Article

Cellular prion protein and amyloid – β oligomers in Alzheimer's Disease – there are connections?

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Abstract: Alzheimer's disease (AD) is the most common cause of dementia worldwide. Pathological deposits of neurotoxin proteins within the brain, such as amyloid-Beta and hyperphosphorylated tau tangles, are prominent features in AD. The prion protein (PrP) is involved in neurodegeneration via its conversion from the normal cellular form PrPc, to the infection form PrP Sc. Some studies indicated that posttranslationally modified PrPc isoforms plays a fundamental role in AD pathological progression. Several studies have shown that interaction of Aβ oligomers with N-terminal residues of the PrPc protein region appears critical for neuronal toxicity. The PrPc-Aβ binding always occur in AD brains and is never detected in nondemented controls and the binding of Aβ aggregates to PrPc is restricted to the N-terminus of PrPc.

Keywords: Alzheimer's disease; cellular prion protein; amyloid β and PrP interaction in Alzheimer's; BACE1; Aβ

1. Introduction

Pathological aggregates of the amyloid-beta (Aβ) peptide and hyperphosphorylated tau are the main changes responsible for developing Alzheimer's Disease (AD), so the question of possible interactions between them seemed obvious. Indeed a lot of studies confirm the relationships between those molecules [1–3]. Not only do monomeric and oligomeric Aβ interact with phosphorylated tau in AD neurons, but what may be even more important is that these interactions progressively increase with the progression of AD [4]. These interactions may cause structural and functional damage, particularly if the interaction occurs at synapses [5]. Because of the ability to bind directly to the receptor, soluble Aβ and tau impair synaptic plasticity, lead to neurite degeneration, and to activation of kinases including Fyn, which itself can enhance tau phosphorylation [1]. The major components of Aβ aggregate in the AD brain are neuritic plaques, diffuse amyloid, and vascular amyloid. Aggregation of Aβ under the form of amyloid fibrils has long been considered central to the pathogenesis of AD [6,7].

However, in recent years, a large body of evidence strongly supports that soluble Aβ oligomers are more detrimental to synaptic plasticity than Aβ that has caused amyloid fibril formation. Soluble Aβ appears to be a more potent seed than fibrillar Aβ aggregates for the transmission of Aβ pathology [8]. Their ability to inhibit long-term potentiation (LTP) and many other critical neuronal activities is responsible for the classic model of synaptic plasticity and memory loss in vivo and in culture cells [9–12]. These studies stoutly defend the idea that soluble Aβ oligomers are the causative agents of AD.

Furthermore, soluble Aβ oligomers have been found to be very high in the AD brain, and their levels correlate strongly with the severity of the disease [13]. The results of clinical trials on mild AD subjects with solanezumab, the antibody that binds to soluble monomers (not to plaques), suggested a statistically significant cognitive benefit [14]. Ample evidence is indicative of the direct attribution of decreased hippocampal LTP and altered memory function to an isolated, biochemically defined, assembly form of human Aβ soluble oligomers in the absence of amyloid fibrils [15]. By binding to receptors on the surface of neurons, Aβ oligomers are thought to initiate signaling pathways that lead to synaptic dysfunction and neuronal death. Interestingly, the mechanism by which Aβ oligomers exert their toxic effects is related to prion protein (PrP), the etiologic protein of prion diseases [16,17], and a glycoprotein in cell membranes [7,18]. PrP is ubiquitously expressed but concentrated in the central nervous system of the brain and spinal cord [19–21], where it functions as a receptor that can mediate the neurotoxic effects of Aβ oligomers. Here we show the latest findings on how the clinical pathology of AD changes depending on the interaction between PrP and Aβ [7,22,23].

2. Cellular prion protein and Alzheimer Disease

The cellular prion protein PrPC is an N-glycosylated GPI-anchored protein founded in lipid rafts. Binding domains and distinct phenotypes present specific mechanisms during AD progression. There have been shown variable ratios of diglycosylated, monoglycosylated, and unglycosylated isoforms [24]. There are some conflicting results regarding the elevation of membrane-binding PrPC levels in brain tissue of AD patients compared with patients with mild cognitive impairment (MCI) or no cognitive impairment (NCI). The discrepancy may arise due to the lack of specificity of the assay for the prion's protein isoform [25].

The soluble Aβ assemblies derived from the brains of individuals with Alzheimer's disease interacted with PrPC at the postsynaptic density to activate the Src kinase Fyn, which phosphorylates the NR2B subunit of NMDA receptor and causes a transient increase of NR2B on the cell surface with consequent excitotoxicity, while rendering destabilization of dendritic spines. This molecular mechanism of PrPC -mediated Aβ toxicity while indicating a prion connection of Aβ and Fyn [26]. Another study demonstrated that soluble Aβ binds to PrPC at neuronal dendritic spines, where it forms a complex with Fyn and results in the activation of the kinase and subsequent Fyn-dependent tau hyperphosphorylation in a PRNP gene dose-dependent manner, making another prion connection [27].

The metabotropic glutamate receptor, mGluR5, a transmembrane protein in the postsynaptic density, could be another protein involved in Aβ oligomer-PrPC binding links Aβ oligomer-PrPC to Fyn [28]. Some data point out that agents like caveolin-1 or the neural cell adhesion molecule (NCAM) could potentially connect PrPC and Fyn from the two opposite sides of the cell membrane [29–31].

3. PrPC and AD stages

PrPC isoforms become modified in various pathological processes of AD. Those diverse phenotypes of PrPC appear to be risk factors for either slow or rapid progression of the disease. The specific PrPC isoforms are participating in the association of modified PrPC interacting proteins with AD pathology. The association between the glycosylation pattern of PrPC and the severity of AD may eventually be a potential diagnostic biomarker for the pathology. A growing body of literature has indicated that PrPC deposits often accompany Aβ plaques in AD and PrPC was the high-affinity receptor to Aβ42 oligomers on cells. The altered expression of PrPC seems to be associated with disease progression. The finding that PrPC is decreased in the hippocampus and temporal cortex in aging and sporadic AD but not in familial AD supports the hypothesis that reduced PrPC expression reflects a main mechanism of disease and is not a consequence of other AD-associated changes [32].

Other studies have shown changes in PrPC expression level in the late stages of AD, probably due to the loss of neurons. PrPC protein expression in the brain increases already in the initial stages of AD and reaches its peak around stage III. Henceforward, PrPC expression declines up to the clinical manifestation of the disease [33]. The impingement of Aβ oligomers with the N-terminal residues of the PrPC protein region appears critical for neuronal toxicity. The PrPC -Aβ binding is regularly present in AD brains, but it has not been found in non-demented controls. The N-terminal residues 23–27 region and the 92–110 region seem to be critically important for PrPC interactions with Aβ42 oligomers because the deletion of either of these regions results in a significant loss of binding. Some preliminary work in this field also suggests that N-terminal residues 23–27 and the 95–110 region of PrPC incorporate the strategic amino acid binding sequence for oligomer Aβ-induced synaptic deterioration and apoptosis of the neurons. Mentioned fragments of PrPC protein strongly impede the Aβ42's both cyto- and synapto -toxic efficiency [24].

4. PrPC and AD prevention

Interactions with the APP cleaving enzyme BACE1 through its N-terminal polybasic domain is another function of PrPC and it inhibits enzyme activity, resulting in a reduction of Aβ production, which indicates a preventive role against AD [34].

Membrane-binding PrPC has been demonstrated to regulate long-term potentiation (LTP) in the hippocampus, which is induced by oligomeric Aβ42. Recently, it was found that PrPC can interact with the different forms of Aβ like synthetic Aβ oligomers, Aβ-derived diffusible ligands (ADDLs). Additionally, PrPC has also been shown to bind to ADDLs, which are tightly related to cognitive impairment in multiple mouse models of Alzheimer's disease. That PrPC is a major component for the inhibition of LTP by ADDLs from AD brains [35,36].

The PrPC -Aβ oligomer interaction is dependent on raft-based complexes. The most important for the interaction between Aβ42 with PrPC is cholesterol-rich lipid rafts. GPI-anchored PrPC is localized to the cholesterol-rich lipid raft microdomains of the plasma membrane. Cholesterol depletion disrupts these rafts with PrPC being redistributed into non raft regions of the membrane. The disruption of the rafts causes a significant reduction in Aβ oligomer binding to cells and prevents the activation of Fyn kinase. Studies indicate that PrPC functions as an extracellular scaffolding protein that is able to organize multiprotein complexes that mediate intracellular signal transduction at the cell surface [37].

5. Conclusions

Interactions between PrPC and Aβ oligomer are one important of the molecular mechanisms that played a role in the pathogenesis of AD. A shift in the profile of PrPC glycosylation plays a role in AD pathological progression. The PrPC appears to be important to mediate the plasticity impairments induced by certain Aβ species or conformations that must be clarified in the future. Further research is needed because it could be crucial to develop new therapies.

Conflicts of Interest: The authors declare no conflict of interest.

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