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Early-Stage Aggregation of Human Islet Amyloid Polypeptide[1]
ASHLEY GUO, JUAN DE PABLO, Institute for Molecular Engineering, University of Chicago — Human islet amyloid polypeptide (hIAPP, or human amylin) is implicated in the development of type II diabetes. hIAPP is known to aggregate into amyloid fibrils; however, it is prefibrillar oligomeric species, rather than mature fibrils, that are proposed to be cytotoxic. In order to better understand the role of hIAPP aggregation in the onset of disease, as well as to design effective diagnostics and therapeutics, it is crucial to understand the mechanism of early-stage hIAPP aggregation. In this work, we use atomistic molecular dynamics simulations combined with multiple advanced sampling techniques to examine the formation of the hIAPP dimer and trimer. Metadynamics calculations reveal a free energy landscape for the hIAPP dimer, which suggest multiple possible transition pathways. We employ finite temperature string method calculations to identify favorable pathways for dimer and trimer formation, along with relevant free energy barriers and intermediate structures. Results provide valuable insights into the mechanisms and energetics of hIAPP aggregation. In addition, this work demonstrates that the finite temperature string method is an effective tool in the study of protein aggregation.

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