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

Title of Project : Cell biological functions of fatty acyl chains in biological membranes

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Research Area : lipid biology
Keyword : biological membrane, fatty acid, phospholipid, acyltransferase

【Purpose and Background of the Research】

Fatty acids in membrane phospholipids of mammalian cells and tissues exhibit considerable structural diversity, including varying chain lengths and degrees of unsaturation. The alteration of the fatty acid composition in cell membranes has also been implicated in a variety of abnormalities, including diabetes, obesity, hypertension, cancer, neurological and heart diseases. However, cell biological functions of fatty acyl chains in biological membranes have remained poorly understood. Through genetic screening in *C. elegans,* we have recently identified a group of enzymes that regulate fatty acid composition in membrane phospholipids.

The objectives of this project are as follows:

(1) To unravel cell phenomena which require a specific fatty acyl chain of membrane phospholipids.
(2) To identify membrane proteins and domains regulated by a specific fatty acyl chain of membrane phospholipids.
(3) To elucidate molecular mechanisms of membrane fatty acyl chain homeostasis.
(4) To clarify molecular mechanisms of pathologies caused by disruption of membrane fatty acyl chain homeostasis.

【Research Methods】

We have generated a deletion mutant library of *C. elegans,* which covers almost all genes involved in phospholipid metabolism. As for some of the newly identified genes, we have generated knockout mice. We have succeeded in establishing comprehensive lipidomic techniques using mass spectrometry, which are indispensable for the study of membrane fatty acyl chains. Using a combination of genetics and lipidomics, we will comprehensively define the biological significance of the hydrophobic environment of biological membranes.

【Expected Research Achievements and Scientific Significance】

Identification of enzymes required for proper membrane fatty acid composition will answer important but so far unresolved questions in membrane biology: "How is the diversity of membrane fatty acid composition formed?" and "What is the biological significance of the hydrophobic environment of biological membranes?" The identification of these enzymes also enables us to manipulate membrane fatty acid composition. This methodology will help us to understand the crosstalk between membrane proteins and the hydrophobic membrane environment.

Recently, much attention has been focused on lipotoxicity caused by saturated fatty acids as an important factor in explaining the metabolic syndrome. Our previous studies revealed that increase of membrane saturated fatty acids contributes to lipotoxicity. Our studies of membrane fatty acyl chain homeostasis will provide the possibility for the discovery of new drug targets in the metabolic syndrome.

【Publications Relevant to the Project】

- Imae R., Inoue T., Kimura M., Kanamori T., H. Tomioka N., Kage-Nakadai E., Mitani S. and Arai H. "Intracellular PLA1 and Acyltransferase, Which Are Involved in *Caenorhabditis elegans* Stem Cell Divisions, Determine the *sn*-1 fatty acyl Chain of Phosphatidylinositol." *Mol. Biol. Cell*, 21, 3114-3124 (2010)
- Ariyama H., Kono N., Matsuda S., Inoue T. and Arai H. "Decrease in membrane phospholipid unsaturation induces unfolded protein response." *J. Biol. Chem.*, 221, 87-95 (2010)
- Lee H. C., Inoue T., Imae R., Kono N., Shirae S., Matsuda S., Gengyo-Ando K., Mitani S. and Arai H. "*C. elegans mboa-7*, a member of the MBOAT family, is required for selective incorporation of polyunsaturated fatty acids into phosphatidylinositol." *Mol. Biol. Cell*, 19, 1174-1184 (2008)

【Term of Project】 FY2011-2015

【Budget Allocation】 165,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~eisei/jp/Home.html