Prion protein as a toxic acceptor of amyloid-β oligomers

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Abstract:

The initial report that cellular prion protein (PrP^C) mediates toxicity of Amyloid-β (Aβ) species linked to Alzheimer's disease was initially treated with scepticism, but growing evidence supports this claim. That there is a high-affinity interaction is now clear and its molecular basis is being unravelled whilst recent studies have identified possible down-stream toxic mechanisms. Determination of the clinical significance of such interactions between PrP^C and disease-associated Aβ species will require experimental medicine studies in humans. Compounds that inhibit PrP-dependent Aβ toxicity are starting to be trialled in humans and, although it is clear that only a fraction of Alzheimer's disease toxicity could be governed by PrP^C, a partial but still therapeutically useful role in human disease may soon be testable.

Introduction

The pathological hallmarks of Alzheimer's disease (AD) are extracellular deposition of cerebral amyloid predominantly composed of amyloid-β protein (Aβ) forming plaques and vascular deposits, and intracellular neurofibrillary tangles mainly composed of hyperphosphorylated Tau protein. Aβ plaques were initially suspected to be directly toxic to neurones, although closer inspection revealed that levels of plaque deposits did not necessarily correlate with the severity of disease (*1*). For this reason, attention has turned to soluble oligomeric forms of Aβ that appear to be more neurotoxic (*2*) and correlate better with disease in AD patients (*3*). The soluble Aβ forms range from monomers to high molecular weight aggregates with different properties and toxic effects (Figure 1). It is possible that distinct conformations or classes of assemblies may also possess different seeding activity (*4;5*). Similarities between Alzheimer's and prion disease have been noted for decades and the recent major growth of interest in the role of so-called "prion-like" mechanisms in other neurodegenerative diseases has led to an explosion in publications linking these diseases (*6*), that are beyond the scope of this review. It remains to be seen if knowledge of the misfolding and seeded aggregation processes will result in new therapeutics for sporadic forms of these diseases. However, a wider understanding of prion pathogenesis and the decades of experience built up in the prion field could facilitate AD research and the development of novel therapies (*7*).

AD itself incorporates a mêlée of genetic and apparently sporadic conditions that can co-exist with an ever greater number of co-pathologies as age-at-onset increases (*8*). The complexities of Aβ oligomer research have been discussed in detail elsewhere (*9*). Some arguments will be emphasised here, but all are relevant to this area of AD research. Poor reproducibility between labs is often blamed on poorly-defined synthetic preparations loosely based on standard "recipes" rather than fully characterising the content of each batch produced. This common assumption can only be tested if all preparations are fully characterised when published (*9;10*). A recent trend towards defining toxic Aβ assemblies by structural fingerprints, rather than the conditions in which they were produced, may help address this problem (*11;12*). As AD patient samples are both precious, and

inherently complex and heterogeneous, it seems pragmatic to continue to test a hypothesis with synthetic or recombinant Aβ that does not contain alternative APP metabolites before confirming the relevance with human samples (*13*). Indeed, Aβ samples from AD brain will always vary in composition, concentration and purity. Native isolation of different Aβ assemblies present in AD brain samples is complex, as purification methods can disrupt and change the conformation of aggregates (*14*). Identification of toxic receptors for such a heterologous disease will, of course, be challenging.

In receptor binding terminology, both receptor and acceptor contain a receptive site for the ligand, although only the receptor induces a biological function. Moreover, the acceptor lacks an endogenous ligand. Many proteins have been described as "receptors" for toxic Aβ assemblies, implying a designed physiological function. It is possible that toxicity is linked to hijacking of a functional interaction with other Aβ assemblies, but until this is demonstrated the candidates are best described as "acceptors" for toxic Aβ assemblies. To date, the majority of research on the PrP:Aβ interaction has focused on the toxic signalling cascades rather than physiological or beneficial roles. Two possible functions of PrP as an Aβ receptor have been suggested: Firstly, as a facilitator of the low-density lipoprotein (LDL) - receptor-related protein-1 (LRP1) mediated Aβ monomer transcytosis out of the brain through the blood-brain barrier (BBB). Secondly, as a protector against Aβ-induced cell death by neutralising oligomeric Aβ (*15-19*). If the Aβ:PrP interaction has a function, it will no doubt unravel as we better understand the true physiological role of PrP (*20*). More research is needed to confirm the consequences of Aβ assemblies binding to PrP, as this will be crucial to develop new therapies targeting the interaction or its downstream effectors.

Prion protein-mediated Aβ toxicity

The Aβ oligomer as a ligand for prion protein

Numerous macromolecules have been identified to bind to different forms of Aβ (*9;21;22*) – not surprising given the inherently sticky nature of this peptide in all forms from monomer through to amyloid plaques. A study by Lauren *et al.* (*23*) stood out because it used an unbiased cell-based

screen of all murine neuronal proteins to identify those that bound to a relatively well-defined preparation of Aβ, based on the "Amyloid-β-derived diffusible ligand" (ADDL) protocol (*2*). The only "hit" was prion protein (PrP). Not only was the interaction confirmed to occur at low nanomolar concentrations, PrP-knockout was also shown to prevent the toxic effect of Aβ in a measure of synaptic plasticity, long term potentiation (LTP). Incubation of nanomolar concentrations of Aβ with wild-type murine brain slices inhibited LTP, whereas in PrP-null mice LTP remained intact. Ironically, after years of effort to find specific, high affinity ligands for PrP, the interaction of PrP with Aβ was discovered from the opposite vantage point. Indeed, Aβ is perhaps the most widely-accepted high-affinity binding partner for PrP.

Confirming PrP-dependent toxicity in vivo

A further study by the same group showed crossing a transgenic mouse model of AD that combines expression of mutant APP_{swe} and presenilin-1 deltaE9 ($PS1_{\Delta E9}$) (both from PrP promoters on a PrP-null background) prevented pathological phenotypes such as neuronal loss and premature death whilst maintaining spatial learning and memory (*24*). Furthermore, a two-week peripheral treatment of another APP/PS1 mouse model ($APP_{swe}PS1_{M146L}$ both with Thy1 promoters) with the 6D11 antibody increased the synaptic density in the hippocampus and improved spatial memory in a radial arm maze (*25*).

Controversy and confirmation

PrP-independent Aβ toxicity

Following the initial report (*23*), a number of groups published seemingly contradictory reports. The first paper to cast doubt on the role of PrP in Aβ toxicity nevertheless confirmed a PrP:Aβ binding interaction (*26*). According to this study, PrP^{c} is not required for Aβ-induced memory impairment in a novel object recognition test when synthetic Aβ oligomers are injected into the brains of mice. That PrP is not critical to all Aβ toxic readouts is not surprising and does not discount a role for this

protein in AD. However, this paper highlights an important point that not all Aβ toxicity is governed by PrP, even when the preparations are known to contain assemblies capable of interacting with PrP. Since the report of PrP as an Aβ oligomer acceptor, numerous other Aβ-interacting candidates have been suggested (see below). These have mainly been identified using a targeted approach rather than the unbiased binding screen used for PrP (*23;27-34*). Only by comparing the candidates side-by-side in the same assays can they be compared for their Aβ oligomer affinity and selectivity. Given that the PrP:Aβ interaction was reported first and the tools to study it are widely available within the molecular neuroscience community, it is not surprising that this interaction was quickly validated. Still, to date, PrP remains by far the most validated Aβ acceptor.

Two studies described PrP-independent pathological, behavioural and electrophysiological changes in the APPPS1^{+} ($APP_{swe}PS1_{L166P}$ both with Thy1 promoters) (*35*) or J20 ($APP_{swe/ind}$ with PDGF-β promoter) (*36*) transgenic models. Potential PrP-specific reasons for these differences include the fact that some, but not all, models express APP using the PrP promoter and that PrP and APP processing may be interrelated (*37*). The contrasting findings might also be the result of differences in the soluble Aβ assemblies present at the ages tested compared to the APP/PS1 lines (APPPS1^{+} mice were used at 2-4 months of age and J20 mice were 6-8 months old). In support of this hypothesis, a later study in the APPPS1^{+} mice showed some PrP-dependent effects at 14 months when soluble Aβ assemblies, including SDS-stable dimers, become abundant (*38*). Another well-studied model, the Tg2576 (APP_{swe} with PrP promoter) mouse (*39*), was recently shown to contain a sub-population of PrP binding Aβ assemblies and displayed a partial recovery of Morris Water Maze deficits when PrP was not expressed (*40*). It is known that J20 mice do not develop large pools of soluble Aβ oligomers until 16 months of age (*41*) and it may be that PrP-dependent effects are observed at this age if they are not overwhelmed by pre-existing PrP-independent effects. In addition, J20-derived Aβ oligomers are mainly recognised by the conformation-specific antibody A11 (*42*) while Aβ oligomers shown to bind PrP (*43*) contain in-register parallel β sheets, recognised by the OC antibody (*44*). It is not known which, if any, of these models better mimic Aβ pathology in AD.

However, confirmation of the involvement of specific proteins in human AD should help select more disease-relevant animal models that may in turn benefit AD research and drug discovery. The corresponding authors of the first two papers reporting PrP-independent Aβ toxicity (*26;35*) have since reported PrP-dependent effects in these models (*38;45*), suggesting that a consensus may be forming (Table 1).

One study directly contradicted the key finding of the original study (*23*) – that the inhibition of LTP by Aβ oligomers was PrP-dependent. Kessels *et al.* produced Aβ following the same protocol, but the inhibition of LTP appeared to be PrP-independent (*46*). In response Lauren *et al.* questioned the similarity of the Aβ preparations that were only characterised by SDS-PAGE (*47*). Although SDS-PAGE has been shown to not reliably represent Aβ assemblies present in solution (*10*), the contradictory studies highlight one problem with studies using synthetic preparations: how do we determine which assemblies are most relevant to the human condition?

Independent confirmation of PrP-dependent toxicity

It was crucial to discover whether synthetic Aβ oligomers could be produced that mimicked the most disease relevant forms of Aβ – those found in the brains of human AD patients that are known to inhibit LTP (*48*). Like some synthetic Aβ oligomers, those purified from AD brain inhibited LTP in wild-type and not PrP-null mice, confirming some relevance to human AD (*49*). Surprisingly, a range of antibodies that bind close to helix-1 of PrP also effectively blocked the interaction, even though it is located on the opposite side of the structured domain of PrP^C from residue 95-105 (Figure 2). Antibodies that bind to 95-105 and helix-1 of PrP, and which are known to be therapeutically active in prion infection (*50*), were found to block Aβ-induced inhibition of LTP in both murine brain slices and live rats (*49;51*). The ability of helix-1 antibodies to block Aβ-induced electrophysiological deficits has now been replicated in a cell-based system (*52*). Previously discovered PrP ligands should now be retested for their ability to disrupt the PrP:Aβ interaction and their potential as AD therapeutics assessed. Indeed, it may be that the identification of the PrP:Aβ interaction may

reinvigorate studies to identify small molecules that bind to PrP^C and arrest prion propagation (*53*). This is firstly because of the increased interest in PrP-binding molecules as possible inhibitors of Aβ and, secondly, from a practical point-of-view, because it is challenging to identify PrP-binding molecules in high-throughput assays. Showing that a compound can block the PrP:Aβ interaction appears to be an acceptable surrogate for identifying molecules that bind to certain sites on PrP (*54*).

The Aβ:PrP interaction

Characterising the PrP binding mode

The fact that there now appears to be a consensus on Aβ:PrP binding does not mean it is a simple interaction; it should not be considered a canonical binary interaction between a PrP monomer and a discreet Aβ oligomer. A single oligomer has the potential to interact with multiple PrP molecules and this could result in further conformational changes to either PrP or Aβ. Kinetic analysis confirmed that the interaction is effectively irreversible on a surface meaning dissociation constants cannot be calculated (*55*), whilst the slow rate of binding observed may be indicative of a conformational change or further Aβ aggregation *in situ* (*55*). The mechanism for helix-1 antibody-mediated inhibition of synaptotoxicity remains obscure (*49*), but hints towards the involvement of multiple PrP molecules (*49*) or a rearrangement of this helix during binding (*53*). A number of groups have suggested a second positively-charged site at the extreme N-terminus of PrP (*45;55*), but it is unclear if this is truly independent or what its relevance is at pathophysiologically pertinent concentration. The basis of the interaction has so far not been resolved at a single amino acid level (*45*). That PrP can disassemble Aβ amyloid fibrils (*56*) and inhibit the assembly of Aβ into toxic oligomeric forms (*57*) at micromolar concentrations confirms the interaction, whilst selective, is not specific at higher concentrations.

Identifying PrP-binding Aβ assemblies

It is known that PrP does not bind as strongly to Aβ monomer or mature fibrils (*26;55*), but numerous synthetic Aβ assemblies have been reported (Figure 1) (*9*), some of which may only vary in their means of preparation rather than their actual composition. Aggregation of ADDL-like preparations for different time periods and then characterising the Aβ assemblies present at different time points allowed the identification of forms that most avidly bind to PrP, as well as those that cause PrP-dependent or PrP-independent synaptotoxicity (*43*). The presence of Aβ protofibrils correlated better with PrP binding than either globular oligomers or amyloid fibrils. Crucially, globular oligomers present at initial time points failed to inhibit LTP, whereas LTP was significantly reduced throughout a time window where protofibrils were present. The protofibrils are not simply chains of globular oligomers, but contain a defined triple helical nanotube structure that could relate to their specific PrP-dependent toxicity (Figure 3). Could the Aβ species in AD brain that cause PrP-dependent toxicity be structurally related to Aβ nanotubes? The presence of SDS-stable dimers in post-mortem brain is strongly associated with AD (*3*) and PrP-dependent toxicity in mice (*38*), whilst synthetic Aβ dimers are known to favour synaptotoxic protofibril formation (*58*). Therefore, it seems plausible that structures similar to Aβ nanotubes can cause PrP-dependent synaptotoxicity in AD brain; although this hypothesis is yet to be tested experimentally. Several studies have, however, compared the PrP binding of different AD brain-derived Aβ species, separated by the hydrodynamic radii using size-exclusion chromatography, but none have confirmed if these species are toxic. Two independent studies have suggested large soluble assemblies with apparent molecular weights greater than 600,000 are the major PrP binding species (*40;59;60*), with a third suggesting SDS-stable dimers are the major PrP binding species (*38*). All this is consistent with a protofibrillar assembly, although this will remain speculation until such species are isolated from AD brain, structurally characterised and shown to cause PrP-dependent toxicity.

PrP-dependent toxic mechanisms

Clearly not all Aβ toxicity is governed by PrP (Table 1) and assemblies can display distinct toxicities in different systems; for example, inhibition of LTP compared with cell membrane disruption (*43*). Furthermore, a variety of non-mammalian protein aggregates induce PrP-dependent cytotoxicity in cellular systems (*61*). Toxicity is mediated through the unstructured N-terminal portion of PrP suggesting some mechanistic overlap with toxic PrP and Aβ species. Such toxicity, caused by interactions with the N-terminus of PrP, yet blocked by ligands binding to the 95-105 or helix-1 regions of PrP, is in contrast to reports of anti-PrP antibody-related toxicity caused by interaction with C-terminal regions of PrP and prevented by ligands binding the N-terminus (*62*). The apparent mechanistic differences between Aβ-induced and anti-PrP antibody-induced toxicity could be explained by the method of incubation. Anti-PrP antibody toxicity was reported after their incubation with brain slices prepared from transgenic mice with a high level of PrP expression for several weeks at high, micromolar concentrations – ~10,000 times those required to engage PrP – suggesting there may be non-specific toxic effects. This effect also appears inconsistent with absence of toxicity seen *in vivo* when up to two micrograms of multiple anti-PrP antibodies are directly injected into the hippocampi of live mice (*63*). Subsequent titration to 6 micrograms of PrP mAbs (*64*), injected directly into brain tissue (estimated volume of distribution 5 mm^3), did however result in apoptosis at the cannula site. As for the brain slice experiments, dose and concentrations in these mouse experiments are high relative to those which might reasonably be expected to be therapeutically relevant. For example, Song *et al.* infused a PrP mAb at 1 microgram/hr into mouse lateral ventricle (estimated volume of distribution 500 mm^3) with clinical benefits against prion disease and no adverse clinical or pathological events (*65*), implying an approximately two-log dose therapeutic window by comparison with Reimann *et al.*'s toxicity. Ohsawa *et al.* demonstrated some evidence of therapeutic potential for established mouse prion disease by peripheral injections of PrP mAb, with no adverse events (*66*). Klyubin *et al.* showed that intravascular injections of PrP mAb were able to block the effects of Aβ on LTP without adverse events (*67*). This paper also reported the single ascending dose study of PrP mAb PRN100 in cynomolgus monkey at intravenous doses up to

200 mg/kg, achieving serum concentrations of 5 mg/ml without significant adverse events (*67*). Overall, these studies suggest that anti-PrP antibodies have a relatively low acute neurotoxicity at likely therapeutic concentrations for prion infection (*65-67*).

Whilst blocking the PrP:Aβ interaction, or the formation of toxic assemblies, appear to be valid approaches to combatting Aβ toxicity, it is also important to understand the cellular mechanisms and how they might be targeted pharmacologically. Identifying whether the binding of a specific Aβ isoform to PrP inhibits a physiological function or triggers a dysfunctional pathway is crucial to drug discovery strategies.

PrP-dependent downstream mediators of toxicity

Phosphorylation of NMDA receptors and their subsequent relocalisation is induced by Fyn activation (*30*). Of all post-synaptic density membrane proteins tested, only mGluR5-dependent Fyn activation was increased by Aβ oligomers (*68*). Formation of this complex may explain the observed clustering of mGluR5 at synapses in the presence of Aβ oligomers (*68;69*). The role of mGluR5 in PrP-dependent Aβ toxicity has now been confirmed in the classic synaptic plasticity paradigm, inhibition of LTP, as well as in the associated facilitation of long-term depression (LTD) (*70*). It is possible that the PrP:mGluR5R interaction includes helix-1 of PrP (*60*) meaning that antibodies that bind helix-1 of PrP could disrupt this complex and have a secondary protective mechanism beyond directly inhibiting the PrP:Aβ interaction. Such serendipity should perhaps be expected in the crowded environment of the synapse. The Aβ:PrP:mGluR5 complex is probably the most studied and independently validated Aβ:PrP pathway and, importantly, its toxicity has been shown to be driven by AD brain extracts (*30;38;68;70*). PrP is linked to Homer1b/c, protein-tyrosine kinase 2β (PTK2B, Pyk2) and calcium/calmodulin-dependent protein Kinase II (CamKII) through mGluR5 in a Aβ-regulated manner (*13*) (*71*). In light of these results, it will be important to examine in more detail the physiological function of PrP:mGluR5 in order to assess the full toxic effect of Aβ oligomers on

synaptic plasticity. It is possible that as well as activating toxic cascades through PrP, Aβ oligomers also alter PrP:mGluR5 interactions crucial for a correct functioning of the synapse.

One effect of PrP may be to increase the local concentration of Aβ or other protein aggregates (*61*) and initiate toxic pathways that it does not directly participate in. PrP could conceivably facilitate the conversion of other Aβ assemblies into those that cause PrP-dependent toxicity (*56*). Likewise anti-PrP antibodies could sterically block interactions with other Aβ-binding proteins closely packed within the synaptic membrane or block access of fibrillar Aβ assemblies that do not exert toxicity through PrP. More targeted site-directed mutagenesis studies where the PrP:ligand interaction is retained yet toxicities are specifically blocked will be required to distinguish between these possibilities.

Other *Aβ* acceptors

Aβ toxicity through other interacting proteins

Numerous Aβ oligomer binding proteins have since been identified (*72;73*) and most of them localise at the synapse, suggesting that binding of Aβ assemblies may cause synaptic dysfunction at least in part by blocking their function. Of course many macromolecules have been shown to bind to some form of Aβ including: GluN1 (*69;74*), GluR2 (*75*), α7nAchR (*76*), RAGE (*77*), insulin receptor (*78*), $p75^{NTR}$ (*79;80*), β_2ARs (*81*), Fz Wnt receptor (*82*), NL1 (*83*), reelin (*84*), GM1 ganglioside (*85*) and LRP1 (*86*).

Although only PrP was identified by an unbiased direct binding assay, two other Aβ oligomer acceptors were recently identified using unbiased functional screening or expression approaches: FcγRIIb (*31*)(*87*) and PGRMC1 (*32;33*) (*88*). Aβ oligomers also bind EphB2 (*27;29*)(*89*). As Eph receptors regulate plasticity and synaptic function, it would not be surprising if more members of the family are involved in AD (*90*). PirB and its human orthologue were also reported as possible Aβ oligomer acceptors (*28*). Finally, NAKα3 binds to patient-derived amylospheroids (*34*). Detailed

discussion of these receptors falls outside the bounds of this review. The heterogeneity in the properties of this small group of recently identified candidates highlights the difficulty in reproducing experiments between labs. Simply acquiring the expertise and reagents required to study one of these proteins and reproducing published experiments could take as long as a standard PhD project. Prioritising which of these acceptors is most relevant for slowing the progress of heterogeneous diseases such as Alzheimer's will be an enormous challenge.

Why might so many receptors be involved in a single disease? Of course there will no doubt be “false positives”, but it is also likely that certain acceptors cause toxicity at different stages – presymptomatic, mild cognitive impairment, early and more advanced AD – as the different aggregates of Aβ accumulate and form in the brain. It is crucial to characterise the Aβ assemblies that bind each protein and their apparent affinity, together with any overlap in the downstream cascade they activate.

Synaptic loss occurs at early stages in AD, therefore protecting, maintaining and restoring the structure of the synapse could be central to AD therapy (*90;91*). Several neurotoxic cascades that are triggered by Aβ:PrP in complex with other proteins, including LRP1, cytoplasmic phospholipase A_2 ($cPLA_2$) and mGluR5, have been described to require lipid rafts organisation (*5;30;92;93*). Interestingly, these results agree with a suggested function for PrP as a scaffold protein on lipid rafts: organising proteins in a complex (*94*). Therefore, finding the scaffold proteins and necessary partners for the different receptors could identify relevant targets to develop therapies. A real challenge of targeting the above receptors is that complete inhibition of a receptor could be detrimental; therefore modulating their function back to physiological levels may be essential.

Future Focus

After initial scepticism and controversy the PrP:Aβ interaction is now becoming accepted as a significant player in Aβ-mediated toxicity *in vitro* and *in vivo*. Its high affinity has not been disputed and the molecular basis of this complex interaction is now being unravelled. Care needs to be taken

to ensure experiments are carried out under the most physiological conditions possible and are described in such a way that they can be faithfully reproduced. More details of the structural basis of the interaction and mechanisms of neurotoxicity, and concrete explanations for reported discrepancies between publications, are required to truly understand the phenomenon. It would aid the field if researchers reported both positive and negative results together to help establish the reasons for PrP-dependent and PrP-independent toxicity. If the hypothesis that PrP is involved in AD cannot be falsified then experimental medicine studies could be considered. The relevance of this interaction to the clinical features and progression of human AD can only be firmly established through clinical trials of drug candidates that block the interaction or down-stream toxicity. This in turn could determine the suitability of individual animal models to AD drug discovery. A humanised anti-PrP monoclonal antibody has now been developed for treatment of prion disease and a preclinical study in live rats demonstrated that intravascular administration of this antibody can block Aβ-induced inhibition of synaptic plasticity without causing acute toxicity (*67*), suggesting it might be suitable for clinical trials in AD should it have a satisfactory safety profile. Likewise, a phase 1b study for a potent inhibitor of src family of kinases, including Fyn, has recently been completed (*95;96*) with a phase IIa trial currently underway. Confirmation of efficacy in human trials would firmly establish a role for PrP^C in AD. It is unlikely that any therapeutic would reverse all symptoms in AD patients, but blocking acute synaptotoxic effects may have an immediate measurable effect in memory and cognitive function. The second question of whether this then slowed rates of neurodegeneration would require major clinical trials. A confirmed disease-modifying therapeutic in the AD field would be a huge step forward after so many disappointments. While the PrP:Aβ interaction was only identified a few years ago, direct examination of its true relevance to AD via experimental medicine may hopefully not be too far away.

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Figure legends:

Figure 1: Diagram depicting the variety of aggregation states of Aβ and sizes. Green lines represent bands in gels, orange structures represent those captured by Atomic Force Microscopy (AFM) and black structures represent those captured by Electron Microscopy (EM). The y-axis identifies the name of the preparation and, where relevant identifies the source. ADDLs are "amyloid-β-derived diffusible ligand", TABFOs are "amyloid-β_{1-42} fibrillar oligomers".

Figure 2: Modelled structure of PrP^C highlighting the Aβ binding site (red) and Helix-1 (yellow). Amino acids in the region 95-105 are required for the interaction and antibodies raised against these epitopes (red and yellow) block the toxic effect of Aβ oligomers on LTP.

Figure 3: Possible PrP^C-dependent (left) and PrP^C-independent pathways (right) for Aβ toxicity as well as possible functional roles for PrP^C in Aβ processing, signalling and transport (centre). Aβ species, such as Aβ nanotubes, are known to bind directly to PrP^C and induce toxicity and several, possibly interconnected, pathways have been identified. The PrP^C:Aβ complex may directly interact with downstream acceptors or PrP^C may raise the local concentrations of certain forms of Aβ thereby sensitising acceptors to Aβ toxicity.

Reference	Direct Aβ:PrP^C interaction		Aβ:PrP^C toxicity		Comment
	Aβ source	Quantitative	Aβ source	System assayed	
Lauren *et al.* (*23*)	Synth	Y	Synth	Cell	Aβ:PrP^C binding in cells and effect on LTP is PrP^C-dependent
Balducci *et al.* (*26*)	Synth	N	Synth	Cell, Mouse *in vivo*	Direct Aβ:PrP^C binding, but no toxicity
Gimbel *et al.* (*24*)			Mouse	Mouse *in vivo*	Ablation of PrP^C reverses cognitive deficits, lifetime and cell death in $APP_{swe}/PS1_{\Delta E9}$ mouse
Chen *et al.* (*55*)	Synth	N			Confirmation of direct binding of Aβ oligomers to $huPrP^C$
Calella *et al.* (*35*)	Synth	N	Mouse	Mouse *in vivo*	Confirmation of Aβ:PrP^C interaction, but disputes PrP^C-dependent behavioural effects in $APP_{swe}/PS1_{L166P}$ mouse
Kessels *et al.* (*46*)	-		Cell	Mouse *ex vivo*	Disputes PrP^C-dependent Aβ-induced LTP inhibition, however, uses ill-defined Aβ oligomers
Lauren *et al.* (*47*)					Reply to Kessels *et al.*
Chung *et al.* (*25*)			Mouse	Mouse *in vivo*	Anti-PrP mAb reverses behavioural effects in $APP_{swe}/PS1_{\Delta E9}$ mouse
Resenberger *et al.* (*61*)	Cell	N		Cell	PrP^C-dependent toxicity of Aβ and amyloid peptides in cells
Zou *et al.* (*100*)	Mouse, Human	N			Aβ mainly interacts with insoluble PrP^C in $APP_{swe/ind}$ mice
Barry *et al.* (*51*)			Human	Rat *in vivo*	Anti-PrP^C mAb reverses effect on AD brain extract-induced LTP inhibition
Freir *et al.* (*101*)	Synth	Y	Synth, Human	Mouse *ex vivo*, rat *in vivo*	Two anti-PrP^C mAbs reverse Aβ-induced LTP defects in rats and mice
Cisse *et al.* (*36*)			Mouse	Mouse *in vivo*	Disputes PrP^C-dependent electrophysiological and lifetime effects in $APP_{swe/ind}$ mice
Bate *et al.* (*93*)	Cell	N	Cell	Cell	Initial report of PrP^C-dependence of synapse damage *via* $cPLA_2$
Alier *et al.* (*52*)			Synth	Cell	PrP^C-dependent electrophysiological effects of Aβ in cells
Caetano *et al.* (*102*)	Synth	N	Synth	Cell	Aβ increases PrP^C at the cell surface
Kudo *et al.* (*103*)			Synth	Mouse *in vivo*	PrP^C-dependent neuronal death *in vivo*
You *et al.* (*104*)			Synth	Cell	Interaction between copper, PrP^C, Aβ oligomers and NMDAr
Pflanzner *et al.* (*15*)	Synth	Y	Synth	Cell	PrP^C-dependent $A\beta_{1-40}$ transcytosis across the BBB
Guillot-Sestier *et al.* (*17*)			Cell, Human	Cell	N1 fragment protects against Aβ-associated cell death
Hyeon *et al.* (*105*)	Synth	N	Synth	Cell	PrP^C-dependent apoptotic cell death

Um *et al.* (*30*)	Human	N	Synth, Human	Cell	Fyn dependent toxicity via NMDAR
Rial *et al.* (*106*)			Synth	Mouse *in vivo*	Overexpression of PrP^C protects against $A\beta_{1-40}$ apoptosis
Nieznanski *et al.* (*57*)	Synth	N			PrP^C N1 fragment inhibits Aβ oligomer formation
Larson *et al.* (*38*)	Human	N	Synth, Human	Cell, Mouse *in vivo*	Fyn dependent toxicity linked to Tau phosphorylation
Younan *et al.* (*56*)	Synth	Y	Synth	Cell, Mouse *in vivo*	PrP^C prevents aggregation and disaggregates Aβ fibrils
Fluharty *et al.* (*45*)	Synth	N			PrP^C-based peptides deactivate Aβ oligomers
Rushworth *et al.* (*92*)	Synth	N	Synth	Cell	Role of lipid rafts and LRP-1 in PrP^C-dependent Aβ toxicity
Ordonez-Gutierrez *et al.* (*107*)			Mouse	Mouse *in vivo*	Confirmation of PrP^C-dependent Aβ toxicity in $APP_{swe}/PS1_{\Delta E9}$ mouse
Chen *et al.* (*108*)	Synth	N	Synth	Cell	Confirmation of Fyn activation
Um *et al.* (*68*)	Synth, Human	N	Synth, Human	Cell, Mouse *in vivo*	mGluR5 as coupling receptor between PrP^C and Fyn
Nicoll *et al.* (*43*)	Synth	N	Synth	Mouse *ex vivo*	Aβ nanotubes correlate with PrP^C-dependent inhibition of LTP
Ostapchenko *et al.* (*109*)	Synth	N	Synth	Cell	STI1 blocks Aβ binding to PrP^C
Rubel *et al.* (*110*)	Synth	N			Confirmation of main binding site for the interaction Aβ:PrP^C
An *et al.* (*111*)	Synth	N	Synth, Human	Rat *in vivo*	Role of exosomes
Nah *et al.* (*112*)			Synth	Cell	Aβ-induced autophagy mediated by presence of PrP^C
Rushworth *et al.* (*113*)	Synth, Cell	Y			Fragment of PrP^C used as biosensor
Dohler *et al.* (*59*)	Synth, Human	N			PrP^C binds to large Aβ species in AD brain
Hu *et al.* (*70*)			Synth, Human	Rat *in vivo*	PrP^C:mGluR5 in Aβ-induced LTD facilitation and LTP inhibition
Beland *et al.* (*16*)	Human	N	Cell	Cell	Secreted PrP^C trap Aβ in amorphous aggregates
Klyubin *et al.* (*67*)	Synth	Y	Human	Rat *in vivo*	Intravascular administration of anti-PrP^C antibody
Haas *et al.* (*60*)	Synth, Mouse	N			Confirmation of interaction between PrP^C and mGluR5
Ganzinger *et al.* (*114*)	Synth	Y	Synth	Cell	Confirmation of Aβ:PrPC interaction by single molecule imaging
Peters *et al.* (*115*)	Synth	N	Synth	Cell	PrP^C-dependent membrane damage and synaptotoxicity
West *et al.* (*116*)	Cell	N	Cell	Cell	Monoacylated PrP^C binds synaptotoxic Aβ oligomers
Risse *et al.* (*54*)	Synth	Y			Disruption of Aβ:PrP^C interaction by small molecule.

Haas *et al.* (*13*)			Synth, Human	Mouse *ex vivo*	Downstream signalling cascade for Aβ:PrP^C:mGluR5
Falker *et al.* (*19*)	Synth	N	Synth	Cell	Protective role of exosomes
Williams *et al.* (*117*)	Synth	N			PrP^C inhibits low molecular weight Aβ oligomers-induced toxicity
Kostylev *et al.* (*40*)	Mouse, Human	Y	Mouse, Human	Mouse *in vivo*	PrP^C interacts with a pool of soluble high molecular weight Aβ to induce PrP^C-dependent cognitive defects
De Mario *et al.* (*118*)			Synth	Cell	Effect of Aβ:PrP^C complex on store-operated Ca^{+2} entry via Fyn
Heiss *et al.* (*119*)	Mouse	Y	Mouse	Mouse	Reverses dendritic spine loss in $APP_{swe}/PS1_{\Delta E9}$ mouse
Beraldo *et al.* (*120*)	Synth	N	Synth	Cell, Mouse *in vivo*	Possible role of Aβ:PrP^C:mGluR5 complex
Pinnock *et al.* (*121*)	Synth	N	Synth	Cell	Reverses Aβ:PrP^C cytotoxicity by LRP/LR antibody
Haas *et al.* (*71*)			Synth	Mouse *ex vivo*	Effect of Aβ:PrP^C:mGluR5 complex on glutamate signalling
Sempou *et al.* (*122*)			Synth	Zebrafish	Src family kinases activation in a Aβ:PrP^C-dependent manner
Scott-McKean *et al.* (*18*)			Synth	Cell, Mouse *ex vivo*	Reverses Aβ-induced synaptic plasticity impairment by PrP^C fragments
Haas *et al.* (*123*)			Synth	Cell, Mouse	Reverses AD mouse phenotypes by mGluR5 selective blocker
Nolan *et al.* (*124*)			Cell	Cell	Role of the glycosylphosphatidylinositol (GPI) anchor attached to PrP^C
West *et al.* (*125*)			Human	Cell	Cholesterol ester cycle regulates Aβ:PrP^C complex
Zhang *et al.* (*126*)			Synth, Rat	Rat *in vivo*	Repetitive anti-PrP^C antibody administration reverses Aβ-induced synaptic plasticity defects on longitudinal studies

Table 1: Summary of publications demonstrating a direct interaction between PrP^c and Aβ (quantitative or not) specifying the source of Aβ oligomers used and also those that reported PrP^c-dependent toxicity (green) and PrP^c-independent toxicity (red), stating source of Aβ oligomers and systems employed. Synth, synthetic.

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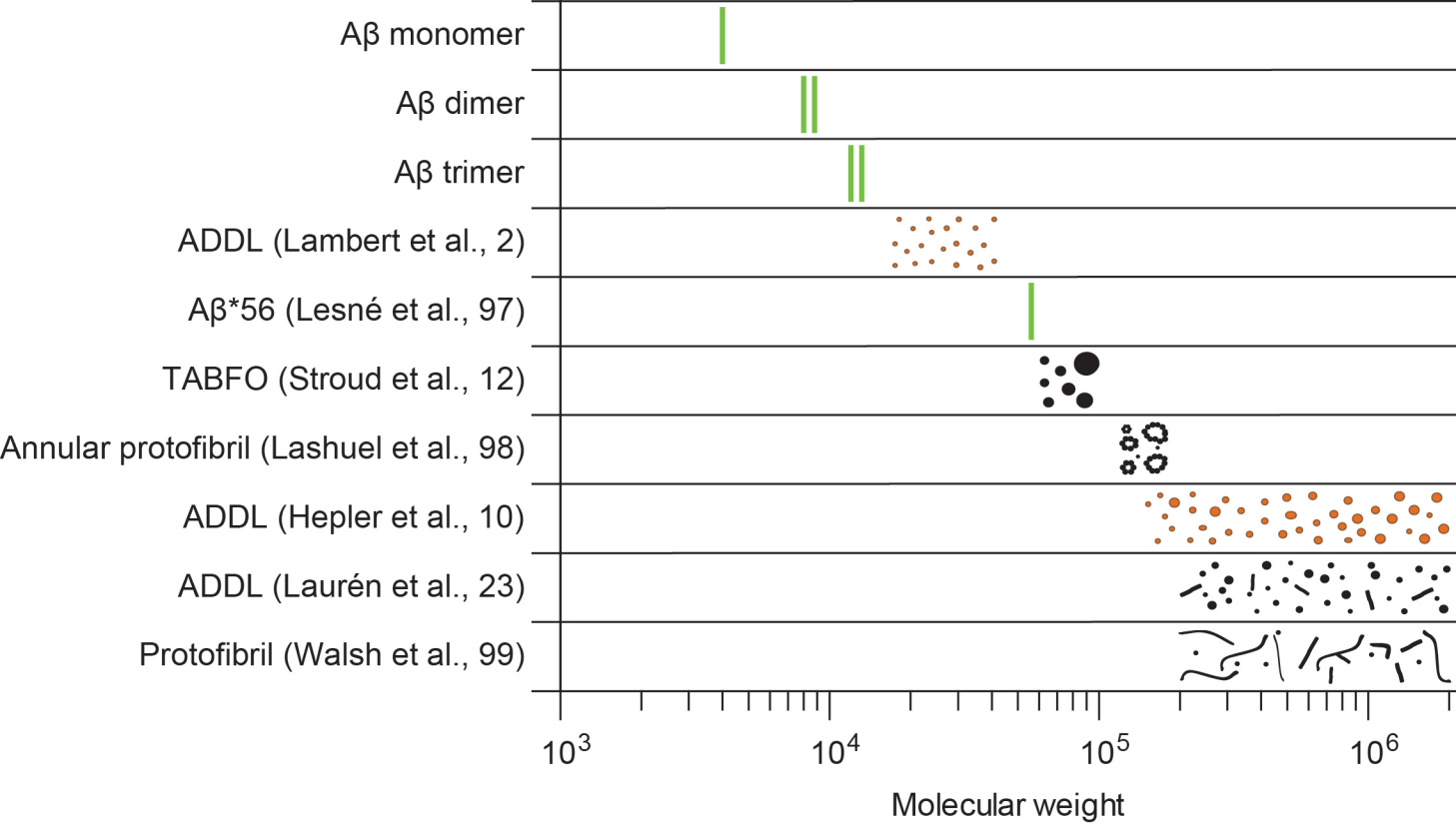
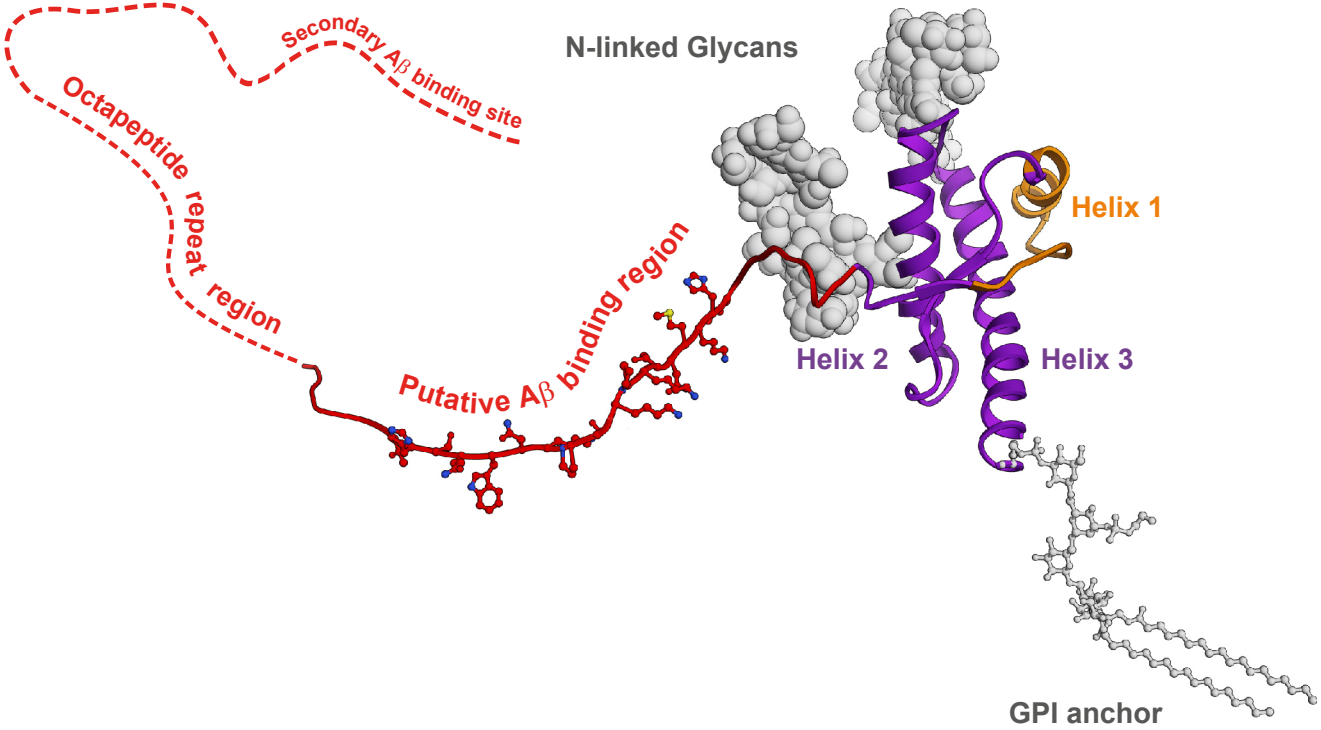
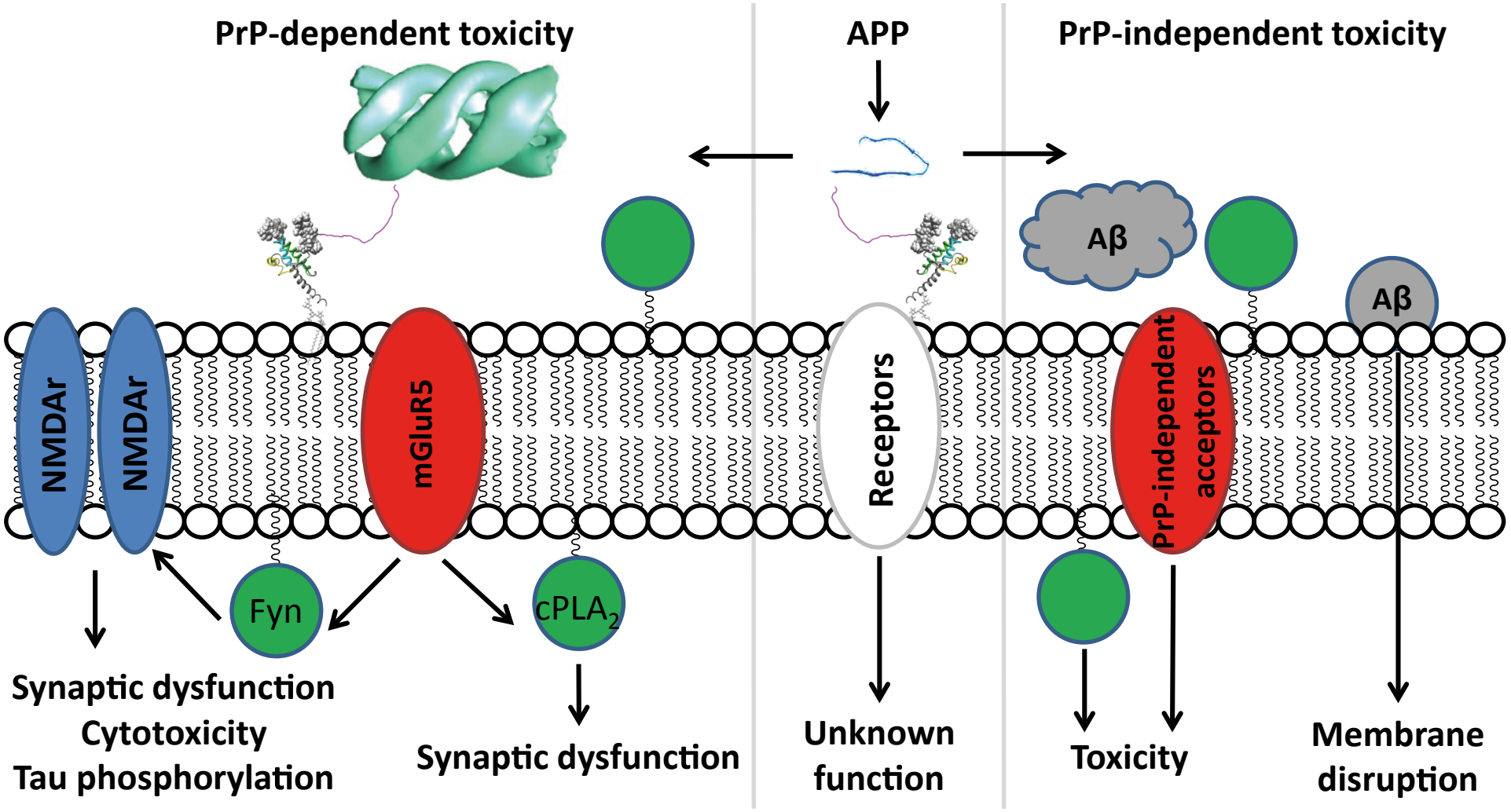

Aβ monomer
Aβ dimer
Aβ trimer
ADDL (Lambert et al., 2)
Aβ*56 (Lesné et al., 97)
TABFO (Stroud et al., 12)
Annular protofibril (Lashuel et al., 98)
ADDL (Hepler et al., 10)
ADDL (Laurén et al., 23)
Protofibril (Walsh et al., 99)
10^3
10^4
10^5
10^6
Molecular weight


Secondary Aβ binding site
Octapeptide repeat region
Putative Aβ binding region
N-linked Glycans
Helix 1
Helix 2
Helix 3
GPI anchor


PrP-dependent toxicity
APP
PrP-independent toxicity
Aβ
Aβ
NMDAr
NMDAr
mGluR5
Receptors
PrP-independent acceptors
Fyn
cPLA2
Synaptic dysfunction
Cytotoxicity
Tau phosphorylation
Synaptic dysfunction
Unknown function
Toxicity
Membrane disruption