【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Functional Analyses of Girdin Family Proteins and their Roles in Psyco-neurologic Disease and Cancer

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Research Project Number : 26221304 Researcher Number : 40183446
Research Area : Experimental Pathology
Keyword : Animal Model, Functional Molecule

【Purpose and Background of the Research】

Cell migration is initiated in response to multiple extracellular cues and regulated by many intracellular molecules. Its dysregulation is involved in the development of various human diseases. We identified the Akt substrate Girdin which is an actin-binding protein, using a yeast two hybrid screening. Girdin is phosphorylated at the leading edge of moving cells by Akt, leading to reorganization of the actin cytoskeleton. The purpose of this study is to further analyze the functions of Girdin and its family protein Daple at the cellular and molecular levels and to elucidate their roles in the development of psyco-neurologic disease and cancer.

【Research Methods】

1. Roles of Girdin and Daple in psyco-neurologic disease and cancer: Using genetically engineered mice, we will investigate the functions of Girdin and Daple (Fig. 1) in neurogenesis and memory formation. By crossing girdin or daple knockout mice with cancer-prone mice, we will elucidate the roles of these molecules in cancer progression.

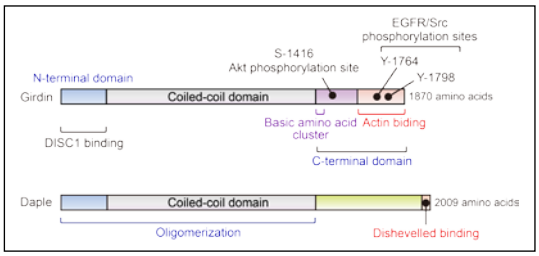

Figure 1 Structure of Girdin and Daple

2. Identification and functional analyses of Girdin or Daple-interacting proteins: To elucidate the functions of Girdin and Daple in cell migration, we will further identify proteins which specifically interact with their N- and C-terminal domains and study the functions of interacting proteins in cancer cell migration and neurogenesis.

3. Regulation of Girdin function by tyrosine phosphorylation: It turned out that Girdin is phosphorylated at tyrosine 1764 and 1798 by Src and EGF receptor. The significance of tyrosine phosphorylation of Girdin will be analyzed at cellular levels as well as in mice.

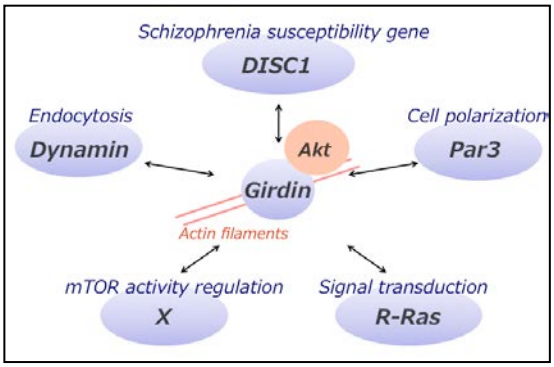

Figure 2 Identification of Girdin-interacting proteins

【Expected Research Achievements and Scientific Significance】

In this project, we will identify new Girdin and Daple interacting proteins (Fig. 2) and generate new genetically engineered mice of the girdin or daple gene. Through these analyses, we will elucidate the roles of Girdin and Daple in the development of psyco-neurologic disease and cancer. In addition, our studies will provide new insights into Girdin and Daple functions in the nervous system.

【Publications Relevant to the Project】

・Ishida-Takagishi, M., Takahashi, M. et al. The Dishevelled-associating protein Daple controls the non-canonical Wnt/Rac pathway and cell motility. **Nature Commun.** 3: 859 (2012).
・Enomoto, A., Takahashi, M. et al. Roles of Disrupted in Schizophrenia 1 interacting protein Girdin in postnatal development of the dentate gyrus. **Neuron** 63: 774-787 (2009).

【Term of Project】 FY2014-2018

【Budget Allocation】 149,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.med.nagoya-u.ac.jp/patho2/