Protein Misfolding and Aggregation in Neurodegenerative Diseases

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Misfolding and aggregation of peptides and proteins has been linked to toxicity in Alzheimer's, Huntington's, and other neurodegenerative diseases. Biochemical and biophysical methods can be used to probe key questions about the mechanisms by which proteins misfold and aggregate. Two systems will be discussed.(1) Huntington's disease (HD) is caused by expansion of the CAG domain in huntingtin, leading to inordinately long polyglutamine stretches in the huntingtin protein. Polyglutamine peptides have been used as model systems to investigate the length-dependence of aggregation. We have examined polyglutamine peptide aggregation and propose a mechanism of aggregation that differs from the widely-held 'monomeric nucleus' hypothesis. We have extended our studies to examine polyglutamine-containing proteins, and demonstrate the critical importance of the position within the host protein in regulating the effect of polyglutamine on misfolding, stability and aggregation.(2) In Alzheimer's disease, aggregation of β-amyloid peptide (Aβ), and its subsequent deposition as fibrils, is believed to be the underlying cause of neurotoxicity. We have carried out extensive investigations into Aβaggregation kinetics. In our current studies, we are pursuing the hypothesis that a naturally occurring homotetrameric protein, transthyretin, may be protective against Aβtoxicity, and we are working to identify the specific residues in TTR that are involved with binding to Aβ.

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