IL-36 alpha Regulates Tubulointerstitial Inflammation in the Mouse Kidney

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Abstract
IL-36 alpha, a member of the IL-1 family, is a crucial mediator of inflammatory responses. We previously found that IL-36 alpha was overexpressed in injured distal tubules (DTs); however, its pathological function remains unclear. Herein, unilateral ureter obstruction (UUO) or folic acid (FA) injection was performed in mouse kidneys to assess the role of IL-36 alpha in kidney injury. IL-36 alpha mRNA and protein expression significantly increased in the kidneys within 24 h after UUO. IL-36 alpha localized to dilated DTs. IL-36 alpha expression significantly correlated with the progression of tubulointerstitial cell infiltration and tubular epithelium cell death in UUO kidneys and with renal dysfunction in FA-induced acute kidney injury mice. At 24 h after UUO, IL-36 alpha(+) DT epithelial cells showed loose intercellular digitations. IL-1RL2, an IL-36 alpha receptor protein, localized to podocytes, proximal tubules, and DTs in the healthy kidney. IL-1RL2 was expressed in interstitial cells and platelets or extended primary cilia of DT epithelial cells in UUO kidneys. IL-36 alpha stimulation promoted the production of IL-6 and Prss35, an inflammatory cytokine and collagen remodeling-associated enzyme, respectively, in cultured NIH3T3 fibroblasts. UUO-treated IL-36 alpha-knockout (KO) mice showed milder kidney injury features than wild-type (WT) mice did. In UUO kidneys from IL-36 alpha-KO mice, the expression of genes associated with inflammatory response and sensory perception was significantly different from that in WT mice. Altogether, our data indicate an association between intrarenal IL-36 alpha overexpression and the progression of tubulointerstitial inflammations and morpho-functional alterations of DT epithelial cells. IL-36 alpha may be a novel kidney injury marker useful for evaluating DT damages.

Keywords
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