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HYPERTENSION

NEW ROLES FOR CUL-3 IN THE KIDNEY

Mutations in cullin-3 (CUL-3) that cause familial hyperkalaemic hypertension (FHHt) have previously been shown to abrogate degradation of WNK kinases, which regulate the renal NaCl cotransporter (NCC). Now, new findings from David Ellison and colleagues demonstrate that CUL-3 403–459del is a gain-of-function mutant that exhibits increased activity compared with wild-type CUL-3.

WNK kinases have been a major focus of Ellison's laboratory for the past 14 years and this study was a continuation of their efforts to understand the association between WNK kinases and FHHt. First, they used a series of *in vitro* techniques to assess the function of CUL-3 403–459del. "Our *in vitro* studies showed that the mutant CUL-3 dramatically enhances binding to, and ubiquitylation of, kelch-like protein 3 (KLHL3), which has a role in WNK kinase degradation," explains Ellison. "The resulting reduction in KLHL3 abundance leads to WNK kinase accumulation."

Next, the researchers used mice with nephron-specific deletion of Cul-3 to test the hypothesis that loss of Cul-3 function leads to FHHt via an increase in WNK kinase levels. "These *Cul3*$^{-/-}$ mice generated some unexpected results that reveal new roles for CUL-3 in the kidney," says Ellison. "Although WNK and NCC were increased, they did not have an FHHt phenotype, but developed polyuria and salt wasting, which was associated with almost complete absence of activated Na-K-Cl cotransporter 2 and aquaporin 2 in the renal medulla." Based on these findings, the researchers suggest that CUL-3 may regulate pathways involved in fluid and electrolyte homeostasis in addition to NCC. *Cul3* deletion also resulted in renal dysfunction, inflammation and fibrosis, indicating a new pathway for kidney injury.

Ellison and colleagues now aim to determine the mechanism by which loss of 57 amino acids in CUL-3 leads to a gain-of-function, and to characterize the regulation of aquaporin 2 and non-distal convoluted tubule ion transport pathways as well as the potential effects of CUL-3 knockout on the nuclear factor erythroid 2-related factor 2/kelch-like ECH-associated protein 1 pathway. They hope that manipulation of CUL-3 effects in the kidney will lead to new avenues for the prevention of chronic kidney disease.

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Original article McCormick, J. A. *et al*. Hyperkalemic hypertension-associated cullin3 promotes WNK signaling by degrading KLHL3. *J. Clin. Invest.* doi: 10.1172/JCI76126