FOXD1 IS AN UPSTREAM REGULATOR OF THE RENIN-ANGIOTENSIN SYSTEM (RAS) DURING METANEPHRIC KIDNEY DEVELOPMENT.

Song R, Preston G, Yosypiv, IV
Department of Pediatrics, Hypertension and Renal Center of Excellence
Tulane University Health Sciences Center, New Orleans, LA

The RAS plays a critical role in ureteric bud (UB) and metanephric kidney morphogenesis. Mutations in the genes encoding components of the RAS in mice or humans cause a spectrum of congenital anomalies of the kidney and urinary tract (CAKUT). However, the mechanisms by which RAS gene mutations result in CAKUT are poorly understood. In this study, we tested the hypothesis that Foxd1, a forkhead box transcription factor essential for normal kidney development, is an upstream regulator of the RAS during UB morphogenesis. The effect of Foxd1 gene dosage on UB branching in vivo was examined on E13.5. Total RNA was isolated from embryonic (E) day E14.5 Foxd1-null and wild-type mouse kidneys and from mesenchymal (MK4) cells transfected or not with Foxd1 expression vector (1.0 μg plasmid DNA). Angiotensinogen (AGT), renin, angiotensin I-converting enzyme (ACE), angiotensin (Ang) II receptor type 1 (AT1R) mRNA levels were determined by real-time qRT-PCR. Cellular distribution of AGT protein was examined in Foxd1+/- and -/- kidneys on E14.5 by immunohistochemistry. The number of UB tips was decreased in Foxd1-/- (n=4) compared with Foxd1+/- (n=6) metanephroi (12±2.1 vs. 24±1.3, p<0.01). AGT mRNA levels were higher in Foxd1-/- than in Foxd1+/- kidneys (2.25±0.05 vs. 1.0±0.02, p<0.05). In contrast, renin, ACE and AT1R mRNA levels were decreased in Foxd1-/- compared with Foxd1+/- metanephroi (Renin: 0.23±0.01 vs. 1.0±0.02, p<0.01, ACE: 0.37±0.02 vs. 1.0±0.01, p<0.01, AT1R: 0.41±0.06 vs. 1.0±0.02, p<0.01). Foxd1 overexpression in MK4 cells decreased AGT and increased renin, ACE and AT1R mRNA levels. In summary, RAS gene expression during metanephric development is differentially regulated by Foxd1 at the transcriptional level. We conclude that the cross-talk between the RAS and Foxd1 plays an important role in UB morphogenesis and pathophysiology of CAKUT.