52c Cell Membrane-Mediated Amyloid-Beta Fibrillogenesis

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Alzheimer's disease (AD) is a protein deposition neurodegenerative disease affecting more than 4.5 million people in the U.S. and to date, no successful treatment is available. Although it is widely accepted that the aggregation of normally monomeric amyloid-β protein (Aβ) into insoluble fibrils is the primary event driving AD pathogenesis, the fundamental mechanism of Aβ fibril formation *in vivo* is still unclear. *In vitro* studies have demonstrated that Aβ aggregation can take place at concentrations three orders of magnitude lower in the presence of phospholipids compared to bulk aggregation studies, suggesting that the cell membrane may mediate Aβ toxicity. We use model lipid monolayers and bilayers to probe Aβ-membrane interactions and their effects on Aβ fibril formation. Lipid monolayers were formed using a custom-made Langmuir trough and lipid bilayers were prepared as vesicles. Aβ-membrane interactions were measured as Aβ insertion into lipid monolayers and Aβ fibril formation was imaged by AFM and monitored by Thioflavin-T binding assay. Electrostatic interactions between Aβ and the phospholipid head groups were found to modulate Aβ insertion into lipid monolayers. Specifically, Aβ exhibited higher insertion into an anionic lipid, which normally only resides in the inner leaflet of the cell membrane. Furthermore, the anionic lipid was shown to induce molecular ordering of adsorbed Aβ at the membrane interface that closely mimic β-sheet ordering of Aβ in amyloid fibrils, revealing an intriguing templating effect of the anionic lipid on Aβ. The consequence of this templating effect on subsequent Aβ fibril formation will be presented and implications for cell membrane-mediated AD pathogenesis will be discussed.