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Structural Studies of the Amyloid State of Proteins

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Amyloid diseases, including Alzheimer's, Parkinson's, and the prion conditions, are each associated with a particular protein in fibrillar form. At the morphological level, these fibers appear similar and are termed "amyloid." We found that the adhesive segments of amyloid fibers are short protein sequences which form pairs of interdigitated, in-register beta sheets. These amyloid fibrils were long suspected to be the disease agents, but evidence suggests that in the neurodegenerative diseases, smaller, often transient and polymorphic oligomers are the toxic entities. We have identified a segment of the amyloid-forming protein, alphaB crystallin, which forms an oligomeric complex exhibiting properties of other amyloid oligomers: beta-sheet-rich structure, cytotoxicity, and recognition by an anti-oligomer antibody. The X-ray-derived atomic structure of the oligomer reveals a cylindrical barrel, formed from six anti-parallel, out-of-register protein strands, which we term a cylindrin. The cylindrin structure is compatible with sequence segments from the Abeta protein of Alzheimer's disease and from other amyloid proteins. Cylindrins offer models for the hitherto elusive structures of amyloid oligomers, and are distinct in structure from amyloid fibrils.

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