

Mechanisms of memory loss in A β and tau mouse models

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Abstract

Although memory loss is the central symptom of Alzheimer's disease, the pathophysiological mechanisms leading to dementia are poorly understood. It is difficult to answer this issue with studies in humans and impossible in cultured cells. Therefore animal models are needed to elucidate the molecular mechanisms leading to dementia. The chief neuropathological changes during Alzheimer's disease, namely neurofibrillary tangles and amyloid plaques, have helped us to determine which molecules to focus upon in the animal models, specifically A β (amyloid β) and tau. This paper presents my perspective on what we have learnt about mechanisms of memory loss from A β and tau mouse models of Alzheimer's disease.

Natural history of Alzheimer's disease

To appreciate the context in which animal models have helped us understand the pathophysiology of memory loss, it is important to delineate the natural history of Alzheimer's disease. Alzheimer's disease has a very insidious onset; we do not know precisely when neural dysfunction begins. The brains of patients dying with Alzheimer's disease are devastated by widespread plaques, tangles and neuron loss. In 1999, it became clear that there is a prodrome to Alzheimer's disease, which is frequently referred to as 'mild cognitive impairment' [1]. These individuals have subjective complaints and mild clinical abnormalities on examination. The brains of individuals at this stage of illness have some plaques and tangles, but neuron loss is restricted to the entorhinal cortex [2,3].

Intriguingly, asymptomatic individuals who were at risk genetically for Alzheimer's disease have shown evidence of brain dysfunction in functional magnetic resonance imaging and positron emission tomography studies [4,5]. This has given rise to the notion of a latent phase of Alzheimer's disease [6]. Although we do not know what kind of brain pathology exists in these individuals, it is likely that they have rare plaques and tangles, because these neuropathological abnormalities appear in autopsy series of cognitively intact individuals after the age of 40 [7]. However, studies on individuals with mild cognitive impairment would lead to the prediction that these asymptomatic individuals would not yet have lost any neurons [2,3].

APP (amyloid precursor protein) transgenic mice modelling of Alzheimer's disease

Three scientific breakthroughs made the creation of the first transgenic mouse models of Alzheimer's disease possible.

First was the isolation and sequencing of the A β (amyloid β) peptide in 1984 [8]. Second was the cloning of the APP and the elucidation of its role in generating the A β peptide [9–12]. Third was the discovery of the first mutation in autosomal dominant familial Alzheimer's disease in APP [13] and the subsequent realization that all autosomal dominant mutations causing Alzheimer's disease increase the amount of the more amyloidogenic A β 42 [14].

This information enabled investigators to create the first APP transgenic mice modelling Alzheimer's disease. Altogether, approx. 20 such mice models have been published (reviewed in [15,16]); many models show progressive plaque deposition and loss of memory. For example, the Tg2576 mouse model recapitulates many of the neuropathological features of Alzheimer's disease, including amyloid plaques [17], oxidative stress [18,19], astrogliosis [20], microgliosis [21], cytokine production [22–24] and dystrophic neurites [20]. Tg2576 mice also show progressive deterioration in spatial reference memory [17,25].

However, within a year or so of the creation of the first APP transgenic mouse models, it became apparent that many important features of Alzheimer's disease were conspicuously absent, including neurofibrillary tangles, neurodegeneration or gross atrophy, and that there was variable neuronal and synaptic loss. Tg2576 mice were virtually devoid of such neurodegenerative changes [20], while synaptic loss was present in J20 and PDAPP mice [26,27], and there was some neuronal loss in APP23 mice [28]. We do not understand the factors that account for these variations between mice, but it is clear that the differences are not attributable to variations in the expression levels of A β . The lack of some important features of Alzheimer's disease led many scientists to challenge the validity of APP transgenic mouse models.

Criteria for validating Alzheimer mouse models

It therefore became important to devise criteria for validating Alzheimer's mouse models. Here, I propose three such

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Abbreviations used: A β , amyloid β ; ALCR, alternating lever cyclic ratio; APP, amyloid precursor protein.

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criteria: (i) theoretical validity, which refers to whether the use of a given transgene is based on sound principles; (ii) factual validity, which refers to how accurately various aspects of the human disease are represented; and (iii) predictive validity, which refers to whether studies using the model predict outcomes seen in human trials. Clearly, predictive validity is the main determinant of the value of a given Alzheimer's mouse model.

Predictive validity of APP transgenic mouse models

Thanks to rapid progress in bench-to-bedside research on Alzheimer's disease, we know more about the predictive validity of APP transgenic mice than of the transgenic mice modelling of any other neurodegenerative illness. $A\beta$ immunotherapy illustrates this point.

In 1999, the scientific community was astonished by the demonstration that young PDAPP mice vaccinated with $A\beta$ failed to develop amyloid deposits and gliosis [29]. This exciting result catalysed an international, multi-centre $A\beta$ vaccine trial in Alzheimer's patients. Autopsy studies of patients receiving the vaccine showed that amyloid plaques are cleared from large patches of the brain in the Alzheimer's disease patients who received an experimental $A\beta$ vaccine [30,31]. However, neurofibrillary tangles were unaffected, and there was persistent neuron loss [32].

When memory was examined in APP transgenic mice receiving either active or passive $A\beta$ immunization, it was clear that memory loss could be prevented, and preexisting memory loss could even be restored to normal [33–36]. However, when the effects of vaccinations on cognitive function were examined in Alzheimer's patients, it was clear that memory is not restored. In one research centre, patients who generated antibodies that stained plaques in Tg2576 mice crossed with mice expressing mutant presenilin-1 had a slower decline in Mini-Mental State Examination and were more likely to remain stable or improve [37]. However, the result is clearly not the same as restoring normal cognitive function in a demented patient.

In summary, when the effects of $A\beta$ immunotherapy in mice and humans are compared and plaques are used as a read-out, the results obtained in mice predict what happens in humans. However, when memory is used as a read-out, there is a striking discrepancy between what occurs in mice and humans. Memory is restored in APP transgenic mice, but not in humans with Alzheimer's disease.

One possible explanation for the discrepancy between the outcome of treatments on memory in mice and Alzheimer's disease patients is that APP transgenic mice have little or no neuronal or synaptic loss. In this respect, APP transgenic mice such as Tg2576 mice most closely resemble individuals in the latent phase of Alzheimer's disease, rather than people with mild cognitive impairment or patients with Alzheimer's disease. If Tg2576 mice were human, they might not even have the subjective complaints or mild cognitive deficits that characterize individuals with mild cognitive impairment.

However, they would, and do, have evidence of brain dysfunction.

The existence of a latent phase of Alzheimer's disease is still speculative, and there is currently no means of identifying individuals in this phase. However, if it were possible to do so, then these individuals would have a condition that would be attractive to treat, because issues related to replacing lost neurons could be avoided, and intervention could potentially prevent neurodegeneration from developing.

An important area of investigation for treating individuals in the latent phase of Alzheimer's disease is to understand how age-related brain dysfunction occurs in the absence of neuron loss. Although Tg2576 and other APP transgenic mice may represent models of the latent phase of Alzheimer's disease, this area of research has attracted very few investigators, because of the dual challenges of performing large-scale, quantitative behavioural measurements in mice combined with the task of isolating candidate $A\beta$ molecular species.

Molecular basis of the memory loss without neurodegeneration in Tg2576 mice

The goal of our initial studies was to determine whether memory loss in Tg2576 mice was caused by fibrillar, insoluble $A\beta$ or soluble $A\beta$ [25]. We identified both age-independent and -dependent behavioural deficits in Tg2576 mice. When the age-independent deficits were excluded, the initial decline in memory in Tg2576 mice coincided with the appearance of fibrillar, insoluble $A\beta$ at approx. 6 months. Moreover, accelerating the production of fibrillar, insoluble $A\beta$ genetically, by crossing Tg2576 mice with the transgenic mice harbouring mutant presenilin-1 genes, resulted in earlier loss of memory. These results suggested the facile interpretation that fibrillar, insoluble $A\beta$ was closely connected with the loss of memory in Tg2576 mice. However, we rejected this notion when we found no correlation whatsoever between memory and fibrillar, insoluble $A\beta$ in Tg2576 mice aged 5–22 months. Since soluble $A\beta$ molecules that were present before 6 months of age did not appear to disrupt memory, we surmised that only specific soluble $A\beta$ molecules present in older mice might be responsible. We therefore hypothesized that small, soluble assemblies of $A\beta$ caused memory deficits in Tg2576, an idea that was supported by data showing significant inverse correlations between fibrillar, insoluble $A\beta$ and memory in Tg2576 mice that were stratified by age. Our data showed that memory deficits in Tg2576 mice are dissociated from plaques and fibrillar, insoluble $A\beta$, and led us to conclude that there may be specific soluble oligomers of $A\beta$ that were capable of disrupting memory without killing neurons or destroying synapses [16,25]. We speculated that these specific soluble oligomers of $A\beta$ were related to $A\beta$ -derived diffusible ligands and to other soluble $A\beta$ assemblies, which have been shown to kill neurons, inhibit fast synaptic transmission and decrease long-term potentiation [26,38–40].

The fact that memory deficits are dissociated from plaques and fibrillar, insoluble $A\beta$ has also been demonstrated in

PDAPP mice, Tg2576 mice crossed with mice expressing mutant presenilin-1, J20 mice and TgCRND8 mice [34,35,41,42]. One of the most remarkable examples was the demonstration that the impaired performance in an object-recognition task shown by 2-year-old PDAPP mice with abundant amyloid plaques rapidly recovered after a single injection of A β antibodies, without reducing the number or size of amyloid plaques [35].

Although the specific A β assemblies in APP transgenic mice responsible for disrupting memory without causing neurodegeneration in the form of neuron or synapse loss have not been identified, recent data support the hypothesis that soluble oligomers of A β are both necessary and sufficient for A β to disrupt cognitive function [43]. Soluble A β oligomers naturally secreted by Chinese-hamster ovary cells in culture were isolated by size-exclusion chromatography and injected intra-cerebroventricularly into rats, which had been trained in an operant task, the ALCR (alternating lever cyclic ratio) test, capable of detecting subtle cognitive effects of very small doses of psychoactive drugs. Injection of fractions containing oligomers, but not monomers, of A β increased the error rates of the rats performing the ALCR test, in a manner that was rapid, potent and transient, and produced impaired cognitive function without inducing permanent neurological deficits. Thus oligomers of A β secreted by cultured cells are capable of disrupting cognitive function without causing apparent neurodegeneration when exogenously introduced into animals.

Whether similar, endogenous A β molecules exist possessing the same capacity to disrupt memory in animals or humans is still a subject of debate. The identity of specific, endogenous, oligomeric forms of A β that seem responsible for cognitive deficits in Tg2576 mice, called A β^* , has been a topic of our recent research (S. Lesné, J. Cleary, L. Kotilinek, R. Kaye, C.C. Glabe and K.H. Ashe, unpublished work).

Neurofibrillary tangles, neurodegeneration and memory loss in transgenic mice

Neurofibrillary tangles have long been associated with neurodegeneration in hereditary and sporadic tauopathies, Alzheimer's disease being the most common of these disorders. However, whether and how neurofibrillary tangles disrupt cognitive function and the extent to which the structural and functional abnormalities caused by neurofibrillary pathology are capable of being modulated are unknown. These questions are more easily addressed in transgenic mouse models than in other experimental systems.

Four important landmarks in tau biology made the creation of transgenic mice producing neurofibrillary pathology possible. First was the isolation and characterization of tau [45], a protein involved in promoting the aggregation and polymerization of tubulin to form microtubules. Second was the cloning of tau [46]. Third was the recognition that tau was the principal protein forming the core of paired helical filaments of neurofibrillary tangles [47,48]. Fourth was the

discovery of mutations in tau linked to familial tauopathies [49].

This knowledge led to the generation of transgenic mice with neurofibrillary pathology, which were developed using both mutant and wild-type tau genes [50,51]. The triple mouse carrying mutant tau, mutant APP and mutant presenilin-1 develops amyloid deposits and neurofibrillary tangles [52]. The htau mouse expressing all human wild-type tau isoforms but no mouse tau is the only one that produces true paired helical filaments [53]. The R406W mouse is the only transgenic mouse in which memory has been carefully examined; very old mice show memory deficits coinciding with the appearance of neurofibrillary pathology [54].

We have recently created transgenic mice expressing mutant tau that can be suppressed with doxycycline. Following the suppression of transgenic tau, memory function recovered and neuron numbers stabilized, but, surprisingly, neurofibrillary tangles continued to accumulate [55].

Conclusions

Animal models are essential for elucidating the pathophysiological and molecular mechanisms leading to dementia in Alzheimer's disease. Transgenic mouse models expressing A β and tau (which are the principal molecular components of the neuropathological hallmarks of Alzheimer's disease, namely amyloid plaques and neurofibrillary tangles) have helped us to determine the molecular and cellular processes involved in producing cognitive deficits. Soluble A β oligomers are the leading candidates of A β species believed to be responsible for disrupting memory in APP transgenic mice. A β oligomers secreted by Chinese-hamster ovary cells have been shown to be necessary and sufficient for A β to disrupt the performance of rats in a complex operant task. However, the identity of the endogenous A β oligomers disrupting cognitive function in animals and humans remains unknown.

The phenotype of APP transgenic mice more closely resembles the latent phase of Alzheimer's disease than the actual disease itself, because the mice exhibit little or no neurodegeneration. In contrast, transgenic mice expressing tau, which develop neurofibrillary tangles and neuron loss, manifest the neurodegenerative aspects of Alzheimer's disease. A successful approach for the prevention and treatment of Alzheimer's disease involves understanding the mechanisms of memory loss in both A β and tau mouse models and applying the knowledge to develop novel interventions.

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