Usage Report for Fiscal Year 2022

Project Title:

Protein-Ligand and Protein-Lipid Interaction

Name:

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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. 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 –

Behaviour of ginsengoside Rh2 in ordered and disordered model membranes

The ginsenoside Rh2 (Rh2) has been reported to act as a saponin. In this study, we investigated the interaction of Rh2 with biological membranes using model membranes. We examined the effects of various lipids on the membrane-disrupting activity of Rh2 and found that cholesterol (Cho) and sphingomyelin (SM) had no significant effect. Further, the effects of Rh2 on acyl chain packing (DPH anisotropy) and water molecule permeability (GP values) did not differ significantly between bilayers containing SM and saturated phosphatidylcholine. These results suggest that the formation of the liquid-ordered (Lo) phase affects the behavior of Rh2 in the membrane rather than a specific interaction of Rh2 with a particular lipid. We investigated the effects of Rh2 on the Lo and liquid-disordered (Ld) phases using surface tension measurements laudan and prodan and fluorescence experiments. In the surface tension-area isotherms, we compared the monolayers of the Ld and Lo lipid compositions and found that Rh2 is abundantly bound to both monolayers, with the amount being greater in the Ld than in the Lo phase. In addition, the hydration state of the bilayers, mainly consisting of the Lo or Ld phase, showed that Rh2 tends to bind to the surface of the bilayer in both phases. At higher concentrations, Rh2 tends to bind more abundantly to the relatively shallow interior of the Ld phase than the Lo phase. The phase-dependent membrane behavior of Rh2 is probably due to the phase-selective affinity and binding mode of Rh2.

4. Schedule and prospect for the future

The specifics of the lipid-lipid and lipid-protein interaction at atomistic levels are still not well understood.

For example, the preferred conformation of lyso-phospholipids in solution state, micelle arrangement or solublized with methyl-β-cyclodextrine remain to be resolved. 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.

Fiscal Year 2022 List of Publications Resulting from the Use of the supercomputer

[Paper accepted by a journal]

1. “Behavior of Triterpenoid Saponin Ginsenoside Rh2 in Ordered and Disordered Phases in Model Membranes Consisting of Sphingomyelin, Phosphatidylcholine, and Cholesterol”; D. Lacanilao Garza, S. Hanashima, Y. Umegawa, M. Murata, M. Kinoshita, N. Matsumori, P. Greimel, *Langmuir*. **2022** ,38(34): 10478-10491.