Renal Structural and Functional Repair in a Mouse Model of Reversal of Ureteral Obstruction

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The end point of immune and nonimmune renal injury typically involves glomerular and tubulointerstitial fibrosis. Although numerous studies have focused on the events that lead to renal fibrosis, less is known about the mechanisms that promote cellular repair and tissue remodeling. Described is a model of renal injury and repair after the reversal of unilateral ureteral obstruction (UUO) in male C57bl/6j mice. Male mice (20 to 25 g) underwent 10 d of UUO with or without 1, 2, 4, or 6 wk of reversal of UUO (R-UUO). UUO resulted in cortical tubular cell atrophy and tubular dilation in conjunction with an almost complete ablation of the outer medulla. This was associated with interstitial macrophage infiltration; increased hydroxyproline content; and upregulated type I, III, IV, and V collagen expression. The volume density of kidney occupied by renal tubules that exhibited a brush border was measured as an assessment of the degree of repair after R-UUO. After 6 wk of R-UUO, there was an increase in the area of kidney occupied by repaired tubules (83.7 ± 5.9%), compared with 10 d UUO kidneys (32.6 ± 7.3%). This coincided with reduced macrophage numbers, decreased hydroxyproline content, and reduced collagen accumulation and interstitial matrix expansion, compared with obstructed kidneys from UUO mice. GFR in the 6-wk R-UUO kidneys was restored to 43 to 88% of the GFR in the contralateral unobstructed kidneys. This study describes the regenerative potential of the kidney after the established interstitial matrix expansion and medullary ablation associated with UUO in the adult mouse.


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Materials and Methods

Male C57bl/6j mice that weighed 20 to 25 g were obtained from Monash University Animal House, Australia. All experiments were approved in advance by a Monash University Animal Ethics Committee, which adheres to the “Australian Code of Practice for the Care and Use of Animals for Scientific Purposes.”

UUO or sham surgery was performed under isofluorane anesthesia (2%; Abbott Australasia Pty Ltd, Kurnell, Australia), whereby the left
ureter was visualized via a flank incision and ligated with a vascular clamp (0.4 to 1.0 mm; S&T Fine Science Tools, Foster City, CA). Mice were allowed to recover for 10 d before tissue collection. The right contralateral unobstructed kidney (CUK) served as the control. Additional groups of mice underwent 10 d of UUO or sham surgery, at which time the clamp was removed under isoflurane anesthesia and the kidney was allowed to recover (R-UUO) for 1, 2, 4, or 6 wk. Animal numbers for each group are outlined in each section.

**Structural Analysis**

Kidneys were collected from mice after 10 d of UUO (n = 5) and sham (n = 6) operations and after R-UUO for 1 wk (n = 5), 2 wk (n = 5), 4 wk (n = 5), and 6 wk (n = 5) for structural analysis.

**Histopathology.** Midcoronal kidney sections were immersion fixed in Carnoy’s solution, embedded in paraffin wax, and cut at 4 μm. Sections were stained with hematoxylin and eosin, Masson’s trichrome, or silver salts stain for histologic analysis.

**Immunohistochemistry.** For determination of macrophage localization, sections were incubated in 20% goat serum (ICN Biomedicals, Aurora, OH) in 10% BSA (Sigma-Aldrich, St. Louis, MO). Rat anti-mouse F4/80 (Serotec, Oxford, UK; 1:50 dilution), incubated overnight at 4°C, was used to localize infiltrating macrophages. Between each incubation period, sections were washed in PBS. A biotinylated goat anti-rat secondary antibody (Santa Cruz Biotechnology, Santa Cruz, CA) diluted 1:200 was used. An avidin-biotin complex (Vector Laboratories, Burlingame, CA) was added followed by diaminobenzidine (Sigma-Aldrich) for signal detection. Sections were counterstained with hematoxylin following by immersion in Scott’s tap water.

For determining the localization of type IV collagen, sections underwent antigen retrieval using Proteinase K (10 μg/ml) followed by incubation with 10% goat serum (Zymed Laboratories Inc., San Francisco, CA) in PBS. A goat anti-human collagen IV primary antibody (Southern Biotech, Birmingham, AL; 1:40 dilution) was added for 1 h. Slides were washed in PBS before peroxidase blocking and incubation with biotinylated horse anti-goat IgG (Vector Laboratories; diluted 1:200). Avidin-biotin complex and VIP substrate (Vector Laboratories) were added for signal detection. Sections were counterstained with Methyl Green Solution.

**Estimation of Macrophage Number.** After immunohistochemical localization of macrophages with F4/80, three sections from each kidney were used to determine the number of macrophage nuclear profiles per mm² of kidney. Immunostained slides were projected onto an unbiased stereologic counting frame (19), and nuclear profiles of F4/80-positive cells were counted at a final magnification of ×670. Macrophages were counted in control kidneys and obstructed kidneys from UUO mice, in comparison with R-UUO mice, in which numbers of interstitial macrophages were assessed in both areas of repair and remodeling. Areas of remodeling were defined as having denuded tubular basement membranes and interstitial expansion. Results were expressed as the number of macrophage nuclear profiles/mm² of sectioned kidney.

**Estimation of Volume Density of Cortical Interstitium.** The volume density of interstitium in the renal cortex is a stereologic assessment of cortical interstitial expansion. Midcoronal 3-μm paraffin sections at 200-μm intervals were stained with Masson trichrome as an indicator of collagen deposition in the renal cortex. Sections were projected onto an orthogonal grid, and fields at 1000 μm intervals were sampled at a final magnification of ×670. Only points that landed on the renal cortex were considered. The interstitium was defined as the area between the cortical tubules and glomeruli, excluding blood vessels. Points that fell on interstitium were expressed as a percentage of points that fell on the renal cortex and used to estimate interstitial volume density.

**Estimation of Volume Density of Repaired Kidney.** The volume density of repaired or normal kidney was measured as an assessment of the degree of repair after R-UUO. The sections that were used for estimation of interstitial volume density were projected onto an orthogonal grid using a microtiche, and whole kidney sections were counted at a final magnification of ×24.25. Points that fell on areas of repaired kidney were expressed as a percentage of points that fell on whole kidney and used to estimate repair after R-UUO. Normal kidney tissue was defined as having a distinct tubular epithelium and a brush border membrane, as opposed to the denuded basement membranes and interstitial expansion seen in areas of remodeling and in damaged tubules after UUO.

**Kidney Collagen Content**

Kidney tissue from sham-operated mice (n = 4) and UUO mice (n = 4) and from mice 2 (n = 4) or 6 (n = 3) weeks after R-UUO was used for the determination of kidney collagen content.

**Hydroxyproline Content.** The total collagen content of the kidney was determined by analysis of hydroxyproline content as described previously (20). Hydroxyproline values were converted to collagen content by multiplying by a factor of 6.94 (as hydroxyproline represents approximately 14.4% of the amino acid composition of collagen) (21) and expressed further as a proportion of the tissue dry weight (collagen concentration/dry weight tissue).

**SDS-PAGE Analysis of Kidney Collagen.** The remaining portions of each sample were diced finely in the presence of liquid nitrogen, and the soluble collagen was extracted (20). Samples were centrifuged at 13,000 rpm for 30 min, and the acetic acid supernatant (which contained the soluble collagen) was discarded, whereas the remaining pellet, which contained the mature cross-linked matrix collagen, were freeze-dried, weighed, and subjected to limited pepsin digestion (enzymesubstrate ratio, 1:10) for 24 h at 4°C. The pepsin-digested (collagen) supernatants were collected after centrifugation, freeze-dried, and dissolved in sample loading buffer, as described previously (20).

The collagen chains were analyzed on 5% (wt/vol) acrylamide gels with a stacking gel of 3.5% (wt/vol) acrylamide. The α1(I) chains were separated from the α1(III) collagen chains by interrupted electrophoresis with delayed reduction of the disulfide bonds of type III collagen (22). The gels were stained overnight at 4°C with 0.1% (wt/vol) Coomassie brilliant blue R-250 and de-stained with 30% methanol that contained 7% acetic acid.

**Physiologic Assessment of R-UUO**

C57bl/6J mice that had undergone 10 d of UUO then reversal for 6 wk (n = 11) or a sham operation (n = 10) were anesthetized with 2% isoflurane and placed on a heating table to maintain body temperature at 37.5°C. The left common carotid artery and left jugular vein were catheterized for measurement of mean arterial pressure and the infusion of fluids (1% BSA that contained 3H-inulin at 5.58 μCi/ml; 0.3 ml/h), respectively. After exposure of the kidneys via a midline incision, the left and then right ureters were catheterized (tapered PE-10: 0.58 mm ID, 0.96 mm OD; SIMS Portex, Hythe, UK) to enable determination of individual kidney function. In sham-operated animals, the bladder was catheterized to allow for total GFR measurements. After a 1-h equilibration period, two timed urine collection periods were performed, after which an arterial blood sample was taken. GFR then was calculated by the renal clearance of 3H-inulin. Experiments were performed as a within-animal design with the functional recovery after 6
wk of reversal of obstruction assessed as the GFR of the left R-UUO kidney expressed as a percentage of the GFR of the right kidney.

Bilateral renal function could not be obtained for some animals as a result of shredding of one of the ureters \((n = 3)\) or of difficulties in maintaining catheter patency associated with relatively low single-kidney urine flows and catheter obstruction by urinary crystals in mice \((n = 4)\) (23). In these kidneys, urine flow within the ureter catheter was initiated but could not be maintained long enough to enable clearance measurements.

**Statistical Analyses**

Values are expressed as mean ± SD. Statistically significant differences were defined as \(P < 0.05\). Data were analyzed via a one-way ANOVA with an accompanying Tukey’s post hoc test performing intergroup comparisons. Hydroxyproline and physiologic data are expressed as mean ± SEM. Physiologic data were analyzed using an unpaired \(t\) test.

**Results**

**Structural Analysis**

- **Histopathology.** The 10 d obstructed kidneys from UUO mice showed ablation of the outer medulla with associated cortical medullary tubular atrophy (Figure 1). Dilated proximal tubules, tubules with denuded basement membranes, interstitial expansion, ECM accumulation, and increased numbers of macrophages were observed in the renal cortex. Basement membrane thickening of both tubules and glomeruli was also evident. As early as 1 wk after R-UUO, epithelial replacement of tubular segments in the outer medulla was evident (Figure 1). After R-UUO at 2 and 6 wk, two distinct areas were apparent in the renal parenchyma: One in which tubules had repaired and a normal histoarchitecture of the kidney was evident and a second area in which the same kidneys demonstrated tubular and matrix remodeling and large numbers of infiltrating macrophages (Figure 2). After R-UUO, renal cortical repair and restoration of nephrons was evident in the outer medulla. The

*Figure 1. Photomicrographs of contralateral unobstructed kidney (CUK), unilateral ureteral obstruction (UUO), and reversal of UUO (R-UUO) kidneys. (A) The CUK displays normal histoharchitecture, with distinct cortex, medulla, and renal papilla. (B) After 10 d of UUO, there is an almost complete ablation of the outer renal medulla (arrow) as well as thinning of the renal cortex. (C) UUO kidneys show proximal tubule dilation (*) and extracellular matrix (ECM) accumulation as a result of collagen deposition (arrow). (D) By 1 wk after UUO, there was cellular replacement of the renal medulla (arrow). (E) After 2 wk of R-UUO, the cortex and the medulla show restoration of renal parenchyma. (F) Masson’s Trichrome staining of 6-wk R-UUO kidney in areas of remodeling adjacent to areas that have undergone epithelial cell replacement and ECM remodeling (arrows). Bars = 1250 μm in A, B, D, and E; 50 μm in C; 500 μm in F.*
Figure 2. Schematic diagram of cross-section of repairing kidney showing the two distinct areas of renal parenchyma apparent at 2 wk of R-UUO. Arrows and adjacent letters indicate the area from which the corresponding photomicrograph is taken. Graph shows volume density of normal kidney tissue. After UUO, there is a dramatic reduction in the relative volume of kidney occupied by normal tubules. This increases as early as 1 wk after the R-UUO. By 4 wk after the R-UUO, there is no statistically significant difference in the relative volume of kidney taken up by normal tubules between the sham-operated controls and kidneys after 4 or 6 wk of R-UUO. Asterisks directly above a column indicate P at least <0.05 compared with all other groups. Asterisk above bracket indicates P < 0.05 between these two groups. (A) After 2 wk of R-UUO, many tubules appear normal; however, there remain some areas of interstitial expansion. (B) F4/80 immunohistochemistry of 2-wk R-UUO kidneys show macrophages in areas that are undergoing remodeling; note the distinct boundary between the two areas (arrow). (C) Silver staining shows evidence of glomerular and tubular basement membrane thickening in areas of remodeling after 2 wk of R-UUO (arrows). In areas that have undergone repair, the basement membranes appear normal. (D) In areas of remodeling, silver salts stain shows thickened denuded basement membranes and ECM expansion (arrow). (E) Collagen IV localization to the peritubular interstitium in sham-operated kidneys (arrow). (F) Accumulated type IV collagen is evident in the interstitium of areas of remodelling (arrow) compared with the areas of the R-UUO kidneys that had undergone re-epithelialization of renal tubules associated with reduced interstitial expansion. Bars = 50 μm in A, E, and F; 200 μm in B; 150 μm in C; 30 μm in D.
denuded basement membranes were found to have re-established their epithelium, and the outer medulla, as well as the cortex, showed restoration of the tubular epithelium by 2 and 6 wk after R-UUO.

Estimation of Macrophage Number and Localization. Macrophages were observed in relatively low numbers in the interstitium of sham-operated kidneys (285.7 ± 56.8/mm²; Figure 3A). After UUO, there was a dramatic increase in macrophage numbers (1595.6 ± 154.0/mm²; P < 0.001 compared with sham), particularly in the periglomerular and peritubular interstitium. By 2 wk of R-UUO, numbers of macrophages had significantly decreased compared with obstructed kidneys of UUO mice (1043.0 ± 246.4/mm²; P < 0.05). After 2 wk of R-UUO, there was a progressive decline in the numbers of macrophages observed in the previously obstructed kidney of R-UUO mice. However, elevated numbers of macrophages were observed in the focal areas of the kidney being remodeled after R-UUO when compared with areas that had undergone repair (2458.4 ± 393.7/mm² versus 575.0 ± 202.6/mm²; P < 0.01; Figure 3A). By 6 wk of R-UUO, there were fewer macrophages observed in focal areas of remodeling than there was in these areas at the 1, 2, or 4 wk time points (P < 0.05).

Estimation of Renal Cortical Interstitial Matrix Expansion. The volume density of interstitium in the renal cortex was measured in all experimental groups as an assessment of the degree of interstitial fibrosis (Figure 3B). There was no difference between sham and CUK kidneys (5.26 ± 1.23 versus 8.71 ± 1.81%; P > 0.05). However, the obstructed kidneys from 10d UUO mice demonstrated a significantly greater interstitial volume density compared with the CUK (29.81 ± 4.40 versus 8.71 ± 1.81%; P < 0.001). After 1 wk of R-UUO, the interstitial volume density was lower than that of the obstructed kidney from mice that underwent 10 d of UUO alone (22.88 ± 1.19 versus 29.81 ± 4.40%; P < 0.05). There was a further reduction in interstitial volume density at 2 wk of R-UUO (17.13 ± 2.95%). However, there was no change in cortical interstitial volume density between 2 wk of R-UUO and mice that were allowed to recover for either 4 (13.25 ± 1.96%) or 6 wk (13.12 ± 1.73%) after R-UUO.

Estimation of Tubular Repair. There were no regions of tubular damage in sham-operated or CUK (volume density of repaired or normal kidney = 100%; Figure 2). There was a dramatic decrease in the volume density of normal kidney tissue after 10 d of UUO (32.6 ± 7.3%; P < 0.001). After 1 wk of R-UUO, there was a significant restoration in the relative volume of kidney occupied by repaired tissue (54.7 ± 17.9%; P < 0.05) as assessed by tubular epithelization and presence of a brush border membrane. There was a further increase at 2 wk of R-UUO (78.6 ± 6.9%; P < 0.01). By 6 wk of R-UUO, there was no statistically significant difference in the volume density of kidney occupied by repaired tubules compared with sham-operated controls (83.7 ± 5.9 versus 100%).

Immunohistochemistry of Type IV Collagen Localization. Type IV collagen localization was seen as a delicate framework in the peritubular interstitium of sham-operated kidneys (Figure 2). After 10 d of UUO, type IV collagen accumulation was observed in the glomerular and tubular interstitium of obstructed kidneys from UUO mice. After R-UUO, type IV collagen accumulation was evident in the tubular and glomerular interstitium in areas that underwent remodeling (Figure 2).

Kidney Collagen Content. A three-fold increase (P < 0.001) in collagen concentration (collagen content/dry weight tissue) was found in the obstructed kidneys from mice that underwent 10 d of UUO in comparison with CUK and sham controls (Figure 4A). This was confirmed by SDS-PAGE analysis, which demonstrated a marked increase in collagen types I, III, and V in obstructed kidneys of R-UUO mice.
The inherent ability of the kidney to recover from ureteral ligation provides insight into mechanisms underlying renal repair. We have established a mouse model of R-UUO resulting in the development of tubulointerstitial fibrosis followed by the resolution of tubular injury and decreased interstitial matrix expansion. The obstructed kidney from 10 d UUO mice demonstrated tubular atrophy; interstitial expansion; types I, III, IV, and V collagen accumulation; and ablation of the outer medulla. By 6 wk after R-UUO, decreased interstitial volume density and collagen content, reduced numbers of macrophages, and epithelial cell replacement of the medullary nephrons were observed. Using bilateral renal function techniques for the first time in mice, this study also demonstrates that 6 wk after R-UUO, these kidneys were capable of glomerular filtration and urine concentration, indicating concomitant functional reversal.

**Table 1. Whole animal comparisons between sham and R-UUO groups**

<table>
<thead>
<tr>
<th></th>
<th>Sham</th>
<th>R-UUO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>27 ± 2</td>
<td>29 ± 1</td>
</tr>
<tr>
<td>Total kidney weight (g)</td>
<td>0.350 ± 0.014</td>
<td>0.385 ± 0.017</td>
</tr>
<tr>
<td>Urine flow (µl/min)</td>
<td>0.942 ± 0.166</td>
<td>0.870 ± 0.207</td>
</tr>
<tr>
<td>GFR (µl/min)</td>
<td>124.8 ± 9.2</td>
<td>102.6 ± 19.5</td>
</tr>
<tr>
<td>FE urine (%)</td>
<td>0.78 ± 0.15</td>
<td>0.81 ± 0.07</td>
</tr>
<tr>
<td>n</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

*R-UUO, reversal of unilateral ureteral obstruction; FE, fractional excretion of urine. Values for R-UUO animals are the combined total for the left and right kidneys. Values are mean ± SEM.
Table 2. Bilateral renal function in 6-wk R-UUO animals

<table>
<thead>
<tr>
<th>Mouse</th>
<th>Body Weight (g)</th>
<th>MAP (mmHg)</th>
<th>Kidney Weights (g)</th>
<th>Urine Flow (μL/min)</th>
<th>GFR (μL/min)</th>
<th>FE Urine (%)</th>
<th>L-UUO GFR Capacity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>199</td>
<td>27</td>
<td>67</td>
<td>0.185</td>
<td>0.181</td>
<td>0.102</td>
<td>0.161</td>
<td>20.9</td>
</tr>
<tr>
<td>212</td>
<td>31</td>
<td>78</td>
<td>0.162</td>
<td>0.200</td>
<td>0.300</td>
<td>0.677</td>
<td>34.3</td>
</tr>
<tr>
<td>563</td>
<td>29</td>
<td>77</td>
<td>0.217</td>
<td>0.219</td>
<td>0.501</td>
<td>0.680</td>
<td>42.7</td>
</tr>
<tr>
<td>564</td>
<td>28</td>
<td>73</td>
<td>0.187</td>
<td>0.188</td>
<td>0.500</td>
<td>0.561</td>
<td>56.4</td>
</tr>
<tr>
<td>Mean</td>
<td>29</td>
<td>74</td>
<td>0.188</td>
<td>0.187</td>
<td>0.351</td>
<td>0.518</td>
<td>38.6</td>
</tr>
<tr>
<td>SEM</td>
<td>1</td>
<td>3</td>
<td>0.011</td>
<td>0.008</td>
<td>0.096</td>
<td>0.106</td>
<td>7.4</td>
</tr>
</tbody>
</table>

*Parameters for individual 6-wk R-UUO mice in which bilateral renal function was obtained. MAP, mean arterial pressure; L-UUO GFR Capacity, GFR of left R-UUO kidney expressed as % of GFR of right kidney; L-RUUO, left kidney 6 wk after R-UUO; R-CUK, the contralateral unobstructed kidney 6 wk after R-UUO.

The obstructed kidney from 10 d UUO mice showed ablation of the outer medulla in conjunction with cortical and medullary tubular atrophy. There was a progressive increase in the relative volume of kidney that had undergone recovery after R-UUO, as evidenced by the re-establishment of proximal tubule epithelium and brush border membrane. Previous studies in the rat have observed that repair after R-UUO depends on the presence of nonatrophied nephrons located in the core of the kidney (24). Until recently, epithelial cells were thought to regenerate by in situ proliferation and migration along denuded basement membranes (25). More recently, the plasticity of tubular and glomerular cells and bone marrow–derived cells to express a range of phenotypes during renal remodeling has gained considerable interest (26). Areas of remodeling in the R-UUO kidneys showed denuded basement membranes, macrophage infiltration, and collagen accumulation. The integrity of tubular basement membranes, expression of integrins and growth factors, and synthesis of type IV collagen all are important factors for successful cell repair and reattachment (27).

In our study, macrophages were evident in large numbers associated with areas of active remodeling in kidneys after R-UUO. The profibrotic role of macrophages is well documented (28). Macrophages secrete a variety of proinflammatory cytokines, including TGF-β, which promotes collagen I, III, and IV production. In addition mice that lack the macrophage chemoattractant osteopontin have a reduced macrophage infiltrate into the kidney that is associated with decreased collagen expression after both ureteral obstruction and ischemia/reperfusion injury (29,30). The alternative activation of macrophages by IL-4 and IL-13 induces a variety of beneficial responses, including the generation of anti-inflammatory cytokines and chemokines, matrix synthesis and stabilization, cell survival and proliferation, and angiogenesis (31,32). Macrophages may be important in the regeneration of tubular epithelial cells (33).

As large defects in the GFR of one kidney are often compensated for by hyperfiltration of the contralateral kidney such that whole animal GFR is normal, we performed bilateral renal function measurements for the first time in mice to examine the degree of functional repair in these kidneys after R-UUO. Mice that had undergone 6 wk of R-UUO demonstrated significant but variable recovery of GFR in the L-RUUO kidney. Furthermore, the normal fractional excretion of urine in the R-UUO kidney is consistent with functional repair of the tubular epithelium of filtering nephrons preventing excessive loss of water and electrolytes. This is in accordance with our stereologic analysis of structural repair indicating that in mice after 6 wk of R-UUO, 84% of the kidney displays normal histologyarchitecture as evidenced by tubular re-epithelization and the presence of a brush border membrane. Whereas L-RUUO kidneys of two animals showed almost normal GFR values (88 and 84%), the L-RUUO kidneys of two animals showed only modest GFR values of approximately 50% of the R-CUK.

Previous studies in adult rats have shown the ability of the postobstructed kidney to return to a normal GFR 4 wk after the reversal of 3 d of UUO (9). Longer term obstruction, however, has led to only a partial recovery of renal function after the relief of UUO (34,35). Recovery of GFR after UUO is most likely dependent on several factors, including the duration of obstruction with studies in neonatal rats suggesting that early relief of obstruction in the developing kidney allows greater preservation of renal function (17,36). Clinically, recovery of renal function after relief of obstruction has been linked to patient age, duration of obstruction, function of the contralateral kidney, and compliance of the ureter and renal pelvis (37).

This study presents the first description of the structural and functional regenerative potential of the adult mouse kidney after interstitial expansion, inflammatory cell infiltration, and medullary ablation associated with UUO in the mouse. Macrophages are shown to be a major cell type associated with both regions of damage and repair. The characterization of the model of R-UUO in the mouse has been used to gain a better understanding of the key events involved in endogenous cellular repair and ECM remodeling.

Acknowledgments

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