Knockout of the interleukin-36 receptor protects against renal ischemia-reperfusion injury by reduction of proinflammatory cytokines

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IL-36, a newly named member of the IL-1 cytokine family, includes 3 isoforms, IL-36α, IL-36β, and IL-36γ, all of which bind to a heterodimer containing the IL-36 receptor (IL-36R). Little is known about the role of the IL-36 axis in acute kidney injury (AKI) pathogenesis. Therefore, we evaluated IL-36 function in the bilateral renal ischemia-reperfusion injury model of AKI using IL-36R knockout and wild-type mice. IL-36R was found to be expressed in the kidney, mainly in proximal tubules. In IL-36R knockout mice, plasma creatinine, blood urea nitrogen, and IL-6 levels after ischemia-reperfusion injury were significantly lower than those in wild-type mice. Immunohistological analysis revealed mild tubular injury. IL-36α/β/γ levels were increased after ischemia-reperfusion injury, and IL-36α was expressed in lymphocytes and proximal tubular cells, but post-ischemia-reperfusion injury mRNA levels of IL-6 and TNF-α were low in IL-36R knockout mice. In primary cultures of renal tubular epithelial cells, IL-36α treatment upregulated NF-κB activity and Erk phosphorylation. Notably, in patients with AKI, urine IL-36α levels were increased, and IL-36α staining in renal biopsy samples was enhanced. Thus, IL-36α/IL-36R blockage could serve as a potential therapeutic target in AKI.

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Acute kidney injury (AKI) is a common disorder associated with a high rate of morbidity and mortality.[1,2] In ischemic AKI, the morphologic changes observed are effacement and loss of the brush border in proximal tubules, patchy loss of tubular cells, proximal tubular dilation, and apoptosis.[3,4] Ischemia is the leading cause of AKI in adults, and the underlying pathogenesis involves injury to nephron segments both from ischemia itself and from the mechanism of survival or death under oxidative stress.[5,6] In response to injury, proximal renal tubular cells release cytokines and chemokines,[7–9] and the numerous potent mediators generated by the injured cells include proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1β, monocyte chemoattractant protein-1, IL-8, and regulated on activation, normal T-cell expressed and secreted.[7–9] However, involvement of the IL-36 system in AKI pathogenesis has not been reported.

IL-36 is a newly identified IL-1 family member comprising IL-36α, IL-36β, IL-36γ, IL-38, and IL-36 receptor antagonist (IL-36Ra).[10–13] IL-36α/β/γ recruit and activate the same receptor, composed of the specific chain IL-36R (previously known as IL-36Rrp2) and the common chain IL-1 receptor accessory protein (IL-1RAcP), and all 3 IL-36 agonists similarly induce proinflammatory cytokines/chemokines.[14,15] Conversely, IL-36Ra binds to IL-36R but does not recruit IL-1RAcP, and thus acts as an IL-36α/β/γ antagonist.[16] IL-38 also binds to IL-36R and exerts antagonistic effects similar to IL-36Ra.[17] IL-36 cytokines play a key role in the pathogenesis of psoriasis,[18-21] rheumatoid arthritis,[18] or inflammatory bowel disease,[22] and they are produced mainly by keratinocytes, although they are also expressed by mononuclear cells, inflammatory macrophages, and dendritic cells.[23-25] Ichii *et al.*[26] reported that IL-36α was related to the development of tubulointerstitial lesions in mice and was expressed in distal convoluted tubules. Chi *et al.*[27] recently showed that IL-36 signaling activated the NLRP3 inflammasome during renal inflammation and fibrosis in the unilateral ureteral obstruction model. However, these studies did not refer to AKI induced by ischemia-reperfusion injury (IRI), and thus the role of

the IL-36 system in IRI-induced AKI pathogenesis remains poorly understood.

Here, we used IL-36R knockout (KO) mice to investigate IL-36α/β/γ expression and IL-36R function in mouse kidney IRI. Furthermore, we measured urine IL-36α levels in patients with AKI and performed immunohistological staining of IL-36α in renal-biopsy samples to determine the pathological role of IL-36α in human AKI. Our findings demonstrate that IL-36α is upregulated in renal tissue in both mouse and human AKI. Moreover, the IL-36R KO mouse data indicate that IL-36 blockage could represent a potential therapeutic target in AKI.

RESULTS

Serum creatinine, blood urea nitrogen, histology, and leukocyte infiltration in the kidney after IRI

IL-36R KO mice were indistinguishable in appearance from age-matched wild-type (WT) controls.[28] Moreover, the mice showed no significant differences in body weight, basal blood urea nitrogen and serum creatinine levels, and renal morphology. In both groups, bilateral renal IRI induced a creatinine and blood urea nitrogen increase that peaked at 24 hours (Figure 1a and b). Renal dysfunction in WT mice was indicated by an increase in serum creatinine from 0.16 ± 0.03 mg/dl before IRI to 1.04 ± 0.15 mg/dl at

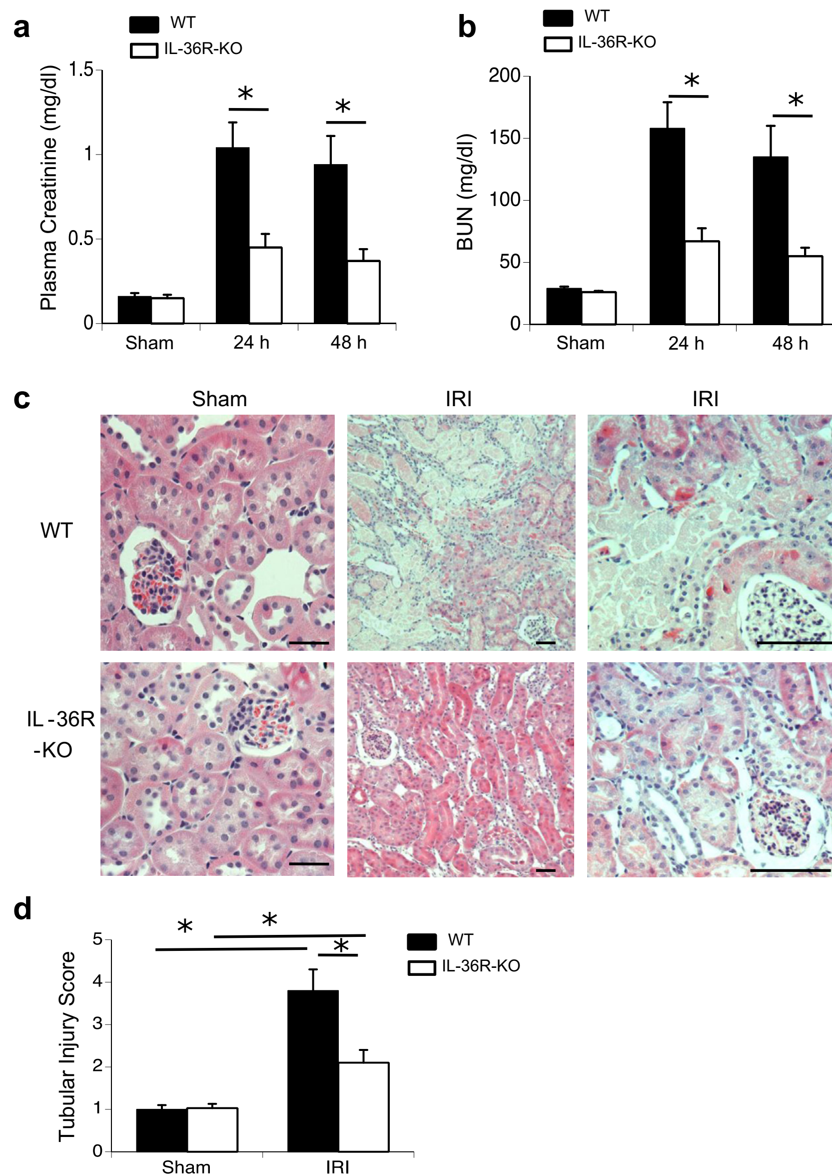

Figure 1 | Interleukin (IL)-36R knockout (KO) mice are protected against renal ischemia-reperfusion injury (IRI). (**a**) Plasma creatinine and (**b**) blood urea nitrogen (BUN) were measured as indicators of kidney function in mice exposed to sham operation or IRI (ischemia followed by 24 or 48 hours of reperfusion). (**c**) Representative morphology (revealed by hematoxylin-eosin staining) of the kidney from wild-type (WT) and IL-36R KO mice after sham operation or IRI. (**d**) Semiquantitative assessment of tubular injury in WT and IL-36R KO mice at 24 hours after sham operation or IRI. Values represent the means ± SEM of evaluation from each group ($n = 6$ per group). *$P < 0.05$. Bars = 50 μm. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

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