Brain cell activity regulates Alzheimer's protein

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Increased brain cell activity boosts brain fluid levels of a protein linked to Alzheimer's disease, according to new research from scientists at Washington University School of Medicine in St. Louis.

Tau protein is the main component of neurofibrillary tangles, one of the hallmarks of Alzheimer's disease. It has been linked to other neurodegenerative disorders, including frontotemporal dementia, supranuclear palsy and corticobasal degeneration.

"Healthy brain cells normally release tau into the cerebrospinal fluid and the interstitial fluid that surrounds them, but this is the first time we've linked that release in living animals to brain cell activity," said senior author David M. Holtzman, MD. "Understanding this link should help advance our efforts to treat Alzheimer's and other neurodegenerative disorders associated with the tau protein.

The study appears online in the *Journal of Experimental Medicine*.

Tau protein stabilizes microtubules, which are long columns that transport supplies from the center of the cell to the distant ends of the cell's branches. Some tau in the cell is not bound to microtubules. This tau can become altered and clump together inside brain cells, forming structures called tangles. Scientists have tracked the spread of these clumps through brain networks in animal models.

"In Alzheimer's disease, you first see clumps of tau in a region called the

entorhinal cortex, and then in the hippocampus, and it continues to spread through the brain in a regular pattern," said Holtzman, the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology. "In another disorder, supranuclear palsy, tau clumps first appear in the brain stem and then spread to regions that the brain stem projects to."

These regular patterns of tau spread through brain networks have led scientists to speculate that dysfunctional tau travels to different brain regions via synapses—the areas where individual nerve cells communicate with each other.

Holtzman's results support this hypothesis, showing that when nerve cells "talk" to each other, tau levels go up in the fluids between those cells, suggesting that brain cells are secreting tau when they send signals.

So far, the researchers only have been able to measure single copies of tau in brain fluid, not the tau clumps. They are looking for a way to detect the clumps. If brain cells can secrete and take in clumps of tau, the scientists believe, these clumps may cause previously normal tau in the receiving cell to become corrupted, fostering the spread of a form of tau involved in disease.

"We also want to know whether brain cells are secreting tau as waste or if tau has a function to perform outside the cell," Holtzman said. "For example, there have been hints that tau may modulate how easy or difficult it is to get brain cells to communicate with each other."

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