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RESEARCH HIGHLIGHT

A Mouse Model of Alzheimer's Disease with Transplanted Stem-Cell-Derived Human Neurons

Yuankai Zhu[1,2,3,4] · Hong Zhang[1,2,3,4]

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Alzheimer's disease (AD), the main cause of dementia, is defined by the combined presence of amyloid-β (Aβ) deposition and abnormal tau aggregation [1]. Experimental models are critical to obtain a better understanding of AD pathogenesis, and to evaluate the potential of novel therapeutic approaches. The most commonly used AD animal models are transgenic mice (Fig. 1). They overexpress human genes associated with familial AD (FAD), which lead to the formation of Aβ plaques. However, AD is defined by the presence and interplay of both Aβ plaques and neurofibrillary tangles (NFTs). In addition to these two main features, an ideal AD model would also incorporate other essential aspects including innate inflammation, a human genetic background, and minimal use of transgenic technology [2].

Recently, a report by Espuny-Camacho *et al.* published in *Neuron* [3] has developed a novel chimeric AD model generated by using human neurons derived from induced pluripotent stem cells (iPSCs). In this model, human iPSC-derived cortical neuronal precursors transplanted into the brain of a mouse AD model were exposed to Aβ plaques. Extensive neuritic dystrophy and alterations of synaptic markers were found in human neuronal transplants surrounding Aβ plaques. In addition, human neurons differentiate and integrate into the mouse brain, express 3R/4R Tau splice forms, show abnormal phosphorylation and conformational Tau changes, and undergo neurodegeneration. But NFTs were not detected in human neurons or in human Tau neurons after 8 months of transplantation. The possible explanation is that an even longer period *in vivo* is required for detectable NFT pathology, or additional seeding is needed to induce the conformation of NFTs. They also showed the upregulation of genes involved in myelination and downregulation of genes related to memory and cognition, synaptic transmission, and neuronal projections. This novel AD chimeric model displays human-specific pathological features and allows the analysis of different genetic backgrounds and mutations during the course of this disease. A particularly important aspect of this approach is innate immunity, which is believed to play an important role in AD pathogenesis. However, the main limitation of this chimeric model is the degeneration and major loss of human neurons without the presence of NFTs, a promising therapeutic target for AD.

Careful examination of the neuropathology and cognitive impairment in various species has shown that AD is a uniquely human disease. The very poor success rate of AD clinical trials with ~99.6% failure can be partly explained by the premature translation of pathology from transgenic mice to humans. Since the development of the first transgenic mouse model with a substantial Aβ plaque burden in 1995, there has been a proliferation of new transgenic models. These models manifest different phenotypes of AD-associated pathology. Rats are experimentally easier to manipulate because of their larger body and brain dimensions. Although the physiological and genetic features of rats are closer to humans than mice, technical

✉ Hong Zhang
hzhang21@gmail.com

[1] Department of Nuclear Medicine, The Second Hospital of Zhejiang University School of Medicine, Hangzhou 310009, China

[2] Zhejiang University Medical PET Center, Hangzhou 310009, China

[3] Institute of Nuclear Medicine and Molecular Imaging of Zhejiang University, Hangzhou 310009, China

[4] Key Laboratory of Medical Molecular Imaging of Zhejiang Province, Hangzhou 310009, China

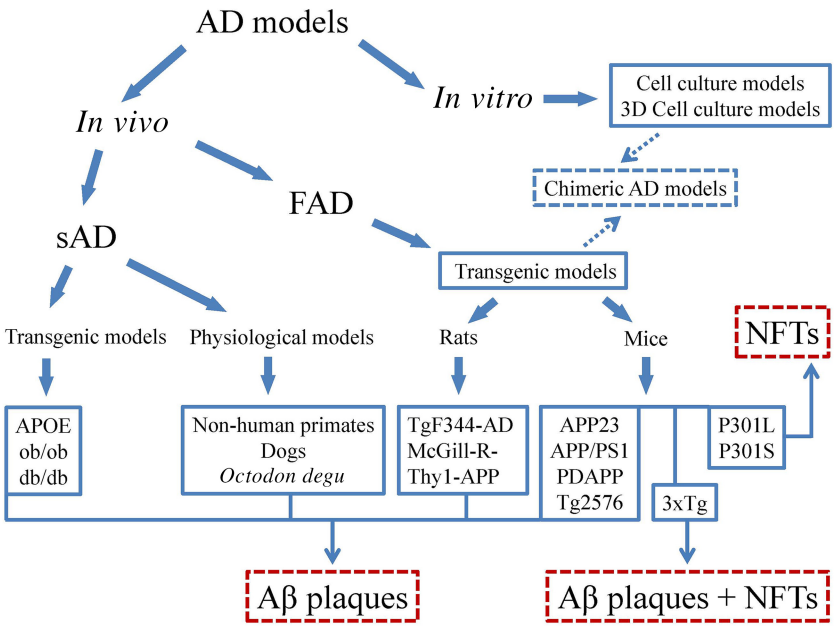

Fig. 1 Schematic of models of Alzheimer's disease (AD). More than 95% of AD cases are sporadic AD (sAD). However, both transgenic and physiological models available for sAD only show Aβ plaques. In addition, the Aβ plaque is also the only pathological change in all transgenic rat models and most transgenic mouse models. The most commonly used models developing neurofibrillary tangles (NFTs) are mice with P301L or P301S mutations. Only 3×Tg mice express both Aβ plaques and NFTs. Induced pluripotent stem cell (iPSC) lines from familial AD and sAD patients show increased accumulation of Aβ, and Tau hyperphosphorylation. The development of 3D cell culture models partly solves the issue that cell culture models do not represent the complex environment *in vivo*. A mouse/human brain chimera model has been established by transplanting human iPSC-derived cortical neuronal precursors into the brain of a mouse AD model.

barriers have slowed the transgenetic development in rats. Since fewer tools are available for genome manipulation than in mice, transgenic technology has been rarely developed in rats. Rodent AD models usually overexpress a mutated form of the FAD-causing genes *APP* and/or *PSEN*, leading to extensive Aβ plaque deposition, Aβ-associated neuroinflammation, and some synaptic dysfunction. However, crucial aspects of the disease, like NFT formation and severe neuronal loss, have never been convincingly demonstrated in rodent models. More importantly, the relevance of these genetic models to the study of sporadic AD (sAD) patients, who do not carry mutations in *APP* or *PEN*, is a matter of debate [4].

A major proportion of AD patients suffer from sAD. Genetically, the *APOE* gene, which encodes the lipid/cholesterol carrier apolipoprotein E (apoE), is the only well-established locus that affects the risk of developing sAD [5]. *APOE* mouse models have been designed, and been combined with FAD mutations in AD studies. On the other hand, glucose intolerance, such as that occurring in type 2 diabetes mellitus (T2DM), is also considered to be a risk factor for dementia. One of the most commonly used T2DM models is the *ob/ob* or obese mouse expressing inactive leptin. These novel sAD models have the potential to explore the genesis of sAD and how it proceeds; and secondly, the generation of animal models that mimic these mechanisms. Although current transgenic models can be very useful for interpreting specific aspects of pathogenic mechanisms, they do not interpret the whole pathophysiology [6]. In addition, since gene expression can be modified by the host genetic background and pharmacokinetics may differ between species, interspecific variability may impose a handicap in the translational application of transgenic models [7]. Results generated from experimental models can be exceptionally informative about specific aspects of AD if researchers are aware of the limitations associated with each model.

Considering these disadvantages of transgenic models, finding a naturally-occurring AD model is appealing because it would more accurately represent the changes that occur in sAD. Many species, including non-human primates, dogs, and *Octodon degus*, naturally develop neuropathological features similar to those seen in the AD brain. However, there are still scientific and practical limitations that preclude widespread application of these models. The non-human primate models have long lifespans, and pathology varies between individual animals. As a result, the selection of animals for preclinical testing may be difficult, and experiments are expensive and time-consuming. Furthermore, cognitive testing is less standardized and can be difficult to perform in these species. Even in the models with most well-characterized AD pathological features, no evidence

supports the widespread presence of NFTs similar to that in AD patients.

The use of experimental models derived from human tissue bypasses concerns associated with confounding effects due to species differences. Neurons derived from pluripotent stem cells from AD patients show an altered Aβ42/Aβ40 ratio and abnormal Tau phosphorylation [8]. The limitations of using human cell-culture models include the lack of standardized protocols to generate and maintain these cell lines. An additional concern is that cell culture models do not accurately represent the complex environment in the brain [9]. It has been reported that neural precursors derived from iPSCs can be transplanted into the rodent brain, resulting in specific patterns of cortical neuronal maturation, connectivity, and synaptic activity, well beyond what can be achieved in a purely *in vitro* condition [10]. Espuny-Camacho *et al*. reported a new approach to exploring how different human genetic backgrounds modulate AD-related features *in vivo*. This model is also of interest to further investigate whether and how Aβ modulates Tau pathology and how this affects neurodegeneration. Another alternative approach is to transplant iPSC-derived cortical neuronal precursors from AD patients into the brain of wild-type rodents. It will be valuable to investigate whether transplanted neurons with potential AD pathology would contaminate the surrounding environment, or be alleviated by the intact host brain.

In conclusion, each animal model mirrors only limited aspects of AD pathology in humans. A better understanding of the strengths and weakness of each model, and the use of more than one model to evaluate potential therapies would help translate preclinical studies to patients. Therefore, it will be necessary to perform preclinical testing in multiple animal models until a more complete physiological animal model of sAD is available, to ensure greater translation of preclinical results to human clinical trials.

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