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Alzheimer's-related protein disrupts motors of cell transport

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A protein associated with Alzheimer's disease clogs several motors of the cell transport machinery critical for normal cell division, leading to defective neurons that may contribute to the memory-robbing disease, University of South Florida researchers report.

In a new study published online in the journal *Cell Cycle*, scientists at the USF Health Byrd Alzheimer's Institute. the Florida Alzheimer's Disease Research Center, and Indiana University also suggest that the protein beta amyloid (amyloid protein) may cause neurons in the brain to malfunction and directly contribute to the memory loss that accompanies Alzheimer's progression. The experiments were conducted using human cell cultures and frog egg extracts.

"By identifying a brand new and extremely important target of the amyloid protein's toxicity, we can develop drugs for Alzheimer's disease that may protect the motors from inhibition and allow the brain to regenerate properly," said principal investigator Huntington Potter, PhD, a professor of Molecular Medicine who holds the Pfeiffer Endowed Chair for Alzheimer's Disease Research.

The latest study builds upon earlier research by Dr. Potter and colleagues showing that the amyloid protein is the culprit that damages the microtubule transport system responsible for moving chromosomes, proteins and other cargo around inside cells. The microtubules are critical for segregating newly duplicated chromosomes as cells divide. When the duplicated chromosomes don't separate properly, they can re-

assemble inside newly created cells in wrong numbers and with an abnormal assortment of genes.

More than 20 years ago Dr. Potter created a storm of controversy with the idea that Down syndrome and Alzheimer's were the same disease. Not only did all people with Down syndrome over age 30 develop the same brain pathology seen in Alzheimer's but perhaps both diseases shared the abnormality of having three copies of chromosome 21, which carries the beta amyloid gene.

Subsequent studies by Dr. Potter and others indicated that Alzheimer's disease was indeed promoted in part by the development of new trisomy 21 cells in the brain, which amplify the nerve-killing buildup of sticky amyloid protein clumps.

The findings in Cell Cycle help to further delineate how interference with cell division could result in a cascade of events that contributes to Alzheimer's pathology. In a series of laboratory experiments, several neuroscientists and cell biologists collaborated to demonstrate how over-production of the amyloid protein attacks several molecular motors that play a role in moving chromosomes along microtubules during normal cell division.

"It's kind of like throwing sand in the gears of the cell's transport machinery," said first author Sergiy Borysov, PhD, a postdoctoral fellow in Dr. Potter's laboratory. "It keeps the wheels from moving, which interferes with the cell division cycle and ultimately leads to the production of degeneration-prone neurons seen in the Alzheimer's disease brain."

The same motors are essential for neuron function as well as production, the researchers suggest.

Properly functioning microtubule motors are especially critical in nerve cells, in which molecules related to learning and memory must travel over long distances, Dr. Potter said. Identifying specific microtubule motors directly inhibited by the amyloid protein could help researchers develop more effective drugs or other therapies for Alzheimer's disease, he added.

More information: "Alzheimer's Aβ Disrupts the Mitotic Spindle and Directly Inhibits Mitotic Microtubule Motors;" Sergiy I. Borysov, Antoneta Granic, Jaya Padmanabhan, Claire E. Walczak, and Huntington Potter, *Cell Cycle*, Volume 10, Issue 9 (May 2011).

Provided by University of South Florida