MAR13-2012-020338

Abstract for an Invited Paper
for the MAR13 Meeting of
the American Physical Society

A physical chemical approach to understanding cellular dysfunction in type II diabetes

ANDREW MIRANKER, Yale University

The conversion of soluble protein into b-sheet rich amyloid fibers is the hallmark of a number of serious diseases. Precursors for many of these systems (e.g. Ab from Alzheimer's disease) reside in close association with a biological membranes. Membrane bilayers are reported to accelerate the rate of amyloid assembly. Furthermore, membrane permeabilization by amyloidogenic peptides can lead to toxicity. Given the b-sheet rich nature of mature amyloid, it is seemingly paradoxical that many precursors are either intrinsically b-helical, or transiently adopt an a-helical state upon association with membrane. We have investigated these phenomena in islet amyloid polypeptide (IAPP). IAPP is a 37-residue peptide hormone which forms amyloid fibers in individuals with type II diabetes. We report here the discovery of an oligomeric species that arises through stochastic nucleation on membranes, and results in disruption of the lipid bilayer. These species are stable, result in all-or-none leakage, and represent a definable protein/lipid phase that equilibrates over time. To characterize the reaction pathway of assembly, we apply an experimental design that includes ensemble and single particle evaluations *in vitro* and correlate these with quantitative measures of cellular toxicity.