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

Broad Section F

Title of Project： Innovative chemical genetics on novel function of endogenous metabolites

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Research Project Number：19H05640　　Researcher Number：80191617
Keyword：Endogenous metabolite, Chemical genetics, Drug target, Posttranslational modification, Metabolic pheromone

【Purpose and Background of the Research】

Many metabolites have cellular function independent of their metabolic roles by acting as cofactors or inhibitors for posttranslational modification enzymes (Fig. 1). Therefore, it seems possible that metabolites in common metabolic pathways possess unexpected activity, and that their dynamic fluctuation upon environmental changes greatly affects the destiny of life through affecting their adaptation and homeostasis. Although fluctuation of metabolites can be analyzed by metabolome, their biological function has been poorly understood because of difficulties in activity measurements. This study aims at elucidating novel function of metabolites by molecular and chemical genetics.

【Research Methods】

In this research, we will uncover new function of metabolites using fission yeast and animal cells with our original screening systems. To this end, we will expand our metabolite compound library.

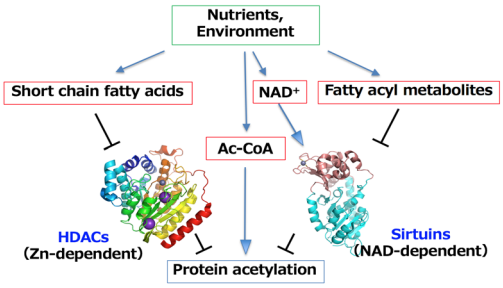

Fig. 1. Protein acetylation regulated by metabolites

(1) Chemical genetics for energy metabolism

We previously showed that SIRT2 has defatty-acylase activity, which requires formation of a large hydrophobic pocket to accommodate the substrate fatty-acyl lysine. However, once the defatty-acylation reaction occurs, it loses deacetylase activity. This is probably because *O*-acyl-ADP ribose, the product of defatty-acylation, binds the hydrophobic pocket thereby inhibiting deacetylase activity. On the other hand, the fatty-acyl lysine substrate may kick it out from the pocket, allowing the next cycle of catalysis. Here we will elucidate the molecular mechanism for the conversion of enzyme activity from deacetylation to defatty-acylation by using synthetic derivatives of *O*-acyl-ADP ribose. In addition, we will analyze the mode of action of a natural product derivative named TLAM, which activates mitochondria respiration and suppresses the Warburg effect in cancer cells.

(2) Chemical genetics for hypoxia response

The eukaryotic translation factor eIF5A is subject to hypusination, a unique posttranslational modification. Hypothesis that hypusination of eIF5A acts as a sensor of hypoxia at the translation level will be examined. Furthermore, we will investigate why defective hypusination under the hypoxic conditions downregulates mitochondrial protein synthesis by ribosome profiling.

(3) Chemical genetics for amino acid metabolism

Based on our previous discovery of a fission yeast pheromone that induces cancellation of nitrogen catabolite repression, we will identify novel signaling small molecules by searching for mutants whose growth can be recovered in the vicinity of the wild-type cell colony.

(4) Chemical genetics for lipid metabolism

We will elucidate the mechanism of cell growth inhibition by fatty acids with odd number carbons or marine microbial lipids by identifying genes that alter their sensitivity.

【Expected Research Achievements and Scientific Significance】

Fluctuation of metabolites upon environmental changes regulates homeostasis through altered posttranslational modification such as acetylation. Uncovering of hidden function of metabolites will lead to the development of novel medical or material production technologies.

【Publications Relevant to the Project】

- Sun *et al.* Identification of novel secreted fatty acids that regulate nitrogen catabolite repression in fission yeast. *Sci. Rep*. 6: 20856, 2016.
- Ito *et al.* The subcellular localization and activity of cortactin is regulated by acetylation and interaction with Keap1. *Sci. Signal.* 8: ra120, 2015.
- Nishimura *et al.* Marine antifungal theonellamides target 3beta-hydroxysterol to activate Rho1 signaling. *Nat. Chem. Biol.* 6: 519-526, 2010.

【Term of Project】 FY2019-2023

【Budget Allocation】 154,700 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.jp/research/labs/csrs/chem_genom/
http://www2.riken.jp/SPD/CG/index.html