UC San Diego Health

Understanding a Protein's Role in Familial Alzheimer's Disease

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Novel genomic approach reveals gene mutation isn't simple answer

Researchers at the University of California, San Diego School of Medicine have used genetic engineering of human induced pluripotent stem cells to specifically and precisely parse the roles of a key mutated protein in causing familial Alzheimer's disease (AD), discovering that simple loss-of-function does not contribute to the inherited form of the neurodegenerative disorder.

The findings, published online in the journal *Cell Reports*, could help elucidate the still-mysterious mechanisms of Alzheimer's disease and better inform development of effective drugs, said principal investigator Lawrence Goldstein, PhD, professor in the Departments of Cellular and Molecular Medicine and Neurosciences and director of the UC San Diego Stem Cell Program.

"In some ways, this is a powerful technical demonstration of the promise of stem cells and genomics research in better understanding and ultimately treating AD," said Goldstein, who is also director of the new Sanford Stem Cell Clinical Center at UC San Diego. "We were able to identify and assign precise limits on how a mutation works in familial AD. That's an important step in advancing the science, in finding drugs and treatments that can slow, maybe reverse, the disease's devastating effects."

Familial AD is a subset of early-onset Alzheimer's disease that is caused by inherited gene mutations. Most cases of Alzheimer's disease – there are an estimated 5.2 million Americans with AD – are sporadic and do not have a precise known cause, though age is a primary risk factor.

In their study, Goldstein and colleagues examined presenilin 1 (PS1), a protein that helps break down other proteins, which is a vital biological necessity for cells and for life. Most notably, PS1 is the catalytic or action-driving component of gamma-secretase, an enzyme that cleaves or splits type-1 transmembrane proteins used to transport cellular material from one side of a cell's membrane to the other, from inside to outside or vice versa.

Among the type-1 proteins cleaved by gamma-secretase is amyloid precursor protein or APP, whose function remains incompletely known. When APP is cleaved by gamma-secretase, peptide fragments called amyloid beta are created. Some researchers believe the accumulation of certain kinds of amyloid beta may result in neuron-killing plaques in the brain, a consequence that has been strongly linked to the development of AD.

Ordinarily, the "molecular scissors" of PS1 do their cutting with no adverse effect, according to Goldstein. But perhaps 20 percent of the time, he said there are "bad cuts" that result in potentially harmful amyloid beta fragments. "Our research demonstrates very precisely that mutations in PS1 double the frequency of bad cuts," he said.

The researchers achieved their unprecedented precision by generating differentiated, purified neurons from stem cells derived from noted biologist Craig Venter, whose genome was fully sequenced and released for public research use in 2007. The created neurons contained different alleles or forms of the mutated gene that produces PS1.

"We were able to investigate exactly how specific mutations and their frequency change the behavior of neurons," said Goldstein. "We took finely engineered cells that we knew and understood and then looked how a single mutation caused changes in the molecular scissors and what happened next."

To exclude potential off-target artifacts observed in previous genome editing work, study co-author Kun Zhang, PhD, associate professor in the Department of Bioengineering at UC San Diego, said he and colleagues used whole exome sequencing to compare the engineered cells with other control cells. They determined that their genome editing approach did not introduce any additional mutations.

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