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

Broad Section H

Title of Project： **Regulatory roles of bioactive lipids driven by the phospholipase A2 family**

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Research Project Number: 20H05691 Researcher Number：60276607
Keyword：Lipid, Enzyme, Biomolecule, Cell, Gene

【Purpose and Background of the Research】

Lipids represent a fundamental biological substance as an energy source, cell membrane components, signaling molecules, and surface barriers (four major functions of lipids), and their qualitative/quantitative changes are associated with various diseases. In our ongoing efforts to clarify the biological roles of the PLA_2 family, we have currently reported that individual PLA_2s are diversely involved in various diseases by regulating the four major functions of lipids (Figure 1). However, the current results obtained so far have only seen the functions of some PLA_2s in very limited situations, and therefore, comprehensive understanding of the *in vivo* functions of a full set of PLA_2s still remains to be a subject to debate.

In this research project, we will continue our current research strategies using gene-manipulated mice for various PLA_2s in combination with metabolome analysis, and accelerate an extrapolation research using human specimens with a view to future clinical derivation. As such, we aim to make a comprehensive systematization of the regulatory roles of various PLA_2-driven lipid pathways in a wide variety of biological responses.

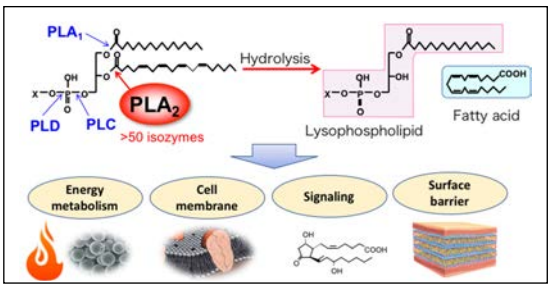

Figure 1 Biological Roles of The PLA_2 family

【Research Methods】

In this study, we will analyze a nearly full set of PLA_2 gene-manipulated mice in combination with lipidomics to identify key lipids responsible for PLA_2-related diseases, and examine their relationships to human diseases (*bench to clinic*). We will extract particular PLA_2s that show correlation with human diseases from clinical specimens and determine their roles in animal models (*clinic to bench*). Furthermore, by collating with the function and regulatory mechanism of each enzyme at the molecular and cellular level, we aim to comprehensively understand the disease-specific lipid metabolism regulated by the PLA_2 family.

【Expected Research Achievements and Scientific Significance】

The most distinctive feature of this study is that we have a lineup of gene-manipulated mice for the PLA_2 family as analytical tools. It is our responsibility as an international hub for the PLA_2-based lipid research to further develop our current research to elucidate new functions of lipids. The approach to comprehensively compare a full set of PLA_2 gene-manipulated mice is unprecedented in the world, and its originality, novelty, and superiority are pretty clear. This research provides a new understanding of various diseases from the viewpoint of lipids, and contributes to the acquisition of new intellectual property and the development of treatment and prevention methods for diseases. Furthermore, this research is expected to contribute to healthy life society and also to have a broad academic impact on a wide range of life science fields.

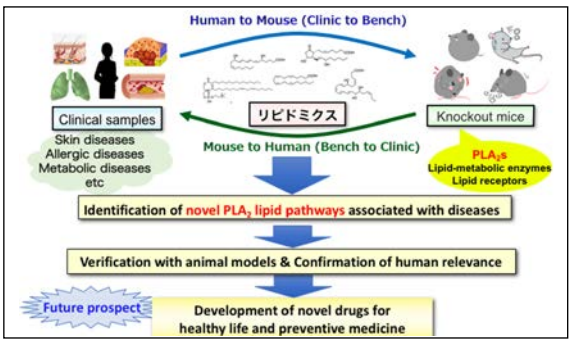

Figure 2 Overall Concept of the Research

【Publications Relevant to the Project】

・ Taketomi Y, Ueno N, Kojima T, Sato H, Murase R, et al. Mast cell maturation is driven via a group III phospholipase A_2-prostaglandin D_2-DP1 receptor paracrine axis. ***Nat. Immunol.*** 14, 554-563, 2013
・ Sato H, Taketomi Y, Ushida A, Isogai Y, Kojima T, et al. The adipocyte-inducible secreted phospholipases PLA2G5 and PLA2G2E play distinct roles in obesity. ***Cell Metab.*** 20, 119-132, 2014

【Term of Project】 FY2020-2024

【Budget Allocation】 151,300 Thousand Yen

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