Molecular analysis of spontaneous glomerulosclerosis in Os/+ mice, a model with reduced nephron mass

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We, Cijiang, Rudolfs K. Zalups, David A. Henderson, Gary E. Striker, and Liliane J. Striker. Molecular analysis of spontaneous glomerulosclerosis in Os/+ mice, a model with reduced nephron mass. Am. J. Physiol. 369 (Renal Fluid Electrolyte Physiol. 38): F266–F273, 1995.—Oligosyndactyly with reduced nephron mass. Am. J. Physiol. 269 (RenaZ Fluid Molecular analysis of spontaneous glomerulosclerosis in Os/+ mice. Glomerulosclerosis in these patients has not been defined.

We studied a mutant strain of mice, ROP Os/+ mice, which are born with a 50% reduction in the number of nephrons and have oligosyndactyly (30, 33). We discovered that these mice develop glomerulosclerosis. Therefore, we examined the expression of several genes coding for the synthesis and degradation of glomerular extracellular matrix. Since ROP Os/+ mice undergo considerable glomerular hypertrophy, we also examined glomerular cell turnover and several growth factors.

MATERIALS AND METHODS

Experimental design. Female ROP Os/+ (Os/+ and ROP +/+ (+/+) mice were obtained from Jackson Laboratories (Bar Arbor, ME). The +/+ mice served as controls for Os/+ mice. Mice were killed at 3 mo according to procedures approved by National Institutes of Health. Six mice from each group were examined for morphological studies and mRNA analysis. The left kidney was perfused with a buffer solution containing collagenase and ribonuclease inhibitors for glomerular microdissection as described previously (27). The right kidney was used for light and immunofluorescence studies. Glomeruli were counted in an additional five mice per group. Finally, 10 additional mice in each group were utilized for electron microscopic analysis. For electron microscopic studies, mice were killed and perfused by intracardiac gravity perfusion (100 mmHg) with 20-s prewash of phosphate-buffered saline (350 mosM, pH 7.4) followed by fixative (1% glutaraldehyde in 0.1 Sorensen's phosphate buffer, 350 mosM, pH 7.4) for 5 min. We have previously shown that glomerular filtration rate, estimated by creatinine clearance, did not differ between 3-mo-old Os/+ and +/+ mice (33). This suggests that there are no early renal functional changes secondary to the 50% reduction in renal mass present in Os/+ mice.

Glomerular number. Glomerular number was determined as described previously (17). Briefly, the kidneys were decapsulated and cut into 2-mm3 pieces. These were incubated in 5 ml of 6 N HCl at 37°C for 90 min. The resultant suspension was diluted to 30 ml with distilled H2O and allowed to stand at 4°C overnight. Glomerular number was determined in duplicate under phase microscopy using a counting chamber.

Light microscopy. Coronal kidney sections were fixed in Carnoy's fixative, embedded in glycol methacrylate, cut at a thickness of 2 μm, and stained with hematoxylin-eosin or periodic acid-Schiff (PAS). The sections were examined by someone without knowledge of the experimental groups to eliminate experimental bias. The degree of mesangial sclerosis was assessed using a scale from 0 to +4 as described previously (18). Forty glomeruli per section were examined in six mice from each group, and the means of scores for individual glomeruli were recorded.

Immunofluorescence microscopy. The kidneys were embedded in low-temperature melting paraffin, and cut at 5 μm. The sections were deparaffinized and rehydrated for immunofluorescence microscopy as described previously (31). After light trypsinization at 37°C, the sections were coated with rabbit anti-mouse type IV collagen (Biodesign, Kennebunkport, ME), rabbit anti rat laminin (Chemicon International, Temecula,
CA), or rabbit anti-human tenasin (GIBCO-BRL, Gaithersburg, MD) followed by biotin-conjugated goat anti-rabbit immunoglobulin G (Tago, Burlingame, CA) and streptavidin-conjugated fluorescein-isothiocyanate (Zymed Laboratories, San Francisco, CA). The sections were examined, coded, and the fluorescence intensity was graded on a 0 to +4 scale as described previously (29).

Light microscopic morphometry. Morphometric analysis was performed on plastic-embedded sections using a digitizing tablet and a video camera, as described previously (3, 7, 29). The mean glomerular volume was derived from the harmonic mean of the glomerular equatorial surface area (7). The surface area fraction of the cortex occupied by the glomeruli was measured as described previously (29).

Glomerular cell number and turnover. The nuclei of 50 successive glomerular profiles were counted by scanning hematoxylin-eosin-stained tissue sections in a serpentine fashion. The relative glomerular cell number was calculated as described previously (26).

The labeling index was determined by measuring [3H]thymidine incorporation in glomeruli as described previously (26). The glomerular labeling index was determined by counting 50 successive glomeruli per section and expressed as the percentage of positively labeled cells (excluding Bowman’s capsular cells) divided by the total glomerular cell number.

Electron microscopy. Four- to 2-mm-thick transverse equatorial slices were cut with sharp single edge razor blades and placed in glutaraldehyde at 4°C. After 1–3 h, the kidney slices were further cut into radially oriented strips that were ~1 mm wide and extended from the capsule at one end to the inner stripe of the outer medulla at the other. The strips were stored overnight in the primary fixative at 4°C. They were rinsed once in 0.1 M Sorenson’s phosphate buffer and twice in 0.1 M sodium cacodylate buffer (pH 7.4) prior to post-fixation in a membrane-enhancing mixture of 1% osmium tetroxide and 0.8% potassium ferrocyanide buffered with 0.1 M sodium cacodylate (pH 7.4) for 2 h at 22°C. The tissue strips were dehydrated in a graded ethanol series, then through propylene oxide to resin (Poly/Bed 812, Polysciences), and polymerized in flat embedding molds at 60°C for 24 h. The embedded strips were cut with a razor blade on a hot plate at 80°C into blocks of 2–4 mm length and glued to the surfaces of plastic stubs so that they could be sectioned longitudinally. Regions of the blocks containing several glomeruli were identified in semithin sections, and after retrimming, 90-µm sections were obtained on a Reichert-Jung Ultracut E ultramicrotome. The thin sections were mounted on high-transmission 200-mesh copper grids and stained with uranyl acetate and lead citrate.

Electron microscopic morphometry. Sections were photographed on an Hitachi H-300 transmission electron microscope, and the magnifications were calibrated. Four to six glomeruli were examined from each animal. There were selected randomly since all glomeruli present in the sections were examined. Due to five mesangial areas from each glomerulus were photographed as encountered at either ×4,000 or ×7,000. Mesangial areas were digitized from the photomicrographs using a SummaSketch II digitizing pad in association with the digitizing component of the IBM PC-Based Three-dimensional Reconstruction System (model HVEM-3D) produced by the Laboratory for High-Voltage Electron Microscopy at the University of Colorado, Boulder. Using this digitizing program in conjunction with Microsoft Excel Version 6.0, the total mesangial cell area and the mesangial matrix area were determined for each micrograph, and the relative matrix area was expressed as percent of the total mesangial area. Basement membrane thickness was measured directly using a ×15 measuring magnifier graduated in 0.1-mm units on micrographs printed at ×24,000. These measurements were performed only at locations where the basement membrane was cut in a plane normal to that of the membrane, as determined by the orientation of the podocyte pedicels and of the endothelial fenestrae. Both total basement membrane and lamina densa thickness were expressed as the mean of three to five regularly spaced sites at each location. Five to ten locations were measured and averaged to provide the mean thickness for a given animal.

Isolation of glomeruli and reverse transcription in situ. Glomeruli were isolated by microdissection, and glomerular cDNA was obtained by in situ reverse transcription, as described previously (27).

Competitive polymerase chain reaction. The primers for mouse α1-chain type IV (α1-IV) collageen, α1-type I (α1-I) collagen, laminin-B1, tenasin, α-smooth muscle actin (α-SMA), β-actin, 72-kDa and 92-kDa collagenases, transforming growth factor-β1 (TGF-β1), and platelet-derived growth factor-B (PDGF-B) were previously described (27, 31). The corresponding polymerase chain reaction (PCR) products were 481 bp for α1-IV collagen, 291 bp for α1-I collagen, 443 bp for laminin-B1, 434 bp for α-SMA, 460 bp for β-actin, 701 bp for 72 kDa collagenase, 472 bp for 92-kDa collagenase, 548 bp for tenasin, 360 bp for TGF-β1, and 435 bp for PDGF-B.

Competitive PCR assays were performed by adding decreasing amounts of mutant templates to glomerular cDNA, as previously described (27). After PCR amplification, the ratio of mutant to cDNA band density was calculated by laser densitometry and plotted as a function of the amount of initial mutant template added to the reaction (27). The amount of glomerular cDNA was derived from linear regression analysis and expressed as mRNA levels. Duplicate or triplicate assays were performed (27, 31). A representative competitive PCR assay is shown in Fig. 1. Glomerular mRNA levels were corrected for glomerular cell number. The mean values obtained for Os/+ mice were expressed as a percentage of those for +/+ mice.

Statistical analysis. All values were expressed as means ± SD. The two tailed unpaired Student’s t test was used to evaluate differences between means for corresponding sets of data obtained from the Os/+ and +/+ mice. Data expressed as a percent, however, were first normalized (made to fit a normal distribution) using the arcsine transformation. The level of significance (P < 0.05) was chosen only for all the analyses performed in the present study. The two-tailed unpaired Mann-Whitney nonparametric test was used to analyzed difference in the immunofluorescence scores between the two groups.

RESULTS

Kidney weight, glomerular volume, and number of glomeruli. There was a 55% reduction in the mean glomerular number per kidney in Os/+ mice (P < 0.001) (Table 1). This was associated with a 24% reduction in kidney weight in Os/+ mice (P < 0.05), in the absence of concomitant change in body and heart weight (Table 1) (33). We measured glomerular cross-sectional areas and found that the mean glomerular volume was increased 1.8-fold (P < 0.001) (Table 1; Fig. 2A). However, the fraction of the cortex occupied by glomeruli did not differ between Os/+ and +/+ mice (Fig. 2B), confirming our previous observation that the entire nephron was hypertrophied (33).

Histology. There was a marked increase in PAS-positive material in the mesangial regions by light microscopy, in all Os/+ mice (Fig. 3). The mesangial sclerosis affected all glomeruli but varied in intensity
between individual tufts. This appearance was called
glomerulosclerosis, since it was due to an excess of
extracellular matrix best seen by immunofluorescence
or electron microscopy. The mesangial sclerosis ap-
peared distributed evenly in the cortical and juxta-
glomerular regions. The mean scores of mesangial sclerosis
were significantly higher in OS/+ mice (2.6 ± 0.4 for
OS/+ vs. 0.5 ± 0.5 for +/+ , P < 0.005).

There was no increase in the thickness of glomerular
basement membranes or basement membranes of Bow-
man’s capsule. Obsolescent glomeruli were not
observed. The interstitium, tubules, and blood vessels
appeared normal.

**Immunofluorescence microscopy.** There was a marked
increase in the amount of type IV collagen (mean score,
2.8 ± 0.4 vs. 1.6 ± 0.5; P < 0.05) and tenascin (mean
score, 3.2 ± 0.4 vs. 1.2 ± 0.4; P < 0.01) in the glomeruli
of OS/+ mice, whereas no change in laminin (mean
score, 2.2 ± 0.4 vs. 1.8 ± 0.5; not significant) was
observed (Fig. 4). The accumulation of type IV collagen
tenascin was restricted to the mesangium.

**Electron microscopy.** The mesangial regions in OS/+ 
mice were expanded by irregularly distributed, homoge-
neous aggregates of increased matrix (Fig. 5). The
excess matrix was less electron dense than the lamina
densa. The laminae of the peripheral basement mem-
brane did not differ from those in the +/+ mice (Fig. 5).
The cells were also similar in appearance to +/+ mice, and
inflammatory cells were not present. The thickness
of the basement membrane and of the lamina densa did
not differ between OS/+ and +/+ mice (Table 2). The
total matrix area, as well as the percentage of mesangial
matrix area, was significantly greater in OS/+ than +/+ 
mice. Finally, the mesangial volume fraction occupied by
cells was smaller in OS/+ mice (Table 2).

**mRNA levels.** Glomerular α1-IV collagen and tenascin
mRNA levels were increased 2.7- and 1.7-fold, respec-
tively, in the OS/+ mice (α1-IV, P < 0.001; tenascin,
P < 0.05) (Fig. 6, A and D; Table 3). There were no
significant changes in laminin B1 mRNA levels (Fig. 6C;
Table 3). α1-1 Collagen was not detectable in either OS/+ 

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**Table 1. Anatomic measurements**

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<tr>
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<th>OS/+ Mice</th>
<th>+/+ Mice</th>
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<tr>
<td>Body wt, g</td>
<td>20.6 ± 0.97</td>
<td>20.4 ± 2.1</td>
</tr>
<tr>
<td>Heart wt, mg</td>
<td>132.6 ± 14.9</td>
<td>127.7 ± 13.7</td>
</tr>
<tr>
<td>Kidney wt, mg</td>
<td>103.5 ± 4.7f</td>
<td>140.4 ± 15.6</td>
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<td>Glomerular volume, ×10⁵ μm³</td>
<td>4.32 ± 0.34f</td>
<td>2.35 ± 0.33</td>
</tr>
<tr>
<td>Glomerular number, ×10³/ kidney</td>
<td>8.54 ± 0.47f</td>
<td>14.34 ± 1.02</td>
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Values are means ± SD; n, no. of measurements. Body weight was
recorded before death. Heart and kidney weights (n = 6) were obtained
after blot drying. Glomerular number (n = 6) and volume (n = 6) were
measured as described in MATERIALS AND METHODS. *P < 0.05, †P < 0.001.
or +/+ mice by PCR amplification, even when the amount of starting cDNA was increased fivefold or the number of PCR cycles was increased to 42.

The 72-kDa collagenase mRNA levels were increased 1.7-fold in Os/+ mice (P < 0.05) (Fig. 6B; Table 3). The 92-kDa collagenase mRNA was barely detectable by standard PCR. Although there were no differences between Os/+ and +/+ mice for this latter molecule, it was not possible to perform quantitative PCR due to the small amount of mRNA present.

The levels of TGF-β1 mRNA in Os/+ mice were increased 1.7-fold (P < 0.05). There were no differences in the levels of PDGF-B mRNA between the two groups of mice (Fig. 7, A and B; Table 3).

α-SMA, considered to be a marker of mesangial cell activation (16), was 1.9-fold higher in Os/+ mice than in +/+ mice (P < 0.01) (Fig. 8B; Table 3).

The β-actin mRNA levels did not differ between the two groups of mice (Fig. 8A; Table 3), when adjusted for cell number.

There was a 34% increase in the mean cell number per glomerulus in Os/+ mice compared with +/+ mice (3,276 ± 411 vs. 2,429 ± 181 cells/glomerulus; P < 0.05, n = 6) (Fig. 9A). However, the cell density was decreased in Os/+ mice, when the mean cell number was adjusted for glomerular volume.

The mean glomerular labeling index was 2.4-fold higher in Os/+ mice than in +/+ mice (0.78 ± 0.25 vs. 0.33 ± 0.066%; P < 0.005, n = 6) (Fig. 9A). Most labeled cells were located in the centrolobular areas, with only occasional podocytes being labeled.

**DISCUSSION**

Oligosyndactyly mice (ROP Os/+) have a radiation-induced mutation that has been linked to chromosome 8. We and others had previously reported that these mice had oligonephronia and enlarged glomeruli (30, 33). We now report that Os/+ mice have glomeruloscle-
Fig. 5. Electron microscopy. Mesangium of an OS/+ mouse is expanded by increased matrix, which displaces mesangial cells. Not all regions are equally affected. Lamina densa does not differ from +/+ mice. A: OS/+ mouse. B: +/+ mouse.

Sclerosis as defined by an increase in the amount of extracellular matrix in the mesangial regions. At 3 mo of age, electron microscopic examination revealed diffuse mesangial expansion and a twofold increase in the amount of mesangial matrix, without a change in the thickness of the peripheral glomerular basement membrane. Thus, in this model, there is a dissociation between extracellular matrix changes in the mesangium and the peripheral basement membrane, with the former being increased and the latter being of normal thickness. This contrasts with that seen in other models of glomerulosclerosis in mice (7, 13, 32) and in diseases such as diabetic nephropathy, in which both compartments are increased (19).

The composition of the sclerosis was unusual in that there was an increased amount of type IV collagen and tenascin detected by immunofluorescence microscopy.

| Table 2. Electron microscopic morphometric analysis of mesangium and basement membranes |
|----------------------------------|------------------------------|-------------------------------|
| Measurement                      | Os/+ Mice                    | +/+ Mice                      |
| Mesangial area, μm²              | 119.5 ± 72.0                 | 81.2 ± 24.4                   |
| Cell area, μm²                   | 80.7 ± 50.4                  | 63.1 ± 18.9                   |
| Matrix area, μm²                 | 45.9 ± 18.8*                 | 18.3 ± 5.8                    |
| Cell area, %                     | 61.3 ± 6.5*                  | 78.4 ± 0.5                    |
| Matrix, %                        | 38.7 ± 6.6*                  | 22.2 ± 3.6                    |
| BM thickness, μm                 | 31.5 ± 2.4                   | 29.7 ± 1.6                    |
| LD thickness, μm                 | 22.1 ± 2.6                   | 19.9 ± 1.2                    |

Values are means ± SD. Glomerular mesangium and basement membranes were quantitated by electron microscopic morphometric analysis as described in MATERIALS AND METHODS. Total mesangial area, cell area, matrix area, basement membrane (BM) and lamina densa (LD) thickness were measured in both Os/+ and +/+ mice. Two sample t-tests with unequal variances were used (α = 0.01). *P < 0.05 (n = 10).
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Fig. 6. Extracellular matrix and collagenase mRNA levels. mRNA levels were determined by competitive reverse transcription-PCR and corrected for glomerular cell number. Mean values obtained for Os/+ mice were expressed as a percentage of those for +/+ mice. A: α1-IV collagen. B: 72-kDa collagenase. C: laminin B1. D: tenascin. *P < 0.05. **P < 0.001.

Table 3. mRNA levels

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<tr>
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<th>Os/+ Mice</th>
<th>+/+ Mice</th>
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<tr>
<td>α1-IV Collagen</td>
<td>635 ± 55*</td>
<td>180 ± 26</td>
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<tr>
<td>Laminin B1</td>
<td>92 ± 29</td>
<td>76 ± 27</td>
</tr>
<tr>
<td>Tenascin</td>
<td>906 ± 232*</td>
<td>424 ± 163</td>
</tr>
<tr>
<td>72-kDa Collagenase</td>
<td>260 ± 94*</td>
<td>118 ± 53</td>
</tr>
<tr>
<td>TGF-β1</td>
<td>85.5 ± 28*</td>
<td>38.5 ± 12</td>
</tr>
<tr>
<td>PDGF-B</td>
<td>14.3 ± 3.2</td>
<td>10.8 ± 3.1</td>
</tr>
<tr>
<td>α-SMA</td>
<td>223 ± 58*</td>
<td>91 ± 32</td>
</tr>
<tr>
<td>β-Actin</td>
<td>599 ± 220</td>
<td>400 ± 126</td>
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Values are absolute means ± SD (×10⁻⁴ amol/glomerulus); n = 6 experimental mice per group. Competitive polymerase chain reaction was performed as described. Assays were performed in duplicate or triplicate. Glomerular cell number was increased 1.3-fold in the Os/+ mice. TGF-β1, transforming growth factor β1; PDGF-B, platelet-derived growth factor-B; α-SMA, smooth muscle α-actin. *P < 0.001. †P < 0.05. ‡P < 0.01.

whereas the amount of laminin appeared unchanged from +/+ littermates. As assessed by competitive PCR on microdissected glomeruli and corrected for cell number, there was a corresponding 3.2- and 1.8-fold increase in the levels of glomerular α1-IV collagen and tenascin mRNAs, respectively. Laminin mRNA levels did not differ from +/+ mice. Type I collagen mRNA was not identifiable. These data are consistent with the results of immunostaining. There was a 1.6-fold increase in the level of 72-kDa collagenase mRNA but no change in the 92-kDa collagenase mRNA. However, it should be noted that the levels were quite low, and a small change might have been undetectable. Finally, there were no differences in β-actin mRNA levels between Os/+ mice and +/+ mice, suggesting that cell hypertrophy was not a major feature of the glomerular changes. The glomerulosclerosis in this model lacked changes in the amount of laminin in the glomeruli and the accumulation of interstitial collagen that are present in the ablation model, in experimental streptozotocin-induced diabetes, or in growth hormone transgenic mice (8, 10, 13, 32).

There was a 1.3-fold increase in cell number and a 2.4-fold increase in the labeling index in Os/+ mice. Most of the labeled cells were in the centrolobular regions, with few parietal or visceral epithelial cells being labeled. There was a 1.8-fold increase in TGF-β1 mRNAs levels but no change in that for PDGF-B. The latter finding was unexpected, since PDGF-B has been shown to be increased in a number of proliferative and sclerosing forms of glomerular disease (11, 15). These data suggest that the glomerular cell proliferation observed in Os/+ mice may not be secondary to increased

Fig. 7. Transforming growth factor-β1 (A) and platelet-derived growth factor-B (B) mRNA levels. mRNA levels were measured and expressed as in Fig. 5. *P < 0.05.

Fig. 8. β-Actin (A) and α-smooth muscle actin (R) mRNA levels. mRNA levels were measured and expressed as in Fig. 5. β-Actin was used to control for the amount of glomerular cDNA. *P < 0.01.

Fig. 9. Glomerular cells. A: mean number of cells/glomerular profile is expressed as a ratio of those in Os/+ vs. +/+ mice. B: [%H]thymidine labeling index in glomerular tufts is expressed as a percentage (labeled cells/total cells × 100). *P < 0.05. **P < 0.005.
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PDGF-B production. However, TGF-β may be implicated in the development of the sclerotic lesions in Os/+ mice. Alternatively, PDGF may have been increased at earlier time points than were investigated in the present work (11, 15). The discrepancy between cell turnover rate and cell number suggests that apoptosis may have been a factor. We have made similar observations in mice transgenic for growth hormone (26).

The cause(s) of glomerulosclerosis is unknown, but it has been postulated that a reduction in glomerular number may be an important factor in the development of progressive glomerular disease (4, 5). We (33) and others (30) have previously found that glomerular number is decreased in Os/+ mice and that the glomeruli were larger than in unaffected littersmates by semiquantitative techniques. In this study we directly counted glomeruli, and found a 2.2-fold decrease in their number in Os/+ mice and a 1.8-fold increase in volume. Interestingly, congenital bilateral renal hypoplasia (oligonephronia) in children is associated with a reduction in the number, as well as the hypertrophy, of nephrons, proteinuria, and glomerulosclerosis leading to end-stage renal failure (2, 5, 9, 28).

Many studies have shown an association between glomerulosclerosis and severe reductions of nephron mass. For instance, in the renal ablation model, five-sixths nephrectomy (~80% reduction) in rats resulted in glomerular hypertrophy, glomerulosclerosis, and glomerular cell proliferation (10). However, unilateral nephrectomy does not produce sclerosis in most animal models (18). The effect of a reduction of nephron mass by surgical techniques after birth may differ from the effects of reduced renal mass based on a genetic defect, i.e., that seen in Os/+ mice. Others have found that the compensatory adaptation to nephron loss was age-dependent; the earlier the nephron loss, the greater the compensation (1, 6, 21, 23). For instance a 20% nephron loss in utero, due to gentamicin toxicity or uterine arterial ligation in the mother, results in glomerulosclerosis in the offspring, whereas a comparable nephron loss in adult animals does not have adverse consequences (5, 14, 18, 20). In that respect, unilateral agenesis is associated with a very high incidence of sclerotic lesions in the unique kidney (1, 22). This observation may partly account for the lesions in Os/+ mice, in which there is a 50% reduction in the number of nephrons.

There is also increasing evidence that glomerular volume may be an important predisposing factor for progressive glomerular diseases. We reported that large glomerular size is associated with an increased risk of end-stage renal disease among different populations (25, 29). A relationship between large glomerular size and subsequent sclerosis has also been found in children with nephrotic syndrome and in patients with nephropathy in insulin-dependent diabetes mellitus (12, 24). Our data in mice transgenic for SV40 Tag and native or mutated growth hormone support a relationship between increased glomerular size and the development of glomerulosclerosis (18, 32), in the absence of a reduced number of nephrons.

In conclusion, these data extend observations on the linkage between a congenital reduction in glomerular number, glomerular hypertrophy, and the development of glomerulosclerosis. This raises the possibility that these events may be linked and may share common genetic determinants.

We thank Dr. Chih-Wei Yang for help in the initiation of these studies.

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REFERENCES


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