

PDF hosted at the Radboud Repository of the Radboud University Nijmegen

The following full text is a publisher's version.

For additional information about this publication click this link.

<http://hdl.handle.net/2066/88845>

Please be advised that this information was generated on 2019-03-20 and may be subject to change.

Review

Do Amyloid β -associated Factors Co-deposit with $A\beta$ in Mouse Models for Alzheimer's Disease?

Nienke M. Timmer^{a,*}, H. Bea Kuiperij^a, Robert M.W. de Waal^b and Marcel M. Verbeek^a

^a*Department of Neurology, Department of Laboratory Medicine, Donders Institute for Brain, Cognition and Behaviour, Alzheimer Centre Nijmegen, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands*

^b*Department of Pathology, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands*

Handling Associate Editor: Gary Arendash

Accepted 29 June 2010

Abstract. Senile plaques and cerebral amyloid angiopathy in Alzheimer's disease (AD) patients not only consist of the amyloid- β protein ($A\beta$), but also contain many different $A\beta$ -associated factors, such as heparan sulfate proteoglycans, apolipoproteins, and complement factors. These factors may all influence $A\beta$ deposition, aggregation, and clearance and therefore seem important in the development of human $A\beta$ deposits. To study AD pathology and test new therapeutic agents, many different mouse models have been created. By transgenic expression of the amyloid- β protein precursor, frequently in combination with other transgenes, these animals develop $A\beta$ deposits that morphologically resemble their human counterparts. Whether this resemblance also applies to the presence of $A\beta$ -associated factors is largely unclear. In this review, the co-deposition of factors known to associate with human $A\beta$ deposits is summarized for several different AD mouse models.

Keywords: Acute-phase proteins, Alzheimer's disease, amyloid- β , apolipoprotein E, complement, heparan sulfate proteoglycans, transgenic mice

INTRODUCTION

To investigate disease mechanisms and test new therapeutic agents, animal models are necessary tools. Even though the use of animals is ethically controversial, there are no other models available that are capable of reproducing the complex nature of human physiology. However, mimicking disease is not easy in animal models, since the biological pathways in animals are

often not identical to those in humans. Therefore, most models are created as transgenics, expressing (mutated) human proteins implicated in human disease. But even in transgenic models, it remains difficult to accurately model symptoms and pathology of a human disease.

Alzheimer's disease (AD) is pathologically characterized by accumulation of the amyloid- β ($A\beta$) protein in senile plaques and cerebral amyloid angiopathy (CAA) [1,2] and by accumulation of hyperphosphorylated tau protein [3]. One of the earliest brain regions affected is the hippocampus, a brain region involved in memory formation. Indeed, memory impairment is one of the main symptoms of AD [4,5]. The importance of $A\beta$ in the pathogenesis of AD, has been emphasized by the discovery of multiple causative muta-

*Correspondence to: Nienke M. Timmer, Department of Neurology, 830 LGEM, Radboud University Nijmegen Medical Centre, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands. Tel.: +31 312 436 18786; Fax: +31 312 436 68754; E-mail: n.timmer@neuro.umcn.nl

tions in A β -related genes (amyloid- β protein precursor (A β PP) and presenilin genes) in familial AD [6].

A β is a cleavage product of A β PP and generally comprises either 40 (A β ₄₀) or 42 (A β ₄₂) amino acids. A β PP is a transmembrane protein that can be cleaved by several different secretases to release A β and a number of other cleavage products [7–9]. In the case of A β , A β PP is first cleaved by a γ -secretase [10] and then by a β -secretase [11,12]. Many of the mutations in A β PP that cause the familial forms of AD are found close to these A β PP cleavage sites [6]. A β is normally cleared from the brain, but when this clearance process becomes impaired, for example due to aging, A β can start to oligomerize and eventually form fibrils. This fibrillization can then result in the formation of A β deposits throughout the brain. Besides mutations in A β PP, pathogenic mutations have also been found in presenilin-1 (PS1) and, to a lesser extent, presenilin-2 [6,13]. Both these presenilins are part of the γ -secretase complex responsible for A β cleavage from A β PP [10,14]. These mutations increase A β production, in particular of the more fibrillogenic A β ₄₂ variant [15].

In more than 99% of AD cases, aging is the most important risk factor to develop AD, whereas in less than 1% of cases the disease can be related to gene mutations. However, there are only a few animal species, including dogs and primates, which naturally develop AD-like pathology with advanced age [16]. To create models for AD with a faster development of A β pathology, transgenic (Tg) mouse models have been generated based on the introduction of human (mutated) A β PP, either alone or in combination with (mutated) presenilin genes [17]. Mice are usually the animals of choice for creating transgenics, since they are not only very susceptible to genetic manipulation, but are also relatively easy and cheap to maintain.

The first AD mouse model that was developed was the PDA β PP model [18]. In this model, starting at an age of 6–9 months immunohistochemically detectable A β deposits developed, that become more dense upon aging and finally morphologically resemble A β deposits found in humans. Furthermore, as seen in humans, the A β deposits in the PDA β PP mice are surrounded by activated astrocytes and microglia and accompanied by a loss of synaptic density. PDA β PP mice also develop cognitive deficits including memory impairment [19], further demonstrating their similarity to human AD patients.

Many more AD mouse models with A β pathology have been created since this first model [17], all char-

acterized by deposition of plaque-like A β and most of them developing cognitive impairment [17]. Due to the different gene combinations and mutations used to create these mice, there are, however, many differences between models. For example, the age of pathology onset in AD models varies greatly. In some mice, such as the TgCRND8 model, deposition starts at an age of 3–6 months [20], while in others, such as the Tg2576 model, it starts at an age of 9–12 months [21]. In general, co-expression of PS1 lowers the age of onset [22], because A β PP in these mice is more readily cleaved by the γ -secretase [23]. Plaque morphology can also vary greatly between different models. For example, A β PP23 mice accumulate mostly compact deposits [24], while parenchymal A β deposits in TgSwDI mice are mostly diffuse [25]. Contrary to A β PP23 mice, which develop CAA next to parenchymal deposits [26], TgSwDI mice, but also A β PPDutch mice, accumulate A β mainly in the brain vasculature with limited parenchymal deposition [25,27]. This characteristic makes these latter models suitable models for familial and sporadic cases of vascular amyloid pathology. A β PP and A β PP/PS1 models do not develop tau pathology, but tau transgenic mice have been developed [28,29]. There is also a triple transgenic mouse model available, overexpressing tau, A β PP, and PS1 [30].

Even though most AD mouse models demonstrate A β pathology that morphologically resembles human AD pathology, the A β deposited in mice is chemically different from human A β . In humans, A β species undergo posttranslational modifications, such as N-terminal degradation, cross-linking, and isomerization. These modifications are either not found in AD mouse models or differ from the human situation [31–33]. Furthermore, A β deposits in mice are usually less compact than in humans, allowing mild extraction buffers to more easily extract A β from mouse brains relative to human brains. Finally, progressive AD pathology in humans is characterized by neurodegeneration, a characteristic that is rarely reproduced in AD mouse models [17]. Only the A β PP23 mouse model has been shown to have some neuronal loss in the CA1 region of the hippocampus [34].

In humans, A β deposits not only contain the A β protein, but immunohistochemical analyses also demonstrated many other proteins [35–37]. It is thought that because of their close association, these co-deposited molecules contribute to A β aggregation and deposition. Although this has not been proven for all co-depositing proteins, *in vitro* studies showed that heparan sulfate proteoglycans (HSPG), apolipoprotein E (ApoE) and

α 1 chymotrypsin (α 1-ACT), can indeed bind to A β , affect its aggregation, stabilize A β deposits and protect deposits against proteolytic degradation [38–40]. Because of their tight association with A β , these (glyco-) proteins may greatly influence the outcome of therapeutic intervention in humans, aimed at reducing A β aggregation and deposition. Since all new potential AD therapeutics are first tested in mouse models, it is important to know if these A β -associated factors are present in the various mouse models. In this review, we aim to examine the validity of AD mouse models with respect to the presence of the main A β co-depositing factors HSPG, ApoE, complement factors, acute-phase proteins, intercellular adhesion molecule (ICAM)-1, cystatin C, and collagenous Alzheimer amyloid plaque component (CLAC). An overview of the co-deposition of these factors in transgenic AD models is shown in Table 1 and discussed below.

Heparan sulfate proteoglycans

More than twenty years ago, close association of HSPG with A β deposits in humans, both parenchymal and vascular, was first described [41]. HSPG consist of a protein core with several highly sulfated glycosaminoglycan chains attached. These glycosaminoglycan chains consist of repeating disaccharide units. There are several different HSPG species, some membrane-associated (glypicans and syndecans) and some associated with the extracellular matrix (agrin, collagen XVIII, and perlecan). HSPG are thought to be involved in numerous (developmental) processes, including neurogenesis, angiogenesis, and blood brain barrier permeability [39]. Of the different HSPG species, agrin, and glypican-1 are the only two HSPG found in association with all different types of A β deposits [42–44]. The association of perlecan with A β deposits is controversial, as one study described this HSPG to have the strongest association [41], whereas we have been unable to detect perlecan in CAA or senile plaques [42,44]. Overall though, HSPG are key components of human A β deposits. Indeed, *in vitro* analysis has demonstrated that HSPG can bind A β with high affinity, mainly through their glycosaminoglycan chains [45]. Through this binding, HSPG can enhance A β deposition [39,43,46], a process that seems to involve HSPG sulfate moieties [47].

There are only a few studies describing co-deposition of HSPG with A β deposits in mouse models. In a characterization study of A β PP23 mice, it is very briefly mentioned that HSPG co-localize with A β de-

posits [48]. A more elaborate study was done using 20-month-old Tg2576 mice [49]. It was demonstrated that antibodies against heparan sulfate stained more than 95% of the “doughnut”-shaped A β deposits visible in this model. Whereas in the A β PP23 mice no distinction was made between individual HSPG species, in the Tg2576 mice it was discovered that glypican-1 and syndecan-3, but not agrin, perlecan, syndecan-1 and -2, were found in the A β deposits. Therefore, in this mouse model the extensive co-deposition of HSPG seen in humans could only partly be reproduced. For example, agrin, a HSPG that is abundantly present in AD senile plaques, was absent from A β deposits in mice, demonstrating that the association of individual HSPG species with A β pathology may not always match the human situation.

We recently studied deposition of several HSPG species in the A β PPswe/PS1dE9 mouse model [50]. In this model, in general HSPG were associated with approximately 30% of A β deposits. Furthermore, co-localization of the different HSPG species (agrin, glypican-1, and perlecan) occurred in less than 10% of A β deposits for each of the species. Therefore, HSPG co-deposition was much less pronounced in this model than in the Tg2576 model or in humans. Due to a low number of detectable vascular deposits, co-deposition of HSPG with CAA vessels could not be determined in this model, nor was it investigated in the Tg2576 model.

Overall, the mouse models seem to differ from human AD pathology in either the type of HSPG species that co-deposit or the number of plaques in which HSPG co-deposition is observed. As previously hypothesized [51], it may be that the lack of glycoproteins, like HSPG, in A β deposits in mice is the reason that these deposits are generally less compact and more easily dissolved. It is important to note that HSPGs are an invariant component of all known human amyloidoses, both cerebral and in peripheral organs, pointing to a very important role in amyloidosis in general [52], a property that is apparently partly lacking in Tg mouse models for AD. As far as we know, co-deposition of HSPG has not been studied in mouse models for other types of amyloidosis.

Apolipoprotein E

ApoE is the most prominent apolipoprotein in the central nervous system and mainly produced by astrocytes [53], although other cell types such as pericytes and smooth muscle cells also contribute to cerebral lev-

els [54,55]. ApoE binds to lipoproteins and mediates their interaction with lipoprotein receptors and endocytosis and in this manner regulates cholesterol homeostasis [56]. There are three isoforms of ApoE (ApoE2, 3, and 4), and the ApoE4 isoform is a well-known risk factor for AD [57], whereas the ApoE2 isoform seems to be protective for the development of AD. The exact role of ApoE in AD, however, is still elusive [58]. *In vitro* studies have demonstrated a direct interaction between A β and ApoE [57] and it is suggested that through this interaction ApoE can influence A β aggregation and mediate A β clearance [38,40,58].

The fact that ApoE can bind A β *in vitro*, suggests an interaction of these two proteins *in vivo*. Indeed, clear co-deposition of ApoE with human A β deposits has been shown. ApoE immunoreactivity is observed in all senile plaques in AD brains, including in diffuse plaques and in the core of amyloid plaques [35,59–61], although some authors described the co-deposition with diffuse deposits to be minor [62]. In these studies, ApoE was also found in CAA vessels [35] and in dystrophic neurites surrounding plaques.

Co-deposition of ApoE with A β deposits in mouse models has been well studied and in several models ApoE was found co-localized with A β . Immunohistochemical analysis of deposits in Tg2576 [63, 64], A β PP23 [48,65], PS/A β PP [66], and A β PP-YAC mice [67] revealed staining for ApoE mostly in (Thioflavin-S positive) fibrillar deposits, with staining of some diffuse deposits. Furthermore, ApoE colocalized with astrocyte markers [64], demonstrating that in mice, as in humans, astrocytes are likely responsible for ApoE production. In the TgSwDI mouse model, that specifically deposits A β in the brain vasculature, ApoE is found in close association with these vascular deposits [33]. All these findings in mice are therefore in concurrence with the ApoE co-deposition found in humans.

Based on studies using brain material of Down syndrome patients, it was suggested that ApoE contributes to plaque maturation [68]. In these patients, A β_{42} was the first A β species to accumulate and ApoE colocalization could be detected in these deposits before A β_{40} accumulates. In the Tg2576 model [64], A β_{42} also seems to be the initial A β species that deposits, with A β_{40} only visible in more mature deposits. Using the Tg2576 model, it was found that all A β deposits positive for ApoE contained A β_{42} , with only some containing A β_{40} . Therefore, since ApoE co-deposition in mice resembles that in humans, this suggests that ApoE has a similar role in plaque maturation in mice as it

has in humans. The function of ApoE in A β deposition has also been investigated using ApoE knockout mouse models. By crossing these knockout mice with AD mouse models [69,70], it was discovered that ApoE expression is key in developing A β deposition.

Recently, an increased risk for AD was linked to another apolipoprotein, ApoJ [71,72]. Indeed, this apolipoprotein, but also ApoD, is known to co-deposit with A β [60,73] and furthermore ApoJ could decrease A β aggregation *in vitro* [74] and *in vivo* [75]. Co-deposition of ApoD has not been studied in AD mouse models. In contrast, in the A β PP-YAC mouse model [67] co-deposition of ApoJ with A β has been described. Therefore, in general, it appears that co-deposition of apolipoproteins with A β is well replicated in Tg mouse models for AD.

Complement factors

The complement system consists of a cascade of factors that can become activated as part of the innate immune response of the body. Although the liver is the main source of complement, brain glial cells can also produce complement factors [76]. The cascade is triggered when either factor C1q (classical pathway), C3 (alternative pathway), or lectins become activated. Ultimately, a membrane attack complex (MAC), consisting of factor C5b-9, is formed that lyses cells by forming a membrane pore. Besides foreign intruders, the A β protein is also known to trigger the complement system by binding to C1q or C3 [77,78]. Indeed, in AD brain, expression of the complement system is upregulated [79] and recently a complement component receptor (CR1) was identified as a risk factor for AD [72]. Furthermore, several components of the complement system, including C1q, C3, and C5b-9, can be found clearly associated with A β deposits [80] and then mostly with fibrillar plaques [81]. Activation of the complement system in turn can stimulate A β aggregation [82]. Although the activated complement system can accelerate (A β -induced) neurodegeneration [83], there is also evidence that it can protect the brain from A β -induced damage [84].

Co-deposition of complement factors in mouse models has been well-studied. In two studies, C1q, C3, and C4 co-deposition in the Tg2576 model was investigated [85,86]. Strong co-deposition of these three complement factors was found with (Thioflavin-S positive) A β deposits. C1q was also strongly expressed in A β deposits of PS/A β PP mice [87] and with the vascular deposits of TgSwDI mice [88]. In A β PP23 mice, not

only was co-deposition of C1q studied, but also that of many more complement factors (C3, C3d, C4, C4d, C7, C9) [65,89]. With the exception of C1q, C3, and C3d, co-deposition of these factors was weak, with co-deposition of complement factors further down in the cascade (C7, C9) being almost absent.

In summary, it appears that, unlike in human A β deposits, only the early components of the complement cascade (C1q, C3) can be detected in A β deposits of Tg mouse models. Although these early complement factors co-deposit with A β in mice, functionally they differ from their human equivalents. For example, it is known that mouse C1q does not bind human A β as efficiently as human C1q does [90] and that mouse C4 cannot activate C5 convertase [91]. Consequently, subsequent activation of the complement system in mice is also less efficient. Since complement can induce neurodegeneration [83], the less efficient activation of this system may explain the relatively low degree of neurodegeneration seen in mouse models [17]. Furthermore, the difference in complement co-deposition and activation between humans and mice may also provide some explanation for the different results that have been found in immunization studies in humans and mice aimed at finding new therapeutic agents [92,93]. Despite the incomplete activation of the complement pathway in mice, it may still play a critical role in A β pathology in mouse models as was demonstrated by a reduction of inflammation and neurodegeneration in an AD mouse model crossed with complement knockout mice [85].

Acute-phase proteins

In AD brains, several acute-phase proteins co-deposit with A β , such as serum amyloid P (SAP), α 2-macroglobulin (α 2M), and α 1-ACT [35,94]. Acute-phase proteins are proteins that become acutely upregulated in plasma in response to inflammation.

SAP is a glycoprotein that is closely associated with all A β deposits in humans [35,95]. The proposed role for SAP in senile plaques is to protect A β fibrils from proteolysis [96]. Besides, SAP may activate the complement system by binding C1q [97]. Only two studies on SAP co-deposition in mouse models have been performed. In one AD mouse model (C57B6/SJL overexpressing A β PP), SAP did not co-localize with amyloid deposits [98,99]. It was postulated that SAP, with a molecular weight of ~250 kDa, failed to readily pass the blood brain barrier (BBB). Only when SAP was administered intranasally to transgenic A β PP mice, could

SAP be detected in association with A β deposits [99]. Since in humans, SAP can be detected in the AD brain and its production is exclusive to the liver, it was suggested that the integrity of the human BBB must be disturbed. In the A β PP23 model [65], SAP was also not detected in A β deposits, although staining in the periphery of deposits was visible. Therefore, functional disturbance of vessels of A β PP23 mice was apparently also not severe enough to allow BBB crossing of SAP into the brain [100]. The reduced transport of complement activator SAP into the brain may in turn contribute to the relative lack of complement activation in AD mouse models [65].

α 2M, a protease inhibitor, co-localized with senile plaques in humans [101] and is thought to prevent accumulation of A β [102]. In a study aimed at investigating the role of α 2M in AD, the co-localization of this protein in the PS/A β PP mouse model was characterized [103]. Starting from 3 months of age, these mice demonstrated A β deposition, with some deposits positive for α 2M. The number of α 2M-positive plaques then increased with age, with α 2M mainly depositing in Thioflavin-S positive fibrillar senile plaques. This demonstrates that α 2M co-deposition resembles the human situation.

Finally, the acute-phase protein α 1-ACT is a serine protease inhibitor that co-deposits with human A β deposits [94]. Whereas some describe α 1-ACT to enhance A β aggregation [104], others demonstrated an inhibition of fibril formation [38], possibly reflecting different effects of α 1-ACT depending on the molar ratio between α 1-ACT and A β [105]. However, as mice do not possess an α 1-ACT homologue [106], co-deposition of this acute-phase protein in AD mouse models is not to be expected. Only by creating double transgenic mice for both human α 1-ACT and A β PP, it was possible to study the *in vivo* role of α 1-ACT on A β aggregation [106]. Thus, it was demonstrated that α 1-ACT increased A β levels and plaque load in these mice.

Thus, co-deposition of acute-phase proteins has been studied in a few mouse models only and in these models co-deposition with A β was restricted to α 2M.

ICAM-1, cystatin C, and CLAC

Besides the above mentioned factors, there are several more proteins that co-deposit with human A β , including ICAM-1, the cysteine protease inhibitor cystatin C, and CLAC. ICAM-1 is closely associated with A β deposits in human AD brains, where it can be found

Table 1
Association of proteins that co-deposit with senile plaques in AD with A β deposits in different mouse models for AD

Co-depositing factor	AD mouse models						Reference
	Tg2576	PS/A β PP	A β PP23 ^a	TgSwDI ^b	A β PP ^{swe} /PS1dE9	A β PP-YAC	
Heparan sulfate proteoglycans			+				[48–50]
<i>HS GAG</i>	+					±	
<i>Perlecan^c</i>	–					±	
<i>Glypican-1</i>	+					±	
<i>Agrin</i>	–						
<i>Syndecans</i>	±						
ApoE	+	+	+	+			[33,63–67]
ApoJ						+	
Complement							[65,85–89]
<i>C1q</i>	+	+	±/+	+			
<i>C3</i>	+		±/+	+			
<i>C3d</i>			±/+				
<i>C4</i>			–				
<i>C4d</i>	+		–	+			
<i>C7</i>			–				
<i>C9</i>			–/±				
Acute phase proteins^d							[65,103]
<i>Serum amyloid P</i>			–				
<i>α2-macroglobulin</i>		+					
ICAM-1	+						[109]
Cystatin-c	+						[110]
CLAC		+ ^e					[116]

(– no co-deposition; ± weak co-deposition; + strong codeposition).

^aonly compact A β deposits visible; ^bco-deposition with vascular A β ; ^cexpression in senile plaques in AD is controversial; ^dmice do not possess an α 1-antichymotrypsin homologue [106]; ^eco-deposition with A β 40- and Thioflavin S-negative plaques.

in both classic and diffuse senile plaques in the cerebrum [107] and, specifically, in classic deposits in the cerebellum [108]. Similarly, co-deposition of ICAM-1 has been described in Tg2576 mice [109], although its expression is restricted to Thioflavin-S positive deposits.

Cystatin C has been found in both vascular and parenchymal A β deposits in AD [110]. On its own, cystatin C can form vascular amyloid deposits, as demonstrated in Icelandic patients suffering from hereditary cerebral hemorrhage with amyloidosis (HCHWA) [111]. Immunohistochemical analysis of 2-year old Tg2576 mice revealed that, similar to the human situation, cystatin C was detected in A β deposits of this model [110]. Other AD mouse models have not yet been investigated for the expression of cystatin C, but the role of cystatin C in A β deposition has been studied by creating AD mouse models that overexpress human cystatin C. In these double transgenic mice, cystatin C reduced A β deposition [112,113]. However, a reduction was also found when cystatin C was ablated [114].

By raising antibodies against extracted amyloid deposits, the co-deposition of CLAC with A β was discovered [115]. A subsequent *in vitro* study demonstrated that CLAC can bind A β , but only when A β is aggregat-

ed [115], making CLAC seemingly more selective in its binding than co-depositing proteins such as HSPG and ApoE. In brain material of AD patients CLAC was found co-deposited with A β ₄₂-positive, but not with A β ₄₀- and Thioflavin S-positive plaques [116]. In the same study, a similar co-deposition of CLAC was found in PS/A β PP mice and it was suggested that CLAC co-deposited with A β in more AD mouse models (unpublished data).

CONCLUSION

Some proteins known to co-deposit with human A β also strongly associate with A β in mice, with ApoE being the most prominent. However, there are also many factors that only partly co-deposit with A β in mice or that do not co-deposit at all, in contrast to the situation in AD brains (Table 1). For example, HSPG can be detected in A β deposits in mice, but their expression in Tg mouse brains is much more restricted than in humans. Since HSPG are known to stimulate A β aggregation and stabilize A β deposits, it seems likely that their limited association with A β deposits in mice is one of the reasons that these deposits are less compact

and easier to dissolve than their human equivalents. Of the complement factors, only the early factors of the cascade co-deposit with A β in mice, resulting in a less efficient activation of the complement system and the lack of formation of the MAC. The absence of a robust complement activation, in turn, may explain the relative absence of neurodegeneration in mouse models for AD. In conclusion, although several transgenic mouse models are far from extensively studied for the association of A β -associated proteins with plaques, it appears that the composition of A β deposits in transgenic mice is markedly different from human A β deposits.

The less pronounced association of the above-mentioned factors may be a consequence of the rapid development of AD pathology in mouse models as compared to human AD patients. Indeed in transgenic mice individual plaques can form within weeks [117] or even within 24 h [118], therefore, there is probably simply not enough time to allow co-deposition of these A β -associated proteins in the relatively constrained time period it takes for A β to accumulate in mice. The incomplete replication of the expression of A β -associated factors in mice and thus, the molecular composition of A β deposits in mice, may in turn imply that the results of A β -targeted therapeutics will likely be different in mice than in men. Indeed, there are many discrepancies in the outcomes of therapeutic interventions in mice and humans, with many human trials demonstrating side-effects not seen in mice [92]. Therefore, when using AD mouse models to study A β deposition or the effects of therapeutic agents on A β deposits, it is necessary to consider the differences in A β deposit composition between mice and humans when translating findings in mouse models to the human situation.

ACKNOWLEDGMENTS

This work was supported by a grant from the Internationale Stichting Alzheimer Onderzoek (ISAO, no. 07510), the Netherlands Organization for Scientific Research (NWO/ZonMW, Vidi program, no. 917.46.331) and the Hersenstichting Nederland (no. 14F06.18).

Authors' disclosures available online (<http://www.j-alz.com/disclosures/view.php?id=518>).

REFERENCES

- [1] Glenner GG, Wong CW (1984) Alzheimer's disease: initial report of the purification and characterization of a novel cerebrovascular amyloid protein. *Biochem Biophys Res Commun* **120**, 885-890.
- [2] Yamaguchi H, Hirai S, Morimatsu M, Shoji M, Harigaya Y (1988) Diffuse type of senile plaques in the brains of Alzheimer-type dementia. *Acta Neuropathol* **77**, 113-119.
- [3] Ballatore C, Lee VM, Trojanowski JQ (2007) Tau-mediated neurodegeneration in Alzheimer's disease and related disorders. *Nat Rev Neurosci* **8**, 663-672.
- [4] Sperling RA, Dickerson BC, Pihlajamaki M, Vannini P, LaViolette PS, Vitolo OV, Hedden T, Becker JA, Rentz DM, Selkoe DJ, Johnson KA (2010) Functional alterations in memory networks in early Alzheimer's disease. *Neuromolecular Med* **12**, 27-43.
- [5] Blennow K, de Leon MJ, Zetterberg H (2006) Alzheimer's disease. *Lancet* **368**, 387-403.
- [6] Tandon A, Rogaeva E, Mullan M, St George-Hyslop PH (2000) Molecular genetics of Alzheimer's disease: the role of beta-amyloid and the presenilins. *Curr Opin Neurol* **13**, 377-384.
- [7] Citron M (2000) Identifying proteases that cleave A β PP. *Ann N Y Acad Sci* **920**, 192-196.
- [8] Wolfe MS (2001) Secretase targets for Alzheimer's disease: identification and therapeutic potential. *J Med Chem* **44**, 2039-2060.
- [9] De Strooper B., Vassar R, Golde T (2010) The secretases: enzymes with therapeutic potential in Alzheimer disease. *Nat Rev Neurol* **6**, 99-107.
- [10] Brunkan AL, Goate AM (2005) Presenilin function and gamma-secretase activity. *J Neurochem* **93**, 769-792.
- [11] Sinha S, Anderson JP, Barbour R, Basi GS, Caccavello R, Davis D, Doan M, Dovey HF, Frigon N, Hong J, Jacobson-Croak K, Jewett N, Keim P, Knops J, Lieberburg I, Power M, Tan H, Tatsuno G, Tung J, Schenk D, Seubert P, Suomensaari SM, Wang S, Walker D, Zhao J, McConlogue L, John V (1999) Purification and cloning of amyloid precursor protein beta-secretase from human brain. *Nature* **402**, 537-540.
- [12] Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiáz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M (1999) Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. *Science* **286**, 735-741.
- [13] Brouwers N, Sleegers K, Van Broeckhoven C (2008) Molecular genetics of Alzheimer's disease: an update. *Ann Med* **40**, 562-583.
- [14] Wolfe MS, Haass C (2001) The Role of presenilins in gamma-secretase activity. *J Biol Chem* **276**, 5413-5416.
- [15] Borchelt DR, Thinakaran G, Eckman CB, Lee MK, Davenport F, Ratovitsky T, Prada CM, Kim G, Seekins S, Yager D, Slunt HH, Wang R, Seeger M, Levey AI, Gandy SE, Copeland NG, Jenkins NA, Price DL, Younkin SG, Sisodia SS (1996) Familial Alzheimer's disease-linked presenilin 1 variants elevate A β 1-42/1-40 ratio *in vitro* and *in vivo*. *Neuron* **17**, 1005-1013.
- [16] Sarasa M, Pesini P (2009) Natural non-transgenic animal models for research in Alzheimer's disease. *Curr Alzheimer Res* **6**, 171-178.
- [17] Games D, Buttini M, Kobayashi D, Schenk D, Seubert P (2006) Mice as models: transgenic approaches and Alzheimer's disease. *J Alzheimers Dis* **9**, 133-149.
- [18] Games D, Adams D, Alessandrini R, Barbour R, Berthelette P, Blackwell C, Carr T, Clemens J, Donaldson T, Gillespie F, Guido T, Hagopian S, Johnson-Wood K, Khan K, Lee M, Liebowitz P, Lieberburg I, Little S, Masliah E, McConlogue L, Montoya-Zavala M, Mucke L, Paganini L, Penniman E, Pow-

- er M, Schenk D, Seubert P, Snyder B, Soriano F, Tan H, Vitale J, Wadsworth S, Wolozin B, Zhao J (1995) Alzheimer-type neuropathology in transgenic mice overexpressing V717F beta-amyloid precursor protein. *Nature* **373**, 523-527.
- [19] Dodart JC, Meziane H, Mathis C, Bales KR, Paul SM, Ungerer A (1999) Behavioral disturbances in transgenic mice overexpressing the V717F beta-amyloid precursor protein. *Behav Neurosci* **113**, 982-990.
- [20] Chishti MA, Yang DS, Janus C, Phinney AL, Horne P, Pearson J, Strome R, Zuker N, Loukides J, French J, Turner S, Lozza G, Grilli M, Kunicki S, Morissette C, Paquette J, Gervais F, Bergeron C, Fraser PE, Carlson GA, George-Hyslop PS, Westaway D (2001) Early-onset amyloid deposition and cognitive deficits in transgenic mice expressing a double mutant form of amyloid precursor protein 695. *J Biol Chem* **276**, 21562-21570.
- [21] Hsiao K, Chapman P, Nilsen S, Eckman C, Harigaya Y, Younkin S, Yang F, Cole G (1996) Correlative memory deficits, Abeta elevation, and amyloid plaques in transgenic mice. *Science* **274**, 99-102.
- [22] Jankowsky JL, Fadale DJ, Anderson J, Xu GM, Gonzales V, Jenkins NA, Copeland NG, Lee MK, Younkin LH, Wagner SL, Younkin SG, Borchelt DR (2004) Mutant presenilins specifically elevate the levels of the 42 residue beta-amyloid peptide *in vivo*: evidence for augmentation of a 42-specific gamma secretase. *Hum Mol Genet* **13**, 159-170.
- [23] Holcomb L, Gordon MN, McGowan E, Yu X, Benkovic S, Jantzen P, Wright K, Saad I, Mueller R, Morgan D, Sanders S, Zehr C, O'Campo K, Hardy J, Prada CM, Eckman C, Younkin S, Hsiao K, Duff K (1998) Accelerated Alzheimer-type phenotype in transgenic mice carrying both mutant amyloid precursor protein and presenilin 1 transgenes. *Nat Med* **4**, 97-100.
- [24] Sturchler-Pierrat C, Abramowski D, Duke M, Wiederhold KH, Mistl C, Rothacher S, Ledermann B, Burki K, Frey P, Paganetti PA, Waridel C, Calhoun ME, Jucker M, Probst A, Staufenbiel M, Sommer B (1997) Two amyloid precursor protein transgenic mouse models with Alzheimer disease-like pathology. *Proc Natl Acad Sci U S A* **94**, 13287-13292.
- [25] Davis J, Xu F, Deane R, Romanov G, Previti ML, Zeigler K, Zlokovic BV, Van Nostrand WE (2004) Early-onset and robust cerebral microvascular accumulation of amyloid beta-protein in transgenic mice expressing low levels of a vasculotropic Dutch/Iowa mutant form of amyloid beta-protein precursor. *J Biol Chem* **279**, 20296-20306.
- [26] Calhoun ME, Burgermeister P, Phinney AL, Stalder M, Tolnay M, Wiederhold KH, Abramowski D, Sturchler-Pierrat C, Sommer B, Staufenbiel M, Jucker M (1999) Neuronal overexpression of mutant amyloid precursor protein results in prominent deposition of cerebrovascular amyloid. *Proc Natl Acad Sci U S A* **96**, 14088-14093.
- [27] Herzig MC, Winkler DT, Burgermeister P, Pfeifer M, Kohler E, Schmidt SD, Danner S, Abramowski D, Sturchler-Pierrat C, Burki K, van Duinen SG, Maat-Schieman ML, Staufenbiel M, Mathews PM, Jucker M (2004) Abeta is targeted to the vasculature in a mouse model of hereditary cerebral hemorrhage with amyloidosis. *Nat Neurosci* **7**, 954-960.
- [28] Gotz J, Chen F, Barmettler R, Nitsch RM (2001) Tau filament formation in transgenic mice expressing P301L tau. *J Biol Chem* **276**, 529-534.
- [29] Lewis J, McGowan E, Rockwood J, Melrose H, Nacharaju P, Van SM, Gwinn-Hardy K, Paul MM, Baker M, Yu X, Duff K, Hardy J, Corral A, Lin WL, Yen SH, Dickson DW, Davies P, Hutton M (2000) Neurofibrillary tangles, amyotrophy and progressive motor disturbance in mice expressing mutant (P301L) tau protein. *Nat Genet* **25**, 402-405.
- [30] Oddo S, Caccamo A, Shepherd JD, Murphy MP, Golde TE, Kaye R, Metherate R, Mattson MP, Akbari Y, LaFerla FM (2003) Triple-transgenic model of Alzheimer's disease with plaques and tangles: intracellular Abeta and synaptic dysfunction. *Neuron* **39**, 409-421.
- [31] Kalback W, Watson MD, Kokjohn TA, Kuo YM, Weiss N, Luehrs DC, Lopez J, Brune D, Sisodia SS, Staufenbiel M, Emmerling M, Roher AE (2002) A β PP transgenic mice Tg2576 accumulate Abeta peptides that are distinct from the chemically modified and insoluble peptides deposited in Alzheimer's disease senile plaques. *Biochemistry* **41**, 922-928.
- [32] Kuo YM, Kokjohn TA, Beach TG, Sue LI, Brune D, Lopez JC, Kalback WM, Abramowski D, Sturchler-Pierrat C, Staufenbiel M, Roher AE (2001) Comparative analysis of amyloid-beta chemical structure and amyloid plaque morphology of transgenic mouse and Alzheimer's disease brains. *J Biol Chem* **276**, 12991-12998.
- [33] Van Vickle GD, Esh CL, Dausgs ID, Kokjohn TA, Kalback WM, Patton RL, Luehrs DC, Walker DG, Lue LF, Beach TG, Davis J, Van Nostrand WE, Castano EM, Roher AE (2008) Tg-SwDI transgenic mice exhibit novel alterations in AbetaPP processing, Abeta degradation, and resilient amyloid angiopathy. *Am J Pathol* **173**, 483-493.
- [34] Calhoun ME, Wiederhold KH, Abramowski D, Phinney AL, Probst A, Sturchler-Pierrat C, Staufenbiel M, Sommer B, Jucker M (1998) Neuron loss in A β PP transgenic mice. *Nature* **395**, 755-756.
- [35] Verbeek MM, Otte-Holler I, Veerhuis R, Ruitter DJ, de Waal RM (1998) Distribution of A beta-associated proteins in cerebrovascular amyloid of Alzheimer's disease. *Acta Neuropathol (Berl)* **96**, 628-636.
- [36] Wilhelmus MM, de Waal RM, Verbeek MM (2007) Heat shock proteins and amateur chaperones in amyloid-Beta accumulation and clearance in Alzheimer's disease. *Mol Neurobiol* **35**, 203-216.
- [37] Abraham CR, Potter H (1989) The protease inhibitor, alpha 1-antichymotrypsin, is a component of the brain amyloid deposits in normal aging and Alzheimer's disease. *Ann Med* **21**, 77-81.
- [38] Ma J, Yee A, Brewer HB, Jr., Das S, Potter H (1994) Amyloid-associated proteins alpha 1-antichymotrypsin and apolipoprotein E promote assembly of Alzheimer beta-protein into filaments. *Nature* **372**, 92-94.
- [39] van Horssen J, Wesseling P, van den Heuvel LP, de Waal RM, Verbeek MM (2003) Heparan sulphate proteoglycans in Alzheimer's disease and amyloid-related disorders. *Lancet Neurol* **2**, 482-492.
- [40] Wisniewski T, Castano EM, Golabek A, Vogel T, Frangione B (1994) Acceleration of Alzheimer's fibril formation by apolipoprotein E *in vitro*. *Am J Pathol* **145**, 1030-1035.
- [41] Snow AD, Mar H, Nochlin D, Kimata K, Kato M, Suzuki S, Hassell J, Wight TN (1988) The presence of heparan sulfate proteoglycans in the neuritic plaques and congophilic angiopathy in Alzheimer's disease. *Am J Pathol* **133**, 456-463.
- [42] van Horssen J, Otte-Holler I, David G, Maat-Schieman ML, van den Heuvel LP, Wesseling P, de Waal RM, Verbeek MM (2001) Heparan sulfate proteoglycan expression in cerebrovascular amyloid beta deposits in Alzheimer's disease and hereditary cerebral hemorrhage with amyloidosis (Dutch) brains. *Acta Neuropathol (Berl)* **102**, 604-614.

- [43] Cotman SL, Halfter W, Cole GJ (2000) Agrin binds to beta-amyloid (A β), accelerates A β fibril formation, and is localized to A β deposits in Alzheimer's disease brain. *Mol Cell Neurosci* **15**, 183-198.
- [44] van Horsen J, Kleinnijenhuis J, Maass CN, Rensink AA, Otte-Holler I, David G, van den Heuvel LP, Wesseling P, de Waal RM, Verbeek MM (2002) Accumulation of heparan sulfate proteoglycans in cerebellar senile plaques. *Neurobiol Aging* **23**, 537-545.
- [45] Snow AD, Kinsella MG, Parks E, Sekiguchi RT, Miller JD, Kimata K, Wight TN (1995) Differential binding of vascular cell-derived proteoglycans (perlecan, biglycan, decorin, and versican) to the beta-amyloid protein of Alzheimer's disease. *Arch Biochem Biophys* **320**, 84-95.
- [46] Castillo GM, Ngo C, Cummings J, Wight TN, Snow AD (1997) Perlecan binds to the beta-amyloid proteins (A β) of Alzheimer's disease, accelerates A β fibril formation, and maintains A β fibril stability. *J Neurochem* **69**, 2452-2465.
- [47] Castillo GM, Lukito W, Wight TN, Snow AD (1999) The sulfate moieties of glycosaminoglycans are critical for the enhancement of beta-amyloid protein fibril formation. *J Neurochem* **72**, 1681-1687.
- [48] Bornemann KD, Staufenbiel M (2000) Transgenic mouse models of Alzheimer's disease. *Ann N Y Acad Sci* **908**, 260-266.
- [49] O'Callaghan P, Sandwall E, Li JP, Yu H, Ravid R, Guan ZZ, van Kuppevelt TH, Nilsson LN, Ingelsson M, Hyman BT, Kalimo H, Lindahl U, Lannfelt L, Zhang X (2008) Heparan sulfate accumulation with A β deposits in Alzheimer's disease and Tg2576 mice is contributed by glial cells. *Brain Pathol* **18**, 548-561.
- [50] Timmer NM, Herbert MK, Kleinovink JW, Kiliaan AJ, de Waal RM, Verbeek MM (2010) Limited expression of heparan sulfate proteoglycans associated with A β deposits in the A β PPswe/PS1dE9 mouse model for Alzheimer's disease. *Neuropathol Appl Neurobiol* **36**, 478-486.
- [51] Kokjohn TA, Roher AE (2009) Amyloid precursor protein transgenic mouse models and Alzheimer's disease: understanding the paradigms, limitations, and contributions. *Alzheimers Dement* **5**, 340-347.
- [52] Snow AD, Wight TN (1989) Proteoglycans in the pathogenesis of Alzheimer's disease and other amyloidoses. *Neurobiol Aging* **10**, 481-497.
- [53] Boyles JK, Pitas RE, Wilson E, Mahley RW, Taylor JM (1985) Apolipoprotein E associated with astrocytic glia of the central nervous system and with nonmyelinating glia of the peripheral nervous system. *J Clin Invest* **76**, 1501-1513.
- [54] Bruinsma IB, Wilhelmus MM, Kox M, Veerhuis R, de Waal RM, Verbeek MM (2010) Apolipoprotein E protects cultured pericytes and astrocytes from D-A β (1-40)-mediated cell death. *Brain Res* **1315**, 169-180.
- [55] Wilhelmus MM, Otte-Holler I, Davis J, Van Nostrand WE, de Waal RM, Verbeek MM (2005) Apolipoprotein E genotype regulates amyloid-beta cytotoxicity. *J Neurosci* **25**, 3621-3627.
- [56] Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH (1987) Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B₁₀₀/LDL receptors in the brain. *J Biol Chem* **262**, 14352-14360.
- [57] Strittmatter WJ, Saunders AM, Schmechel D, Pericak-Vance M, Enghild J, Salvesen GS, Roses AD (1993) Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. *Proc Natl Acad Sci U S A* **90**, 1977-1981.
- [58] Kim J, Basak JM, Holtzman DM (2009) The role of apolipoprotein E in Alzheimer's disease. *Neuron* **63**, 287-303.
- [59] Namba Y, Tomonaga M, Kawasaki H, Otomo E, Ikeda K (1991) Apolipoprotein E immunoreactivity in cerebral amyloid deposits and neurofibrillary tangles in Alzheimer's disease and kuru plaque amyloid in Creutzfeldt-Jakob disease. *Brain Res* **541**, 163-166.
- [60] Navarro A, Del VE, Astudillo A, Gonzalez del RC, Tolivia J (2003) Immunohistochemical study of distribution of apolipoproteins E and D in human cerebral beta amyloid deposits. *Exp Neurol* **184**, 697-704.
- [61] Wisniewski T, Frangione B (1992) Apolipoprotein E: a pathological chaperone protein in patients with cerebral and systemic amyloid. *Neurosci Lett* **135**, 235-238.
- [62] Sheng JG, Mrak RE, Griffin WS (1996) Apolipoprotein E distribution among different plaque types in Alzheimer's disease: implications for its role in plaque progression. *Neuropathol Appl Neurobiol* **22**, 334-341.
- [63] Kuo YM, Crawford F, Mullan M, Kokjohn TA, Emmerling MR, Weller RO, Roher AE (2000) Elevated A β and apolipoprotein E in A β PP transgenic mice and its relationship to amyloid accumulation in Alzheimer's disease. *Mol Med* **6**, 430-439.
- [64] Terai K, Iwai A, Kawabata S, Sasamata M, Miyata K, Yamaguchi T (2001) Apolipoprotein E deposition and astrogliosis are associated with maturation of beta-amyloid plaques in betaA β PPswe transgenic mouse: Implications for the pathogenesis of Alzheimer's disease. *Brain Res* **900**, 48-56.
- [65] Schwab C, Hosokawa M, McGeer PL (2004) Transgenic mice overexpressing amyloid beta protein are an incomplete model of Alzheimer disease. *Exp Neurol* **188**, 52-64.
- [66] Burns MP, Noble WJ, Olm V, Gaynor K, Casey E, LaFrancois J, Wang L, Duff K (2003) Co-localization of cholesterol, apolipoprotein E and fibrillar A β in amyloid plaques. *Brain Res Mol Brain Res* **110**, 119-125.
- [67] Kulnane LS, Lamb BT (2001) Neuropathological characterization of mutant amyloid precursor protein yeast artificial chromosome transgenic mice. *Neurobiol Dis* **8**, 982-992.
- [68] Lemere CA, Blusztajn JK, Yamaguchi H, Wisniewski T, Saito TC, Selkoe DJ (1996) Sequence of deposition of heterogeneous amyloid beta-peptides and APO E in Down syndrome: implications for initial events in amyloid plaque formation. *Neurobiol Dis* **3**, 16-32.
- [69] Bales KR, Verina T, Cummins DJ, Du Y, Dodel RC, Saura J, Fishman CE, DeLong CA, Piccardo P, Petegnief V, Ghetti B, Paul SM (1999) Apolipoprotein E is essential for amyloid deposition in the A β PP(V717F) transgenic mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **96**, 15233-15238.
- [70] Holtzman DM, Fagan AM, Mackey B, Tenkova T, Sartorius L, Paul SM, Bales K, Ashe KH, Irizarry MC, Hyman BT (2000) Apolipoprotein E facilitates neuritic and cerebrovascular plaque formation in an Alzheimer's disease model. *Ann Neurol* **47**, 739-747.
- [71] Harold D, Abraham R, Hollingworth P, Sims R, Gerrish A, Hamshere ML, Pahwa JS, Moskvin V, Dowzell K, Williams A, Jones N, Thomas C, Stretton A, Morgan AR, Lovestone S, Powell J, Proitsi P, Lupton MK, Brayne C, Rubinsztein DC, Gill M, Lawlor B, Lynch A, Morgan K, Brown KS, Passmore PA, Craig D, McGuinness B, Todd S, Holmes C, Mann D, Smith AD, Love S, Kehoe PG, Hardy J, Mead S,

- Fox N, Rossor M, Collinge J, Maier W, Jessen F, Schurmann B, van den Bussche H, Heuser I, Kornhuber J, Wiltfang J, Dichgans M, Frolich L, Hampel H, Hull M, Rujescu D, Goate AM, Kauwe JS, Cruchaga C, Nowotny P, Morris JC, Mayo K, Sleegers K, Bettens K, Engelborghs S, De Deyn PP, Van Broeckhoven C, Livingston G, Bass NJ, Gurling H, McQuillin A, Gwilliam R, Deloukas P, Al-Chalabi A, Shaw CE, Tsolaki M, Singleton AB, Guerreiro R, Muhleisen TW, Nothen MM, Moebus S, Jockel KH, Klopp N, Wichmann HE, Carrasquillo MM, Pankratz VS, Younkin SG, Holmans PA, O'Donovan M, Owen MJ, Williams J (2009) Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet* **41**, 1088-1093.
- [72] Lambert JC, Heath S, Even G, Campion D, Sleegers K, Hiltunen M, Combarros O, Zelenika D, Bullido MJ, Tavernier B, Letenneur L, Bettens K, Berr C, Pasquier F, Fievet N, Barberger-Gateau P, Engelborghs S, De DP, Mateo I, Franck A, Helisalmi S, Porcellini E, Hanon O, de Pancorbo MM, Lendon C, Dufouil C, Jaillard C, Leveillard T, Alvarez V, Bosco P, Mancuso M, Panza F, Nacmias B, Bossu P, Piccardi P, Annoni G, Seripa D, Galimberti D, Hannequin D, Licastro F, Soininen H, Ritchie K, Blanche H, Dartigues JF, Tzourio C, Gut I, Van BC, Alperovitch A, Lathrop M, Amouyel P (2009) Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet* **41**, 1094-1099.
- [73] Choi-Miura NH, Ihara Y, Fukuchi K, Takeda M, Nakano Y, Tobe T, Tomita M (1992) SP-40,40 is a constituent of Alzheimer's amyloid. *Acta Neuropathol* **83**, 260-264.
- [74] Matsubara E, Soto C, Governale S, Frangione B, Ghiso J (1996) Apolipoprotein J and Alzheimer's amyloid beta solubility. *Biochem J* **316** (Pt 2), 671-679.
- [75] DeMattos RB, O'dell MA, Parsadanian M, Taylor JW, Harmony JA, Bales KR, Paul SM, Aronow BJ, Holtzman DM (2002) Clusterin promotes amyloid plaque formation and is critical for neuritic toxicity in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci U S A* **99**, 10843-10848.
- [76] Morgan BP, Gasque P (1996) Expression of complement in the brain: role in health and disease. *Immunol Today* **17**, 461-466.
- [77] Bradt BM, Kolb WP, Cooper NR (1998) Complement-dependent proinflammatory properties of the Alzheimer's disease beta-peptide. *J Exp Med* **188**, 431-438.
- [78] Jiang H, Burdick D, Glabe CG, Cotman CW, Tenner AJ (1994) beta-Amyloid activates complement by binding to a specific region of the collagen-like domain of the C1q A chain. *J Immunol* **152**, 5050-5059.
- [79] Yasojima K, Schwab C, McGeer EG, McGeer PL (1999) Up-regulated production and activation of the complement system in Alzheimer's disease brain. *Am J Pathol* **154**, 927-936.
- [80] Eikelenboom P, Stam FC (1982) Immunoglobulins and complement factors in senile plaques. An immunoperoxidase study. *Acta Neuropathol* **57**, 239-242.
- [81] Loeffler DA (2004) Using animal models to determine the significance of complement activation in Alzheimer's disease. *J Neuroinflammation* **1**, 18.
- [82] Webster S, O'Barr S, Rogers J (1994) Enhanced aggregation and beta structure of amyloid beta peptide after incubation with C1q. *J Neurosci Res* **39**, 448-456.
- [83] Shen Y, Halperin JA, Lee CM (1995) Complement-mediated neurotoxicity is regulated by homologous restriction. *Brain Res* **671**, 282-292.
- [84] Wyss-Coray T, Yan F, Lin AH, Lambris JD, Alexander JJ, Quigg RJ, Masliah E (2002) Prominent neurodegeneration and increased plaque formation in complement-inhibited Alzheimer's mice. *Proc Natl Acad Sci U S A* **99**, 10837-10842.
- [85] Fonseca MI, Zhou J, Botto M, Tenner AJ (2004) Absence of C1q leads to less neuropathology in transgenic mouse models of Alzheimer's disease. *J Neurosci* **24**, 6457-6465.
- [86] Zhou J, Fonseca MI, Pisalyaput K, Tenner AJ (2008) Complement C3 and C4 expression in C1q sufficient and deficient mouse models of Alzheimer's disease. *J Neurochem* **106**, 2080-2092.
- [87] Matsuoka Y, Picciano M, Malester B, LaFrancois J, Zehr C, Daeschner JM, Olschowka JA, Fonseca MI, O'Banion MK, Tenner AJ, Lemere CA, Duff K (2001) Inflammatory responses to amyloidosis in a transgenic mouse model of Alzheimer's disease. *Am J Pathol* **158**, 1345-1354.
- [88] Fan R, DeFilippis K, Van Nostrand WE (2007) Induction of complement proteins in a mouse model for cerebral microvascular A beta deposition. *J Neuroinflammation* **4**, 22.
- [89] Reichwald J, Danner S, Wiederhold KH, Staufenbiel M (2009) Expression of complement system components during aging and amyloid deposition in A β PP transgenic mice. *J Neuroinflammation* **6**, 35.
- [90] Webster SD, Tenner AJ, Poulos TL, Cribbs DH (1999) The mouse C1q A-chain sequence alters beta-amyloid-induced complement activation. *Neurobiol Aging* **20**, 297-304.
- [91] Ebanks RO, Isenman DE (1996) Mouse complement component C4 is devoid of classical pathway C5 convertase subunit activity. *Mol Immunol* **33**, 297-309.
- [92] Orgogozo JM, Gilman S, Dartigues JF, Laurent B, Puel M, Kirby LC, Jouanny P, Dubois B, Eisner L, Flitman S, Michel BF, Boada M, Frank A, Hock C (2003) Subacute meningoencephalitis in a subset of patients with AD after Abeta42 immunization. *Neurology* **61**, 46-54.
- [93] Schenk D, Barbour R, Dunn W, Gordon G, Grajeda H, Guido T, Hu K, Huang J, Johnson-Wood K, Khan K, Kholodenko D, Lee M, Liao Z, Lieberburg I, Motter R, Mutter L, Soriano F, Shopp G, Vasquez N, Vandeventer C, Walker S, Wogulis M, Yednock T, Games D, Seubert P (1999) Immunization with amyloid-beta attenuates Alzheimer-disease-like pathology in the PDA β PP mouse. *Nature* **400**, 173-177.
- [94] Abraham CR, Selkoe DJ, Potter H (1988) Immunochemical identification of the serine protease inhibitor alpha 1-antichymotrypsin in the brain amyloid deposits of Alzheimer's disease. *Cell* **52**, 487-501.
- [95] Kalaria RN, Grahovac I (1990) Serum amyloid P immunoreactivity in hippocampal tangles, plaques and vessels: implications for leakage across the blood-brain barrier in Alzheimer's disease. *Brain Res* **516**, 349-353.
- [96] McGeer EG, Yasojima K, Schwab C, McGeer PL (2001) The pentraxins: possible role in Alzheimer's disease and other innate inflammatory diseases. *Neurobiol Aging* **22**, 843-848.
- [97] Ying SC, Gewurz AT, Jiang H, Gewurz H (1993) Human serum amyloid P component oligomers bind and activate the classical complement pathway via residues 14-26 and 76-92 of the A chain collagen-like region of C1q. *J Immunol* **150**, 169-176.
- [98] Shi J, Perry G, Aliev G, Smith MA, Ashe KH, Friedland RP (1999) Serum amyloid P is not present in amyloid beta deposits of a transgenic animal model. *Neuroreport* **10**, 3229-3232.
- [99] Shi J, Perry G, Berridge MS, Aliev G, Siedlak SL, Smith MA, LaManna JC, Friedland RP (2002) Labeling of cerebral

- amyloid beta deposits *in vivo* using intranasal basic fibroblast growth factor and serum amyloid P component in mice. *J Nucl Med* **43**, 1044-1051.
- [100] Winkler DT, Bondolfi L, Herzig MC, Jann L, Calhoun ME, Wiederhold KH, Tolnay M, Staufenbiel M, Jucker M (2001) Spontaneous hemorrhagic stroke in a mouse model of cerebral amyloid angiopathy. *J Neurosci* **21**, 1619-1627.
- [101] Van Gool D., De Strooper B., Van Leuven F., Triau E, Dom R (1993) alpha 2-Macroglobulin expression in neuritic-type plaques in patients with Alzheimer's disease. *Neurobiol Aging* **14**, 233-237.
- [102] Hughes SR, Khorkova O, Goyal S, Knaeblein J, Heroux J, Riedel NG, Sahasrabudhe S (1998) Alpha2-macroglobulin associates with beta-amyloid peptide and prevents fibril formation. *Proc Natl Acad Sci U S A* **95**, 3275-3280.
- [103] Kondo T, Tooyama I (2003) Deposition of Alpha2-Macroglobulin in Fibrillar Type of Senile Plaques in the Brain of PS/A β PP-Transgenic Mice. *Acta Histochem Cytochem* **36**, 215-220.
- [104] Eriksson S, Janciauskiene S, Lannfelt L (1995) Alpha 1-antichymotrypsin regulates Alzheimer beta-amyloid peptide fibril formation. *Proc Natl Acad Sci U S A* **92**, 2313-2317.
- [105] Janciauskiene S, Rubin H, Lukacs CM, Wright HT (1998) Alzheimer's peptide A β 1-42 binds to two beta-sheets of alpha1-antichymotrypsin and transforms it from inhibitor to substrate. *J Biol Chem* **273**, 28360-28364.
- [106] Nilsson LN, Bales KR, DiCarlo G, Gordon MN, Morgan D, Paul SM, Potter H (2001) Alpha-1-antichymotrypsin promotes beta-sheet amyloid plaque deposition in a transgenic mouse model of Alzheimer's disease. *J Neurosci* **21**, 1444-1451.
- [107] Verbeek MM, Otte-Holler I, Westphal JR, Wesseling P, Ruiters DJ, de Waal RM (1994) Accumulation of intercellular adhesion molecule-1 in senile plaques in brain tissue of patients with Alzheimer's disease. *Am J Pathol* **144**, 104-116.
- [108] Verbeek MM, Otte-Holler I, Wesseling P, Ruiters DJ, de Waal RM (1996) Differential expression of intercellular adhesion molecule-1 (ICAM-1) in the A β containing lesions in brains of patients with dementia of the Alzheimer type. *Acta Neuropathol* **91**, 608-615.
- [109] Apelt J, Lessig J, Schliebs R (2002) Beta-amyloid-associated expression of intercellular adhesion molecule-1 in brain cortical tissue of transgenic Tg2576 mice. *Neurosci Lett* **329**, 111-115.
- [110] Levy E, Sastre M, Kumar A, Gallo G, Piccardo P, Ghetti B, Tagliavini F (2001) Codeposition of cystatin C with amyloid-beta protein in the brain of Alzheimer disease patients. *J Neuropathol Exp Neurol* **60**, 94-104.
- [111] Olafsson I, Thorsteinsson L, Jensson O (1996) The molecular pathology of hereditary cystatin C amyloid angiopathy causing brain hemorrhage. *Brain Pathol* **6**, 121-126.
- [112] Kaeser SA, Herzig MC, Coomaraswamy J, Kilger E, Selenica ML, Winkler DT, Staufenbiel M, Levy E, Grubb A, Jucker M (2007) Cystatin C modulates cerebral beta-amyloidosis. *Nat Genet* **39**, 1437-1439.
- [113] Mi W, Pawlik M, Sastre M, Jung SS, Radvinsky DS, Klein AM, Sommer J, Schmidt SD, Nixon RA, Mathews PM, Levy E (2007) Cystatin C inhibits amyloid-beta deposition in Alzheimer's disease mouse models. *Nat Genet* **39**, 1440-1442.
- [114] Sun B, Zhou Y, Halabisky B, Lo I, Cho SH, Mueller-Stener S, Devidze N, Wang X, Grubb A, Gan L (2008) Cystatin C-cathepsin B axis regulates amyloid beta levels and associated neuronal deficits in an animal model of Alzheimer's disease. *Neuron* **60**, 247-257.
- [115] Hashimoto T, Wakabayashi T, Watanabe A, Kowa H, Hosoda R, Nakamura A, Kanazawa I, Arai T, Takio K, Mann DM, Iwatsubo T (2002) CLAC: a novel Alzheimer amyloid plaque component derived from a transmembrane precursor, CLAC-P/collagen type XXV. *EMBO J* **21**, 1524-1534.
- [116] Kowa H, Sakakura T, Matsuura Y, Wakabayashi T, Mann DM, Duff K, Tsuji S, Hashimoto T, Iwatsubo T (2004) Mostly separate distributions of CLAC- versus A β 40- or Thioflavin S-reactivities in senile plaques reveal two distinct subpopulations of β -amyloid deposits. *Am J Pathol* **165**, 273-281.
- [117] Yan P, Bero AW, Cirrito JR, Xiao Q, Hu X, Wang Y, Gonzales E, Holtzman DM, Lee JM (2009) Characterizing the appearance and growth of amyloid plaques in A β PP/PS1 mice. *J Neurosci* **29**, 10706-10714.
- [118] Meyer-Luehmann M, Spires-Jones TL, Prada C, Garcia-Alloza M, de CA, Rozkalne A, Koenigsnecht-Talboo J, Holtzman DM, Bacskai BJ, Hyman BT (2008) Rapid appearance and local toxicity of amyloid-beta plaques in a mouse model of Alzheimer's disease. *Nature* **451**, 720-724.