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New Therapeutic Strategy of Salt-Sensitive Hypertension in Chronic Kidney Disease by Functionally Selective Modulation of Inflammatory Signaling Via Receptor Binding Molecule

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Summary

Angiotensin II type 1 receptor-associated protein (ATRAP) promotes AT1R internalization along with suppression of hyperactivation of tissue AT1R signaling. Here, we provide evidence that renal ATRAP plays a critical role in suppressing hypertension in a mouse remnant kidney model of chronic kidney disease. The effect of 5/6 nephrectomy on endogenous ATRAP expression was examined in the kidney of C57BL/6 and 129/Sv mice. While 129/Sv mice with a remnant kidney showed decreased renal ATRAP expression and developed hypertension, C57BL/6 mice exhibited increased renal ATRAP expression and resistance to progressive hypertension. Consequently, we hypothesized that downregulation of renal ATRAP expression is involved in pathogenesis of hypertension in the remnant kidney model of chronic kidney disease. Interestingly, 5/6 nephrectomy in ATRAP-knockout mice on the hypertension-resistant C57BL/6 background caused hypertension with increased plasma volume. Moreover, in knockout compared to wild-type C57BL/6 mice after 5/6 nephrectomy, renal expression of the epithelial sodium channel α-subunit and tumor necrosis factor-a was significantly enhanced, concomitant with increased plasma membrane angiotensin II type 1 receptor in the kidneys. Thus, renal ATRAP down-regulation is involved in the onset and progression of blood pressure elevation caused by renal mass reduction, and implicates ATRAP as a therapeutic target for hypertension in chronic kidney disease.