Understanding fibrillogenesis at a molecular level requires detailed structural characterization of amyloid fibrils. Protein structural transformations on the molecular level during in vitro fibril formation are accompanied by substantial changes in macroscopic properties, such as formation of a gelatinous phase and the formation of insoluble particles. These changes limit the application of classical tools of structural biology, solution NMR and X-ray crystallography. The combination of deep UV resonance Raman (DUVRR) spectroscopy and postmortem hydrogen-deuterium exchange (HX) was utilized for probing parallel vs. anti-parallel β-sheet in fibrils prepared from full-length Aβ1-40 and Aβ34-42 peptides, respectively.1 Using previously published structural data based on solid state NMR analysis, we verified the applicability of Asher's approach2 for the quantitative characterization of peptide conformation in the Aβ1-40 fibril core. We found that the conformation of the parallel β-sheet in Aβ1-40 fibril core is atypical for globular proteins while, in contrast, the anti-parallel β-sheet in Aβ32-42 fibrils is a common structure in globular proteins. In contrast to globular proteins, the conformations of parallel and anti-parallel β-sheet in Aβ fibril cores are substantially different, and their differences can be distinguished by DUVRR spectroscopy.

Application of DUVRR spectroscopy allow us to discover a new protein folding/aggregation phenomenon, spontaneous refolding of amyloid fibrils.3 Mature fibrils prepared from apo-α-lactalbumin spontaneously refold from one polymorph to another as a result of a mild alteration in solution temperature and salinity. This discovery changes the very concept of the extraordinary stability of amyloid fibrils and presages a new approach for potentially regulating the biological activity of fibrils and their associated toxicity.

The controlled reversal of supramolecular helical chirality in protein fibrils was observed using vibrational circular dichroism (VCD).4 Normal or reversed insulin fibrils were grown by precise adjustment of pH. AFM images show two polymorphs corresponding to opposite senses of helical twist of the supramolecular structure with the same cross-β core.


