【Grant-in-Aid for Scientific Research (S)】

Integrated Disciplines (Complex Systems)

Title of Project : Dynamic structure and domain formation of membrane lipids in model bilayer systems

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Research Area : Complex systems
Keyword : Conformational mobility, domain structure, lipid bilayer, sphingomyelin, lipid rafts

【Purpose and Background of the Research】

Lipid-lipid and lipid-protein interactions have been recently revealed to play key roles in cell physiology such as signal transduction and substance transportation. Because lipids are highly flexible molecules, the elucidations of their 3D structures surrounding membrane proteins and self-assembly called 'lipid rafts' are extremely difficult even with the use of X-ray and NMR. We have studied to elucidate the active structure of lipids in and around proteins by using solid-state NMR techniques combined with ultrahigh-resolution X-ray crystallography, organic synthesis and protein engineering. This breakthrough is expected to advance our knowledge in biological and biomedical sciences over the next decade, and also contribute the researches and developments for medical and pharmaceutical applications.

【Research Methods】

a) Conformation of lipid molecules in lipid rafts: The pair of ^{2}H and ^{13}C is site-specifically introduced to a fatty acyl chain. Magnetic dipole-dipole interaction is determined by REDOR, which provides the mobility and orientation of a labeled segment that has not been obtainable from conventional ^{2}H NMR. In addition, we focus on saponin aglycone mimicking the Cho structure to evaluate structural factors that are responsible for Cho-ordering effects.

b) Lipid molecules in rafts in atomic resolution molecular interaction: we attempt the direct observation of molecular interactions using solid state NMR. A ^{13}C-^{15}N pair in the SM amide induces greater relaxation, by which the correlation time can be determined with much higher precision. Correlation time and domain size as experimental data are compared with those from molecular simulation results.

c) Interactions between proteins and lipids: Bacteriorhodopsin (bR) as a model membrane proteins is used for investigating lipid-protein interactions. We try to establish a methodology to evaluate the conformation of surrounding lipids based on molecular dynamics simulations (Figure 1) and NMR measurements of a biomembrane model containing integral proteins.

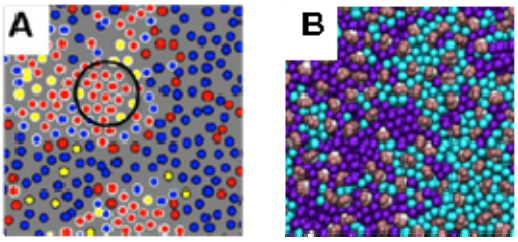

Figure 1. Molecular simulations of raft domains by two groups. Red in A and cyan in B are raft lipid molecules to segregate from the other lipids (the circled lipids is forming raft-like structure).

【Expected Research Achievements and Scientific Significance】

The molecular mechanism underlying the selective recruitment of proteins to lipid rafts plays an important role in the intracellular signal transduction. By this research, a deeper understanding of lipid-protein interactions could be achieved and the structure and functions of lipids in biological membranes would help promote the understanding of the molecular basis of biological membranes, and eventually lead to drug discovery and diagnostic development.

【Publications Relevant to the Project】

・Nakagawa, Y., Umegawa, Y., Tsuchikawa, H., Hanashima, S., four coauthors、Murata, M. *Biochemistry* (2016). Published online.
・Matsumori, N.; Yamaguchi, T.; Maeta, Y.;Murata, M. *Biophys. J.* 108(12), 2816-2824 (2015).

【Term of Project】 FY2016-2020

【Budget Allocation】 140,600 Thousand Yen

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