Abstract

hIAPP (human islet amyloid polypeptide), also called amylin, is a hormone cosecreted with insulin. It is associated with type II diabetes (T2D) for its amyloid deposits are commonly found in the T2D patients and its aggregates are highly toxic to beta-cells that produce insulin. It has been shown that not the mature amyloid fibrils, but the aggregation intermediates are most cytotoxic for the membrane damage. However, the mechanism is still not clear. e.g. some evidence showed the damage is through pore-formation on the membrane, which changes the cell permeability, while others supported a detergent-like mechanism, which involves large scale of membrane defects. To identify the toxic species is a daunting problem for experiments due to the heterogeneity of oligomers. Experimental results largely indicated hIAPP monomer is random coil as an intrinsically disordered peptide, however, it is hard to have detailed descriptions from the ensemble-averaged results.

To understand the structural ensemble as well as the dynamics of transitions, Markov state model analysis on extensive atomistic Molecular Dynamics simulations of hIAPP monomer in solution was performed and we found there are multiple equally-populated metastable states without a dominant one. Though as a random coil overall, hIAPP monomer can transiently sample alpha helix and beta hairpin structures. Different from the folded protein, there is no transition hub and the transition time among different metastable states is at several microseconds or above, which is comparable for the folding time of the proteins with similar length. This reflects the ruggedness of the free energy landscape of a protein without its native structure. i.e. even though the interactions are not strong enough to stabilize the protein, the breaking and reforming of non-specific contacts still take a long time due to the large volume of configurational space. The microsecond transition timescales also indicate the aggregation may involve both the induced fit and conformational selection (the diffusion encounter time at 1 micromolar concentration is around tens of microseconds for hIAPP). Furthermore, the beta hairpin structures identified have extended hydrophobic surface area exposed with a flat geometry and may serve as a precursor for the aggregation.