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Amyloid precursor protein and tau transgenic models of Alzheimer's disease: insights from the past and directions for the future

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Abstract

During the last 20 years, our understanding of the mechanisms underlying Alzheimer's disease (AD) has considerably improved, in part owing to both *in vitro* and *in vivo* model systems. Studies in mice expressing both human amyloid precursor protein and human tau have provided clear evidence that amyloid- β and tau interact in the pathogenesis of AD. Moreover, amyloid- β toxicity has been shown to be tau-dependent since reducing tau levels prevents behavioral deficits and sudden death in amyloid precursor protein transgenic mice. As tau pathology preferentially develops in specific sites and spreads in a predictable manner across the brain, understanding the mechanism underlying tau dysfunction should be a focus in AD mouse modeling. A defined effort must be made to develop therapies that directly address the impact of tau dysfunction in the pathogenesis of AD. Finally, early diagnosis of AD is essential and this must be made possible by identification of early biomarkers, behavioral changes or use of novel imaging techniques.

Keywords

amyloid cascade hypothesis; amyloidosis; brain imaging techniques; clinical diagnosis; cognitive dysfunction; neuronal loss; tauopathy

Alzheimer's disease

Alzheimer's disease (AD) is a common form of dementia characterized by loss of memory and other intellectual abilities serious enough to interfere with daily life. Alzheimer's disease accounts for 50–70% of dementia cases [101]. Other types of dementia include vascular dementia, mixed dementia, dementia with Lewy bodies and frontotemporal dementia (FTD). The diagnosis of AD is confirmed after postmortem examination and is dependent on the identification of senile plaques composed of amyloid- β (A β) peptides and neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau [1]. Several genes have been implicated in AD, most notably, those encoding amyloid precursor protein (APP), presenilin (PSEN)1 and 2 (reviewed in [2]). In addition, the ApoE has been associated with sporadic AD [3,4] and mutant tau has been shown to cause the related tauopathy FTD with

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Parkinsonism linked to chromosome 17 (FTDP-17) demonstrating that tau dysfunction can cause neurodegeneration and lead to cognitive and/or behavioral deficits [5–7].

Which came first, the amyloid or the tau?

Our understanding of the mechanisms underlying AD has progressed considerably during the last 20 years, especially with regard to the role of A β in the pathogenesis of this disease. Originally proposed in 1991, one of the central hypotheses in the AD field is the amyloid cascade hypothesis, which posits that abnormal accumulation of A β plays a causal role in triggering the full spectrum of AD neuropathology, which includes neuronal death, and formation of amyloid plaques and NFTs [8,9]. Recent works have refined this hypothesis, with some now suggesting that soluble A β oligomers rather than A β deposits primarily contribute to synaptic dysfunction, neuronal death, NFT formation and memory impairment in AD [10,11]. The precise toxic species of A β (i.e., monomeric, oligomeric and fibrillar A β) have not been defined, yet this clarification may have an important impact on the development of AD therapeutics [12,13]. Current AD therapy driven by the amyloid cascade hypothesis primarily focuses on reducing toxic A β levels by blocking A β generation and by removing A β through immunotherapy. However, the human Phase IIa clinical study was halted after 6% of the subjects developed meningoencephalitis [14]. The follow-up study of the original Phase I A β 42 immunization trial revealed no evidence of a delay in disease progression [15]; however, significant plaque removal was clearly confirmed in human subjects. This suggests that A β immunization may only show substantial therapeutic benefit if it is initiated at earlier stages of the disease, perhaps before mild cognitive impairment [16].

On the other hand, NFTs reflect intraneuronal changes and the extent of NFTs correlates with the progression of dementia; therefore, the mechanism underlying NFT formation represents a factor that appears to contribute to the cognitive dysfunction observed in individuals affected by AD. Indeed, NFTs are a key neuropathological feature of AD and other neurodegenerative diseases, collectively termed tauopathies (reviewed in [17]). During normal aging, NFTs first appear in the entorhinal cortex [18]. However, as dementia progresses, NFTs appear in neocortical and limbic areas, including the hippocampus. Individuals with NFTs in limbic regions show learning and memory difficulties. Moreover, the presence of NFTs in neocortex correlates with more severe levels of dementia [19]. Interestingly, Braak and Braak found that, in the entorhinal cortex, NFT formation is independent of A β deposition, while in limbic and neocortical areas, NFT formation only occurs after A β deposition [20]. Their analysis suggests that the chronology of pathological changes appears to start with NFTs developing in entorhinal cortex in the absence of A β and continues with A β deposition, which then triggers the appearance of NFTs into limbic and neocortical areas. This hypothesis would imply that brain aging is characterized by NFT development in the entorhinal cortex, and that A β can accelerate NFT formation, resulting in AD; however, this suggestion is based on the end stage pathologies and not necessarily the molecular events and interactions leading to the pathologies.

Our lack of a clear understanding of these molecular and biochemical events leading to amyloidosis and tauopathy, as well as the interaction between the two has prompted the field to create mouse models to mimic key events in the development of AD. The field has yet to develop a perfect mouse model of AD given the fundamental differences between mice and humans; however, many of the currently existing mouse models closely replicate salient aspects of the disease. Here, we review some of the most widely studied mouse models of AD-related pathologies.

Modeling amyloidosis

Derived from the protein encoded by the *APP* gene, A β is a hydrophobic peptide that pathologically deposits in the brains of individuals affected by AD. Sequential cleavage of APP by β - and γ -secretases releases A β into the luminal/extracellular space [21]. Owing to the loose site specificity of γ -secretase-mediated proteolysis, various C-terminal truncated A β species, including two major species, A β 40 and A β 42, are also generated. A β 40 is the most predominant species of secreted A β ; however, A β 42 is hypothesized to be the trigger species for AD-related amyloid patho-physiology owing to a faster aggregation potential compared with A β 40 [22,23]. The significant neurotoxicity of oligomeric and/or fibrillar A β aggregates indicates that accumulation of A β is a central pathogenic event in AD [24]. Indeed, histochemical and biochemical studies have revealed that A β 42 primarily deposits within the brains of both AD patients and several animal models. In 1991, the first *APP* missense mutation in familial AD (FAD) was identified in a British kindred [25]. In mutation carriers, a valine was replaced by an isoleucine at codon 717 (V717I). To date, 20 missense mutations in the *APP* gene have been identified (reviewed in [26]). Moreover, more than 160 mutations in the *PSEN* genes have been identified in early-onset FAD (reviewed in [2]). *PSEN* are central components of the atypical aspartate protease complexes responsible for the γ -secretase cleavage of APP [27,28]. Identification of these genetic deficits that can underlie the development of AD has allowed the development of cell and mouse models for AD as mutations in the *APP*, *PSEN1* and *PSEN2* genes have been found to specifically increase the A β 42:A β 40 ratio and accelerate the parenchymal accumulation of A β [29–34]. The mechanism through which FAD mutations modify overall γ -secretase-mediated cleavage of APP, leading to increased A β 42:A β 40 ratios, remains unclear. The increased A β 42:A β 40 ratio may possibly result from direct alterations in the cleavage reactions catalyzed by mutant *PSEN* such that A β 42 generation is facilitated, A β 40 generation is attenuated, or both A β 40 and A β 42 generation change in a different manner. Recently, several groups observed that decreasing A β 40 levels without an increase in A β 42 was associated with a subset of AD-causing *PSEN* mutations [32,33,35,36]. Several *in vitro* studies suggest that A β 40 directly interferes with A β 42 aggregation by delaying the A β 42-mediated nucleation step at an early stage in the fibrillogenesis process [37–40].

Transgenic mice overexpressing mutant human APP, which reproduce A β plaque formation, have been extensively used to study AD-related pathogenic mechanisms *in vivo* [41–44]. The most successful APP transgenic mouse models have employed expression of full-length human *APP* with FAD mutations. The first transgenic mouse exhibiting AD-like plaques was the PDAPP mouse, expressing human *APP* containing the V717F Indiana mutation under the control of the PDGF promoter [42]. This mouse exhibited extracellular A β plaques of varying morphology, many plaques having dense compact cores, with others being much more diffuse in appearance. The plaques appeared from approximately 6 to 9 months of age. The second successful mouse line was the Tg2576 mouse that overexpressed the 695 isoform of human *APP* with the Swedish double mutation (*APP*^{Swe}; K670N/M671L) under the control of the hamster prion protein promoter [43]. In this mouse model, both diffuse and dense core amyloid plaques were found in the cortex and hippocampus at 9–11 months of age. As an additional model, the APP23 mouse expressing *APP*⁷⁵¹^{Swe} cDNA coupled to the murine *thy-1* gene developed congophilic deposition of A β in parenchyma from 6 months of age [44] and in the cerebral vasculature beyond 1 year of age [45]. Subsequently, many more APP transgenic models have been developed, such as the TgCRND8, which overexpressed the 695 isoform of human *APP* with both the Swedish and Indiana mutations under the control of the hamster prion protein promoter [46], or J20 mice, which expresses a human *APP* minigene with the Swedish and Indiana mutations under control of the PDGF promoter (Figure 1) [41].

In a novel attempt to understand the specific role of either A β peptide in AD pathogenesis, that eliminated complicating factors such as the APP processing derivatives and the sub-cellular localization of processing, a protein chimera was used to drive expression of either human A β 40 or A β 42 in transgenic mice in the absence of human APP [47]. Using this paradigm, BRI-A β 40 transgenic mice did not develop amyloid pathology at any age, while BRI-A β 42 transgenic mice have high levels of A β 42 with considerable amyloid plaque pathology. When the authors crossed Tg2576 with the BRI-A β 40 mice, the resultant bigenic BRI-A β 40/Tg2576 mice had dramatic reductions in both immuno-histochemical A β loads and thioflavin S-positive plaques compared with age-matched Tg2576 littermates. These observations indicate that A β 40 has protective effects against the aggregation of A β 42. Increased levels of either A β 40 or A β 42 in BRI-A β /Tg2576 mice failed to enhance axonal defects observed in Tg2576 mice alone, suggesting that APP-induced axonopathy was not due to A β [48].

Modeling tauopathy

Tau is a phosphoprotein that belongs to the family of the microtubule-associated proteins. The primary function of tau protein (reviewed in [49]), which is normally localized in the axons of neurons, is to stabilize microtubules (MTs). With its ability to modulate MT dynamics, tau contributes to key structural and regulatory cellular functions, such as maintaining neuronal processes and regulating axonal transport, respectively. The normal dynamic equilibrium of MT-bound tau is primarily determined by the phosphorylation state of tau. MT-bound tau is promoted by dephosphorylation of tau and detachment of tau from MT is promoted by phosphorylation of tau. There are six major isoforms in the adult human brain, all of which are derived from a single gene located on human chromosome 17. The six tau isoforms differ from each other in the number of tubulin-binding repeats (either three or four, referred to as 3R and 4R tau isoforms, respectively) and in the presence or absence of either one or two 29-amino acid-long inserts at the N-terminal portion of the protein. This protein is abnormally accumulated as filamentous inclusions in a number of neurodegenerative diseases, including AD, progressive supranuclear palsy, corticobasal degeneration, Pick's disease and FTDP-17 (reviewed in [17]). These tau inclusions, which appear as paired helical filaments (PHF), twisted ribbons or straight filaments, are detergent-insoluble and predominantly composed of hyperphosphorylated tau [50–54]. In AD, NFTs and neuronal cell loss typically coincide within the same brain regions [55]. The progressively expanding anatomical distribution of NFTs reflects progressive brain dysfunction in disease, suggesting that NFT formation and neuronal cell loss may share a common mechanism [56]. Initial attempts to model tauopathy relied on the over-expression of wild-type human tau protein [57]. While many of these wild-type tau transgenic models mimicked the pretangle pathology that is observed in early stage AD and other tauopathies, mature tauopathy and profound neuronal loss was not observed in these models.

The most impressive mouse model of wild-type tauopathy (termed Htau) relied on a human Pl artificial chromosome containing the entire human *tau* gene; however, tauopathy was not observed in this model until the human *tau* transgene was introduced onto a murine *tau*-deficient background [58]. The tauopathy in the Htau model is somewhat slow to develop; mice older than 15 months of age developed tau-opathy, DNA fragmentation and a quantitative loss of neurons [58,59]. The failure of the Htau mice to develop significant tauopathy in the context of murine tau expression suggested that murine tau may reduce the propensity of human tau to become hyperphosphorylated at the levels expressed in the transgenic line. While it is conceivable that higher levels of wild-type human tau expression, even in the context of murine tau, may eventually result in rapidly progressing tauopathy, this model does not yet exist.

The finding that patients with FTDP-17 harbor *tau* mutations [5–7] strongly suggested that tau dysfunction itself can cause neurodegeneration. As with models of amyloidosis, the identification of *tau* mutations in association with the tauopathy FTDP-17 has proven essential in the development of models of mature tauopathy. Indeed, overexpression of mutant tau in various animal models has been demonstrated to induce neurodegeneration [60–67]. More recently, the rTg4510 mouse model was developed to generate a model with significant forebrain tauopathy, a feature that was absent in most previous models of tauopathy [68]. The rTg4510 model uniquely employed the CaMKII α promoter-driven tetracycline effector transgene to focus human mutant P301L tau overexpression in the forebrain and provide conditional control of the transgenic tau expression. The rTg4510 mice developed robust neurofibrillary pathology in the cortico-limbic area, which is physiologically relevant to AD and other tauopathies. The amount of P301L tau protein in mouse forebrains at 2.5 months of age was approximately 13-times the level of endogenous tau in littermates. The rTg4510 mice develop pretangle pathology at 2.5 months and mature neurofibrillary tangles at 4 months in the cortex and at 5.5 months in the hippocampus. The progressive accumulation of biochemically abnormal, sarkosyl insoluble tau corresponds to the severity of tau pathology, with the emergence of a robust 64-kDa species that correlates with the presence of mature neurofibrillary tangles. In addition to the development of neuropathologically and biochemically abnormal tau, approximately a 50% loss of CA1 neurons was observed in the 5.5-month rTg4510 mice by using unbiased stereological analysis [68,69]. The rTg4510 mice also showed profound deficits in cognition related to disease progression (Figure 1), thereby providing a robust behavioral measurement related to tau dysfunction, a quality that had not been shown in wild-type tau transgenic mouse models. In rTg4510 mice, suppression of P301L tau to its basal level of human tau (2.5-fold endogenous owing to a leaky transgene) reversed behavioral impairments, although NFTs continued to increase [68]. This suggested that NFTs were unlikely to be the initial neurotoxic species.

Most recently, Clavaguera *et al.* reported that injection of brain extract from mutant P301S tau transgenic mice into the brain of transgenic ALZ17 mice expressing wild-type tau induced assembly of wild-type tau into filaments and spreading of pathology from the site of injection to neighboring brain regions [70]. This work has brought attention to an intriguing view that a small amount of aggregated tau seeding was able to promote wild-type tau aggregation in a prion-like fashion. Interestingly, even though the injected ALZ17 mice developed tau pathology, it did not lead to neuronal loss, suggesting transitioning of wild-type tau did not facilitate neuronal toxicity. Nevertheless, it is worthwhile to test any other models, such as Htau mice by the injection of post-mortem brain extracts from tauopathy patients.

Modeling Alzheimer's disease

Although amyloidosis, tauopathy, neuronal loss and cognitive dysfunction had each been recapitulated in either amyloid or tau transgenic models, only a few studies have successfully yielded a system in which the relationship between amyloid and tau could be examined within the same model. In 2001, two critical studies were published supporting the role of amyloid in AD pathogenesis. Intercrossing the Tg2576 model of amyloidosis with the JNPL3 mouse model of tauopathy demonstrated that high levels of APP or A β could enhance tauopathy (Figure 1) [71]. In a parallel publication, intracerebral injection of A β 42 into the P301L tau transgenic strain pR5 [72] resulted in similar findings that could be directly attributed to A β 42. Most recently, tangle formation was aggravated by infusing brain extracts of aged APP23 mice intracerebrally in JNPL3 mice or by crossing APP23 and JNPL3 mice [73]. Additional mouse models have now been created combining aspects of both amyloidosis and tauopathy including the dual expression of APP^{Swe} and P301L tau on

a PSEN1^{M146V/-} background in the 3xTg-AD mice [71,72,74], and the regulatable transgenic mouse model rTg3696AB expressing both APP with the Swedish and London (V717I) mutations and P301L tau driven by the CaMKII promoter system [75]. While these models have largely been utilized to investigate that impact of A β on tauopathy, a groundbreaking study was reported in 2007, which demonstrated that reduction of endogenous tau ameliorated A β -induced deficits in an APP transgenic mice (Figure 1) [76]. This was achieved by crossing the J20 line onto hetero- and homozygous tau-knockout background. Tau reduction also protected both transgenic and nontransgenic mice against the GABAA receptor antagonist pentylentetrazole (PTZ)-mediated excitotoxicity. The results suggest that A β toxicity is tau dependent (Figure 1). Although crosstalk between A β and tau was confirmed in these mouse models, it is still unclear which forms of A β are related to the NFT formation and how A β and/or APP processing derivatives contribute to the hyperphosphorylation of tau leading to tau aggregation.

Conclusion

Previous mouse models of AD have been developed to reproduce crucial features of the disease such as amyloid plaques, NFTs, cognitive degeneration, atrophy and neuronal loss. While the APP single transgenic mouse models develop neither NFT nor exhibit massive neuronal loss, studies in mice expressing both mutant APP and tau clearly replicate the main pathological hallmarks of AD. Some researchers in the field debate the significance of these models since these models employ several strategies that do not represent 'true' AD in aggregate. To appreciate the validity of such an argument, one must realize that we are seeking to recreate a human disease that normally requires decades to develop by manipulating an animal that lives for a mere 2 years. Given this, it is not surprising that such strategies are needed to yield these essential research animals. For example, amyloidosis is generally modeled in these transgenic mice by the expression of APP containing FAD mutations, which account for less than 1% of the total number of AD cases. Rapidly progressing, mature tauopathy has only been modeled in transgenic mice expressing tau with a mutation associated with FTDP-17. In addition, most of the tau models have relied on high levels of expression and a single isoform of human tau to drive tauopathy, each of which has been suggested by some experts in the field as being physiologically irrelevant. Most mouse models of tauopathy have not accurately reproduced the age-dependent, anatomical distribution of the lesions starting in the trans-entorhinal cortex in human brain according to Braak NFT staging. Each of these issues is something that should be appreciated when using tau and amyloid model systems; however, simply dismissing the utility of these animal models may be a mistake. Interestingly, cell lines (i.e., M17 and N2a cells), which are routinely utilized for the study of AD and other neurodegenerative disease have similar, if not more extreme, deviation from normal physiology, yet those models have been embraced by the field as essential research tools.

Future perspective

There are a number of techniques that may improve our ability to assess current mouse model systems in a more clinically appropriate manner. These techniques should be more readily applied so that the field can move past the end stage neuropathological hallmarks such as amyloid plaques and NFT in order to address the earliest features of the disease. In addition, AAV can now be employed to refine our understanding of the interplay between tau and A β as well as their interaction with other proteins.

Validation for Alzheimer's disease models

While neuropathologically characterized by amyloid and tau pathologies, AD is clinically characterized by early memory deficits, followed by the gradual erosion of other cognitive

functions. In order to evaluate clinical aspects in mouse models of AD, researchers have employed behavioral studies such as the Morris water maze (MWM) test [77]. Although there are some disadvantages and limitations [78], the MWM allows assessment of spatial learning and memory in transgenic mice in relation to progression of disease or therapeutic trials. Partnering of such behavioral tests with more technologically sophisticated measures of pathology and brain functioning may enhance our ability to validate and utilize disease models. Imaging techniques, such as PET, MRI and multiphoton imaging, have been recently applied for the visualization of A β deposition in transgenic mouse brains. The PET tracer ^{11}C -labeled Pittsburgh Compound-B (PIB) was used in APP23 mice to show an age-dependent increase in radioligand binding in parallel with progressive A β accumulation [79]. There are several limitations of PET, including a high variability in normal controls, low spatial resolution and long scanning periods. In contrast to visualizing pathological structures, manganese-enhanced MRI (Mn-enhanced MRI) was newly developed to assess neural activity of the mouse brain responding to novel environments [80]. As manganese enters into neurons through calcium channels and accumulates in neurons, positive magnetic resonance signals can be detected to show active regions of the brain during behavior to be sampled with MRI [81,82]. Kimura *et al.* observed that the activity of the parahippocampal area in aged (20–24 months old) transgenic mice overexpressing wild-type human 4R tau isoform (termed Wtau-transgenic) was strongly correlated with the decline in memory as assessed by the MWM test. As the entorhinal and hippocampal circuit is essential for the formation of place memory, it is quite reasonable to show reduced neural activity in perirhinal, lateral and medial entorhinal cortices of aged Wtau transgenic mice. In the future, these imaging techniques will be able to provide high spatial resolution that is compatible with the size of mouse brain structure. Overall, combining behavioral and imaging techniques may lead to better clinical and pathological staging of AD mouse models, both in the context of disease development and in therapeutic trials.

Somatic brain transgenesis

Recent advances in molecular biology have made it possible to investigate neurological disorders at the molecular and genetic level. The use of viral vectors as agents for gene delivery provides a direct approach to manipulate gene expression in the mammalian CNS. Most of the vector systems used in the early days of gene therapy research, for example, herpesvirus and adenoviral vectors, suffered from immunogenicity and direct neuronal toxicity. Recently, the development of AAV vectors has conquered these problems [83]. Direct injection of AAV serotype 2 (AAV2) vector into the brain [84] appears to be nontoxic and results in the persistent transduction of neural tissue, preferentially in neurons [85]. The performance of different types of AAV vector appears to be tissue-dependent and probably related to the abundance of serotype-specific AAV receptor. Passini *et al.* reported that widespread gene delivery can be achieved by injecting an AAV serotype 1 (AAV1) vector directly into the cerebral lateral ventricles at birth on postnatal day 0, and allowing the cerebrospinal fluid to deliver the virus throughout the CNS [86]. Based on this newly established technology (termed as somatic brain transgenesis [SBT]), Levites *et al.* generated AAV1 vectors encoding anti-A β single-chain variable fragments (scFvs), which were then injected into the ventricles of postnatal day 0 TgCRND8 mice [87]. This strategy allowed complete prevention of pathology in all areas of the TgCRND8 mouse brain for at least 1 year, suggesting stable expression of the delivered transgene for the lifetime of the animal [87]. Previously, Lawlor *et al.* examined AAV-mediated gene transfer of BRI-A β 40, BRI-A β 42 and APP^{Swe} into the hippocampi of adult rats to define the contribution of A β peptide itself [88]. AAV-BRI A β 40 and A β 42 transduction can be used in established mouse models of tauopathy such as the Htau mice or rTg4510 mice to determine the impact of A β peptide on the development of NFT, neuronal loss and cognitive impairment. In the future, SBT technology should allow us to design cost- and time-effective experimental strategies

to refine our understanding of the interaction between tau and A β as well as with other proteins.

Transduction knockout technique with AAV-Cre

Inactivating genes *in vivo* is an important technique for establishing their function in the adult CNS. However, conventional null mutations of genes that have important functions during development often show an embryonic lethal phenotype, such as PSEN, making experiments on adult animals impossible. The Cre-loxP system is well suited for this problem because it can be used to produce conditional gene deletions in particular cell types at specific times [89,90]. Cre recombinase catalyzes recombination between short loxP sequences, thus deleting any sequence flanked by loxP sites [91]. Recently, as described previously, AAV vectors provide a useful tool to mediate delivery and stable transduction of genes to the brain. Injection of AAV-Cre, which is now commercially available, into the specific brain region of the mice with loxP-flanked genes of interest will cause region-specific recombination. Using this technique, for example, Scammell *et al.* reported that focal deletion of the adenosine A1 receptor in the hippocampus of AAV-Cre injected inducible *A1R*-knockout mice induced local expression of Cre and a marked decrease in *A1R* mRNA [92]. They observed that deletion of A1 receptor CA3 neurons abolished the postsynaptic response to adenosine, but deletion of A1 receptors from CA1 neurons had no effect, demonstrating a presynaptic site of action. Park *et al.* also reported that deletion of phosphatase and tensin homolog (PTEN) in adult retinal ganglion cells of AAV-Cre injected PTEN^{f/f} mice promotes robust axon regeneration after optic nerve injury [93]. This experimental approach will provide novel mouse modeling in the AD research field, as well as wide applicability in neuroscience.

Executive summary

The amyloid cascade hypothesis

- A refined hypothesis now posits that soluble amyloid β (A β) oligomers rather than A β deposits primarily contribute to synaptic dysfunction, neuronal death, neurofibrillary tangle (NFT) formation and memory impairment in Alzheimer's disease (AD).
- The extent of NFTs correlates with the progression of dementia.

Mouse modeling for amyloidosis

- Several transgenic mouse lines overexpressing human amyloid precursor protein (APP) with familial AD (FAD) mutations were successfully developed to exhibit extracellular A β plaques of varying morphology.
- The transgenic mouse expressing BRI-A β 42 fusion developed considerable amyloid plaque pathology suggesting that overproduction of A β 42; however, mice expressing BRI-A β 40 did not.

Mouse modeling for tauopathy

- Htau mice expressing wild-type human tau successfully replicated tauopathy.
- The rTg4510 mouse model was developed in order to generate a model with significant forebrain tauopathy including mature NFT formation, neuronal loss and cognitive dysfunction.
- Suppression of P301L tau expression in rTg4510 mice reversed behavioral impairments although NFTs continued to increase suggesting that NFTs might not be the initial neurotoxic species.

- Transmission and spreading of tauopathy in transgenic ALZ17 mice expressing wild-type tau was observed after injection of brain extract from mutant P301S tau transgenic mice.

Mouse modeling for Alzheimer's disease

- Studies in mice expressing both mutant *APP* and mutant *tau* replicate the main pathological hallmarks of AD.
- Impact of A β and/or APP on enhanced tauopathy was confirmed by several mouse models.
- Reduction of endogenous tau ameliorated A β -induced deficits in APP transgenic mice.

Future perspective

- Early diagnosis of AD is essential in humans and therefore in the mouse models mimicking the disease. Early behavioral analyses and brain imaging techniques should improve the assessment of preclinical stages in existing and future mouse models.
- The use of adenovirus (AAV) technology provides a direct approach to manipulating gene expression in the mouse brain.
- The recently established technology of somatic brain transgenesis will refine our understanding of the interaction between tau and A β , as well as with other proteins.
- The transduction knockout technique with AAV-Cre also provides a novel mouse modeling strategy in AD with brain regional specific gene recombination.

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Website

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Figure 1. Disease cascades leading to amyloidosis and tauopathy in humans and mouse models Mutations in *APP* and *PSEN* genes can lead to AD; however, the discovery of mutations within the *MAPT* gene encoding tau protein demonstrated that tau dysfunction alone could cause neurodegeneration, at least in FTDP-17. It is still unclear how amyloid influences the tau cascade to yield both amyloid and tau pathology within the same disease (AD). Given this, a number of Tg mice have been generated to provide models in which we can examine the origin of the main pathological features of these diseases and ultimately test therapeutics aimed at abrogating toxic species of amyloid or tau. A number of different models are listed under the cascade that they attempt to model. Tau levels are noted in each of these models where endogenous is represented as (+), overexpression is represented as (+++), and degree of tau deficiency is either (-) or (+/-). Salient features of AD or FTDP-17 that are recapitulated within each model are noted. Aβ: Amyloid β; AD: Alzheimer's disease; APP: Amyloid precursor protein; PSEN: Presenilin; FAD: Familial AD; FTDP: Frontotemporal Dementia with Parkinson's; tg: Transgenic.