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Review Article

Experimental Neurobiology

An Update of Animal Models of Alzheimer Disease with a Reevaluation of Plaque Depositions

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Animal models of Alzheimer disease (AD) are used to study the mechanisms underlying AD pathogenesis, genetic interactions with genes of interest, and environmental risk factors that cause sporadic AD as well as to test the therapeutic effects of AD drug-candidates on neuropathology and cognitive function. To attain a comparative view on the AD models developed, representative AD lines were selected and summarized with respect to transgenic constructs and AD-related pathology. In addition, age-dependent plaque deposition data available in the literature for six representative AD models such as Tg2576, PDAPP, TgAPP23, Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD mice were reevaluated using a photographic plaque reference scale method that was introduced recently. Tg2576, PDAPP, and TgAPP23 mice, which carry the amyloid precursor protein (APP) transgene, produced initially slow, but progressively accelerated plaque deposition as they aged, resulting in logistic plaque deposition. In contrast, Tg-APPswe/PS1dE9 and 3xTg-AD mice, which carry both APP and PS1 transgenes, developed abruptly accelerated plaque formation from the beginning, resulting in logarithmic plaque deposition. 5XFAD mice, which also carry both the APP and PS1 transgenes, developed a logarithmic deposition beginning at 2 months. This comparative analysis suggests that AD models may be classified into two distinct plaque deposition groups, and that early plaque models such as APPswe/PS1dE9, 3xTg-AD and 5XFAD might be useful to study the biochemical aspects of APP metabolism, whereas late plaque models such as Tg2576, PDAPP, and TgAPP23 might be useful to study more physiological and environmental aspects of AD pathogenesis, which occur on a longer time scale.

Key words: Alzheimer disease, plaque deposition, APP models, APP and PS1 models, comparison of plaque levels

INTRODUCTION

Alzheimer's disease (AD) is a progressive neurodegenerative disease characterized by neuropathological changes such as amyloid plaque deposition, neurofibrillary tangles (NFTs), neuronal loss, dystrophic neurites, and gliosis, as well as behavioral phenotypes such as learning and memory impairment, anxiety, depression, and other psychological symptoms [1, 2]. AD is a typical age-dependent neurodegenerative disease that affects 5% of individuals >65 years, 20% of those >85 years, and more than one-third of those >90 years [3]. Therefore, in the absence of proper preventative and therapeutic efforts, its prevalence will continue to increase as life expectancy increases.

Early onset familial AD (FAD) accounts for only a small percentage of AD cases. At least 232 different mutations in genes for amyloid precursor protein (APP), presenilin 1 (PS1 or PSEN1) or presenilin 2 (PS2 or PSEN2) (33, 185, and 13 mutations in, respectively, APP, PS1 and PS2) have been identified in FAD [4].

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In vitro and *in vivo* studies suggest that amyloid-β (Aβ) peptides are the primary causative agents in AD pathogenesis [5, 6]. Aβ is produced as a result of the sequential cleavage of APP by β-secretase and γ-secretase. This Aβ-producing amyloidogenic pathway is active when APP has mutations at the cleavage sites by β-secretase or γ-secretase [7, 8]. In contrast, α-secretase cleaves APP within the Aβ domain, precluding the generation of Aβ in normal APP metabolism. Presenilins are the core part of the protein complex known as γ-secretase [9]. FAD mutations in presenilins increase production of amyloidogenic Aβ peptides in both transfected cells and transgenic mice, supporting the Aβ amyloid hypothesis [10]. The apolipoprotein E (APOE) gene is believed to be a genetic risk factor. The APOE gene occurs in >3 different alleles including E2, E3, and E4. The E4 allele has been identified as a risk factor for AD in late-onset families [11]. Individuals with one copy (15% of total population) or two copies (2% of total population) of the E4 allele have an increased chance of developing AD by, respectively, 3 times and 10-20 times, compared to those not carrying any E4 alleles [11, 12].

Most AD cases are late-onset sporadic. Although the exact cause of most sporadic AD cases is not known, several risk factors have been proposed. Clinical and epidemiological studies suggest that aging, stress, gender (female), acid-forming food containing high dietary fat or total energy, dioxins, aluminum, lead, and viral infections could act as risk factors for AD [13], although it remains to be seen if dioxins, aluminum, lead, and viral infections can be salient non-genetic risk factors for people in developed countries.

Animal models of AD play an important role in all areas of AD studies. Proper AD models are needed to study the mechanisms underlying AD pathogenesis, the genetic interactions of the genes of interest, and environmental risk factors that cause sporadic AD, as well as to test the therapeutic effects of AD drug-candidates on neuropathology and cognitive function. First, animal models of AD need to show histopathology such as plaques, NFTs, neuronal loss, and behavioral pathology including cognitive deficits, thus AD models need to show *face validity*. Second, animal models of AD need to fulfill a substantial similarity between mechanisms underlying changes in behavioral, pathophysiological, and neuronal components in the model and those in AD, thus AD models need to show *construct validity*. Third, animal models of AD need to provide predictive value of AD pathogenesis, allowing extrapolation of the effects of an experimental manipulation, thus AD models need to show *predictive validity*. Good predictive value may help unravel a new mechanism and identify putative therapeutics [14-16]. Ideal animal models of AD may have homology to the neurobehavioral pathology and underlying mechanisms of human AD, which include the full blown etiology, pathology, syndrome, and specific mechanisms underlying age-dependent neurobehavioral changes in AD. Several dozens of AD models have been developed to mimic the genetic cause of human AD by generating transgenic mice that overexpress mutant forms of human APP, presenilins, and/or tau protein in the brain. The list of transgenic AD models produced thus far can be found in many excellent reviews [17-21] and at the web site of the Alzheimer Research Forum [http://www.alzforum.org/res/com/tra/default.asp]. Many of the transgenic AD models developed display Aβ accumulation, plaque pathogenesis, gliosis, neuronal loss, tau pathology, and/or cognitive impairments, but no single transgenic AD model recapitulates all aspects of AD pathology. Despite that ideal AD models have not been developed, currently available AD models drive our interest to move from model building to model evaluation and use. AD models have proven useful with respect to investigating mechanisms underlying a certain aspect of AD pathology, evaluating the predictive value of AD pathogenesis, and developing a strategy and drugs to treat AD. In the use of AD models, some scientists tend to seek early-plaque models at the expense of aging effects. However, familial and sporadic AD all occur in an age-dependent manner (Fig. 1), an important feature that can be simulated by current AD models and that should not be compromised with early plaque deposition in the choice of an

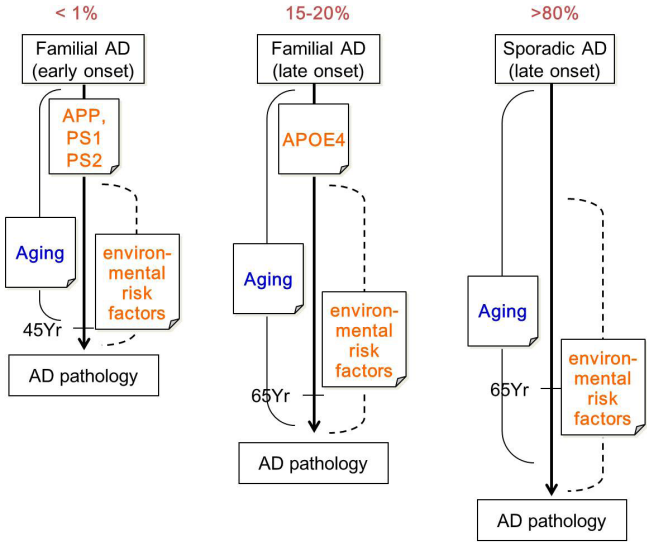

Fig. 1. Gene, age and other environmental factors on the development of Alzheimer disease (AD). Age-dependent pathogenesis of AD is an important common factor in early-onset familial AD (FAD; carrying mutations at APP, PS1 or PS2), late-onset FAD (carrying ApoE4 allele), and sporadic AD. In all cases of AD, aging or age-related accumulation of undefined factors appears to trigger AD pathogenesis. Environmental risk factors may include besides aging, stress, gender (female), acid-forming food containing high dietary fat or total energy, dioxins, aluminum, lead, and viral infections.

AD animal model for certain types of research.

In the present review, we classify AD animal models as APP models, CTF models, Aβ models, presenilin models, APP+PS1 double transgenic models, tau models, and a triple (APP+PS1+tau) transgenic model, with presenting a summary of key features relevant to AD pathology (Table 1).

APP MODELS

APP models are transgenic mice that express mutant forms of human APP under the control of strong brain-driving promoters, which include platelet-derived growth factor β-chain (PDGFβ), prion protein (PrP), and thymocyte differentiation antigen 1 (Thy-1) genes. APP is a transmembrane protein that contains Aβ42. Mutations in APP around the cleavage sites by β-secretase or γ-secretase increase Aβ42 secretion in the brain. Indeed, overexpression of mutant forms of human APP in the brains of mice results in Aβ42 accumulation, plaque deposition, Aβ-triggered pathology, and cognitive impairment, which have some similarities to those in human AD. The mouse lines PDAPP, Tg2576, TgAPP23, TgCRND8, J20, and TgAPP(Sw,V717F) were all produced using this strategy.

PDAPP

Mice express the human APP695/751/770 with the mutation V717F at the γ-cleavage site under the regulatory control of the PDGFβ promoter. PDAPP mice develop increased expression of APP mRNA levels and plaque deposition in the brain at 6-9 months [22] and develop behavioral defects at 13-15 months of age [23].

Tg2576

Mice express the human APP695 with the Swedish double mutations (K670N/M671L) at the β-secretase cleavage site under control of the hamster PrP promoter. Tg2576 mice show accumulation of Aβ40 and Aβ42 at 6-9 months and plaque deposition beginning at 9 months of age [24, 25]. Tg2576 mice develop cognitive impairment beginning at 6 months of age [26]. Tg2576 mice are widely used partly due to the initial generosity of Dr. K Hsiao to users and later commercial availability from Taconic Inc.

TgAPP23

Mice express the human APP751 containing the Swedish double mutations (K670N/M671L) at the β-secretase cleavage site driven by the mouse Thy-1 promoter. TgAPP23 mice show typical plaques at 6 months[27] and neuritic and synaptic degeneration as well as tau hyperphosphorylation in aged brains [28]. TgAPP23 mice develop cognitive decline at 10 months [29].

J20

Transgenic lines express the human APP695/751/770 containing the Swedish double mutations (K670N/M671L) at the β-secretase cleavage site and the V717F mutation at the γ-secretase cleavage site. The transgene is driven by the PDGFβ promoter [30]. J20 mice develop plaque deposition at 5-7 months and cognitive deficit at 6-7 months [30, 31].

TgCRND8

Mice express the human APP695 containing the Swedish mutations (K670N/M671L) at the β-secretase cleavage site and the V717F mutation at the γ-secretase cleavage site. The transgene is driven by the hamster PrP promoter [32]. TgCRND8 mice develop plaque deposition and cognitive deficits at 3 months [32].

TgAPP(Sw,V717F)

Mice express the human APP751 containing the Swedish mutations (K670N/M671L) at the β-secretase cleavage site and the V717F mutation at the γ-secretase cleavage site driven by the PDGFβ promoter. TgAPP (Sw,V717F) mice show behavioral deficits at 11-14 months in the absence of Aβ42 accumulation and plaque deposition [33].

CTF MODELS

TgCTF104

Mice express the carboxyl terminal fragment of APP (CTF104 of APP591-695) under control of the human NF-L neurofilament promoter [34]. TgCTF104 mice develop plaque deposition at 8-10 months, severe cognitive deficits at 8 months, and neuronal loss at 18-22 months [34].

TgβCTF99

Mice express the β-secretase-cut carboxyl terminal fragment (βCTF99) with the V717F mutation under control of the PDGFβ promoter. TgβCTF99 mice display no plaque deposition but develop cognitive deficits at 11-14 months and neuronal loss in the hippocampus and cerebral cortex at 16-18 months [35].

Aβ MODELS

BRI-Aβ42

Mice express Aβ1-42 that is fused to the C-terminus of the BRI protein at the furin cleavage site under control of the mouse PrP promoter [36]. Mice carrying BRI-Aβ42A, but not BRI-Aβ40,

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Table 1. Transgenic Alzheimer disease (AD) models were classified with respect to transgenic constructs and AD-related pathology

	Transgenic mouse line	Transgene	Promoter	Genetic background (original line)
APP model	PDAPP	APP695, 751, 770-V717F	Human PDGF-β	C57BL/6×DBA/2
	Tg2576	APP695-K670N/M671L	Hamster PrP	C57BL6×SJL
	TgAPP23	APP751-K670N/M671L	Mouse Thy-1	C57BL/6J
	J20	APP695, 751, 770-K670N/M671L, V717F	Human PDGF-β	C57BL/6×DBA/2
	TgCRND8	APP695-K670N/M671L, V717F	Hamster PrP	C3H/He-C57BL/6
	TgAPP (Sw, V717F)/B6	APP751-K670N/M671L, V717F	Human PDGF-β	C57BL/6
CTF model	TgCTF104	APP591-695	Human neurofilament NF-L	B6C3
	TgβCTF99/B6	βCTF99 (V717F in APP751)	Human PDGF-β	C57BL/6
Aβ model	BRI-Aβ42A	C-terminus of the BRI protein	Mouse PrP	B6C3
PS model	Tg-PS1 M146L or M146V	PSEN1-M146L or M146V	Human PDGF-β	SW×B6D2
	pNSE-hPS2m	PSEN2 -N141I	Rat NSE nromoter	BDF1
APP+PS model	APPswe/PS1dE9	APP695-K670N/M671L, PSEN1-M146L	Mouse PrP	C57BL6×C3H
	5X FAD	APP695-K670N/M671L, I716V, V717I, PSEN1-M146L, L286V	Mouse Thy-1	C57BL/6×SJL
Tau model	JNPL3	FTDP-17 - P301L	Mouse PrP	C57BL6×DBA2×SW
	V337M Tg	FTDP-17 - V337M	Human PDGF-β	B6SJL
APP+PS+tau model	3xTg	APP695-K670N/M671L, PSEN1-M146V, Tau- P301L	Mouse Thy-1	C57BL/6/129S

	Transgenic mouse line	Aβ		Plaque deposition		Tau (NFT)		Neuronal loss	
		Month	Ref.	Month	Ref.	Month	Ref.	Month	Ref.
APP model	PDAPP	8-10	62	6-9	22			No	64
				12-15	63				
	Tg2576	6-9	25, 54	9-12	25, 54, 67	No	68	No	68
		6	26	11	68				
	TgAPP23	6	72	6	27, 72	12	27	14-16 (CA1)	73
								12 (CA3)	27
	J20	2-4	30	5-7	30				
	TgCRND8	3	32	3	32				
		4.5-5.5	75	3.5	75				
	TgAPP (Sw, V717F)/B6			No	33				
CTF model	TgCTF104			8-10	34			18-22 (CA1)	34
	TgβCTF99/B6	No	35	No	35			16-18	35
Aβ model	BRI-Aβ42A	3	36	12	36				
PS model	Tg-PS1 M146L or M146V			No	37				
	pNSE-hPS2m	12	77	12	77				
APP+PS model	APPswe/PS1dE9	7	45	6	44, 45			No	78
				4.5-6	55				
	5X FAD	1.5	47	2	47			9	47
								18	82
Tau model	JNPL3					3	49		
						4.5	48		
	V337M Tg					11	50	11 (HP)	50
APP+PS+tau model	3xTg	13	51	6	51, 86	12-15	51		
		6	85	4	52	9	85		
		4	52	3	59, 85	6	59, 86		

Table 1. Continued

	Transgenic mouse line	Behavior test			Vendor
		Month	Behavior	Ref.	
APP model	PDAPP	6	Delay eye-blink conditioning	65	
		3	Bar-press learning task	66	
		13-15	Morris water maze	23	
	Tg2576	6	Morris water maze	26	Taconic
		7	16-hole circular platform task	69	
		16-18	T-maze	70	
		16-18	Pavlovian fear conditioning	70	
		9	Water maze visible platform acquisition task	71	
		9	Passive avoidance memory retention	71	
	TgAPP23	3	Morris water maze	72	57
		10	Complex maze	29	
		11	Rota-rod	57	
		11	Morris water maze	57	
	J20	6-7	Morris water maze	31, 74	Jax.
	TgCRND8	3	Morris water maze	32, 76	
		3.5-5	Y-maze	75	
		9	Morris water maze	75	
	TgAPP(Sw,V717F)/B6	13	Open field	33	
		14	Passive avoidance	33	
		14	Morris water maze	33	
		13	Elevated plus maze	33	
CTF model	TgCTF104	8	Morris water maze	34	
	TgßCTF99/B6	12.5-14.5	Morris water maze	35	
		13	Elevated plus maze	35	
		7	Passive avoidance	35	
Aβ model	BRI-Aβ42A				
PS model	Tg-PS1 M146L or M146V				
	pNSE-hPS2m	12	Morris water maze	77	
APP+PS model	APPswe/PS1dE9	8	Morris water maze	79	Jax.
		18	Morris water maze	45	
		6	Radial arm water maze	80	
		12	Morris water maze	80	
		7.5	Morris water maze	46	
		7.7	Passive avoidance test	46	
		7.8	Marble burying test	46	
	5X FAD	4-5	Y-maze	47	Jax.
		6	Y-maze	81	
		15-18	Y-maze	82	
		6	Contextual fear conditioning	83	
		9-10	Conditioned taste aversion test	84	
		6-7	Contextual fear conditioning	84	
Tau model	JNPL3				
	V337M Tg	11	Elevated plus maze	50	
APP+PS+tau model	3xTg	6	Morris water maze	52, 86	Jax.
		6	Contextual fear conditioning	52	
		9	Y-maze	85	

Aβ42 accumulation, plaque depositions, neurofibrillary tangles (NTFs), neuronal loss, and behavioral impairments for each line are summarized with references. APP, amyloid Precursor Protein; PS or PSEN, presenilins; CTF, carboxyl terminal fragment; PDGF-β, platelet-derived growth factor β–chain; PrP, prion Protein; Thy-1, Thymocyte differentiation antigen 1.

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develop amyloid deposits at 3 months and neuropathology at 12 months [36].

PS1 AND PS2 TRANSGENIC MODELS

PS1 and PS2 transgenic lines

(Tg-PS1 M146L/or M146V and Tg-pNSE-hPS2) carrying FAD mutant forms of PS1 and PS2 (M146L or M146V), respectively, under control of the PDGFβ and NSE promoter show enhanced levels of Aβ42, supporting the hypothesis that the presenilin mutations cause AD pathogenesis through a gain of deleterious function [9, 10, 37]. However, transgenic mice carrying FAD mutant forms of presenilins or gene-targeted mice carrying FAD-mutant PS1 ($PS1^{P264L/P264L}$) do not develop plaques, although when crossed with plaque-forming APP lines (eg., Tg2576), the presenilin FAD mutations produce elevated levels of Aβ42 and cause earlier and more extensive plaque deposition [38-41].

APP+PS TRANSGENIC MODELS

APP and PS1 bigenic or monogenic transgenic mice carrying the transgene for both mutant APP and mutant PS1 show increased Aβ42 production and more extensive plaque deposition, which was reviewed well by Hall and Roberson [20].

Tg-APPswe/PS1dE9

Mice express the human APP with the Swedish mutations (K670N/M671L) at the β-secretase cleavage site and PS1 (PS1dE9), which result in plaque deposition in the brain starting at 6 months of age [42-44]. Despite the plaque deposition and behavioral deficits at 6-8 months of age [45, 46], Tg-APPswe/PS1dE9 mice do not develop NFTs or neuronal loss. Tg-APPswe/PS1dE9 mice became popular partly due to the early availability from JAX (Table 1).

5XFAD

Mice express the human APP with the Swedish mutations (K670N/M671L) at the β-secretase cleavage site and two FAD-associated mutations (I716V/V717I) at the γ-secretase cleavage site, and human PS1 with the M146V and L286V mutations under control of the mouse Thy-1 promoter [47]. 5XFAD mice develop plaque deposition at 2 months and cognitive deficits at 4-6 months [47]. 5XFAD mice are now available from JAX (Table 1).

TAU MODELS

Transgenic mice overexpressing mutant tau produce tau pathology, but not Aβ deposits.

JNPL3

Mice express the human tau with the most common mutation (P301L), which causes the fronto-temporal dementia and parkinsonism-linked to chromosome 17 (FTDP-17 mutation) in human, under control of the mouse PrP promoter. JNPL3 mice develop NFTs at 6.5 months and progressive motor disturbance in hemizygous animals [48]. When JNPL3 are crossed with Tg2576, the resulting double mutant (tau/APP) progeny and the Tg2576 parental mice develop Aβ deposits at the same age; however, the tau/APP double mutants exhibit enhanced NFT pathology in the limbic system and olfactory cortex compared to that of the JNPL3 parent strain [49].

TauV337M

Mice express the human tau with the V337M mutation under control of the PDGFβ promoter. TauV337M mice develop NFT and hippocampal neuronal loss at 11 months [50].

TRIPLE (APP+PS+TAU) TRANSGENIC MODEL

3xTg-AD

Mice express the human APP695(Swe), PS1(M146V), and Tau(P301L) under control of the mouse Thy-1 promoter. 3xTg-AD mice develop plaques beginning at 6 months of age and NFTs at 12 months. 3xTg-AD mice display synaptic dysfunction, including long-term potentiation deficits before plaque and tangle pathology [51]. 3xTg-AD mice show memory deficits at 4.5 months, which are correlated with the accumulation of intraneuronal Aβ in the hippocampus and amygdala [52].

REVALUATION OF PLAQUE DEPOSITION PATTERNS IN THE BRAIN OF SIX REPRESENTATIVE AD MODELS USING PHOTOGRAPHIC PLAQUE REFERENCE PANELS

The plaque models Tg2576, PDAPP, TgAPP23, Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD are widely used in many laboratories as they display robust age-dependent plaque deposition in the brain, but their relative plaque deposition patterns and features have not been clearly analyzed due to technical difficulties. In this review, we attempted to re-evaluate plaque deposition levels in each line using a photographic plaque reference scale method [44] and analyzed the resulting data.

We searched for studies describing plaque deposition in brain sections of AD models and re-evaluated plaque levels in each line using plaque reference panels. Despite that the plaque deposition

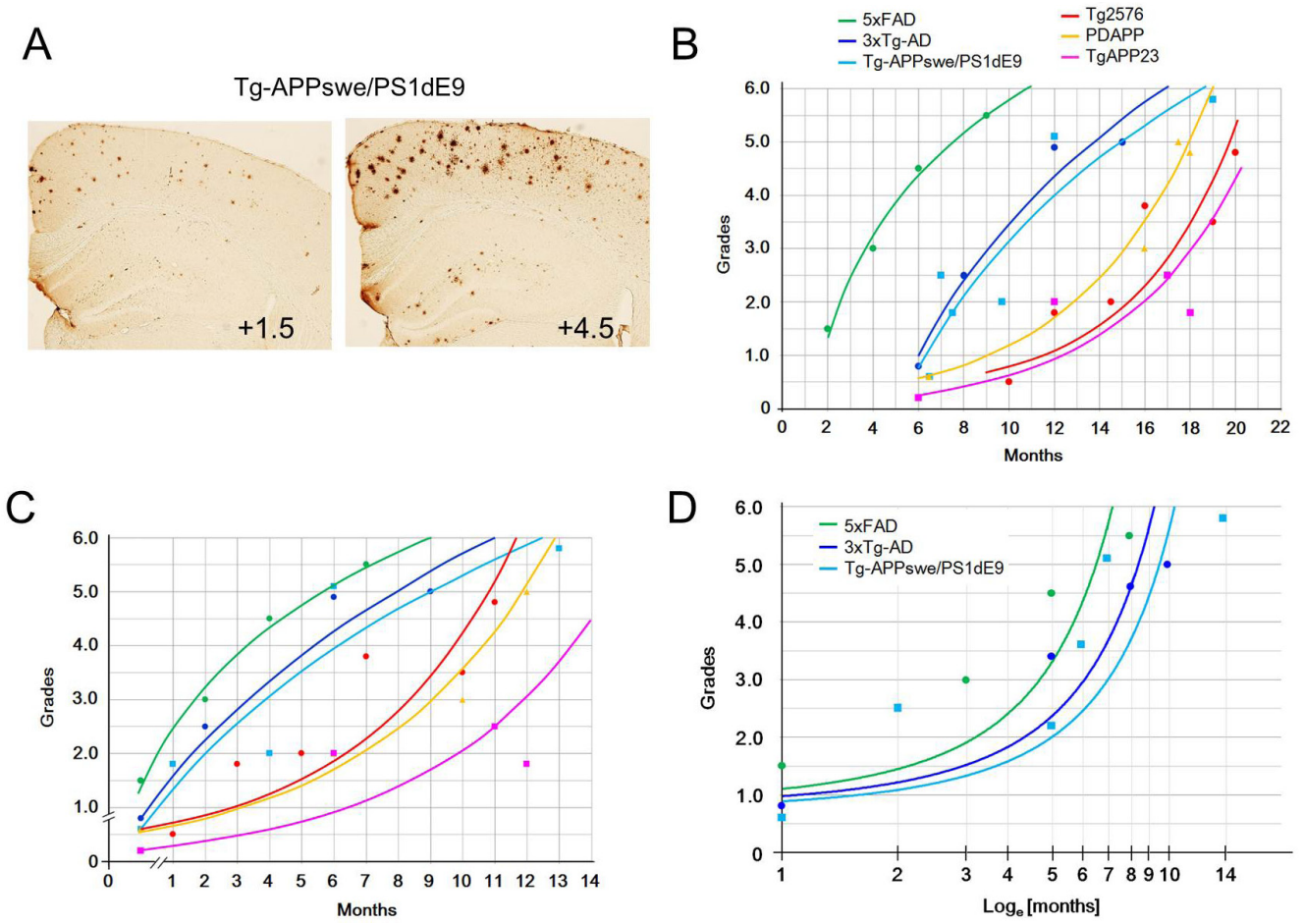

Fig. 2. Temporal plaque deposition patterns in the brains of six representative AD models. (A) Examples of quantifying plaque deposition levels in the brain of Tg-APPswe/PS1dE9 mice using the six-scale photographic plaque reference panels [44]. (B) Age-dependent plaque deposition in the brains of Tg2576, PDAPP, TgAPP23, Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD mice are plotted with age. Photomicrographs showing plaque deposition in the parietal cortices for each line were searched for in the literature and their plaque deposition levels were re-evaluated using the six-scale photographic plaque reference panels. Plaque deposition levels for each line was reassessed using both the Tg2676 panels and Tg-APPswe/PS1dE9 panels [44], and plaque scores were averaged [25, 27, 44, 45, 47, 55-61]. (C) Age-dependent plaque deposition was re-evaluated using the six-scale reference panels in the brains of Tg2576, PDAPP, TgAPP23, Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD mice and were aligned over the month showing first plaque deposition. Rapid and abrupt plaque accumulation was evident in the AD models that carry both APP and PS1 transgenes compared to the lines that carried the APP transgene. (D) Plaque deposition levels in Tg-APPswe/PS1dE9, 3xTg-AD, and 5xFAD mice plotted over log values of time (loge[months]) produced new plaque deposition patterns that were similar in shape to the un-converted plaque deposition profiles displayed by Tg2576, PDAPP, and TgAPP23 mice.

information contained in the photographic images published in the literature was available at low resolution in most cases, immunostaining of brain sections was not carried out in the same condition, and animals were reared in different laboratories probably under different microenvironments, plaque depositions evaluated for each AD model plotted against age resulted in either logistic or logarithmic curves (Fig. 2A-C). The age-dependent plaque deposition patterns of Tg2576, PDAPP, and TgAPP23 similarly produced logistic curves, whereas the temporal plaque deposition patterns of Tg-APPswe/PS1dE9 and 3xTg-AD produced logarithmic curves. The temporal plaque deposition in 5XFAD mice (Fig. 2B) was left-shifted (that is, time-shifted) and was basically similar to the patterns of Tg-APPswe/PS1dE9 and 3xTg-AD mice. In fact, Tg2576, PDAPP, and TgAPP23 belonged to APP models, whereas Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD belonged to lines carrying both APP and PS1 transgenes in an individual. This interpretation was supported by previous reports describing the plaque loading data between Tg2576 and bi-transgenic mice genetically produced by crossing Tg2576 with Tg-PS1$^{P264L/P264L}$ mice [38] and the plaque loading data between Tg2576 and 5XFAD [47]. The present analysis was primarily based on existing image data available in the literature; thus, it may be

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an estimate. Nevertheless, the results of this analysis indicate that Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD mice, which carry the APP and PS1 transgenes, produce rapid and logarithmic accumulation of plaques, whereas Tg2576, PDAPP, and TgAPP23 mice, carrying the APP transgene, produce slow and logistic accumulation of plaques in the brain (Fig. 2B, C).

Considering that the transgenic cassettes carrying hAPP in Tg-APPswe/PS1dE9 and 3xTg-AD mice are similar to the hAPP transgenic cassettes carried by Tg2576, PDAPP, and TgAPP23 mice, accelerated plaque deposition in Tg-APPswe/PS1dE9 and 3xTg-AD is likely driven by the added action of enhanced γ-secretase activity onto the mutant form of human APP. Plaque depositions in Tg-APPswe/PS1dE9 and 3xTg-AD appear to have some time-accelerated process aspects, and there are 5-8 months of aging difference when plaque levels in each group reach to level +3.0 (Fig. 2B, C). Re-plotting the plaque deposition levels in Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD over the log values of time (loge[months]) resulted in new plaque deposition profiles (Fig. 2D) which are increasing rapidly after 3 months compared to the slopes of the unconverted plaque depositions in Tg2576, PDAPP, and TgAPP23 mice (Fig. 2B, C). Thus, the plaque deposition pressure in Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD appears to occur too strongly to be cleaned up even by young healthy brains. On the other hands, presumably 5-8 months of aging is a long period that involves numerous changes besides altered APP metabolism. Therefore, a simple time-accelerated process of APP metabolism may not be proper to explain the rapid plaque deposition in Tg-APPswe/PS1dE9 and 3xTg-AD.

Consistent with this interpretation, it was reported that the plaque deposition pattern in Tg2576 mice was qualitatively different from that in Tg-APPswe/PS1dE9 mice. The brains of Tg2576 mice started to accumulate predominantly small plaques, whereas the brains of Tg-APPswe/PS1dE9 mice began to deposit relatively large plaques [44]. Because accelerated APP metabolism has been proven in the brains of Tg-APPswe/PS1dE9, 3xTg-AD, and 5XFAD, these early plaque deposition models might be useful to study biochemical aspects of APP metabolism and the resulting plaque deposition, whereas Tg2576, PDAPP, and TgAPP23 might be useful for more physiological and environmental aspects of AD pathogenesis, which occur over a longer time scale. As we reported previously, indeed accelerated plaque pathology by behavioral stress in Tg-APPswe/PS1dE9 [53] was less prominent than that in Tg2576 [54]. The aging factor in AD pathogenesis should not be compromised by taking advantage of accelerated plaque deposition, but it should be seriously considered as an important part of AD pathogenesis in choosing AD models. Many AD studies can be successfully performed if provided with a proper AD model after a careful consideration of the plaque deposition profile. AD models displaying more delayed and slow plaque deposition might model the brains of late-onset sporadic AD more closely.

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