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New protein linked to Alzheimer's disease

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After decades of studying the pathological process that wipes out large volumes of memory, scientists at The Feinstein Institute for Medical Research discovered a molecule called c-Abl that has a known role in leukemia also has a hand in Alzheimer's disease. The finding, reported in the June 14th issue of the *Journal of Alzheimer's Disease*, offers a new target for drug development that could stave off the pathological disease process.

Peter Davies, PhD, head of the Feinstein Institute's Litwin-Zucker Center for Research in Alzheimer's Disease, became interested in c-Abl when he found that the protein was part of the plaques and tangles that crowd the brains of Alzheimer's patients. The protein c-Abl is a tyrosine kinase involved in cell differentiation, cell division and cell adhesion. In patients with chronic myeloid leukemia (CML), c-Abl is turned up in B cells. Inhibiting c-Abl with the cancer drug Gleevec prevents cell division. There was quite a lot known about c-Abl when Dr. Davies began thinking about its possible role in Alzheimer's. He was looking at kinases that phosphorylate tau, the protein that accumulates inside of the neurons during the disease process.

Dr. Davies questioned whether activated c-Abl turned on the cell cycle and could kill adult cells. He designed the study to test this idea and found that turning on the cell cycle in adult brain damages the cells. In their current study, the investigators devised a clever way to activate c-Abl in neurons of normal adult mice. They turned on human c-Abl genes in two different regions – the hippocampus and the neocortex – in adult mice and discovered abundant cell death, especially in the hippocampus.

"You don't even need to count, you can just look and see holes in the cell layers of the hippocampus," said Dr. Davies. "It is stunning. Even before the neurons die, there is florid inflammation."

He said that the animal model is ideal for testing the benefit of drugs that turn off c-Abl. While Gleevec works in CML, it does not cross the blood-brain barrier so it would not be useful. Dr. Davies and his colleagues are looking for other drugs that inhibit c-Abl and can get into the brain. "We have a great model to test compounds for Alzheimer's disease. Will regulating c-Abl make a difference for patients? We won't know unless we try it in double blind clinical trials."

The researchers are now working to understand the mechanism of cell death. They are also investigating why males die considerably sooner than females – 12 to 15 weeks compared to 24 to 26 weeks. "It is an incredibly interesting model," said Dr. Davies. "If c-Abl is important we can learn how it works."

More information: The paper detailing the findings has been published in an early online version. It is scheduled for publication in the June 14th issue of the *Journal of Alzheimer's Disease* (www.j-alz.com).

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