NEURODEGENERATIVE DISEASE

A chimeric approach

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It has proved difficult to recapitulate the neuronal loss that is observed in Alzheimer disease (AD) in rodent models of the disorder. In a new study, however, De Strooper, Vanderhaeghen and colleagues generated a chimeric model of AD in which human neurons were transplanted into an AD mouse model and found that the human neuronal grafts not only were associated with amyloid- β -related and some other pathologies that are characteristic of the disease but also showed robust neurodegeneration.

The authors generated human cortical precursor cells from human pluripotent stem cells (PSCs) that had been engineered to express green fluorescent protein and implanted these into the frontal cortices of newborn AD mice and their wild-type littermates. The AD mice used in the experiment expressed mutant forms of the amyloid precursor protein (APP), from which amyloid- β is derived, and presenilin 1, which is involved in the cleavage of APP to produce amyloid- β .

Many of the transplanted human cells expressed various neuronal markers, and electron microscopy revealed that the human neurons formed synapses with host neurons, indicating that they had become integrated into the murine brain. The AD mice developed amyloid- β plaques in the host brain tissue and among the transplanted human neurons, and these plaques were surrounded by dystrophic neurites. Similar pathology was observed in AD mice transplanted with neurons derived from mouse PSCs, but wild-type mice transplanted with human neurons showed no plaque development. These findings indicate that amyloid- β plaque formation can be recapitulated in the human neuronal grafts but is not a consequence of human neuron transplantation.

Astrogliosis and microgliosis are pathological features of AD. In the AD mice with transplanted human neurons, amyloid- β deposits in the host tissue and human neuronal grafts were surrounded by microglia and astrocytes. Ultrastructural analysis of these glia revealed that most of these cells were enlarged and/or had a phagocytic phenotype, potentially signifying astrogliosis and microgliosis. By contrast, few glia in the wild-type mice with transplanted human neurons had a similar appearance. These findings suggest that the human neuronal grafts in AD mice are associated with AD-relevant glial phenotypes but that the transplanted neurons do not induce them.

Strikingly, the authors noticed that, in mice that had received human neurons, the density of the transplanted cells was similar in both groups before the emergence of amyloid- β pathology at about 2 months but was reduced by ~50% in AD mice compared

with wild-type mice at 6 months after transplantation. By contrast, murine host neurons in both groups of animals showed no difference in density at the 6-month time point. Further analysis revealed that many of the human neurons at 6 months in the AD mice showed a necrotic phenotype. Finally, transplanted murine neurons in AD mice showed no signs of degeneration. Together, these data indicate that human, but not mouse, neurons exposed to amyloid- β pathology can undergo degeneration in AD mice.

Tau-containing neurofibrillary tangles (NFTs) represent one of the hallmark pathologies of AD and have often been linked to neuronal loss in the disease. Here, the authors found no NFT pathology in the AD mice with human transplanted neurons. They repeated the transplantation experiment with human neurons expressing a tau mutation that is associated with frontal temporal dementia. Although the human neurons still underwent neurodegeneration and now showed abnormal tau phosphorylation and some conformational changes in this protein, no NFTs could be detected. Thus, the neurodegeneration observed in this model does not result from NFT formation.

This study presents a novel, chimeric model for AD and shows that amyloid- β pathology can be associated with human neuron degeneration in the absence of NFTs. In doing so, it also indicates that human and murine neurons respond differently to amyloid- β .

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