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Lipid Modulation in the Formation of β-Sheet Structures. Implications for De Novo Design of Human Islet Amyloid Polypeptide and the Impact on β-Cell Homeostasis

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Abstract: Human islet amyloid polypeptide (hIAPP) corresponds to a 37-residue hormone present in insulin granules that maintains a high propensity to form β-sheet structures during co-secretion with insulin. Previously, employing a biomimetic approach, we proposed a panel of optimized IAPP sequences with only one residue substitution that shows the capability to reduce amyloidogenesis. Taking into account that specific membrane lipids have been considered as a key factor in the induction of cytotoxicity, in this study, following the same design strategy, we characterize the effect of a series of lipids upon several polypeptide domains that show the highest aggregation propensity. The characterization of the C-native segment of hIAPP (residues F_{23}-Y_{37}), together with novel variants F_{23}R and I_{26}A allowed us to demonstrate an effect upon the formation of β-sheet structures. Our results suggest that zwitterionic phospholipids promote adsorption of the C-native segments at the lipid-interface and β-sheet formation with the exception of the F_{23}R variant. Moreover, the presence of cholesterol did not modify this behavior, and the β-sheet structural transitions were not registered when the N-terminal domain of hIAPP (K_1-S_{20}) was characterized. Considering that insulin granules are enriched in phosphatidylserine (PS), the property of lipid vesicles containing negatively charged lipids was also evaluated. We found that these types of lipids promote β-sheet conformational transitions in both the C-native segment and the new variants. Furthermore, these PS/peptides arrangements are internalized in Langerhans islet β-cells, localized in the endoplasmic reticulum, and trigger critical pathways such as unfolded protein response (UPR), affecting insulin secretion. Since this phenomenon was associated with the presence of cytotoxicity on Langerhans