Extended Abstract
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Role of aromatic interaction in adhesion of amyloid beta peptides on glycolipid containing membrane

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Abstract

The CH−π and OH−π interaction of aromatic residues of amyloid beta (Aβ) with GM1 oligosaccharide is concluded to be effective to keep Aβ peptides attached to the membrane surface and play an important role to initial stages of Alzheimer's disease pathology. In this work, molecular dynamics (MD) simulations for Aβ42 were performed to investigate the behaviors of Aβ42 on GM1-ganglioside-containing lipid membrane. As far the computational model, the initial atom coordinate of Aβ42 were extracted from one of the conformations which had been determined by solution nuclear magnetic resonance (NMR) spectroscopy (PDB accession code: 1Z0Q/1IYT). A computational model for mixed membrane was composed of 48 monosialotetrahexosylganglioside (GM1), 96 sphingomyelin (SM), and 96 cholesterol(CHL). A 1000 ns simulation was executed with NAMD 2.9 programs to analyze the probability of the Aβ binding to the mixed lipid membrane. The hydrogen bond occupancy was calculated using visual molecular dynamics (VMD) software. The results showed that binding affinity of Aβs were increases with GM1 in lipid membrane, suggesting the involvement of OH−π and CH-π interaction between the aromatic side chains of sugar carbohydrate moieties of GM1 with aromatic rings of Aβs.

The aromatic rings of Phe4, Tyr10, Phe19, and Phe20 of Aβ was within distance that enabled CH−π and/or OH−π stacking interaction with to the GM1 head groups. In this seminar, I will discuss the cluster of GM1-ganglioside containing lipid membrane model and how effect to amyloid beta tightly connection with lipid membrane and subsequently, conformation transformation to toxicity folding shape, in recent study.

Alzheimer, Parkinson and other neurodegenerative diseases involve a series of brain proteins, referred to as 'amyloidogenic proteins', with exceptional conformational plasticity and a high propensity for self-aggregation. Although the mechanisms by which amyloidogenic proteins kill neural cells are not fully understood, a common feature is the concentration of unstructured amyloidogenic monomers on bidimensional membrane lattices. Membrane-bound monomers undergo a series of lipid-dependent conformational changes, leading to the formation of oligomers of varying toxicity rich in β-sheet structures (annular pores, amyloid fibrils) or in α-helix structures (transmembrane channels). Condensed membrane nano- or microdomains formed by sphingolipids and cholesterol are privileged sites for the binding and oligomerisation of amyloidogenic proteins. By controlling the balance between unstructured monomers and α or β conformers (the chaperone effect), sphingolipids can either inhibit or stimulate the oligomerisation of amyloidogenic proteins. Cholesterol has a dual role: regulation of protein–sphingolipid interactions through a fine tuning of sphingolipid conformation (indirect effect), and facilitation of pore (or channel) formation through direct binding to amyloidogenic proteins. Deciphering this complex network of molecular interactions in the context of age- and disease-related evolution of brain lipid expression will help understanding of how amyloidogenic proteins induce neural toxicity and will stimulate the development of innovative therapies for neurodegenerative diseases.

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