

Lipids are major players in Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder affecting over 36 million people worldwide. Alzheimer's patients suffer from dementia and memory loss and go through a progressive, irreversible and eventually fatal loss of cognitive functions. When Alois Alzheimer firstly described the disease over 100 years ago, he identified abnormal protein deposits as well as fat tissue inclusions and altered lipid composition in the brains of his patients. These observations suggested a possible relation between Alzheimer's disease and lipid imbalance, which was established decades later when the strongest genetic risk factor in Alzheimer's disease was linked to apolipoprotein E, the major lipid transporter in the central nervous system. Presently it is well known that cholesterol and many other lipids are involved in various ways in key aspects of the disease. For example, lipids strongly interfere with a protein crucial to Alzheimer's disease, called "amyloid- β precursor protein" (APP). APP is located inside the fatty membranes surrounding nerve cells and can be cut into a smaller protein segments called "amyloid-beta" ($A\beta$). This smaller protein is very unstable and easily aggregates into clumps that can become large and sticky, depositing as plaques in the brain (protein deposits initially observed by Alzheimer). Some of those protein clumps can also remain as small, free and permeable structures easily interacting with fatty membranes and interfering with synapses and cell-to-cell communication in the brain.

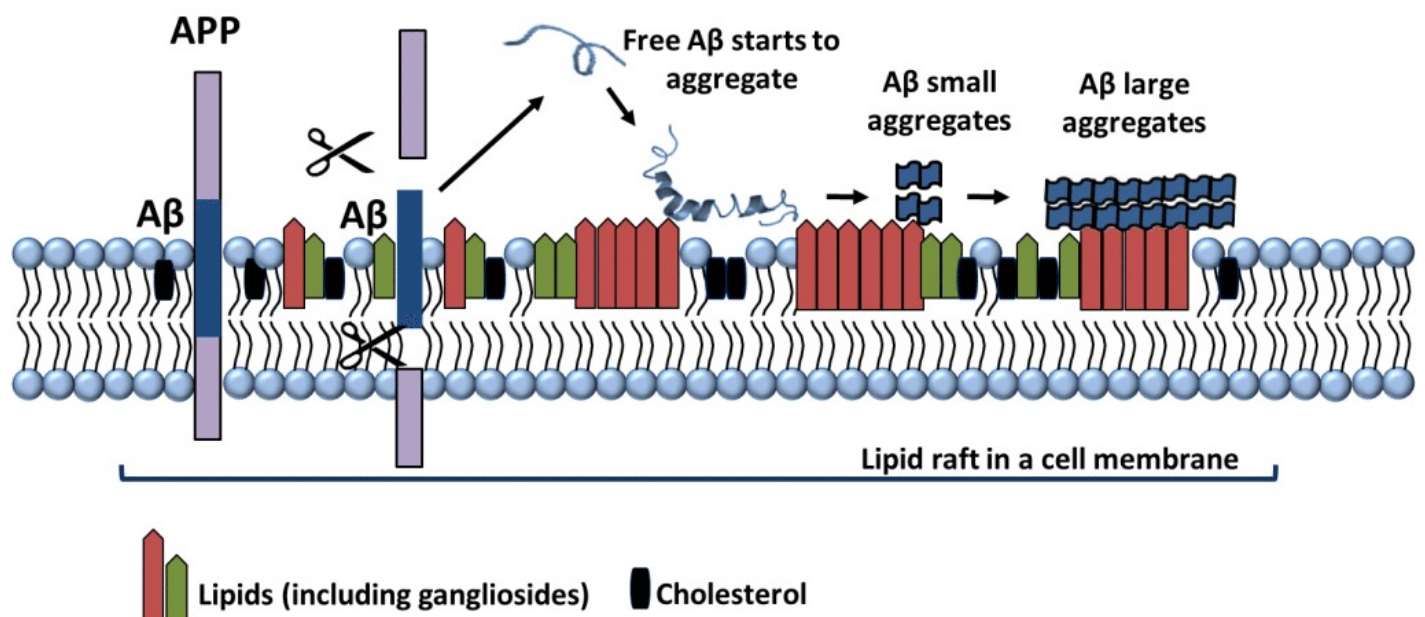


Fig. 1. Cell membrane contains regions called lipid rafts that are rich in cholesterol and gangliosides. These regions provide an environment that promotes cleavage of the precursor protein, APP, into the smaller fragment, A β . A β is released and can aggregate into clumps together with cholesterol and other lipids. These protein aggregates damage the cell membrane and disturb the communication between cells in the brain, leading to the loss of memory and cognitive function in Alzheimer's disease.

The potentially toxic process of A β formation and aggregation occurs preferentially in lipid rafts, which are regions of fatty membrane that are rich in cholesterol and a particular type of lipids named gangliosides. Cholesterol plays a major role here as it binds APP promoting its localization in lipid rafts and helping other molecules to cut APP into the toxic A β . The lipid rafts are also believed to serve as templates for A β aggregation (Fig. 1) because lipid-rich environments can change the structure of A β turning it into a more aggregation-prone molecule. Moreover, the toxic action of small A β aggregates is thought to include the formation of pores in the membranes of brain cells. These holes perturb the flow of ions and other vital molecules in and out of the cells and can lead to cell death. Cholesterol may importantly influence the insertion of A β into the cell membranes, its aggregation and pore formation.

Although the molecular role of cholesterol in Alzheimer's disease is not entirely clear, clinical evidence indicates that cholesterol has a major influence on the disease progression. In fact, elevated blood levels of cholesterol are a risk factor for Alzheimer's disease, and cholesterol-rich diet promotes accumulation of A β inside the cells and increases its cerebral load. Cholesterol levels in the human brain were also reported to increase in the early stages of the disease. This apparent connection between the elevated blood cholesterol and the Alzheimer's disease raised the possibility that cholesterol-lowering drugs may benefit the patients. Furthermore, some cell and animal model studies report that cholesterol-lowering drugs can reduce levels of A β in brain cells. Limited clinical studies report decreased risk of Alzheimer's disease or improved cognitive function in patients. However, more studies are needed to draw unequivocal conclusions about possible role of lipid-lowering drugs in Alzheimer's treatment.

Clarifying the role of specific lipids and their body balance in Alzheimer's disease is a challenge addressed by many scientists hoping to reveal possible disease-predisposing factors and provide new methods for improved diagnostics, treatment and ultimate prevention of Alzheimer's disease.

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Publication

[Lipids in Amyloid- \$\beta\$ Processing, Aggregation, and Toxicity.](#)

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