The Expanding Amyloid Family: Structure, Stability, Function, and Pathogenesis

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The hidden world of amyloid biology has suddenly snapped into atomic level focus revealing over 80 amyloid protein fibrils, both pathogenic and functional. Many of the most prevalent degenerative diseases, including Alzheimer's, Parkinson's, ALS, and type 2 diabetes are associated with particular proteins in amyloid fibril form. Fibrils structures determined X-ray and electron crystallography, as well as particle averaging by cryoEM, and solid-state NMR have contributed to deepened understanding of the formation, stability, and pathology of structures have led to design of compounds that inhibit fibril formation as well as some compounds that disaggregated fibrils. A subclass of functional amyloid-like fibrils are formed by reversible interaction of low complexity domains, having underrepresented members of the 20 coded amino acids. When mutated or at high concentration reversible amyloid fibrils can transition to irreversible pathogenic form. Unlike globular proteins, amyloid proteins flatten and stack into unbranched fibrils. Also unlike globular proteins, a single protein sequence can adopt wildly different two-dimensional conformations, yielding distinct amyloid fibril polymorphs. Hence, an amyloid protein may define distinct diseases depending on its conformation.

I will describe the energetic basis for the great stability of pathogenic amyloid, the structural differences found in reversible amyloid, and chemical methods for inhibiting and disaggregating amyloid. Our database of amyloid structure and energy is available at https://people.mbi.ucla.edu/sawaya/amyloidatlas/

Reference: The Expanding Amyloid Family: Structure, Stability, Function, and Pathogenesis. Michael R. Sawaya, Michael P. Hughes, Jose A. Rodriguez, Roland Riek, David S. Eisenberg. Cell, in press.

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