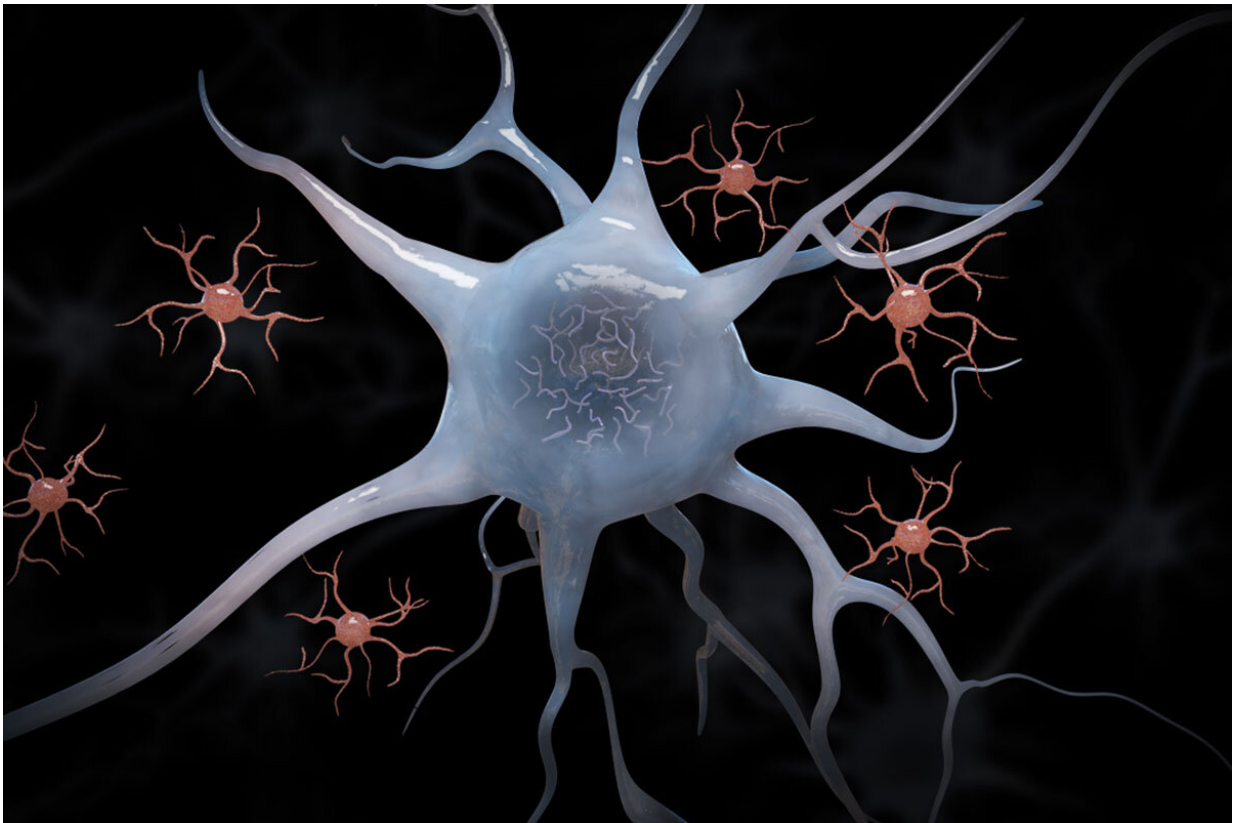


Targeting immune cells may be potential therapy for Alzheimer's

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A neuron containing tangles of tau protein is surrounded by immune cells known as microglia in this computer-generated image. A study from Washington University School of Medicine in St. Louis has found that microglia drive neurodegeneration in diseases, including Alzheimer's disease, that are linked to tau protein. Targeting microglia may help treat such diseases. Credit: Mark Hallett

Messy tangles of a protein called tau can be found in the brains of people with Alzheimer's disease and some other neurodegenerative diseases. In Alzheimer's, the tangles coalesce just before tissue damage becomes visible in brain scans and people start to become forgetful and confused.

Now, a new study has found that [brain immune cells](#) called microglia—which are activated as tau tangles accumulate—form the crucial link between protein clumping and brain damage. The research, published Oct. 10 in the *Journal of Experimental Medicine*, shows that eliminating such cells sharply reduces tau-linked brain damage in the mice—and suggests that suppressing such cells might prevent or delay the onset of dementia in people.

"Right now many people are trying to develop new therapies for Alzheimer's [disease](#), because the ones we have are simply not effective," said senior author David Holtzman, MD, the Andrew B. and Gretchen P. Jones Professor and head of the Department of Neurology. "If we could find a drug that specifically deactivates the microglia just at the beginning of the neurodegeneration phase of the disease, it would absolutely be worth evaluating in people."

Under ordinary circumstances, tau contributes to the normal, healthy functioning of brain neurons. In some people, though, it collects into toxic tangles that are a hallmark of [neurodegenerative diseases](#) such as Alzheimer's and [chronic traumatic encephalopathy](#), a progressive brain disease often diagnosed in football players and boxers who have sustained repeated blows to the head. Holtzman and colleagues previously had shown that microglia limit the development of a harmful form of tau. But the researchers also suspected that microglial cells could be a double-edged sword. Later in the course of the disease, once the tau tangles have formed, the cells' attempts to attack the tangles might harm nearby neurons and contribute to neurodegeneration.

To understand the role of microglial cells in tau-driven neurodegeneration, Holtzman, first author and postdoctoral researcher Yang Shi, Ph.D., and colleagues studied genetically modified mice that carry a mutant form of human tau that easily clumps together. Typically, such mice start developing tau tangles at around 6 months of age and exhibiting signs of neurological damage by 9 months.

Then, the researchers turned their attention to the gene APOE. Everyone carries some version of APOE, but people who carry the APOE4 variant have up to 12 times the risk of developing Alzheimer's disease compared with those who carry lower-risk variants. The researchers genetically modified the mice to carry the human APOE4 variant or no APOE gene. Holtzman, Shi and colleagues previously had shown that APOE4 amplifies the toxic effects of tau on neurons.

For three months, starting when the mice were 6 months of age, the researchers fed some mice a compound to deplete microglia in their brains. Other mice were given a placebo for comparison.

The brains of mice with tau tangles and the high-risk genetic variant were severely shrunken and damaged by 9½ months of age—as long as microglia were also present. If microglia had been eliminated by the compound, the mice's brains looked essentially normal and healthy with less evidence of harmful forms of tau despite the presence of the risky form of APOE.

Further, [mice](#) with microglia and mutant human tau but no APOE also had minimal [brain damage](#) and fewer signs of damaging [tau tangles](#). Additional experiments showed that microglia need APOE to become activated. Microglia that have not been activated do not destroy brain tissue or promote the development of harmful forms of tau, the researchers said.

"Microglia drive neurodegeneration, probably through inflammation-induced neuronal death," Shi said. "But even if that's the case, if you don't have microglia, or you have microglia but they can't be activated, harmful forms of tau do not progress to an advanced stage, and you don't get neurological damage."

The findings indicate that microglia are the linchpin of the neurodegenerative process—and an appealing target of efforts to prevent cognitive decline in Alzheimer's disease, chronic traumatic encephalopathy and other neurodegenerative diseases. The compound Holtzman and Shi used in this study has side effects that make it a poor option for drug development, but it could point the way to other compounds more narrowly tailored to microglia.

"If you could target [microglia](#) in some specific way and prevent them from causing damage, I think that would be a really important, strategic, novel way to develop a treatment," Holtzman said.

More information: *Journal of Experimental Medicine* (2019). [DOI: 10.1084/jem.20190980](https://doi.org/10.1084/jem.20190980)

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