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NEURODEGENERATIVE DISEASE

New dimensions in Alzheimer's modelling

> a three-dimensional culture system might encourage amyloid-β accumulation and produce a more useful human cellular model of the disease

The development of *in vitro* models that are better able to recapitulate key aspects of complex neurodegenerative diseases in human cells is expected to benefit both basic research and drug development. In a new paper published in *Nature*, Choi *et al.* report that, by adding a third dimension to a cell culture model of Alzheimer's disease, they have succeeded in reproducing the two key features of the disease — amyloid-β plaques and neurofibrillary tangles — in human cells for the first time.

The amyloid hypothesis of Alzheimer's disease suggests that the accumulation of amyloid-β into plaques drives the aggregation of hyperphosphorylated tau into neurofibrillary tangles. However, two-dimensional human cell culture models of Alzheimer's disease have failed to produce both plaques and tangles in the same culture, making it difficult to test this hypothesis. Here, the authors hypothesized that a three-dimensional culture system might encourage amyloid-β accumulation and produce a more useful human cellular model of the disease.

Choi *et al.* created their three-dimensional model by overexpressing variants of human amyloid-β precursor protein (APP) and/or presenilin 1 (PSEN1; a key regulator of APP processing) that carry mutations linked to familial Alzheimer's disease in a human neural progenitor cell line. The cells were grown in a gel that was up to 4 mm thick and that contained high levels of proteins typically present in the brain's extracellular matrix. The authors found that the cells differentiated into neurons and glia more effectively than they did in two-dimensional cultures. Importantly, the differentiated cultures also contained higher levels of the adult isoforms of tau that are present in neurofibrillary tangles.

A series of immunohistochemical and biochemical analyses showed that the three-dimensional cultures recapitulated many of the key aspects of Alzheimer's disease, including amyloid-β aggregation and increased levels of phosphorylated tau. When the cultures were created using only those cells expressing the highest levels of mutant *APP* and *PSEN1*, there was a dramatic increase in phosphorylated tau in neurites and neuronal cell bodies. Extracts from these enriched cultures contained high levels of insoluble tau aggregates, which transmission electron microscopy revealed to be very similar in appearance to the neurofibrillary tangles present in Alzheimer's disease.

The authors also showed that drugs known to modify amyloid and tau pathology in animal models of Alzheimer's disease were effective in the cultures. Treatment with β- or γ-secretase inhibitors, which modulate APP processing, decreased amyloid-β accumulation and tau phosphorylation, whereas inhibitors of glycogen synthase kinase 3β (GSK3β) decreased tau phosphorylation without affecting amyloid-β levels. These findings thus provide support for the amyloid hypothesis by suggesting that GSK3β is involved in the generation of tau pathology downstream of APP processing abnormalities.

This new culture system is the first to reproduce both amyloid-β accumulation and neurofibrillary tangles in human cells. It may provide a system to further investigate the links between these two aspects of Alzheimer's pathology, as well as a tool for the screening of drugs designed to modulate these processes.

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