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Elucidation of Epigenetic Factors Contributing to Suppression of Chronic Kidney Diseases Caused by Salt-Loaded Hypertension

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Summary

1. Research Background and Objectives Excessive salt intake is known to exacerbate kidney injury through mechanisms such as elevated blood pressure, increased sympathetic nervous system activity, and abnormal blood coagulation, thereby contributing to the progression of chronic kidney disease (CKD). Animal studies have also demonstrated that salt loading promotes kidney dysfunction by raising blood pressure and increasing proteinuria. Elucidating the mechanisms underlying CKD progression and identifying new therapeutic approaches remain urgent global challenges. In this study, we employed an AKI-to-CKD transition mouse model—where acute kidney injury (AKI) progresses to CKD—with the aim of exploring novel therapeutic targets by focusing on epigenetic molecular mechanisms.

2. Methods An AKI model was established by performing bilateral renal ischemia-reperfusion (IR) for 18 minutes, with evaluations of AKI and CKD conducted at 48 hours and 6 weeks post-IR, respectively. Renal tubular epithelial cells were isolated from the kidneys, and RNA-seq and ATAC-seq analyses were performed to investigate changes in gene expression and chromatin accessibility. In parallel, primary human renal proximal tubular epithelial cells (RPTECs) were subjected to hypoxic stimulation, and chromatin immunoprecipitation (ChIP-qPCR) using an anti-HIF1 antibody was conducted to assess hypoxia-induced chromatin changes. A candidate enhancer region located 91 kb upstream of the **PTPN12** gene (designated **PTPN12-E**) was identified and knocked out using CRISPR/Cas9 technology in mice, which were then subjected to the same IR model.

3. Results RNA-seq analysis revealed distinct gene expression clusters among sham, AKI, and CKD samples. A total of 133 genes were found to be commonly upregulated in both the AKI and CKD stages. ATAC-seq identified 229 chromatin regions that were closed under sham conditions, became open after AKI, and remained open during CKD progression. Among these, a region located 91 kb upstream of the **PTPN12** gene appeared to function as an enhancer. ChIP-qPCR of RPTECs demonstrated sustained recruitment of HIF1 to this region under hypoxic conditions, even after reoxygenation. Preliminary data indicated that **PTPN12-E** knockout mice exhibited attenuation of CKD phenotypes following IR injury.

4. Discussion This study suggests the presence of “hypoxic memory,” wherein chromatin structural changes induced by AKI persist into the CKD phase and contribute to disease progression. Specifically, we propose that the sustained open chromatin status of certain enhancer regions, including PTPN12-E, plays a key role in the pathogenesis of CKD. Our findings support the potential of targeting such epigenetic alterations as a novel therapeutic strategy for preventing CKD progression.