The islet amyloid polypeptide: biophysical studies of interactions, structures and aggregation

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Amyloid proteins are involved in many pathologies. One of these proteins is the human islet amyloid polypeptide (hIAPP), which is the main constituent of the amyloid fibrils found in the pancreas of type 2 diabetes mellitus (T2DM) patients. Under certain conditions, hIAPP is able to form amyloid fibrils that play a role in the progression of T2DM. The molecular mechanism of hIAPP-induced cell death is not yet understood and the factors that induce hIAPP fibril formation and hIAPP toxicity are not yet all defined.

Here, I'll and shed a light on the understanding of the behaviour of extrinsic (propeptides, flanking peptides) and intrinsic factors (pH, insulin, zinc) that modulate hIAPP fibril formation during its secretion in the granules of the pancreatic β cells. We have established that the components of the β-cell granules such as zinc, insulin, low pH, propeptides affect hIAPP fibril formation [1-4].
During the secretion, hIAPP will interact with membranes composed mainly of lipids. Thus, I also focused my research on the interaction between hIAPP and different membrane models. I tested micelles, bicelles, small and large vesicles containing saturated and/or unsaturated chains, as well as different polar lipid head groups. I also included cholesterol and sphingomyelin. I was able to propose a global interacting mechanism between hIAPP and membranes. The first interaction is driven by electrostatic interactions and is favoured by the lipid membrane curvature [5, 6].
I also showed that amino acids composition of hIAPP is crucial both for the fibril formation and the interaction with membrane and that the specific mutation of charged residue 18 can block the fibril formation. This residue 18 is important for specific intra- and intermolecular interactions that occur during fibril formation [6-8].
Finally, we used kinetic analysis to elucidate the aggregation mechanism of hIAPP in the presence of membranes. The results converge to a model in which aggregation on the membrane is strongly dominated by secondary nucleation, that is, the formation of new nuclei on the surface of existing fibrils [9-11].

References

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