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

Biological Sciences (Medicine, Dentistry, and Pharmacy)

Title of Project : Development of a Novel Strategy for Life Style Disease through Exploration of the Roles of Mineral- and Gluco-Corticoids in Hypertension and Organ Dysfunction

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Research Area : Medicine, Dentistry, and Pharmacy
Keyword : Nephrology, Hypertension

【Purpose and Background of the Research】

We have been studying about the organ dysfunction related to life style disease from many aspects. Excess of adrenal hormones, aldosterone and cortisol, induces hypertension and kidney injury. We clarified that activation of the receptors of these hormones plays a key role in hypertension and organ dysfunction, independent of serum concentrations of the hormones. We showed that a small GTP binding protein Rac1 (1) and decrease of histone deacetylase 8 (2) induces hypertension by activating MR and GR, respectively.

We will explore the mechanisms underlying activation of MR and GR by investigating 3 points described below and aim to develop a novel strategy for treatment of hypertension and kidney injury. 1) Exploration of the role of Rac1-MR pathway in the organ dysfunction. Activation of Rac1- MR pathway in the kidney induces glomerular damage and hypertension. We will clarify the respective sites of Rac1 activation involved in glomerular damage and hypertension. We also investigate the roles of Rac1-MR pathway in cardiac dysfunction. 2) Exploration of novel targets of MR and GR pathways. Using kidney-specific MR and GR knockout mice, we will identify the novel disease modifying genes regulated by MR and GR. 3) We also clarify the mechanisms underlying MR and GR activation by analyzing receptor modifications and epigenetic changes of the promoter regions of genes newly identified in 2).

【Research Methods】

Site-specific (glomerular and tubular) knockout mice will be analyzed for determining the role of Rac1-MR pathway of the kidney. Cardiomycyte-specific Rac1 and MR knockout mice will also be analyzed. The role of pendrin in hypertension will be determined by genetically modified mice.

Novel target genes of MR and GR will be clarified by analyzing site-specific MR and GR knockout mice. Furthermore, novel switch mechanisms for MR and GR will be discovered by analyzing the promoter modifications by MR, GR, and epigenetic states of the novel target genes using technics including ChIP sequencing. Finally, the findings obtained from mice will be proved by using human kidney biopsy samples.

【Expected Research Achievements and Scientific Significance】

The novel genes regulated by MR and GR and mechanisms underlying MR and GR activation identified in the present study are expected to be the targets for novel therapy against hypertension and organ dysfunction. Exploration of the mechanisms underlying aberrant epigenetic changes would pave the way for the development of novel means for prevention and/or reversal of pathologic states considered to be irreversible.

【Publications Relevant to the Project】

1) Shibata S, Nagase M, Yoshida S, Kawarazaki W, Kurihara H, Tanaka H, Miyoshi J, Takai Y, Fujita T. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. Nat Med. 2008;14:1370-6
2) Mu S, Shimosawa T, Ogura S, Wang H, Uetake Y, Kawakami-Mori F, Marumo T, Yatomi Y, Geller DS, Tanaka H, Fujita T. Epigenetic modulation of the renal β-adrenergic-WNK4 pathway in salt-sensitive hypertension. Nat Med. 2011;17:573–80
3) Fujita T. Mechanism of Salt-Sensitive Hypertension: Focus on Adrenal and Sympathetic Nervous Systems. J Am Soc Nephrol. 2014;25:1148-55

【Term of Project】 FY2015-2019

【Budget Allocation】 153,800 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.c-epi.rcast.u-tokyo.ac.jp/index.html