Atomic models of de novo designed ccbeta-met amyloid-like fibrils

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The common characteristics of amyloid and amyloid-like fibrils from disease- and non-disease-assocd. proteins offer the prospect that well-defined model systems can be used to systematically dissect the driving forces of amyloid formation. We recently reported the de novo designed ccbeta peptide model system that forms a native-like coiled-coil structure at low temps. and which can be switched to amyloid-like fibrils by increasing the temp. Here, we report a detailed mol. description of the system in its fibrillar state by characterizing the ccbeta -Met variant using several microscopic techniques, CD spectroscopy, X-ray fiber diffraction, solid-state NMR, and mol. dynamics calcns. We show that ccbeta -Met forms amyloid-like fibrils of different morphologies on both the macroscopic and at. levels, which can be controlled by variations of assembly conditions. Interestingly, heterogeneity is also obsd. along single fibrils. We propose at. models of the ccbeta -Met amyloid-like fibril, which are in good agreement with all exptl. data. The models provide a rational explanation why oxidn. of methionine residues completely abolishes ccbeta -Met amyloid fibril formation, indicating that a small no. of site-specific hydrophobic interactions can play a major role in the packing of polypeptide-chain segments within amyloid fibrils. The detailed structural information available for the ccbeta model system provides a strong mol. basis for understanding the influence and relative contribution of hydrophobic interactions on native-state stability, kinetics of fibril formation, fibril packing, and polymorphism. [on SciFinder (R)]

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