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

Broad Section H

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

MURAKAMI Makoto
(The University of Tokyo, Graduate School of Medicine, Professor)

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.

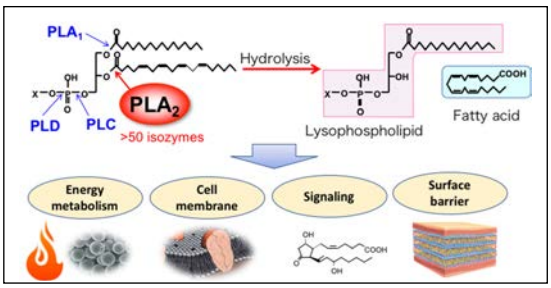


Figure 1 Biological Roles of The PLA_2 family

【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.

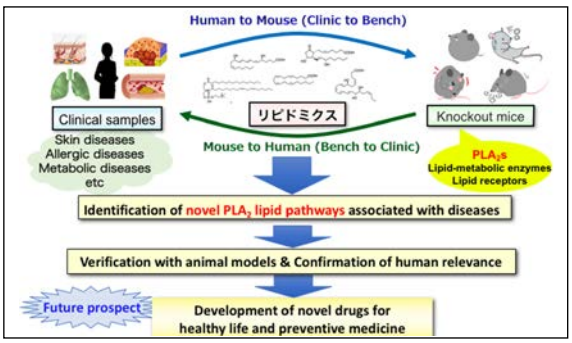


Figure 2 Overall Concept of the Research

【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

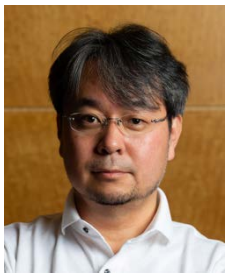
【Budget Allocation】 151,300 Thousand Yen

【Homepage Address and Other Contact Information】

http://lmmhs.m.u-tokyo.ac.jp/

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

Broad Section H



Title of Project： **Integrated molecular basis for herpesvirus replication and pathogenesis**

KAWAGUCHI Yasushi
(The University of Tokyo, The Institute of Medical Science, Professor)

Research Project Number: 20H05692 Researcher Number：60292984
Keyword：Virus, proliferation mechanism, pathological expression mechanism

【Purpose and Background of the Research】

Herpes simplex virus (HSV) is a medically important virus that causes various diseases in humans, such as encephalitis, mucosal and skin diseases, and eye diseases. Moreover, HSV infections increase the risk of human immunodeficiency virus infections by 2–4 times and are also involved in the exacerbation of dementia. Although antiviral drugs have been developed for HSV infections, the effects are not sufficient for some infection-related diseases and vaccines have not been developed either. Furthermore, repeated latency and recurrence render the complete cure of HSV infections difficult, and the unmet medical needs are high. Considering that the "overall picture of the proliferation and pathogenic mechanisms of HSV"—a universal question in HSV research—is the "sum of complex infection phenomena," it is not difficult to understand why it would be impossible to elucidate this simply by analyzing "fragmented individual infection phenomena." In this study, we aim to integrate multilayered knowledge into *in-depth* analyses at the biological level by applying basic research knowledge on various HSV infection phenomena that the principal investigator has accumulated over many years. Furthermore, we aim to understand each infection phenomenon unraveled by leading-edge technology in an integrated manner as an "overall picture of the proliferation and pathogenic mechanisms of HSV." Additionally, using the unique knowledge unraveled from HSV research, we will attempt to elucidate new life phenomena that are not bound by conventional virology.

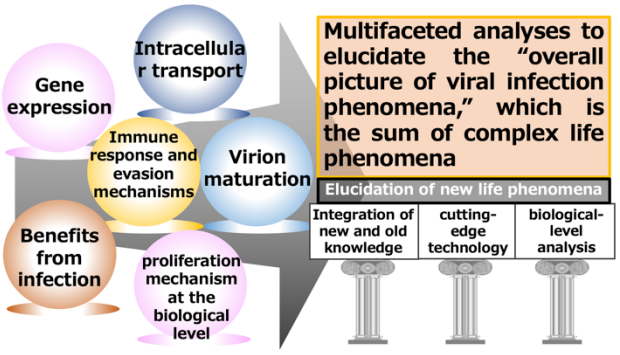


Figure 1 Concept diagram of this research project

【Research Methods】

In addition to conventional virological, molecular biology, cell biology, and experimental zoological methods, this study will be conducted by making full use of advanced technologies, such as single-cell analysis, proximity-dependent labeling for interactome analysis, quantitative phosphoproteomics, microbiome analysis, and gene editing and screening at the cellular and viral levels.

【Expected Research Achievements and Scientific Significance】

Research on HSV has been actively promoted for many years owing to the high unmet medical needs caused by infection-related diseases. Nevertheless, the "overall picture of the proliferation and pathogenic mechanisms of HSV" remains unclear, with the lack of "panoramic forms of research on various infectious phenomena" being suggested as one of the reasons. Following in this research trend, we have performed multifaceted analyses of various infection phenomena. This study, which promotes the elucidation of the "overall picture of viral infection phenomena" (Fig. 1), is not only important internationally but also highly significant in terms of ongoing foundation building in this field. Moreover, by using viruses as biological probes, our approach in elucidating cellular and biological mechanisms that cannot be clarified by conventional research on host cells has the potential to lead to the discovery of new biological phenomena that will have an impact not only on virology but also on general biology.

【Publications Relevant to the Project】

· Maruzuru Y, et al., Herpes simplex virus 1 VP22 inhibits AIM2-dependent inflammasome activation to enable efficient viral replication. ***Cell Host & Microbe*** 23: 254-65, 2018.
· Arii J et al., ESCRT-III mediates budding across the inner nuclear membrane and regulates its integrity. ***Nat. Commun.*** 9: 3379, 2018.

【Term of Project】 FY2020-2024

【Budget Allocation】 152,100 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.ims.u-tokyo.ac.jp/Kawaguchi-lab/KawaguchiLabTop.html

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

Broad Section H

Title of Project： Comprehensive understanding of Regnase-1-mediated mRNA surveillance system

AKIRA Shizuo

(Osaka University, Immunology Frontier Research Center, Specially Appointed Professor)

Research Project Number: 20H05693 Researcher Number：50192919

Keyword：Regnase-1, mRNA stability, metabolic regulation, tissue homeostasis

【Purpose and Background of the Research】

The discovery of microRNAs and non-coding RNAs has led to increase in the study of mRNA regulatory mechanisms. We identified an endoribonuclease, named Regnase-1, which binds to the 3'UTR of *IL-6* mRNA and degrades its mRNA (Figure 1). So far, RNA-binding proteins that reported to be involved in mRNA stability have no own endoribonuclease activity, but instead promote the degradation by recruiting to exosomes via interactions with target mRNAs. Besides those involved in microRNA biogenesis, Regnase family is the only RNA-binding protein possessing endoribonuclease activity in mammals. Subsequent studies have shown that Regnase-1 regulates the production of not only IL-6 but also many other mRNAs associated with inflammatory and immune responses and plays essential roles in immune system. Furthermore, it is becoming clear that Regnase-1 is involved in the regulation of various metabolic processes other than inflammatory and immune responses, suggesting that Regnase-1 participates in various biological processes. However, it is not yet known how Regnase-1 discriminates the target specificity of mRNAs. In this study, we investigate whether Regnase-1 is involved in the regulation of homeostasis and cell activation in various organs, based on the accumulated knowledge of Regnase-1. The purpose of this project is to gain a comprehensive understanding of Regnase-1-mediated mechanism of mRNA regulation.

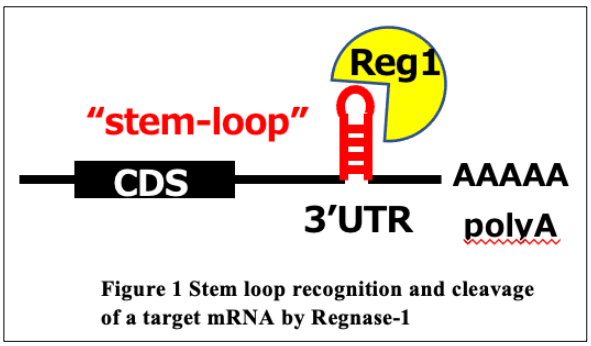


Figure 1 Stem loop recognition and cleavage of a target mRNA by Regnase-1

【Research Methods】

We generate cell-type and tissue-specific knockout and various mutation knock-in mice to elucidate the *in vivo* roles of Regnase-1, a novel mechanism for the regulation of immune and inflammatory responses. We will examine the role of Regnase-1 by using these mice-derived immune analyze the Regnase-1-mediated regulatory mechanisms, including its role in metabolism. In addition, we will search for novel molecules and small compounds that inhibit the endonuclease activity of Regnase-1, examine their effects, and explore their potential application in drug discovery.

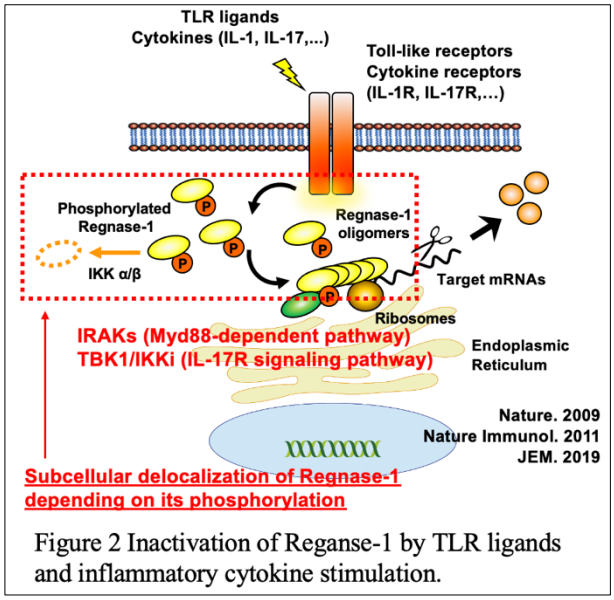


Figure 2 Inactivation of Reganse-1 by TLR ligands and inflammatory cytokine stimulation.

【Expected Research Achievements and Scientific Significance】

By understanding the regulation of immune and inflammatory responses by Regnase-1 as well as its metabolic regulation, we hope to explore new areas of RNA biology. Furthermore, it is important to explore and develop small compounds that regulate immune function via Regnase-1 for the conquest of diseases.

【Publications Relevant to the Project】

・ Tanaka H et al, J. Exp. Med. (2019)
・ Nagahama Y et al, PNAS (2018)

【Term of Project】 FY2020-2024

【Budget Allocation】 152,400 Thousand Yen

【Homepage Address and Other Contact Information】

http://hostdefense.ifrec.osaka-u.ac.jp/en/index.html