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レプリカ交換アンブレラサンプリングシミュレーションで調べるアミロイド前駆体 C99 のコレステロール分子との相互作用による構造変化の誘起

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Inducing structural changes by interactions of Amyloid-Precursor-Protein-C99 (C99) with cholesterol studied by replica-exchange umbrella sampling (REUS) simulations

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【Introduction】

The amyloid beta (Aβ) peptide associated with Alzheimer's Disease (AD) is produced by he stepwise processing off Amyloid=Precursor=Protein (APP) (see Fig. 1). ,Given the importance to AD research, step in this process has been intensely studied[1-3]. Of particular interest is the cleavage of C99 peptide by γ−secretase to produce Aβ, which may result in enhanced production of a more amyloidogenic form of Aβ and the early onset of AD. Understanding the role of membrane conditions (including cholesterol) and C99 sequence (including familial mutations) in the cleavage of C99 and production of is a critical goal for AD research. It is known that increased levels of cholesterol lead to enhanced production of more amyloidogenic lengths of Aβ. Moreover, it has been shown that C99 binds cholesterol leading to structural changes in the transmembrane region of the peptide which is recognized by γ-secretase (see Fig. 2)[4-7].

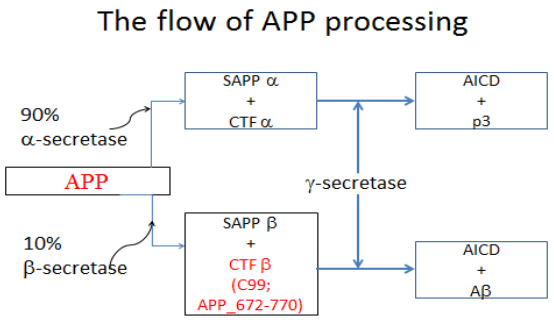

Fig. 1: The process of APP cleavage by enzymes into amyloid beta (Aß).

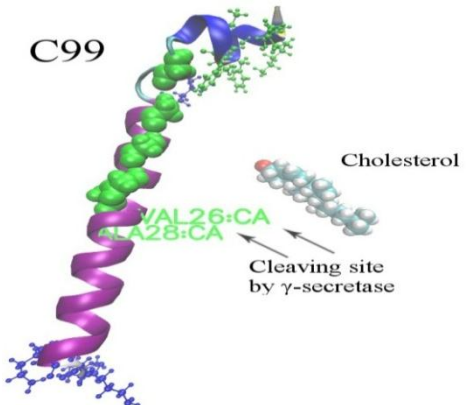

Fig. 2: The initial states of complex molecule and the cleaving site of C99 structure.

A goal of our research is to understand how C99-cholesterol interactions affect the recognition and cleavage of C99 by γ-secretase and to explore the design of cholesterol analogs that may serve as AD therapeutics by modulating the production of Aβ.

【Method】

This research investigated structures of the C99-cholesterol complex, including the structural change of C99 (15-55 fragment, APP 686-726) monomer by interactions with one cholesterol molecule using all-atom replica-exchange umbrella sampling (REUS) simulations. The umbrella potential imposes a systematic sampling of conformations between C99 and cholesterol as a function of their relative separation. The heterogeneous dielectric generalized Born (HDGB) model is used as the treatment of the membrane environment, which models the membrane through a continuously varying dielectric constant and surface area based "cavity" contribution. [8]

【Results and discussions】

To validate our model, we compared the spatial distribution of cholesterol across the membrane normal axis for a single cholesterol molecule, comparing our results with those of all-atom simulations of cholesterol in a POPC lipid bilayer. We further explored the interaction of cholesterol with C99 molecules to determine the nature of interaction and binding as well as the impact on the structure of C99.

Results of REUS simulations were compared with those of NMR experiments by the Sanders laboratory, with a particular emphasis on the specific interactions between cholesterol and the GXXGXXG motif in the transmembrane region of C99 molecule. REUS calculations allow for an evaluation of contact information as a function of the separation of C99 and cholesterol as well as the strength of binding (that can be compared with experimental binding constants). In the simulation model significant interaction of cholesterol with the GXXGXXG motif of the transmembrane region of C99 was observed, in agreement with experimental results. Further insight into the nature of the C99-cholesterol interactions was also derived, and should serve in the development of structure-activity correlations characterizing the nature of C99-cholesterol interactions. Future work involving the evaluation of C99 interactions with cholesterol analogs, in the context of developing therapeutics for the treatment of AD, is discussed.

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