Diametric shift in 2 protein levels spurs Alzheimer's plaque accumulation

1 December 2011

A diametric shift in the levels of two proteins involved in folding, moving and cutting other proteins enables accumulation of the destructive brain plaque found in Alzheimer's disease, researchers report.

VPS35 is a protein that folds others into specific positions to unleash their functions. When levels are reduced as they are in aging, it unleashes the normally dormant BACE1, a protein responsible for beta amyloid plaque production, Georgia Health Sciences University researchers report in The Journal of Cell Biology.

When researchers modified a mouse model of Alzheimer's so that VPS35 production was essentially cut in half, BACE1 activity was increased, accelerating aging and development of related problems such as memory deficits and poor communication between brain cells as well as beta amyloid accumulation, said Dr. Wen-Cheng Xiong, developmental neurobiologist and Weiss Research Professor at GHSU and the study's corresponding author.

It was known that expression of VPS35 was down and BACE1 was up in Alzheimer's but the direct relationship was unknown, Xiong said. "We believe impaired function of VPS35 could be a risk factor for Alzheimer's and Parkinson's diseases," Xiong said. Discovering the relationship makes VPS35 a potential biomarker for the diseases as well as a target for new therapies to keep VPS35 elevated. The accelerated aging model Xiong developed and patented will enable these future drug studies.

This unhealthy balance causes cells to accumulate more waste than their recycling systems can handle. Additionally misfolded proteins end up in the wrong cell compartment where they form aggregates that eventually kill the cell. Being in the wrong place is what enables BACE1 activity to increase: it ends up stuck in a cell compartment called the endosome where high acidity levels activate the protein. As BACE1 becomes more numerous and active, it chops up more potentially productive proteins, turning them into garbage.

"Each protein knows its destination, lifespan and when it should be degraded; everything is controlled. With aging, their trafficking, their control system is disrupted," Xiong said.

Future questions include what reduces VPS35 levels, such as increased levels of reactive oxygen species that come with age, and whether exercise can help keep them up. 'We think VPS35 will be a new, hot and hopefully productive area for Alzheimer's and Parkinson's research," Xiong said.

The protein is classified a retromer. Retromers are important to recycling inside cells. While silent in healthy adults, BACE1 plays an important role in brain development.

Provided by Georgia Health Sciences University