and that its three isoforms, including apoE4, have different effects on neurobiology and neurodegenerative disease.

Other co-authors of the paper are Shengjun Chang, Tian ran Ma, Maureen E. Balestra and Dennis Miranda of the Gladstone Institutes. This work was supported in part by the National Institutes of Health and by a research grant from GlaxoSmithKline.

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