No. 1545

Role of Macrophage Mineralocorticoid Receptor in the Pathogenesis and Target Organ Complications of Salt-Sensitive Hypertension

Miki NAGASE

Juntendo University

Summary

I had been engaged in the research exploring the mechanisms of salt-sensitive hypertension and its target organ complications, and found pivotal roles of Rac1-mediated mineralocorticoid receptor (MR) activation. Recently, association of salt and the immune system have been highlighted. In the present study, I created salt-loaded uninephrectomized aldosterone infused model in macrophage-specific MR KO mice and their control Fc mice, and explored the role of macrophage MR in the pathogenesis of salt-induced hypertension and renal injury.

I generated macrophage-specific MR KO mice (M-MR KO; $LysM^{cre/+}$ $MR^{flox/flox}$) and their flox control (M-MR Fc: $LysM^{+/+}$ $MR^{flox/flox}$), using the Cre-loxP system. M-MR KO mice did not develop obvious kidney abnormalities. Therefore, we created the uninephrectomy/salt/aldosterone model. After 6 weeks, there were no significant differences in body weight, BUN, serum creatinine, systolic blood pressure, or urinary albumin excretion. The results suggest that macrophage MR did not play a central role in the pathogenesis of salt-induced hypertension or albuminuria of this model.

On the other hand, the expression of renal fibrosis markers, such as collagen I, collagen III, and fibronectin, was more pronounced in the kidney of M-MR KO mice. The expression of PAI-1 and CCN5 was significantly greater in the KO group. Gene expression of podocyte-related molecules did not differ between Fc and KO mice.

As for macrophage properties, the expression of TNFα and IL1β, M1 macrophage markers, did not differ between Fc and KO mice, and the expression of IL6 was rather enhanced in the KO mice. The expressions of M2 macrophage markers (IL10, Fizz1, Mannose receptor, Arg1) were enhanced in the kidney of salt-loaded uninephrectomized aldosterone model, which was further enhanced in the KO group.

Salt is known to promote accumulation of bone marrow-derived immune cells. The expression of macrophage-specific marker F4/80, a T lymphocyte subset marker CD4, as well as MCP-1, a macrophage chemoattractant, were significantly increased in the KO group.