Study finds how Alzheimer's-associated protein tangles spread through the brain
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Massachusetts General Hospital (MGH) investigators have discovered a mechanism behind the spread of neurofibrillary tangles - one of the two hallmarks of Alzheimer's disease - through the brains of affected individuals. In a report that has been released online in the journal *Nature Communications*, the research team describes finding that a particular version of the tau protein, while extremely rare even in the brains of patients with Alzheimer's disease, is able to spread from one neuron to another and how that process occurs.

"It has been postulated that tangles - the abnormal accumulation of tau protein that fills neurons in Alzheimer's disease - can travel from neuron to neuron as the disease progresses, spreading dysfunction through the brain as the disease progresses. But how that happens has been uncertain," says Bradley Hyman, MD, PhD, director of the MGH Alzheimer's Disease Research Center and senior author of the report. "Our current study suggests one mechanism at play is that a unique and rare type of tau has the properties we were looking for - it is released from neurons, taken up by other neurons, transported up and down axons, and then released again."

Previous research has shown that tau tangles first appear in a structure located deep within the brain called the entorhinal cortex, which is a hub for signals passing between the hippocampus and the cerebral cortex. Tangles appear later in other nearby structures involved with memory and cognition, but whether that progression reflected the movement of tau proteins through adjacent neurons or some other process was uncertain. Several 2013 studies from Hyman's group and others showed the movement of a mutant form of tau between brain structures and resultant neurodegeneration in a mouse model. One of Hyman's papers also suggested that the process could be halted, but exactly how the cell-to-cell transport takes place still needed to be demonstrated.

The current study revealed that, when brain sample from that mouse model were applied to cultured neurons, only 1 percent of the tau in those samples was taken up by the neurons. The tau proteins that were taken up were high molecular weight - meaning that a number of smaller proteins are bound together into a larger molecule - soluble, and studded with a large number of phosphate molecules, a known characteristic of the tau in Alzheimer's-associated tangles. Similar results were seen in experiments using brain samples from Alzheimer's patients, both in cultured neurons and in living mice. The process by which this version of tau passes between neurons was illustrated using a microfluidic device developed at the MGH BioMEMS Resource Center.

The device consists of three chambers, the first two containing mouse neurons, connected by microgrooves through which axons - the fibers that carry signals from one neuron to another - can extend. The team found that applying this rare form of tau from the brains of the mouse model to neurons in the first chamber resulted in the protein's being taken up by those neurons and, within five days, being present at the ends of first-
chamber-neuron axons and in neurons in the second chamber. A few days later, tau was detected at the end of axons extending from the second to the third chamber, which contained no neurons.

Removal of tau from the first chamber did not cause it to disappear from the second chamber, indicating that once a certain amount of the pathologic version of the protein has been taken up, neurons can continue passing it along even after the original source has been removed. Additional experiments with tau from the brains of Alzheimer's patients confirmed that the high-molecular-weight, soluble, phosphate-bearing version was taken up and passed between neurons.

"Our findings suggest that that the release and uptake of this form of tau is an important step in the spread of disease from one brain region to another," says Hyman, the John Penny Professor of Neurology at Harvard Medical School. "Since that spread likely underlies clinical progression of symptoms, targeting the mechanisms of the spreading might hold promise to stabilize disease."

Provided by Massachusetts General Hospital

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