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Application of APP/PS1 Transgenic Mouse Model for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD), the most common neurodegenerative disorder, will not only reduce quality of life severely, but also bring heavy economic burden to the family and society. Slow progress in AD therapies partially due to lack of appropriate animal models. APP/PS1 transgenic mouse, a widely used animal model for AD, can be used in lots of aspects for AD related study, such as neuronal apoptosis, inflammation, cholinergic abnormal, neurogenesis disorder and synaptic plasticity. Despite all this, APP/PS1 transgenic mice model is not a perfect model, and more suitable animal model according to the aim of research should be established.

Keywords: APP/PS1; Alzheimer's disease; Transgenic mouse

Introduction

Alzheimer's disease (AD), also known as senile dementia, is a neurodegenerative disease of the central nervous system, and the most common cause of dementia, characterized by a progressive loss of cognitive function and behavioral disorders clinically. The pathogenesis of AD is complicated, and there is still no effective treatment for it. Studies of etiology, pathology, and related pharmacology on AD are based on appropriate animal models, which should have three characters: A. pathological changes marked by senile plaques (SP), neurofibrillary tangles (NFTs), and loss of neurons and synapses; B. other pathological features such as inflammation and astrocytosis; and C. memory and cognitive dysfunction. Taken into account the months in age of animal, if the animal model of AD also fits the three aspects mentioned above, it will be proper to meet the requirements of the experiment of AD.

Transgenic (Tg) animal models of AD

With the deepening in the research of the AD pathology and rapid progress of molecular neurobiology, more and more AD animal models have been established. They can be divided into two categories: non-Tg models and Tg models, the former focus on mouse, rat, dog or monkey, because these species can develop plaques and tangles; the latter usually adopt mouse and rat because of their reproducibility. Non-Tg models include aging animal model [1], senescence-accelerated prone 8 mice (SAMP8), exogenous harmful material injection models [2,3], knock-in (KI) mouse model, and so on. These models can analog AD pathological changes to a certain extent as well as apparent flaws. Aging animal models analog the aging process and exhibit neurologic changes that are generally milder and more variable in nature, such as synaptic dysfunction and Ca^{2+} dysregulation [4], but they often lack of characteristic pathological changes of AD. SAMP8 mice exhibit progressive synaptic loss and develop deficits in learning and memory as early as 4 months of age [5], develop an age-dependent accumulation of Aβ deposits in the hippocampus as early as 6 months of age [6], however, the life span are shortened accordingly. To the models induced by exogenous harmful material injection, NFTs caused by aluminum have been shown to possess an actual accumulation of neurofilaments (and not tau) [7]; Aβ peptide injection does not directly reproduce the lesions of AD [8]. APP/PS1 KI mice can replicate much of the Aβ-dependent pathologies seen clinically in AD [9,10], but the onset of cognitive deficits start at 11 months of age[11], and the AD-related motor deficits does not develop. In contrast to the APP/PS1 KI mutant, the APP KI mutation alone does not affect markers for adult hippocampal neurogenesis [12]. PS1 KI mice, a model that shows cognitive decline developed in an Aβ-independent way, therefore plaque-dependent pathology cannot be expected [13].

Tg models are important models for the AD study. They are established on the basis of genetics, mainly involves amyloid precursor protein(APP) gene on chromosome 21, presenilin1 (PS1) gene on chromosome 14, presenilin 2 (PS2) gene on chromosome 1, Tau protein gene on chromosome 17 and Apolipoprotein E (ApoE) gene on chromosome 19 [14]. By transgenesis, the course of AD can be simulated steadily at molecular level. Meanwhile, this technique can produce many animals at the same time, so the reliability and repeatability of experimental results can be ensured. Tg models have three types: single transgenic models such as APP Tg mouse model, double Tg models such as APP/PS1 Tg mouse model and triple Tg mouse models such as APP/ PS1/Tau Tg mouse model [15]. Although the emergence of Tg model is a hot spot of AD research in recent years, there are still problems in the application of Tg AD models, such as lack of aging process, poor reproductive ability and immunity. Therefore, compared with the real AD pathological changes, there is still a long way to go.

APP/PS1 Tg mouse model

Double Tg mouse from a cross line between APP and PS gene is an acknowledged method that β-amyloid (Aβ) deposition fastest in the brain [16]. Double Tg APP/PS1 mouse model mainly include five kinds: APPswe × PS1, APPSL × PS1M146L, APPswe × PS1dE9, 5 × FAD and APPSL × PS1ki [17], of which $APPs_{we}$ × PS1dE9 is the most widely used AD model. APPswe is a Swedish family mutation. Leu and Lys are substituted by Asn and Met at the end sites of 670 and 671 coding sequence of APP. PS1dE9 is the ninth exon deletion in the

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familial AD. These mutations are believed to have a close relationship with the excessive formation of Aβ plaques. Extracellular Aβ deposition can be detected in such Tg mouse models at 2.5 months [18,19], long-term potentiation impairment at 3 months[20], apparent dysfunction of learning and memory at 6 ~ 8 months [21,22], and a small amount of Aβ deposition in hippocampus at 6 months[23], SP in hippocampus at 8 months and cerebral cortex similar with AD patients and neuron loss at 12 ~ 18 months [24]. However, some studies found that along with the growth of mice, cerebral glucose uptake increased, especially around the SP, and the mechanism of which need to be further explored [25]. In contrast, single Tg AD mice reach a peak of memory damage at 12 ~ 15 months or even older [26,27], and it failed to show any significant sign of neuronal loss in affected brain regions. Although APP/PS1 Tg mice showed accelerated amyloid deposits, the expression of Tau and NFTs are not obvious compare with APP/PS1/tau triple Tg AD model[28], but it has advantages in price and technology.

Application of APP/PS1 Transgenic Mouse Model

The etiological mechanisms of AD remain unclear, and there are many views and hypothesis, including inflammatory reaction, neurotoxicity of Aβ, neuron apoptosis, synaptic plasticity, and etc. Therefore, it is difficult for us to establish and select an ideal AD model. Due to the similarities of many of its multiple pathological changes to AD, the application of APP/PS1 Tg mouse model becomes more extensive in recent years.

Apoptosis of neurons

Neuronal apoptosis is considered to be extremely important in the pathogenesis of AD [29]. Multiple factors are involved in the apoptosis of neurons [30], including neurotoxicity of Aβ, oxidative stress injury (such as free radicals, lipid peroxidation and reduced polyunsaturated fatty acids), mutation of PS genes, calcium dyshomeostasis and endoplasmic reticulum stress[31-33]. Abnormal Ca^{2+} level and ryanodine receptor mediated Ca^{2+} release have been found increased in dendritics and cell bodies of cortex neuron in APP/PS1 Tg mice [34,35]. Some researchers have found that clearance of extracellular Aβ by the monoclonal antibody 3D6 or reactive oxygen species by *N*-tert-butyl-phenylnitrone (PBN) did not rescue the cellular oxidative stress in neurites surrounding Aβ plaques in APP/PS1 mouse. This non-rescue event suggests that once the redox potential increased within cells that the effect of external anti-oxidants are ineffective .This non-rescue event implies that prevention therapies will be more effective than treatment therapies or that longer durations of treatment will be necessary[36].

Neurotoxicity of Aβ

Aβ cascade hypothesis indicated that the excessive accumulation of aggregated Aβ and subsequent pathological events are the key points of occurrence and development of AD [37]; and the levels of free Aβ were more closely related to the severity of cognitive function compared to Aβ fibers [38]. γ-secretase is an important enzyme that cleaves APP to Aβ peptide. It was demonstrated that by inhibition PS1 and nicastrin (NCT), two components of γ-secretases, the cognitive function of APP/PS1 Tg mice improved [39]. However, many researchers believe that the severity of cognitive impairment is more closely related to NTFs in the cortical nerves, which might be one of the possibilities that many clinical trial targeting Aβ failed [40,41]. Nevertheless it is undeniable that Aβ deposition plays a key role in the pathogenesis of AD [42].

Inflammation response

Neuroinflammation, in the way of glial activation (especially in the vicinity of amyloid plaques), is one of the major pathological changes in the brain of AD patients, which may be involved in the pathogenesis of AD and has played an important role in the progression of AD [43]. The levels of various inflammatory factors and signaling molecules have been found alterations in APP/PS1 Tg mice, including the interleukins, complement C1q and TNF-α [44-47]. Chemokine ligand 4(CCL4) is overexpressed in *APP/PS1* brains and that levels of CCL4 mRNA and protein are positively correlated with the age-related progression of cerebral insoluble Aβ deposition in these mice [48]. Other studies showed that long term over-expression of IL-1β could improve the pathological changes of Aβ, increase the expression of microglia associated with Aβ plagues, and induce the entry of peripheral immune cells into the brain [49].

Cholinergic system

To a certain degree, vulnerability of basal forebrain cholinergic system is associated with the severity of AD [50], especially the decline of acetylcholine levels [51]. Choline acetyl transferase (ChAT) in hippocampus and cortex tissue of 10 months APP/PS1 mice decreased significantly. Acetylcholinesterase (AChE) activity began to decline at 16 months, and this decrease is correlated with the degree of dementia [52].

Neurogenesis

It has been demonstrated that neuron loss is most closely related to the cognitive impairment in AD pathological features [53]. Therefore, to promote and increase neurogenesis in hippocampus may be a potential pathway to delay or reverse the progression of AD. Neurogenesis includes 3 aspects: cell proliferation, differentiation and survival. Compared with age-matched controls, there was a decrease in neurogenesis in APP/PS1 Tg mice at 3-6 months, no significant difference between 12 ~ 15 months, which is consistent with the pathological features of brain in AD patients [54-56]. It is indicated that hippocampal neurogenesis may increase during the development of AD [57]. It is suggested that neurogenesis in APP/PS1 mice might be a compensatory effect for pathologic changes, and AD brain tissue may exist some toxic factors on neurogenesis [58]. Therefore, it is necessary to give some appropriate stimulus for the neurogenesis of neurons.

Synaptic plasticity

Synaptic plasticity is the basis of learning and memory. Synapses loss, especially dendritic spines loss which manifests as morphological changes is closely correlated with cognitive impairment [59]. The decrease of synaptic efficacy in the hippocampus is much earlier than the appearance of neuron degeneration [60]. Previous work has reported that the loss of synapses in the dendritic spines and dendrites was the main reason for the decrease of the synapse in APP/PS1 Tg mice [61].

Conclusion

APP/PS1 Tg mice, a proper AD model, has been highly valued by medical researchers, and has been applied in other studies besides AD. Some scholars have found that cholesterol levels in the hippocampus of APP/PS1 Tg model mice began to increase at 7 months, and mitochondrial cholesterol content increased significantly at 10 months [62,63]. Because the complex pathogenesis and pathological mechanisms of AD, the differences between autosomal-dominant AD and sporadic AD, most of the animal models including APP/PS1 Tg model can only simulate part of the pathological characteristics of AD. Compared to the AD patients, the reduced inflammatory response and ferric iron concentration were found

in the APP/PS1 neural tissue, which suggest that the Tg model loosely fits within the current framework of the amyloid cascade model [64].It is necessary to have a good understanding of the model when adopted. With the study and development of molecular biology mechanisms of AD, some novel and more proper AD animal models will certainly be established in future, which will in turn greatly accelerate the study and therapy progress of AD.

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