Alms1 (Alstrom Syndrome 1), a Novel Gene Involved in Blood Pressure Regulation, Renal Na Handling and Thick Ascending Limb (TAL) Function

Ankita Bachhawat Jaykumar, Wayne State Univ/ Henry Ford Hosp, Detroit, MI; Paulo Caceres, Gustavo Ares, Henry Ford Hosp, Detroit, MI; William H Beierwaltes, Wayne State Univ/Henry Ford Hosp, Detroit, MI; Pablo A Ortiz, Wayne State Univ/ Henry Ford Hosp, Detroit, MI

Single nucleotide polymorphisms in the Alstrom syndrome 1 (ALMS1) gene are associated to hypertension, renal dysfunction, and obesity in the general population. The role of ALMS1 in regulating blood pressure or renal Na handling is unknown. In a proteomics screen, we identified ALMS1 as an interacting protein with the Na/K/2Cl cotransporter NKCC2. NKCC2 mediates NaCl reabsorption by the TAL. Thus, we hypothesized that ALMS1 regulates NKCC2 endocytosis and activity as well as blood pressure. First, we confirmed the expression of ALMS1 in isolated perfused TALs. To study ALMS1 function, we generated ALMS1 knockout (KO) rats in collaboration with the rat genome editing consortium at MCW and confirmed deletion of the ALMS1 gene. We found that 3 month old ALMS1 KO rats are hypertensive compared to wild type littermates (ALMS1 MAP: 141 ± 5 mmHg vs WT: 99 ± 6 mmHg, $p< 0.005$) fed a normal Na diet. We measured surface and intracellular NKCC2 and found a higher percentage of NKCC2 at the surface in TALs from ALMS1 KO (ALMS1: 13.8 ± 1.2% vs WT: 9.1 ± 1.0%, $p<0.05$, n=6). The increase in surface NKCC2 is due to lower endocytosis because the rate of NKCC2 internalization was lower in TALs from ALMS1 KO (ALMS1: 13.1 ± 1.2% vs WT: 28.2 ± 2.8% over 20 min, $p<0.01$, n=6). To study NKCC2-mediated Na transport *in vivo*, we measured bumetanide-induced natriuresis and diuresis. ALMS1 KO rats exhibited higher bumetanide-induced natriuresis (ALMS1: 1292 ± 65 vs WT: 564 ± 31 µmoles, $p<0.01$, n=5) and diuresis (ALMS1: 3.1 ± 0.32 vs WT: 1.6 ± 0.13 ml, $p<0.05$), indicative of higher TAL Na reabsorption. To study if this decreases the ability to excrete a volume and Na load in ALMS1 KO, we instrumented anesthetized rats and measured sodium excretion ($U_{Na}V$) and urine volume (UV) over 150 min after an acute saline load. We found that the cumulative $U_{Na}V$ was lower in ALMS1 KO rats (ALMS1: 72 ± 38 vs WT: 219 ± 55 µmoles, $p<0.05$, n=8) as was the UV (ALMS1: 0.70 ± 0.24 vs WT: 1.78 ± 0.39 ml, $p<0.05$). We conclude that deletion of ALMS1 decreases NKCC2 endocytosis and increases TAL Na reabsorption. Thus, the hypertension observed in ALMS1 KO rats may be in part due to higher renal Na reabsorption. It is not known whether the expression of ALMS1 protein is decreased in hypertensive patients or lowered by dietary factors that increase BP in humans.

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