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Investigation of the Role of NFAT5 in Renal Tubular Cells in Salt-Sensitive Hypertension

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Summary

Nuclear factor of activated T-cells 5, NFAT5, is a transcription factor, which is activated by hyperosmolality and induces the expression of osmoprotective genes, contributing to cell survival even in extremely high osmolality conditions such as renal inner medulla. In skin tissue, involvement of NFAT5 activation in the alleviation of salt-sensitive hypertension has been suggested. High-salt diet induces the accumulation of sodium (Na) in interstitium of the skin, which activate NFAT5 in macrophage. The activation of NFAT5 increases the expression of vascular endothelial growth factor-C (VEGF-C) and cause its secretion by macrophages. VEGF-C induces lymphangiogenesis and increases lymph capillary, resulting in the alleviation of hypertension induced by high-salt diet. Recently, we generated renal tubular cell-specific NFAT5 conditional knock out (KO) mice, which exhibited polyuria, decrease in urinary sodium excretion, and hypernatremia.

In the present study, we investigated the roles of renal tubular NFAT5 in salt-sensitive hypertension and VEGF-C expression in the kidney. *In vitro* experiments, NaCl-added hypertonicity (500 mOsm/kg•H_2O) induced the expression of NFAT5 protein and VEGF-C mRNA in HEK293 and NRK52E cells. *In vivo* experiments, the expression of VEGF-C protein in the kidney was increased by 1%NaCl drinking and subcutaneous administration of aldosterone with uninephrectomy in wild type mice (C57BL/6J). NFAT5 KO mice subjected to 1%NaCl drinking and administration of aldosterone with uninephrectomy died in a week, being suspected extreme hypernatremia, hypokalemia, and dehydration by aldosterone. Therefore, WT and KO mice were fed with regular diet or 8% NaCl containing high-salt diet and all mice survived for a month. High-salt diet induced hypertension both in WT and KO mice. Systolic blood pressure in KO mice with high-salt diet was significantly higher than that in WT mice with high-salt diet.

In conclusion, renal tubular NFAT5 could regulate urine concentration and urinary sodium excretion, which is important to alleviate hypertension induced by high-salt diet. The investigations of causative sodium-related transporter and VEGF-C expression in the kidney of NFAT5 KO mice are ongoing.