

### **Structural Studies of Amyloid**

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Numerous soluble proteins convert to insoluble amyloid fibrils having common properties. These fibrils are associated with neurodegenerative diseases, such as Alzheimer's and Parkinson's, and can also be formed in vitro. In the case of the yeast protein Sup35, conversion to amyloid fibrils is associated with a transmissible infection akin to that caused by mammalian prions. A seven-residue peptide segment from Sup35 forms both amyloid fibrils and closely related microcrystals, which reveal the atomic structure of an amyloid spine. It is a double  $\beta$ -sheet, with each sheet formed from parallel segments stacked in-register. Sidechains protruding from the two sheets form a dry, tightly self-complementing steric zipper, bonding the sheets. Within each sheet, every segment is bound to its two neighbouring segments via stacks of both backbone and sidechain H-bonds. The structure illuminates the stability of amyloids as well as their self-seeding characteristic.

Amyloid structure has also presented long-standing, fundamental puzzles of protein structure. These include whether amyloid-forming proteins have two stable states, native and amyloid, and whether all or only part of the native protein refolds as it converts to the amyloid state. We find that a designed amyloid of the well-characterized enzyme ribonuclease A contains native-like molecules capable of enzymatic activity. Also these functional molecular units are formed from a core ribonuclease A domain and a swapped complementary domain. These findings are consistent with the zipper-spine model for amyloid3 in which the fibrils are formed from 3D domain-swapped functional units, retaining native-like structure.

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