

# Chemical engineers help decipher mystery of neurofibrillary tangle formation in Alzheimer's brains

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Neurofibrillary tangles – odd, twisted clumps of protein found within nerve cells – are a pathological hallmark of Alzheimer's disease. The tangles, which were first identified in the early 1900s by German psychiatrist and neuropathologist Aloysius Alzheimer, are formed when changes in a protein called tau cause it to aggregate in an insoluble mass in the cytoplasm of cells. Normally, the tau protein is involved in the formation of microtubules, hollow filaments that provide cells with support and structure; abnormal tau tangles, however, cause that structure to break down, and lead to cell death.

Researchers have long puzzled over just what produces the tangles – and, indeed, if they are a cause or a side effect of Alzheimer's and similar neurodegenerative diseases. Now, new research by Eva Chi, an assistant professor of chemical engineering at the University of New Mexico, and her colleagues suggests that changes to the lipid membranes of [nerve cells](#) initiate tangle formation.

"Proteins in the brain do not aggregate spontaneously to form amyloid fibrils to cause diseases," says Chi. Rather, she says, "there are physiological triggers that cause these proteins to start aggregating and the lipid membrane may serve such a role." At the AVS Symposium in Nashville, Tenn., held Oct. 30 – Nov. 4, Chi will discuss these tangling triggers and their implications for the development of new Alzheimer's therapies.

Using a combination of techniques, including fluorescence microscopy and X-ray and neutron scattering imaging, Chi and her colleagues found that tau proteins inside nerve cells interact strongly with negatively charged lipids, which are found on the inner surface of cell membranes. "In diseased brains, tau proteins become hyperphosphorylated" – adorned with multiple phosphate ( $\text{PO}_4^{3-}$ ) groups – "and detach from microtubules. They can then interact with the negatively charged lipids on the cell membrane and start to aggregate into fibrils and cause disease."

When tau proteins interact with the lipid membrane, they can damage the structure of the membrane, "which can possibly make the membranes 'leaky' and cause neurons to die," Chi explains. "There has been much uncertainty about what causes neurodegeneration in these diseases, but now the field is converging on the idea that neuronal death in [Alzheimer's disease](#) is caused by the proteins acquiring toxicity as they aggregate."

The researchers suggests that compounds that prevent the proteins from interacting with the lipid membrane – or protect the membrane from being disrupted – could offer hope to Alzheimer's patients. "We are currently looking at how naturally occurring flavonoids [antioxidants found in plants] can protect the cells from protein aggregate-induced toxicity and have found that they reduce protein interaction with membranes," Chi says.

**More information:** The AVS 58th International Symposium & Exhibition will be held Oct. 30 – Nov. 4 at the Nashville Convention Center. Presentation NT+AS-WeA8, "Interaction of Alzheimer's Disease Tau Protein with Model Lipid Membranes," is at 4:20 p.m. on Wednesday, Nov. 2.

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