Genes Expressed by Both Mesangial Cells and Bone Marrow–Derived Cells Underlie Genetic Susceptibility to Crescentic Glomerulonephritis in the Rat

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The Wistar-Kyoto (WKY) rat shows marked susceptibility to crescentic glomerulonephritis. In the model of nephrotoxic nephritis (NTN) that is induced by a small dose of nephrotoxic globulin, WKY rats developed crescents in 80 ± 2% of glomeruli at day 10, whereas no crescents were seen in Lewis rats. This was associated with marked increase in monocyte chemoattractant protein-1 synthesis in WKY glomeruli. It was posited whether susceptibility depended on circulating or intrinsic renal cells. Bone marrow (BM) isografts from WKY to WKY or Lewis to Lewis did not affect susceptibility to NTN. When BM was transferred from WKY to Lewis rats, crescents developed in 35 ± 9% of glomeruli 10 d after induction of NTN, indicating that susceptibility could be transferred by BM cells. However, crescents were also seen in WKY rats that were given Lewis marrow. For assessment of the contribution of intrinsic renal cells, kidneys from WKY or Lewis rats were transplanted into F1 animals. In NTN, the ratio of crescents in the transplanted kidney to the native kidney was significantly higher for WKY-to-F1 than for Lewis-to-F1 transplants, demonstrating that the kidney itself also influences susceptibility. Mesangial cell responses were then examined in the two strains. Mesangial cells that were derived from WKY rats synthesized significantly more monocyte chemoattractant protein-1 basally and after stimulation with heat-aggregated rabbit IgG or TNF-α. These results show that susceptibility to NTN in the WKY rat depends on both circulating and intrinsic renal cells and that there are genetic differences between the strains in mesangial responses to inflammatory stimuli.

on other chromosomes and were designated Cgrn3 through Cgrn7.

The locus on chromosome 13 included the gene that codes for the α subunit of the activatory Fc receptor Fcgr3. We showed that most laboratory strains of rat express two forms of Fcgr3 but that, in the WKY rat, a newly identified paralogue, Fcgr3-related sequence (Fcgr3-rs), was absent. Loss of Fcgr3-rs leads to enhanced antibody-dependent cytotoxicity in macrophages from WKY rats, a phenomenon that was originally described by Renneke et al. (3).

These data indicate that one major determinant of susceptibility to crescentic glomerulonephritis in the rat is an enhanced Fc-receptor–driven macrophage response to intraglomerular Ig. However, the role of genes at the other QTL that we have identified remains unknown, and neither is it clear whether susceptibility to crescents is entirely determined by circulating cells or whether intrinsic renal factors also make a contribution. In an attempt to elucidate this, we carried out bone marrow (BM) and kidney transplants between the susceptible WKY and resistant Lewis strains. Our results show that susceptibility depends on both circulating cells and the kidney itself. We also demonstrate that mesangial cells from WKY rats show enhanced proinflammatory responses that may partly explain the contribution of the kidney to susceptibility to crescent formation.

Materials and Methods

Animals

Wistar-Kyoto (WKY/NCr) and Lewis (LEW/Cr) rats were purchased from Charles River (Margate, UK). F1 rats were generated by intercrossing the two strains. All procedures were performed in accordance with the United Kingdom Animals (Scientific Procedures) Act.

BM Transplantation

Femurs were removed from donor rats. Marrow was flushed out using RPMI with 10% FBS (Sigma-Aldrich, Poole, UK), 100 U/ml penicillin, and 100 g/ml streptomycin (Invitrogen, Paisley, UK). Cells were then washed, resuspended in fresh medium at 5 × 10^7 cells/ml, and kept on ice.Recipient rats were irradiated with 12 Gy at 0.57 Gy/min, using gamma rays from a cesium source irradiator (IBL 637; CIS Bio International, Saclay, France). They were administered an intravenous injection of 0.2 ml of BM cell preparation within 2 h of irradiation. Rats were left a minimum of 8 wk to recover and to reconstitute their BM. Rats were weighed every 2 wk and at the end of the experiment.

Renal Transplantation

Orthotopic transplantation of the left kidney was performed as described previously (14) with removal of the recipient’s own left kidney at the time. After transplantation, rats were allowed to recover for 6 to 8 d before induction of NTN.

NTN

NTS was prepared in rabbits by standard methods. NTN was induced in male rats by intravenous injection of 0.1 ml of NTS. Nine days later, urine was collected by placing rats into metabolic cages for 24 h with free access to food and water. Proteinuria was determined by the sulfosalicylic acid method (15). On day 10 after induction of NTN, rats were killed under isoflurane anesthesia and blood was collected from the abdominal aorta. Samples of kidney, skin, liver, colon, and lung were fixed in 10% formal saline, processed, and embedded in paraffin wax. In some cases, glomeruli were isolated by sieving as described previously (16), and 2000 glomeruli were plated in six-well plates (Nunc, Roskilde, Denmark) in DMEM (Life Technologies, Paisley, UK). After 48 h of incubation, supernatants and cell layers (glomeruli + cells) were collected for sandwich ELISA and quantitative reverse transcription–PCR (qRT-PCR), respectively.

Assessment of BM Chimerism

Genomic DNA was extracted from whole blood using the Puregene DNA Purification kit (Genentech Systems, Minneapolis, MN). A total of 100 ng of DNA from the BM transplant recipient was amplified by PCR using fluorescence-labeled primers for a polymorphic marker (D13Rat77) that distinguishes the donor allele from the recipient allele. A standard curve was prepared by mixing varying percentages of WKY and Lewis genomic DNA. After separation of PCR products in an automated DNA sequencer, ABI 3700 or 3730XL (Applied Biosystems, Warrington, UK), allelic-peak height ratios were calculated for each sample using GeneMapper Software 3.7 (ABs, Warrington, UK), and the percentage of donor or recipient DNA of the sample was determined from the standard curve.

Histology and Immunohistochemistry

Crescent formation was assessed by counting the number of crescents in 100 consecutive glomeruli in periodic acid-Schiff–stained sections. Macrophages were identified by immunoperoxidase staining with mAb ED-1 (Serotec, Oxford, UK) and CD8^+ cells were stained with mAb MRC OX8 (Serotec) as described previously (9). The total number of immunostained cells in 25 consecutive glomeruli was counted and converted to a mean count per glomerular cross section (gcs).

BM-Derived Macrophage Culture

Femurs from adult WKY and Lewis rats were isolated and flushed with Hanks buffer (Life Technologies). Total BM-derived cells were plated and cultured for 7 d in DMEM (Life Technologies) that contained 25 mM HEPES (Sigma), 25% L929 conditioned medium, 25% decomplemented FBS (F-539; M.B. Meldrum, Bourne End, UK), penicillin (100 U/ml; Invitrogen), streptomycin (100 μg/ml; Invitrogen), Paisley, UK), and 1-glutamine (2 mM; Invitrogen). These cells were characterized as macrophages by ED-1 staining. Macrophages were made quiescent in serum-free medium for 24 h and then stimulated with TNF-α (2 ng/ml). Control macrophages were unstimulated. Monocyte chemoattractant protein 1 (MCP-1) protein and mRNA levels were measured by sandwich ELISA and qRT-PCR, respectively.

Mesangial Cell Culture

Glomeruli from Lewis and WKY rats were isolated by sieving. Purified glomeruli were digested with collagenase type 1 (Sigma; 750 U/ml) for 20 min. Partially digested glomeruli were cultured in 25-cm^2 tissue culture flasks at 600 glomeruli/ml in RPMI 1640 medium (Invitrogen) that contained 20% decomplemented FBS (F-539), penicillin (100 U/ml; Invitrogen), streptomycin (100 μg/ml; Invitrogen), and 1-glutamine (2 mM, Invitrogen) and was supplemented with insulin-transferrin-selenite (Sigma). The cultures were maintained at 37°C with 5% CO_2 for 6 d, allowing glomerular mesangial cells to grow out. Medium was changed every 2 to 3 d thereafter. By days 21 to 28, when the cell outgrowth reached confluence, cells were subcultured. These cells were characterized by both FACS staining and immunofluorescence staining using cells that were cultured on coverslips. They were
positive for Thy-1.1 antigen, myosin, and desmin and negative for pancytokeratin, OX-1, ED-1, and OX-23.

**Comparison of Mesangial Cell Responses between Strains**

For making the culture conditions comparable, mesangial cells from different strains of rats were passaged into 48-well culture plates at the same time. Passage 10 cells were used for each experiment. Confluent mesangial cells were stimulated with either heat-aggregated rabbit IgG (Sigma) or TNF-α (R&D, Abingdon, UK) in serum-free medium. Heat-aggregated IgG was prepared as described previously, with modifications (17). After stimulation for 24 h, mesangial cell supernatants were harvested and centrifuged to remove cellular contaminants. These supernatants were either examined immediately with sandwich ELISA or stored at −20°C. In each experiment, two wells of cells from each group were trypsinized and counted in a hemocytometer. The viability of the cells was checked by 0.2% trypan blue stain (Invitrogen). MCP-1 was measured in the supernatant by sandwich ELISA as described previously (10).

**RNA Extraction and qRT-PCR**

Total RNA was isolated from the whole kidney, isolated glomeruli, or macrophages using the Trizol-method. Total RNA concentration was determined by using Nanodrop spectrophotometer (Labtech Int., Rungmer, UK). MCP-1 and glyceraldehyde-3-phosphate dehydrogenase genes forward and reverse primers were as follows: MCP-1 forward primer 5’TGGATGCGTATGGCCCCACTC-3’, MCP-1 reverse primer 5’TCCCTTTATGGGGTGCACGC-3’.

Real-time RT-PCR was performed on a ABI 7500 Sequence Detection System (Applied Biosystems, Warrington, UK) using SYBR Green (Stratagene, Cambridge, UK). A total of 200 ng of total RNA was used for qRT-PCR, and all of the samples were amplified in triplicate. After the initial reverse transcription (30 min at 50°C and 10 min at 95°C), the samples were cycled 40 times at 95°C for 30 s and 60°C for 45 s. Results were then exported to 7500 Fast system SDS software (ABS), and Ct values were determined for MCP-1 and glyceraldehyde-3-phosphate dehydrogenase. The relative expression levels were then determined by using the $2^{\Delta\Delta C_t}$ method.

**Statistical Analyses**

Results are expressed as means ± SEM. Comparisons between groups were analyzed by Mann-Whitney U test.

**Results**

**MCP-1 Synthesis by Glomeruli from Native Kidneys with NTN**

We previously showed that, after a small dose of NTS, WKY rats develop severe crescentic glomerulonephritis, whereas no crescents are seen in Lewis rats. It is known that administration of antibodies to MCP-1 reduces crescent formation in WKY with NNT (18). We therefore studied glomerular MCP-1 synthesis and mRNA levels in WKY and Lewis rats 5 d after induction of NTN. As shown in Figure 1, glomeruli from WKY rats showed markedly higher levels of secreted MCP-1 protein and mRNA compared with Lewis rats.

**BM Transplantation**

BM transplants were carried out from WKY to Lewis and from Lewis to WKY. As controls, we carried out isologous transplants in each strain. In WKY-to-Lewis transplants, the reconstitution, as measured as a percentage of donor DNA in peripheral blood cells, was 95 ± 3% (n = 6), and in Lewis-to-WKY transplants, it was 90 ± 1% (n = 6). To monitor for graft-versus-host disease, we assessed body weight and histology of skin, liver, colon, and lung (19,20). We found no evidence of graft-versus-host disease on histologic examination. Percentage weight gain from before transplantation to the end of the experiment was similar in WKY rats that were given WKY marrow (16 ± 3%) or Lewis marrow (17 ± 2%). In Lewis rats, percentage weight gain was higher in those that were given WKY marrow (47 ± 4%) than in those with an isologous transplant (34 ± 4%), although this did not reach statistical significance (P = 0.064). Figure 2 shows the results of NTN induction in the rats that received a transplant at 10 d, and Figure 3 shows representative histology. We found that Lewis rats that received Lewis BM showed no crescents (Figures 2 and 3A), whereas WKY rats that were given WKY BM showed marked crescent formation that was comparable to that seen in unmanipulated WKY rats (Figures 2 and 3B). Therefore, the BM transplantation procedure itself did not affect susceptibility to nephritis. In resistant Lewis rats that were given WKY BM, there was clear and significant glomerulonephritis with proteinuria, macrophage infiltration, and crescent formation (Figures 2 and 3C). The number of glomerular CD8+ cells was also significantly higher in WKY-to-Lewis than in Lewis-to-Lewis transplants (5.5 ± 0.4 versus 0.7 ± 0.3 cells/gcs; P = 0.001). However, the numbers of crescents that were seen in these rats were still considerably less than in WKY rats. In WKY rats that were given Lewis BM, there was a significant reduction in crescent formation compared
with WKY rats after isologous transplantation. These results show that susceptibility to crescent formation can be transferred by BM-derived cells but suggest that, as well as the effect of BM-derived factors, there are other factors, possibly intrinsic to the kidney, that may also affect development of crescents.

Kidney Transplantation

To investigate the possibility that the kidney itself contributes to susceptibility to glomerulonephritis, we examined NTN in kidney transplants. We first performed control isografts from Lewis to Lewis (n = 2) and showed that these rats did not develop crescents after induction of NTN, whereas crescentic glomerulonephritis did develop in WKY-to-WKY grafts (n = 4). We then transplanted kidneys from WKY to Lewis and vice versa but found, despite that these strains share the same MHC haplotype, that there was acute cellular rejection, presumably associated with mismatches at minor histocompatibility antigens. We previously showed (13) that F1 rats that are derived from crossing WKY with Lewis have an intermediate susceptibility to NTN, so we decided to study transplants from the parental strains into F1 rats, which do not undergo rejection. NTN was given 6 to 8 d after transplantation, and rats were killed 10 d later. Crescents were found in resistant Lewis kidneys that were transplanted into F1 rats (31 ± 10% crescents; n = 5; Figure 3D). There is some variability in the susceptibility of F1 rats to crescentic nephritis; however, if there were no effect of the kidney itself on susceptibility, then we would expect the ratio of the percentage of crescents in the transplanted kidney to the native kidney to be the same whatever the strain of the donor kidney. In fact, as shown in Figure 4, there is a significantly higher ratio in transplants of WKY kidneys, demonstrating that kidneys from this strain develop more crescents in F1 rats than Lewis kidneys. There were also significantly more macrophages in glomeruli of WKY kidneys that were transplanted into F1 rats than in Lewis kidneys that were transplanted into F1 rats (33 ± 2 versus 25 ± 3 cells/gcs; P = 0.015). We extracted RNA from transplant and native kidneys and measured MCP-1 mRNA by real-time qRT-PCR. As shown in Figure 5, the relative expression of MCP-1 in transplanted compared with native kidneys was significantly higher when the donor was WKY.

Mesangial Cell Studies

We reasoned that if susceptibility to crescent formation depended in part on the kidney, then this might be due to a difference in mesangial cell responses to inflammatory stimuli.

Figure 2. NTN after bone marrow (BM) transplantation. Rats received a transplant of BM after 12 Gy of irradiation. After 8 wk, rats were given NTS and killed 10 d later. Glomerular crescents (A), proteinuria (B), and glomerular macrophages (C) were analyzed. Lewis-to-Lewis control transplants did not develop crescents. In WKY rats that were given WKY BM, crescent formation was similar to that in unmanipulated WKY rats. There was crescentic glomerulonephritis in Lewis rats that were given WKY BM. In WKY rats that were given Lewis BM, the severity of disease was reduced.

Figure 3. Renal histology in NTN after BM or kidney transplantation. No crescents were seen in glomeruli in a Lewis rat that was given a Lewis BM transplant (A). In a WKY rat that was given a WKY BM transplant, there was crescent formation similar to that seen in unmanipulated WKY rats (B). Crescents were seen in Lewis rat kidneys after transplantation of WKY BM (C) or when transplanted into an F1 (WKY × Lewis) rat (D). All periodic acid-Schiff stain. Magnification, ×200.
Mesangial cells synthesize MCP-1, and administration of antibodies to MCP-1 reduces crescent formation in WKY NTN (18). In addition, as we have shown here that there is considerably enhanced glomerular synthesis of MCP-1 in NTN in WKY compared with Lewis rats. We therefore studied mesangial cell synthesis of MCP-1 in WKY and Lewis rats. Figure 6 shows MCP-1 production by mesangial cells that were stimulated with heat-aggregated IgG. Significantly more MCP-1 is secreted by WKY compared with Lewis mesangial cells, but, interesting, unstimulated WKY mesangial cells also produced more MCP-1 than Lewis mesangial cells. Stimulation with TNF-α also led to significantly more MCP-1 secretion by WKY mesangial cells (Figure 7). These experiments were carried out by using replicate wells of cell lines that were derived from single WKY or Lewis rats. We were concerned that this might not represent a true strain difference but merely incidental selection during the process of deriving the cell lines. We therefore set up mesangial cell lines from several rats, and Figure 8 shows a comparison of MCP-1 production by mesangial cell lines that were derived from four Lewis rats and five WKY rats. There was significantly higher MCP-1 synthesis by WKY mesangial cells with or without stimulation by rabbit IgG. Therefore, experiments from multiple mesangial cell lines that were derived from several Lewis and WKY rats confirmed that WKY rat mesangial cells produced more MCP-1 than those from Lewis rats. We also compared the synthesis of MCP-1 by BM-derived macrophages from WKY and Lewis rats and found that macrophages from WKY rats contained more MCP-1 mRNA and secreted more MCP-1, but, in contrast to mesangial cells, there was no effect of TNF-α (Figure 9).

**Discussion**

The unique susceptibility of the WKY rat to crescentic glomerulonephritis has made it a very useful model system for studying therapeutic interventions, but little attention has been paid to the reasons for why this strain is so susceptible. We believe that understanding this is likely to lead to important insights into the mechanisms of crescent formation. We previously reported the results of a genome-wide linkage study that showed that crescent formation was strongly linked to QTL on chromosomes 13 and 16 (13) with less strong linkage to five other QTL. We further showed that Fcgr3, a candidate gene in the chromosome 13 QTL, has multiple copies in the rat and that a novel form of Fcgr3, which we have named Fcgr3-rs, is absent from the WKY genome. Loss of Fcgr3-rs is associated with enhanced macrophage antibody–dependent cytotoxicity and Fc-mediated phagocytosis. We therefore hypothesized that susceptibility to NTN depended, at least in part, on increased reactivity of circulating macrophages to antibody bound in glomeruli. However, our genetic analysis showed that there must be other genes contributing to the phenotype, so we thought that it was important to discover whether susceptibility was entirely dependent on the functions of circulating cells.

We initially used BM transplant experiments to test the role of circulating cells. These experiments showed unequivocally that the susceptibility to crescents could be transferred to resistant Lewis rats by WKY BM. This is consistent with a major role
for Fc receptor–mediated responses in susceptibility but, of course, does not exclude the possibility that there may be other functional differences in WKY and Lewis macrophages or other leukocytes that contribute to susceptibility. However, even with 95% reconstitution by donor BM, we saw crescents in only a mean of 35% of glomeruli of Lewis rats compared with 89% in control WKY rats that received isologous BM. Similarly, although transplantation of Lewis BM into WKY rats led to significantly fewer crescents (51%), it did not abolish the susceptibility to crescent formation. This suggested that there was an important contribution to severity of crescentic glomerulonephritis that was not dependent on BM-derived cells. This intrinsic contribution could be either from the kidney itself or possibly from an extrarenal, BM-independent effect, for example from the endocrine system. To test directly whether there was an intrinsic renal influence, we therefore studied kidney transplants.

The kidney transplant experiments were made more complex by the fact that there was rejection when we transplanted kidneys between the strains. We therefore made use of the fact, which we had shown previously, that F1 rats have an intermediate susceptibility to glomerulonephritis compared with the parental strains. It is possible to transplant from parental strains into F1 animals without rejection because the recipient animals share all of the antigens of the donor. It may be that the process of transplantation itself could have an effect on the severity of crescentic glomerulonephritis compared with the parental strains. It is possible to transplant from parental strains into F1 animals without rejection because the recipient animals share all of the antigens of the donor. It may be that the process of transplantation itself could have an effect on the severity of crescentic glomerulonephritis in the transplanted kidney, and, in addition, there is some variability between the susceptibility of the F1 animals. Therefore, to take account of this, we compared the severity of glomerulonephritis in the transplanted kidney with that in the native kidney. The results with kidney transplantation confirmed the findings with BM transplantation, in that Lewis kidneys developed crescentic glomerulonephritis when placed in an appropriate (WKY) environment.

However, the severity of glomerulonephritis in transplanted Lewis kidneys relative to native kidneys in F1 recipients was significantly less than that of transplanted WKY kidneys, indicating that the kidney itself makes a contribution to susceptibility to glomerulonephritis. It is noteworthy that whereas four of six WKY transplanted kidneys showed similar disease severity to the recipient F1 kidneys, the Lewis transplanted kidneys showed clearly less disease, suggesting the presence of protective factors in Lewis kidney. We found a similar effect on MCP-1 mRNA levels and glomerular macrophage numbers, which were higher in WKY kidneys than in Lewis kidneys that were transplanted into F1 animals. This contrasts with experiments in the Thy-1 model of mesangial proliferative glomerulonephritis in rats using kidney transplants, which showed that influx of macrophages was entirely dependent on circulating cells (21). Conversely, in the same Thy-1 model, experiments that used two substrains of Lewis rat with different susceptibility to glomerulosclerosis showed that this susceptibility is governed by genes that are expressed by the kidney (22). As far as we are aware, our study is the first to show a naturally occurring genetic susceptibility to glomerular inflammation that is dependent on the kidney.

There is considerable evidence from studies in mice that intrinsic glomerular cells contribute to the severity of glomerular inflammation. For example, in a series of elegant experiments, the group of Tipping and Holdsworth studied mice in which BM is transplanted between wild-type mice and mice that are genetically engineered to lack selected cytokines, allowing the construction of chimeras with cytokine deficiency in BM-derived cells or intrinsic renal cells (23). They showed that intrinsic renal cell production of TNF-α (24), IFN-γ (25), and IL-12 (26) and intrinsic renal cell expression of CD40 (27) contribute to induction of crescentic glomerulonephritis in a mouse model of NTN. It is not possible to be certain from their experiments, but a likely intrarenal source of these cytokines is
the glomerular mesangial cell. We previously showed that rat mesangial cells that are stimulated with IL-1β produce macrophage chemotactic factors, including MCP-1, and that culture supernatants from stimulated mesangial cells are able to suppress macrophage activation as assessed by nitric oxide synthesis (28). All of these studies indicate an important cross-talk between mesangial cells and inflammatory cells in the mediation of glomerulonephritis. It is therefore not entirely unexpected that in the WKY rat, where several different genes are involved in susceptibility, one or more of these could control mesangial cell function.

To define further the possible role of the mesangial cell in the susceptibility of the WKY rat to crescentic glomerulonephritis, we examined the response of cultured mesangial cells to various stimuli. We first studied responses to aggregated rabbit IgG because rabbit IgG is used as the nephrotoxic globulin in our model. In response to aggregated IgG, we found that WKY mesangial cells made considerably more MCP-1 than did Lewis mesangial cells. One possible explanation for this result is that it is due to the absence of Fcgr3-rs, as we have shown for WKY macrophages. However, our previous studies in mice showed no role for intrinsic renal cell expression of Fc receptors in mouse NTN (29). We therefore looked at responses to other stimuli and showed that there was also enhanced synthesis of MCP-1 by WKY mesangial cells in response to TNF-α (Figure 6) and LPS (data not shown). It is interesting that we also showed enhanced MCP-1 synthesis by WKY macrophages, although this was not further increased by TNF-α. The cellular mechanism that determines this enhanced response remains to be elucidated. We are currently breeding rats that are congenic for the QTL that we have described on chromosomes 13 and 16, and these should allow us to determine which of these loci are responsible for the phenotypes shown by macrophages and mesangial cells in the WKY rat.

### Conclusion

Our results indicate that the unique susceptibility of the WKY rat to crescentic glomerulonephritis is due to several genes. One of these is Fcgr3, which is responsible for the enhanced responses of WKY macrophages to immune complexes, although other genes may also be involved in the macrophage phenotype. Transfer of BM-derived cells is sufficient to transfer susceptibility to crescentic glomerulonephritis to a nonsusceptible strain, but the full-blown crescentic nephritis that is seen in the WKY rat is also dependent on genes that control intrinsic renal cell responses and in particular the response of mesangial cells to proinflammatory stimuli. This is the first demonstration of naturally occurring genetic differences in mesangial cell phenotype and raises the intriguing possibility that similar genetic variation may occur in human mesangial cell responses and could influence development of glomerulonephritis.

### Acknowledgments

This work was supported by grants from the Medical Research Council and the Mason Medical Research Foundation.

This work was presented as an abstract at the annual meeting of the American Society of Nephrology; November 14 through 19, 2006; San Diego, CA.
Disclosures

None.

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