Title:	Preferential Recruitment of Conformationally Distinct Amyloid-β Oligomers by the Intrinsically Disordered Region of the Human Prion Protein
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Abstract:	Soluble oligomeric species of the amyloid-β (Aβ) peptide exhibit pronounced neurotoxic effects in Alzheimer's disease. Recent studies have indicated that the prion protein (PrP) is one of the cell-surface receptors, so-called a bad receptor, of Aβ oligomers that mediates downstream cellular toxicity. A rational classification of Aβ oligomers on the basis of conformation indicates that there are two distinct types of oligomers, namely, prefibrillar and fibrillar oligomers that are positive to A11 and OC conformation-dependent antibodies, respectively. The mechanism of heterotypic assembly of conformationally distinct oligomers and PrP is poorly understood. In this work, using an array of biophysical and biochemical tools, we dissect the molecular mechanism of the interaction of A11- and OC-positive Aβ42 oligomers with human PrP. Using site-specific binding titrations, we show that the recruitment of Aβ oligomers primarily occurs via the electrostatic interaction between the N-terminal intrinsically disordered region of PrP and Aβ oligomers. Our results demonstrate that OC-positive fibrillar oligomers possessing in-register parallel β-sheet packing displayed ~30 times stronger binding with PrP compared to A11-positive oligomers. We also show that these OC-positive oligomers exacerbate their toxic effects on mammalian cells upon binding to PrP. On the contrary, the addition of PrP does not alter the toxicity exhibited by A11-positive oligomers. Our findings suggest that strategies targeting the interaction between PrP and OC-positive oligomers, which have been shown to be highly concentrated in the vicinity of amyloid plaques, may have therapeutic potential against Alzheimer's disease.
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