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NEURODEGENERATIVE DISEASE

Dishing up Alzheimer's disease

Until recently, researchers striving to understand the pathogenesis of neurodegenerative disorders that strike late in life, such as Alzheimer's disease, have been restricted to using post-mortem human tissue or animal models. However, the advent of techniques to 'reprogram' skin cells into pluripotent stem cells has brought with it the promise of a greater understanding of disease mechanisms. In a paper published in *Nature*, Goldstein and colleagues exploit this approach to investigate mechanisms of sporadic and familial Alzheimer's disease.

Current hypotheses regarding the causes of Alzheimer's disease suggest that aberrant processing of amyloid precursor protein (APP), which leads to increased amyloid-β production, and the hyperphosphorylation of tau are key disease mechanisms; however, the interactions between these pathogenic pathways are unclear. Although most Alzheimer's disease cases are sporadic, the rarer familial forms of Alzheimer's disease have received greater research attention owing to the availability of animal models of these forms of the disease. However, these models do not accurately mimic all of the symptoms of the human disease. Insights into disease mechanisms have been gained from human post-mortem tissue, but this approach prohibits the study of early stages of disease pathogenesis. Thus, there is a growing impetus to develop methods to study the neurons of living patients and to examine sporadic forms of Alzheimer's disease.

A recent study used cell reprogramming techniques to create neurons from the fibroblasts of patients with familial Alzheimer's disease. Goldstein and colleagues have now extended this approach by reprogramming fibroblasts of two patients with sporadic Alzheimer's disease, two with familial Alzheimer's disease and two individuals without dementia. The fibroblasts were converted to induced pluripotent stem cells (iPSCs), and a novel fluorescence-activated cell sorting procedure was used to obtain cultures containing more than 90% neurons and possessing the molecular and electrophysiological characteristics of mature neurons.

The authors found that, compared with control cultures, iPSC-derived neurons from both patients with familial Alzheimer's disease and one of the two individuals with sporadic Alzheimer's disease exhibited elevated levels of amyloid-β, phosphorylated tau (p-tau) and the activity of glycogen synthase kinase 3β (GSK3β; thought to be responsible for tau hyperphosphorylation). Thus, reprogrammed neurons can successfully recapitulate many of the hallmarks of Alzheimer's disease within a timeframe amenable to experimental analysis.

Next, the authors used their cultures to examine the relationship between APP processing and tau hyperphosphorylation. They found that treatment of the patient-derived neurons with an inhibitor of β-secretase — the enzyme responsible for the first step in the 'amyloidogenic' processing of APP — significantly reduced levels of GSK3β activity and p-tau, suggesting that APP processing can induce GSK3β-mediated phosphorylation of tau. This assertion was supported by the observation of increased numbers of large endosomes, a major site of APP processing. However, amyloid-β may not mediate this link as treatment with an inhibitor of γ-secretase (the enzyme responsible for amyloid-β production) had no effect on GSK3β activity or p-tau.

This study illustrates how iPSC technology can be harnessed to gain insights into the mechanisms of neurodegenerative conditions that are difficult to obtain by studying post-mortem tissues or animal models. The differences between the cells derived from the two individuals with spontaneous forms of Alzheimer's disease may indicate that different disease mechanisms are involved. The testing of cells from more patients might resolve this issue and further enhance our understanding of Alzheimer's disease pathology.

Katherine Whalley

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ORIGINAL RESEARCH PAPER Israel, M. A. *et al.* Probing sporadic and familial Alzheimer's disease using induced pluripotent stem cells. *Nature* 25 Jan 2012 (doi:10.1038/nature10821)
FURTHER READING Qiang, L. *et al.* Directed conversion of Alzheimer's disease patient skin fibroblasts into functional neurons. *Cell* **146**, 359–371 (2011) | Ittner, L. M. & Götz, J. Amyloid-β and tau – a toxic *pas de deux* in Alzheimer's disease. *Nature Rev. Neurosci.* **12,** 67–72 (2011)

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