The renal retinoid system: time-dependent activation in experimental glomerulonephritis

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The renal retinoid system: time-dependent activation in experimental glomerulonephritis. Am J Physiol Renal Physiol 286: F458–F465, 2004. First published October 28, 2003; 10.1152/ajprenal.00173.2003.—Retinoids reduce renal damage in rat experimental glomerulonephritis. It is unknown, however, how local and systemic retinoid pathways respond to renal damage in rat experimental glomerulonephritis. We examined the extrarenal and glomerular retinoid concentration patterns. On days 3, 7, and 14, we compared nonnephritic rats (control group; CON) to THY-GN rats with respect to systolic blood pressure and glomerular cell count per cross section. Systolic blood pressure and glomerular cell count were significantly higher in THY-GN rats on days 7 and 14 (P < 0.001). We found a 60% reduction in expression levels for retinoid receptors and dehydrogenases in nephritic glomeruli on day 3, but a threefold increase on day 7 (P < 0.001 vs. CON). The same applies to RARα protein. Hepatic expression of retinoid receptors was not influenced. On day 14, glomerular expression levels for retinoid receptors and retinoid-metabolizing enzymes had returned to a normal level, glomerular cell count being still increased. Administering 13-cis retinoic acid (isotretinoin) lowered blood pressure and glomerular cell count in nephritic rats but failed to influence the glomerular expression of retinoid receptors or retinoid-metabolizing enzymes. Our data document a stimulation of glomerular retinoid-synthesizing enzymes and expression of retinoid receptors in the early repair phase of THY-GN, suggesting activation of this system in acute renal disease.

retinoid receptors; retinol dehydrogenase; retinal dehydrogenase; isotretinoin; acute anti-Thy1.1-glomerulonephritis; rat

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the consequences of isotretinoin treatment for this condition. Features applying to both investigations include the following.

We chose male Wistar rats (Charles River, Sulzfeld, Germany), weighing 150–160 g, as the object of our investigations. All animal experimentation was performed according to the “Deutsches Tier- schutzgesetz” (German Animal Protection Law). The experimental groups represented nephritic groups. We induced acute anti-Thy1.1-

mesangioproliferative glomerulonephritis by administering 500 μg of Moab 1-22-3 dissolved in PBS (15) as a single-shot injection into the tail vein of the rats on day 0. Moab 1-22-3 is a monoclonal antibody directed against the Thy1.1-like antigen on the surface of rat mesangial cells (14). In contrast to the monoclonal antibody OX-7, Moab 1-22-3 induces more severe mesangial cell injury, resulting in earlier mesangiolytic changes, matrix expansion, and higher proteinuria (35).

Between groups, pair-feeding of the rats was used to ensure that all animals received identical amounts of nutrients.

At the end of the experiments, the rats were given intramuscular injections of 5 mg/kg body wt xylazine (Bayer Vital, Leverkusen, Germany) and 100 mg/kg body wt ketamine 10% (WDT, Garbsen, Germany). The rats were then perfused with saline solution containing 0.5 g/l procaine hydrochloride via a cannula retrogradely inserted into the abdominal aorta (45). To drain blood, the inferior vena cava was incised. The perfusion pressure was adjusted to the individual systolic blood pressure (SBP). Glomeruli were isolated by a fractional sieving technique as described elsewhere (37). The kidneys of each rat were sieved individually. We used three grids with a final mesh size of 53 μm for glomeruli. The yield and purity of isolated glomeruli were comparable between groups at any time (purity >90%).

In the first investigation, three experimental (THY; n = 8) and three control groups (CON; n = 6) were established. Day 3, 7, or 14 after the injection of the antibody represented the experimental end point when SBP was determined by tail-cuff plethysmography (tail plethysmograph built by the University of Heidelberg) under light ether anesthesia. SBP was also taken on day 0. The SBP for each rat was calculated as the average of three separate measurements at each session.

In the second investigation, we established two experimental and two control groups. One experimental (THY; n = 8) and one control (CON; n = 6) group was pretreated with 10 mg/kg body wt isotretinoin (F. Hoffmann-La Roche, Basel, Switzerland) orally for 3 days before Moab 1-22-3 or PBS administration. Isotretinoin-chow was prepared according to Schäfer et al. (32). The other groups received a placebo (vehicle) chow.

On day 7 the experiment was terminated. SBP was measured on days −3, 0, and 7.

Table 1. Sequence, hybridization position of primers, annealing temperature, and cycle numbers used for quantitative RT-PCR of retinoid receptors and retinoid-metabolizing enzymes

<table>
<thead>
<tr>
<th>Gene</th>
<th>Primer Sequence (5′ → 3′)</th>
<th>Hybridization Position</th>
<th>Annealing Temperature</th>
<th>No. of Cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>RARα</td>
<td>S: AGT TCT GAA GAG ATA GTG CCC</td>
<td>301</td>
<td>57°C</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>AS: TGT TCT GAG CTT TGC TTT</td>
<td>749</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RARβ</td>
<td>S: AGA GCT ATG AGA TGA CAG CGG</td>
<td>703</td>
<td>58°C</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>AS: GTG ATG TCT TCG TGC TCT GG</td>
<td>1030</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RARγ</td>
<td>S: AAC AAG GTG ACC AGG AAT CG</td>
<td>817</td>
<td>57°C</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>AS: AGA AGG TCA TGG TGG TCT CG</td>
<td>1279</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RXRα</td>
<td>S: TCC TGA GGC AAG CAC TAT GG</td>
<td>606</td>
<td>57.5°C</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>AS: GCA TCT TGG ACA CAA GCT CC</td>
<td>1254</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RoD 1</td>
<td>S: AGC TGA GGA GCA AGA CAT CG</td>
<td>497</td>
<td>55°C</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>AS: TGG GAG ATG CAA TAA CCA CC</td>
<td>833</td>
<td></td>
<td></td>
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<tr>
<td>RoD 2</td>
<td>S: ACA GAG AGT ATT GTG GCA GCC</td>
<td>487</td>
<td>55°C</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>AS: TGG GAG ATG CAG TAA CCA CC</td>
<td>767</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RaD 1</td>
<td>S: AGC GAT TTC TGC CAT GGG</td>
<td>720</td>
<td>55°C</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>AS: CAT TTC ATG GAG ATT TG</td>
<td>1290</td>
<td></td>
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<tr>
<td>RaD 2</td>
<td>S: TGG GTT TTC TGT GGA GAA G</td>
<td>274</td>
<td>55°C</td>
<td>34</td>
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<tr>
<td></td>
<td>AS: TGT GTA TCA CAA CCT GAG ACG</td>
<td>777</td>
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<td></td>
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S, sense; AS, antisense; RAR, retinoic acid receptor; RXR, retinoid X receptor; RoD and RaD, retinol and retinal dehydrogenase, respectively.
DNA was determined. Each sample was measured in two individual PCR assays for every investigated gene.

**Immunoblotting.** Proteins were isolated from frozen glomeruli according to the manufacturer’s instructions provided together with an immunoblotting kit (Santa Cruz Biotechnology, Santa Cruz, CA). After fractionating by SDS-PAGE in a 10-slot gel chamber, proteins were electrotransferred onto nitrocellulose filters that were blocked with 5% milk-0.05% Tween 20. Membranes were incubated with RARα antibody (1:250) for 1 h and then with 1:5,000 dilution of goat anti-rabbit IgG-horseradish peroxidase (both antibodies: Santa Cruz Biotechnology) and finally detected by chemoluminescence (11).

**Statistical analyses.** All values are expressed as means ± SE. Data were analyzed by using the nonparametric Mann-Whitney test or multivariate ANOVA and Bonferroni’s posttest, as indicated. Statistical significance was accepted at \( P < 0.05 \).

## RESULTS

**SBP and glomerular cell count in the course of THY-GN: effect of isotretinoin.** THY-GN rats experienced a significant and steady rise in SBP after Moab 1-22-3 injection, whereas SBP values in CON rats remained constant at all times (Fig. 1A).

Isotretinoin treatment reduced the steepness of the rise in SBP in THY-GN rats but did not have any effect in nonnephritic CON on day 7 \( (P < 0.01; \text{Fig. 1B}) \).

Compared with CON, the glomerular count of cell nuclei was significantly lower in THY-GN rats on day 3 \( (P < 0.01) \) but doubled in value on day 7 and thus was significantly higher than in the CON groups on days 7 and 14 \( (P < 0.001; \text{Fig. 1C}) \). Again, isotretinoin treatment of THY-GN rats reduced the increase in glomerular numbers of cell nuclei, whereas elevated values in vehicle-treated THY-GN rats were retained \( (P < 0.01; \text{Fig. 1D}) \).

**Serum and tissue retinoid concentrations.** Serum 13-cis RA and all-trans RA levels were higher in isotretinoin-treated than in vehicle-treated groups (Fig. 2, A and B).

13-Cis RA and all-trans RA levels in isolated glomeruli of vehicle-treated groups were close to or below the detection limit of the assay but made a shift to detectable values in the case of isotretinoin treatment (Fig. 2, C and D).

**Time-dependent changes in glomerular gene expressions of retinoid receptors in the course of acute THY-GN.** On day 3, levels of glomerular expression of the retinoid receptors RXRα, RXRβ, and RXRγ significantly fell below control values in THY-GN rats \( (P < 0.01) \), RXRα being the only receptor expressed at control levels. On day 7, all receptors showed obvious similarities to the expression pattern of RA levels in isolated glomeruli of THY-GN and RXRα expression was less compared with the other receptors. It remained minimally elevated in THY-GN vs. CON \( (P < 0.001; \text{Fig. 3, A–D}) \).

**Hepatic mRNA expression of RXRα and RXRγ in THY-GN.** No difference in the hepatic expression of RXRα and RXRγ could be observed between nephritic and nonnephritic groups on day 7.

**Time-dependent changes in glomerular gene expressions of retinoid-metabolizing enzymes in the course of acute THY-GN.** The glomerular expression pattern of all retinoid-metabolizing enzymes (RalDH 1 and 2, RoDH 1 and 2) showed obvious similarities to the expression pattern of retinoid receptors: a 80% decline in relation to control values on day 3 \( (P < 0.0001; \text{RoDH 1: 83.04%, RoDH 2: 77.53%, RoDH 1: 75.71%, RoDH 2: 82.0%}) \), a surge to values about four times the control values on day 7 \( (\text{RoDH 1: 5.56×, RoDH 2: 8.3×, RoDH 1: 2.79×, RoDH 2: 1.65×}) \), and the return to or below control levels on day 14 (Fig. 4, A–D).

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**Fig. 1.** A: time course of systolic blood pressure (SBP) 3, 7, and 14 days after induction of anti-THY1.1-glomerulonephritis (THY-GN). Values are means ± SE. SBP was measured in THY-GN rats compared with nonnephritic controls (CON). **■** \( P < 0.001 \). B: influence of isotretinoin treatment on SBP. Isotretinoin reduced SBP in rats with THY-GN significantly on day 7. *\( P < 0.01 \), **■** \( P < 0.001 \). C: total glomerular count of cell nuclei was significantly lower in THY vs. CON rats on day 3, whereas on days 7 and 14 it was elevated nearly 2-fold in THY vs. CON rats. *\( P < 0.01 \), **■** \( P < 0.001 \). D: effects of isotretinoin treatment on total glomerular count of cell nuclei. Isotretinoin reduced glomerular cell number in rats with THY-GN. *\( P < 0.01 \), **■** \( P < 0.001 \).
Effect of isotretinoin treatment on the glomerular expression of retinoid receptors and retinoid-metabolizing enzymes in the course of acute THY-GN. Oral supplementation with isotretinoin did not influence glomerular gene expression of retinoid receptors and of retinoid-synthesizing enzymes in nonnephritic rats. Isotretinoin did not influence the threefold elevation of the expression of these genes in THY-GN rats on day 7 (Table 2).

Glomerular protein expression of RARα on day 7. The glomerular expression of protein RARα was analyzed in vehicle- and isotretinoin-treated CON and THY-GN rats. RARα

Fig. 2. A and B: serum retinoid concentrations. 13-Cis and all-trans retinoic acid (RA) were more abundant in isotretinoin- than in vehicle-treated groups. Values are expressed as ng retinoid/ml serum. The detection limit was 1 ng/ml; however, values over 10 ng/ml can only be considered as confident. C and D: glomerular retinoid concentrations. 13-Cis and all-trans RA were nearly undetectable in untreated groups, but they could be shown under isotretinoin treatment. The values are presented as pmol retinoid/g tissue. The detection limit was 0.7 pmol/g tissue (wet weight); however, values over 7 pmol/g tissue (wet weight) can only be considered as confident.

Fig. 3. A–D: glomerular gene expression of retinoid receptors in the course of acute THY-GN. Values are means ± SE. On day 3, the expression of the retinoic acid receptor RARα decreased significantly in nephritic glomeruli vs. nonnephritic CON rats, whereas on day 7 the glomerular expression of all receptors was 3-fold higher in THY-GN vs. CON rats. In contrast, on day 14, glomerular RARβ and RARγ mRNA reached the level in CON rats, whereas gene expression of RARα and retinoid X receptor RXRα remained elevated in THY-GN vs. CON rats. The dotted line demonstrates normalized control level. *P < 0.01, **P < 0.001.
was found in glomeruli, where it was more abundant in THY-GN than in nonnephritic rats. Isotretinoin treatment did not alter RAR expression levels ($P < 0.05$; Fig. 5, A and B).

**DISCUSSION**

Our data document a time-dependent response of the endogenous retinoid system to acute glomerular damage at different times in the course of acute mesangio proliferative glomerulonephritis in the rat. The results of this study complement previous findings, in which there had been shown that isotretinoin reduces the blood pressure increase in acute THY-GN (43). The fact that the number of resident glomerular cells is reduced on day 3, reflecting early mesangiolysis in response to antibody-mediated injury, is characteristic of the model (14). In contrast, on day 7 the number of mesangial cells is increased again as a result of mesangial cell proliferation (12). This course of THY-GN was confirmed in our model.

In agreement with our earlier work, treatment with isotretinoin lowered blood pressure, proliferation of mesangial cells,

Table 2. Effects of isotretinoin treatment on glomerular gene expression of retinoid receptors and retinoid-metabolizing enzymes in acute THY-GN on day 7

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Isotretinoin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CON</td>
<td>THY</td>
</tr>
<tr>
<td>RARα</td>
<td>0.82 ± 0.09</td>
<td>1.52 ± 0.05†</td>
</tr>
<tr>
<td>RARβ</td>
<td>0.69 ± 0.07</td>
<td>1.81 ± 0.15†</td>
</tr>
<tr>
<td>RARγ</td>
<td>0.61 ± 0.05</td>
<td>1.63 ± 0.13†</td>
</tr>
<tr>
<td>RXRα</td>
<td>0.56 ± 0.05</td>
<td>1.90 ± 0.23†</td>
</tr>
<tr>
<td>RoDH 1</td>
<td>0.57 ± 0.07</td>
<td>2.22 ± 0.18†</td>
</tr>
<tr>
<td>RoDH 2</td>
<td>0.37 ± 0.08</td>
<td>1.64 ± 0.23†</td>
</tr>
<tr>
<td>RalDH 1</td>
<td>0.74 ± 0.05</td>
<td>1.41 ± 0.11*</td>
</tr>
<tr>
<td>RalDH 2</td>
<td>0.43 ± 0.09</td>
<td>1.96 ± 0.23*</td>
</tr>
</tbody>
</table>

Values are means ± SE. THY-GN, anti-Thy-1.1 nephritis; CON, control. In THY-GN rats, oral isotretinoin (10 mg/kg body wt) did not influence expression of either RARs and RXRs or of RoDHs and RalDHs. THY vs. CON: $*P < 0.01$; $†P < 0.001$. $\star P < 0.05$. 

Fig. 4. A–D: glomerular gene expression of retinoid-metabolizing enzymes in the course of acute THY-GN. Values are means ± SE. On day 3, the glomerular gene expression of retinol and retinal dehydrogenases (RoDHs and RalDHs) decreased by 80% in THY-GN vs. CON rats. In contrast, on day 7 the mRNA expression of these enzymes was 4-fold higher in nephritic glomeruli than that in nonnephritic controls. On day 14, RalDH 1 and RoDH 2 returned to CON levels, whereas RalDH 2 and RoDH 1 were significantly lower in THY-GN vs. CON rats. The dotted line demonstrates normalized control level. $**P < 0.001$. 

Fig. 5. A and B: immunoblotting of glomerular RARα. Values are means ± SE. On day 7, RARα protein is more abundant in THY than in CON groups. Isotretinoin treatment had no influence on RARα protein levels. kD, kDa.
and glomerular damage (8, 22, 43). The mechanism of the antihyperpertensive effect of retinoids has not yet been clarified. The retinoid-mediated decrease in SBP is not specific for isotretinoin, because synthetic retinoids also lowered blood pressure in the THY-GN model (16). It may reflect alleviation of renal damage by retinoids, allowing the kidney to normalize SBP. Additionally, however, retinoids lower the expression of the angiotensin receptor in vitro and in vivo. They block the effects of angiotensin II (8, 11). This suggests another possible mechanism of blood pressure-lowering action by retinoids.

Antiproliferative effects of retinoids were demonstrated in different cell types, e.g., mesangial, vascular smooth muscle, endothelial, and tubular cells (11, 28, 36). The mechanisms of the antiproliferative action of retinoids have not been completely elucidated. One pathway is the interference with AP-1 by protein-protein interaction of retinoid receptors or by down-regulation of its units c-Jun and c-Fos (35). Thus proliferation by AP-1-dependent genes, e.g., angiotensin II, PDGF, or endothelins, is lowered by retinoids (11, 20, 46).

Changes in the endogenous retinoid system in response to acute glomerular injury were observed at the level of retinoid receptor expression, serum and glomerular retinoid levels, and glomerular expression of retinoid-metabolizing enzymes.

Regulation of the different subtypes of retinoid receptors under different circumstances has been described in the past (4, 5, 17). On day 3, we observed a uniform decrease in glomerular retinoid receptor gene expression, with the exception of RARα. Because receptor expression was determined in isolated glomeruli and expressed per microgram RNA, it is obvious that this decrease does not reflect merely the effects of mesangiolysis but indicates either a relative reduction in retinoid receptor-expressing cells within the glomeruli or a reduced expression of the receptor number per cell.

Mesangial cells are known to express retinoid receptors (11), but do so endothelial and inflammatory cells, i.e., monocytes/macrophages. In contrast to the other receptors, RARα was not affected. Because this receptor is supposed to be ubiquitously expressed, its expression might not have been influenced by a shift in the relative distribution of glomerular cells, although it cannot be excluded that these are receptor subtype-specific differences in receptor regulation.

Similar to the expression of glomerular retinoid receptors on day 3, the expression of retinoid-metabolizing enzymes was reduced as well. The cellular origin of expression of these enzymes in the glomerulus has not yet been determined. The reduction of gene expression of these enzymes may suggest a decrease in the local production of retinoids in the state of early glomerular damage in THY-GN. Whether these alterations locally influence the level of retinoids in the glomeruli is unknown.

On day 7, a completely different expression pattern of the retinoid receptors and retinoid-metabolizing enzymes was observed: In contrast to day 3, the expression of all retinoid receptors and retinoid-metabolizing enzymes was significantly higher in nephritic compared with nonnephritic glomeruli. On the mRNA level, retinoid receptor and RalDH expression was increased about threefold, and RoDHs expression about fivefold. On day 7, both mRNA expression and protein expression of RARs in the glomeruli were increased.

Because at that time the number of mesangial cells was elevated as a result of the ongoing repair processes, it cannot be decided whether the enhanced receptor and enzyme expression was due to an increased glomerular number of retinoid receptor-expressing cells or an enhanced expression per cell. The findings on day 14, however, answer this question, because at that point the expression of retinoid system components and glomerular cell number did not go in parallel. On day 14, the expression of the different retinoid receptors had almost returned to normal, whereas the number of glomerular cells was still elevated. Similar findings were obtained with respect to the retinoid-metabolizing enzymes.

These changes, therefore, cannot be explained on the basis of the number of retinoid receptor-expressing cells but strongly suggest a regulated cellular expression of these receptors. This interpretation is also supported by the fact that hepatic expression of RARα and RXRα was not altered on day 7, when their expression in the glomeruli was significantly elevated, suggesting time-specific regulation. Because the expression of these two receptors did not change in the liver on the day of maximal change in the kidney, we took this as further evidence that the changes in the retinoid system are induced locally in the kidney due to renal disease.

A regulated response of the retinoid system to glomerular damage is further supported by the findings of a decreased amount of 13-cis RA and all-trans RA in the serum on day 7 in vehicle-treated nephritic rats. This may indicate “consumption” of the retinoids. A local reduction in available retinoids at the site of inflammation may trigger increased expression of retinoid receptors and of metabolizing enzymes. In the glomeruli, the endogenous retinoid levels were low or at the detection limit of these assays, precluding further analysis.

We therefore applied isotretinoin to overcome a potential local reduction in retinoids. As a result of this maneuver, the elevated concentrations of 13-cis RA and its isomer all-trans RA were meshed in the serum of nonnephritic and nephritic rats as well as in the glomeruli. In the past, isotretinoin had been shown to reduce the number of glomerular cells and the level of SBP as surrogate markers of glomerular damage (22, 32, 42, 43). The fact that isotretinoin influenced neither the glomerular expression of retinoid receptors nor that of metabolizing enzymes is puzzling, because isotretinoin is metabolized to all-trans RA in the glomeruli. 13-Cis RA binds neither CRABP nor retinoid receptors (48), but it has been shown to act as a prodrug for all-trans RA in the skin (40). These findings indicate that retinoid supplementation is not the trigger for retinoid receptor expression in this model. Our results are in conflict with the results of other investigators, who had demonstrated that the levels of vitamin A or of retinoids can influence retinoid receptor expression (13). On the other hand, induction of retinoid receptors on day 7 may render renal tissue more sensitive to the action of isotretinoin, further supporting its anti-inflammatory and antiproliferative effects.

The results of our experiments indicate an active and specific response of the renal retinoid system in the early repair phase of acute mesangioliproliferative glomerulonephritis.

Retinoids have long been associated with wound healing. In dermatology, for instance, retinoids are used for the treatment of psoriasis, acne, and seborrhoea (26, 27). Previous work has indicated that retinoids play a role in the control of inflammation and wound healing, because they exert strong anti-inflammatory and antiproliferative effects (7, 11, 21). Therefore, a local reduction in available retinoids at the site of inflammation...
may trigger increased expression of retinoid receptors and of metabolizing enzymes.

Conversely, a deficiency of vitamin A retards tissue repair. Retinoids reverse the inhibitory effects of glucocorticoids on wound healing by promoting epithelization and synthesis of collagen and ground-substance (1). Paquette et al. (29) have recently shown that topical all-trans RA treatment of patients with chronic leg ulcers stimulates formation of granulation tissue, angiogenesis, and synthesis of new collagen.

Above all, our findings suggest that renal tissue responds to exogenous retinoids and that the endogenous retinoid system is altered in response to renal injury. Whether these changes reflect the activation of this system or the response to local deprivation of retinoids after renal injury remains to be elucidated. Clearly, the changes in the endogenous system suggest an active role of retinoids in glomerular damage repair.

GRANTS

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