



GLADSTONE STUDY REVEALS HOW GENETIC FACTOR MAY INCREASE ALZHEIMER RISK

Scientists at Gladstone Institute of Neurological Disease Zero in on Toxicity of Key Protein, apoE4

San Francisco, Calif. (March 23, 2004)--Researchers at the Gladstone Institute of Neurological Disease have identified processes that may explain how a key protein, apolipoprotein E4 (apoE4), contributes to the development of Alzheimer's disease. Their findings, described in the *Journal of Neuroscience* (March 10, 2004), include identifying where in the brain apoE4 is broken down into toxic fragments that can impair the function and survival of nerve cells. Results of their study may point the way to a new therapeutic strategy for prevention and treatment of Alzheimer's disease.

ApoE4 is the best known genetic risk factor for Alzheimer's disease, but, until now, the mechanism by which it increases that risk has remained a mystery. The key finding of the current study relates to apoE4's tendency to be broken down into toxic fragments when it is produced in neurons, the brain cells responsible for cognitive functions.

Proteins can be broken into small pieces by enzymes known as proteases in a process termed proteolysis. While the degradation of proteins is important for many cell processes, it can be harmful when it occurs inappropriately, not only because it destroys the protein, but also because abnormally high levels of fragments can damage cells.

In the new study, involving the examination of genetically engineered mice, Gladstone researchers have established that:

- only apoE4 produced by neurons is susceptible to fragmentation, unlike apoE4 produced by other brain cells;
- fragmentation is correlated with age, occurring more frequently the older the animal, similar to the effect of age on Alzheimer risk in humans;
- fragmentation of apoE4 occurs predominantly in the very parts of the brain that are most vulnerable to Alzheimer's disease, the neocortex and hippocampus. In contrast, fragmentation does not occur in the cerebellum, which is much less vulnerable to Alzheimer's;

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- the apoE4 fragments cause an abnormal change to the protein tau, which is also heavily affected by Alzheimer's disease. Both apoE4 fragments and Alzheimer's disease lead to the abnormal attachment of phosphate groups on tau that can end up contorting the shape of brain cells.

The investigators suspect that the fragmentation of apoE4 is caused by a neuron-specific enzyme, which they are now trying to identify and block with drugs.

“From this and our previous studies, we believe that the protease that cleaves apoE4 may serve as a therapeutic target for the prevention and treatment of Alzheimer's disease, especially in patients who are impacted by apoE4,” said the senior author of the study, Yadong Huang, M.D., Ph.D., staff research investigator at the Gladstone Institute of Neurological Disease (GIND) and assistant professor of pathology at the University of California, San Francisco (UCSF).

“With this work, we're a significant step closer to solving the key riddle of apoE4, namely, what is occurring at the molecular level that makes this protein so active in causing neurodegenerative disease,” explained Dr. Robert Mahley, president of the J. David Gladstone Institutes and a co-author of the paper. “Research of this kind is essential for the development of better treatments for Alzheimer's disease.”

This work was supported in part by grants from the National Institutes of Health and by a MetLife Foundation award. The paper, “Neuron-Specific Apolipoprotein E4 Proteolysis Is Associated with Increased Tau Phosphorylation in Brains of Transgenic Mice,” was co-authored by GIND staff members Walter J. Brecht, senior research associate; Faith M. Harris, research associate; Shengjun Chang, postdoctoral fellow; Ina Tesseur, postdoctoral fellow; Gui-Qiu Yu, senior research associate; Qin Xu, postdoctoral fellow; Jo Dee Fish, research technologist; Tony Wyss-Coray, former staff research investigator; Manuel Buttini, former research scientist; and Lennart Mucke, GIND director and senior investigator, professor of neurology, UCSF, along with Mahley and Huang.

The Gladstone Institute of Neurological Disease is one of three research institutes of The J. David Gladstone Institutes, a private, nonprofit biomedical research institution affiliated with UCSF. For further information, visit www.gladstone.ucsf.edu.

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