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

Title of Project : Dissection of Rho-mDia pathway-mediated mechanisms of tissue organization and homeostasis

Shuh Narumiya
(Kyoto University, Graduate School of Medicine, Professor)

Research Area : General medical chemistry
Keyword : Rho, mDia , Actin cytoskeleton, cell motility, cell adhesion, homeostasis

【Purpose and Background of the Research】

Actin cytoskeleton plays important roles in cell morphogenesis, migration, proliferation and adhesion. During the past 20 years, the molecular mechanism of assembly and regulation of actin cytoskeleton has been largely elucidated. However, most of those studies were done in vitro in cultured cells and it remains still largely unknown how the principles discovered in cultured cells are utilized in tissue organization and homeostasis in intact body. mDia is an actin nucleator functioning downstream of Rho. In this study, we examine mice deficient in three mDia isoforms either alone or in combination, and unravel actions and action mechanisms of the actin cytoskeleton in organization and maintenance of tissue structures.

【Research Methods】

We examine mice deficient in mDia1, mDia2 or mDia3 either alone or in combination and analyze the role of Rho-mDia pathway in neural stem cell homeostasis, axon guidance, neural plasticity, homeostasis of hematopoietic stem cells, enucleation, DMBA/TPA-induced skin cancer and regulation of coat color. In these experiments, we combine in vivo analysis of intact animals with in vitro nalaysis of cultured cells to reveal molecular mechanisms of each action. We also use in utero electroporation of exogenous genes and siRNA to complement our knockout mice studies and generate conditional knockout mice that lacks gene expression in a time- and tissue-specific manner by exploiting the Cre/LoxP system.

【Expected Research Achievements and Scientific Significance】

1. Elucidation of mechanisms of stem cell proliferation and differentiation: We plan to identify the common actin-dependent niche mechanism or structure that regulates the proliferation of neural stem cells and hematopoetic stem cells by analyzing the abnormal proliferation phenotype of each stem cell in mDia-deficient mice. Results obtained by this analysis may promote our understanding of pathogenesis of congenital brain anomalies, pediatric brain tumor and leukemia. In addition, mDia-deficient mice exhibit impaired apical-basal polarity of neural stem cells. By analyzing this phenotype, we expect to clarify the maintenance mechansm of this plarity and its significance to brain morphogenesis.

2. Unraveling the physiological importance of Rho-mDia pathway in neural plasticity: In this study, we subject our KO mice to cocaine-induced addiction and chronic stress-induced depression, both of which involve plastic change of neural structure. By examining heir phenotype, we expect to find how Rho-mDia contributes to neural plasticity and behavioral change associated with drug-addiction and depression.

3. Determination of the role of Rho-mDia pathway in skin homeostasis: While Rho is overexpressed in several types of clinical cancer, and mutation of a RhoGAP, DLC-1, is the most frequently found mutation in cancer next to p53, the precise role of Rho in carcinogenesis is still largely unknown. We plan to identify the role of Rho in this process by subjecting our KO mice to DMBA/TPA-induced skin cancer model.

In conclusion, this study will elucidate in vivo function of Rho signaling and actin cytoskeleton in intact body.

【Publications Relevant to the Project】

1. Narumiya, S., Tanji, M. & Ishizaki, T. (2009) Rho signaling, ROCK and mDia1, in transformation, metastasis and invasion. Cancer Metastasis Rev., 28, 65-76.
2. Sakamoto, S et al. Liprin-α controls stress fiber formation by binding to mDia and regulating its membrane localization.
J. Cell Sci., in press

【Term of Project】 FY2011-2013

【Budget Allocation】 126,000 Thousand Yen

【Homepage and Other Contact Information】

http://www5.mfour.med.kyoto-u.ac.jp/
snaru@mfour.med.kyoto-u.ac.jp