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REVIEW

Binding between Prion Protein and Aβ Oligomers Contributes to the Pathogenesis of Alzheimer's Disease

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Abstract

A plethora of evidence suggests that protein misfolding and aggregation are underlying mechanisms of various neurodegenerative diseases, such as prion diseases and Alzheimer's disease (AD). Like prion diseases, AD has been considered as an infectious disease in the past decades as it shows strain specificity and transmission potential. Although it remains elusive how protein aggregation leads to AD, it is becoming clear that cellular prion protein (PrP^C) plays an important role in AD pathogenesis. Here, we briefly reviewed AD pathogenesis and focused on recent progresses how PrP^C contributed to AD development. In addition, we proposed a potential mechanism to explain why infectious agents, such as viruses, conduce AD pathogenesis. Microbe infections cause Aβ deposition and upregulation of PrP^C, which lead to high affinity binding between Aβ oligomers and PrP^C. The interaction between PrP^C and Aβ oligomers in turn activates the Fyn signaling cascade, resulting in neuron death in the central nervous system (CNS). Thus, silencing PrP^C expression may turn out be an effective treatment for PrP^C dependent AD.

Keywords Alzheimer's disease (AD) · Amyloid-β protein · Neurodegenerative disease · Cellular prion protein (PrP^C)

Introduction

Alzheimer's disease (AD), which was first reported by Dr. Alois Alzheimer in 1906 (Maurer *et al*. 1997), is a chronic neurodegenerative disease and one of the most common forms of dementia (Lane *et al*. 2018). In 2015, approximately 29.8 million AD patients were diagnosed worldwide, and it has been predicted that there will be more than 113 million AD patients worldwide by 2050 (Jellinger and Attems 2010; Vos *et al*. 2016). The incidence of AD is particularly high in the elderly; approximately 10% of people older than 60 years shows AD symptoms. In people older than 85 years, the prevalence is 50% (Gonsalves *et al*. 2012). Typical features of AD include short-term memory loss, visual-spatial perception disorders, and impairment of language and executive function (Pohanka 2018). The pathological features of AD include plaques formed by the deposition of amyloid β protein (Aβ) and neurofibrillary tangles formed by hyperphosphorylated tau protein (Glenner and Wong 1984; Lee *et al*. 1991; Martin *et al*. 2013; Ow and Dunstan 2014).

According to the time of onset, AD is classified as early-onset AD (EOAD) or late-onset AD (LOAD) (Bateman *et al*. 2011). EOAD, in which the age at onset is between 30 and 65 years, accounts for less than 0.1% of all AD cases (Blennow *et al*. 2006). LOAD, in which the age at onset is more than 65 years, is the most common form of AD. Both EOAD and LOAD can occur in people with a positive family history of AD; approximately 60% of patients with EOAD have multiple AD patients in their family, and 13% of these familial EOAD cases are inherited by autosomal dominant inheritance and affect at least three generations (Campion *et al*. 1999; Brickell *et al*. 2006). EOAD may also occur in LOAD families (Bird

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2008). Only 1% to 5% of AD cases can be simply diagnosed genetically, whereas most AD cases are complex and may involve multiple susceptibility genes and their interactions with environmental factors (Serretti *et al*. 2005; Roses 2006; Reitz and Mayeux 2014).

In this review, we briefly reviewed the pathogenesis of AD with an emphasis on how cellular prion protein (PrP^C) attribute to AD development. More importantly, we propose the interactions between PrP^C and Aβ oligomers may be the underline mechanism for AD caused by other infectious agents, such as viruses. Finally, we point out potential studies to corroborate the role this interaction plays *in vivo*.

Factors Influencing AD Development

Even after many years of intensive research, the cause of AD is not completely understood. It is believed that 70% of risk is genetic and involves multiple genes (Ballard *et al*. 2011). In addition, other factors such as age and genders are also involved. Age is one of the most important factors affecting the pathogenesis of AD (Seshadri *et al*. 1997; Hebert *et al*. 2001). The incidence of AD increases significantly with age: 3% of people aged 65–74 years, 17% of people aged 75–84 years, and 32% of people of 85 years or older develop AD (Hebert *et al*. 2013). However, ageing *perse* does not cause AD. Gender is another important factor determining the risk of AD; more women than men suffer from AD (Mielke *et al*. 2014). However, as the average life expectancy of women is longer than that of men and as age is a big risk factor for AD, it is difficult to assign the effect only to gender. What confounds the effect of gender further is the observation that men aged 45–65 years have higher cardiovascular mortality than women (Chene *et al*. 2015). Because cardiovascular disease is a risk factor for AD (Kivipelto *et al*. 2006), men older than 65 years who do not have cardiovascular disease have a healthier cardiovascular condition, which reduces the risk of developing AD (Chene *et al*. 2015). In addition, environmental factors, such as air pollution or aluminum pollution, or personal habits, such as smoking, greatly influence the occurrence of AD (Markesbery and Ehmann 1993; McLachlan *et al*. 1992; Shin *et al*. 1995; Pratico *et al*. 2002; Banks *et al*. 2006; Zatta *et al*. 2009; Cataldo *et al*. 2010; Bolognin *et al*. 2011; Moulton and Yang 2012).

Genes Associated with AD

Various genes associated with AD have been identified to date, including genes encoding amyloid precursor protein (*APP*), presenilin-1 (*PSEN-1*), presenilin-2 (*PSEN-2*), *CD2AP*, apolipoprotein E (*ApoE*), clusterin (*CLU*), complement receptor 1 (*CR1*), prion protein (*PRNP*), and tumor necrosis factor (*TNF*) (Bertram *et al*. 2007; Carrasquillo *et al*. 2010; Corneveaux *et al*. 2010; Hooli *et al*. 2012; *Kruger et al*. 2012; Lambert *et al*. 2013; Sproul *et al*. 2014; Wang *et al*. 2016; Bi *et al*. 2018; Mukherjee *et al*. 2018; Rao *et al*. 2018; El Bitar *et al*. 2019).

ApoE has three alleles, *ε2*, *ε3*, and *ε4*, which encode ApoE2, ApoE3, and ApoE4, respectively. Among the three alleles, ε3 is the most common, whereas ε2 is the least common (Mahley and Rall 2000). People with the ε4 allele are more likely to develop AD than those with the ε2 or ε3 allele (Spinney 2014). It is estimated that people with one ε4 allele are three times more likely to develop AD than those with two ε3 alleles, whereas people with two ε4 alleles have a 8–12 times higher risk of developing AD (Holtzman *et al*. 2012; Loy *et al*. 2014). Comparing to those individuals having mutation in *APP*, *PSEN-1*, or *PSEN-2*, individuals expressing *APOE-ε4* have slightly higher risk of developing AD (Chouraki and Seshadri 2014). Only 1% or less of AD cases are caused by mutation of *APP*, *PSEN-1*, or *PSEN-2*, which directly causes more $A\beta_{42}$ production (Bekris *et al*. 2010), leading to Aβ oligomerization and consequently, neuron death. People with mutated *APP* or *PSEN-1* will definitely develop AD if the mutations are AD-prone, whereas approximately 95% people with mutated *PSEN-2* develop AD (Goldman *et al*. 2011).

Aggregated Proteins Contribute to AD

Like Aβ, α-synuclein, tau, and prion protein are aggregation-prone proteins that are implicated in AD.

α-Synuclein Cross-seeds Tau fibrillization, Contributing to AD Pathogenesis

α-Synuclein is the major structural component of Lewy body fibrils, however, it was originally identified in senile plaques as a non-Aβ component from AD brain (Ueda *et al*. 1993). α-Synuclein pathology has been reported in sporadic and familial cases of AD (Yokota *et al*. 2002; Willingham *et al*. 2003). The protein was first identified from *Torpedo californica* (Maroteaux *et al*. 1988). In humans, α-synuclein is encoded by the *SNCA* gene localized on chromosome 4. α-Synuclein is a 14.5-kDa protein and consists of 140 amino acids (Ueda *et al*. 1993; Xia *et al*. 2001). The mRNA of α-synuclein is selectively spliced to produce three isoforms, α-synuclein-140, α-synuclein-126, and α-synuclein-112. The most common is α-synuclein-140, which is the full transcript of the *SNCA*

gene; α-synuclein-126 lacks residues 41–54 due to loss of exon 3; and α-synuclein-112 lacks residues 103–130 due to deletion of exon 5 (Ueda *et al*. 1994; Beyer 2006) (Fig. 1). α-Synuclein is abundant in the brain—it accounts for 1% of total proteins in the cytoplasm of brain cells (Iwai *et al*. 1995)—but is less abundant in the heart, muscles, and other tissues. In the brain, α-synuclein is mainly present at the tips of nerve cells at the presynaptic terminals (Iwai *et al*. 1995), where it interacts with phospholipids via its amino (N)-terminus (Clayton and George 1998; Chandra *et al*. 2003; Burre *et al*. 2012). In neurons, approximately 15% of α-synuclein is bound to the membrane, whereas the remainder is cytosolic, without a stable structure (McLean *et al*. 2000; Lee *et al*. 2002). Membrane-bound α-synuclein has amphipathic α-helix structures composed of 11 residues (XKTKEGVXXXX) (George *et al*. 1995; Weinreb *et al*. 1996; Kim 1997). α-Synuclein can interact with tubulin (Alim *et al*. 2002) and shows molecular chaperone activity to facilitate soluble N-ethylmaleimide-sensitive fusion protein attachment protein receptor (SNARE) complex formation (Chandra *et al*. 2005). Although cytosolicα-synuclein is unstructured and thus soluble, under pathological conditions α-synuclein can aggregate as insoluble fibrils, leading to Parkinson's disease, Lewy body dementia, and multiple system atrophy, the pathological feature of Lewy body (Spillantini *et al*. 1997). Remarkably, different strains of synthetic α-synuclein fibrils showed significant differences in efficiency in cross-seeding tau aggregation *in vitro* and *in vivo* (Guo *et al*. 2013).

Hyperphosphorylated Tau Forms Neurofibrillary Tangles, Leading to AD

Identified in 1975, tau protein was first thought to be essential for microtubule assembly (Weingarten *et al*. 1975; Cleveland *et al*. 1977). The structure of tau is stabilized when the protein is bound to tubulin. Binding also hinders its phosphorylation. Human tau is encoded by the *MAPT* gene, which is located on chromosome 17q21 and is composed of 14 exons (Goedert *et al*. 1988, 1989). In the adult brain, tau mRNA is selectively spliced to produce six tau isomers composed of 352, 381, 383, 410, 412, and 441 amino acids, respectively (Buee *et al*. 2000) (Fig. 2). In neurons in the central nervous system, tau binds to tubulin via the positively charged carboxyl (C)-terminus to form microtubules. Besides promoting tubulin assembly, thus stabilizing microtubule structure, it also regulates synaptic synthesis and inter synaptic signal transmission (Iqbal *et al*. 2005).

Tau has 79 potential phosphorylation sites, and as much as 31 residues can be phosphorylated in tau protein (Billingsley and Kincaid 1997). In normal adult human brain, tau contains two to three phosphate groups per molecule. However, in AD, tau is 3–4-fold more phosphorylated than in control brains, leading to hyperphosphorylation containing approximately 8 mol PO_4/mol tau (Kopke *et al*. 1993). The levels of total and phosphorylated tau in the cerebrospinal fluid are elevated in AD and correlate with a decrease in neuropsychological functions. Increased levels of phosphorylated tau protein threonine (t)181, t231, and total tau in the cerebrospinal fluid can be used to predict progression of mild cognitive impairment to AD (Mattsson *et al*. 2009). The extent of tau phosphorylation is regulated by protein kinase and phosphatase such as protein kinase A (PKA), protein kinase C (PKC), Ca^{2+}/calmodulin-dependent kinase (CaM kinase) II, protein phosphatase 1 (PP1) and protein phosphatase 2A (PP2A) (Matsuo *et al*. 1994; Billingsley and Kincaid 1997; Taniguchi *et al*. 2001; Ballatore *et al*. 2007). Phosphorylated tau can dimerize *in vivo*, potentially leading to cross-linking and the formation of pairs of helical filaments. These pairs of helical filaments can compete with microtubules to bind normal tau and other macromolecular microtubule-associated proteins, leading to cytoskeletal abnormalities and axonal transport disorders, causing

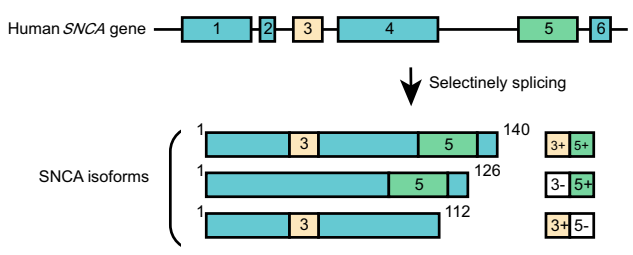

Fig. 1 Schematic representation of the human *SNCA* gene. *SNCA* gene contains 6 exons, selectively spliced to produce three isoforms: α-synuclein-140, α-synuclein-126, and α-synuclein-112.

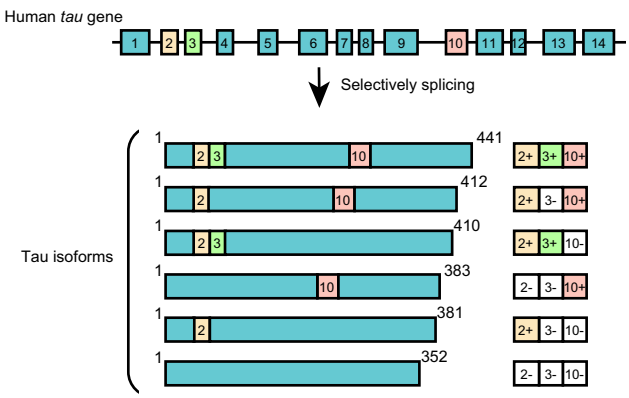

Fig. 2 Schematic representation of the human *tau* gene (modified from Buee *et al*. 2000). The human *tau* gene contains 14 exons, selectively spliced to produce six tau isomers composed of 352, 381, 383, 410, 412, and 441 amino acids, respectively.

synaptic loss and finally leading to dementia (Alonso *et al*. 1997). Hyperphosphorylated tau accumulates to form neurofibrillary tangles, which are an important pathological feature of AD (Alonso *et al*. 1997; Martin *et al*. 2013) (Fig. 3).

Amyloid Beta Can Form Aggregates Resulting in Neuron Damage in the Central Nervous System

The gene encoding APP is located on chromosome 21 in the human genome. APP is a transmembrane protein that can be processed via two pathways (Fig. 4). In the non-amyloid pathway, APP is cleaved by α-secretase between the 16th and 17th amino acids from the N-terminus to form soluble sAPPα and α-C-terminal fragments (α-CTFs). The α-CTF is further degraded by γ-secretase to produce P3 and incomplete Aβ ($A\beta_{17–40}$ and $A\beta_{17–42}$), which do not form amyloid deposits (Allinson *et al*. 2003). In the amyloid pathway, APP is cleaved by β-site amyloid precursor protein-cleaving enzyme 1, a transmembrane aspartyl protease that cleaves APP in the extracellular region to produce the N-terminus of Aβ, to form sAPPβ and β-C-terminal fragments (β-CTFs). The β-CTF is further cleaved by γ-secretase in the membrane to form the 3-kDa protein p3 and $A\beta_{40}$ (major component) or $A\beta_{42}$ (minor component) (Edbauer *et al*. 2003; Vassar 2004). Overexpression of APP in the brain of AD patients leads to the production of Aβ, which is cleaved by β-and γ-secretases (Masters *et al*. 1985). Aβ can exist as monomer, soluble oligomer, or insoluble fiber. Aβ monomer and insoluble Aβ fibers do not significantly change synaptic plasticity. However, soluble Aβ oligomers, including Aβ dimer and especially, OC antibody-positive oligomers from AD brain, can effectively impair synaptic structure and function (Shankar *et al*. 2008; Tomic *et al*. 2009). With ageing, the rate of Aβ production increases, whereas the rate of clearance decreases, resulting in Aβ deposition, which activates protein kinase II to hyperphosphorylate tau, resulting in tau aggregation and eventually leading to neurotoxicity and synaptic damage (Gotz *et al*. 2001; Jack *et al*. 2010; Falker *et al*. 2016).

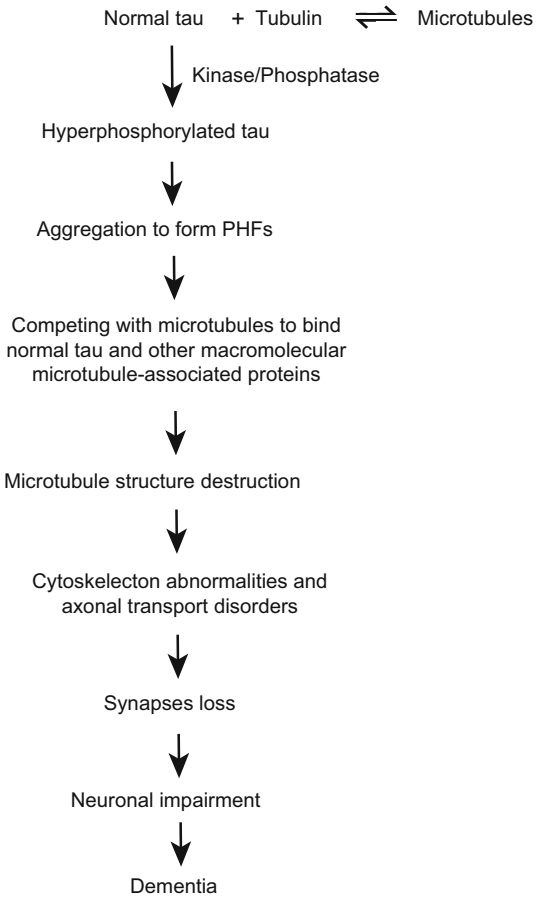

Fig. 3 Schematic representation of the process of Tau-induced neurofibrillary degeneration.

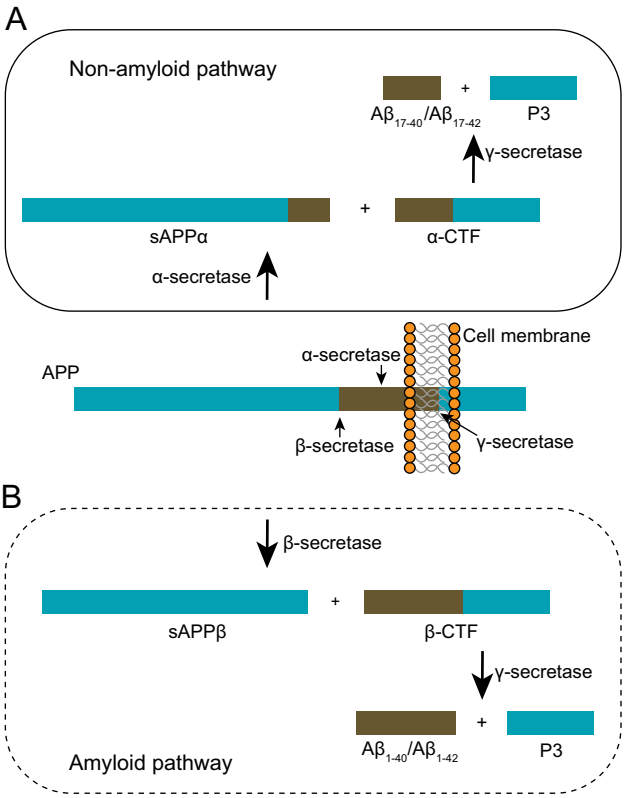

Fig. 4 Metabolic pathways of APP. **A** Non-amyloid pathway. APP is cleaved by α-secretase and γ-secretase to produce incomplete Aβ ($A\beta_{17–40}$ and $A\beta_{17–42}$). **B** Amyloid pathway. APP is cleaved by β-secretase and γ-secretase to produce $A\beta_{40}$ or $A\beta_{42}$.

PrP^C-Bound Aβ Oligomers Lead to Loss of Neuron Plasticity

Although Aβ seems to play a central role in AD pathogenesis, it requires other molecules to cause neurotoxicity. One of these proteins is PrP^C, a GPI-anchored glycoprotein located in lipid rafts in cell membranes (Yang *et al*. 2014). PrP^C is highly conserved in mammals (Basler *et al*. 1986; Schatzl *et al*. 1997). The *PRNP* gene is a single-copy gene with one exon (Basler *et al*. 1986) localized on chromosome 20p13 in the human genome.

Similarities between AD and Prion Disease

Although criteria for the clinical diagnosis of AD have been clearly outlined, there is considerable overlap in the clinicopathological features of AD and prion disease, a rare neurodegenerative disease, which leads to difficulties in diagnosis (Watson 1979; Ball 1980; Masters *et al*. 1981; Brown *et al*. 1982; Van Everbroeck *et al*. 2004; Armstrong *et al*. 2005). In one study, more than half of patients who were diagnosed as having Creutzfeldt–Jakob disease were fully compliant with the criteria of AD (Tschampa *et al*. 2001). In addition, some subjects with hereditary prion diseases show obvious signs of AD (Ghetti *et al*. 1996; Zheng *et al*. 2008). Especially, patients without a family history of prion diseases can show clinical features similar to those of other neurodegenerative diseases, such as AD, in earlier phases (Kovacs *et al*. 2002). Like AD, most human prion diseases are sporadic and hereditary; less than 1% is acquired. Hereditary prion diseases with *PRNP* mutation account for 10%–15% of all prion diseases (Prusiner 1998; World Health Organization (WHO) 2003).

Misfolded Aβ Behaves as Prion

Besides clinicopathological similarity, Aβ and PrP^{SC} (scrapie prion) share significant similarities at the molecular level. Like PrP^{SC}, Aβ can aggregate to form oligomers, which can form insoluble amyloid fibers that form depositions (Sakono and Zako 2010). A synthetic Aβ with distinct morphology and molecular structure reportedly possessed self-propagating capability when seeded to grow fibrils (Petkova *et al*. 2005). In addition, Aβ aggregates are capable of self-propagation when inoculated into susceptible transgenic mice (Stohr *et al*. 2012), a character reminiscent of different prion strains (Jones and Surewicz 2005). Studies have also suggested that some cases of familial AD can be transmitted as prion disease. After supernatant of superior frontal gyrus or lateral orbital cortex homogenate from four AD patients or two neurologically normal controls was unilaterally injected into the right hippocampus and neocortex of 3-month-old male APP transgenic mice (Tg2576) for 5 months, the cerebral hemispheres injected with the AD supernatant, but not the control supernatant, formed a large number of senile plaques and vascular deposits formed by Aβ aggregation. Although Aβ deposits were the most concentrated in the injection area, some deposits appeared in areas far from the injection site, even along the corpus callosum in the contralateral hemisphere in some mice, indicating that Aβ had spread among and multiplied in cells, again a character reminiscent of PrP^{SC} (Kane *et al*. 2000). Similarly, 10% of brain extracts from AD patients or brain lysates from Aβ-laden APP23 transgenic mice caused robust β-amyloid deposition in the hippocampus when injected into the hippocampus of young male APP23 mice (Cook and Austin 1978; Wisniewski *et al*. 1984; Kane *et al*. 2000; Meyer-Luehmann *et al*. 2006). More importantly, distinct Aβ strains can produce consistently different amyloid deposits when inoculated into bigenic mice. It has been shown that synthetic $A\beta_{40}$ or $A\beta_{42}$ strains, or brain lysates of "Arctic" or "Swedish" AD, which harbor E693G mutation or G670T/A671C double mutations, respectively, produced distinct but reproducible pathological attributes when inoculated into susceptible mice (Stohr *et al*. 2014; Watts *et al*. 2014; Watts and Prusiner 2018). These results strongly indicated that Aβ oligomers caused a transmission, but not a seeding effect.

Expression of PrP^C is Required for AD Pathogenesis in Mice and Drosophila

Similarities in biophysical properties between Aβ and PrP^{SC}, together with similarities in clinicopathological features between AD and prion disease suggest that these diseases share certain etiological mechanisms implicated in protein-misfolding diseases (Gajdusek 1994). In a transgenic AD mouse model, deletion of *PRNP* did not alter APP and Aβ expression levels, and astrocyte proliferation remained unchanged, with no axonal degeneration and synaptic loss. In contrast, AD transgenic mice with intact PrP^C expression exhibited dysfunction and memory deficits. Transgenic mice lacking PrP^C, but containing Aβ plaques showed no dysfunction and memory impairment (Gimbel *et al*. 2010). Treatment of aged APPswe/PSen1ΔE9 transgenic AD mice with anti-PrP^C antibody restored synaptic density (Chung *et al*. 2010). In *Drosophila*, PrP^C exacerbates AD pathogenesis (Younan *et al*. 2018). Thus, like prion disease, which requires PrP^C to show neurotoxicity, PrP^C is required for AD pathogenesis. These results suggest that PrP^C plays an important role in mediating learning and memory deficits in the AD model.

PrP^C Binds to Aβ

The requirement of PrP^C expression in AD pathogenesis in the mouse and *Drosophila* models suggests a potential interaction between PrP^C and Aβ. To investigate the mechanism of Aβ-mediated neuron toxicity, synthetic biotin-$A\beta_{42}$ oligomers were used to screen binding partners on the surface of COS-7 cells expressing cDNAs from an adult mouse brain library (Lauren *et al*. 2009). It was found that PrP^C expression was required for binding (Lauren *et al*. 2009). Further studies indicated that recombinant PrP^C binds to soluble $A\beta_{42}$ oligomers via two motifs, which span residues 23–27 and residues 95–110 (Calella *et al*. 2010; Chen *et al*. 2010; Fluharty *et al*. 2013; Younan *et al*. 2013; Ganzinger *et al*. 2014). However, it does not bind effectively to Aβ monomer and Aβ fibrils (Balducci *et al*. 2010; Chen *et al*. 2010). In fact, PrP^C inhibits Aβ fiber formation by promoting Aβ oligomer stability (Younan *et al*. 2018). Unlike binding between recombinant small $A\beta_{42}$ oligomers and PrP^C, larger $A\beta_{42}$ oligomers from AD brain lysate bind PrP^C efficiently (Dohler *et al*. 2014; Haas *et al*. 2014; Kostylev *et al*. 2015), and this binding requires lipid raft integrity (Rushworth *et al*. 2013).

Aβ-affects PrP^C-related Signaling Pathway

Binding between soluble $A\beta_{42}$ oligomers and PrP^C requires lipid rafts, the platform for cell signaling regulation (Simons and Toomre 2000; Mollinedo and Gajate 2015), suggesting that cellular signaling may be activated upon this binding. In neuron cells expressing PrP^C, addition of Aβ oligomers activated synaptic cytoplasmic phospholipase A (2) to translocate into lipid rafts and to form a complex with PrP^C and Aβ oligomers, leading to synapse damage (Bate and Williams 2011). The Src tyrosine kinase Fyn has been shown to colocalize with PrP^C in lipid rafts, and aggregation of PrP^C activates Fyn kinase in some cell lines (Pantera *et al*. 2009). When Aβ oligomers were added to PrP^C-expressing neurons, they bound PrP^C with high affinity, and activated Fyn (Thomas and Brugge 1997) to phosphorylate the NR2B subunit of the *N*-methyl-D-aspartate receptor, leading to its degradation (Um *et al*. 2012; You *et al*. 2012). Overexpression of Fyn enhanced Aβ-induced toxicity in a transgenic AD mouse model by inducing hyperphosphorylation of tau or neuronal Ca^{2+}-dyshomeostasis. Accordingly, when Fyn activity is inhibited, Aβ-induced damage can be reduced (Chin *et al*. 2005; Larson *et al*. 2012; De Mario *et al*. 2015). Another protein involved in Aβ oligomer-PrP^C binding is the metabotropic glutamate receptor, mGluR5, a transmembrane protein in the postsynaptic density, which links Aβ oligomer-PrP^C to Fyn. The addition of Aβ oligomers to neurons expressing PrP^C and mGluR5 activates Fyn and calcium signaling to enhance eEF2 phosphorylation, leading to Arc translation and dendritic spine loss (Um *et al*. 2013) (Fig. 5).

PrP^C-mediated Aβ Oligomer Inhibits Long-term Potentiation

Maintaining long-term potentiation (LTP) is widely accepted as one of the major cellular mechanisms that underlie learning and memory (Cooke and Bliss 2006). Soluble Aβ oligomers can inhibit LTP, leading to contraction of dendritic spines from pyramidal cells and causing spatial memory impairment. Hippocampal slices from *PRNP* null mice when tested for synaptic reactivity did not show Aβ oligomer-induced LTP damage (Lauren *et al*. 2009). Similarly, when binding between Aβ oligomers and PrP^C was prevented by anti-PrP^C antibodies, synaptic plasticity was rescued (Lauren *et al*. 2009). Remarkably, when administrated intracerebroventricularly, antibodies directed against the putative Aβ-binding site on PrP^C prevented Aβ-mediated inhibition of LTP (Barry *et al*. 2011). In contrast, a Fab fragment directed against the PrP^C region not involved in Aβ binding did not rescue LTP caused by Aβ oligomers (Barry *et al*. 2011).

Infectious Agents Activate PrP^C Expression Associated with AD

In addition to Aβ–PrP^C complex, many other factors contribute to AD pathogenesis, among which immune response and inflammation play critical roles (Sochocka *et al*. 2017). Infectious agents activate immune responses and inflammation; thus, it is not surprising that infectious agents have been suspected to play a role in AD (Himmelhoch *et al*. 1947; Cleobury *et al*. 1971; Lycke *et al*. 1974; Renvoize *et al*. 1979; Middleton *et al*. 1980; Renvoize and Hambling 1984; Wisniewski *et al*. 1984; Mirra *et al*. 1986; Mozar *et al*. 1987; Dittrich *et al*. 1989; Miklossy 1993; Miklossy *et al*. 1994, 2006; Balin *et al*. 1998; Price *et al*. 2001; Sauder *et al*. 2001; Riviere *et al*. 2002; Wojtowicz *et al*. 2002; Kountouras *et al*. 2006; Carbone *et al*. 2014; Schott 2015; McNamara and Murray 2016; Itzhaki 2017; Westman *et al*. 2017; Dominy *et al*. 2019). Herpes simplex virus (HSV) has been investigated extensively in AD (Sequiera *et al*. 1979; Jamieson *et al*. 1991, 1992; Itzhaki *et al*. 1997; Lin *et al*. 2002; Wozniak *et al*. 2005). In a HSV-infected mouse model, Aβ deposits were detected in the brain as a result of increased levels of β-site amyloid precursor protein-cleaving enzyme 1 in neuronal and glial cells (Wozniak *et al*. 2007). Although HSV-1 can also be detected in normal aged brain, in AD,

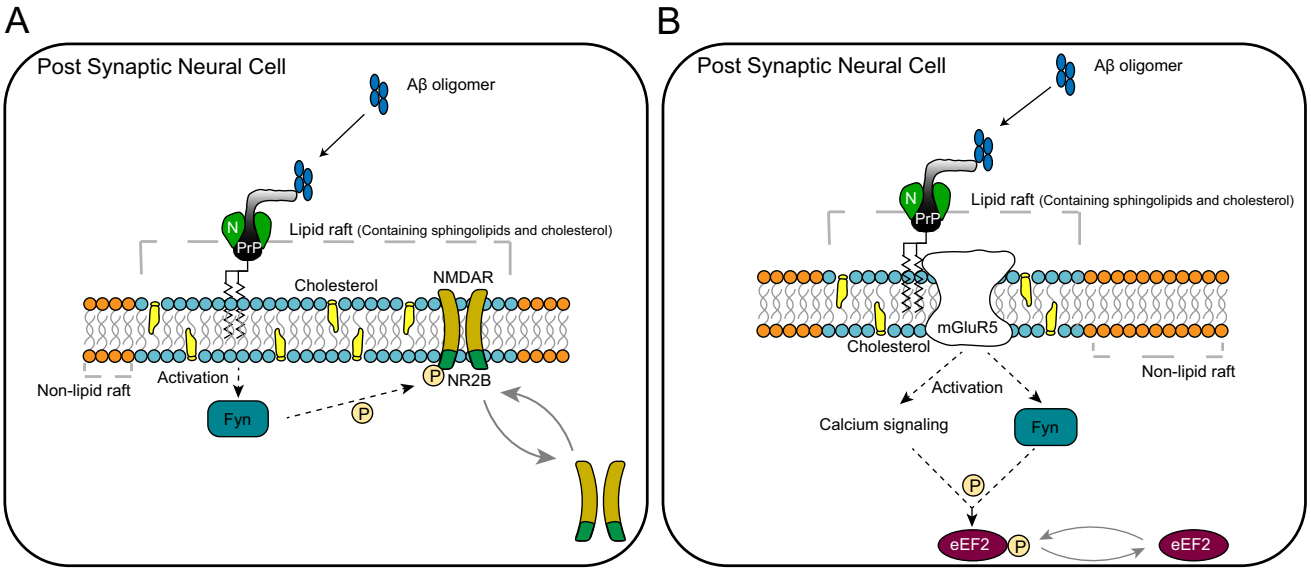

Fig. 5 Signaling cascades mediated by the interaction between PrP^C and Aβ oligomers. **A** Binding between PrP and Aβ oligomers activates Fyn, which phosphorylates the NR2B subunit of the *N*-methyl-D-aspartate receptor, leading to its degradation. **B** An alternative pathway induced by PrP binding to Aβ oligomers, recruiting mGluR5, activating Fyn and leading to calcium accumulation and phosphorylation of eEF2, resulting in loss of neuron plasticity. The correlation between these two pathways remains to be determined.

infection by HSV-1 is restricted to particular regions, such as frontal and temporal cortices and the hippocampus, which suggests a causal relationship between HSV-1 infection and AD occurrence (Denaro *et al*. 2003). In addition, HSV-1 infection causes inflammatory cytokine IL-6 production, which may worsen AD (Luterman *et al*. 2000; Oshima *et al*. 2001). Finally, the presence of anti-HSV IgM indicates a reactivation of the infection, at which point the risk of developing AD is doubled (Lovheim *et al*. 2015). However, as the frequency of *APOE ε4* is higher in AD patients with HSV-1 infection (Itzhaki *et al*. 1997; Corder *et al*. 1998), HSV-1 alone is not a risk factor for AD. Recently, human herpes virus-6A and-7 were found to be closely related to AD, possibly by regulating APP metabolism (Readhead *et al*. 2018). Interestingly, infection by *Helicobacterpylori* and human immunodeficiency virus (HIV) has been shown to upregulate the expression of PrP^C (Muller *et al*. 1992; Konturek *et al*. 2005; Dohler *et al*. 2014), which has been implicated in inflammation (Pammer *et al*. 1998; de Almeida *et al*. 2005; Tsutsui *et al*. 2008; Hu *et al*. 2010; Gourdain *et al*. 2012; Petit *et al*. 2012; Ding *et al*. 2013; Liu *et al*. 2015; Wu *et al*. 2017). Thus, PrP^C expression induced by infectious agents may contribute to neuron death by inducing an inflammation response. In addition, virus infection has been shown to induce Aβ deposition (Wozniak *et al*. 2007; Readhead *et al*. 2018), during which an interaction between Aβ oligomers and PrP^C is possible. This interaction may initiate a signaling cascade leading to neuron apoptosis (Um *et al*. 2013).

Concluding Remarks and Perspectives

Multiple receptors for Aβ have been identified, among which PrP^C shows the highest affinity. As PrP^C itself is prone to oligomerization (Priola *et al*. 1995; Pan *et al*. 2005; Rambold *et al*. 2008; Gao *et al*. 2019), it remains to be investigated whether Aβ oligomers, when formed on the membrane of a neuron, bind to PrP^C monomer or PrP^C dimer first, as this may have implications for the activation of downstream signaling, thus affecting AD pathogenesis. Another issue that remains to be investigated is how posttranslational modification of PrP^C affects its interaction with Aβ on a neuron. It is known that most PrP^C on the cell surface has complex-type N-linked glycans, which prevent its oligomerization (Yi *et al*. 2018). It is unclear whether Aβ oligomers prefer non-glycosylated or glycosylated PrP^C. Furthermore, cell-surface glycosaminoglycan (GAG) has been shown to recruit PrP^C (Pan *et al*. 2002; Gao *et al*. 2016), thus forming a PrP^C pool behaving as PrP^C oligomers, whereas GAG also binds Aβ and is critical for Aβ fibril formation (Castillo *et al*. 1999). Interestingly, Aβ oligomers and GAG bind to the same motif on PrP^C, but how GAG affects AD pathogenesis via modifying PrP^C–Aβ interaction warrants further investigation.

By binding to PrP^C, Aβ oligomers inhibit LTP, leading to cognitive decline in AD. Furthermore, the Aβ–PrP^C oligomer complex can interact with the mGluR5 receptor, causing abnormal phosphorylation of eEF2 and resulting in loss of dendritic spines (Fig. 6).

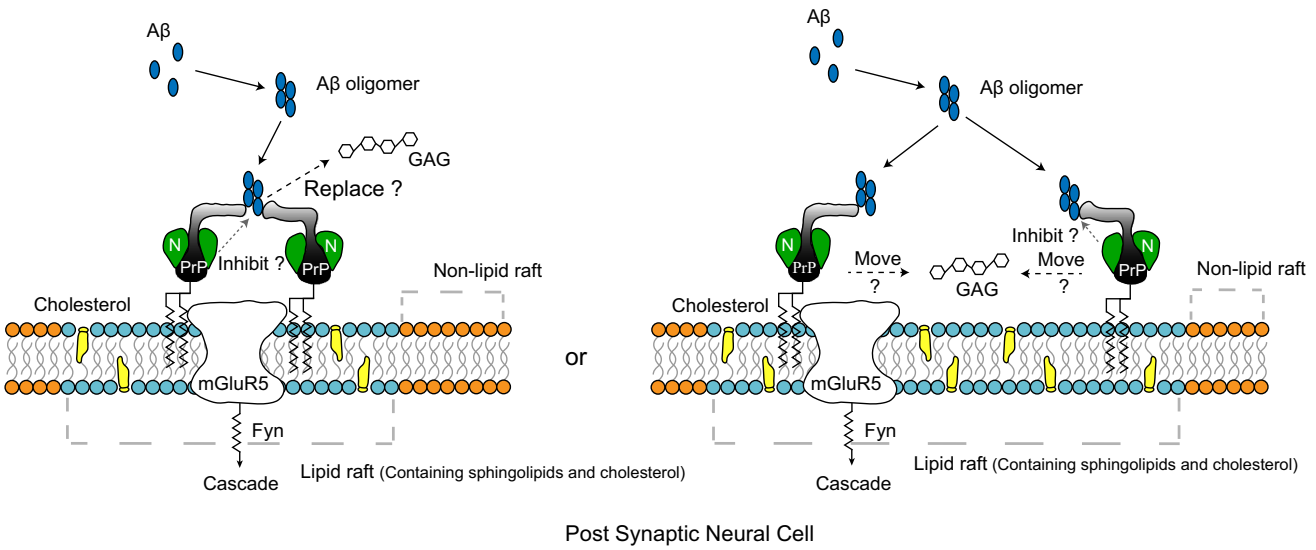

Fig. 6 Potential interactions between Aβ oligomers and PrP^C on neurons. Left panel: *in vivo*, GAG might bind PrP^C before Aβ oligomer formation. Aβ oligomers might replace GAG owing to its higher affinity for PrP^C. Right panel: Aβ oligomers may bind PrP^C monomer, GAG facilitates Aβ fibrilization by pulling PrP^C monomer to oligomerize. In either case, N-linked glycans may resist PrP^C oligomerization.

Besides binding to PrP^C on neuronal cells, Aβ oligomers may also interact with PrP^C on glia, which has been shown to be induced by HIV-1 infection. In the early stage of AD onset, activated microglia gather around Aβ plaques, producing neurotoxic molecules, such as NO, ROS, proteases, adhesion molecules, and pro-inflammatory cytokines TNF-α, IL-1β, IL-6 (Veerhuis *et al*. 2003; Trotta *et al*. 2014). Whether the binding of PrP^C to Aβ oligomers has any role in generating neurotoxic molecules remains incompletely understood. Current data suggest that the interaction between Aβ and PrP^C plays an important role in the pathophysiology of AD and might be a novel therapeutic target for of AD.

Aβ plaques occur many years before clinical symptoms can be detected. This suggests that either Aβ–PrP^C complex requires a long time to form *in vivo*, or the threshold for triggering the signaling cascade to initiate AD *in vivo* is high. In addition, there is a variety of Aβ proteins, including $Aβ_{37}$, $Aβ_{38}$, $Aβ_{40}$, $Aβ_{42}$, and $Aβ_{43}$, which can be further processed by aminopeptidase, glutaminyl cyclase or isomerase, and kinase (Kumar *et al*. 2011). How those modifications affect PrP^C–Aβ oligomer interaction remains to be investigated.

Since binding between PrP^C and Aβ oligomers plays an important role in ageing related AD and may also be responsible for infectious agents caused AD, understanding the interaction *in vivo* is of great importance for AD treatment.

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Compliance with Ethics Standards

Conflict of interest The authors declare that they have no conflict of interest.

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