

Scientists find new causes for neurodegeneration

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Diseases that cause neurons to break-down, such as Alzheimer's, Multiple Sclerosis and Creutzfeldt-Jakob disease (Mad Cow Disease), continue to be elusive to scientists and resistant to treatments.

A new finding from University of Michigan researchers demonstrates an unpredicted link between a virtually unknown signaling molecule and neuron health.

In a study released in *PNAS*, the journal of the National Academy of Sciences this week, graduate student, Yanling Zhang, postdoctoral fellow Sergey Zolov and Life Sciences Institute professor Lois Weisman connect the loss of this molecule to massive neurodegeneration in the brain.

The molecule PI(3,5)P2 is a lipid found in all cells at very low levels. Lipids are a group of small organic compounds. While the best studied lipids are fats, waxes and oils, PI3,5P2 is a member of a unique class of lipids that signal the cell to perform special tasks.

Weisman said it was surprising to find that PI(3,5)P2 plays a key role in the survival of nervous system cells.

"In mice, lowered levels of PI(3,5)P2 leads to profound neurodegeneration," said Weisman. "It suggests that we have a good place to look to find treatments for neurodegenerative diseases such as Alzheimer's."

Weisman, who is also professor of Cell & Developmental Biology at the U-M Medical School and her colleagues, began from clues that were hidden in a conserved genetic pathway in yeast (a pathway that has remained the same in yeast, plants and humans over evolutionary time). Studies in yeast showed that the enzyme that manufactures the lipid is governed by the FIG4 and VAC14 genes, which exist in yeast, mice and humans.

Working with two independently derived mouse models, Weisman's team and collaborators including graduate student Clement Chow and Professor Miriam Meisler of the Department of Human Genetics at the U-M Medical School, reached the same conclusions in a pair of important papers for neuroscience research.

Building on research from Meisler, a mouse geneticist, and Weisman, a yeast geneticist, the collaborators published a paper in *Nature*, July 5, 2007, showing that in mice, the FIG4 gene is required to maintain normal levels of the signaling lipid and to maintain a normal nervous system. Importantly, they found that human patients with a very minor defect in their FIG4 genes had serious neurological problems.

The signaling lipid PI(3,5)P2 (short for phosphatidylinositol 3,5-bisphosphate) is part of a communication cascade that senses changes outside the cell and promotes actions inside the cell to accommodate to the changes.

Weisman's team found that mice missing the VAC14 gene, which encodes a regulator of PI(3,5)P2 levels, suffer massive neurodegeneration that looks nearly identical to the neurodegeneration seen in the FIG4 mutant mice. In both cases the levels of PI(3,5)P2 are one half of the normal levels. The fact that both mice have half the normal levels of the lipid and also have the same neurodegenerative problems provides evidence that there is a direct link between the lipid

and neuronal health.

The new findings indicate that when Vac14 is removed, the cell bodies of many of the neurons appear to be empty spaces and the brain takes on a spongiform appearance.

Source: University of Michigan

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