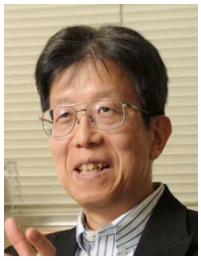
【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Agricultural Sciences)



Title of Project : Development of Novel Methods for Target Identification of Natural Products and their Application to Chemical Epigenetics

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Research Project Number : 26221204　Researcher Number : 80191617
Research Area : Boundary Agriculture
Keyword : Epigenetics, Proteome, Target molecule

【Purpose and Background of the Research】

Naturally occurring bioactive small molecules (natural products) contain substances showing extremely potent and specific bioactivity. As in the case of penicillin, elucidation of the target molecules and mode of action has provided great impacts on biology. However, most of these studies were accomplished through a trial and error strategy and no rapid and systematic methodology for efficient drug target identification has been established. This project aims to develop a novel technology to detect the chemical-target interaction, thereby enabling systematic elucidation of the mode of action of target-unknown natural products and the function of the target molecules such as epigenetics. In addition, we establish a system to identify therapeutic targets based on information about genes responsible for the disease onset by using the concept of synthetic lethality.

【Research Methods】

An integrated system to identify target molecules of bioactive natural products will be developed. Specifically, we will establish barcode sequencing methods to determine chemical genomic profiles using a barcoded fission yeast gene deletion mutant collection and human cell culture infected with a pooled, barcoded shRNA library (Fig. 1) and bimolecular fluorescent complementation (BiFC) imaging to screen for protein-protein and chemical-protein interactions. By employing this target identification system integrated with affinity beads technology, the target molecules of microbial or marine natural products and their functional pathways will be systematically identified. In addition, we will find compounds with novel activities including epigenetic regulation.

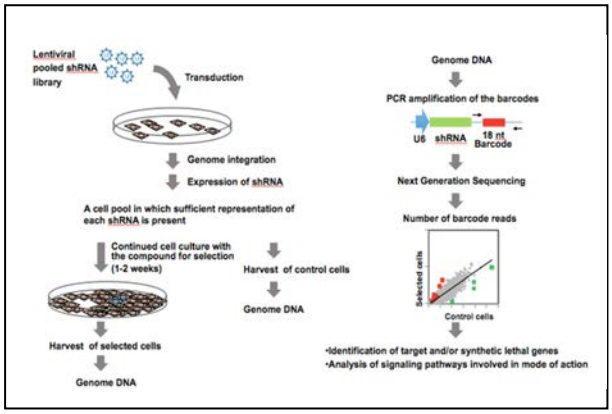

Fig. 1. Target identification by barcoded shRNA

【Expected Research Achievements and Scientific Significance】

A huge variety of microbes and plants in nature synthesize natural products with marvelous bioactivities. Their target identification has provided deep insights into drug discovery. As the process for the target identification resembles classical genetics, it is called chemical genetics, which generally uses compound-bound affinity probes. However, it is not always successful due to the unstable binding to the probes. It is therefore necessary to establish chemical genomics, an unbiased genome-wide methodology to screen for target molecules. This project will contribute to problem resolution in health, medicine, and environment, by facilitating an efficient use of bioactive substances.

【Publications Relevant to the Project】

- Nishimura, S., *et al.* Marine antifungal theonellamides targets 3β-hydroxysterol to activate Rho1 signaling. Nature Chem. Biol., 6: 519-526, 2010.
- Ito, T., *et al.* Real-time imaging of histone H4K12-specific acetylation determines the modes of action of histone deacetylase and bromodomain inhibitors. Chem. Biol., 18: 495-507, 2011.

【Term of Project】

FY2014-2018

【Budget Allocation】

150,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.riken.jp/en/research/labs/chief/chem_genet/
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