342a Assembly State-Dependent Insertion of Amyloid-Beta Protein into Lipid Monolayers

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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 accumulation of monomeric amyloid-β (Aβ) protein into insoluble deposits is the primary event driving pathogenesis of AD the underlying mechanism by which Aβ aggregates result in neurotoxicity is still unclear. One proposed mechanism for Aβ neurotoxicity is membrane disruption and depolarization mediated by ion-channel formation, resulting in the alteration of ion homeostasis and disregulation of neuronal signal transduction, leading to cell death. However, direct evidence of Aβ incorporation and membrane disruption have not been provided and characterization of the Aβ species responsible for channel formation have not been elucidated. We use lipid monolayers as model membranes to probe Aβ-membrane interactions. We found that insertion of monomeric Aβ into pure lipid monolayers formed in a Langmuir trough depend on the electrostatic interaction between Aβ and phospholipid head group. Aβ insertion and disruption of lipid monolayers were directly visualized for the first time with fluorescence microscopy. Aβ was shown to selectively insert at lipid domain boundaries, disrupting the integrity of lipid monolayer. Furthermore, insertion of Aβ into lipid monolayers was found to depend on its assembly state – an oligomeric Aβ species exhibited enhanced membrane insertion propensity compared to monomeric Aβ. We will present findings of the characterization of this oligomeric species and discuss implications of the molecular mechanism of Aβ neurotoxicity.