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Linking 2 molecular pieces of the Alzheimer's puzzle

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Researchers have uncovered a biological link between the protein whose mutation causes early-onset Alzheimer's disease (AD) and a gene variant linked to late-onset AD. The researchers said their finding could lead to new approaches to treating AD.

Guojun Bu and colleagues published their findings in the October 4, 2007 issue of the journal *Neuron*.

In their studies, the researchers sought to link the function of two known causative factors in AD—amyloid precursor protein (APP) and a particular form of the gene for the protein apolipoprotein E (apoE) that has been linked to higher late-onset AD risk.

Mutations in APP are known to cause early-onset AD when cleavage of the protein produces a short toxic protein called Aâ peptide that builds up in the brain, killing brain cells.

And a specific variant of the gene for apoE, which produces a version called apoE4, has been linked to late-onset AD, although how this predisposes individuals to the disease is largely unknown. However, the normal function of the apoE protein is known. It carries cholesterol and other lipids into nerve cells, where they act as essential building blocks for neuronal membranes.

In their experiments with mice and cultured mouse cells, the researchers linked APP to the regulation of apoE and its cholesterol transport

function. Specifically, they found that the normal cleavage of APP in the cell gives rise to a nontoxic fragment (called AICD) that suppresses the gene that produces the cell receptor for apoE—called LRP1. This receptor, which nestles in the membrane of nerve cells, enables the apoE protein to transport its cholesterol cargo into the cell.

The researchers speculated that the loss of LRP1 function in AD might cause a loss of cholesterol that causes malfunction of neurons. Thus, they suggested that treatments to restore the activity of the receptor gene might be a useful treatment strategy for AD. One such treatment, they said, consists of drugs that inhibit the enzyme that cleaves APP to produce the regulatory protein fragment that suppresses the LRP1 gene.

The researchers concluded that “Our results provide important insights into APP biological function and its potential implications for neuronal dysfunction in AD and may lead to the design of better therapeutic strategies to treat this devastating disease.”

Source: Cell Press