Title:	Conserved features of intermediates in amyloid assembly determine their benign or toxic states
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Abstract:	Some amyloid-forming polypeptides are associated with devastating human diseases and others provide important biological functions. For both, oligomeric intermediates appear during amyloid assembly. Currently we have few tools for characterizing these conformationally labile intermediates and discerning what governs their benign versus toxic states. Here, we examine intermediates in the assembly of a normal, functional amyloid, the prion-determining region of yeast Sup35 (NM). During assembly, NM formed a variety of oligomers with different sizes and conformation-specific antibody reactivities. Earlier oligomers were less compact and reacted with the conformational antibody A11. More mature oligomers were more compact and reacted with conformational antibody OC. We found we could arrest NM in either of these two distinct oligomeric states with small molecules or crosslinking. The A11-reactive oligomers were more hydrophobic (as measured by Nile Red binding) and were highly toxic to neuronal cells, while OC-reactive oligomers were less hydrophobic and were not toxic. The A11 and OC antibodies were originally raised against oligomers of Aβ, an amyloidogenic peptide implicated in Alzheimer's disease (AD) that is completely unrelated to NM in sequence. Thus, this natural yeast prion samples two conformational states similar to those sampled by Aβ, and when assembly stalls at one of these two states, but not the other, it becomes extremely toxic. Our results have implications for selective pressures operating on the evolution of amyloid folds across a billion years of evolution. Understanding the features that govern such conformational transitions will shed light on human disease and evolution alike.
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