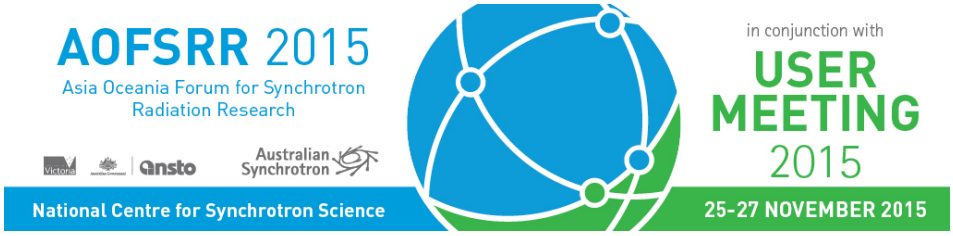

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Amyloid Fibril Morphology: Relevance to Disease and Materials Science

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Amyloid fibrils are implicated in over 20 neurodegenerative diseases. The mechanisms of fibril structuring and formation are not only of medical and biological importance but are also relevant for material science and nanotechnologies due to the unique structural and physical properties of amyloids. We found that hen egg white lysozyme (HEWL), homologous to the disease-related human lysozyme, can form left-handed giant amyloid ribbons, closing into nanotubes. To obtain an improved understanding of the molecular processes that underpin fibril assembly we identified an amyloidogenic peptide from HEWL and with a combination of nanoscale analytical techniques we were able to follow its assembly. These results will improve our understanding of structure-function relationships of amyloids in relation to neurodegenerative disease and materials science.

Using matrix-assisted laser desorption ionization mass spectrometry analysis, we identified a peptide sequence, which drives amyloid formation in HEWL, namely the ILQINS hexapeptide. By combining atomic force microscopy, circular dichroism and synchrotron based small angle X-ray scattering, we found that this fragment, also forms amyloid fibril structures, with rapid assembly kinetics. Additionally, all fibrillar structures formed possessed an unexpected right-handed twist, a rare chirality within the corpus of amyloid experimental observations. We confirm by wide-angle X-ray scattering and molecular dynamics simulations that these fibrils are composed of conventional left-handed β-sheets, but that packing stresses between adjacent sheets created this unusual chirality. We also show that the right-handed fibrils represent a metastable state present before the formation of β-sheet-based microcrystals.

Keywords

Amyloid Fibril, Chirality, Neurodegenerative Disease, SAXS, WAXS, Molecular Dynamics, AFM

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