Protein accumulation on fat droplets implicated in late-onset Alzheimer's disease

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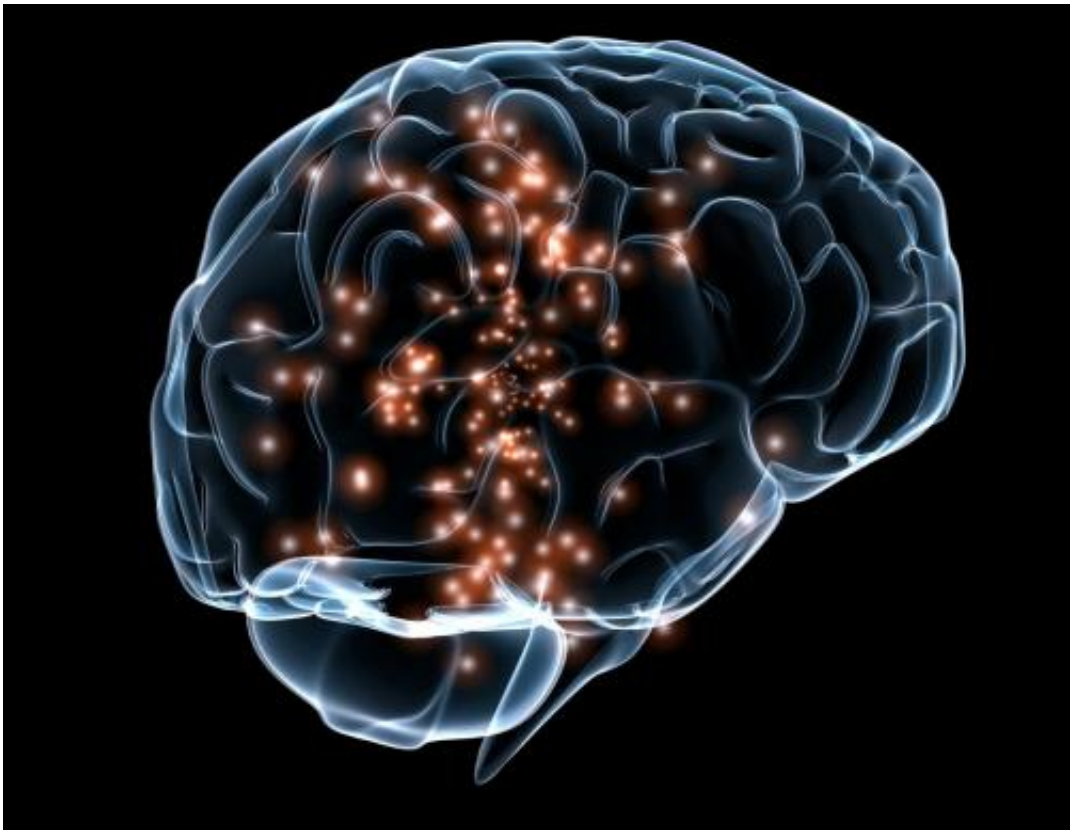

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UNC School of Medicine researcher Sarah Cohen, Ph.D., and Ian Windham, a former Ph.D. student from the Cohen lab, have made a new discovery about apolipoprotein E (APOE)—the biggest genetic risk factor for late-onset Alzheimer's disease.

Older people who inherited a genetic variant called APOE4 from their parents have a two- or three-times greater risk of developing late-onset neurodegenerative disease. If researchers can better understand how APOE4 affects brain cells, it may help them design effective therapeutics and target the mechanisms causing the enhanced disease risk.

Cohen and Windham performed an exceptionally thorough, five-year-long study to understand better and visualize the relationship between APOE4, Alzheimer's Disease, and fat molecules called lipids in the brain.

"We discovered that brain cells known as astrocytes are more vulnerable to damage and may even go dysfunctional when APOE4 surrounds their lipid storage centers," said Cohen, assistant professor of cell biology and physiology and senior author on the paper published in the *Journal of Cell Biology*. "This mechanism could explain why exactly APOE4 increases one's risk of Alzheimer's on the cellular level."

The role of lipids in the brain

Sixty percent of the brain's dry mass is composed of lipids, which play important roles in the brain, such as storing cellular energy and forming myelin, which surrounds and insulates neurons. Lipids can be found in specialized fat storage compartments known as lipid droplets within astrocytes.

As helpful as they may be, lipids can also become toxic if the conditions are right. When excited or stressed, neurons release toxic lipids into the environment. Astrocytes are tasked with cleaning up the free-floating toxic lipids and preventing them from accumulating in the brain.

If astrocytes were to become damaged or dysfunctional in any way, they

cannot perform their cleaning duties. As a result, other brain cells, called microglia, cannot clean up amyloid beta plaques in the brain either, another driving factor for Alzheimer's disease.

Seeing APOE in real-time

APOE is produced by astrocytes. Much like a taxi or Uber, the protein oversees the release and transport of lipids between cell types in the brain. Windham and Cohen wanted to see what exactly happens with the lipids in the astrocytes. Windham led the charge, creating a labeling and tagging system that would allow them to see the innards of astrocytes in action under the microscope.

"Tagging APOE with green fluorescent protein allowed us to see the different places APOE goes while inside living cells," said Windham, now a postdoctoral fellow at The Rockefeller University and first author on the paper.

The team first fed astrocytes oleic acid, an omega-9 fatty acid naturally produced in the body. Using a microscope, the team observed the usual formation of lipid droplets. APOE4, surprisingly, zipped over to the lipid droplets like a magnet and changed the shape and size of the droplets.

It became abundantly clear to the researchers that APOE4 can escape secretion, lock itself inside astrocytes, and migrate to lipid droplets within astrocytes. Windham and Cohen hypothesize that the altered composition of the lipid droplets could be causing astrocyte dysfunction and affecting the microglia's ability to clear amyloid beta.

Lipids: The next frontier

However, more research needs to be done to know the specifics. Cohen hopes their findings will further emphasize the role of lipid droplets in Alzheimer's disease and other neurodegenerative diseases.

"In Alois Alzheimer's first paper, he described three characteristics of neurodegenerative disease: amyloid beta plaques, tau tangles, and accumulations of lipids," said Cohen. "The first two have gotten a lot of attention. The next frontier is lipids. With APOE being the biggest genetic risk factor, we think it holds the clues for how lipids fit into the story."

More information: Ian A. Windham et al, APOE traffics to astrocyte lipid droplets and modulates triglyceride saturation and droplet size, *Journal of Cell Biology* (2024). DOI: 10.1083/jcb.202305003

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