MedicalXpress

Alzheimer's brains found to have lower levels of key protein

September 1 2011

Researchers have found that a protein variation linked by some genetic studies to Alzheimer's disease is consistently present in the brains of people with Alzheimer's. In further biochemical and cell culture investigations, they have shown that this protein, known as ubiquilin-1, performs a critical Alzheimer's-related function: it "chaperones" the formation of amyloid precursor protein, a molecule whose malformation has been directly tied to Alzheimer's pathology.

"What we saw here is that in all 20 of the Alzheimer's brains we examined the ubiquilin-1 protein level was lower, and that's completely new," said University of Texas Medical Branch at Galveston assistant professor José Barral, co-author of a paper on the study now online in the Journal of Biological Chemistry. "Our experiments looked at the consequences of decreased ubiquilin-1, and showed that it's necessary for the proper handling of amyloid precursor protein."

APP has been a major focus of Alzheimer's investigators for almost two decades, ever since scientists identified it as the source of so-called "protein plaques," abnormal aggregations of proteins nearly always found in the brains of Alzheimer's victims. Ubiquilin-1's significance was revealed after the UTMB researchers established ubiquilin-1's status as a chaperone protein for APP.

In the origami-like folding process by which proteins arrive at their proper shape, chaperone proteins act as, well, chaperones: they bind to their client proteins and make sure they don't misbehave.

The kind of APP misbehavior Alzheimer's researchers are most concerned about is the formation of toxic aggregations of the protein or its breakdown products, both inside and outside brain cells. Through a series of biochemical and cell-culture experiments, the UTMB team was able to show that ubiquilin-1 decreased this aggregation.

"Ubiquilin-1 prevents the APP molecule from falling into a conformation it's not supposed to be in," said UTMB associate professor Darren Boehning, co-author of the *Journal of Biological Chemistry* paper. "This fits with a theme we're seeing across the neurodegenerative disorders and the disorders of aging - the idea that many of these disorders are associated with decreased quality control by chaperones."

Provided by University of Texas Medical Branch at Galveston