Usage Report for Fiscal Year 2021

Project Title:

Protein-Ligand and Protein-Lipid Interaction

Name:

○ GREIMEL Peter

Laboratory at RIKEN:

Center for Brain Science, Laboratory for Cell Function Dynamics

1. Background and purpose of the project, relationship of the project with other projects

The cellular membrane represents the most important border in the biological world and provides an essential barrier between the intracellular space and the outside world. Membranes protect the function of life within its boundaries and separate different areas within a cell to give rise to specialized cellular compartments. While biological membranes are crowded with proteins, their main constituents are a wide variety of lipids.

To allow the exchange of nutrients and information between the interior and the surrounding environment, a barrier or wall requires windows and doors. In a cellular context, this task is conducted by proteins, embedded in the lipid membranes of cells, such as receptors and transporters to convey signals or transport nutrients across this barrier respectively.

2. Specific usage status of the system and calculation method

Quantum mechanics (QM) simulations utilizing the Gaussian 09 and Gaussian 16 software package have been performed. Molecular dynamics simulations were performed utilizing the NAMD software package and results were visualized with VMD.

3. Result & Conclusion –

Cholesteryl-β-D-glucoside (ChoGlc)

ChoGlc is a mammalian glycolipid that is expressed in brain tissue and formed by the glycosylation of cholesterol (Chol). The effects of ChoGlc on lipid ordering were examined in membranes composed of N-stearoyl sphingomyelin (SSM), which is abundant in the brain as well as dioleoyl-sn-glycero-3-phosphocholine (DOPC). To investigate the possible molecular mechanism involved in these interactions, differential scanning calorimetry revealed that ChoGlc was miscible with SSM and DOPC in a similar extent of Cho. Solid-state 2H NMR of deuterated SSM and fluorescent anisotropy using 1,6-diphenylhexatriene demonstrated that the glucosylation of Cho significantly reduced the effect of the sterol tetracyclic core on the ordering of SSM chains. The orientation of the sterol core was further examined by solid-state NMR analysis of deuterated and fluorinated ChoGlc analogues. ChoGlc had a smaller tilt angle between the long molecular axis (C3-C17) and the membrane normal than Cho in the probed bilayers, and the alteration of the mean tilt angle was restricted even at high temperatures. This orientation of the sterol core of ChoGlc lead to reduce sterol-lipid interactions. The MD simulation results suggested that the Glc moiety perturbs the lipid-sterol interactions, which reduces the umbrella effect of the phosphocholine headgroup because the hydrophilic glucose moiety resides at the same depth as the amide group in sphingolipids and glycerol moiety in glycolipids. These differences between ChoGlc and Cho also weaken the lipid-ChoGlc interactions. Thus, the distribution and localization of Cho and ChoGlc possibly control the stability of sphingomyelin-based domains that transiently occur at specific locations in biological membranes.

4. Schedule and prospect for the future

Specifics of the lipid-lipid and lipid-protein interaction at atomistic levels are still not well understood and thus remain under investigation.

For example, preferred conformation of lyso-phospholipids in solution state, micelle arrangement or solublized with methyl-β-cyclodextrine are still not well understood. To gain a more complete atomistic understanding of this lipid conformation, we will probe lyso-phospholipid conformation by MD simulation in different solution states and correlate our results with experimental observation such as nuclear magnetic resonance spectroscopy.

Additionally, conformational preference and restraints of transitionstates during chemical reactions exert a significant influence on the steoerchemistry of the reaction product. To exploit these restrictions during the chemical synthesis of glycolipids QM simulations of associated reaction paths will be performed. The results of the QM simulations will be correlated with nuclear magnetic resonance spectroscopy evidence of reaction intermediates.

Fiscal Year 2021 List of Publications Resulting from the Use of the supercomputer

[Paper accepted by a journal]

1. “β-Glucosylation of Cholesterol Reduces Sterol-Sphingomyelin Interactions”; S. Hanashima, N. Fukuda, R. Malabeda, M. Murata, M. Kinoshita, P. Greimel, Y. Hirabayashi, *BBA – Biomembranes*, **2021**, 1863 (2), 183496.