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ALZHEIMER DISEASE

A novel human–mouse chimaeric model of Alzheimer disease

> human neurons might react differently from mouse neurons in response to amyloid deposition

Alzheimer disease (AD)-like amyloid pathology has been modelled with some success in transgenic rodents, but these models fail to recapitulate some of the key features of AD, such as neurodegeneration and tau pathology. In new research reported in *Neuron*, Bart De Strooper, Pierre Vanderhaeghen and colleagues have attempted to address these limitations by generating a human–mouse chimaeric model of AD.

"The fact that transgenic rodents do not develop full AD made us think that human neurons might react differently from mouse neurons in response to amyloid deposition," says De Strooper. "Pierre Vanderhaeghen's laboratory had published several nice papers on mouse chimaeras to study cortical neuronal differentiation, and we decided to work together to address this question."

For the new study, the researchers generated cortical precursor cells by differentiating human pluripotent stem cells (PSCs) *in vitro*. These cells were injected into the brains of newborn AD mice or their wild-type littermates. The AD mouse line was derived from APP/PS1-21 transgenic mice, which were crossed with immunodeficient NOD-SCID mice to prevent rejection of the human xenografts.

In both mouse lines, the grafted cells underwent differentiation into mature neurons and initially integrated effectively into the brain. However, the onset of amyloid-β (Aβ) deposition in the AD mice was accompanied by neuroinflammation orchestrated by host-derived astrocytes and microglia, and resulted in the induction of AD-like changes in the grafted cells.

"The human neurons transplanted into AD mice undergo major neurite dystrophy, neurodegeneration, tau pathological conformational changes and severe cell death," explain lead authors Ira Espuny-Camacho and Amaia Arranz Mendiguren. "These important AD hallmarks have not been shown to this extent in previous AD mouse models."

The investigators also used RNA-seq analysis to examine gene expression patterns in the grafted neurons. Several AD-related gene modules were found to be differentially expressed between the AD and control mice. Intriguingly, the cells transplanted into the AD mice showed substantial upregulation of two noncoding RNAs, *LINC01007* and *RP11-89N17.4*, which could warrant further exploration with regard to a potential role in neurodegeneration.

In contrast to the human cells, mouse PSC-derived neurons injected into the brains of AD mice did not degenerate in response to Aβ deposition. This finding indicates that mouse neurons are less susceptible to Aβ-mediated toxicity than are human neurons, which might explain why previous mouse models of amyloidosis have exhibited an incomplete AD phenotype.

"We can now use this model to investigate the 'cellular phase of AD'; for example, what happens if we suppress the microglial response in these mice, and how do human astrocytes or microglia respond to amyloid plaques *in vivo*?" comments De Strooper. "In addition, we can do a genetic screen in human cells to identify drug targets that protect the neurons from dying, and we can analyse blood and cerebrospinal fluid from the animals and see whether human proteins appear that can serve as biomarkers."

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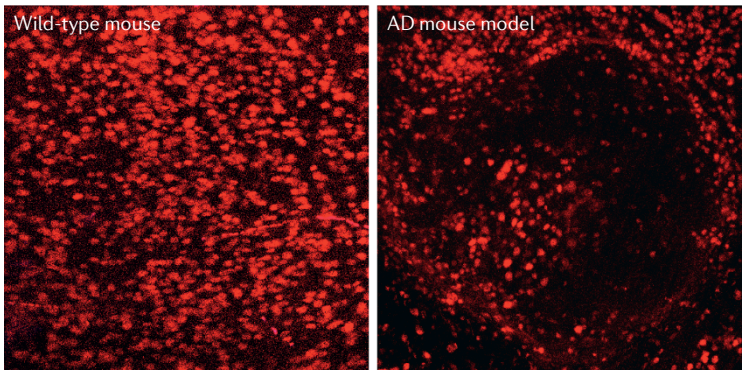

Nuclear staining reveals degeneration of transplanted human neurons in the brain of an Alzheimer disease (AD) mouse model. Image courtesy of I. Espuny-Camacho.

ORIGINAL ARTICLE Espuny-Camacho, I. *et al.* Hallmarks of Alzheimer's disease in stem-cell-derived human neurons transplanted into mouse brain. *Neuron* http://dx.doi.org/10.1016/j.neuron.2017.02.001 (2017)

FURTHER READING De Strooper, B. & Karran, E. The cellular phase of Alzheimer's disease. *Cell* **164**, 603–615 (2016) | Espuny-Carmacho, I. *et al.* Pyramidal neurons derived from human pluripotent stem cells integrate efficiently into mouse brain circuits *in vivo*. *Neuron* **77**, 440–456 (2013)