Nature and Severity of the Glomerular Response to Nephron Reduction Is Strain-Dependent in Mice

Ciro Esposito,* Ci-Jiang He,* Gary E. Striker,[†]
Rudolfs K. Zalups,[‡] and Liliane J. Striker[†]

From the Division of Nephrology,* IRCCS Policlinico San Matteo, University of Pavia, Pavia, Italy, Renal Cell Biology Laboratory,[†] Department of Medicine, University of Miami School of Medicine, Miami, Florida, and Division of Basic Medical Sciences,[‡] Mercer University, School of Medicine, Macon, Georgia

**Nephron reduction is an important factor in the development of glomerulosclerosis. In a study of the oligosyndactyly (Os) mutation that causes a congenital 50% reduction in nephron number, we previously found that ROP Os/+ mice developed glomerulosclerosis whereas C57Bl/6J Os/+ mice did not. We concluded that the predisposition to glomerulosclerosis depended largely on the genetic background, the ROP being sclerosis-prone whereas the C57 strain was sclerosis-resistant. In the current experiments we asked whether the intensity of the sclerotic response to nephron reduction in the ROP strain was related to the time at which it occurred, ie, a pre- or post-natal event. We also determined whether the absence of lesions in C57 Os/+ mice was caused by a higher threshold for the induction of a sclerotic response in C57 mice. We further examined the relationship between glomerular hypertrophy and sclerosis. C57 +/+, C57 Os/+, ROP +/+, and ROP Os/+ mice were uninephrectomized (NX) at age 10 weeks and followed for 8 weeks. We found no sclerotic changes in NX C57 +/+ and C57 Os/+ mice, despite a 75% reduction in nephron number in the latter. In contrast, both NX ROP +/+ and NX ROP Os/+ mice had glomerulosclerosis, which was more severe in the NX ROP Os/+ mice. Examination of extracellular matrix synthesis and degradation at the mRNA level revealed that synthesis exceeded degradation in ROP Os/+ mice. The lesions in NX ROP +/+ were less severe than in sham-operated ROP/Os mice, suggesting that the timing of nephron reduction affected the amplitude of the sclerotic response in this strain. Following NX, an increase in glomerular volume was found in C57 +/+, ROP +/+, and ROP Os/+ mice. However, NX did not lead to a further increase in glomerular volume in C57 Os/+ mice. We make three conclusions: 1) sclerosis was more severe in the ROP strain when nephron reduction occurred *in utero*; 2) the absence of glomerulosclerosis in C57 mice was not related to a higher threshold for a sclerosis response in this strain; and 3) whereas glomerular size continued to increase as nephron number decreased in ROP mice, it reached a plateau in C57 mice.   *(Am J Pathol 1999, 154:891–897)*

Because the shortage of cadaver kidneys has prompted an increase in the use of kidneys from living donors for transplantation,[1] it is important to know whether this practice places donors at risk.[2–6] Many,[5,6] but not all,[2–4] retrospective studies have demonstrated that adult donors do not have a significant decline of renal function in follow-up periods of up to 45 years. It is possible that the risk to the donor depends on their susceptibility to a reduction in renal mass. In fact, patients undergoing unilateral nephrectomy who have a family history of renal disease and hypertension appear to carry a higher risk of long-term renal insufficiency than those without familial antecedents.[7] There is increasing evidence that genetic factors play an important role in the development of a large number of glomerular diseases.[8–10] Furthermore, we recently found that the renal response to an inborn deficit in nephron number was strain-dependent.[11] We studied renal lesions in sclerosis-prone (ROP) and sclerosis-resistant (C57) mice carrying a radiation-induced mutation associated with a 50% reduction in nephron number and oligosyndactyly (the Os mutation).[11] ROP Os/+ mice had glomerular hypertrophy and glomerulosclerosis at age 3 months with an increase in both cell turnover rate and extracellular matrix (ECM) synthesis.[12] In contrast, C57 Os/+ mice developed only minimal glomerulosclerosis, despite an identical reduction in nephron number and an equal increase in both glomerular size and glomerular cell-labeling index.[11] These data suggested that whereas hypertrophy and increased cell turnover were common responses to congenital nephron reduction, the development of glomerulosclerosis was largely dependent upon the genetic background. In the current study, we asked whether nephrectomy in adulthood induced an equal sclerotic response in ROP and C57 mice, whether the sclerotic response in ROP mice to nephron reduction in adults resembled that *in utero*, if the lack of a sclerotic response in C57 mice was because the

threshold for sclerosis-induction had not been reached in our previous experiments, and if there was a relationship between glomerular hypertrophy and glomerulosclerosis.

Materials and Methods

Experimental Design

Female ROP Os/+ (ROP/Le-*Os Es*[1b]/+ *Es*[1a]), ROP +/+, C57 Os/+ (C57BL/6J-Os +/+ *Cchala*[tg-la]) and C57 +/+ mice were obtained from Jackson Laboratories (Bar Harbor, Maine). ROP +/+ and C57 +/+ littermates served as controls for ROP Os/+ and C57 Os/+ mice. The left kidney was removed at age 10 weeks in each group as described.[13] Control mice matched for age, sex, and strain were sham operated. Nephrectomized (NX) and sham-operated mice were fed standard diet throughout the experimental period. Each group consisted of six animals, and they were sacrificed according to NIH approved procedures either 2 weeks or 8 weeks after NX, at which time they were 12 weeks or 18 weeks old. After removing one pole for light microscopy, the remainder of the solitary kidney was perfused with a buffer containing 0.1% collagenase and RNase inhibitors for glomerular microdissection and molecular analysis as described previously.[14]

Light Microscopy

Kidney sections were fixed in Carnoy's fixative, embedded in glycol methacrylate, cut at a thickness of 2 μm and stained with hematoxylin/eosin (H&E) and periodic acid-Schiff (PAS). One investigator examined the sections without knowledge of the experimental groups to eliminate experimental bias. Mesangial sclerosis was graded using a scale from 0 to 4+ as described previously.[10] Forty glomeruli per section were examined in six mice from each group, and the mean of scores for individual glomeruli was recorded. Arteries were examined, and the number affected was expressed as a percent of the total. The interstitial changes were mild and not quantitated.

Light Microscopic Morphometry

Glomerular volume was assessed by examining plastic-embedded sections using a digitizing tablet and video camera, as described previously.[15] The mean glomerular volume was derived from the harmonic mean of the glomerular equatorial surface area.

Glomerular Cell Number and Turnover (18-Week Mice Only)

The nuclei of 50 consecutive glomerular profiles were counted by scanning H&E-stained tissue sections in a serpentine fashion. The relative glomerular cell number was calculated as described previously.[15] The labeling index was determined using [^{3}H]thymidine incorporation and autoradiography. A cell was considered labeled when the number of grains per nucleus exceeded 3 to 4. The glomerular-labeling index was calculated by counting 50 successive glomeruli per section and expressed as the percentage of labeled cells (excluding Bowman's capsular cells) divided by the total glomerular cell number.

Isolation of Glomeruli and Reverse Transcription in Situ

Glomeruli were isolated by microdissection at 4°C in a solution containing RNase inhibitors.[14] After sonication, cDNA was obtained by *in situ* reverse transcription.

Competitive Polymerase Chain Reaction (PCR)

The primers for mouse α1 type IV collagen, laminin β1, tenascin, β-actin, and 72 kd collagenase were previously described.[14,16] The expected PCR products were 484 bp for α1 type IV collagen, 443 bp for laminin β1, 460 bp for β-actin, 701 bp for 72 kd collagenase, and 548 bp for tenascin. Decreasing amounts of mutant template competed for specific primers with a fixed amount of the test glomerular cDNA during PCR amplification. The ratio of mutant to cDNA band density was calculated by laser densitometry and plotted as a function of the initial amount of mutant template added to the reaction. The amount of glomerular cDNA was derived from linear regression analysis. Duplicate or triplicate assays were performed. The mean values obtained for all mice were expressed as attomol $\times 10^{-4}$/glomerulus. All reverse transcription (RT)-PCR data were normalized to β-actin and the results expressed as ratios.

Statistical Analysis

All values were expressed as mean $\pm$ SD. The two-tailed unpaired Student's *t*-test was used to evaluate differences between means for corresponding sets of data obtained from oligosyndactyly (Os) and control mice. As level of significance $P < 0.05$ was chosen.

Results

Body Weight and Glomerular Volume (Table 1)

Body weight did not differ between nephrectomized and sham-operated mice at either 2 weeks or 8 weeks post-NX. There was a significant increase (30 to 40%) in glomerular volume in ROP +/+ and C57 +/+ mice 2 weeks and 8 weeks post-NX ($P < 0.01$). There was no change in glomerular volume 2 weeks post-NX in either ROP Os/+ or C57 Os/+ mice. Whereas there was an increase in glomerular volume in ROP Os/+ mice (54%) 8 weeks post-NX, there were no differences between sham and NX C57 Os/+ mice 8 weeks post-NX.

Table 1.   Body Weight and Glomerular Volume

Age		ROP +/+	C57 +/+	ROP Os/+	C57 Os/+
12 weeks (2 weeks after NX)					
Body weight (g)	Sham	19.9 ± 1.2	19.7 ± 0.4	20.6 ± 0.97	18.9 ± 2.1
	NX	19.9 ± 1.6	19.1 ± 0.7	18.8 ± 0.8	18.0 ± 1.1
GV (×10^5 μm^3)	Sham	2.19 ± 0.35	2.01 ± 0.34	4.31 ± 0.26†	4.02 ± 0.81†
	NX	2.83 ± 0.6*	2.85 ± 0.3*	4.32 ± 0.76†	4.34 ± 0.28†
18 weeks (8 weeks after NX)					
Body weight (g)	Sham	20.3 ± 1.3	21.3 ± 0.89	22.3 ± 1.7	22.9 ± 1.6
	NX	21.9 ± 1.8	22.4 ± 0.94	23.1 ± 1.1	23.5 ± 1.3
GV (×10^5 μm^3)	Sham	2.54 ± 0.34	2.17 ± 0.29	6.20 ± 0.81†	6.75 ± 0.72†
	NX	3.75 ± 0.3*	2.82 ± 0.5*	9.5 ± 1.4*†‡	7.15 ± 0.83*†

Body weight was measured before sacrifice. Glomerular volume was measured as described. There were six experimental mice in each group.
*P < 0.05, nephrectomized mice *versus* sham controls.
†P < 0.01, C57 Os/+ sham *versus* C57 +/+ sham (either at 2 weeks and at 2 months), C57 Os/+ NX *versus* C57 +/+ NX (either at 2 weeks and at 2 months), ROP Os/+ sham *versus* ROP +/+ sham (either at 2 weeks and at 2 months), ROP Os/+ NX *versus* ROP +/+ NX (either at 2 weeks and at 2 months).
‡P < 0.01, ROP Os/+ NX *versus* C57 Os/+ NX.

Light Microscopy (Table 2)

C57 +/+ Mice

There were no glomerular, tubulointerstitial, or vascular changes in sham or nephrectomized mice except for the increase in size in the NX group.

ROP +/+ Mice

Sham operated mice had a slight increase in the amount of PAS-stained material in the mesangial areas of 50% of glomeruli, which was most noticeable in the vicinity of the vascular pole 8 weeks post-NX (score: 0.6 ± 0.4). Two weeks after nephrectomy, the mesangial sclerosis was unchanged in ROP +/+ mice. Eight weeks post-NX, the mesangial matrix score was 0.9 ± 0.15. The sclerotic glomeruli were found distributed throughout the cortex. There were no tubulointerstitial or vascular lesions (Figure 1).

C57 Os/+ Mice

As reported previously, there was a minimal increase in the mesangial matrix in sham-operated mice (score: 1.2 ± 0.5), similar to values found in non-nephrectomized control mice.[11] There was no significant change in mice post-NX (score: 1.3 ± 0.6).

ROP Os/+ Mice

Twelve- and 18-week-old sham-operated ROP Os/+ mice had glomerular lesions (score 2.23 ± 0.26 and 2.7 ± 0.2, respectively), similar to nonoperated mice previously described.[12] At 8 weeks post-NX most glomeruli exhibited increased mesangial sclerosis. In the more severely affected glomeruli there was a marked decrease in the patency of the vascular loops, apparently caused by the presence of large subendothelial masses of hyalin material (score: 3.75 ± 0.1). A small number of arterioles showed smooth muscle and intimal cell prolif-

Table 2.   Histological Score

Age		ROP +/+	C57 +/+	ROP Os/+	C57 Os/+
12 weeks (2 weeks after NX)					
Glomeruli	Sham	0.6 ± 0.3	0.35 ± 0.2	2.23 ± 0.26†	1.2 ± 0.5‡
	NX	0.64 ± 0.2	0.33 ± 0.1	2.80 ± 0.6†	1.2 ± 0.5‡
Blood vessels	Sham	0.15 ± 0.1	0.08 ± 0.1	0.32 ± 0.2	0.25 ± 0.08
	NX	0.13 ± 0.11	0.12 ± 0.11	0.25 ± 0.18	0.21 ± 0.12
Interstitium	Sham	0.15 ± 0.1	0.17 ± 0.2	0.31 ± 0.2	0.2 ± 0.18
	NX	0.16 ± 0.1	0.2 ± 0.1	0.24 ± 0.08	0.3 ± 0.2
18 weeks (8 weeks after NX)					
Glomeruli	Sham	0.85 ± 0.2	0.35 ± 0.2	2.7 ± 0.2*	1.2 ± 0.5‡
	NX	0.9 ± 0.15	0.33 ± 0.1	3.75 ± 0.1†	1.32 ± 0.6‡
Blood vessels	Sham	0.2 ± 0.09	0.18 ± 0.1	1.1 ± 0.3†	0.29 ± 0.18
	NX	0.19 ± 0.13	0.13 ± 0.1	1.2 ± 0.25†	0.34 ± 0.16
Interstitium	Sham	0.16 ± 0.17	0.16 ± 0.1	0.35 ± 0.2	0.2 ± 0.18
	NX	0.17 ± 0.15	0.21 ± 0.15	0.31 ± 0.16	0.3 ± 0.2

Glomerular, vascular, and tubulointerstitial lesions were graded on a scale from 0 to 4 according to the extent of the involvement. Six mice were studied for each group.
*P < 0.001, ROP Os/+ 2 months sham *versus* ROP +/+ 2 months NX.
†P < 0.001, ROP Os/+ 2 weeks sham *versus* C57 Os/+ 2 weeks sham, ROP Os/+ 2 weeks NX *versus* C57 Os/+ 2 weeks NX. ROP Os/+ 2 months sham *versus* C57 Os/+ 2 months sham, ROP Os/+ 2 months NX *versus* C57 Os/+ 2 months NX.
‡P < 0.05, C57 Os/+ sham and C57 Os/+ NX *versus* C57 +/+ sham and C57 +/+ NX respectively.

ROP +/+   C57 +/+
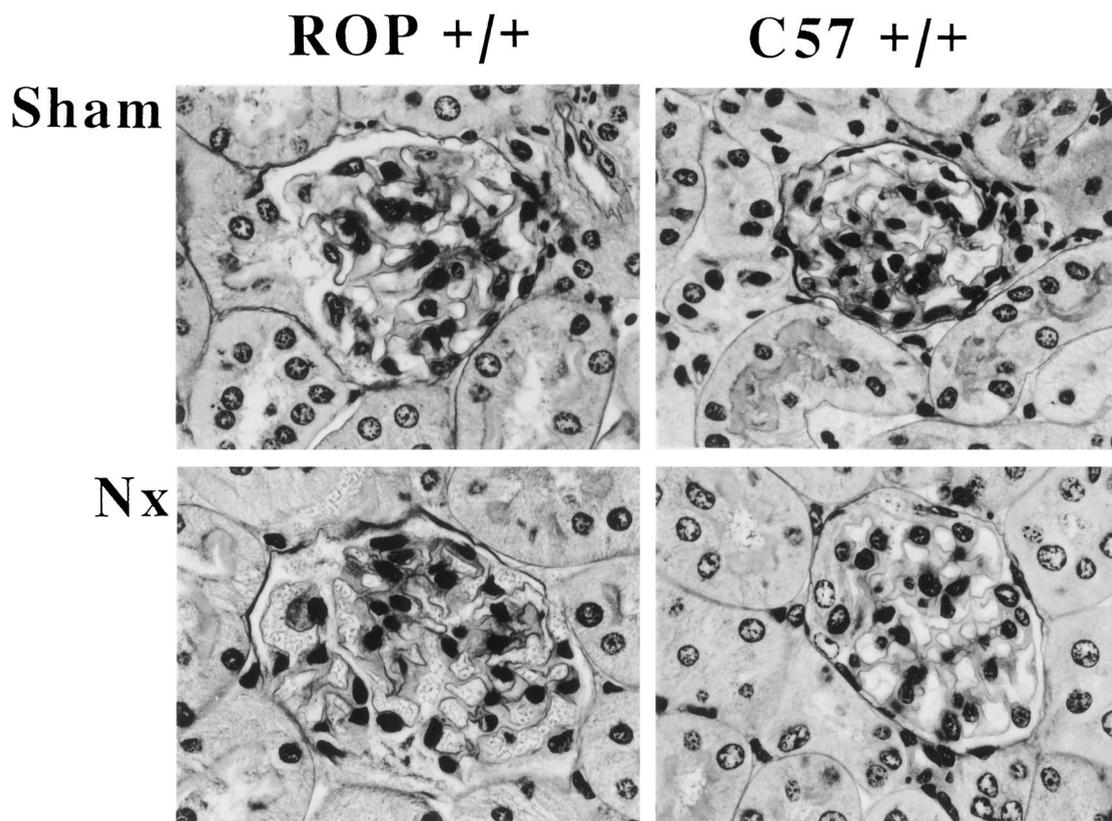
Figure 1. Light microscopy. Methacrylate-embedded sections were stained by periodic acid-Schiff methenamine (×400). Sections of C57 +/+ and ROP +/+ mice sacrificed 2 months after NX are shown.

eration with reduction of the lumen. There were no tubulointerstitial lesions (Figure 2).

Glomerular Cell Number and Turnover

Glomerular cell number and labeling index were determined 8 weeks post-NX (Table 3).

ROP +/+ and C57 +/+ Mice

There was no change in the mean cell number per glomerulus between nephrectomized and sham-operated mice, despite an increase in glomerular volume in both groups of mice. Approximately 30% of the labeled cells were situated on the external surface of the glomerular tufts. It was not possible to differentiate between mesangial and endothelial cell labeling within the tufts.

ROP Os/+ and C57 Os/+ Mice

Sham-operated ROP Os/+ and C57 Os/+ mice had a higher labeling index than ROP +/+ and C57 +/+ mice. As noted above, approximately 30% of the labeled cells were situated on the external surface of the glomerular tufts. There was no increase in the labeling index post-NX in either ROP Os/+ or C57 Os/+ mice.

While there was an increased number of cells in the enlarged glomeruli of both ROP Os/+ and C57 Os/+

mice compared with littermates without the Os gene, no further increase was found post-NX. Glomerular cell number did not change in ROP Os/+ mice post-NX, despite a further increase in glomerular volume (Table 1).

Glomerular mRNA Levels

Glomerular $\alpha 1$ IV collagen, laminin $\beta 1$, tenascin, and 72 kd collagenase mRNAs, measured by competitive PCR, were normalized to β-actin mRNA levels (Table 4).

ROP +/+ and C57 +/+ Mice

There was a significant increase in $\alpha 1$ IV collagen mRNA at both 2 and 8 weeks post-NX in ROP +/+ and C57 +/+ mice. The levels were higher in ROP +/+ than in C57 +/+ mice at 8 weeks post-NX ($P < 0.05$). There was no significant change observed in laminin $\beta 1$ and tenascin mRNA levels at either 2 or 8 weeks post-NX. There was a significant increase in 72 kd collagenase mRNA levels 8 weeks post-NX in both groups of mice.

ROP Os/+ and C57 Os/+ Mice

The levels of $\alpha 1$ IV collagen mRNA were higher in both groups of mice compared with their non-Os littermates, as we had previously found.[11] In addition, the laminin $\beta 1$ and tenascin mRNA levels were higher in ROP Os/+

ROP Os/+   C57 Os/+
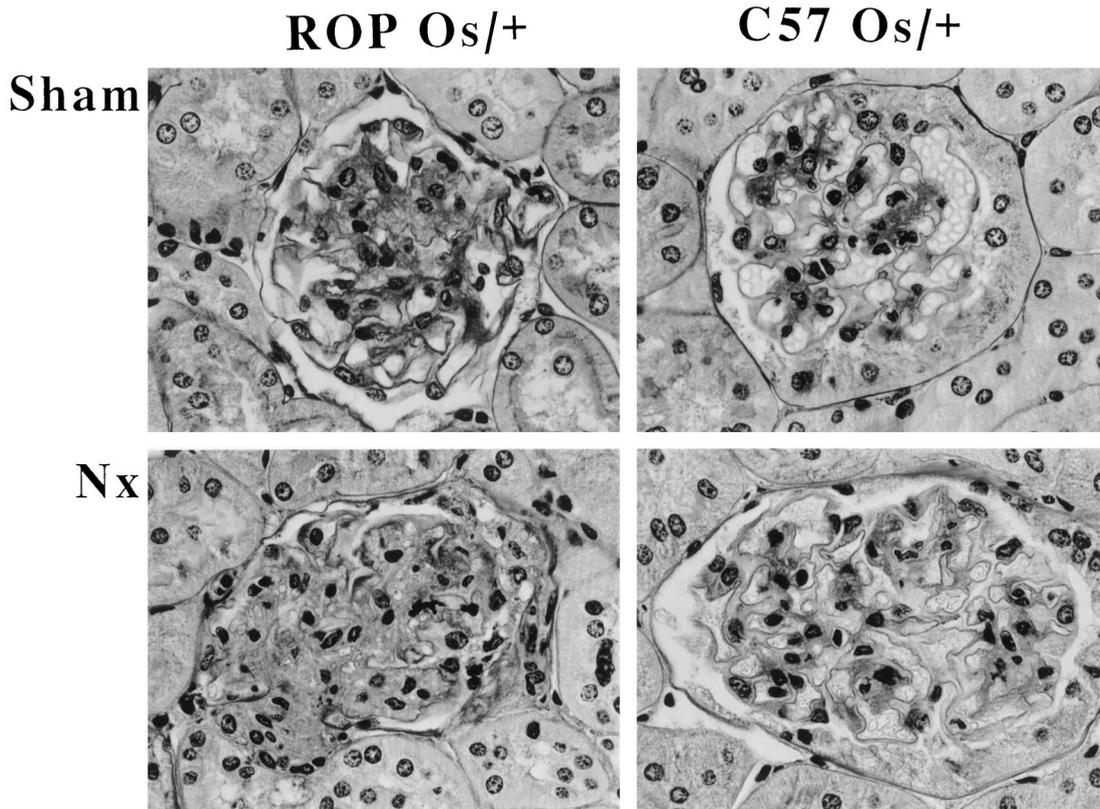
Figure 2. Light microscopy. Methacrylate-embedded sections were stained by periodic acid-Schiff methenamine (×400). Sections of C57 Os/+ and ROP Os/+ mice sacrificed 2 months after NX are shown.

compared with ROP +/+ mice, as shown previously.[12] There was a significant increase in α1 IV collagen, laminin, and tenascin mRNAs in ROP Os/+ mice but not in C57 Os/+ mice 8 weeks post-NX. 72 kd collagenase mRNA levels were slightly but significantly increased in both ROP Os/+ and C57 Os/+ mice at 8 weeks post-NX.

Discussion

We previously studied mice with a mutation (Os) causing a 50% reduction in nephron number during development and showed that glomerulosclerosis occurred in sclerosis-prone mice (ROP +/+), but not in sclerosis-resistant mice (C57).[11] In the current study we show that when a 50% reduction in nephron number was induced by uni-nephrectomy in adult mice, glomerulosclerosis occurred only in the sclerosis-prone mouse strain. This finding was independent of the presence of the Os gene. Interest-

ingly, ROP Os/+ mice had more severe lesions than ROP +/+ mice, which had been nephrectomized as adults, despite the fact that both had a 50% reduction in nephron number. The cause of this difference is not known, but it has been previously found that the response to nephrectomy is age dependent.[17] The fact that glomerulosclerosis was found only in the sclerosis-prone strain carrying the Os gene, provided evidence that this mutation was not directly associated with the sclerotic lesions.

We found that the lack of a sclerotic response in the resistant strain (C57) was not a threshold effect, because even a 75% reduction in nephron number did not induce sclerosis. Although nephrectomy did not induce significant sclerosis in C57 mice at either the histological or ECM mRNA levels, glomerular volume and labeling index were both increased. Thus, cell turnover, glomerular hypertrophy, and the accumulation of ECM were not tightly linked. This is consistent with our previous *in vivo* and *in*

Table 3.   Glomerular Cell Number and Labeling Index

Age: 18 weeks (8 weeks after NX)		ROP +/+	C57 +/+	ROP Os/+	C57 Os/+
Cells/50 glomeruli	Sham	2429 ± 181	2599 ± 319	3276 ± 411†	3139 ± 400
	NX	2396 ± 223	2379 ± 123	3132 ± 146†	3403 ± 101†
Labeled cells (%)	Sham	0.26 ± 0.06	0.29 ± 0.03	0.78 ± 0.25†	0.76 ± 0.28†
	NX	0.64 ± 0.1*	0.54 ± 0.1*	0.84 ± 0.18	0.80 ± 0.05

Glomerular cell number and labeling index were measured as described. Data are means of six experimental mice per group.
*$P < 0.001$; ROP +/+ NX and C57 +/+ NX *versus* sham-operated littermates.
†$P < 0.001$; ROP Os/+ NX *versus* ROP +/+ NX, ROP Os/+ sham *versus* ROP +/+ sham, C57 Os/+ NX *versus* C57 +/+ NX, C57 Os/+ sham *versus* C57 +/+ sham.

Table 4. Glomerular mRNA Levels (Competitive PCR)

Age		ROP +/+	C57 +/+	ROP Os/+	C57 Os/+
12 weeks (2 weeks after NX)					
α1-IV collagen	Sham	0.61 ± 0.16	0.66 ± 0.30	1.38 ± 0.27	0.87 ± 0.17
	NX	1.13 ± 0.3*	0.84 ± 0.1*	1.29 ± 0.21	1.02 ± 0.10
Laminin β1	Sham	0.19 ± 0.17	0.10 ± 0.04	0.26 ± 0.08†	0.13 ± 0.04
	NX	0.23 ± 0.07	0.12 ± 0.04	0.26 ± 0.05†	0.12 ± 0.03
Tenascin	Sham	1.00 ± 0.10	1.75 ± 0.44	2.38 ± 0.3†‡§	1.80 ± 0.23
	NX	1.25 ± 0.20	1.48 ± 0.26	2.88 ± 0.56‡	2.27 ± 0.30
72 kd collagenase	Sham	0.44 ± 0.19	0.56 ± 0.16	0.60 ± 0.23	0.71 ± 0.14
	NX	0.45 ± 0.12	0.47 ± 0.13	0.77 ± 0.22	0.63 ± 0.17
18 weeks (8 weeks after NX)					
α1 IV collagen	Sham	0.66 ± 0.08	0.51 ± 0.160	1.23 ± 0.1†‡	0.78 ± 0.20
	NX	1.2 ± 0.14*	0.80 ± 0.16*	2.17 ± 0.4*‡	0.97 ± 0.13
Laminin β1	Sham	0.21 ± 0.02	0.13 ± 0.03	0.29 ± 0.07	0.19 ± 0.04
	NX	0.28 ± 0.07	0.16 ± 0.06	0.58 ± 0.1*†‡	0.25 ± 0.07
Tenascin	Sham	1.40 ± 0.05	1.81 ± 0.45	1.88 ± 0.25‡	1.87 ± 0.15
	NX	1.52 ± 0.23	1.42 ± 0.22	3.02 ± 0.1*†‡	2.01 ± 0.26‡
72 kd collagenase	Sham	0.35 ± 0.03	0.35 ± 0.09	0.59 ± 0.09‡	0.61 ± 0.16‡
	NX	0.54 ± 0.1*	0.52 ± 0.1*	0.75 ± 0.16‡	0.90 ± 0.15‡

Competitive PCR was performed as described. The means of six experimental mice for each group are shown. Data represent means of the ratio of the indicated molecule to β-actin.

*$P < 0.05$; when NX mice were compared with sham control mice and when ROP +/+ NX mice were compared with C57 +/+ NX mice at 2 months.

†$P < 0.05$; ROP Os/+ 2 weeks sham *versus* C57 Os/+ 2 weeks sham, ROP Os/+ 2 weeks NX *versus* C57 Os/+ 2 weeks NX, ROP Os/+ 2 months sham *versus* C57 Os/+ 2 months sham, ROP Os/+ 2 months NX *versus* C57 Os/+ 2 months NX.

‡$P < 0.05$; when ROP Os/+ and C57 Os/+ mice were compared with ROP +/+ and C57 +/+, respectively.

§$P <$ ROP Os/+ 2 weeks sham *versus* ROP +/+ 2 weeks NX.

vitro data and that of others.[11,18,19] There was an increase in α1 IV collagen mRNA in both C57 +/+ and ROP +/+ mice at both 2 and 10 weeks NX, the increase being higher in the ROP +/+ mice at 10 weeks.

Glomerular hypertrophy has been proposed to be an important factor in the development of glomerulosclerosis in rats and mice.[9,13,20,21] In mice transgenic for bovine growth hormone (bGH) we found that glomerular size was greater than expected for body size and that it continued to increase as glomerulosclerosis progressed.[22,23] These mice die in renal failure.[22] In the current study we found that glomerular hypertrophy occurred in both sclerosis-prone and sclerosis-resistant mice. However, there was a sharp difference between the two strains in the degree of hypertrophy ultimately attained. Whereas glomerular size increased by approximately 50% in nephrectomized adult C57 +/+ mice, nephrectomy of littermate C57 Os/+ mice resulted in no further increase in glomerular size even though there was a 75% decrease in nephron number. However, there was a substantial increase in glomerular size in ROP Os/+ mice after adult nephrectomy. This relationship between continuously increasing glomerular size and glomerulosclerosis is in agreement with our observations in mice transgenic for bGH. The data from these two animal models suggest that glomerular size does not exceed a certain size in sclerosis-resistant mice following nephron reduction. However, in sclerosis-prone mice glomerular size continues to increase as nephron number decreases, and this is associated with the development of progressive glomerulosclerosis. It is not possible, at present, to determine whether there is a causal link between the progressive glomerular lesion and the lack of a plateau in glomerular size in sclerosis-prone mice. A similar relationship between glomerular size and suscep-

tibility to glomerulosclerosis was noted in diabetic mice following the induction of hyperglycemia.[24]

There was an increase in α1 IV collagen mRNA in both ROP +/+ (1.8 fold) and C57 +/+ (1.6 fold) mice ($P < 0.05$) 8 weeks after nephrectomy, and the levels were higher in ROP +/+ mice. The 72-kd collagenase mRNA levels were similar in sham-operated ROP +/+ and C57 +/+ mice. Although the levels were increased 8 weeks post-NX, they were not significantly different from one another. There was a further increase in α1 IV collagen, laminin β1, and tenascin mRNA levels in ROP Os/+ mice 8 weeks after NX but not in C57 Os/+ mice. There was an increase in 72-kd collagenase mRNA levels of similar magnitude in both ROP Os/+ mice and C57 Os/+ mice 8 weeks after nephrectomy. These data show that there was an increase in the synthesis of several matrix components in the NX ROP Os/+ mice, relative to the other groups. Furthermore, the changes in 72-kd collagenase mRNA levels were parallel in all groups, providing evidence that the cause of the glomerulosclerosis could have been a relative imbalance in matrix turnover, favoring deposition.

Genetic factors have been reported to be important in determining the response to adult nephrectomy. Dahl salt sensitive rats with 5/6 renal ablation had significantly more severe hypertension and focal glomerulosclerosis than salt-resistant rats.[25] Male Wistar rats and several other rat strains developed glomerulosclerosis after adult uninephrectomy,[19] whereas male PVG/c rats did not.[8]

In summary, these data show that nephrectomy in adulthood resulted in a sclerotic response only in a susceptible mouse strain and that in this strain, a 50% reduction in nephron number during development resulted in more prominent glomerulosclerosis than did an equal reduction occurring during adulthood. The data also

show that a 75% reduction in nephron number in the sclerosis-resistant strain did not induce sclerosis, suggesting that the different responses between the two strains was not simply a difference in a threshold. Finally, the data show that glomerular hypertrophy in response to nephron reduction in the sclerosis-resistant strain was limited, reaching a plateau at a 50% reduction in number. However, glomerular size continued to increase in the sclerosis-prone strain as nephron number decreased.

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