Negative Data

REVIEW
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The next generation mouse models of preclinical Alzheimer's disease

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ABSTRACT

Since 1995, more than 100 transgenic (Tg) mouse models of Alzheimer's disease (AD) have been generated in which mutant amyloid precursor protein (APP) or APP/presenilin 1(PS1) cDNA is overexpressed (1st generation models). Although many of these models successfully recapitulate major pathological hallmarks of the disease such as amyloid β peptide (Aβ) deposition and neuroinflammation, they have suffered from artificial phenotypes in the form of overproduced or mislocalized APP/PS1 and their functional fragments, as well as calpastatin deficiency-induced early lethality, calpain activation, neuronal cell death without tau pathology, endoplasmic reticulum stresses, and inflammasome involvement. Such artifacts bring two important uncertainties into play, these being [1] why the artifacts arise, and [2] how they affect the interpretation of experimental results. In addition, destruction of endogenous gene loci in some Tg lines by transgenes has been reported. To overcome these concerns, we developed single App knock-in mouse models harboring the Swedish and Beyreuther/Iberian mutations with or without the Arctic mutation (*App*$^{NL-G-F}$ and *App*$^{NL-F}$ mice) (2nd generation models). While these models are interesting given that they exhibit AB pathology, neuroinflammation, and cognitive impairment in an age-dependent manner, the model with the Artic mutation, which exhibits an extensive pathology as early as 6 months of age, is not suitable for investigating AB metabolism and clearance because the AB in this model is resistant to proteolytic degradation and is therefore prone to aggregation. Moreover, it cannot be used for preclinical immunotherapy studies owing to the discrete affinity it shows for anti-Aβ antibodies. The weakness of the latter model (without the Arctic mutation) is that the pathology may require up to 18 months before it becomes sufficiently apparent for experimental investigation. Nevertheless, this model was successfully applied to modulating AB pathology by genome editing, to revealing the differential roles of neprilysin and insulin-degrading enzyme in AB metabolism, and to identifying somatostatin receptor subtypes involved in AB degradation by neprilysin. Intriguingly, neprilysin deficiency did not have any significant effect on the levels of major neuropeptides, indicating that neprilysin's action is specific to AB in brain. In addition to discussing these issues, we also provide here a technical guide for the application of *App* knock-in mice to AD research. We have subsequently generated a new double knock-in line carrying the *App*$^{NL-F}$ *and Psen1*^{P301S} mutations, the pathogenic effect of which was found to be synergistic. A characteristic of this 3rd generation model is that it exhibits more cored plaque pathology and neuroinflammation than the *App*$^{NL-G-F}$ line, and thus is more suitable for preclinical studies of disease modifying medications targeting AB. We also created a derivative *App*^{GF} line devoid of Swedish mutations which can be utilized for preclinical studies of β- secretase modifier(s). This line has also provided insights into the etiological role of the C-terminal fragment of APP generated by β-secretase (CTF-β). In addition, we introduce a new model of cerebral amyloid angiopathy that may be useful for analyzing amyloid-related imaging abnormalities that can be

caused by anti-Aβ immunotherapy. Use of the App knock-in mice also led to identification of the α-endosulfine-K_{ATp} channel pathway as components of the somatostatin-evoked physiological mechanisms that reduce Aβ deposition via the activation of neprilysin. Such advances have provided new insights for the prevention and treatment of preclinical AD. Because tau pathology plays an essential role in AD pathogenesis, we created knock-in mice with human tau wherein the entire murine *Mapt* gene has been humanized. Using these mice, we discovered the carboxy-terminal PDZ ligand of neuronal nitric oxide synthase (CAPON) as a mediator linking tau pathology to neurodegeneration and showed that tau humanization promoted pathological tau propagation. Finally, we describe and discuss the current status of mutant human tau knock-in mice and a non-human primate model of AD that we have successfully created (1).

Reference

1. H. Sasaguri *et al.*, Recent Advances in the Modeling of Alzheimer's Disease. *Front Neurosci* **16**, 807473 (2022).