A molecular dynamics analysis of human and porcine Islet Amyloid Polypeptides

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Amylin (or IAPP) is a 37-residue Intrinsically Disordered Polypeptide (IDP) acting as a putative hormone. It is co-secreted by pancreatic islet beta-cells with insulin, to whom it is a synergistic partner limiting after-meal glucose excursions and reducing nutrient intake. As a calcitonin-family hormone, IAPP presents highly conserved sequence on its N-terminus (residues 1-19), which is related to membrane and insulin binding, as well as in the C-terminal region (residues 30-37) involved in peptide self-association. Nevertheless, mutations are usual in the middle segment (residues 20-29), which might induce the formation of citotoxic amyloids in some mammalian species. In such cases, this leads to insufficient insulin secretion due to a progressive apoptotic loss of pancreatic beta-cells, resulting in the onset of Type 2 Diabetes (T2D).

Islet transplantation is a promising treatment for T2D in humans, however its success is impaired by progressive graft loss, likely due to citotoxic aggregation of human Islet Amyloid Polypeptide (hIAPP) secretated by the endocrinious pancreas. Alternatively, the effectiveness of porcine xenotransplantations might be explained by the fibrillization-resistance of porcine IAPP (pIAPP). To better elucidate such mechanisms, we perform comparative Replica-Exchange Molecular Dynamics (REMD) simulations of both IAPP isoforms. The usage of accurate force field Charmm22* with explicit solvation TIP4P/Ew ensure minimal structural bias. We find direct helix-to-strand thermal interconversions during the folding of hIAPP, which is absent on pIAPP. Furthermore, the usually amyloidogenic segment 20–29, hosting 5 out of the 10 overall mutations of pIAPP is strongly depleted of beta-strand structures. Such pIAPP propensities anti-correlate with hIAPP monomeric state features that lead to a transient beta-sheet intermediate found during its oligomerization. Such findings corroborate our previous thermostatistical investigations employing advanced Monte Carlo methods [Phys. Chem. Chem. Phys., 19 (2017) 25617], as well as unveil further dynamic details leading to aggregation-resistance mechanisms observed in some IAPP isoforms.