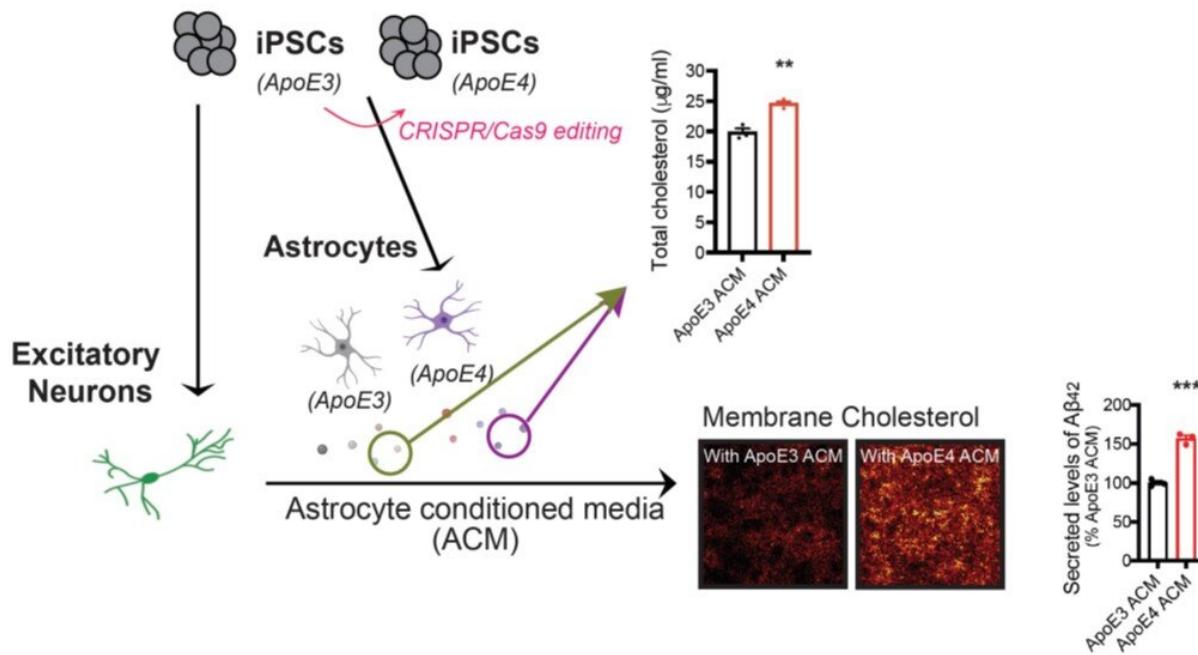


Stem cells model genetic risk for developing Alzheimer's disease

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Cholesterol oversupply from ApoE4 astrocytes promote Aβ production in neurons. Credit: Jinsoo Seo

New research published in *Stem Cell Reports* has found elevated cholesterol supply from astrocytes to neurons in the model of Alzheimer's disease (AD) brains, suggesting that modulating brain cholesterol could be explored in the search of treatment options for the

devastating, degenerative disease.

AD, the most frequent cause of dementia, affects an estimated 24 million people worldwide. With very limited treatment options, scientists are looking for ways to understand the disease better. One hallmark of AD is the emergence of so-called [beta-amyloid plaques](#), clumps of beta-amyloid protein accumulating in the brain and thought to be toxic to adjacent neurons. The causes for Alzheimer's disease and the formation of beta-amyloid plaques are still largely unknown but genetic studies found that a gene called APOE, which is involved in cholesterol metabolism and transport, is linked to AD in the elderly. The APOE gene exists in different versions in people, APOE2, APOE3 and APOE4, but the APOE4 gene comes with a relatively higher risk of developing AD.

Curiously, in the brain, it's mostly the [supporting cells](#) called astrocytes rather than the neurons that make ApoE protein. To find out if the APOE4 gene in astrocytes relates to AD, Jinsoo Seo and colleagues with the Daegu Gyeongbuk Institute of Science and Technology (DGIST), South Korea, used human-induced [stem cells](#) carrying different versions of the APOE gene to make neurons and astrocytes in the lab, and to study their interaction. The researchers found that astrocytes carrying the AD-associated APOE4 gene released more cholesterol than astrocytes with APOE3.

The scientists noticed that the neurons exposed to higher cholesterol had distinct changes to their cell membranes, the outer layers of the cell which normally contain cholesterol. Further, this high cholesterol content in cell membranes was directly related to the increased production and secretion of beta-amyloid by the neurons. This work illustrates how different versions of the APOE gene in astrocytes can influence beta-amyloid production in neurons, and how cholesterol oversupply from ApoE4 astrocytes might promote the formation of toxic

beta-amyloid plaques in AD patients.

More information: APOE4-carrying human astrocytes oversupply cholesterol to promote neuronal lipid rafts expansion and A β generation, *Stem Cell Reports* (2021). [DOI: 10.1016/j.stemcr.2021.07.017](https://doi.org/10.1016/j.stemcr.2021.07.017)

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