# Cholesterol and the Amyloid Precursor Protein

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**Country**

USA

**Title of project or programme**

Cholesterol and the Amyloid Precursor Protein

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NIH (NIA)

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01/05/2013

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4

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

Amyloid beta-Protein Precursor, Cholesterol, Membrane Microdomains, gamma secretase, cholesterol analog

**Research Abstract**

DESCRIPTION (provided by applicant): The amyloidogenic pathway is widely believed to be closely linked to most forms of Alzheimer’s disease. In this pathway the full length amyloid precursor protein (APP) is cleaved by ß-secretase to release a 99 residue transmembrane C-terminal domain known as “”C99?”. C99 is then cleaved by ?-secretase to release the amyloid-ß

(Aß) polypeptides. There is a considerable body of data that elevated cholesterol in neuronal membranes promotes the amyloidogenic pathway, but there has not been a mechanistic explanation. In our recent work we have shown that C99 forms a specific 1:1 complex with cholesterol, with a dissociation constant well within the physiological concentration range of cholesterol in mammalian membranes. This observation, combined with a large body of literature evidence that the ß- and ?-secretases tend to be associated with cholesterol-rich membrane domains often referred to as “”lipid rafts””, suggests a compelling hypothesis for how cholesterol promotes amyloidogenesis. We hypothesize that formation of a complex between cholesterol and C99 (or full length APP) results in enhanced partitioning of C99/APP to lipid rafts, where ß- and ?-secretase reside. This enhances the rate of amyloid-ß production relative to conditions in which C99/APP is not complexed with cholesterol and the protein resides in bulk membranes. Aims are: Aim 1. Determine the structure of the C99/cholesterol complex in both bulk membranes and in “”lipid rafts””. This aim will provide the structural basis for molecular recognition of cholesterol by C99 and will also provide the first ever comparison of the structure of a membrane protein under model membrane conditions that mimic lipid rafts versus bulk membranes. Aim 2. Elucidate the structural determinants in cholesterol that drive its association with C99. This will involve binding studies between C99 and a variety of cholesterol analogs/metabolites and will further illuminate the basis for molecular recognition between C99 and cholesterol. It will also provide a starting point for developing compounds that mimic cholesterol but that bind even more avidly to C99. Moreover, we will test the possibility that cholesterol analogs known to be “”raft-phobic”” can compete effectively with cholesterol for binding to C99. Aim 3. Determine whether binding of cholesterol to C99 and APP increases partitioning of these proteins into lipid rafts. Both giant unilamellar vesicles and cell-derived vesicles will be employed. These studies will test the hypothesis that association of cholesterol with the C99 and APP drives partitioning of these protein into rafts. Moreover, using selected compounds from Aim 2 that compete effectively with cholesterol but that have no avidity for rafts, we will also test whether raft association of C99/APP can be suppressed.

**Lay Summary**
PUBLIC HEALTH RELEVANCE: Successive cleavage of the amyloid precursor protein (APP) by ß-secretase and ?-secretase results in the production of the amyloid-ß polypeptides, which are thought to underlie the genesis of most forms of Alzheimer’s disease. It is widely believed that cholesterol in neuronal membranes somehow promotes amyloid-ß production. Here we follow up on the recent discovery that APP forms a complex with cholesterol by conducting additional studies devoted to determining exactly how formation of this complex promotes amyloid-ß production and Alzheimer’s disease.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**
Alzheimer's disease & other dementias

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