Abstract:
The aggregation of proteins is tightly controlled in living systems, and misfolded proteins are normally removed before aggregation of the misfolded protein can occur. But for reasons not clearly understood, in some individuals this degradation process breaks down, and misfolded proteins accumulate in insoluble protein aggregates (amyloid deposits) over time. Of the many proteins expressed in humans, a small but growing number have been found to form the long, highly ordered $\beta$-sheet protein fibers that comprise amyloid deposits. Despite a lack of obvious sequence similarity, the amyloid forms of diverse proteins are strikingly similar, consisting of long, highly ordered insoluble fibers with a characteristic crossed $\beta$-sheet pattern. Amyloidogenesis has been the focus of intense basic and clinical research, because a high proportion of amyloidogenic proteins have been linked to common degenerative diseases, including Alzheimer’s disease, type II diabetes, and Parkinson’s disease. The apparent link between amyloidogenic proteins and disease was initially attributed to the amyloid form of the protein; however, increasing evidence suggests that the toxicity is due to intermediates generated during the assembly of amyloid fibers. These intermediates have been proposed to attack cells in a variety of ways, such as by generating inflammation, creating reactive oxygen species, and overloading the misfolded protein response pathway. One common,
well-studied mechanism is the disruption of the plasma and organelle membranes. In this Account, we examine the early molecular-level events in the aggregation of the islet amyloid polypeptide (IAPP, also called amylin) and its ensuing disruption of membranes. IAPP is a 37-residue peptide secreted in conjunction with insulin; it is highly amyloidogenic and often found in amyloid deposits in type II diabetics. IAPP aggregates are highly toxic to the \( \beta \)-cells that produce insulin, and thus IAPP is believed to be one of the factors involved in the transition from early to later stages of type II diabetes. Using variants of IAPP that are combinations of toxic or non-toxic and amyloidogenic or nonamyloidogenic forms, we have shown that formation of amyloid fibers is a sufficient but not necessary condition for the disruption of \( \beta \)-cells. Instead, the ability to induce membrane disruption in model membranes appears to be related to the peptide's ability to stabilize curvature in the membrane, which in turn is related to the depth of penetration in the membrane. Although many similarities exist between IAPP and other amyloidogenic proteins, one important difference appears to be the role of small oligomers in the assembly process of amyloid fibers. In many amyloidogenic proteins, small oligomers form a distinct metastable intermediate that is frequently the most toxic species; however, in IAPP, small oligomers appear to be transient and are rapidly converted to amyloid fibers. Moreover, the aggregation and toxicity of IAPP is controlled by other cofactors present in the secretory granule from which it is released, such as zinc and insulin, in a control mechanism that is somehow unbalanced in type II diabetics. Investigations into this process are likely to give clues to the mysterious origins of type II diabetes at the molecular level.