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Defective Cell Transport Suggested in Alzheimer's Disease

Over the last few years, scientists have been successful in identifying genes implicated in Alzheimer's disease, but they are just beginning to piece together what the Alzheimer's-disease-related proteins do in the cell, and how they may cause disease.

Now, Howard Hughes Medical Institute investigator Lawrence Goldstein and his colleagues at the University of California, San Diego, report in the December 6, 2001, issue of the journal *Nature* that several of these proteins are involved in trafficking cargo inside nerve cells. In a related report published in the November 8, 2001, issue of the journal *Neuron*, a team of researchers led by Goldstein showed that disruption of the transport system caused by defects in these proteins can lead to nerve cell death.

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"If you look at the history of breakthroughs in disease, often the understanding of what proteins normally do gives important clues to what is aberrant in disease," said Goldstein. "This has been much less useful so far in understanding neurodegenerative diseases. Neurologists see protein aggregations in diseased brains, but there is a big gulf in understanding whether the generation of protein aggregates causes the disease per se."

In the brains of patients with Alzheimer's disease, a peptide called amyloid-beta accumulates in areas of the brain where nerve cells die en masse, leading to progressive dementia. Goldstein and his colleagues studied the role of amyloid precursor protein (APP), which gives rise to the abnormal amyloid clumps.

Using mouse neurons as a model, the scientists showed that APP serves as an attachment point for a molecular motor called kinesin, which transports packets of protein from the main cell body along the length of the cell. This

cell transport mechanism is crucial to nerve cells, which have the unique property of sending out tendrils, called axons, up to several feet from the main cell body to innervate distant parts of the body. Communication in these cells is long distance, explained Goldstein.

“If you imagine the cell body as a 50-foot room, the axon could extend up to 200 miles away,” he said. “The cell would have to ship cargo along rather narrow 20-foot pipes and keep track of everything that is happening along the route.”

When something goes wrong with this transport process, the cell often cannot cope and sends out a distress signal that initiates cell death. Goldstein and his colleagues have studied this process and conclude that APP may be involved in a signaling process that leads to cell death when nerve cells are damaged.

Furthermore, the scientists discovered that two other key Alzheimer’s-disease-related proteins, beta-secretase and presenilin-1, are found together with APP inside the packet. Beta-secretase and presenilin-1 are thought to be the main enzymes that process APP and create amyloid-beta peptide. Finding them together inside the cell suggests that APP processing may be part of a normal cell transport function that is somehow disrupted in Alzheimer’s disease, according to Goldstein.

The scientists compared cell transport in neurons of normal mice and mutant mice in which the APP protein is missing. In nerve cells of the mutant mice, they found that APP, beta-secretase and other cellular cargo, in addition to the motor protein kinesin, stay mainly in the cell body, suggesting that when APP is missing, normal cell cargo transport is stalled.

The scientists also found that amyloid-beta and another portion of APP, called the C-terminus, are made in these compartments inside living cells and inside compartments isolated from nerve cells. The C-terminus is the portion of APP where the motor molecule kinesin attaches. Goldstein and his colleagues found that when enzymes break off the C-terminus, kinesin is liberated and the transport process is disrupted. These results also represent one of the first detailed studies of amyloid-beta being formed in compartments inside living nerve cells.

To complement the mouse studies, the researchers studied the effects of various *APP* gene mutations in fruit flies. As reported in the *Neuron* article, Goldstein’s team showed that excess APP containing amyloid-beta region and the C-terminus caused neural cell death, but amyloid-beta containing APP alone did not. These results and research by other investigators led Goldstein’s team to conclude that the C-terminus may carry a cell death signal that can be initiated when transport fails.

“Our results suggest maybe it is the cleavage to liberate this C-terminal piece that is sending a signal back to the cell body to die,” said Goldstein. “It certainly is an interesting clue and makes sense in the context that if a cell is damaged it needs to be able to signal to the nucleus.”

The results also are consistent with the epidemiological observation that people who suffer trauma to the brain are more susceptible to developing Alzheimer's disease, Goldstein added. The investigators are now trying to isolate the death signal for further study.

While Goldstein says the results are not definitive, he suggests studies such as these should help sort out the question of which protein products lead down the path to cell death seen in Alzheimer's disease.