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APP transgenic modeling of Alzheimer's disease: mechanisms of neurodegeneration and aberrant neurogenesis

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Abstract Neurodegenerative disorders of the aging population affect over 5 million people in the US and Europe alone. The common feature is the progressive accumulation of misfolded proteins with the formation of toxic oligomers. Alzheimer's disease (AD) is characterized by cognitive impairment, progressive degeneration of neuronal populations in the neocortex and limbic system, and formation of amyloid plaques and neurofibrillary tangles. Amyloid- β ($A\beta$) is the product of proteolysis of amyloid precursor protein (APP) by β and γ -secretase enzymes. The neurodegenerative process in AD initiates with axonal and synaptic damage and is associated with progressive accumulation of toxic $A\beta$ oligomers in the intracellular and extracellular space. In addition, neurodegeneration in AD is associated with alterations in neurogenesis. $A\beta$ accumulation is the consequence of an altered balance between protein synthesis, aggregation rate, and clearance. Identification of genetic mutations in APP associated with familial forms of AD and gene polymorphisms associated with the more common sporadic variants of AD has led to the development of transgenic (tg) and knock out rodents as well as viral vector driven models of AD. While APP tg murine models with mutations in the N- and C-terminal flanking regions of $A\beta$ are characterized by increased $A\beta$ production with plaque formation, mutations in the mid-segment of $A\beta$ result in increased formation of oligomers, and mutations toward the C-terminus (E22Q)

segment results in amyloid angiopathy. Similar to AD, in APP tg models bearing familial mutations, formation of $A\beta$ oligomers results in defective plasticity in the perforant pathway, selective neuronal degeneration, and alterations in neurogenesis. Promising results have been obtained utilizing APP tg models of AD to develop therapies including the use of β - and γ -secretase inhibitors, immunization, and stimulating neurogenesis.

Keywords Transgenic · Neurodegenerative disease · Aging · Alzheimer · APP · Synapse loss · Neurogenesis

Introduction

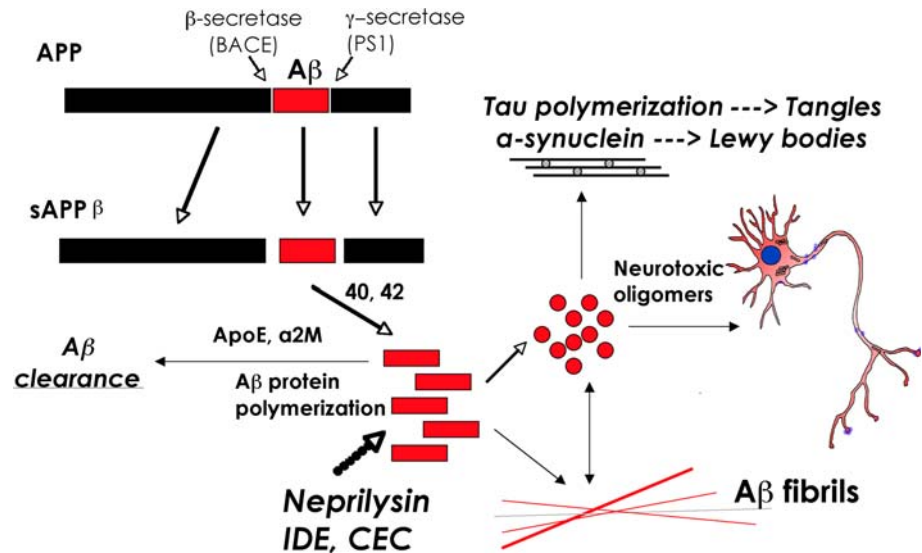
Alzheimer's disease (AD) is the most common neurodegenerative disorder in the aging population. It is characterized by the progressive and irreversible deafferentation of the limbic system, association neocortex, and basal forebrain (Perry et al. 1977; Hyman et al. 1984; Wilcock et al. 1988; Hof et al. 1990; Palmer and Gershon 1990; Masliah et al. 1993), accompanied by the formation of neuritic amyloid plaques, amyloid angiopathy, neurofibrillary tangles (NFTs), and neuropil threads (Terry et al. 1994). This neurodegenerative process is followed by reactive astrogliosis (Dickson et al. 1988) and microglial cell proliferation (Rogers et al. 1988; Masliah et al. 1991).

Loss of synapses (DeKosky and Scheff 1990; Masliah 2001; Scheff and Price 2001) and axonal pathology (Raff et al. 2002) are probably key neuropathological features leading to dementia in these neurodegenerative disorders. In addition, recent evidence suggests that alterations in the niches for neurogenesis in the adult brain might also contribute to the neurodegenerative process (Haughey et al. 2002; Tatebayashi et al. 2003; Dong et al. 2004;

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Fig. 1 Schematic diagram of APP processing and accumulation of toxic $A\beta$ species. β - and γ -secretase cleavage of APP results in the production of $A\beta_{1-40}$ and $A\beta_{1-42}$, which accumulates into neurotoxic oligomers



Jin et al. 2004; Wen et al. 2004; Chevallier et al. 2005; Donovan et al. 2006). The unique patterns of cognitive impairment that characterize AD, in turn, depend on the neural circuitry specifically affected (Hof and Morrison 1994), the extent of the synapto-dendritic damage, and the speed with which the injury propagates (Terry et al. 1991; DeKosky et al. 1996). Recent evidence supports the contention that neuronal cell death might occur later in the progression of neurodegeneration and that damage to the synapto-dendritic apparatus might be one of the earliest pathological alterations (Masliah and Terry 1993, 1994; Masliah 1998, 2001; Honer 2003; Scheff and Price 2003). This is accompanied by the abnormal accumulation of neuronal proteins in the extracellular space (e.g., plaques, cerebral amyloid angiopathy [CAA]) or in intracellular compartments (e.g., tangles and Lewy bodies [LBs]). Abnormal accumulation and misfolding (toxic conversion) of these synaptic and cytoskeletal proteins are being explored as key pathogenic events leading to neurodegeneration (Koo et al. 1999; Ramassamy et al. 1999; Ferrigno and Silver 2000).

In AD, amyloid- β peptide 1–42 ($A\beta_{1-42}$), a proteolytic product of amyloid precursor protein (APP) metabolism (Fig. 1), accumulates in the neuronal endoplasmic reticulum (ER) (Cuello 2005) and extracellularly (Selkoe et al. 1996; Trojanowski and Lee 2000; Walsh et al. 2000). The primary pathogenic event triggering synaptic loss and selective neuronal cell death in these disorders is not yet completely clear (Masliah 2000, 2001), however, recent studies suggest that nerve damage might result from the conversion of normally non-toxic monomers to toxic oligomers (Volles et al. 2001; Volles and Lansbury 2002; Walsh and Selkoe 2004) (Fig. 2), whereas larger polymers and fibers that often constitute the plaques might not be as toxic (Lansbury 1999; Walsh et al. 2002). An example of a

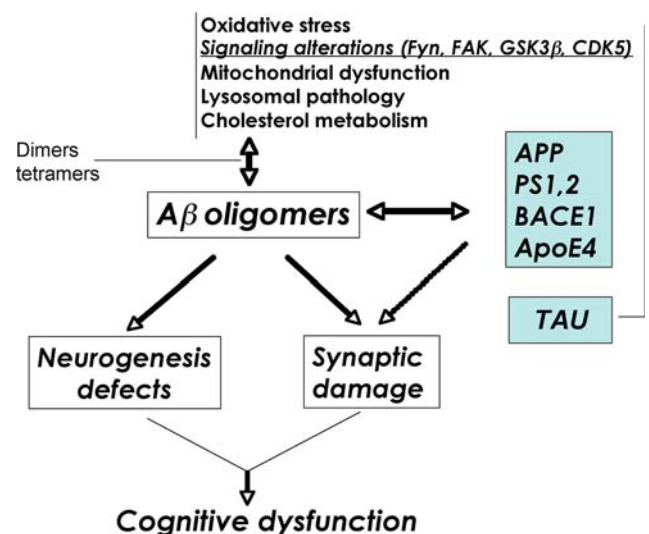


Fig. 2 Schematic diagram of factors contributing to $A\beta$ oligomerization. Defective cellular processes can lead to the accumulation of $A\beta$ dimers, trimers, and oligomers, which in turn contribute to neurogenesis defects and synaptic damage

naturally occurring oligomer species is $A\beta^{*56}$, which has been shown to promote age-dependent memory deficits (Lesne et al. 2006). $A\beta^{*56}$ and $A\beta$ trimers secreted by cultured cells could share common synaptotoxic properties (Selkoe 2008). Previous studies have shown that the $A\beta$ dimers, trimers, and higher-order oligomers secreted by cultured neurons inhibit LTP and damage spines (Klein et al. 2001; Walsh and Selkoe 2004; Townsend et al. 2006; Selkoe 2008). Additional studies have shown that $A\beta$ dimers derived from human CSF disrupt synaptic plasticity and inhibit hippocampal LTP in vivo (Klyubin et al. 2008). Together, these studies indicate that $A\beta$ oligomers ranging in size from 2 to 12 subunits might be responsible for the

synaptic damage and memory deficits associated with AD (Lacor et al. 2007).

Thus, when developing transgenic (tg) models of AD it is important to consider the following outcome features: (1) targeting the selective neuronal populations in the neocortex and limbic system involved in learning and memory; (2) favoring production of high levels of $A\beta_{1-42}$ over $A\beta_{1-40}$; (3) promoting accumulation of $A\beta$ oligomers; (4) inducing post-transcriptional modifications (e.g., pyroglutamate $A\beta$); (5) evaluating abnormal accumulation of intracellular $A\beta$; (6) evaluating development of amyloid plaques and CAA; (7) evaluating neurodegeneration with synaptic loss, axonal damage, and defects in neurogenesis; and (8) behavioral and electrophysiological impairments that correspond to the pattern of neurodegeneration.

Experimental modeling of Alzheimer's disease

Although dramatic progress has been made in understanding the pathogenesis of neurodegenerative conditions of the aged population, such as AD, Parkinson's disease (PD), and Lewy body disease (LBD), most of these disorders remain incurable. Because of the near epidemic proportion in the aging population, these disorders pose a serious challenge to the health care system. Identification of new targets and development of biological mouse models holds the promise of better understanding their pathogenesis and discovering and testing new treatments.

Experimental models of AD could mimic individual or multiple alterations found in AD; however, to date not a single model mimics all the alterations observed in AD. The best model is probably the aged monkey (Price et al. 1994), however, because of the time and cost involved in utilizing this model, most studies have been focused on developing murine models. Most of the tg animal models of AD are based on the targeted overexpression of single or multiple mutant molecules associated with familial AD (FAD) (Table 1, Fig. 3). Currently, mutations in three genes have been described, namely APP, presenilin (PS)1, and PS2 (Hutton and Hardy 1997; Cruts and Van Broeckhoven 1998; Rocchi et al. 2003; Bertoli-Avella et al. 2004; Pastor and Goate 2004). Other APP and PS tg models have been developed in rats, drosophila, and *C. elegans*, either using constitutively active or regulatable promoters, or viral vectors. The main focus of this review will be dedicated to murine APP tg models and the corresponding neurodegenerative pathology and alterations in neurogenesis, however, it is important to emphasize that this represents one aspect of the disease; other components, such as NFT pathology will be addressed by others.

Experimental APP transgenic murine models of Alzheimer's disease

In AD, APP mutations as well as mutations in PS1 and 2 and polymorphisms in apolipoprotein E (ApoE) have also been linked with AD (Fig. 2) and as such are important targets. Most efforts toward developing tg models have been focused on overexpression of mutant APP (Table 1) in combination with mutant PS1. A summary of the FAD mutations reproduced in tg mouse models is presented in Fig. 3. Previously developed tg animal models have shown that it is possible to reproduce certain aspects of AD pathology over a shorter period of time (Masliah et al. 1996; Games et al. 1997; Price et al. 2000). In this model, the platelet-derived growth factor (β chain) (PDGF- β) promoter drives an alternatively spliced human APP (hAPP) minigene (PDAPP) encoding mutated (Indiana, V717F) hAPP695, 751, and 770 (Games et al. 1995; Rockenstein et al. 1995). This confers a high ratio of mRNA encoding mutated hAPP versus wild-type mouse APP (Rockenstein et al. 1995), which promotes development of typical amyloid plaques, dystrophic neurites, loss of presynaptic terminals, astrogliosis and microgliosis (Games et al. 1995, 1997; Masliah et al. 1996).

Other models have expressed mutant hAPP under the regulatory control of either the human or murine (m)Thy1 promoter (Andra et al. 1996; Sturchler-Pierrat et al. 1997; Moechars et al. 1999; Bornemann and Staufenbiel 2000) or the prion protein (PrP) promoter (Hsiao et al. 1996; Borchelt et al. 1997). Amyloid deposition begins at 12 months of age; however, co-expression of mutant PS1 accelerates amyloid deposition, beginning at 4 months of age (Borchelt et al. 1996, 1997; Holcomb et al. 1998). Another previously developed model, where hAPP is also expressed under the control of the PrP promoter, displays even earlier onset of amyloid deposition, starting at 3 months and progressing to mature plaques and neuritic pathology from 5 months of age, accompanied by high levels of $A\beta_{1-42}$ (Chishti et al. 2001). While the PrP promoter has provided several models that mimic aspects of FAD, other promoters targeting expression of APP to neurons provide alternative models demonstrating pathology that recapitulate similar and additional aspects of FAD. In this regard, we have generated lines of tg mice expressing hAPP751 cDNA containing the London (Lon, V717I) and Swedish (Swe, K670N/M671L) mutations under the regulatory control of the mThy1 gene (mThy1-hAPP751) (Rockenstein et al. 2001; Fig. 4). While expression of mutant hAPP under the PDGF- β promoter results in the production of diffuse (and some mature) plaques (Games et al. 1995; Mucke et al. 2000), tg expression of mutant hAPP under the mThy1 (Andra et al. 1996) and PrP (Hsiao et al. 1996; Borchelt et al. 1997)

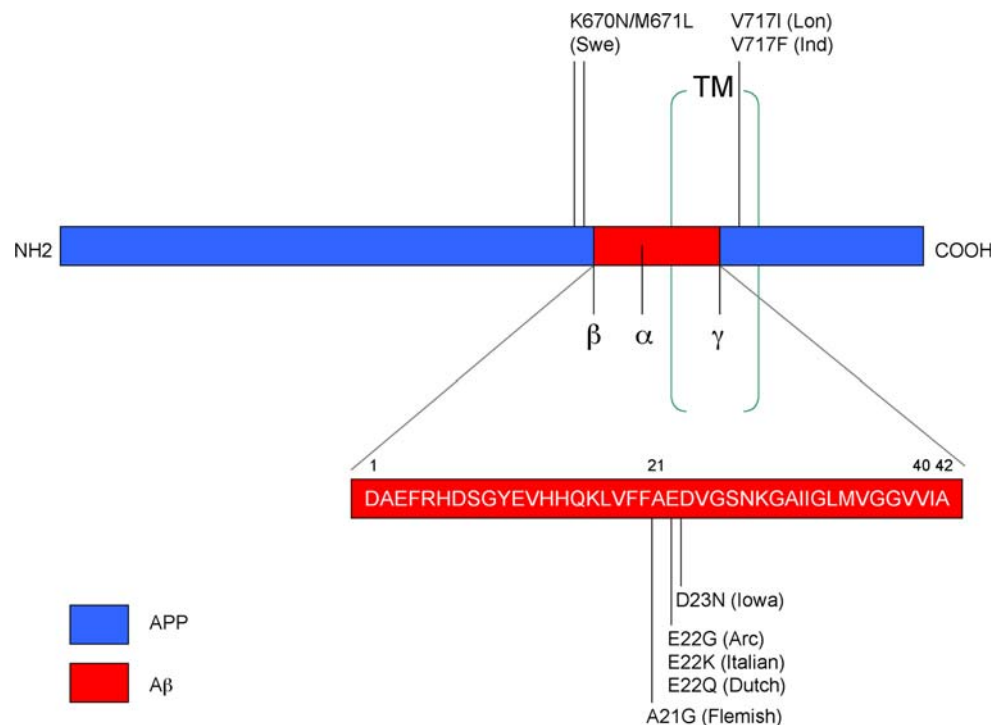
Table 1 Representative animal models of AD pathology

Model	Gene/Mutation	Species	Strategy	Promoter	Phenotype	References
PDAPP tg	hAPP695, 751, 770 V717F (Ind)	Mouse	Overexpression	PDGF- β	Increased expression of APP, accumulation of diffuse amyloid plaques, synaptic damage, and astro/microgliosis	Games et al. (1995), Rockenstein et al. (1995), Mucke et al. (2000)
Thy1-APP751 Swe/Ind tg	hAPP751 K670N/M671 (Swe) + V717F (Ind)	Mouse	Overexpression	Thy1	Amyloid deposition (6 mos), gliosis and tau hyperphosphorylation	Andra et al. (1996), Sturchler-Pierrat et al. (1997)
Thy1-APP695 Swe/Lon tg	hAPP695 K670N/M671 (Swe) + V717I (Lon)	Mouse	Overexpression	Thy1	Amyloid deposition (12 mos), high levels of A β _{1–42} accumulation	Moechars et al. (1999)
Thy1-APP751 Swe/Lon tg	hAPP751 K670N/M671 (Swe) + V717I (Lon)	Mouse	Overexpression	Thy1	Amyloid deposition (3 mos) and mature plaque formation in hippocampus and neocortex	Rockenstein et al. (2001)
Tg2576	hAPP695 K670N/M671 (Swe)	Mouse	Overexpression	PrP	Amyloid deposition (9–12 mos), some vascular A β deposition	Hsiao et al. (1996), Borchelt et al. (1997)
Tg2576/PS1 mut	hAPP695 K670N/M671 (Swe) PS1 M146L	Mouse	Overexpression	PrP-hAPP PDGF β -PS1	Early (4 mos) amyloid deposition, elevation of A β 42(43) levels	Borchelt et al. (1997), Holcomb et al. (1998)
TgCRND8	hAPP695 K670N/M671 (Swe) + V717F (Ind)	Mouse	Overexpression	PrP	Early (3–5 mos) amyloid deposition, high levels of A β _{1–42} accumulation	Chishtii et al. (2001)
3xTg-AD	hAPP695 K670N/M671 (Swe) hTau4R0N P301L PS1 M146V	Mouse	Overexpression of hAPP, hTau Knockin PS1	Thy1	Amyloid deposition (9 mos), some intraneuronal A β accumulation, tangle-like pathology in the hippocampus, behavioral deficits	Oddo et al. (2003a, b)
Rat PDGF β -APP751 tg	hAPP751 K670N/M671 (Swe) + V717F (Ind) PS1 M146L	Rat	Overexpression	PDGF- β	Intracellular amyloid accumulation, CREB activation and tau pathology	Echeverria et al. (2004a, b)
Rat UbC-APP _{swe} tg	hAPP695 K670N/M671 (Swe)	Rat	Overexpression	UbC	Extracellular amyloid deposition at 15–18 mos, some cerebrovascular A β accumulation	Folkesson et al. (2007)

Table 1 continued

Model	Gene/Mutation	Species	Strategy	Promoter	Phenotype	References
Rat UbC-APP ^{Swe} /Ind tg	hAPP695 K670N/M671 (Swe) + V717F (Ind)	Rat	Overexpression	UbC	High levels of APP expression, A β detected in serum	Agca et al. (2008)
Rat Synapsin-APP/PS1 tg	hAPP695 K670N/M671 (Swe) PS1 M146V A β 3Q-42	Rat	Overexpression	Synapsin 1	Amyloid deposition at 7 mos in double tg	Flood et al. (2009)
TBA2 tg	Chimeric mo/hAPP695 K670N/M671 (Swe) + V717F (Ind)	Mouse	Overexpression of pyroglutamate A β	Thy1	Accumulation of intraneuronal pyroglutamate A β , extensive neuronal loss, no tangles or hippocampal degeneration	Wirhbs et al. (2009)
Tet-APP tg	Humanized A β in mo APP K670N/M671 (Swe)	Mouse	Regulatable overexpression	tetO	Abundant plaques remain after abolition of APP expression	Jankowsky et al. (2005)
APP ^{Swe} KI		Mouse	Knockin	Endogenous	Ninefold greater A β levels than in normal human brain, spatial and temporal expression patterns of human A β are reproduced	Reaume et al. (1996)
Arctic mut A β tg	hAPP K670N/M671 (Swe) + V717F (Ind) +A β E22G (Arc)	Mouse	Overexpression of hAPP, generation of mut A β	PDGF- β	Accumulation of oligomeric and fibrillar mut A β , extensive plaque formation	Cheng et al. (2004)
APP Dutch tg	hAPP751 A β E22Q (Dutch)	Mouse	Overexpression of hAPP, generation of mut A β	Thy1	Model of CAA; accumulation of primarily cerebrovascular amyloid, little parenchymal amyloid	Herzig et al. (2004)

Fig. 3 Diagram showing common mutations in the APP gene that are utilized in the generation of animal models of AD. Mutations in the N- and C-terminal domains of APP result in the accumulation of intracellular and/or extracellular A β species, while mutations in the A β region lead to the development of amyloid angiopathy. *Swe* Swedish mutation, *Lon* London mutation, *Ind* Indiana mutation, *Arc* Arctic mutation, *TM* transmembrane domain



promoters favors the formation of mature plaques in the hippocampus and neocortex. This suggests that the differential patterns of A β deposition might be dependent on the specific neuronal populations selected by the promoter, levels of expression and topographical distribution of the transgene, and levels of A β_{1-40} and A β_{1-42} . Consistent with this, in FAD and Down syndrome, production of high levels of A β_{1-42} results in early plaque formation (Citron et al. 1997). This suggests that early age of onset and plaque formation depends on high levels of A β_{1-42} production (Rockenstein et al. 2001). Finally, of considerable interest and wide attention is the triple tg mouse model developed by LaFerla et al. (2007) (3xTg-AD) that involves overexpression of mutant APP (Swe) and Tau (P301L) under the Thy1.2 promoter in homozygous mutant PS1 (M146V) knockin mice. These mice develop neurological deficits, amyloid deposition, and tangle-like pathology in the hippocampus (Oddo et al. 2003a, b).

Models with accumulation of intracellular A β have also been developed. Among the most interesting ones is a rat tg model that expresses Swe/Ind mutant hAPP751 (K670N/M671L, V717F) alone or with mutant PS1 (M146L) under the control of the PDGF- β promoter (Echeverria et al. 2004a, b). These animals are characterized by extensive intracellular amyloid accumulation, CREB activation, and tau pathology (Echeverria et al. 2004a, b). Other APP tg rat models express mutant hAPP695 (K670N/M671L) under the control of the ubiquitin-C (UbC) promoter, which shows a similar ubiquitous expression pattern as the human APP promoter (Folkesson et al. 2007); (Agca et al. 2008).

These animals have been shown to develop extracellular amyloid deposits at 15–18 months. A third rat line carrying both mutant APP (K670N/M671L) and a human PS1 transgene with the FAD M146V mutation under the control of the rat synapsin 1 promoter develops plaques at 7 months of age (Flood et al. 2009). While these models show promising results recapitulating the intracellular accumulation of A β that is observed in AD patients, more detailed neuropathological examination is necessary to fully characterize these models. Interestingly, the 3xTg-AD model described earlier has also been shown to accumulate intraneuronal A β , and more recent studies have focused on this as a mouse model of intracellular A β deposition. In these animals, accumulation of intraneuronal A β leads to progressive degeneration and death of neurons in the brains of tg mice (LaFerla et al. 2007).

Remarkably, post-transcriptionally modified A β also accumulates in substantial quantities intraneuronally (Fig. 5). In particular, pyroglutamate A β_{3-42} triggers a lethal phenotype with neurodegeneration in a mouse model that expresses A β_{3-42} peptides under the control of the Thy1 promoter (TBA2 tg) (Wirhth et al. 2009). This model expresses A β with N-terminal glutamine (A β_{3Q-42}) as a fusion protein with the murine thyrotropin-releasing hormone (mTRH), for transport via the secretory pathway (Cynis et al. 2006). The levels of converted A β (3(pE)-42) in TBA2 mice are comparable to the APP/PS1 knockin mouse model (Casas et al. 2004), with extensive neuron loss and associated behavioral deficits (Wirhth et al. 2009). Eight weeks after birth, TBA2 mice develop neurological

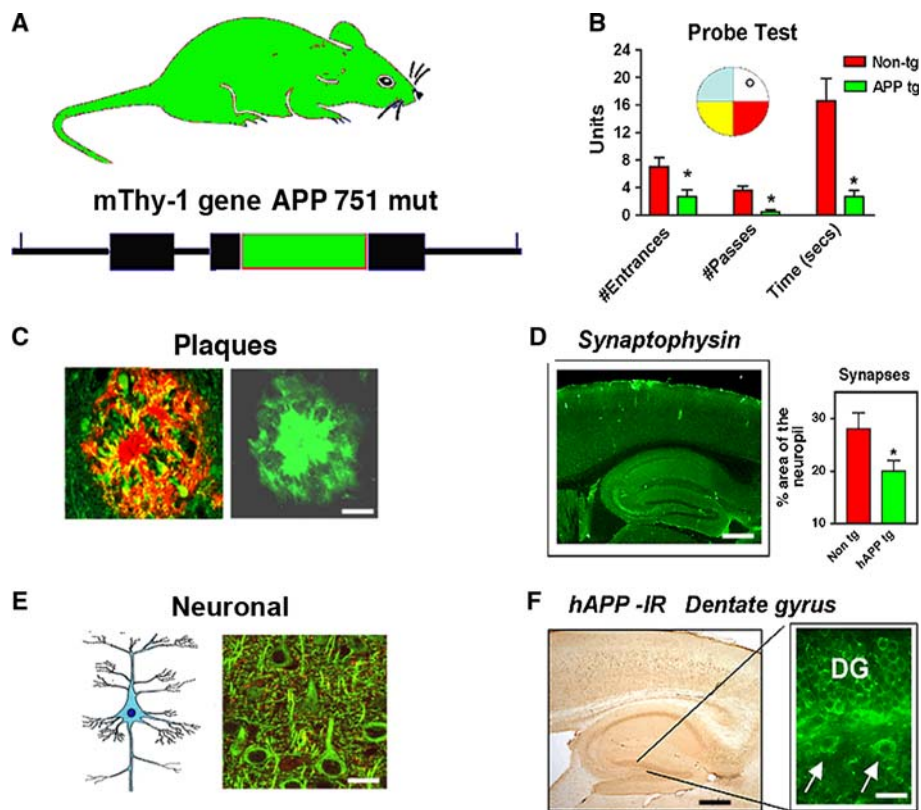


Fig. 4 Characterization of cognitive and neuropathological alterations in the brains of mThy1-hAPP tg mice. **a** Structure of mutant hAPP transgene under the control of the mThy-1 promoter. **b** Memory portion of the water maze behavioral test where the platform was removed (Probe test) to evaluate the number of entrances into the target quadrant where the platform was previously located (# Entrances), the number of times the animal passed over the location, where the platform was (# Passes), and time spent (Time) swimming in the target quadrant where the platform was previously located. APP tg mice exhibited reduced performance compared to

non-tg controls in all three measures of memory retention in this behavioral test. **c** $A\beta$ -immunoreactive deposits in the cortex of an APP tg mouse. *Scale bar* 50 μ m. **d** Reduced synaptophysin immunoreactivity in the brain of an APP tg mouse. *Scale bar* 0.2 mm. **e** Degeneration of the MAP2-immunoreactive dendritic arbor in the cortex of an APP tg mouse. *Scale bar* 10 μ m. **f** hAPP immunoreactivity in the dentate gyrus (DG) of an APP tg mouse. *Scale bar* 1 mm (left panel), 20 μ m (right panel). * $p < 0.05$ compared to non-tg controls by Student's *t*-test ($n = 4$ mice per group)

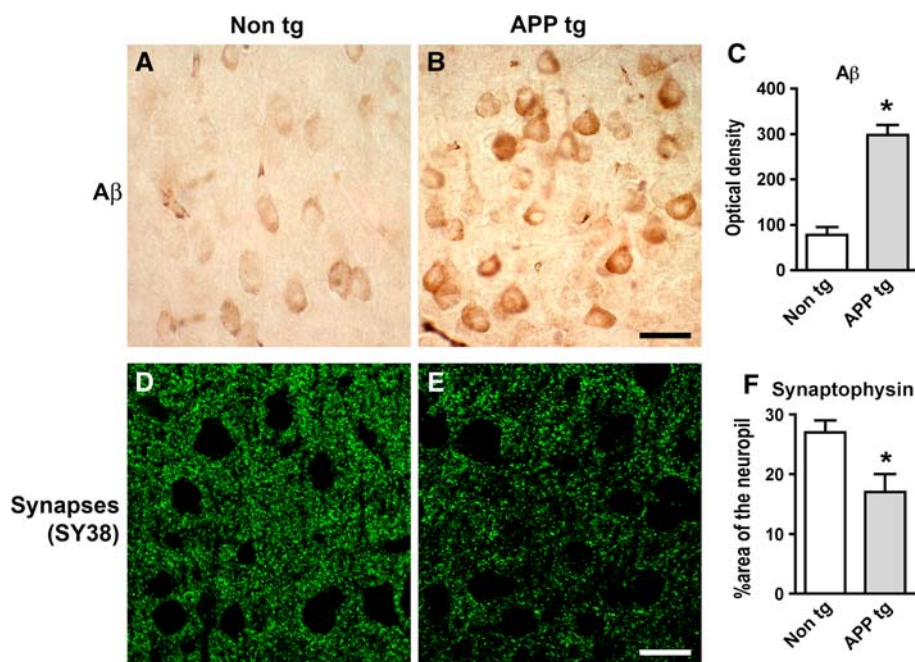
impairments together with abundant loss of Purkinje cells (Wirhth et al. 2009). Although the TBA2 model lacks important AD-typical neuropathological features like tangles and hippocampal degeneration, it clearly demonstrates that intraneuronal $A\beta$ (3(pE)-42) is neurotoxic in vivo (Wirhth et al. 2009).

To further understand the mechanisms involved in $A\beta$ deposition and clearance, a unique model of neuronal APP expression has been developed that expresses mutant (Swe/Ind) hAPP695 under the control of a tetracycline-sensitive promoter (Jankowsky et al. 2005). This approach allows the instantaneous abolition (95%) of hAPP expression upon treatment with doxycycline. Animals were treated with antibiotic after plaques were already formed and in this model, very little new hAPP—and subsequently, $A\beta$ —is produced after antibiotic treatment, so the natural rate of $A\beta$ clearance can be assessed. Notably, even after 12 months of suppression of APP production, amyloid

deposits in the brains of treated mice remained abundant (Jankowsky et al. 2005). This indicates that, once formed, amyloid plaques are highly resistant to dissolution in the brain, and further suggests that therapeutic approaches based solely on reducing amyloid production may not be effective, and may need to be combined with clearance-based treatments.

While most animal models of AD involve ectopic expression or overexpression of FAD-related genes, some pathological features of AD have been recapitulated in mutant and knockin animals in which FAD-causing mutations are targeted into their endogenous genes. One advantage to gene-targeted and knockin models is that developmental and tissue-specific expression patterns of human $A\beta$ are relatively preserved because the gene encoding the mutant precursor protein remains in its normal chromosomal location. One of the first models to express mutant APP in its endogenous location in the

Fig. 5 Increased intracellular pyroglutamate- $A\beta$ immunoreactivity and synaptic deterioration in mThy1-hAPP tg mice. **a–c** Sections from the brains of non-tg and APP tg mice were immunolabeled with an antibody against pyroglutamate $A\beta_{3-42}$ and developed with DAB. Increased intraneuronal immunoreactivity was detected in the cortex of APP tg mice compared to non-tg controls. *Scale bar* 20 μ m. **d–f** Reduced synaptophysin (SY38) immunoreactivity in the neuropil of APP tg mice compared to non-tg controls. *Scale bar* 20 μ m. * $p < 0.05$ compared to non-tg controls by Student's *t*-test ($n = 4$ mice per group)



mouse genome used site-specific mutagenesis to transform murine APP into “humanized” APP bearing the Swe mutation (K670N/M671L) (Reaume et al. 1996). In this model, amyloidogenic processing was somewhat enhanced and measurable increases in $A\beta$ production were detected (Siman et al. 2000), however, the effects were not as robust as in APP tg models. Interestingly, in the gene-targeted mutant APP animals, the pathological process is markedly enhanced upon introduction of a PS1 P264L knockin mutation in these mutant APP animals, characterized by a large increase in $A\beta_{1-42}$ levels and an acceleration of age-dependent onset of amyloid pathology (Siman et al. 2000).

It is still controversial which $A\beta$ species is responsible for the neurodegenerative process in AD. While most recent studies support a role for small oligomers (dimers, trimers, up to dodecamers) (Walsh and Selkoe 2004; Glabe 2005; Glabe and Kaye 2006), others emphasize an important role for the accumulation of intracellular $A\beta$ and for post-transcriptional modifications, such as pyroglutamate changes (Cynis et al. 2008; Schilling et al. 2008). Models reproducing the formation of $A\beta$ oligomers include those expressing APP bearing the Arctic mutation (E22G) under the control of the PDGF- β promoter (Cheng et al. 2004). This mutation is highly fibrillogenic in vivo, and these mice rapidly develop extensive plaque formation (Cheng et al. 2004). Mutations that increase oligomers and protofibril formation include the E22G (Arctic), E22K (Italian), E22Q (Dutch), and the D23N (Iowa) amino acid substitutions (Demeester et al. 2001; Lashuel et al. 2003; Betts et al. 2008; Fig. 3). Interestingly, all of these mutations are located within the $A\beta$ -containing sequence of APP, and in addition to the apparent oligomer-promoting

effect of these mutations, it has been proposed that the pathogenic effect may also be related to a resistance in proteolysis of $A\beta$ (Tsubuki et al. 2003). In support of this possibility, another familial APP mutation, A21G (Flemish), exhibits a significantly reduced rate of proteolysis by the $A\beta$ -degrading enzyme Neprilysin (Betts et al. 2008).

Most emphasis has been placed on the amyloid deposition in the intracellular compartment and in the plaques. However, patients with AD also develop amyloid deposition around blood vessels, a process that ultimately leads to a condition known as cerebral amyloid angiopathy (CAA). This can cause vascular fragility and hemorrhages (reviewed in Pezzini et al. (2009)), and it is important to note that therapeutic anti- $A\beta$ vaccination strategies may increase susceptibility to developing CAA (Boche et al. 2008). Patients who have hereditary cerebral hemorrhage with amyloidosis-Dutch type (HCHWA-D) generate both wild-type $A\beta$ and E22Q-mutant $A\beta$ ($A\beta$ Dutch) (van Duinen et al. 1987; Levy et al. 1990). The brains of patients with HCHWA-D show CAA with very little parenchymal amyloid deposition (Herzig et al. 2006). To date, there are several mouse models that deposit amyloid in the blood vessels, including some models more widely used to study parenchymal $A\beta$ accumulation, such as the Tg2576 mouse (Hsiao et al. 1996; Frackowiak et al. 2003). The only mouse model that develops significant cerebrovascular amyloid with virtually no parenchymal amyloid is the APPDutch mouse, which overexpresses hAPP751 bearing the E693Q (E22Q in $A\beta$) mutation under the control of the Thy1 promoter (Herzig et al. 2004). More recently, the same group has also developed a new model of CAA by crossing the APPDutch mutant mice with

APP23 mice that express mutant hAPP751 (Swe) under the control of the Thy1 promoter (Herzig et al. 2009). While the classical APP23 mice display extracellular A β plaques, double-tg APP23/APPDutch mice co-deposited A β Dutch (mainly A β Dutch1-40) and wild-type A β at twofold levels in the vasculature, with reduced parenchymal deposition (Herzig et al. 2009). Hemorrhages were also significantly increased in the double-tg mice. These studies suggest that A β Dutch1-40 increases vascular deposits and reduces parenchymal amyloidosis similar to HCHWA-D patients.

For a comprehensive review of these and additional tg models of neurodegenerative disease, please visit the Alzheimer's forum website at: <http://www.alzforum.org/res/com/tra>.

Alterations in APP processing, synaptic plasticity, and neurogenesis in APP tg models

The most significant correlate to the severity of the cognitive impairment in AD is the loss of synapses in the frontal cortex and limbic system (DeKosky and Scheff 1990; Terry et al. 1991; Masliah and Terry 1994; DeKosky et al. 1996; Figs. 2, 4). The pathogenic process in AD involves alterations in synaptic plasticity that include changes in formation of synaptic contacts, changes in spine morphology, and abnormal area of synaptic contact (Scheff and Price 2003). However, other cellular mechanisms necessary to maintain synaptic plasticity might also be affected in AD (Cotman et al. 1993; Masliah 2000; Masliah et al. 2001). Recent studies indicate that neurogenesis in the mature brain plays an important role maintaining synaptic plasticity and memory formation in the hippocampus (van Praag et al. 2002). In the adult nervous system, motor activity and environmental enrichment (EE) have been shown to stimulate neurogenesis in the hippocampal dentate gyrus (DG) (Gage et al. 1998; van Praag et al. 2002). Physiological neurogenesis in the adult brain is regulated by numerous cell extrinsic and intrinsic factors, including local cytokine/chemokine signals and intracellular signal transduction (Johnson et al. 2009). In this context, recent studies have shown that, among other pathways, the Notch (Breunig et al. 2007; Crews et al. 2008), cyclin-dependent kinase-5 (CDK5) (Jessberger et al. 2008; Lagace et al. 2008), and wnt/bone morphogenetic protein (BMP) (Lim et al. 2000; Lie et al. 2005) cascades are involved in regulating adult neurogenesis. Interestingly, studies of human brains (Tatebayashi et al. 2003) and tg animal models have demonstrated significant alterations in the process of adult neurogenesis in the hippocampus in AD (Dong et al. 2004; Jin et al. 2004; Wen et al. 2004; Chevallier et al. 2005; Donovan et al. 2006). The deficient neurogenesis in the subgranular zone

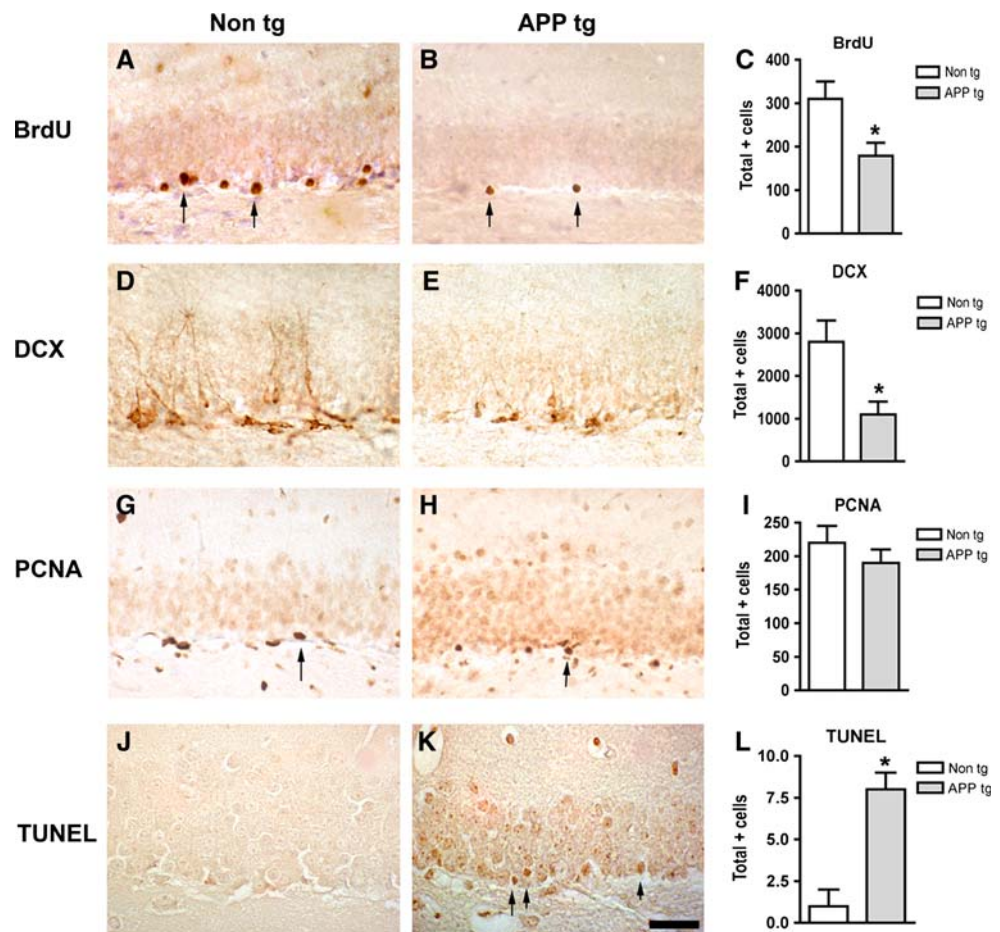
(SGZ) of the DG found in our APP tg mice (Rockenstein et al. 2007; Fig. 6) is consistent with studies of other lines of APP tg mice and other models of AD that have shown decreased markers of neurogenesis, such as bromodeoxyuridine (BrdU)+, and doublecortin (DCX)+ cells, with an increase in the expression of markers of apoptosis (Feng et al. 2001; Haughey et al. 2002; Dong et al. 2004; Wang et al. 2004).

A different study reported increased neurogenesis in the PDAPP model (Jin et al. 2004). Another recent study showed that in 5-month-old APP23 tg mice prior to amyloid deposition, there was no robust difference in neurogenesis relative to wild-type control mice, but 25-month-old amyloid-depositing APP23 mice showed significant increases in neurogenesis compared to controls (Ermini et al. 2008). In contrast, 8-month-old amyloid-depositing APP/PS1 tg mice revealed decreases in neurogenesis compared to controls. Furthermore, 8-month-old nestin-GFP \times APP/PS1 mice exhibited decreases in quiescent nestin-positive astrocyte-like stem cells, while transient amplifying progenitor cells did not change in number (Ermini et al. 2008). Strikingly, both astrocyte-like and transient-amplifying progenitor cells revealed an aberrant morphologic reaction toward congophilic amyloid deposits. A similar reaction toward the amyloid was no longer observed in doublecortin-positive immature neurons (Ermini et al. 2008). These results provide evidence for a disruption to neuronal progenitor cells (NPCs) in an amyloidogenic environment and support findings that neurogenesis is differentially affected among various tg mouse models of AD, probably due to variations in promoter cell type specificity, expression levels, and other factors. A more comprehensive analysis of neurogenesis in APP tg mice showed that while in the molecular layer (ML) of the DG there is an increased number of NPC, in the SGZ markers of neurogenesis are decreased, indicating that in PDAPP animals there is altered migration and increased apoptosis of NPC that contributes to the deficits in neurogenesis (Donovan et al. 2006).

The molecular mechanisms of aberrant neurogenesis in AD are unclear, however, several signaling pathways that control physiological adult neurogenesis are known to be dysregulated in AD. For example, CDK5 is hyperactivated in AD by A β peptide-mediated calcium influx (Lee et al. 2000). In mature neurons, this contributes to neurodegeneration by promoting aberrant phosphorylation of downstream targets of CDK5 such as tau (Ahlijanian et al. 2000), however, the direct effects on NPCs are unknown. It is possible that kinases, such as CDK5 that are disturbed in mature neurons in AD may also play a role in the mechanisms of disrupted neurogenesis in the adult AD brain.

While a considerable body of work is currently emerging on neurogenic alterations associated with the pathogenesis

Fig. 6 Reduced markers of neurogenesis and increased apoptosis in the hippocampus of APP tg mice. **a–c** Reduced BrdU immunoreactivity in the hippocampal dentate gyrus of APP tg mice treated with BrdU compared to non-tg controls treated with BrdU. **d–e** Reduced doublecortin (DCX) immunoreactivity in the hippocampal dentate gyrus of APP tg mice compared to non-tg controls. **g–i** Reduced proliferating cell nuclear antigen (PCNA) immunoreactivity in the hippocampal dentate gyrus of APP tg mice compared to non-tg controls. **j–l** Increased TUNEL-positive cells in the hippocampal dentate gyrus of APP tg mice compared to non-tg controls. *Scale bar* 50 μ m for all panels. * $p < 0.05$ compared to non-tg controls by Student's *t*-test ($n = 4$ mice per group)



of AD, it is important to keep the role of neurogenesis in perspective given the relatively limited number of brain regions that are neurogenic. It is an exciting prospect that new neurons from progenitor cells in the hippocampus could replace cells damaged during the pathogenesis of AD. However, the extent to which progenitor cells might integrate into already-established neural circuitry is unclear, and the problem of re-establishing long inter-regional connections is considerable. Furthermore, taking into account the distribution of AD pathology among various non-neurogenic brain regions, such as the entorhinal cortex and neocortex, it is possible that neurogenesis may not be an ideal target for repairing global neuronal damage in the brain. However, given the critical role of the hippocampus in the processes of learning and memory, and the recent studies showing that neurogenesis plays an important part in these functions (van Praag et al. 2002), it is possible that modulation of neurogenesis in this area might have therapeutic potential. Moreover, it is important to consider the interconnected circuitry that characterizes the brain's architecture. Although AD pathology in the hippocampus primarily affects the non-neurogenic pyramidal cell layers, the granular cells extend processes into the pyramidal layers, and additionally affect the connectivity of the

entorhinal cortex via the perforant pathway. Taken together, much further work will be necessary to fully understand the role of neurogenesis in the pathogenesis of AD and the therapeutic potential of harnessing the regenerative capacity of progenitor cells.

Alterations in synaptic plasticity in AD might involve not only direct damage to the synapses but also interference with adult neurogenesis (Fig. 2). The mechanisms of synaptic pathology in AD are the subject of intense investigation. Studies of experimental models of AD and in human brain support the notion that aggregation of $A\beta$, resulting in the formation of toxic oligomers rather than fibrils, might be ultimately responsible for the synaptic damage that leads to cognitive dysfunction in patients with AD (Walsh and Selkoe 2004; Glabe 2005; Glabe and Kaye 2006; Fig. 1). Supporting this notion, it has been shown that $A\beta$ oligomers reduce synaptic transmission and dendritic spine movement (Lacor et al. 2004; Moolman et al. 2004; Walsh and Selkoe 2004), and interfere with axoplasmic flow and activate signaling pathways that might lead to synaptic dysfunction, tau hyperphosphorylation, and cell death. Moreover, a dodecameric $A\beta$ complex denominated *56 has been recently characterized (Lesne et al. 2006) in brains from APP tg mice and shown

to contribute to the behavioral alterations in these animals. The differential effects of this and other toxic oligomeric species of $A\beta$ in mature and developing neurons and synapses awaits further investigation.

The accumulation of $A\beta$ in the CNS and the formation of toxic oligomers most likely depend on the rate of $A\beta$ aggregation, synthesis, and clearance (Fig. 7). Although most effort has been concentrated at elucidating the mechanisms of $A\beta$ production and aggregation (Luo et al. 1999; Sinha et al. 1999; Vassar et al. 1999; Selkoe 2000; Cai et al. 2001), less is known about the mechanisms of $A\beta$ clearance. As previously discussed in the section on tg models, the conditional APP tg model showed that enhancing clearance of $A\beta$ may actually be more critical than preventing its production when considering potential therapies. This is also important because while most familial forms of AD might result from mutations that affect the rate of $A\beta$ synthesis and aggregation, sporadic AD might be the result of alterations in $A\beta$ clearance (Fig. 7). Pathways involved in $A\beta$ clearance include LDLR-related protein (LRP) ligands, such as apolipoprotein E (ApoE) (Holtzman et al. 1995, 1999), lysosomal degradation (Nixon et al. 1992, 2005) and cleavage by proteolytic enzymes, such as Neprilysin, insulin-degrading enzyme (IDE), endothelin-converting enzyme (ECE), angiotensin converting enzyme (ACE), and matrix metalloproteinase-9 (MMP9) (Iwata et al. 2000, 2001; Selkoe 2001; Carson and Turner 2002; Leissring et al. 2003; Marr et al. 2004; Eckman and Eckman 2005; Saito et al. 2005; Fig. 7).

Functional correlations to the structural pathology in APP tg mice

The relationship among the patterns of $A\beta$ production, amyloid deposition, neurodegeneration, and behavioral deficits in the tg models of AD is complex. One important finding common to several of these APP tg models is that there is no obvious neuronal dropout in early stages of pathogenesis (Irizarry et al. 1997a, b). In fact, the earliest

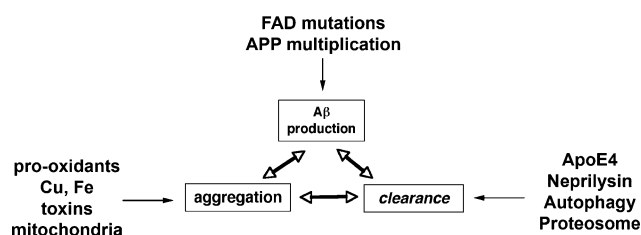


Fig. 7 Schematic diagram showing several factors involved in the regulation of $A\beta$ accumulation into oligomers, including production, aggregation, and clearance

neuronal pathology before amyloid deposition is the loss of synapses and dendrites in the limbic system and neocortex (Hsia et al. 1999; Mucke et al. 2000). This is accompanied by neurophysiological deficits and alterations in long-term potentiation (LTP) and field potential (Chapman et al. 1999; Hsia et al. 1999). Since the synaptic damage in these mice correlates better with the levels of soluble $A\beta_{1-42}$ than with plaques, it has been proposed that neurodegeneration might be associated more with the neurotoxic effects of $A\beta$ oligomers than with fibrillar amyloid (Mucke et al. 2000). In agreement with this possibility, studies of brain slices have shown that $A\beta$ oligomers rather than fibrillar amyloid are toxic to synapses and depress LTP, leading to cognitive impairment (Walsh et al. 2002).

Other recently developed models have also focused on defining the effects of APP and its products on functional markers, including behavioral performance and LTP. These studies have shown that overexpression of the C-terminal APP fragment C100 under the control of neurofilament (NF) promoter results in amyloid-like production and electrophysiological alterations (Nalbantoglu et al. 1997). Although these, as well as the other APP tg animal models, have been shown to be of significant interest, the basic principle for their success rests in the ability to overexpress high levels of mutant APP, which is in a way rather non-physiological event. With the exception of Down syndrome, in sporadic AD there is no evidence for upregulation of APP expression but rather a shift in the ratio between APP770 and 751 to APP695. In this regard, a previous study (van Leeuwen et al. 1998) has shown frame shift mutations in APP and ubiquitin genes are present in some AD patients. It is conceivable that future tg models might utilize this mechanism in an attempt to reflect the more common sporadic forms of the disease.

Conclusions

In summary, a number of known mutations in the APP gene associated with familial forms of amyloid disorders have made it possible to recapitulate several features of amyloid pathology in the brains of tg animal models. While other genes, such as PS1 and tau have been manipulated alone or in combination with APP mutations, a large portion of the current literature describing the AD-like neurodegenerative phenotypes in animal models has been based on animal models expressing high levels of mutant APP. While APP tg murine models with mutations in the N- and C-terminal flanking regions of $A\beta$ are characterized by increased $A\beta$ production with plaque formation, mutations in the mid-segment of $A\beta$ result in increased formation of oligomers, and mutations toward the C-terminus (E22Q) segment results in amyloid angiopathy. Several lines of evidence

suggest that formation of A β oligomers reduces neuroplasticity and contributes to neuronal degeneration and alterations in neurogenesis. Specifically targeting these toxic oligomeric species of A β with β - and γ -secretase inhibitors, immunization, and neurogenesis-stimulating therapies may provide individual or combination treatments that ameliorate multiple features of AD pathology.

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