【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Medicine, dentistry, and pharmacy I)

Title of Project : Analysis of the regulation and mode of action of atypical G-protein cycles

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Research Area : Biological pharmacy, Functional biochemistry
Keyword : Biochemistry, Cell signal transduction

【Purpose and Background of the Research】

G proteins, which cycle between the two different GTP- and GDP-bound conformations (G cycles), play important roles as a "molecular switch" in many signaling pathways. G proteins have been classified into three major families, 1) translation factors, 2) trimeric G proteins, and 3) small GTPases, based on their structural features. The small GTPases, such as Ras, Rab, Arf, and Rho/Rac family, are involved in the regulation of cell growth/ differentiation, intracellular vesicle trafficking, and cell shape/adhesion. However, there are many other small GTPases, of which functions are still unknown. Recently, several Ras-type GTPases appear to function in vesicle trafficking and/or cell-shape regulation. In addition, we have also identified many atypical G proteins that exhibit unique biochemical properties and/or structures different from previously characterized small GTPases. These findings indicate there are new regulatory mechanisms and physiological roles of the atypical G proteins.

In this research project, we analyze the atypical G proteins, which include 1) Arl8 and Di-Ras exhibiting unique biochemical properties, 2) Arl13b and Rab45 that contain many functional regions other than G domain, and 3) Rag hetero-dimer involved in the mTOR-signaling pathway. We are planning to elucidate how G cycles of the atypical G proteins are regulated dependent on their structure and modes of actions in intracellular signaling pathways.

【Research Methods】

To achieve this research objective, we plan to carry out the following analyses at different organization levels.

1) Biochemical characterization of the atypical G proteins: We will purify the recombinat and native proteins from baculo-virus-transfected Sf-9 cells and mammalian tissues to identify their regulators and effectors.

2) Physiological roles of the atypical G proteins: We will identify their roles at intact-cell and animal levels with the techniques of molecular biology, cell biology, and molecular genetics. We also analyze in *C. elegans*, since the number of each G protein family is limited.

【Expected Research Achievements and Scientific Significance】

Our goal is to understand a common mechanism underlying various G cycles by revealing the regulation and functions of the atypical G proteins. These G proteins appear to mostly function in endosome dynamics, such as lysosome biogenesis, endocytosis, and exocytosis. Furthermore, mutations in genes encoding the atypical G proteins are responsible for ciliary and lysosomal diseases. Thus, our research progress will contribute not only to the understanding of organelle formation, which is precisely regulated by many small GTPases, but also to the diagnosis and therapy for the diseases.

【Publications Relevant to the Project】

1. Saito K, *et al.* cTAGE5 mediates collagen secretion through interaction with TANGO1 at endoplasmic reticulum exit sites. *Mol. Biol. Cell.* 2011 Apr 27 [Epub ahead of print]
2. Nakae I, *et al.* The Arf-like GTPase Arl8 mediates delivery of endocytosed macro-molecules to lysosomes in *Caenorhabditis elegans. Mol. Biol. Cell* **21**: 2434–2442 (2010)
3. Cevik S, *et al.* Joubert syndrome Arl13b functions at ciliary membranes and stabilizes protein transport in *Caenorhabditis elegans. J. Cell Biol.* **188**: 953–969 (2010)

【Term of Project】 FY2011–2015

【Budget Allocation】 173,700 Thousand Yen

【Homepage Address and Other Contact Information】

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