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Review

The pathogenesis of soluble PrP fragments containing Aβ binding sites

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ABSTRACT

Prion protein (PrP) has proven to bind amyloid beta (Aβ) oligomers with high affinity, changing our understanding of both prion diseases (PD) and Alzheimer's disease (AD) at the molecular and phenotypic levels, although the latter currently lacks sufficient attentions. Transgenic mice expressing anchorless PrP developed unusual diseases reminiscent of AD with tremendous amyloid plaque formation. In this review, we described two interesting observations at the phenotypic level. First, common pathogenic mutations of the PRNP gene in Gerstmann–Sträussler–Scheinker (GSS) syndrome were clustered at PrP95-105. Meanwhile, all nonsense PRNP mutations that generated soluble PrP 95-105 exhibited phenotypes with abundant amyloid formations. We speculate that PrP-Aβ oligomers binding might be the underlying mechanism of the predominant amyloid phenotypes. Second, soluble PrP-Aβ oligomer complexes might exist in the extracellular space at the beginning of both PD and AD and subserve an initial neuroprotective function. Thus, the diseases would only present after long-term accumulation. This might be the central common pathogenic event of both PD and AD.

Contents

1. Prion diseases and Alzheimer's Disease are the most unusual and most common neurodegenerative diseases, respectively

Prion diseases (PD) are unusual fatal neurodegenerative diseases that present with dementia as the most common and earliest symptom. The causal agents of PD are abnormal isoforms of cellular prion protein (PrP^{Sc}), produced by a conformational transformation from the normal isoform (PrP^{C}). PrP^{C} is a 253-aa-long glycosyl-phosphatidylinositol (GPI)-anchored protein that is expressed in many tissues, though at its highest levels in neurons (Brown, 2001).

Abbreviations: PD, prion diseases; AD, Alzheimer's disease; PrP, prion protein; GSS, Gerstmann–Sträussler–Scheinker; GPI, glycosyl-phosphatidylinositol; APP, amyloid precursor protein; LTP, long-term potentiation; CJD, Creutzfeldt–Jakob disease.

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Although it was cloned almost 30 years ago, the full normal functions of PrP^C are still unclear.

Alzheimer's disease (AD) is the most common neurodegenerative disease and is affecting millions of people worldwide. AD is characterized by the deposition of senile plaques in the brain that consist predominantly of the amyloid-β (Aβ) peptide 40–42 amino acids long, produced by the cleavage of amyloid precursor protein (APP). APP is a type I transmembrane protein expressed in many tissues and concentrated in the synapses of neurons, whose primary function is still unclear.

PD and AD are neurodegenerative diseases that demonstrate synaptic failure as their earliest and most predominant pathogenic event (Ferrer, 2002; Fournier, 2008; Mallucci, 2009; Small et al., 2001; Westergard et al., 2007). Amyloid plaques are present in both AD and some types of PD (Schwarze-Eicker et al., 2005; Kellett and Hooper, 2009). PrP^{Sc} can be deposited in the brain as large fibrillar amyloid plaques and/or as small diffuse punctate non-amyloid deposits. The non-amyloid form is prevalent in many patients with sporadic Creutzfeldt–Jakob disease (sCJD) (Chesebro et al., 2010) while the amyloid plaque form is present in patients with Gerstmann–Sträussler–Scheinker (GSS) syndrome and about 10% of sCJD cases (Wisniewski et al., 2002). Other common phenotypic features of PD and AD include: numerous kindred carrying point mutations in an amyloidogenic protein, the presence of polymorphisms that influence disease susceptibility, and more sporadic occurrences than inherited cases (Castellani et al., 2004).

2. PrP95-105 can bind Aβ oligomers with high affinity

Abundant research has explored the connections between PrP and APP. PrP^C overexpression in transgenic mice significantly increased the number of Aβ plaques while the levels of Aβ40 and Aβ42 were slightly higher (Schwarze-Eicker et al., 2005). Cellular PrP^C overexpression inhibited β-secretase mediated cleavage of APP and reduced Aβ generation. Depletion of PrP^C in N2a cells increased Aβ levels in the culture medium. Aβ levels also significantly increased in the brains of PrP null mice and scrapie infected mice (Parkin et al., 2007).

The real breakthrough was made by Lauren et al. (Lauren et al., 2009). Aβ oligomers failed to block Long-Term Potentiation (LTP) in young adult PrP null mice while they inhibited LTP in wild-type PrP mice. Anti-PrP^C antibodies, or deletion of 11 amino acids at positions 95-105 of PrP, prevented Aβ oligomers from binding to PrP^C and rescued synaptic plasticity in hippocampal slices from Aβ oligomers. In addition, immunohistochemistry data suggested that the co-localization of PrP and Aβ42 oligomers extensively overlapped, which can indicate protein–protein binding, and that both proteins were most concentrated at post-synaptic densities. They concluded that PrP^C could bind Aβ oligomers with high affinity via PrP 95-105.

Since these findings, there have been fierce debates regarding whether PrP^C is a mediator or receptor of Aβ oligomers(Calella et al., 2010; Chen et al., 2010; Chung et al., 2010; Gimbel et al., 2010; Kessels et al., 2010). The developing consensus suggests that PrP^C can bind Aβ oligomers with high affinity, and that PrP 95-105 is the main binding site. Currently, the focus of research has moved to the downstream intracellular molecular events, which are not covered in this paper(Chen et al., 2013; Kudo et al., 2012a,b; Ostapchenko et al., 2013; Um et al., 2012).

Data on soluble PrP^C from Calella et al. (2010) provided vital information. First, they confirmed that PrP^c could bind Aβ oligomers. Second, their data showed that soluble PrP could rescue APPPS1-related LTP impairment in transgenic mice co-expressing both anchorless PrP and APPPS1, whereas the GPI-anchored PrP failed to rescue LTP impairment.

3. Anchorless/soluble PrP enhance amyloid formation

Chesebro et al. (2005) established a series of transgenic mouse models expressing anchorless PrP. After scrapie infection, PrP^{Sc} was deposited in amyloid plaques in heterozygous transgenic mice expressing anchorless PrP. The amyloid plaques induced brain damage reminiscent of AD (Trifilo et al., 2008), and the mice developed an amyloid heart disease (Trifilo et al., 2006). Furthermore, after scrapie infection, homozygous transgenic mice expressing two-fold anchorless PrP developed a new fatal disease with dense amyloid PrP^{res} plaque deposition in the gray matter, but without spongiosis. Pathogenic amyloid angiopathy was found as described for the heterozygous mice (Chesebro et al., 2005), and which was similar to that found in AD. Co-localization of PrP^{res} and APP was also observed within these amyloid plaques.

The above anchorless, or soluble, PrP seemed to enhance the formation of amyloid plaques. Given the high affinity between PrP95-105 and Aβ oligomers, we speculate that soluble PrP 95-105 might play the amyloidogenic function and enhance the formation of amyloid plaques noted above. Then how does PrP become soluble? Does soluble PrP exist under natural conditions?

4. Soluble PrP95-105 could be produced by two mechanisms

PrP^C can be processed by different pathways, including alpha- or beta-cleavage and shedding. Alpha cleavage and shedding could produce soluble/truncated fragments containing Aβ binding sites (Liang and Kong (2012)) (No.1 in Fig. 2).

Alpha cleavage occurs at PrP residue 110/111 and is mediated by proteases such as ADAM10, ADAM17, TACE and ADAM 8. These produce two fragments, termed N1 and C1. N1 contains the Aβ oligomer binding site and is secreted into the extracellular space while C1 attaches to the membrane.

Beta cleavage occurs at PrP residue 90/91, and is mediated by reactive oxygen species in the presence of divalent copper ions (Kang and Kim, 1997; Mange et al., 2004; McMahon et al., 2001; Watt et al., 2005). It produces two fragments, termed N2 and C2, with N2 being secreted to the extracellular space, and C2 attaches to the membrane. Beta cleavage does not produce soluble PrP fragments containing Aβ oligomer binding sites. However, beta cleavage has been considered to be the amyloidogenic pathway (Forloni et al., 1993; Kuwata et al., 2003; Walsh et al., 2009a).

Shedding occurs at or near the GPI-anchor and is mediated by ADAM10, AMAM9 (indirectly via ADAM10), and phospholipase. Shedding releases full length PrP into the extracellular space, which produces soluble PrP fragments containing Aβ oligomer binding sites.

Soluble PrP^C was detected in human cerebrospinal fluid, seminal fluid, and serum (Parizek et al., 2001; Picard-Hagen et al., 2006; Roberts et al., 2010; Tagliavini et al., 1992). The soluble PrP^C detected in seminal fluid was cleaved at residue 203, indicating that it was produced by the shedding pathway (Shaked et al., 1999). Immunochemical methods revealed that soluble PrP levels were higher in plasma from patients with CJD and other neurodegenerative diseases than in healthy subjects (Volkel et al., 2001). Notari et al. found two fragments in brain tissue from patients with sCJD and variant CJD (vCJD) patients' brain tissues that shared the primary N-terminal sequence but lacked a few amino acids at the very end of the C-terminus as well as the GPI-anchor (Notari et al., 2008).

Evidently, the soluble PrP coexisted with GPI-anchored PrP under natural conditions, but with higher levels in patients with PD patients. This suggests that it also has normal physiological functions, an important one of which might be the binding of Aβ oligomers.