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Role of Cholesterol in β-Amyloid Precursor Protein Processing and Oligomerization

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The relationship between cholesterol and β-amyloid precursor protein (APP) processing is an attractive mystery in the Alzheimer's disease (AD) field. It has been hypothesized that there is a direct interaction between cholesterol and APP, which can be processed into Aβ in its pathogenic pathway. To assess the importance of APP-cholesterol interaction in regulating APP processing, we generate several cholesterol-binding-deficient mutant APP proteins via introducing single-site mutations in the putative cholesterol recognition amino acid consensus (CRAC) sequence of APP. Our preliminary result reveals that smaller portion of APP-S622L, which has a lower binding affinity for cholesterol than APP wild-type, is co-fractionated with lipid raft marker flotillin-1 compared to wild-type. The C99/C83 ratio is also influenced by this S622L mutation. Further study shows these mutations influence the oligomerization properties of APP as well. These data suggest the interaction between cholesterol and APP could be a driving force for distributing APP into lipid raft, which makes APP more accessible to the pathogenically critical protein BACE1.