MedicalXpress

Study identifies therapeutic target for Alzheimer's disease, revealing strategy for slowing disease progression

April 11 2022

Credit: Pixabay/CC0 Public Domain

About 11% of the U.S. population 65 and older has been diagnosed with Alzheimer's disease (AD), the most common form of dementia that results in memory loss and cognitive impairment, according to the Alzheimer's Association.

And the World Health Organization predicts the number of people living with Alzheimer's will grow by millions each year.

Despite decades of research, scientists don't fully understand what causes the brain condition. And there is no known therapeutic treatment.

But a new study published recently in *Nature Communications* by a team of researchers from the Case Western Reserve University School of Medicine suggests a key protein molecule plays a major role in the accumulation of brain cholesterol, triggering the development of Alzheimer's.

The lab of Xin Qi, professor of physiology and biophysics at the School of Medicine, developed and patented a peptide inhibitor earlier in hopes of treating AD and Huntington's disease. She said this study found that mice, when treated with the peptide inhibitor, demonstrated 50% restored memory function, based on testing such as navigating mazes.

The impact of Alzheimer's disease

AD is an age-related neurodegenerative disorder that results in progressive cell death, leading to memory loss and cognitive dysfunction.

The numbers around the disease are staggering—more than 5.7 million people have AD, and that group is estimated to reach 14 million by 2050, according to the Alzheimer's Association. That number is expected to balloon to 16 million by 2050. The cost of annual out-of-pocket healthcare for Alzheimer's totals more than $250 billion.

Understanding the pathology

Risk factors that contribute to AD include vascular diseases that impact the heart and blood vessels. While some risk factors are well known—aging, for example—others, such as brain cholesterol, play a key role in understanding how the disease develops.

Brain cells communicate through cholesterol-rich cell membranes, a process that occurs naturally and is essential for healthy brain function. Research shows the brain contains 23-25% of the body's cholesterol.

"Cholesterol accumulates in the brain and causes damage to the neuron—it's long been understood as playing a role in Alzheimer's disease pathology," Qi said. "However, what causes the cholesterol accumulation in the brain continues to be unknown and could hold answers."

The study

The paper is the result of more than five years of research into the role of brain cholesterol and its relationship with AD.

The researchers set out to tackle two main questions:

- What role does brain cholesterol play in the disease?
- How can this new pathway be used for future treatment options?

Qi, the paper's senior author, said the study centered on the protein coding gene, ATAD3A. Much is unknown about how the protein functions within neurodegenerative diseases.

"In Huntington's disease, the molecule ATAD3A becomes hyperactive

and is oligomerized (repeated), which is a cause of the disease," Qi said. "We worked with data scientists to see if ATAD3A also has a link to Alzheimer's disease and, to our surprise, we found that the molecule is a top candidate linked to Alzheimer's."

From there, researchers gathered data by analyzing models and found a pathway linking ATAD3A and brain cholesterol. The researchers found that once ATAD3A forms repeating similar or identical parts through a process called oligomerization, it suppresses another protein called CYP46A1. The new protein then prevents cholesterol from being metabolized in the brain, meaning it accumulates. Researchers have linked the accumulation of brain cholesterol to disease progression in neurodegenerative diseases.

The findings

The data shows that ATAD3A—especially during oligomerization—could be the cause of AD development.

With a possible target identified, Qi believes the next step to treatment lies in peptide inhibitors, which bind to ATAD3A and block it in action.

"Models treated with the peptide showed improved performance on the memory tests," Qi said. "They showed increased memory retention, stronger cognitive activity and up to 50% restored damage to the memory."

This means that targeting ATAD3A oligomerization can likely slow the progression of Alzheimer's disease, Qi said. Further testing is underway.

More information: Yuanyuan Zhao et al, ATAD3A oligomerization promotes neuropathology and cognitive deficits in Alzheimer's disease models, *Nature Communications* (2022). DOI:

10.1038/s41467-022-28769-9