Neurodegenerative Diseases

Neurodegenerative Dis 2012;10:298–300
DOI: 10.1159/000332596

Received: June 28, 2011
Accepted: August 25, 2011
Published online: December 9, 2011

Cellular Prion Protein Mediates Toxic Signaling of Amyloid Beta

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Key Words

Prion · Alzheimer's disease · N-methyl-D-aspartate · Intrinsically disordered N-terminal domain of PrP^C · Neurodegeneration · β-Sheet

Abstract

Prion diseases in humans and animals comprise a group of invariably fatal neurodegenerative diseases characterized by the formation of a pathogenic protein conformer designated PrP^{Sc} and infectious particles denoted prions. The cellular prion protein (PrP^C) has a central role in the pathogenesis of prion disease. First, it is the precursor of PrP^{Sc} and infectious prions and second, its expression on neuronal cells is required to mediate toxic effects of prions. To specifically study the role of PrP^C as a mediator of toxic signaling, we have developed novel cell culture models, including primary neurons prepared from PrP-deficient mice. Using these approaches we have been able to show that PrP^C can interact with and mediate toxic signaling of various β-sheet-rich conformers of different origins, including amyloid β, suggesting a pathophysiological role of the prion protein beyond prion diseases.

Results and Discussion

PrP^C Mediates Toxic Signaling of Homologous and Heterologous PrP^{Sc}

By employing transgenic mice, it has been convincingly shown that the expression of PrP^C is essential for the formation of PrP^{Sc} and infectious prions [1]. Moreover, neuronal PrP^C is required to mediate neurotoxic effects of scrapie prions [2–4]. Using a novel cell culture model, we could corroborate that PrP^C localized at the cell surface is a mediator of proapoptotic signaling induced by PrP^{Sc} [5]. This assay is based on the cocultivation of PrP^C-expressing cells with scrapie-infected cells that release PrP^{Sc} and infectious prions into the cell culture medium. To test whether the toxic effects required sustained de novo formation of PrP^{Sc}, we modified our cell culture model in order to minimize the possibility that propagation of infectious prions occurs. To this end, we exposed cells expressing hamster, human, cervid or bovine PrP^C to mouse PrP^{Sc}. Based on previous studies in transgenic mice and cell culture models [6, 7], it is highly unlikely that mouse PrP^{Sc} can induce efficient conversion of heterologous PrP^C molecules into PrP^{Sc}. Strikingly, heterologous PrP^C, be it of hamster, human, cervid or bovine origin, could efficiently mediate toxic signaling of mouse

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PrP^{Sc} in our model. These findings provided experimental evidence that toxic signaling of PrP^{Sc} via PrP^{C} appears to be independent of PrP^{Sc} propagation [8].

PrP^{C} Binds to and Mediates Toxic Signaling of β-Sheet-Rich Conformers of Different Origins

Some observations already suggested a possible connection between Alzheimer's disease and prion diseases [9], but the first mechanistic insight into a possible role of PrP^{C} in amyloid beta (Aβ)-induced toxicity was provided by the Strittmatter group. They identified PrP^{C} as a high-affinity receptor for oligomeric conformers of Aβ and showed that expression of PrP^{C} is required to mediate Aβ-induced inhibition of long-term potentiation and memory impairment in transgenic Alzheimer mice [10, 11]. Initially, these results could not be reproduced by other groups [12–14]. However, in the meantime, independent studies, including one from our group, provided additional experimental evidence for the concept that PrP^{C} can act as a mediator of Aβ-induced toxicity [8, 15–18].

In our study, we did not only focus on the role of PrP^{C} as a possible mediator of Aβ-induced toxicity, but we also addressed the possibility that PrP^{C} can mediate toxic signaling of diverse β-sheet-rich conformers. In particular, we tested toxic assemblies formed by (a) Aβ peptide, (b) the NM domain of the yeast prion protein Sup35 [19] and (c) designed β-sheet peptides [20]. Indeed, employing established cell lines and primary neurons prepared from wild-type or $PrP^{0/0}$ mice, we could show that the expression of PrP^{C} sensitizes cells to toxic effects of different β-sheet-rich conformers [8].

The mechanisms underlying the toxic activity of β-sheet-rich conformers are far from being understood, but it is conceivable that different upstream events converge at similar neurotoxic signaling pathways. We therefore started to define components downstream of PrP^{C} involved in toxic signaling. Interestingly, Aβ-, PrP^{Sc}- and β-peptide-induced toxicity was significantly reduced by pharmacological blockage of N-methyl-D-aspartate receptor activity. In addition, we observed that PrP^{Sc} can induce mitochondrial alterations in neurons, such as perinuclear clustering of mitochondria.

Another important issue is to define domains of PrP^{C} involved in signal transmission. This involves interactions of PrP^{C} with the pathogenic protein assemblies and with cellular factors required for signal transmission. A consistent finding of different groups is that the primary binding site of oligomeric Aβ lies within the intrinsically disordered N-terminal domain of PrP^{C}. Further fine mapping indicated a prominent role of the region between amino acids 90 and 119 [10, 18, 21]. We could corroborate that PrPΔN, a mutant lacking a large portion of the N-terminal domain, is impaired in both binding to Aβ and mediating its toxic effects. Moreover, a secreted version of the N-terminal domain of PrP^{C} efficiently interacted with β-sheet-rich conformers and interfered with toxic signaling via PrP^{C}. However, binding of β-sheet-rich conformers to PrP^{C} at the plasma membrane is not sufficient to induce toxic signaling. PrP-CD4, a PrP mutant anchored to the plasma membrane by a heterologous C-terminal transmembrane domain, binds to β-peptides but cannot mediate toxic effects. Thus, targeting of PrP^{C} to specific microdomains by a GPI anchor could be a prerequisite to induce intracellular signaling pathways, for example via Fyn kinase [8, 22]. While there is increasing support for a role of PrP^{C} as a mediator of Aβ-induced synaptic dysfunction, further research is required to better characterize the toxic protein assemblies and to identify the underlying mechanisms disrupting neuronal homeostasis.

Acknowledgements

Work of the authors was supported by grants from the Deutsche Forschungsgemeinschaft (SFB 596), the Max Planck Society and the BMBF (BioDisc, DIP5.1).

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