

## mir-192-5p in the Kidney is Protective Against the Development of Hypertension

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MicroRNAs (miRs) are short RNAs that primarily reduce protein abundance by base-pairing with their target mRNA. The role of most miRs in the development of hypertension remains unknown. We performed a deep sequencing analysis of miR expression in human kidney biopsies with hypertensive nephrosclerosis or without any significant injury. miR-192-5p was one of the most abundant miRs detected and was down-regulated in hypertensive nephrosclerosis. Previous studies have shown that miR-192-5p targets the beta 1 subunit of Na/K-ATPase which drives renal tubular reabsorption. We hypothesized that miR-192-5p in the kidney protects against hypertension. We used the Dahl salt sensitive (SS) rat and a congenic rat SS.13BN26 (L26) with reduced salt sensitivity as well as Mir192 knockout mice (KO) to test this hypothesis. SS rats had a decreased level of abundance of miR-192-5p in the renal cortex compared to the L26 rats (n=9, p<0.05). The protein abundance of the beta 1 subunit of Na/K-ATPase was higher in the SS rat compared to the L26 rat (n= 3, p<0.05). Treatment with anti-miR-192-5p, delivered directly into the kidney through renal artery injection, in uninephrectomized L26 rats significantly exacerbated hypertension. Mean arterial blood pressure (MAP) of L26 rats treated with anti-miR-192-5p reached 151+/-5 mmHg at day 14 post anti-miR treatment and 4% NaCl (HS) diet, which was significantly higher than L26 rats treated with a control anti-miR and HS (135+/-5 mmHg, n=6 and 8, p<0.05). Tissues were collected in additional groups of rats at 9 days after anti-miR injection, which was just before MAP became significantly different between the two groups, for analysis of Na/K-ATPase activity. Na/K-ATPase activity was increased in the renal cortex of rats treated with anti-miR-192-5p compared to control anti-miR (9.8 +/-1.8 μmole/min/μg vs 7.2 +/-1.3 μmole/min/μg, n=5 and 6, p<0.05). Furthermore, Mir192 KO mice treated with 1 μg/Kg/min of Angiotensin II and HS for 14 days exhibited an increased MAP compared to wild-type (WT) mice (190 +/-4 mmHg vs 167 +/-12 mmHg; n= 3 WT and 5 KO, p<0.05). In conclusion, miR-192, particularly miR-192-5p in the kidney, confers significant protection against the development of hypertension.

Disclosure Block:

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