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Early-Stage Aggregation of Islet Amyloid Polypeptide on Membrane Surfaces Probed by Label-Free Chiral Sum Frequency Generation Spectroscopy ZHUGUANG WANG, LI FU, ELSA YAN, Yale University — The aggregation of human islet amyloid polypeptide (hIAPP) into fibrils is associated with type II diabetes. It can be catalyzed by interactions with membranes. Recent studies have shown that cytotoxicity arises from the intermediates of aggregation instead of mature fibrils. However, the pathogenic mechanism is still unknown and it remains challenging to probe structures of the intermediates on membrane surfaces due to a lack of biophysical methods that are sensitive to both protein secondary structures and interfaces. Here, we used label-free chiral sum frequency generation spectroscopy (cSFG) to probe the intermediates. Recently, we have discovered cSFG provides highly specific peptide vibrational signatures that can distinguish protein secondary structures at interfaces. Using cSFG, we observed in situ and in real time the aggregation of hIAPP from disordered structures to α-helices and then β-sheets on membrane surfaces. We also obtained the orientation of the β-sheet aggregates inserted into the membranes. We further studied the S20G mutant, which is linked to the early onset of type II diabetes among Asian populations. We compared the mutant with the wild-type hIAPP to evaluate the effect of S20G in the early-stage aggregation on membrane surfaces.

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