NEURODEGENERATIVE DISEASE

A new mouse model to study late-onset Alzheimer's disease

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Most mouse models of Alzheimer's disease (AD) consist of transgenic mice that overexpress human genes associated with familial AD, an early-onset form of the disease caused by rare and fully penetrant mutations in the genes *APP*, *PSEN-1* and *PSEN-2*. The PD-APP transgenic mouse, which overexpresses human amyloid precursor protein (APP 717V→F), was the first APP-based model to reproduce amyloid β-peptide (Aβ) pathology in the form of amyloid plaques in mice; since then researchers have created and characterized more than 170 genetically modified mouse models containing AD-linked mutations.

Although these mice have provided valuable insights into disease mechanisms, early-onset AD accounts for less than 5% of AD cases and new mouse models that mimic the late-onset progression seen in sporadic human AD, the most common form of the disease, are needed.

In a new study published in *Nature Communications*, a team of investigators led by Frank M. LaFerla from University of California, Irvine generated a new mouse model in which they substituted the mouse Aβ peptide for its human counterpart (hAβ). The mice, which carry no familial AD mutation and develop age-dependent behavioral and phenotypic alterations, might represent an important step towards modeling late-onset AD.

The investigators used a knock-in (KI) strategy to humanize the murine *App* gene by changing 3 amino acids within the sequence of the Aβ peptide, a product of APP processing. In these mice, hAβ-KI allele is integrated in the *App* locus, under the control of endogenous gene-regulatory elements; therefore humanized *App* is expressed at murine physiological levels. "These results are significant because APP is not overexpressed in human sporadic AD, and the hAβ-KI mouse model recapitulates this salient feature," explain the investigators in their report.

Detailed phenotypic characterization of the mice showed that substitution of mouse Aβ with the wild-type human isoform was sufficient to produce significant changes in cognition, synaptic plasticity, inflammation, OC+/PAS granule formation and gene expression in hAβ-KI mice. These changes were associated with an age-associated increase in insoluble Aβ and decrease in soluble Aβ in the brain of the mice. However, the investigators could not detect amyloid aggregates in hAβ-KI brains, which suggests that additional factors are required for the formation of amyloid plaques.

The investigators conclude that the hAβ-KI mouse line will be a useful platform to investigate the many genetic, aging, and environmental factors that drive the development of AD and lead to formation of plaques.

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