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RAGE-DNA aptamer improves renal injury through Rac1-mediated MR activation in DOCA-salt hypertensive mice

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Background: Uncontrolled blood pressure accelerates the progression of chronic kidney disease (CKD). Activation of mineralocorticoid receptor (MR) plays a central role for the progression of hypertensive nephropathy (HN) independent of circulating aldosterone (Aldo). Advanced glycation end products (AGEs) and the receptor for AGEs (RAGE) system activates in the kidneys of patients with HN as well. However, causal relationship between MR axis and AGEs-RAGE system on renal injury has not been known. In this study, we examined whether activation of MR induces renal injury through the activation of AGEs-RAGE system in deoxycorticosterone acetate (DOCA)-treated hypertensive mice. Further, we explored an effect of DNA-aptamer directed against RAGE (RAGE-aptamer) on the progression of HN in this model.
Methods: Protocol 1: Uninephrectomized 8-week-old male C57Bl/6J and RAGE KO mice were divided into 3 groups as follows; 4% salt diet (control), 4% salt diet with DOCA (DOCA/salt) (50mg, 21days release, Innovation Research®), RAGE KO mice treated with DOCA/salt. DOCA was administrated subcutaneously in the right flank region. Protocol 2: RAGE-aptamer was constructed by Systematic Evolution of Ligands by EXponential enrichment (SELEX) method, and was administrated in DOCA/salt mice by osmotic mini pump for 21days. Protocol 3: Conditionally immortalized mouse podocytes were cultured with Aldo (1 μM) in a presence or absence of RAGE-aptamer and spironolactone.
Results: Systolic blood pressure, urinary albumin excretion (UAE), and an accumulation of Nε-Carboxymethyllysine (CML), one of the well characterized AGEs, were exacerbated in DOCA/salt mice compared with control. Genetic deletion of RAGE improved DOCA/salt-induced UAE in association with decreased accumulation of CML in podocytes of DOCA/salt mice without any changes of blood pressure. Administration of RAGE-aptamer improved DOCA/salt-elicited UAE and podocyte injury. CML accumulation and cortical RAGE expression were attenuated by RAGE-aptamer as well. Further, RAGE-aptamer suppressed GTP-bound Rac1 activation and MR overexpression in podocytes of DOCA/salt mice. In cultured podocytes, Aldo induced ONOO- production and CML accumulation within 30min, which were abolished by the treatment with RAGE-aptamer and spironolactone, suggesting that Aldo might accelerate oxidative stress generation through the activation of MR-AGEs-RAGE axis, thereby being involved in podocyte injury.
Conclusion: Crosstalk between AGEs-RAGE system and Rac-1-MR axis could accelerate podocyte injury in the kidney of HN. RAGE-aptamer might be a novel therapeutic strategy for the progression of MR-induced renal injury in HN.