Title of Project : Activation mechanisms of the aldosterone / mineralocorticoid receptor system in metabolic syndrome

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Research Area : Medicine, dentistry, and pharmacy

Keyword : Nephrology, Endocrinology

【Purpose and Background of the Research】

Aldosterone has recently been recognized as an important mediator of target organ damage, in addition to its role in salt and blood pressure homeostasis. Recent epidemic of obesity and high salt diet in our modern society are postulated to cause inappropriate activation of the aldosterone/mineralocorticoid receptor (MR) system, leading to cardiovascular and renal disease. We demonstrated that metabolic syndrome rat is susceptible to renal and cardiac injuries, especially when fed a high salt diet, due to inappropriate aldosterone/MR activation. Adipocyte-derived aldosterone-releasing factors (ARF) may account for aldosterone excess in this model. We further identified small GTPase Rac1 as a novel activator of MR, and reported that the ligand-independent MR activation by Rac1 contributes to the nephropathy of several chronic kidney disease (CKD) models (**Nature Medicine** 14:1370,2008).

The aim of the present study is to elucidate the molecular mechanisms for target organ damage in metabolic syndrome, focusing on "cross-talk between Rac1 and MR", and to promote translational research to verify the clinical significance of Rac1/MR activation and to develop epoch-making diagnostic and therapeutic strategies.

【Research Methods】

(1) Analysis of Rac1-MR interaction and target organ injury, using experimental models of metabolic syndrome (KKAy, SHR/cp, diet-induced obesity, etc.). Search for stimuli causing Rac1 activation.
(2) Generation of cell type-specific (ex. podocyte-specific) Rac1 Tg / KO mice.
(3) Identification of ARF, based on the comparative analysis of fat cell conditioned media from obese SHR and non-obese SHR.
(4) Elucidation of other mechanisms of MR activation.
(5) Development of drugs (reagents to inhibit Rac1, ARF, and newly-identified target molecules), diagnostic tools (indicators of MR activation in the target organ), specification of clinical conditions in which Rac1-MR overactivation is involved. Execution of large-scale clinical trial and analysis of genetic polymorphisms for tailor-made medicine.

【Expected Research Achievements and Scientific Significance】

Recent clinical studies indicate the participation of aldosterone/MR system in metabolic syndrome. However, not all patients have elevated plasma aldosterone, which might be explained by ligand-independent activation of MR. Therefore, we consider that elucidation of these alternative pathways of MR activation would be clinically important.

We expect that our basic experimental study will provide deeper insight into the mechanisms of target organ damage in metabolic syndrome. Our translational research will bring about improved life prognosis in patients at high risk for cardiovascular disease, and prolonged kidney survival in CKD patients who have increased risk for dialysis. Because the number of CKD patients is estimated to be ~4 million, we expect that our study will offer beneficial impact on our society from medico-economic aspect as well.

【Publications Relevant to the Project】

Shibata S, Fujita T et al. Modification of mineralocorticoid receptor function by Rac1 GTPase: implication in proteinuric kidney disease. ***Nature Medicine*** 14:1370-1376, 2008.
Nagase M, Fujita T et al. Enhanced aldosterone signaling in the early nephropathy of rats with metabolic syndrome: possible contribution of fat-derived factors. ***J Am Soc Nephrol*** 17:3438-3446, 2006.

【Term of Project】 FY2009-2013

【Budget Allocation】 162,900 Thousand Yen

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