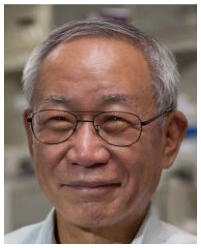
【Grant-in-Aid for Scientific Research (S)】
Biological Sciences (Medicine, Dentistry, and Pharmacy)



Title of Project : Physiological Roles and Action Mechanisms of mDia-induced Actin Cytoskeleton in the Body

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Research Project Number : 26221302 Researcher Number : 70144350
Research Area : General medical chemistry
Keyword : Biomolecular medicine

【Purpose and Background of the Research】

Actin cytoskeleton plays critical roles in cell morphogenesis, adhesion, migration, proliferation and division. While much has been elucidated on how actin cytoskeleton is formed and functions in cultured cells, it remains largely unknown how actin cytoskeleton functions in tissue homeostasis in the body. We have generated mice deficient in each of three isoforms of mDia that catalyzes actin polymerization downstream of Rho in the cell, and revealed that the actin cytoskeleton produced by the Rho-mDia pathway functions in shaping brain structure and cytokinesis of erythroblasts. Here we combine analysis in KO mice and cultured cells, and further examine the functions of this mDia-induced actin cytoskeleton in processes such as neural plasticity in the presynapse, TCR signaling in lymphocytes, sperm morphogenesis and malignant cell transformation and cancer.

【Research Methods】

Here we examine the functions of mDia in four biological processes; 1, neural plasticity at the presynaptic terminal; 2, TCR signaling in lymphocytes; 3, sperm morphogenesis in the testis ; 4, malignant cell transformation and tumor formation in the skin. In 1, we already observed mDia 1/3-dependent contraction of the presynaptic terminal in primary culture of hippocampal neurons under tetrodotoxin treatment (Fig. 1), and examine the underlying mechanism of this phenomenon. We also examine physiological relevance of this mechanism by analyzing the stress behavior and synaptic response of mice that lack mDia1/3 specifically in nucleus accumbens. In 2, we already found impaired TCR signaling in thymocytes obtained from mDia1/3 double knockout (DKO) mice (Fig. 2). We examine how actin cytoskeleton induced by mDia/3 functions in immunological synapse formation and TCR microcluster dynamics there.

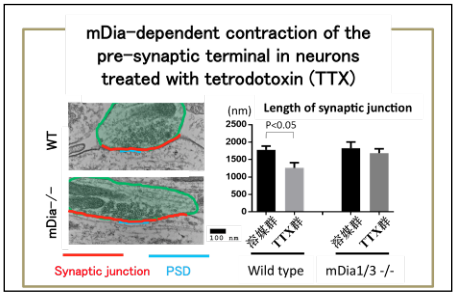

Figure 1

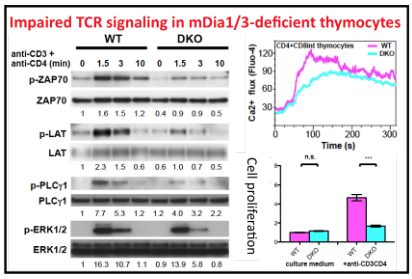

Fig. 2

In 3, we already observed impaired morphogenesis of sperm in mDia1/3 DKO testis, and this is due to the defect in Sertoli cells. We examine underlying mechanism. In 4, we combine cell transformation assay in vitro and DMBA/TPA-dependent skin carcinogenesis in vivo, and examine the role of mDia1 in cancer.

【Expected Research Achievements and Scientific Significance】

The above-mentioned experiments are expected to reveal, 1. a mechanism of neural plasticity at the presynapse and its physiological significance, 2, how mDia-induced actin is involved in TCR signaling, 3, how actin plays in interaction of Sertoli cells and sperm, and 4, how mDia-mediated actin is involved in transformation and cancer.

【Publications Relevant to the Project】

Thumkeo D, Watanabe S, Narumiya S. (2013) Physiological roles of Rho and Rho effectors in mammals. *Eur J Cell Biol.* **92**:303-315.

【Term of Project】 FY2014-2016

【Budget Allocation】 132,400 Thousand Yen

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