Peritubular capillary preservation with COMP-angiopoietin-1 decreases ischemia-reperfusion-induced acute kidney injury

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ACUTE KIDNEY INJURY (AKI), characterized by rapid decline in glomerular filtration rate, is associated with high morbidity and mortality. Ischemia-reperfusion renal injury is the major pathogenic mechanism of AKI and is usually caused by kidney transplantation, treatment of hypotension, and major surgery. Despite new insights into the pathogenesis of acute renal failure, morbidity and mortality have not declined in decades (33, 40).

Renal endothelial cells play a vital role in the pathogenesis of early and chronic ischemic kidney injury (2). Acute ischemia-reperfusion injury impairs the integrity of endothelial cells (14, 18, 30) and permanently damages peritubular capillaries (3). Renal vascular endothelial cell injury results in a loss of the vasorelaxing effect of acetylcholine (10, 28) and increases the microvascular permeability secondary to capillary leakage (37). It also decreases renal function through changes in vascular reactivity, decreased capillary barrier function, and regulation of the inflammation and coagulation pathways. Amelioration of renal endothelial cell dysfunction prevents the renal injury seen in acute renal failure (4). Recently, Kwon et al. (25) demonstrated that preservation of renal peritubular capillary endothelium integrity and an increase in the number of pericytes can be an important mechanisms for recovery from ischemic AKI in humans. Leonard et al. (27) also reported that the administration of vascular endothelial cell growth factor-121 protects against ischemic vascular structure injury and decreased chronic renal function after AKI.

Ischemia-reperfusion renal injury increases renal inflammation by increasing proinflammatory adhesion molecules and cytokines and renal vascular congestion after AKI. Because the endothelial cells are the major site of initiation of inflammation, adhesion molecules and chemokines produced by renal endothelial cells are critical factors in the inflammatory processes of renal ischemia-reperfusion injury. Kelly et al. (21) have demonstrated that regulation of intercellular adhesion molecule-1 (ICAM-1) by the vascular endothelium of the ischemic kidney significantly decreases the renal injury. Therefore, a therapy that targets the endothelium to improve renal hemodynamics, regulate renal inflammation, and decrease renal microvascular permeability may be expected to decrease the acute and chronic effects of ischemia-reperfusion renal injury and subsequently improve the mortality rate in AKI patients.

Angiopoietin-1 (Ang1) is an angiogenic factor essential for embryonic vascular development through its actions on an endothelial receptor tyrosine kinase, Tie2 (1, 36). Ang1 also decreases vascular permeability (41) and has anti-inflammatory (13) as well as antiapoptotic (22) properties. Cartilage oligomeric matrix protein (COMP)-Ang1, an engineered variant of native Ang1, is more potent than native Ang1 in phosphorylating Tie2 and signaling via Akt in primary cultured endothelial cells; this signaling pathway regulates endothelial cell survival, migration, sprouting, and tube formation (6). Recently, our group (23, 26) has reported that treatment with COMP-Ang1 can decrease the progression of renal fibrosis in a unilateral ureteral obstruction model and cyclosporine-induced renal injury. Thus COMP-Ang1 may have potential as an endothelium-oriented therapeutic agent in renal disease (23). On the other hand, Long et al. (29) reported that treatment with Ang1 had no protective effect in folic acid-induced renal injury and suggested that the effect of Ang1 treatment may
depend on the animal model. Thus there are conflicting data about the role of Ang1 in the pathogenesis of AKI.

In this study, we examined whether COMP-Ang1 has renoprotective effects in a murine model of acute ischemia-reperfusion injury. Our results demonstrate that COMP-Ang1 treatment preserves renal peritubular endothelial cell integrity and improves renal function and renal histology by regulating renal hemodynamics, macrophage infiltration, and decreasing the injury-induced increase in renal vascular permeability. Our data also suggest that COMP-Ang1 decreases renal interstitial fibrosis 30 days after the ischemia-reperfusion injury.

MATERIALS AND METHODS

Animal experiments. Male C57BL/6 mice (Charles River Korea, Seoul, Korea; 20–30 g body wt) were used in these experiments. All animal studies were reviewed and approved by the Institutional Animal Care and Use Committee of Chonbuk National University. Recombinant adenoviruses expressing COMP-Ang1 or LacZ were constructed using previously published methods (8). For adenoviral treatment, COMP-Ang1 adenovirus (Ade-COMP-Ang1), vehicle adenovirus (Ade-LacZ), or sTie2-Fc adenovirus (Ade-sTie2-Fc) diluted in 50 μl of sterile 0.9% NaCl was injected intravenously through the tail vein. In our previous experiments (23), circulating serum levels of COMP-Ang1 increased 3 days after treatment, peaked at 5 days, and declined thereafter. To evaluate the effect of high levels of COMP-Ang1 in the ischemia-reperfusion injury model, mice therefore received an intravenous injection of COMP-Ang1 adenovirus or vehicle adenovirus 3 days before the ischemia-reperfusion injury. sTie2-Fc adenovirus was administered 1 day before Ade-COMP-Ang1 injection.

Protocol 1: bilateral ischemia-reperfusion acute injury model. After an intramuscular injection of ketamine (100 mg/kg) and xylazine (10 mg/kg), the bilateral renal arteries were clamped with microvascular clips for 22 min, and then circulation was restored by removing both clips. After 1, 2, 3, 5, or 7 days of reperfusion, the animals were reanesthetized, blood samples were collected from the left ventricle, and kidneys were removed for morphological analyses (n = 10 mice per group each day). Part of each kidney was immediately fixed in 4% paraformaldehyde. The other renal tissues were...
immediately frozen in liquid nitrogen and kept at −80°C. Mice in the sham operation group after administration with COMP-Ang1 adenovirus or vehicle adenovirus only were sampled in the same way as in the ischemia-reperfusion groups.

Protocol 2: renal interstitial fibrosis model after ischemia-reperfusion injury. An ischemic injury was induced using the same method as described in protocol 1. Additional COMP-Ang1 adenovirus or vehicle adenovirus was not administered after ischemia-reperfusion injury. Mice treated with COMP-Ang1 (n = 8) or vehicle (n = 8) were euthanized 30 days after the ischemia. The corresponding control group was euthanized 30 days after the sham operation (n = 8). The kidney was removed and tissue taken for histology. The presence of interstitial fibrosis was assessed in slides stained with Masson’s trichrome.

Immunohistochemistry. Immunohistochemical analyses were performed as previously described (23). The kidney blocks were stained with anti-ER-HR3 antibodies (BMA, Augst, Switzerland) and anti-Ly-6G (Gr-1) antibodies (BD Biosciences, Franklin Lakes, NJ). Anti-platelet endothelial cell adhesion molecule (PECAM-1; Chemicon International, Temecula, CA) and anti-desmin (Dako, Glostrup, Denmark) were used on frozen sections. Digital images of desmin and PECAM-1 staining were obtained with a Zeiss LSM 510 confocal microscope (Carl Zeiss, Göttingen, Germany). The extent of fibrosis, analyzed using Masson’s trichrome stain, was examined using a computer-assisted image system with a Zeiss Z1 microscope (Carl Zeiss) and a digital image analysis program (AnalySIS). Ten digital images of every other nonoverlapping ×400 microscopic field across the renal cortex and medulla were captured with a Zeiss Z1 microscope.

Histology. Sections were stained with periodic acid-Schiff and viewed with a Zeiss Z1 microscope. Tubular injury was scored by estimating the percentage of tubules in the cortex or the outer medulla that showed epithelial necrosis or had luminal necrotic debris and tubular dilatation as follows: 0, none; 1, <5%; 2, 5–25%; 3, 25–75%; and 4, >75% (17). All evaluations were made on 10 fields (×200) per section and 10 sections per kidney.

Measurement of biochemical parameters. Blood samples were centrifuged (3,300 g for 3 min) to separate serum. Serum levels of
urea and creatinine were measured by automatic analyzer (Hitachi 7180; Tokyo, Japan) using an enzymatic method.

**Measurement of mean arterial pressure, renal blood flow, and renal vascular resistance.** Measurements of mean arterial pressure (MAP) and renal blood flow (RBF) were performed as described previously (15). The renal vascular resistance was calculated as MAP/RBF.

**Measurement of renal cortical and medullary blood flow.** Changes in the blood flow in the superficial renal cortex and medulla were measured using a laser-Doppler flow probe (1.2-mm diameter; type N; Transonic Systems, Ithaca, NY) as described previously (23). Renal cortical and medullary blood flow were measured 2 h and 2 days after the ischemia-reperfusion injury. The average laser-Doppler flow signal from the renal cortex and medulla was expressed as a percentage of the systemic arterial pressure measurement from that region.

**Vascular permeability measurement using Evans blue dye.** The microvascular leakage of Evans blue dye was assessed as described previously (43).

**Immunoblotting.** Immunoblotting was performed as previously described (35). Whole kidneys were homogenized, and immunoblot analysis of protein expression was carried out using routine procedures. The primary antibodies to phospho-Akt and Akt (Cell Signaling Technology, Danvers, MA) were used. The results of densitometric analyses are reported as the relative ratio of phospho-Akt to Akt. The relative ratio measured in kidney treated with control buffer is arbitrarily presented as 1.

**ELISA of transforming growth factor-β1.** Kidney tissue levels of transforming growth factor (TGF)-β1 were measured at 0, 1, 2, and 4 wk after ischemia-reperfusion injury following treatment with COMP-Ang1 adenovirus as described previously (23).

**Statistical analysis.** Data are means ± SD. Multiple comparisons were examined for significant differences using ANOVA, followed by individual comparisons with the Tukey post hoc test. Statistical significance was set at P < 0.05.

**RESULTS**

COMP-Ang1 preserves renal peritubular capillary endothelial cells without pericyte recruitment after ischemia-reperfusion injury. To evaluate whether COMP-Ang1 preserves peritubular capillary endothelial cells after ischemia-reperfusion injury, we stained kidney sections with an antibody to renal PECAM-1 after ischemia-reperfusion injury. After 1 day, peritubular PECAM-1-positive endothelial cell expression was decreased in ischemia-reperfusion-injured kidneys compared with sham-operated kidneys (Fig. 1). The addition of COMP-Ang1 prevented the decrease in the expression of PECAM-1-positive endothelial cells induced by ischemia-reperfusion injury (Fig. 1). Treatment with sTie2-Fc reversed the effect of COMP-Ang1 on the expression of PECAM-1 in peritubular capillaries (Fig. 1). We stained the same kidney sections with desmin, a marker for pericytes, to evaluate the changes in pericytes in this ischemia-reperfusion injury model. The percentage of kidney tissue positive for desmin was not different 1 day after ischemia-reperfusion injury than after a sham operation (Fig. 1). Treatment with COMP-Ang1 did not affect the density of desmin-positive pericytes in the ischemia-reperfusion-injured kidney.

To confirm the protective effect of COMP-Ang1 on the endothelium, we also stained the kidney sections with an antibody to another endothelial antigen, von Willebrand factor (vWF). The vWF-positive area in the kidney after ischemia-reperfusion injury was 17% of that after the sham operation (Supplementary Fig. 1). Administration of COMP-Ang1 in-
increased the density of vWF by about twofold after ischemia-reperfusion injury (Supplementary Fig. 1). COMP-Ang1 alone did not change the vWF-positive area in sham-operated kidneys. These results indicate that COMP-Ang1 preserves renal peritubular endothelial cells after ischemia-reperfusion injury.

COMP-Ang1 ameliorates renal functional after ischemia-reperfusion injury. Mice that underwent bilateral renal ischemia-reperfusion injury exhibited significant increases in blood urea nitrogen (BUN) and serum levels of creatinine 1, 2, 3, 5, and 7 days after ischemia-reperfusion injury compared with the levels in sham-operated mice (Fig. 2, A and B). Serum creatinine and BUN peaked 2 days after the ischemia-reperfusion injury (maximum increases of 14.3-fold in BUN and 7.4-fold in serum creatinine compared with levels in sham-operated mice). The pretreatment with COMP-Ang1 attenuated the increase of BUN and creatinine levels in 1, 2, and 3 days after the ischemia-reperfusion, whereas those levels in mice treated with COMP-Ang1 alone did not differ from those of sham-operated mice.

COMP-Ang1 prevents tissue damage after ischemia-reperfusion injury. Marked tubular damage, such as exfoliation of epithelial cells, brush border loss, interstitial edema and inflammatory cell infiltration, tubular cast formation, and tubular dilatation, was observed in the kidney 1, 2, 3, 5, and 7 days after ischemia-reperfusion injury (Fig. 3, A and B). The injury score was significantly higher on 1, 2, 3, and 5 days after ischemia-reperfusion injury than in sham-operated mice. Treatment with COMP-Ang1 attenuated the increase of BUN and creatinine levels in 1, 2, 3, and 5 days after ischemia-reperfusion injury (Fig. 3, A and B). Treatment with sTie2-Fc reversed the effect of COMP-Ang1 on the renal tubular injury (Fig. 3 C). COMP-Ang1 alone did not change the injury score in the kidneys of sham-operated mice.

COMP-Ang1 increases RBF and MAP and decreases renal vascular resistance after ischemia-reperfusion injury. Ischemia-reperfusion injury significantly lowered RBF, but mice treated with COMP-Ang1 had significantly higher RBF after ischemia-reperfusion than those treated with vehicle (Fig. 4A). The MAP was significantly lower after ischemia-reperfusion injury than after the sham operation. However, there was no significant difference in MAP between mice treated with vehicle or COMP-Ang1 after ischemia-reperfusion injury (Fig. 4B). The renal vascular resistance (calculated as MAP/RBF) was significantly higher in the ischemia-reperfusion-injured mice than in sham-operated mice (Fig. 4C). COMP-Ang1 significantly suppressed the increase of renal vascular resistance induced by ischemia-reperfusion injury (Fig. 4C). COMP-Ang1 alone did not alter MAP, RBF, or renal vascular resistance from the levels seen in sham-operated mice. These data suggest that COMP-Ang1 ameliorates both the decrease of RBF and MAP, and therefore, the increase of renal vascular resistance was decreased after treatment with COMP-Ang1.

COMP-Ang1 increases tissue perfusion. We also measured the influence of COMP-Ang1 on renal cortical and medullary blood flow by using a laser-Doppler flow probe in ischemia-reperfusion-injured kidneys. Ischemia-reperfusion injury did not significantly change renal cortical blood flow 2 h after the operation but significantly decreased renal medullary blood flow to 83% of control at this time point (Fig. 4D). COMP-Ang1 treatment ameliorated the decrease of renal medullary blood flow induced by ischemia-reperfusion-injury (Fig. 4D). The renal cortical and medullary blood flow 2 days after the operation decreased to 70.0 and 77.9%, respectively, of that in sham-operated kidneys (Fig. 4D). COMP-Ang1 treatment increased the renal cortical and medullary blood flow by 1.25-

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**Fig. 5. Renal vascular permeability (A), interferon (IFN)-γ (B), IL-6 (C), and IL-10 (D) after IRI. COMP-Ang1 and vehicle were administered as described in MATERIALS AND METHODS. Renal vascular permeability was quantified with Evans blue dye. Data are means ± SD (n = 4 for each experimental group). *P < 0.05; **P < 0.01 vs. sham + vehicle. †P < 0.05; ‡P < 0.01 vs. IRI + vehicle.**
and 1.22-fold, respectively, in ischemia-reperfusion-injured kidneys (Fig. 4D) but did not change cortical or medullary blood flow in sham-operated kidneys.

**COMP-Ang1 decreases renal microvascular permeability and ameliorates IL-10 level in kidney.** Because of the association of ischemia-reperfusion-induced AKI with increased microvascular leakage in the kidney, we examined the effect of COMP-Ang1 on the kidney vasculature in ischemia-reperfusion-induced AKI by measuring the leakage of Evans blue dye (16). Renal vascular permeability was higher in ischemia-reperfusion-injured kidneys than in sham-operated kidneys (Fig. 5A). However, COMP-Ang1 treatment prevented a significant portion of the ischemia-reperfusion-induced increase in renal vascular permeability (Fig. 5A). No significant differ-

**Fig. 7.** Immunoblot analyses of Akt and phospho-Akt from kidneys after IRI. A: COMP-Ang1 or vehicle was injected 3 days before IRI or sham operation. Kidneys were harvested 1 or 3 days after IRI or sham operation. B: mice were pretreated with sTie2-Fc 24 h before treatment with COMP-Ang1. Kidneys were harvested 1 day after IRI. Blots (top) were probed with an anti-phospho-Akt antibody. The membrane was stripped and reprobed with an anti-Akt antibody to control for protein loading in each lane. Densitometric analyses (bottom) are presented as the relative ratio of phospho-Akt to Akt. The relative ratio measured in sham kidneys treated with vehicle is arbitrarily presented as 1. Results from 3 independent experiments were similar. Data are means ± SD. **P < 0.01 vs. sham + vehicle. †P < 0.05; ‡P < 0.01 vs. IRI + vehicle. §P < 0.05 vs. IRI + COMP-Ang1.
ence in renal vascular permeability was observed in sham-operated and COMP-Ang1-treated mice. We also evaluated the changes of tissue levels of interferon-γ, IL-6, and IL-10 in the kidney with and without COMP-Ang1 treatment. Interferon-γ tissue level was not changed 2 and 5 days after ischemia-perfusion injury (Fig. 5B). Although COMP-Ang1 treatment did not suppress the ischemia-reperfusion injury-induced increase of IL-6 in the kidney (Fig. 5C), COMP-Ang1 ameliorated the ischemia-reperfusion injury-induced decrease of IL-10 in the kidney (Fig. 5D).

COMP-Ang1 suppresses Gr-1-positive neutrophils infiltration and ER-HR3-positive macrophage infiltration. We performed immunohistochemical studies to evaluate the changes in the number of Gr-1-positive neutrophils and ER-HR3-positive macrophages in ischemia-reperfusion-induced AKI. The number of Gr-1-positive neutrophils in kidney 1 day after injury peaked at about 67-fold compared with sham-operated kidney (Fig. 6C). Ischemia-reperfusion injury increased the infiltration of ER-HR3-immunopositive macrophages into the kidney by 109-fold 5 days after injury over with the amount of infiltration in sham-operated mice (Fig. 6, A and B). COMP-Ang1 treatment decreased the ischemia-reperfusion-induced accumulation of Gr-1-positive neutrophils and ER-HR3-positive macrophages in kidney by about 61 and 46%, respectively, whereas COMP-Ang1 alone had no effect (Fig. 6).

COMP-Ang1 increases renal Akt phosphorylation after ischemia-reperfusion-induced AKI. Phosphorylation of Akt in endothelial cells is a downstream pathway of COMP-Ang1. Renal Akt phosphorylation was higher 1 and 3 days after ischemia-reperfusion-induced AKI than after the sham operation (Fig. 7A). However, COMP-Ang1 also increased renal Akt phosphorylation 1 and 3 days after ischemia-reperfusion-induced AKI compared with that in mice treated with vehicle (Fig. 7A). The mean increases in Akt phosphorylation after treatment with COMP-Ang1 were found to be 3.1- and 3.6-fold at 1 and 3 days, respectively (Fig. 7A). COMP-Ang1 itself increased phosphorylation of Akt in sham-operated kidneys, but not significantly. Treatment with sTie2-Fc decreased COMP-Ang1-induced increase of Akt phosphorylation in kidney (Fig. 7B).

COMP-Ang1 decreases renal interstitial fibrosis 30 days after ischemia-reperfusion injury and decreases renal TGF-β1 level after ischemia-reperfusion injury. To evaluate the effect of COMP-Ang1 on interstitial fibrosis 30 days after ischemia-reperfusion injury, we stained slides with Masson’s trichrome and measured the deposition of blue-stained collagen (Fig. 8A).

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**Fig. 8.** Effects of COMP-Ang1 in renal interstitial fibrosis 30 days after IRI. A: light-field photomicrographs of Masson’s trichrome-stained (MTS) sections 30 days after IRI or sham operation. Scale bar, 50 μm. B: semi-quantitative score of tubulointerstitial fibrosis in MTS sections. Ten randomly selected high-power fields were quantified and averaged to obtain the value for each animal. Data are means ± SD (n = 8 for each experimental group). C: tissue level of activated transforming growth factor (TGF)-β1 measured by ELISA. Data are means ± SD (n = 4 for each experimental group). *P < 0.05; **P < 0.01 vs. sham + vehicle. †P < 0.01 vs. IRI + vehicle.
Thirty days after the ischemia-reperfusion, collagen deposition was 39.5-fold higher in the injured kidneys than in the sham-operated kidneys, especially in the outer medullary interstitial area. Fibrosis was not observed in kidneys from sham-operated mice. COMP-Ang1 treatment significantly suppressed collagen deposition in ischemia-reperfusion-injured kidneys by 45% (Fig. 8B). COMP-Ang1 itself did not affect collagen deposition in sham-operated kidneys.

To evaluate whether renal tissue levels of TGF-β1 were changed after treatment with COMP-Ang1, we measured tissue levels of TGF-β1 1, 2, and 4 wk after ischemia-reperfusion injury (Fig. 8C). COMP-Ang1 significantly decreased the ischemia-reperfusion injury-induced increase of renal TGF-β1 level 1 wk after the injury. These results suggest that COMP-Ang1 decreases renal interstitial fibrosis through downregulation of renal TGF-β1 level 1 wk after ischemia-reperfusion injury.

**DISCUSSION**

In this study, we have demonstrated that COMP-Ang1 preserves renal endothelial cells positive for PECAM-1 or vWF and prevents renal injury from the ischemia-reperfusion.

Kwon et al. (25) demonstrated that human kidney recipients with abundant peritubular pericytes/myofibroblasts positive for α-smooth muscle actin are more likely to recover than patients with fewer peritubular pericytes. This suggests that increased numbers of pericytes can be an important factor in renal recovery after postsischemic AKI in humans, but in our data in mice, COMP-Ang1 preserved renal endothelial cells without increasing the number of desmin-positive pericytes after ischemia-reperfusion injury. Therefore, further studies are necessary to evaluate the role of pericyte in AKI.

Recently, Long et al. (29) demonstrated that Ang1 treatment stabilizes peritubular capillaries along with the increase in fibrotic and inflammatory processes in folic acid-induced acute renal injury, whereas our results demonstrate that COMP-Ang1 has an anti-inflammatory effect after an ischemia-reperfusion injury model. Moreover, Long et al. suggested that the response to the treatment with endothelial growth factor differs according to the kidney disease model. It is reasonable to discuss that COMP-Ang1 was developed as a more potent agent than native Ang1 and has higher efficiency for phosphorylating Tie2 and signaling via Akt in primary cultured endothelial cells (6, 7); hence, we suggest that the difference in the effect of Ang1 in kidney may be due to structural variation between Ang1 and COMP-Ang1.

Ischemia-reperfusion renal injury increases renal microvascular permeability in animal models (16, 38). Increased renal vascular permeability in turn induces interstitial edema, which contributes to decreased RBF, hemoconcentration, and an inflammatory cell-induced inflammatory cascade in kidneys (20, 24). Thus increased renal microvascular permeability eventually contributes to increased renal injury. Ang1 acts as an anti-permeability factor to prevent leakage from vessels induced by vascular endothelial cell growth factor or tumors (19, 34, 41). In an endotoxemic model of lung injury, Ang1 significantly decreased the lipopolysaccharide-induced increase in lung water content (42). Consistent with this finding, our results demonstrate that COMP-Ang1 significantly prevents the ischemia-reperfusion-induced increase of renal microvascular permeability.

Numerous strategies have been developed to inhibit the movement of inflammatory cells into renal tissue after ischemia-reperfusion injury. Several studies have demonstrated the effectiveness of using antagonists to adhesion molecules to decrease the vascular endothelium-mediated infiltration of inflammatory cells into the kidney tissue (31, 39). ICAM-1 has an important role in increasing tissue injury during reperfusion of the ischemic kidney, and downregulation of ICAM-1 ameliorates renal injury in ischemia-reperfusion AKI (21, 31). We found in this study that COMP-Ang1 decreased ischemia-reperfusion-induced ICAM-1 protein expression in renal tubules and interstitial space (data not shown) and macrophage infiltration in kidney. COMP-Ang1 may therefore prevent ischemia-reperfusion-induced renal injury in part by regulating inflammation.

Progressive renal fibrosis may occur 4–8 wk after severe ischemia-reperfusion injury (5, 11, 32). It has been reported that neutrophils and CD4+ T cells persistently infiltrate 6 wk after the initial injury (5, 12). Persistent renal inflammation after ischemia-reperfusion injury is an important mechanism of chronic interstitial renal fibrosis. Given that serum levels of COMP-Ang1 are elevated for 2 wk after a single adenovirus injection, COMP-Ang1 treatment produces long-lasting tracheal vascular enlargement and increases blood flow and wound healing in diabetic mice (23, 8, 9). We therefore evaluated the long-term effect of COMP-Ang1 on fibrosis after ischemia-reperfusion injury. Administration of COMP-Ang1 decreased renal fibrosis 30 days after ischemia-reperfusion as observed using Masson’s trichrome stain (Fig. 8). COMP-Ang1 may therefore found to have a long-term protective effect after ischemia-reperfusion injury.

In conclusion, COMP-Ang1 protects against ischemia-reperfusion-induced AKI by significantly improving renal hemodynamics, renal function, and renal tissue blood flow in mice. COMP-Ang1 may be considered for use as an endothelium-targeted therapy for preventing ischemia-reperfusion-induced AKI.

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