Novel culture system replicates course of Alzheimer's disease, confirms amyloid hypothesis

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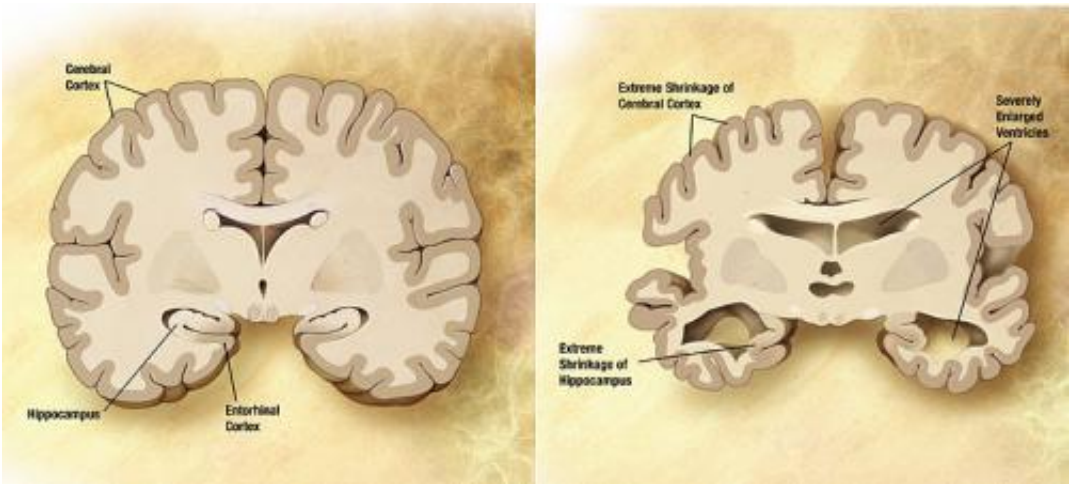

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

An innovative laboratory culture system has succeeded, for the first time, in reproducing the full course of events underlying the development of Alzheimer's disease. Using the system they developed, investigators from the Genetics and Aging Research Unit at Massachusetts General Hospital (MGH) now provide the first clear evidence supporting the hypothesis that deposition of beta-amyloid plaques in the brain is the first step in a cascade leading to the devastating neurodegenerative disease. They also identify the essential

role in that process of an enzyme, inhibition of which could be a therapeutic target.

"Originally put forth in the mid-1980s, the amyloid hypothesis maintained that beta-amyloid deposits in the brain set off all subsequent events – the neurofibrillary tangles that choke the insides of neurons, neuronal cell death, and inflammation leading to a vicious cycle of massive cell death," says Rudolph Tanzi, PhD, director of the MGH Genetics and Aging Research Unit and co-senior author of the report receiving advance online publication in *Nature*. "One of the biggest questions since then has been whether beta-amyloid actually triggers the formation of the tangles that kill neurons. In this new system that we call 'Alzheimer's-in-a-dish,' we've been able to show for the first time that amyloid deposition is sufficient to lead to tangles and subsequent cell death."

While the mouse models of Alzheimer's disease that express the gene variants causing the inherited early-onset form of the disease do develop amyloid plaques in their brains and memory deficits, the neurofibrillary tangles that cause most of the damage do not appear. Other models succeed in producing tangles but not plaques. Cultured neurons from human patients with Alzheimer's exhibit elevated levels of the toxic form of amyloid found in plaques and the abnormal version of the tau protein that makes up tangles, but not actual plaques and tangles.

Genetics and Aging Research Unit investigator Doo Yeon Kim, PhD, co-senior author of the *Nature* paper, realized that the liquid two-dimensional systems usually used to grow cultured cells poorly represent the gelatinous three-dimensional environment within the brain. Instead the MGH team used a gel-based, three-dimensional culture system to grow human neural stem cells that carried variants in two genes – the amyloid precursor protein and presenilin 1 – known to underlie early-onset familial Alzheimer's Disease (FAD). Both of those genes were co-

discovered in Tanzi's laboratory.

After growing for six weeks, the FAD-variant cells were found to have significant increases in both the typical form of beta-amyloid and the toxic form associated with Alzheimer's. The variant cells also contained the neurofibrillary tangles that choke the inside of nerve cells causing cell death. Blocking steps known to be essential for the formation of amyloid plaques also prevented the formation of the tangles, confirming amyloid's role in initiating the process. The version of tau found in tangles is characterized by the presence of excess phosphate molecules, and when the team investigated possible ways of blocking tau production, they found that inhibiting the action of an enzyme called GSK3-beta – known to phosphorylate tau in human neurons – prevented the formation of tau aggregates and tangles even in the presence of abundant beta-amyloid and amyloid plaques

"This new system – which can be adapted to other neurodegenerative disorders – should revolutionize drug discovery in terms of speed, costs and physiologic relevance to disease," says Tanzi. "Testing drugs in mouse models that typically have brain deposits of either plaques or tangles, but not both, takes more than a year and is very costly. With our three-dimensional model that recapitulates both plaques and tangles, we now can screen hundreds of thousands of drugs in a matter of months without using animals in a system that is considerably more relevant to the events occurring in the brains of Alzheimer's patients."

More information: A three-dimensional human neural cell culture model of Alzheimer's disease, *Nature* , DOI: 10.1038/nature13800

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