

## Modes of A $\beta$ toxicity in Alzheimer's disease

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**Abstract** Alzheimer's disease (AD) is reaching epidemic proportions, yet a cure is not yet available. While the genetic causes of the rare familial inherited forms of AD are understood, the causes of the sporadic forms of the disease are not. Histopathologically, these two forms of AD are indistinguishable: they are characterized by amyloid- $\beta$  (A $\beta$ ) peptide-containing amyloid plaques and tau-containing neurofibrillary tangles. In this review we compare AD to frontotemporal dementia (FTD), a subset of which is characterized by tau deposition in the absence of overt plaques. A host of transgenic animal AD models have been established through the expression of human proteins with pathogenic mutations previously identified in familial AD and FTD. Determining how these mutant proteins cause disease *in vivo* should contribute to an understanding of the causes of the more frequent sporadic forms. We discuss the insight transgenic animal models have provided into A $\beta$  and tau toxicity, also with regards to mitochondrial function and the crucial role tau plays in mediating A $\beta$  toxicity. We also discuss the role of miRNAs in mediating the toxic effects of the A $\beta$  peptide.

**Keywords** Alzheimer · Amyloid · Frontotemporal dementia · Fyn · miRNA · Mitochondria · Oligomer · Proteomic · Tau · Transgenic

### Introduction

One of the major burdens associated with advanced age is dementia, a pathological condition defined as the significant loss of intellectual abilities—such as memory functions—that is severe enough to interfere with social or occupational functioning. The relentless neuronal degeneration that is associated with Alzheimer's disease (AD) and the more than two dozen related disorders affects a steadily increasing percentage of the population worldwide. More than 26 million people worldwide are currently living with AD, a number that will quadruple to more than 106 million by 2050 unless effective treatments or a cure are found. Of all dementing disorders, AD is the most common form, comprising 50–70% of all reported cases. Frontotemporal dementia (FTD), in comparison, is less frequent, but may account for up to 50% of all dementia cases presenting before the age of 60 years [1]. At the present time, neither AD nor FTD can be cured although lifestyle choices, such as of diet and exercise, confer some form of protection [2].

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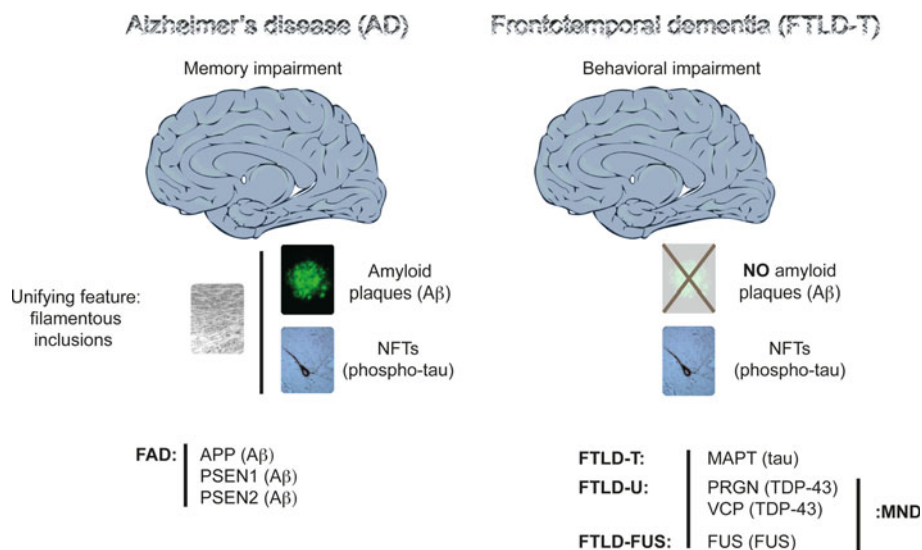
### Neuropathological features of AD and FTD

When in the years of 1992 and 1997, the 100-year-old histological slides of Alois Alzheimer's original cases were rediscovered in the basement of the Institute of Neuropathology of the University of Munich [3], they revealed what Alzheimer had described in his first case, Auguste D,

as the key features of the disease named after him: the presence of overt neurofibrillary tangles (NFTs) and amyloid plaques. While Alzheimer was the first to describe NFTs [4], the credit of reporting amyloid plaques for the first time goes to Fischer and Redich [5]. Plaques and NFTs are the key histopathological hallmarks of AD (Fig. 1). The AD brain is further characterized by massive neuronal cell and synapse loss at specific predilection sites [6]. The major proteinaceous component of the plaques is a 40–42 amino acid polypeptide amyloid- $\beta$  ( $A\beta$ ; ( $A\beta_{40}$  and  $A\beta_{42}$ ) that is derived by proteolytic cleavage from the larger amyloid precursor protein APP [7, 8]. The enzyme  $\beta$ -secretase generates the amino terminus of  $A\beta$ , while  $\gamma$ -secretase cleavage at the carboxy-terminus dictates its length.  $A\beta_{40}$  is the most common species and  $A\beta_{42}$  the more fibrillogenic.  $\beta$ -Secretase activity has been attributed to a single protein, BACE 1 [9], whereas  $\gamma$ -secretase activity depends on four essential components, namely, presenilin, nicastrin, APH-1, and PEN-2, which together form a proteolytic complex [10].  $\alpha$ -Secretase is the enzyme that is involved in the non-amyloidogenic pathway, by

cleaving APP within the  $A\beta$  domain and thus precluding  $A\beta$  formation [11].

The second histopathological hallmark of AD are the neurofibrillary lesions that are found in cell bodies and apical dendrites as NFTs, in distal dendrites as neuropil threads, and in the abnormal neurites that are associated with some plaques (neuritic plaques). NFTs are also abundant, in the absence of overt plaques, in over two dozen tauopathies that represent a significant subset of FTD [12]. The neurofibrillary lesions are mainly composed of highly phosphorylated, aggregated assemblies of the protein tau [13, 14]. Tau belongs to the family of microtubule-associated proteins (MAPs) that includes MAP2. As neurons develop, tau segregates into axons, and MAP2 into dendrites [15]. In the axon, tau stabilizes the microtubules. Under pathological conditions tau dissociates from the microtubules, causing them to collapse, and tau starts accumulating in the somatodendritic compartment. The precise steps of this process are not fully understood. The established axonal localization of tau does not exclude the fact that under physiological conditions, this protein exerts



**Fig. 1** Histopathological and genetic features of Alzheimer's disease (AD) and frontotemporal dementia (FTD). Memory impairment characterizes AD at a clinical level, and the presence of amyloid ( $A\beta$ ) plaques and phospho-tau-containing neurofibrillary tangles (NFTs) in brain at a histopathological level. A unifying feature of the plaques and tangles is that their major proteinaceous components,  $A\beta$  and tau, respectively, are fibrillar. Plaques are scarce in FTD. The prominent feature in FTD is a behavioral impairment, with memory functions often being preserved until late in disease. Compared to AD, FTD is a highly heterogeneous group of related dementias, as reflected both by the function of the mutated genes, and by the proteins that are deposited as insoluble aggregates, and by the clinical syndromes, with language and behavioral variants known. A subset of FTD, known as frontotemporal lobar degeneration with tau deposits (FTLD-T) or FTD with Parkinsonism linked to chromosome 17

(FTDP-17), is characterized by tau inclusions. The first FTD mutations were identified in the tau-encoding *MAPT* gene causing FTLD-T. Mutations have been subsequently identified in the *PGRN* gene encoding progranulin, and in the *VCP* gene encoding valosin-containing protein. TDP-43 is the deposited protein, and these deposits are shared with motor neuron disease (MND), also known as amyotrophic lateral sclerosis (ALS). Fused in sarcoma (*FUS*) is another pathological protein that has been identified in a small subset of patients with either ALS or a form of FTD. In familial AD (FAD), mutations have been identified in the *APP* gene encoding the amyloid precursor protein from which  $A\beta$  is derived by proteolytic cleavage, and in the genes encoding presenilin 1 and 2 (*PSEN1* and *PSEN2*), which form part of the  $A\beta$  cleavage machinery. In AD, no mutations have been identified in the tau-encoding *MAPT* gene

important functions outside of the axon, such as in the dendrite, as we have recently shown [16].

Tau contains an unusually high number of putative phosphorylation sites (45 serines, 35 threonines, and 4 tyrosines), and for many of these, specific antibodies are available [17]. Under physiological conditions, there are on average 2–3 mol of phosphate per mol of tau, whereas under pathological conditions this ratio is increased to 7–8 mol [18]. This posttranslational modification has been termed ‘hyperphosphorylation’: some sites are phosphorylated to a higher degree in the diseased than in the healthy brain; others are de novo phosphorylated. Phosphorylation tends to dissociate tau from microtubules. Tau also undergoes a conformational change that is likely to assist in differential phosphorylation [19]. Both tau and A $\beta$  undergo nucleation-dependent fibril formation [20]. In the course of this process, initially dispersed polypeptide chains slowly come together to form a diverse array of fibrillation nuclei that enable the rapid outgrowth into higher order assemblies, including fibrils [21–23]. Tau is generally perceived as a neuronal protein; however, in tauopathies such as progressive supranuclear palsy (PSP) or corticobasal degeneration (CBD), the protein forms aggregates in non-neuronal cells [24], emphasizing the important role of glia in neurodegenerative disease [25].

In AD, the most severe neuropathological changes occur in the hippocampal formation, followed by the association cortices and subcortical structures, including the amygdala and the nucleus basalis of Meynert [26]. NFTs develop and spread in a predictable manner across the brain, providing the basis for distinguishing six stages of disease progression: the transentorhinal Braak stages I–II represent clinically silent cases; the limbic stages III–IV, incipient AD; the neocortical stages V–VI, fully developed AD. By using phosphorylation-dependent anti-tau antibodies, such as AT8, neuronal changes can be visualized well before the actual formation of NFTs [27, 28]. In FTD, there is atrophy of the frontal and temporal cortex that is often asymmetrical.

### Genetic causes of AD and FTD

What is causing AD is not understood, with the exception of the rare, familial (FAD) forms; the latter, however, account for less than 1% of all cases [29]. In FAD, autosomal dominant mutations have been identified in three genes: in *APP* itself, and in the presenilin 1- (*PSEN1*) and presenilin 2-encoding (*PSEN2*) genes (Fig. 1). In addition to the FAD genes, a series of susceptibility genes have been identified in sporadic AD (SAD); these include *apolipoprotein E* (*APOE*) as the most established risk gene [30] *CLU* encoding clusterin, *PICALM* encoding the

phosphatidylinositol-binding clathrin assembly protein, and *CRI* encoding the complement component (3b/4b) receptor 1 [31–33]. Clinically and histopathologically, early-onset FAD cannot be discriminated from late-onset SAD [24].

Compared to AD, FTD is a highly heterogeneous group of related dementias, as reflected both by the function of the mutated genes, by the proteins that are deposited as insoluble aggregates, and by the clinical syndromes, with language and behavioral variants known [34]. The first FTD mutations were identified in FTDP-17 (FTD with Parkinsonism linked to chromosome 17) in the tau-encoding *MAPT* gene [35–37]. This subset of FTD, also known as FTLT-T (frontotemporal lobar degeneration with tau deposits) is characterized by tau inclusions (Fig. 1). There is also a subset of FTD that lacks tau aggregates but presents with an abundance of ubiquitin-positive lesions. The nature of the aggregating protein was not known until recently. This ‘dementia lacking distinctive histology’ (now termed FTLT-U or FTDU-17) is caused by loss-of-function mutations in the *PGRN* gene that encodes the pleiotropic protein progranulin, and in the *VCP* gene that encodes valosin-containing protein [38, 39]; the aggregating protein is TDP-43 (TAR DNA-binding protein 43), a highly conserved heteronuclear ribonucleoprotein (hnRNP) [40]. Fused in sarcoma (FUS) is another pathological protein that has been identified in a small subset of patients with either amyotrophic lateral sclerosis (ALS) or a form of FTD [41]. Finally, mutations in *CHMP2B* that encodes chromatin-modifying protein 2B cause FTD in the absence of either tau or TDP-43 inclusions [42]. For detailed information and an update on the genes and mutations in familial AD and FTD, we refer the reader to two websites—<http://www.molgen.ua.ac.be/ADMutations> and <http://www.molgen.ua.ac.be/FTDMutations>—both of which are continually updated resources.

### Clinical features of AD and FTD

The accurate differential diagnosis of AD and FTD remains a difficult yet important clinical issue, particularly with the advent of treatments that are designed to target the causes and/or consequences of specific types of dementia [43]. With the recent advent of positron emission tomography (PET) imaging, it has become possible to assess A $\beta$  deposition longitudinally and explore its relationship with cognition and disease progression. For example, in one study that involved over 200 subjects and a 20-month clinical follow-up after [<sup>11</sup>C]Pittsburgh compound B (PiB)-PET and two additional follow-ups for up to 3 years with lower numbers of subjects, at baseline, 97% of AD, 69% of mild cognitive impairment (MCI), and 31% of healthy

control (HC) subjects showed high PiB retention [44]. At the 20-month follow-up, small but significant increases in PiB standardized uptake value ratios were observed in the AD and MCI groups, as well as in the HCs with high PiB retention at baseline (5.7, 2.1, and 1.5%, respectively). There was a weak correlation between PiB increases and the decline in cognition when all groups were combined. Progression to AD occurred in 67% of MCI with high PiB versus 5% of those with low PiB, but 20% of the low PiB MCI subjects progressed to other dementias. Of the high PiB HCs, 16% developed MCI or AD within 20 months and 25% by 3 years. One low PiB HC developed MCI. Taken together, these results indicate that A $\beta$  deposition increases slowly from cognitive normality to moderate severity AD. Extensive A $\beta$  deposition precedes cognitive impairment and is associated with a higher risk of cognitive decline in HCs and progression from MCI to AD over 1–2 years. Importantly, the cognitive decline is only weakly related to the change in A $\beta$  plaque burden, suggesting that downstream factors have a more direct effect on symptom progression [44]. One of these down-stream factors may well be differences in protein levels of tau, with low levels conferring protection [45].

AD is characterized by deficits in memory, visuospatial ability, language, and executive function. While cognitive deficits have traditionally been emphasized in defining AD, there are a variety of neurobehavioral symptoms that are also commonly associated with the disease, including increased apathy, agitation, anxiety, and psychiatric symptoms, such as delusions or hallucination [46]. In contrast to AD, which is predominantly characterized by memory loss, FTD is mainly initiated by behavioral impairment (Fig. 1). The neurobehavioral symptoms include overeating, apathy or euphoria, disinhibition, depression, stereotyped behaviors, reduced empathy, and antisocial and aggressive behaviors. Patients with FTD also show a variety of cognitive problems, such as language and memory impairments, which are often coupled with a lack of insight into these changes [47]. In a significant subset of FTD, late Parkinsonism is found [12]. The diagnosis is based on the person's clinical presentation, the medical history and examination, neuropsychological assessments and, increasingly, brain imaging. However, due to its insidious and gradual onset, the diagnosis of FTD can be difficult. Furthermore, the behavioral symptoms, such as apathy or impulsive responding, that are associated with FTD can have a negative impact on cognitive performance, and patients may be quite often wrongly diagnosed with AD [48]. At present, AD and FTD can only be definitively diagnosed at autopsy. The average age of diagnosis of FTD is about 60 years, which is in the order of 10 years before the average SAD patient is diagnosed [49, 50].

## Animal models of AD and FTD

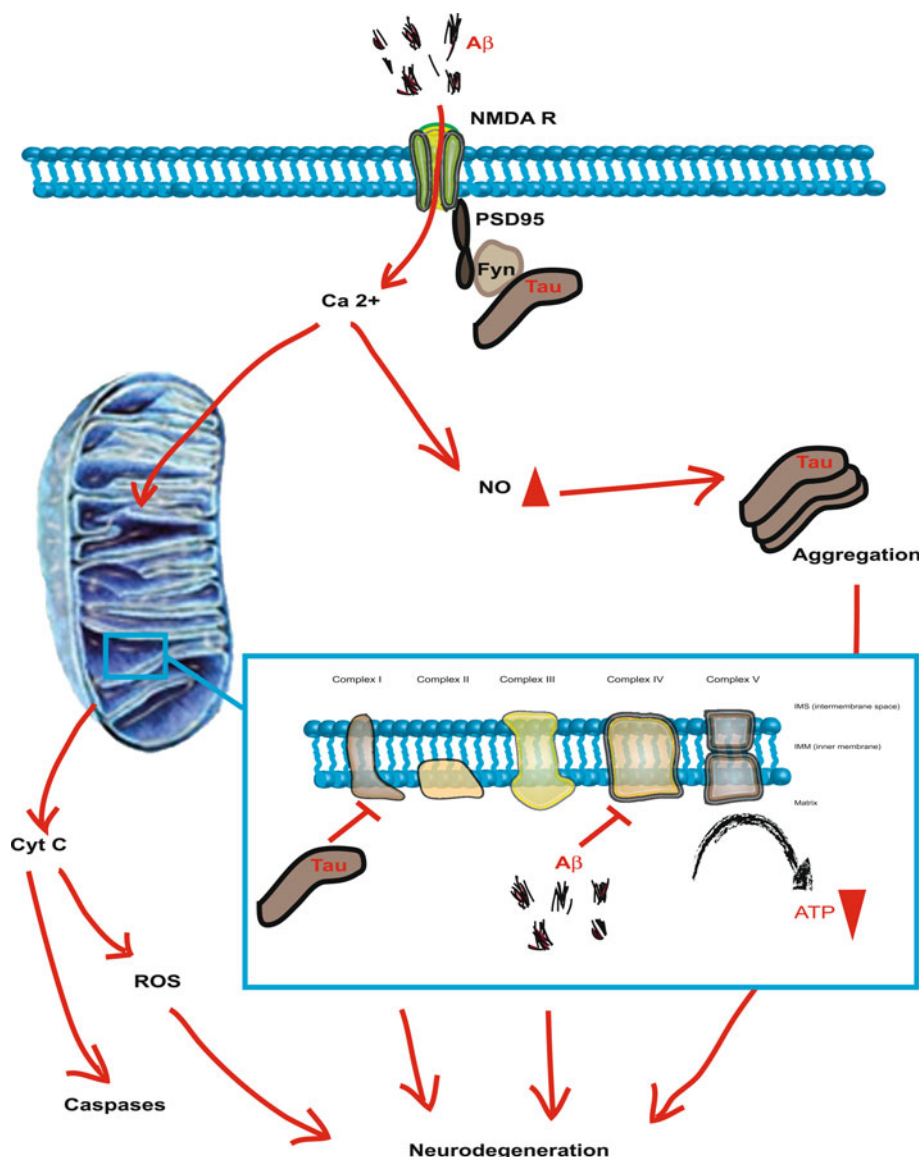
To better understand the role of A $\beta$  and tau in AD and related disorders, experimental animal models have been developed, in particular in mice, that reproduce the major aspects of the neuropathological characteristics of these diseases [11, 51]. Massive neuronal cell loss, however, has only been achieved for a small subset of mouse strains.

In 1995, Games and coworkers established the first A $\beta$  plaque-forming mouse strain through expression of the disease-linked V717F mutant form of APP in the brain, under control of the platelet-derived growth factor mini-promoter. These PDAPP mice showed many of the pathological features of AD, including extensive deposition of extracellular amyloid- $\beta$  plaques, astrogliosis, and neuritic dystrophy [52]. Similar features were observed in the Tg2576 strain established by Hsiao and coworkers, by expressing the APP<sup>sw</sup> mutation inserted into a hamster prion protein cosmid vector [53]. The plaque-forming APP23 strain was established by expressing APP<sup>sw</sup> under the control of the neuronal mThy1.2 promoter [54, 55]. The common features of these strains is the development of amyloid plaques that are associated with memory impairment [11]. Subsequently, many other models have been developed with a pronounced plaque pathology, such as the TgCRND8 or the J20 mice [56, 57].

In the same year in which the first plaque-forming mice were established, the first tau transgenic mouse model was also generated, by expressing the longest human wild-type brain tau isoform, htau40, under control of the neuronal hThy1 promoter [58]. Despite the lack of an NFT pathology, the mice reproduced the somatodendritic localization of hyperphosphorylated tau in AD. They presented a pathology that is best described as an early 'pre-tangle' phenotype. A more pronounced tau phenotype was eventually achieved through the use of stronger promoters [59–62]. NFT formation, however, was only reproduced in mice in 1998, following the identification of pathogenic FTDP-17 mutations in the *MAPT* gene, by targeting FTD mutant tau expression to both neuronal and glial cells [11]. Our group, for example, expressed two mutant forms of tau, G272V and P301L, in separate strains that both developed NFTs [63–67], while mice with pseudophosphorylated tau fail to develop NFTs [68]. The P301L tau-expressing pR5 mice showed a behavioral impairment in amygdala- and hippocampus-dependent tasks; aspects of the behavioral impairment could be correlated with the aggregation pattern of the transgene [67, 69–71]. K369I transgenic mice, on the other hand, model Parkinsonism in FTD, in parts owing to expression of the transgene in the substantia nigra, among other brain areas [72, 73].



**Fig. 2** Modes of Aβ toxicity as illustrated for the signaling through the NMDA (*N*-methyl-D-aspartate) receptor (*NMDAR*). Tau is perceived as an 'axonal' protein, although a fraction of it is present in dendrites. Tau functions in targeting the kinase Fyn to this compartment. Fyn then phosphorylates the NMDAR subunit NR2B, thereby mediating complex formation of NMDARs with the post-synaptic density protein 95 (*PSD95*). The over-activation of the NMDAR complex (excitotoxicity) results in excessive nitric oxide (*NO*) levels. This causes down-stream protein misfolding and aggregation, as well as mitochondrial fragmentation. The toxic signaling pathway also involves the release of mitochondrial cytochrome *c* (*Cyt c*) and the activation of down-stream caspases as well as the formation of reactive oxygen species (*ROS*). The excitotoxicity complex mediates Aβ's toxic functions and subsequent neurodegeneration, a process that depends on the presence of tau. *Inset*: Components of the mitochondrial respiratory chain itself are targets of Aβ and tau and, together, these toxic entities synergistically impair mitochondrial functions



To achieve a more complete model of AD, the plaque and NFT pathology has been combined in 3xtg-AD mice that express APP<sup>sw</sup> and P301L-tau expression on a mutant PS1<sup>M146V</sup> knock-in background [74, 75]. These mice have been used extensively to dissect pathogenic mechanisms and more recently for gene therapeutic approaches [76]. Remarkably, cognitive function is improved without altering Aβ or tau pathology. Instead, the mechanism underlying the improved cognition involves a robust enhancement of hippocampal synaptic density, mediated by brain-derived neurotrophic factor (BDNF). Another model with combined pathologies addresses the role of tau phosphorylation at the pathogenic epitope S422 [77]. These tripleAD mice have been used by us to assess the effects of Aβ and tau on mitochondrial functions (Fig. 2a) [78].

**Aβ and down-stream signaling**

The amyloid cascade hypothesis claims, in simplistic terms, that there is a pathogenic degenerative cascade in AD, with Aβ being upstream of tau [79]. To address the interaction of Aβ and tau [80], Aβ plaque-forming Tg2576 mice were crossed with NFT-forming P301L tau-transgenic JNPL3 mice [65, 81]; also, P301L tau transgenic pR5 mice were intracerebrally injected with fibrillar preparations of Aβ<sub>42</sub>. Both strategies caused an increased tau phosphorylation at pathological epitopes and increased NFT formation, thereby establishing a link between Aβ and tau in vivo [65, 81]. These findings have been reproduced in vitro [82, 83]. Similarly, NFT formation was aggravated by infusing brain extracts of aged plaque-forming APP23 mice intracerebrally in P301L tau transgenic mice or by

crossing  $A\beta$  plaque-forming APP23 and P301L tau transgenic mice [84]. Together, these studies established that  $A\beta$  exaggerates a pre-existing tau pathology supporting, at least in part, the amyloid cascade hypothesis in mice. They proved an essential role for  $A\beta$  in disease.

However, there is also an important role for tau. When hippocampal neurons from tau knockout and transgenic as well as wild-type control mice were cultured in the presence of  $A\beta$ , it was found that the knockout neurons were resistant to  $A\beta$  toxicity, while those from tau transgenic mice were more susceptible [85]. In a next step towards showing an essential role for tau in mediating  $A\beta$  toxicity, Mucke and colleagues crossed plaque-forming APP transgenic mice onto hetero- and homozygous tau knockout backgrounds [86]. They found that this prevented the memory impairment that characterizes the APP mutant mice and, importantly (and somewhat surprisingly), that this improvement was achieved without any changes to  $A\beta$  levels or  $A\beta$  plaque load. Tau reduction also protected against pentylentetrazole (PTZ)-mediated excitotoxicity, as shown by a reduced seizure severity and increased latency. Excitotoxicity describes a signaling cascade that is induced by the over-activation of the *N*-methyl-D-aspartate (NMDA) receptor (NMDAR), resulting in neuronal damage and death due to the generation of excessive nitric oxide (NO) (Fig. 2). This process has been implicated as one patho-mechanism underlying  $A\beta$ -mediated neurodegeneration in AD, despite a lack of evidence for a direct binding of  $A\beta$  to NMDARs [87, 88]. Toxicity mediated by any particular receptor may not necessarily involve the direct binding of  $A\beta$ , but it could be due to an indirect modulation of receptor properties, possibly through membrane association. This mechanism may explain why  $A\beta$  has been reported to bind to distinct receptors under certain conditions and not to others depending on the experimental design [89, 90]. Results from recent studies suggest that excessive NO can mediate excitotoxicity in part by triggering down-stream protein misfolding and aggregation, as well as mitochondrial fragmentation. S-Nitrosylation, or covalent reaction of NO with specific protein thiol groups, represents a convergent signal pathway contributing to NO-induced protein misfolding and aggregation, as well as mitochondrial fragmentation through  $A\beta$ -related S-nitrosylation of proteins, such as dynamin-related protein-1 (Drp1) [91]. The toxic signaling pathway also involves the release of mitochondrial cytochrome c and the activation of down-stream caspases [92, 93]. Excessive NMDAR activation thus precipitates the neuronal degenerative process, in part by mitochondrial dysfunction [94].

Coming back to the interaction of tau and  $A\beta$ , the important question arises how tau in fact mediates  $A\beta$  toxicity and why its removal prevents it? In order to decipher the underlying mechanisms, we generated a

mouse strain that expresses the projection domain of tau, while lacking the microtubule-binding domain [16]. When these so-called  $\Delta$ tau mice were crossed with  $A\beta$  plaque-forming APP23 mice, the high susceptibility to excitotoxicity that characterizes the APP23 strain was rescued; also rescued was early mortality. In addition, the memory phenotype of these mice improved; and again, the rescue occurred in the absence of any changes to APP mRNA levels, or  $A\beta$  plaque load. Similarly, crossing the APP23 mice onto a second tau knockout background confirmed the previous findings of Mucke and colleagues on the protective role of not having tau [16, 86]. When we analyzed the subcellular localization of the projection domain tau in  $\Delta$ tau mice, we found that it accumulated in the soma, while it was excluded from the dendrite. What links tau and the NMDAR is the non-receptor tyrosine kinase Fyn, establishing a toxic triad [95]. We found by enhanced immunohistochemistry that already under physiological conditions a fraction of tau is present in the dendrites (Fig. 2) [16]. It functions in targeting the kinase Fyn to the dendrite where the enzyme phosphorylates the NMDAR subunit NR2B, thereby mediating complex formation of the NMDAR with the post-synaptic density protein 95 (PSD95) [96]. In the presence of  $\Delta$ tau, this truncated version of tau competes with endogenous (full-length) tau in the binding to Fyn, trapping it in the soma and preventing it from entering the dendrites. Therefore, Fyn is not available for phosphorylation of NR2B's Y1472 and hence, the excitotoxic signaling complex cannot be formed. Likewise, in tau knockout mice, tau is not available in the first place, and Fyn is thus not targeted to the dendrite. While excitotoxic signaling is impaired in  $\Delta$ tau over-expressing or tau knockout mice, we found no significant changes in synaptic NMDAR expression levels and NMDA currents [16]. In addition to the genetic approach, we tested the pharmacological uncoupling of the NMDAR/PSD95 complex in APP23 mice by delivering a small peptide, Tat-NR2B9c, composed of the carboxy-terminal amino acids of NR2b (including Y1472) fused to a HIV1-Tat peptide [97], using an osmotic pump. This approach permanently protected the APP23 mice from experimentally induced seizures and memory impairment and extended their lifespan to that of wild-type mice. However, crossing the APP23 mice with P301L tau mutant pR5 mice that are characterized by tau accumulation in the soma and, importantly, in the dendrites, caused a dramatic effect in that none of the mice survived beyond the age of 4 months [16]. Tau reduction has subsequently been shown to further prevent the  $A\beta$ -induced defects in the axonal transport of mitochondria [98].

Together, these findings lead us to propose the 'tau axis hypothesis' [45] which postulates that progressively increasing levels of dendritic tau make neurons more

vulnerable to A $\beta$ : at the onset of AD, A $\beta$  levels in the brain increase. The presence of tau at low levels in the dendrites (low compared to levels in the axon) renders, to some degree, the dendrites (and their spines) vulnerable to postsynaptic A $\beta$  toxicity (Fig. 2b). With disease progressing, tau becomes increasingly phosphorylated (a process driven in part by A $\beta$ ), and tau accumulates in the soma and the dendrites. In fully manifested AD, levels of tau in the dendrite (dendritic spine) are high, and this is associated with an increased neuronal vulnerability to A $\beta$  toxicity. As A $\beta$  increases further, it exacerbates tau's phosphorylation and somatodendritic accumulation, thereby hypersensitizing the synapses to A $\beta$ 's toxicity. Ultimately, this process results in the loss of synapses and causes neuronal degeneration [6]. There is an increasing understanding that in AD the neuronal network is disturbed and as the disease is initiated at one particular site, it is spreading through the brain via synaptic connections. This concept has been addressed in mice by targeting transgene expression to distinct subregions of the brain, such as the entorhinal cortex (EC) [99]. In this brain area, NFT formation was found to be initiated in AD. Transgenic overexpression of APP/A $\beta$  in the EC elicited abnormalities in synaptic functions and activity-related molecules in the hippocampal dentate gyrus and CA1 regions, as well as epileptiform activity in the parietal cortex. Soluble A $\beta$  was observed in the dentate gyrus, and A $\beta$  deposits in the hippocampus were localized to terminal fields of the perforant pathway. Thus, the authors concluded that APP/A $\beta$  expression in EC neurons causes transsynaptic deficits that may initiate a cortico-hippocampal network dysfunction in both mouse models and human patients with AD [99].

What is the identity of the A $\beta$  receptor(s) and what are the down-stream effectors of its toxicity? At present it is not understood whether A $\beta$  acts via a receptor or whether membrane binding alone is sufficient [100]. If A $\beta$  acts via a receptor, this receptor may have specificity for A $\beta$  or it may bind proteins or peptides with shared amyloid properties. Work on primary cortical and hippocampal cultures treated with the amyloidogenic peptides A $\beta$  and human amylin, respectively, indicates that the latter may be the case, as rat amylin, which is not amyloidogenic, turns out not to be toxic, while both A $\beta$  and human amylin are [101]. These findings underscore commonalities between AD and type 2 diabetes mellitus [102]. Membrane interaction of A $\beta$  can occur via its hydrophobic carboxy-terminal domain [103, 104] or by electrostatic interactions mediated by the charged amino acids in the amino-terminal domain [105]. A $\beta$  may bind to the cell membrane to form channels or pores that disrupt ion homeostasis, hence leading to neuronal dysfunction [103, 106–109]. As several molecules associated with disease, such as the Prion protein, the

British peptide, or human amylin, can form soluble oligomers, bind to membranes, and subsequently disrupt ion homeostasis, this may be an inherent property of amyloidogenic proteins or peptides [110].

As discussed above, toxicity mediated by the NMDAR may not necessarily involve direct binding of A $\beta$ , rather it could be due to an indirect modulation of receptor properties, possibly through membrane association [89, 90]. Normal NMDAR signaling is a multi-step process, with contributions by the fast acting nuclear Ca<sup>2+</sup>/calmodulin-dependent protein (CaM) kinase pathway and the slower acting, longer lasting Ras-extracellular signal-regulated kinase 1/2 (ERK1/2) pathway, which translocate to the nucleus and ultimately result in activation of the transcription factor CREB [111]. Too much calcium influx via the NMDAR, such as under excitotoxic conditions, leads to neuronal death. While a long-standing view is that neuronal responses to NMDAR activity follow a bell-shaped curve, in which both too much and too little response is potentially harmful, this view has been recently revisited in that the location of the NMDAR may influence whether its activation is coupled to pro-death or pro-survival signals [111].

A $\beta$  may induce synaptic and neuronal degeneration via a plethora of pathways [112]. A $\beta$ 's anti-LTP (long-term potentiation) activity can be modulated by antagonists of the p38 MAP kinase [113] and the Jun NH<sub>2</sub>-terminal kinase (JNK) pathways [114], both of which have been implicated in the hyperphosphorylation of tau [115, 116]. In one study, inhibitors of p38, JNK, GSK-3 $\beta$ , and phosphatidylinositol 3-kinase showed either no or only minor inhibition of A $\beta$  oligomer-mediated cell death in mouse hippocampal slices, but inhibitors of MAPK kinase kinase (MAPKKK), which is upstream of the extracellular ERKs, significantly inhibited A $\beta$ -mediated neuronal death [117]. Another interesting kinase is Fyn, as it links A $\beta$  and tau [45]. Not only is Fyn an interaction partner of tau [118], it also phosphorylates tau at Y18 [119]. Fyn is necessary for the toxicity of A $\beta$ -derived diffusible ligands (ADDL, an oligomeric form of A $\beta$ ) as Fyn knockout neurons are resistant to ADDL-mediated neuronal cell death [120]. Moreover, when crossed with APP transgenic mice, Fyn knockout mice display reduced synaptotoxicity without affecting aberrant sprouting [121, 122]. Fyn has a role in modulating synaptic activity and plasticity through its phosphorylation of NMDAR [123]. While tau reduction prevents cognitive deficits in A $\beta$ -forming APP transgenic mice, Fyn overexpression exacerbates them.

Using electroencephalography (EEG) to examine network effects, researchers have recorded whole-cell currents in acute hippocampal slices from APP mice in the presence or absence of tau. APP mice with tau had increased spontaneous and evoked excitatory currents, reduced

inhibitory currents, and NMDAR dysfunction. Tau reduction increased inhibitory currents and normalized the excitation/inhibition balance and NMDAR-mediated currents in the APP mutant mice [124]. These findings are consistent with the fact that A $\beta$  oligomers alter the transport of NMDAR by promoting its endocytosis, resulting in decreased receptor activity both in vitro and in the APP transgenic mice [125]. Work on neuronal and astrocyte cultures further suggests that A $\beta$  causes Ca<sup>2+</sup>-dependent oxidative stress by activating an astrocytic NADPH oxidase, with neuronal death following through a failure of antioxidant support [126]. Together, these results suggest a fine-balanced network of molecular interactions [100].

### Neurotoxicity of different A $\beta$ species

Alzheimer's disease is believed to be a disease of the synapses and has hence been termed a 'synaptic failure' [6]. While A $\beta$  can kill neurons, synaptotoxicity may be more relevant for the earlier stages of AD that are best characterized by synaptic loss rather than neuronal death. Loss of synaptic terminals or dendritic spines could cause the associated decline in cognitive functions that characterizes AD. Whether the neurotoxic and synaptotoxic actions of A $\beta$  are separate activities or whether they share common mechanisms is not known [100].

The interpretation of A $\beta$  toxicity studies is complicated by the fact that different preparations are being used, such as A $\beta$ 42 versus the less amyloidogenic A $\beta$ 40 versus the shorter, cheaper A $\beta$ 25-35 version, aged versus fresh preparations, monomers versus oligomers versus fibrils; on top of that, different concentrations, incubation times, and cellular system add additional levels of complexity [127, 128]. For example, it was found early on that while A $\beta$  peptide added at micromolar concentrations to primary neuronal cultures induces cell death [129], low, subnanomolar concentrations are neurotrophic, arguing in favor of a physiological function of A $\beta$  [129]. When A $\beta$  aggregation was induced, this aggregation increased the neurotoxic activity of the A $\beta$  peptide, suggesting that the toxic species are associated with the formation of fibrils [130–132]. At present, however, major research efforts of many groups concentrate on non-fibrillar soluble A $\beta$  as the major toxic species in AD [120, 133–135]. These have been given different names, including ADDLs [120], globulomers [136], and the dodecameric A $\beta$  species A $\beta$ \*56 [137]. Recent structural analysis has revealed that pentameric and hexameric oligomers may be the building blocks of the more toxic decameric and dodecameric complexes [138]. To assist in identifying the different A $\beta$  species, conformational antibodies have been developed that not

only stabilize the A $\beta$  protofibrils but also prevent mature amyloid fibril formation [135, 139].

A $\beta$  can inhibit long-term potentiation (LTP), a model system for synaptic strengthening and memory [120, 133, 140–142]. When cell medium containing abundant A $\beta$  monomers and putative oligomers—but not amyloid fibrils—was microinjected into rat brain, this markedly inhibited hippocampal LTP [133]. Immunodepletion of all A $\beta$  species from the medium completely abrogated this effect. Pretreatment of the medium with insulin-degrading enzyme (IDE), which degrades A $\beta$  monomers but not oligomers, did not prevent the inhibition of LTP, indicating a crucial role for A $\beta$  oligomers. These were shown to disrupt synaptic plasticity in vivo at concentrations found in the human brain and cerebrospinal fluid, in the absence of monomeric or fibrillar amyloid. When cells were treated with  $\gamma$ -secretase inhibitors at doses which prevented oligomer formation but allowed appreciable monomer production, LTP was not longer inhibited, indicating that synaptotoxic A $\beta$  oligomers can be targeted therapeutically [133, 143]. Oligomers caused a tenfold greater toxicity in Neuro-2A cells than in fibrils [144]. However, whereas LTP seems to be inhibited by oligomeric A $\beta$  only and not by fibrillar A $\beta$ , in a different experimental paradigm, the two species seem to have both toxic, yet diverse effects [145]. Using rat astrocyte cultures, oligomeric A $\beta$ 42 was shown to induce initial high levels of the pro-inflammatory molecule interleukin (IL)-1 $\beta$  that decreased over time, whereas fibrillar A $\beta$  caused increased levels over time [145]. With respect to mitochondrial functions, we observed that fibrillar and oligomeric species demonstrated a very similar degree of toxicity (see below). It has been suggested that the neurotoxic activity of oligomers is associated with dimeric and trimeric species [133, 142] and, in a recent study, A $\beta$  dimers were found to be the most abundant form of soluble oligomer detectable in the human brain [146]. They were isolated from the cortices of typical AD subjects, at subnanomolar concentrations, they first induced tau hyperphosphorylation in hippocampal neurons, subsequently disrupting the microtubule cytoskeleton, and they caused neuritic degeneration—all in the absence of amyloid fibrils.

The relative contribution of the two forms of A $\beta$ —A $\beta$ 40 and A $\beta$ 42—to disease is a matter of debate. One of the major puzzles in the AD field is that a difference of just two residues between A $\beta$ 40 and A $\beta$ 42 markedly changes toxicity and aggregation properties. A structural study showed that the hydrophobic carboxy-terminal residues in A $\beta$ 42 stabilize the neurotoxic low-order oligomers in a non- $\beta$ -sheet secondary structure and that the conversion to protofibrils and fibrils having  $\beta$ -sheet secondary structure reduces toxicity [138]. In *Drosophila*, A $\beta$ 42 expression causes the formation of diffuse amyloid deposits,



age-dependent learning deficits, and neurodegeneration. A $\beta$ 40 causes similar learning deficits without aggregation and neurodegeneration [147]. On the other hand, rational mutagenesis applied to the A $\beta$ 42 peptide confirmed that the rate of aggregate formation in vitro is linked to brain toxicity [148]. Furthermore, flies expressing wild-type or E22G A $\beta$ 42 had a median survival of 24 and 8 days, respectively, whereas A $\beta$ 40-expressing flies had a median survival of 30 days, indicating that A $\beta$ 40 may be non-toxic, and possibly protective [147]. This possibility is supported by nuclear magnetic resonance (NMR) studies which revealed that A $\beta$ 40 prevents A $\beta$ 42 from aggregating in vitro [149]. Thus, this aspect of toxicity and the relative role of monomeric, oligomeric, and fibrillar species are far from being resolved.

### A $\beta$ -binding proteins and mitochondrial targets

A number of A $\beta$ -binding proteins have been identified on the outside of the plasma membrane of neurons and glial cells that are limited to dealing with a highly sticky peptide, such as A $\beta$ 42. These proteins include the  $\alpha$ 7-nicotinic acetylcholine receptor, the receptor for advanced glycosylation end-products (RAGE), APP itself, NMDAR, the P75 neurotrophin receptor (P75NTR), CD36, and low-density lipoprotein receptor-related protein (LRP) members [150]. LRP, apoE, and the serum protein  $\alpha$ 2-macroglobulin ( $\alpha$ 2M) probably modulate A $\beta$  toxicity via clearance of apoE:A $\beta$  and  $\alpha$ 2M:A $\beta$  complexes or A $\beta$  alone from the brain and hence reduce A $\beta$  levels [151, 152]. Interestingly, in a study involving metabolic labeling, A $\beta$  clearance rates were found to be relatively impaired in the central nervous system (CNS) of AD patients compared with controls, while production was unaffected [153]. Specifically, late-onset AD was associated with a 30% impaired clearance of both A $\beta$ 42 and A $\beta$ 40, indicating that clearance mechanisms may be critically important in the development of AD. Estimates based on a 30% decrease in A $\beta$  clearance rates suggest that the AD brain accumulates A $\beta$  over a period of about 10 years. The impaired clearance of both A $\beta$ 40 and A $\beta$ 42 is consistent with prior findings of the deposition of both A $\beta$ 40 and A $\beta$ 42 in parenchymal amyloid plaques and the substantial deposition of A $\beta$ 40 in cerebral amyloid angiopathy in about 80% of cases of AD [154].

P75NTR can bind a variety of A $\beta$  oligomeric species and modulate A $\beta$  toxicity in a cell type- and P75 isoform-dependent manner [155, 156]. Full-length P75NTR blocks toxicity of both fibrillar and non-fibrillar A $\beta$  preparations in primary neuronal cultures [157], but promotes toxicity of fibrillar A $\beta$  in neuroblastoma cells [158]. The binding of A $\beta$  oligomers to neurons can be blocked with an anti-

NMDAR antibody and, as a consequence, reactive oxygen species (ROS) stimulation in hippocampal cultures is reduced [159]. These results indicate different modes of toxicity in different cell types.

There is an increasing amount of data being published on intracellular sites of A $\beta$  production and targeting, including intracellular organelles, such as mitochondria [160–164], whose function it impairs [165–169]. When we analyzed the total brain proteome of P301L tau transgenic pR5 and wild-type mice, we discovered that it consisted mainly of metabolically related proteins, including mitochondrial respiratory chain complex components, antioxidant enzymes, and synaptic proteins, that were modified. This deregulation could be functionally validated in the pR5 mice as mitochondrial dysfunction, and the reduction in mitochondrial complex V levels was confirmed in human P301L FTDP-17 brains [166]. In one study, we found that P301L tau mitochondria displayed an increased vulnerability towards fibrillar A $\beta$ 42 compared to control mitochondria, suggesting a synergistic action of tau and A $\beta$  pathology on the mitochondria [166]. In a follow-up study we investigated the toxicity of oligomeric A $\beta$  species [127, 128]. Interestingly, in cortical pR5 brain cells, both oligomeric and fibrillar—but not monomeric—A $\beta$ 42 caused a decreased mitochondrial membrane potential. This was not observed with cerebellar preparations, indicating selective vulnerability of cortical neurons [167]. We also measured reductions in state 3 respiration, the respiratory control ratio, and uncoupled respiration when P301L tau mitochondria were incubated with either oligomeric or fibrillar preparations of A $\beta$ 42. We found that aging specifically increased the sensitivity of mitochondria to oligomeric A $\beta$ 42 damage, indicating that while oligomeric and fibrillar A $\beta$ 42 are both toxic, they exert different degrees of toxicity in mitochondria from older animals [167]. When we performed a comparative, quantitative iTRAQ proteomic analysis of single-transgenic pR5, double-transgenic APP/PS2 mutant, and <sup>triple</sup>AD (pR5/APP/PS2) mice, as well as of wild-type controls, we found that one-third of the deregulated proteins were mitochondrial. Notably, deregulation of complex I was tau dependent, while deregulation of complex IV was A $\beta$  dependent, both at the protein and activity levels. Synergistic effects of A $\beta$  and tau were evident in 8-month-old <sup>triple</sup>AD mice as only they showed a reduction of the mitochondrial membrane potential at this early age. At the age of 12 months, the strongest defects on the oxidative phosphorylation system, the synthesis of ATP, and ROS levels were exhibited in the <sup>triple</sup>AD mice, again emphasizing synergistic, age-associated effects of A $\beta$  and tau in perishing mitochondria [78]. Synergistic effects were also found by us in the neuroblastoma cell system in promoting aberrant cell cycle reentry [170].

Mitochondrial dysfunction has been linked to full-length and carboxy-terminally truncated APP, which was shown to accumulate exclusively in the protein import channels of mitochondria of human AD, but not age-matched control brains [163]. Similarly, the accumulation of full-length APP in the mitochondrial compartment in a transmembrane-arrested form, but not lacking the acidic domain, was shown to cause mitochondrial dysfunction and impair energy metabolism [171]. A $\beta$  can disrupt mitochondrial cytochrome *c* oxidase activity [161, 172] in a sequence- and conformer-dependent manner [161]. The A $\beta$  binding protein alcohol dehydrogenase (ABAD, also known as ERAB) is a short-chain alcohol dehydrogenase that binds to A $\beta$  in the mitochondrial matrix. ABAD can bind to oligomeric A $\beta$ 42 present in the cortical mitochondria of APP transgenic mice [173]. This interaction promotes leakage of ROS, mitochondrial dysfunction, and cell death—potentially underlying the mechanism of A $\beta$ -induced mitochondrial toxicity [160]. The results of protease sensitivity assays suggest that A $\beta$  indeed gains access to the mitochondrial matrix rather than being simply adsorbed to the external mitochondrial surface [162]. The interaction between A $\beta$  and mitochondria may explain how A $\beta$  induces apoptosis and caspase activation [160, 174, 175]. In general, intracellular A $\beta$  may be derived either from internalized extracellular A $\beta$  or from intracellularly generated A $\beta$  [176–178]. As it stands, the putative existence of intracellular A $\beta$  adds a further level of complexity to the mechanism of A $\beta$  toxicity, obtaining direct access to organelles that are vital for the function and viability of neurons [179].

### A $\beta$ , altered gene expression and miRNA deregulation

The last years have seen vast improvements in the methods available for functional genomics studies. The effects of A $\beta$  on the proteome and transcriptome can be assessed with increasingly smaller sample sizes and a higher sensitivity, and these methods have been applied successfully to AD and its model systems [180, 181]. Previously, we and others identified deregulated genes and proteins either in human AD tissue itself, or in tissue culture systems and animal models [182–184]. This approach not only identified deregulated genes and proteins but also pathogenic mechanisms, such as mitochondrial dysfunction, impaired unfolded protein responses, and changes in microRNA (miRNA) expression [185]. MicroRNAs (miRNAs) add another level of complexity to gene regulation. While initially identified for their roles in development and cellular identity, the role of miRNAs in human neurodegenerative disease has been increasingly acknowledged in more recent times [186–188]. miRNAs are evolutionarily conserved

non-coding RNAs that are approximately 22 nucleotides and which negatively regulate gene expression in a sequence-specific manner [189, 190]. Changes in miRNA profiles have been reported for postmortem human AD brain tissue, where they include miRNAs that regulate genes such as *APP* itself or *BACE1*, which encodes the  $\beta$ -secretase involved in APP processing and A $\beta$  formation [191–194]. Although the role of genes such as *APP* and *PSEN* in familial AD is firmly established, little is known about the molecular mechanisms affecting A $\beta$  generation in sporadic AD. A deficiency in A $\beta$  clearance is a possibility, as discussed above, but an increased expression of proteins such as APP or BACE1 may also be associated with the disease: a study of miRNA expression profiles in sporadic AD patients revealed that several miRNAs potentially involved in the regulation of APP and BACE1 expression appear to be decreased in the diseased brain. Of these, miR-29a, -29b-1, and -9 can regulate BACE1 expression in vitro. The miR-29a/b-1 cluster was significantly (and AD-specific) decreased in AD patients displaying abnormally high BACE1 protein. Similar correlations between the expression of this cluster and BACE1 were found during brain development and in primary neuronal cultures. These results suggest that the loss of specific miRNAs can contribute to increased BACE1 and A $\beta$  levels in sporadic AD [192]. In a comparison of human brain tissue to A $\beta$ -treated primary neuronal cultures or brain tissue derived from A $\beta$ -depositing APP mutant APP23 transgenic mice, we found a remarkable overlap in deregulated, mostly down-regulated miRNAs [185]. The down-regulation of approximately 50% of the miRNAs tested in response to A $\beta$  was also observed, including down-regulation of miR-9 and 181c, which are also down-regulated in human AD brain tissue [192, 195, 196]. Whether changes in miRNA profiles are specific for sporadic AD, or whether they are a cause or a consequence of the disease process, remains to be investigated: the interesting opportunity that is offered, however, is that miRNAs, similar to protein markers, can be used for diagnostic purposes [192], as is the case for cancer patients [197].

### Conclusions

What can be expected in the forthcoming years? Some of the current therapeutic trials targeting A $\beta$  may come to fruition [11]. The mode of A $\beta$  uptake and/or binding by neurons and other cell types will be elucidated and interacting proteins, both under physiological and pathologic conditions, will be identified. With the advent of new tools, it will likely become easier to discriminate A $\beta$  conformations and hence allow the role of specific conformers in

toxicity to be defined [139]. Moreover, the role that tau plays in mediating A $\beta$  toxicity in disease will assist in the development of treatment strategies for AD and related disorders [45].

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