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Aggregation Matters: Insulin Behavior on Model Lipid Raft Membranes

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Diabetes mellitus currently affects over 420 million people globally, with diabetes-related deaths expected to double by 2030. Insulin, a key therapeutic agent in diabetes, may aggregate into fibrillary deposits, complicating treatment and serving as a model for protein aggregation studies. Here, we investigated interactions between insulin and biomimetic lipid membranes enriched with ganglioside GM3, a component of lipid rafts implicated in insulin resistance in type 2 diabetes. We also considered zinc ions, abundant in pancreatic β-cells, known to influence insulin stability and aggregation. Lipid raft models were prepared from DOPC, sphingomyelin, cholesterol, and optionally GM3. Insulin aggregation states (from monomers to fibrils) were characterized by Thioflavin T fluorescence. Interactions with model lipid membranes were studied using Langmuir monolayers and ATR-FTIR spectroscopy on immobilized bilayers, evaluating membrane stability, fluidity, and lipid miscibility. AFM was applied to observe insulin structural changes in time. Results showed that monomeric insulin partially integrates into membranes, whereas aggregated forms mainly remain surface-bound. GM3 notably modulates these interactions independently of zinc ions and hexameric zinc-insulin complexes accumulate at the surface, altering lipid orientation.