Genetic Mouse Models of Alzheimer's Disease

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SUMMARY

In the current minireview, we focus on genetic mouse models of Alzheimer's disease (AD). Because various excellent, up-to-date reviews, special issues, and reliable websites are already dedicated to the genetics of Alzheimer's disease in general and of animal models in particular, this review is not meant to be comprehensive. Rather, we aim to steer the Alzheimer's novice through the recent mouse literature on AD. Special attention will be paid to genetic models that have been tested behaviorally.

INTRODUCTION

Alzheimer's disease (AD) is the most common cause of dementia in the elderly, the fourth most common cause of death in western industrialized nations, and one of the major contributors to the global burden of disease (WHO, 2000). No disease-modifying treatment is currently available. The onset of dementia in AD is insidious, and its course is relentlessly progressive and characterized by global cognitive decline, involving memory, orientation, judgment, and reasoning. Nearly 4.5 million individuals are currently afflicted in the United States (U.S.), an incidence expected to rise to up to 16 million by the year 2050 (Hebert et al., 2003).

Extracellular neuritic plaques and intraneuronal neurofibrillary tangles (NFTs) are the two classical hallmark microscopic pathologies of AD (Lovestone & McLoughlin, 2002; Selkoe, 2004). Neuritic plaques comprise a dense amyloid core of β-amyloid peptide (Aβ) that is surrounded by dystrophic neurites. These plaques precipitate and deposit around neurons, mainly those in the limbic system and cortex (Glenner & Wong, 1984a, 1984b; Glenner et al., 1984). This 'choking' mechanism will ultimately lead to neuronal death, which is believed to be responsible for phenotypical dementia in affected patients (Wilquet & De Strooper, 2004).

The microtubule-associated protein, tau, is the principal component of NFTs (Stoothoff & Johnson, 2005). Tau function is regulated by phosphorylation and in AD, tau is abnormally hyperphosphorylated, leading to disruption of microtubule dynamics, impaired axonal transport, and tau polymerization, which results in the formation of intraneuronal NFTs and ultimately neuronal death. For a pathological diagnosis of AD, both neuritic plaques and NFTs are required.

It is now generally believed that abnormal production and aggregation of Aβ (especially the more fibrillogenic $A\beta_{42}$ isoform) are primary pathogenic events in AD and that NFTs are farther downstream in the pathogenesis, commonly referred

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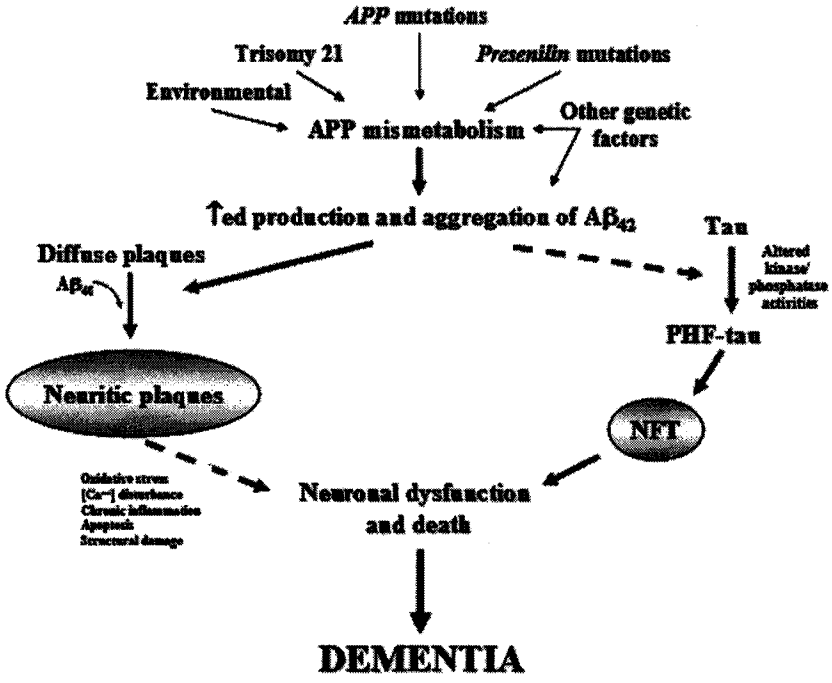

Fig. 1: Schematic overview of the amyloid cascade hypothesis See text for more information.

to as the "amyloid hypothesis" (Fig. 1). This hypothesis is to some extent controversial as plaques and tangles have been found in the brains of non-demented individuals as well (albeit in lower abundance). Moreover, the exact sequence and implication of the different biological processes involved in AD are not yet entirely clear. Although neurodegeneration, amyloid plaques, and NFTs are widely accepted as part of the disease, to determine to what extent those factors contribute to dementia and to what extent they are interconnected to each other remains difficult. Nevertheless, recent studies have revealed that soluble oligomers of Aβ can disrupt synaptic function (Walsh & Selkoe, 2004), mediate neuronal dysfunction in AD (Walsh & Selkoe, 2004), and are both necessary and sufficient to disrupt learning behavior in a manner that is both rapid, potent and transient (Cleary et al., 2005). For a detailed discussion on the amyloid hypothesis, the reader is referred to Hardy & Selkoe (2002) and Marchesi (2005).

GENETICS

As in most complex disorders, genes play an important role in the pathogenesis of AD. One of the most effective methods to ascertain the input of genetic factors is the classical twin method. By comparing genetically related individuals, e.g. monozygotic and dizygotic twins, this method is able to estimate the relative contribution of both genetic and environmental factors, as well as their

interaction for more detailed information, see, among others Boomsma et al., 2002). Studies over the last decades have rendered estimates of the heritability of AD, i.e. the proportion of phenoltypic variation that can be attributed to genetic effects—between 48 and 75% (Bergem et al., 1997; Raiha et al., 1996), depending on, among others, the age of the population under investigation (early-onset vs. late-onset) and the type of study (incidence vs. prevalence).

The search for the actual genes has proven to be difficult. To date, possession of the β4 allele of ApoE is the most robust genetic susceptibility factor for late-onset AD but is neither necessary nor sufficient to cause disease (Tanzi & Bertram, 2005). Other genes involved are the genes encoding amyloid precursor protein (APP), presenilin-1 (PSEN1), and presenilin-2 (PSEN2). Specific mutations in these genes cause early-onset familial AD (EOFAD). First discovered in 1991 (Goate et al., 1991), the number of these fully penetrant mutations has expanded exponentially.[1]

Although such mutations are rare (< 5% of all AD cases), the affected genes—and the biochemical pathways they represent—are excellent starting points for the genetic and functional analysis of AD. Mutations in the gene encoding tau, however, cause a range of different disorders, which are collectively referred to as "tauopathies" (Ingram & Spillantini, 2002). None of these disorders has any appreciable AD pathology, confirming the contribution of tau to be further downstream in the pathogenesis of AD.

Another advantage, from a genetic point of view, in the study of AD is the central role of Aβ in the amyloid hypothesis. Hence, by definition (but in contrast to most psychiatric disorders), a clearly defined neuronal intermediate phenotype, also called an endophenotype, can be further explored. This approach is extremely useful in the genetic analysis of a complex disorder because identifying the effect of a gene on a more elementary (neuro)biological trait is easier than identifying its effect on a complex trait with dichotomous diagnostic categories.

Aβ is a 40-42 amino acid peptide derived from proteolytic processing of a much larger precursor molecule, the amyloid precursor protein (APP). The proteases catalyzing this reaction are termed "secretases": β-secretase (BACE1) first cleaves at the N-terminus of Aβ and then β-secretase cleaves at the C-terminus (Fig. 2). The bulk of APP, however, is cleaved by α-secretase within the Aβ domain to produce the C-terminal fragment, C83, which can be further cleaved intramembranously by γ-secretase to produce peptide P3 and the APP intracellular domain (AICD), which can translocate to the nucleus to participate in gene transcription events (Cao & Sudhof, 2001; see Fig. 2).

Mismetabolism of APP, especially an increase of the more fibrillogenic cerebral Aβ ending at position 42 ($A\beta_{42}$) compared with the one ending at position 40 (Aβ40), can lead to an abnormal production and aggregation of Aβ and as a result to AD. In consequence, the genes encoding the α-, β-, and γ-secretases can be considered candidate genes for AD. Other candidate genes are those that code for proteins affecting Aβ clearance and degradation, as well as Aβ toxicity and inflammation. For a review on the genetics of the amyloid cascade, the reader is referred to Tanzi & Bertram (2005).

ANIMAL MODELS

Many AD studies have been aimed at the analysis and manipulation of Aβ peptides. In this respect, animal models have been very valuable as nearly all studies in humans are necessarily based on postmortem tissues where there is considerable variation in quality because of the technical (agonal state of the brain, post-mortem interval, tissue fixation and storage, tissue pH) and

[1] for more information http://www.molgen.ua.ac.be/ADMutations

biological (age at death, gender, medication and substance abuse) state of the autopsy brain (for detailed information, see Katsel et al., 2005). There are other reasons, though, why animal models are indispensable. Their environment can be controlled and hence manipulated. Sample sizes can be increased when necessary. Perhaps most important, animals can be experimented upon and, accordingly, can provide answers to questions that cannot be answered in humans.

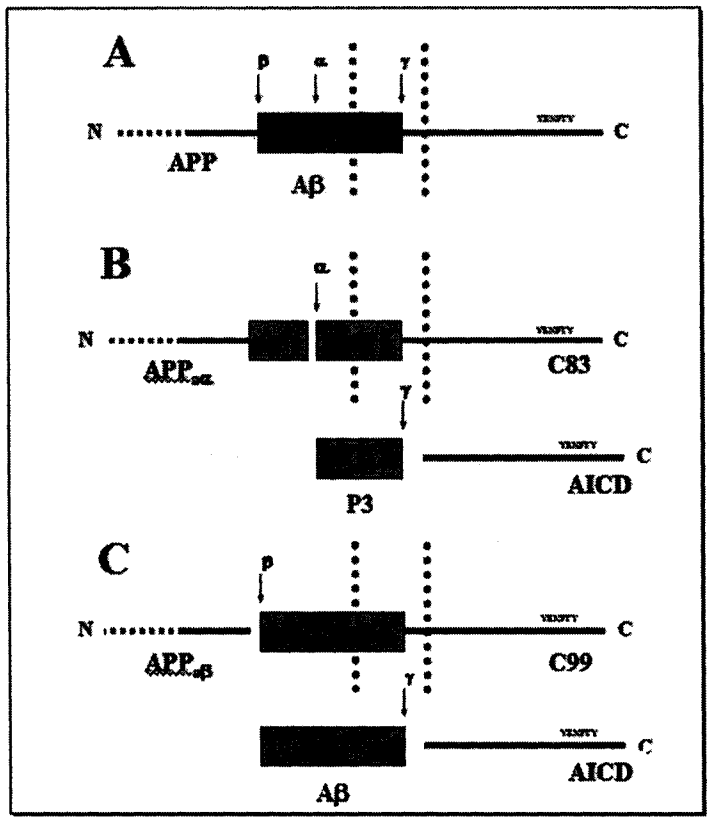

Fig. 2: APP processing pathways. A: APP is an integral transmembrane protein (N-terminal is extracellular; C-terminal is cytoplasmatic). The C-terminal of Aβ (red 'block') is embedded within the cell membrane (area between dashed lines). B: Non-amyloidogenic pathway. APP is cleaved by the membrane-associated metalloprotease α-secretase within the Aβ domain, thereby preventing the formation of Aβ. This results in the release of the large soluble extracellular N-terminal portion of APP (APPsα) and C83 (C-terminal fragment of 83 residues). C83 might be further processed by γ-secretase to release the p3 peptide, which is considered non-amyloidogenic, and the APP intracellular domain (AICD). C: Amyloidogenic pathway. APP is cleaved by two distinct proteases: β- and γ-secretase. First, β-Secretase, (BACE1 = β-site APP-cleaving enzyme) cleaves APP at the N-terminal region of the Aβ sequence, resulting in the soluble APPsβ and the amyloidogenic C99 (C-terminal fragment of 99 residues). Second, γ-secretase cleaves C99, resulting in AICD and Aβ.

Although this review will concentrate on mouse models of AD, invertebrate models such as *Drosophila sp.* and *C. elegans* should not be discarded too easily. Despite their clear disadvantages —they are not mammals and therefore lack the brain structures typical of those—they do have added value in the study of AD, especially at a practical level. They are smaller, cheaper to house and breed, and have shorter generation times than any mammal, which allows the breeding of many generations in a short time span. Last, but certainly not least, is the advantage of a less stringent legislation. Thus, transgenic fly and worm AD models exist both with regard to Aβ and tau expression (for recent reviews, see Brandt et al., 2005; Lee et al., 2005; Link, 2005).

Mice are the most popular animal models for AD nowadays, the main reason being that their genome can be manipulated relatively easily. This advantage has resulted in a variety of genetic mouse models, although rat models do exist as well (see for instance, Hu et al., 2004). Before we dive into the pool of knockouts, knockins, and transgenics, we would like to remind the reader of what a good animal model for AD theoretically should be like.

1. First, this model should be reliable, which refers to the stability and reproducibility of the phenotype, across time and preferably also across laboratories, although the latter is far from easy (Crabbe et al., 1999).
2. Second, this model should have validity with AD. Validity implies four different features. Face validity refers to the similarity between the animal model and the disease of interest, i.e. AD. Hence, the model should mimic the behavioral characteristics of AD—e.g. cognitive decline—as well as possible.
3. Construct validity is another factor and exists when the model either relies or elucidates the same basic underlying mechanism as AD, such as the accumulation of Aß peptides and/or hyperphosphylation of tau. Genetic validity exists when the risk for a disease is known to involve similar genetic components both in humans and in the animal model, whereas predictive validity usually refers to how useful animal models are for predicting the efficacy and safety of drugs.

MOUSE MODELS FOR ALZHEIMER'S DISEASE

At the start of this outline, it is important to realize that both in (semi-) natural and in laboratory conditions mice do not develop plaques and tangles, hence the development of mouse models for AD implies manipulations by the experimenter. Such manipulations can be either genetic or invasive, the latter generally being the exogenous administration of different Aβ peptides into the normal rodent brain. Both techniques have their advantages and handicaps but are essentially complementary. In this review, we will focus on genetically modified mouse models of AD. For a recent review on mouse models of AD involving exogenous Aβ administration and their comparison to transgenic models, the reader is referred to Stephan & Phillips (2005).

Genetically modified strains

The amyloid hypothesis has also played a major role in the development of transgenic mouse models. By definition, genes that code for APP and the enzymes involved in the processing of APP to Aβ are good candidates for manipulation; therefore, not surprisingly, to date, a multitude of genetically modified strains exist that attempt to unravel specific parts of the amyloid pathway. The genetically modified strains entail the following:

(a) *Classical and conditional knockouts (KO).* In classical KOs, the function of the gene under investigation is abolished from a very early stage of development. In conditional KOs, there is either a temporal restriction (gene

function is abolished at certain premeditated time windows) or a regional restriction (no gene function in certain brain regions). A combination of both is also possible;

(b) *Transgenics*, in which a foreign gene, e.g. human APP, is inserted into the genome;

(c) *K nockins*, in which very specific mutations are introduced in the gene leading to a loss of activity of the proteins encoded by the targeted gene (although the gene expression *per se* is not voided as it is in KOs).

Moreover, combinations of (a), (b), and (c) are possible. Strains having one gene knocked out and another inserted into the genome and overexpressed (KO/Tg) are quite common nowadays. Even triple transgenics are being used in mouse models of AD.

APP transgenics

The first successful genetically modified mouse models in AD research were transgenic and increased the load of Aβ by increasing the load of its precursor APP. In general, a human APP (hAPP) gene—usually a mutant form linked to inherited early onset forms of AD—is inserted into the genome. If successful, this procedure leads to the overexpression of the transgene in question and, consequently, to increased levels of APP. To our knowledge, five distinct hAPP transgenics have been developed: PDAPP, Tg2576, APP23, TgCRND8, and J20. Each transgenic has its own genetic characteristics (different mutations, different promoters, different background), which leads to different expression levels and both qualitatively and quantitatively different levels of neuroanatomical abnormalities. All have been tested behaviorally; some extensively, others not. A close look at those lines that have been tested in great detail, such as PDAPP and Tg2576, demonstrates that (genetically induced) high APP levels lead to high Aβ levels, which, in turn, lead to robust cognitive disturbances. Thus, both lines can show learning deficits over time and in different laboratories. This point is rather important as the replicability of the (endo)phenotype over time and across laboratories are essential conditions for a reliable animal model. An additional strength of these particular lines is that they show deficits in several different cognitive tests, which indicates that the behavioral consequences of high Aβ levels, i.e. poorer performance in cognitive tests compared with control animals, are general rather than test specific. For instance, Tg2576 mice, developed by Hsiao et al. (1996), have comparatively more difficulties in a specific version of the water navigation task than their control littermates. Both their acquisition of hidden platform locations and their retention of spatial reference information are affected. This effect is progressive and starts as early as 6 months of age (Westerman et al., 2002). In a different laboratory, the same transgenics also show performance deficits in an adapted version of the Barnes maze (Pompl et al., 1999), whereas in yet another lab they perform poorer in a T-maze alternation task and are impaired at acquiring fear to the conditioning context (Corcoran et al., 2002).

Not unexpectedly, the search for biochemical targets has widened beyond overexpression of mutant forms of the human APP gene. From a genetic point of view, all the genes encoding the secretases that cleave the APP molecule can be considered compelling candidate genes for AD. Especially interesting are the β- and γ-secretases, which catalyze the processing of APP to the various Aβ peptides, and α-secretase, which is part of the non-amyloidogenic pathway.

β-secretase

BACE1 is the most important β-secretase in neurons. Both transgenic and knockout BACE1 mice have been developed and, interestingly, their

phenotypic changes are opposite: The KOs are more anxious than controls and transgenics are bolder. This observation suggests the involvement of BACE in anxiety and not so much in cognition as might have been expected. The next step in elucidating the role of β-secretase in AD was the development of double transgenics, in this case the crossbreeding of mice overexpressing hAPP with those either lacking or overexpressing BACE1 (BACE/Tg2576 and hBACE/Tg2576, respectively). As expected, double transgenics (hBACE/Tg2576) have accelerated amyloid pathology, high levels of both total Aβ and Aβ42, and greater numbers of plaques than hAPP mice alone. The removal of BACE1 in the presence of hAPP, however, rescues certain of the cognitive deficits associated with Aβ (for references, see Kobayashi & Chen, 2005).

γ-secretase

The secondary cleavage in the processing from APP to Aß42 requires the activity of the γ-secretase enzyme. In fact, functional γ-secretase is a complex holoenzyme consisting of several individual enzymes, including PS1, PS2, Nicastrin, Aph-1, and Pen-2 (De Strooper & Woodgett, 2003; Francis et al., 2002). Especially the presenilins (PS1, PS2) have been the target of intense investigation. KOs, transgenics, and KIs have been used, as well as double and even triple transgenics. Although PS1 KO mice are not viable (Shen et al., 1997), this problem was circumvented by the development of conditional KOs (cKO), in which the loss of the gene was limited to the postnatal forebrain. PS1cKO animals showed modest cognitive impairments in long-term spatial reference memory and retention (Yu et al., 2001).

Mice overexpressing PS1 (hPS1), however, show only minor behavioral disturbances. Interestingly, KIs with a directed missense mutation in the endogenous murine PS1 overproduce Aβ42, but develop no plaques. These mice show poorer performance in the object recognition test, but not in the water-navigation task, suggesting changes of PS1 to affect non-hippocampal memory systems (Huang et al., 2003; Janus et al., 2000). PS2 KOs are both viable and fertile and do not appear to show any neurobehavioral abnormalities, whereas PS2 transgenics and KIs perform more poorly in the water-navigation task.

Following an experimental concept similar to that of the hAPP x BACE1, both double transgenics and $cPS^{-/-}$/APP have been developed. Compared with controls, double transgenics accumulate Aβ quicker and at higher levels and, consequently, perform poorer in a multitude of cognitive tests (see Kobayashi & Chen, 2005). Mechanistically in line with the hAPP x PS findings is the observation that $cPS^{-/-}$/APP mice, which carry a conditional postnatal neuron-specific cre/lox KO version of the PS1 gene, develop no amyloid plaques and behave normally in an object recognition task (Dewachter et al., 2002), suggesting γ-secretase inhibition is a promising target for putative treatment strategies.

α-secretase

The third secretase involved in APP processing is the α-secretase, which metabolizes about 90% of APP. To a certain extent, the α-secretase can be considered the 'good' secretase as it produces peptides not—or far less than the Aβs–associated with amyloid toxicity (see Fig. 2). Thus, although the P3 fragment is also a component of certain amyloid plaques in AD, there have been very few reports of P3 having apoptotic or any other kind of deleterious activity in neurons. As a result, the α-secretase-processing pathway has been described as the non-amyloidogenic pathway (Naslund et al., 1994; Wei et al., 2002). A number of enzymes can act as α-secretase in the brain, including the ADAM proteins (ADAM9, ADAM10, and ADAM17). ADAM stands for A Disintegrin and Metallo-

proteinase; its members have apparently redundant α-secretase cleavage activities but differential expression patterns (Buxbaum et al., 1998; Karkkainen et al., 2000; Lammich et al., 1999).

ADAM10 and ADAM17 single knockouts have been shown to be lethal embryonically, whereas ADAM9 knockouts are viable and show no apparent abnormalities. While overexpression of α-secretase, i.e. ADAM10, itself is not harmful, it restores basic neural function in a transgenic model of AD. Thus in an extensive study Postina et al. (2004) showed that enhanced α-secretase expression prevents the development of plaques in old animals overexpressing hAPP. In contrast, overexpression of a largely inactive ADAM10 on an APP background exacerbates amyloid deposition. The authors also tested these animals in the water navigation task and observed deficits in the acquisition phase of place learning and in the probe trial, whereas the double transgenics—both overexpressing ADAM10 and hAPP—performed as well as control animals. Long term potentiation (LTP) was also improved in the double transgenics as opposed to single APP transgenics, suggesting a fundamental rescue of synaptic function via the increased activity of α-secretase. Their results on the neuroprotective role of α-secretase are in line with previous findings from Moechars et al. (1996) on a double transgenic overexpressing hAPP with a disturbed α-secretase cleavage site. The resulting APP/RK mice had increased APP expression in their brains with a shift toward β-site cleavage amyloid peptides and had shorter life spans than control animals (Moechars et al., 1999). APP/RK mice also showed neuroanatomical abnormalities in the amygdala, cortex, and hippocampus and were observed to be more aggressive and hyperactive.

Tau

In addition to these 'Aβ transgenics', various transgenic mouse models have been developed that overexpress human wild-type tau and/or mutated forms of human tau known to be associated with frontotemporal dementia and parkinsonism (abbreviated FDTP.[1] In humans, tau proteins are encoded by a single gene on chromosome 17. Alternative splicing of the mRNA generates six different brains isoforms, which can be divided in two classes: proteins that contain three C-terminal imperfect repeat domains (3R) and proteins that contain 4 repeats (4R). Most transgenic models overexpress the mutated 4R tau form in one way or another, varying from 'normal' 4R tau to one mutated form (P301L, P301S, V337M) to multiple mutations. Although numerous tau pathologies have been found in the brains of these transgenics (for reviews see Brandt et al., 2005; Lee et al., 2000), few studies have exposed these mice to extensive behavioral testing.

Interestingly, Tanemura et al. (2002) found 11-mo-old transgenics overexpressing the V337 mutant gene to be less anxious than control littermates on the elevated-plus maze, whereas no difference was observed in the water-navigation task. This result suggests the presence of a very specific (non-spatial) cognitive deficit in which Tg mice may not be able to discriminate fearful conditions from fearless ones. Supporting this interpretation, the transgenics showed little habituation to the elevated plus maze and open field, whereas control animals showed clear habituation patterns. Further studies on neurodegeneration in the hippocampus of these transgenics—irregular shaping o 30% to 70% of the neurons, as well as diminishec neural responses recorded from hippocampa slices—might shed some light on the differentia functional (spatial vs. non-spatial) implications.

The same laboratory also tested the behavic of mice overexpressing another mutated 4R ta gene, R406W, which in humans causes a tauc pathy that clinically resembles AD. Within 48

[1]see again http://www.molgen.ua.ac.be/AD Mutations for mc information

after conditioning, the transgenics showed reduced levels of fear response during the cued but not the contextual testing in comparison with control littermates at an age of 16–23 months. Fifteen days after conditioning, the animals also showed lower levels of fear response during the contextual testing, suggesting that memory loss may be more pronounced in longer retention delays in aged transgenics. Taken together, the results of that study suggest the presence of associative memory impairments in mice overexpressing the mutated tau gene. This effect seems to be rather specific as transgenics either did not differ or differed only slightly from controls with regard to other behavioral and sensorimotor tests. Neuroanatomically, transgenics are characterized by congophilic tau inclusions, predominantly in the hippocampus, amygdala, and neocortex, areas that are well established to be involved in memory formation (Tatebayashi et al., 2002).

Triple Transgenics

To study the interaction between Aβ and tau, Oddo et al. (2003) went one step further and developed a triple-transgenic using a novel strategy in which two transgenes, Tg2576 and tauP301L, were microinjected into single-cell embryos obtained from homozygous PS1-knockin mice. Triple-transgenic (3xTg) mice develop age-related and progressive neuropathologies, including plagues and tangles. The pattern of progression—Aβ first in cortical regions, then later in hippocampus and amygdala; tau the other way around—closely mimics that observed in AD. One of the main findings in their study is that presynaptic dysfunction, including LTP deficits, precede the accumulation of extracellular Aβ deposits, which, in turn, precede tau alterations, the latter sequence of events being in line with the amyloid cascade hypothesis. Moreover, the results of this study suggest an important role for intracellular Aβ, in the absence of structural changes, in cognitive decline in AD. Recently, 3xTg mice have also been studied for their cognitive behavior at different time points (Billings et al., 2005). The earliest cognitive impairment manifests at 4 months as a deficit in long-term retention and correlates with the accumulation of intraneuronal Aβ in the hippocampus and amygdala. No plaques or tangles are apparent at this age, suggesting that they contribute to cognitive dysfunction at later time points. Clearance of the intraneuronal Aβ pathology by immunotherapy rescues the early cognitive deficits on a hippocampal-dependent task, whereas reemergence of the Aβ pathology again leads to cognitive deficits. Triple-transgenic mice are now being investigated at various, different levels and are likely to provide more insight on the exact sequence of pathological events leading to Alzheimer (LaFerla & Oddo, 2005).

CONCLUSIONS

The use of genetic mouse models has certainly been effective in research on the pathogenesis of AD and has led to important insights into the underlying pathological processes. In comparison to 10 years ago, genetic mouse models have evolved both in a qualitative and in a quantitative way and seem to mimic AD neuropathology better than the first genetically altered models. For instance, the generation of the 3xTg-AD mice is a step forward in animal modeling because such transgenics develop both plaques and tangles in the same order as AD patients do. The 3xTg-AD model strongly implicates intraneuronal Aβ in the onset of cognitive dysfunction, which might facilitate therapeutic evaluations.

Another interesting line of research is the inclusion of environmental factors in a genetic design, which allows for the detection of gene-environment interactions. In this respect, recent studies by Lazarov et al. (2005) and Jankowski et

al. (2003) are worth mentioning. Both groups subjected double transgenics co-expressing APPswe and PS1 polypeptide variants, to an enriched environment for longer periods and examined the brains afterward. Although the results were not in agreement for various reasons (see Lazarov et al. (2005) for discussion), clearly environmental factors can affect amyloid deposition in a genetic-dependent way. The identification of such factors would certainly be valuable in the treatment (or prevention) of Alzheimer's disease.

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