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CYSTIC KIDNEY DISEASE

A new osmoregulatory role for HNF-1β

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The transcription factor HNF-1β is crucial for kidney development and adult renal function. Ablation of HNF-1β causes kidney cysts in mice and heterozygous human HNF-1β mutations lead to structural and functional renal abnormalities such as multicystic dysplastic kidneys. In a new study, Peter Igarashi and colleagues found a novel role for HNF-1β in osmoregulation through modulation of gene expression and protein localization.

The researchers assessed the function of HNF-1β in the renal collecting ducts (CDs) using a new CD-specific transgenic mouse model. Unlike removal in the nephron, which results in early cyst formation and perinatal lethality, CD-specific depletion of HNF-1β led to slow progressive cystic kidney disease, renal fibrosis and nephrogenic diabetes insipidus but did not affect long-term survival.

Before structural renal changes were visible, HNF-1β-depleted mice developed hydronephrosis owing to polyuria and altered urinary concentration, which persisted after 24 h of water restriction and desmopressin administration. The levels of vasopressin and solute excretion were comparable in mutant and control mice; however, mutant kidneys had increased levels of aquaporin-2, which was mislocalized to the cytoplasm, and decreased expression of the urea transporter UT-A and of collectrin, which is involved in apical membrane vesicle trafficking. The researchers also showed that HNF-1β binds to the *Nr1h4* promoter in wild-type kidneys. *Nr1h4* encodes FXR, the expression of which was inhibited in HNF-1β-deficient inner medullary CD cells exposed to hypertonic NaCl and reduced in CD-specific HNF-1β-depleted kidneys.

The researchers conclude that loss of HNF-1β produces defects in urinary concentration through direct and indirect downregulation of osmosensitive genes. This finding reveals a novel function of HNF-1β in osmoregulation and expands the spectrum of renal disorders caused by HNF-1β mutations.

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