Title:	Mechanistic Insights into the Interaction of Conformationally Distinct Amyloid-β Oligomers with the Prion Protein and Lipid Membranes
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Abstract:	Alzheimer's disease is an age-related neurodegenerative disorder that is characterized by memory dysfunctions and cognitive decline. A pathological characteristic of Alzheimer's disease is the extracellular fibrillar deposits of amyloid-beta (Aβ) peptides, known as amyloid plaques. Soluble oligomers of Aβ are recognized as the key intermediates that cause synaptic dysfunction and neurotoxicity. A wide variety of soluble Aβ oligomers were characterized based on their morphology, size, toxicity, and secondary structural contents. A rational classification of oligomers based on the structure has emerged to identify the fundamental structural attributes of these soluble oligomers. Two conformation-specific antibodies, namely, anti-amyloid oligomer (A11) antibody and anti-amyloid fibril (OC) antibody recognize mutually exclusive structural epitopes of two structurally distinct oligomers, prefibrillar and fibrillar oligomers, respectively. Previous studies have described various mechanisms by which soluble oligomers exhibit their neurotoxic effects. However, the mechanisms by which two conformationally distinct Aβ oligomers exhibit toxicity remain poorly understood. Recent studies have indicated that the prion protein (PrP) is one of the cell-surface receptors of soluble Aβ oligomers that mediate downstream cellular toxicity. A growing body of research has also revealed that the interaction of soluble Aβ oligomers with the lipid membrane leads to the formation of annular pores and causes membrane permeabilization. Using an array of molecular biology, biophysical, and biochemical tools, I embarked upon studies aimed at dissecting the detailed molecular mechanisms of interactions of structurally distinct, A11-positive prefibrillar and OC-positive fibrillar Aβ42 oligomers with PrP as well as with lipid membranes derived from the brain total lipid extract. My thesis work underscores the importance of designing the therapeutic strategies that target the interaction of conformationally distinct Aβ42 oligomers with PrP and lipid membranes.
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