Usage Report for Fiscal Year 2023

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 provides the essential barrier between the intracellular space and the outside world. In addition, lipid membranes separate different areas within a cell to give rise to specialized cellular compartments. Taken together, lipid membranes protect the function of life within its boundaries and thus represent the most important border in the biological world. While biological membranes are crowded with proteins, their main constituents are a wide variety of lipids.

A protective barrier or wall requires windows and doors to allow the exchange of nutrients and information between the interior and the surrounding environment. 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. Pre-assembly of transport and signaling complex in the membrane is facilitated by specific lipid-protein interactions.

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

Ginsenoside Rh2 (Rh2) is a ginseng saponin with a single sugar unit and has attracted much attention for its diverse pharmacological activities. Following a previous report (Garza et al. Langmuir 2022, 38, 10478), we investigated the interaction of Rh2 with membrane lipids in a model membrane in liquid-disordered (Ld) phase combining molecular dynamics (MD) simulations with solid-state NMR and small angle X-ray diffraction experimental results. ^{31}P NMR showed that Rh2 disrupts the packing structure of phospholipids, while ^{2}H NMR revealed that Rh2 slightly lowered the order of palmitoyloleoylphosphatidylcholine. The electron density profile of the studied model membrane determined by X-ray diffraction supports binding of Rh2 near the interface of the membrane often referred to as the shallower part of the bilayer interior. The experimental results were in good agreement with MD simulations indicate that Rh2 interacts weakly with membrane lipids, including cholesterol, and relaxes the packing of lipid chains due to its presence in the shallow part of Ld phase bilayers resulting in increased wobbling of the molecular axis of cholesterol relative to the bilayer normal.

4. Schedule and prospect for the future

From an atomistic point of view, the specifics of the lipid-lipid and lipid-protein interaction remains poorly understood. For example, the conformation of lyso-phospholipids solubilized by methyl-β-cyclodextrine remains to be resolved. To gain a more complete atomistic understanding, we employ MD simulations and correlate our results with experimental observation such as NMR spectroscopy.

Fiscal Year 2023 List of Publications Resulting from the Use of the supercomputer

[Paper accepted by a journal]

1. Yilmaz N, Panevska A, Tomishige N, Richert L, Mély Y, Sepčić K, Greimel P, Kobayashi T. Assembly dynamics and structure of an aegerolysin, ostreolysin A6. J Biol Chem. 2023 Aug;299(8):104940. doi: 10.1016/j.jbc.2023.104940. Epub 2023 Jun 19. PMID: 37343702; PMCID: PMC10366546.