Probing the sources of the apparent irreproducibility of amyloid formation: drastic changes in kinetics and a switch in mechanism due to micellelike oligomer formation at critical concentrations of IAPP

The aggregation of amyloidogenic proteins is infamous for being highly chaotic, with small variations in conditions sometimes leading to large changes in aggregation rates. Using the amyloidogenic protein IAPP (islet amyloid polypeptide protein, also known as amylin) as an example, we show that a part of this phenomenon may be related to the formation of micellelike oligomers at specific critical concentrations and temperatures. We show that pyrene fluorescence can sensitively detect micellelike oligomer formation by IAPP and discriminate between micellelike oligomers from fibers and monomers, making pyrene one of the few chemical probes specific to a prefibrillar oligomer. We further show that oligomers of this type reversibly form at critical concentrations in the low micromolar range and at specific critical temperatures. Micellelike oligomer formation has several consequences for amyloid formation by IAPP. First, the kinetics of fiber formation increase substantially as the critical concentration is approached but are nearly independent of concentration below it, suggesting a direct role for the oligomers in fiber formation. Second, the critical concentration is strongly correlated with the propensity to form
amyloid: higher critical concentrations are observed for both IAPP variants with lower amyloidogenicity and for native IAPP at acidic pH in which aggregation is greatly slowed. Furthermore, using the DEST NMR technique, we show that the pathway of amyloid formation switches as the critical point is approached, with self-interactions primarily near the N-terminus below the critical temperature and near the central region above the critical temperature, reconciling two apparently conflicting views of the initiation of IAPP aggregation.