



GLADSTONE INSTITUTE OF NEUROLOGICAL DISEASE NEWS

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GLADSTONE SCIENTISTS PROVE NEURONS PRODUCE ALZHEIMER'S-LINKED APOLIPOPROTEIN E

Unique Mouse Model Helps Solve Protein Mystery

A question long debated among Alzheimer's disease researchers has been definitively answered by scientists at the Gladstone Institute of Neurological Disease in San Francisco.

Using a unique mouse model, Gladstone Investigator Yadong Huang, MD, PhD, and his team have proven that, under certain conditions, neurons produce Alzheimer's-linked apolipoprotein E.

Also known as apoE, this cholesterol-carrying protein has three common forms, one of which, apoE4, is the major known genetic risk factor for Alzheimer's disease, according to studies published around the world in recent years. Until now, most researchers have believed that apoE is synthesized in the brain solely in such cells as astrocytes, microglia, and ependymal layer cells. Controversial for the last decade has been the question of whether or not neurons, which make thought and memory possible by transmitting electrical signals, can produce apoE.

The Gladstone study, published in the May 10 issue of the *Journal of Neuroscience* and highlighted in its "This Week in the Journal" section, proves that neurons, too, produce apoE, but only in response to injury to the brain.

Key to the finding has been the development of a mouse model that is uniquely capable of alerting researchers whenever and wherever the apoE gene is expressed. Huang and his team have succeeded in making one of the two alleles of the apoE gene produce a green fluorescent protein that represents apoE, while the remaining allele functions normally. Thus, under a microscope, the bright green fluorescence, dubbed EGFPapoE, shows researchers wherever the apoE gene is expressed.

"This study lays to rest a long-standing controversy concerning the neuronal expression of apoE," says senior author Huang, an assistant professor of pathology and neurology at UCSF. "Our study proves clearly that neurons produce apoE in response to injury. They support the notion that an understanding of how apoE expression is regulated in neurons is important for unraveling the mechanisms underlying apoE4-related neurodegenerative disorders."

"ApoE expression can be detected with unprecedented sensitivity and resolution in these mice," explains Qin Xu, PhD, a Gladstone postdoctoral scholar and first author of the paper. "This mouse model, known as the 'EGFP knock-in,' is a new and extremely promising approach to monitor gene expression *in vivo*."

"Our EGFPapoE reporter mice can be used to track apoE expression in any tissue at any stage of development," adds Huang. "They will be a valuable tool for investigating the normal functions of apoE

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SCIENTISTS PROVE NEURONS PRODUCE ALZHEIMER'S-LINKED APOE/2-2-2

and the regulatory mechanisms that govern its expression.”

Still to be determined is the exact mechanism by which apoE4 wreaks havoc on the brain, playing roles not only in Alzheimer's disease but also in a number of other neurological diseases. Studies in Huang's lab have revealed a possible scenario. It appears that apoE in neurons is subject to processing by an enzyme that clips off a portion of the protein, resulting in toxic fragments that escape the secretory pathway and enter the cytosol (the fluid portion of a cell's cytoplasm). Studies now underway at Gladstone and elsewhere indicate that those fragments may interfere with glucose metabolism in the mitochondria (small intracellular organelles responsible for energy production, among other functions), leading to mitochondrial dysfunction and neuronal cell death.

The paper, “Profile and Regulation of Apolipoprotein (Apo) E Expression in Central Nervous System in Mice with Targeting of Green Fluorescent Protein Gene to the apoE Locus,” was authored by Aubrey Bernardo, David Walker, and Tiffany Kanegawa of the Gladstone Institute of Neurological Disease, Gladstone Institutes President Robert W. Mahley, and Xu and Huang. This work was supported in part by grants from the National Institutes of Health and a postdoctoral fellowship from the John Douglas French Alzheimer's Foundation.

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