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A Cellular Iron Receptor in Vascular Cells and Salt Sensitive Hypertension

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Summary

Background: We have previously reported that iron and a cellular iron transport protein, transferrin receptor 1 (TfR1) is associated with hypertensive vascular remodeling in salt sensitive hypertensive rats. In addition, we have shown increased renal TfR1 expression in salt sensitive hypertensive rats. However, the role of TfR1 in the pathophysiology of hypertensive vascular remodeling and renal dysfunction remains completely unknown. In this study, we investigated the role of TfR1 in hypertensive vascular remodeling and renal dysfunction using genetic TfR1 knockout mice.

Methods and Results: First, to assess the role of TfR1 in vascular smooth muscle cells in the pathophysiology of hypertension, we generated vascular smooth muscle cells specific TfR1 heterozygous deleted (SMC-TfR1$^{+/-}$) mice. To create SMC-TfR1$^{+/-}$ mice, TfR1$^{flox/+}$ mice were crossbred with congenic C57BL6 mice that express Cre recombinase under the control of the endogenous SM22 promoter (SM22-Cre mice). Systolic blood pressure and aortic morphology were not different between SMC-TfR1$^{+/-}$ mice and control mice. Then, angiotensin II was administered for 28 days in SMC-TfR1$^{+/-}$ and control mice. Systolic blood pressure was elevated in both control and SMC-TfR1$^{+/-}$ mice after angiotensin II infusion; however, hypertensive aortic remodeling was increased to a lesser extent in SMC-TfR1$^{+/-}$ mice compared to control mice.

Second, we assessed blood pressure and renal morphology in TfR1 heterozygous deleted (TfR1$^{+/-}$) mice after 5/6 nephrectomy or unilateral ureteral obstruction. Systolic blood pressure did not differ significantly between control and TfR1$^{+/-}$ mice, while the extent of renal fibrosis was less in *TfR1*$^{+/-}$ mice than control mice after both 5/6 nephrectomy or unilateral ureteral obstruction.

Conclusions: These results indicate that TfR1 in SMC plays a role in the pathophysiology of hypertensive vascular remodeling. In addition, TfR1 is associated with the mechanism of hypertensive renal dysfunction, particularly renal fibrosis.