

# New findings suggest alternative mechanisms behind Alzheimer's disease

August 12 2024

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In the Alzheimer's affected brain, abnormal levels of the beta-amyloid protein clump together to form plaques (seen in brown) that collect between neurons and disrupt cell function. Abnormal collections of the tau protein accumulate and form tangles (seen in blue) within neurons, harming synaptic communication between nerve cells. Credit: National Institute on Aging, NIH

New findings out of Emory University are challenging existing theories about the origins of Alzheimer's, the leading cause of dementia in the elderly worldwide. A team led by researchers at the Goizueta Brain Health Institute has found strong evidence supporting a new understanding of the mechanism behind Alzheimer's disease.

In a [paper](#) published August 9 in *Cell Reports Medicine*, Todd E. Golde and Yona Levites explain how the [amyloid](#) beta deposits long known to build up in the brains of Alzheimer's patients serve as a kind of scaffold for the accumulation of other proteins. Because many of these proteins have known signaling functions, their presence around the amyloid accumulations, known as plaques, could be the culprit causing [brain cell damage](#) rather than the amyloid itself.

In the brains of those who suffer from Alzheimer's, amyloids accumulate and build up into sticky plaque that disrupts brain functions and causes cognitive decline. The big unknown has been exactly how that occurs. According to the most widely adopted hypothesis, the amyloid beta buildup disrupts cell-to-cell communication and activates immune cells in a process that eventually destroys brain cells.

In the study, Golde, director of the Emory Center for Neurodegenerative Disease in the Goizueta Institute, Levites, associate professor in Emory University's School of Medicine, and their colleagues presented a new hypothesis, emphasizing a different role for amyloid beta, a simple [protein](#) that forms in all brains but normally dissolves out by natural processes.

In experiments, they used cutting-edge analytical technologies to identify and measure the level of more than 8,000 proteins in human brains with Alzheimer's, as well as similar proteins in mice. Focusing on proteins whose levels increased most dramatically, they identified more than 20 proteins that co-accumulate with amyloid beta in both the human brains

with Alzheimer's and the mice. As the research continues, they suspect they'll find more.

"Once we identified these new proteins, we wanted to know whether they were merely markers of Alzheimer's or if they could actually alter the disease's deadly pathology," says Golde.

"To answer that, we focused on two proteins, midkine and pleiotrophin. Our research showed they accelerated amyloid aggregation both in the test tube and in mice. In other words, these additional proteins may play an important role in the process that leads to brain damage rather than the amyloid itself. This suggests they might be a basis for new therapies for this terrible brain affliction that's been frustratingly resistant to treatment over the years."

While the basics of Alzheimer's have been understood for more than a century, the search for a cure has been slow, often marked by repeated cycles of initially promising treatments that didn't work in trials, as well as continuing controversy over competing theories to best explain how the disease damages the brain.

As the researchers put it, "The initial notion of a purely linear amyloid cascade is now recognized as simplistic. Studies have unveiled the vast complexity of changes occurring over decades in the brains of individuals as Alzheimer's pathologies emerge."

Significantly, multiple kinds of amyloid buildup, besides [amyloid beta](#), have been implicated in more than 30 human disorders affecting tissues and organs throughout the body. Because this new research proposes a novel process by which Alzheimer's develops, it may allow for fresh approaches to discovering treatment targets for other diseases as well.

**More information:** Yona Levites et al, Integrative proteomics

identifies a conserved A $\beta$  amyloid response, novel plaque proteins, and pathology modifiers in Alzheimer's disease, *Cell Reports Medicine* (2024). [DOI: 10.1016/j.xcrm.2024.101669](https://doi.org/10.1016/j.xcrm.2024.101669)

Provided by Emory University

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