Study uncovers key factor in Alzheimer's progression

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(Medical Xpress)—A new study from researchers at the University of Florida may have uncovered a critical factor that drives the relentless progression of Alzheimer's disease — a discovery that could eventually slow its progression.

For more than 15 years, scientists have known that two types of brain lesions form in patients with Alzheimer's disease, one type of lesion forming only after the other. David R. Borchelt, a professor of neuroscience, and Guilian Xu, an assistant research scientist at the UF College of Medicine, have used a mouse model to find a potential explanation for how the first type of brain lesion may trigger the second. They report their findings in the current issue of the journal *Human Molecular Genetics*.

"Understanding how this sequence of events works is thought to be critical and could lead to new therapeutic approaches," said Borchelt, director of the SantaFe HealthCare Alzheimer's Disease Research Center at UF and the McKnight Brain Institute.

The lesion that appears first is an amyloid plaque, an incorrectly folded protein structure that forms when a small peptide called the amyloid-beta peptide clumps together. However, scientists have known that amyloid alone does not produce Alzheimer's disease, and all patients with symptoms have a second type of brain lesion called a neurofibrillary tangle. This second lesion appears later in the disease, and as more of these lesions develop, patient symptoms get worse.

Finding an explanation for the sequential appearance of these lesions has challenged scientists, but understanding how the amyloid plaques trigger the tangles could help scientists devise ways to slow disease progression.

The explanation lies at the heart of how cells function. All cells produce proteins, the molecular workhorses of the cell. Proteins have specific, three-dimensional shapes critical to proper function. This is so important that large amounts of cell energy go into making correctly folded proteins and eliminating incorrectly folded ones. The study by the Borchelt laboratory provides evidence that the abnormal accumulation of the amyloid peptide in the brain that produces the plaque lesions also interferes with brain cells' ability to keep proteins correctly folded.

"This deficiency in cell function could set the stage for allowing the formation of the neurofibrillary tangles that seem to be the key pathology to symptoms," Borchelt said.

These tangles form when a protein called tau loses its normal shape and folds into a shape that allows it to bind to other tau proteins. This becomes a runaway process that fills the cell with abnormally shaped tau clumps that produce the tangles.

In recent years, pharmaceutical and biotech companies have begun to look for drugs that could stimulate better protein folding in brain cells. The study by Xu suggests that these companies may be on the right track. Borchelt cautions that more work is needed to fully understand how amyloid pathology is linked to the tangle pathology, but this recent study offers a new avenue of investigation that could lead to a clearer picture.

Provided by University of Florida

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