Low-dose mTOR inhibition by rapamycin attenuates progression in anti-thy1-induced chronic glomerulosclerosis of the rat


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Low-dose mTOR inhibition by rapamycin attenuates progression in anti-thy1-induced chronic glomerulosclerosis of the rat. Am J Physiol Renal Physiol 294: F440–F449, 2008. First published December 19, 2007; doi:10.1152/ajprenal.00379.2007.—Treatment options in human mesangioproliferative glomerulonephritis, mostly IgA nephropathy, are limited. Progressive mesangioproliferative nephropathy represents a major cause of end-stage kidney disease. The present study explores the efficacy of low-dose mTOR inhibition by rapamycin in a chronic-progressive model of mesangioproliferative glomerulosclerosis (cGS). cGS was induced by high-dose anti-thy1 antibody injection into uninephrectomized rats. Rapamycin administration (2.5 mg·kg⁻¹·body wt⁻¹) was started 10 days after antibody injection and continued until week 20. cGS was characterized by advancing proteinuria, increased blood pressure, marked tubulointerstitial and glomerular fibrosis, cell proliferation and round cell infiltration, and impaired renal function. Kruskal-Wallis and Mann-Whitney U-tests were used for statistical analysis. The course of chronic anti-thy1-induced glomerulosclerosis was significantly attenuated by low-dose rapamycin treatment. In week 20, this was demonstrated by improvements in proteinuria (−38%), systolic blood pressure (−16 mmHg), tubulointerstitial and glomerular histological matrix accumulation (−61 and −24%), transforming growth factor-β1 overexpression (−41 and −47%), collagen I deposition (−53 and −65%), cell proliferation (−90 and −76%), and leukocyte number (macrophages −52 and −53%; lymphocytes −58 and 51%), respectively. Rapamycin improved renal function as well (blood creatinine −0.68 mg/dl, urea −66.7 mg/day, and creatinine clearance +0.13 ml·min⁻¹·100 g body wt⁻¹). In conclusion, low-dose mTOR inhibition by rapamycin limits the progressive course of anti-thy1-induced renal disease toward chronic glomerulosclerosis, tubulointerstitial fibrosis, and renal insufficiency. Renoprotection by rapamycin involved significant beneficial effects on multiple key pathways in the progression of chronic renal disease, i.e., proteinuria, extracellular matrix accumulation, renal cell proliferation, and inflammatory cell infiltration.
tubulointerstitial fibrosis, and renal insufficiency in a not primarily immune-mediated manner (17, 21, 27). This model has been termed anti-thy-1-induced chronic glomerulosclerosis or anti-thy-1-induced renal fibrosis (17, 27). The course of experimental progressive anti-thy-1-induced chronic glomerulosclerosis mimics to a relevant degree advancing mesangio-proliferative nephropathy in humans and thus can act as an experimental model for studying human disease. Treatment with low-dose rapamycin was started 10 days after antibody injection, i.e., after the initial marked glomerular proliferation of mesangial cells had passed. Proteinuria was determined monthly as a disease follow-up. In week 20 after disease induction, the actions of rapamycin on key pathways of renal disease progression, such as proteinuria, fibrogenesis, cell proliferation, and round cell infiltration, were measured. Blood pressure and renal function served as additional measures of disease severity and therapeutic efficacy.

METHODS

Materials. Unless otherwise indicated, materials, chemicals, or culture media were purchased from Sigma-Aldrich (Taufkirchen, Germany).

Animals. Male Wistar rats (150–180 g) were obtained from Charles River (Sulzfeld, Germany). The animals were fed a normal protein diet (22.5% protein, A1311, Altromin, Lage, Germany) for at least 3 days before the experiment to allow equilibration. Animals were housed in a constant-temperature room with a 12:12-h dark-light cycle. Body weight was determined weekly. Food and water intakes were monitored daily. Animal care and treatment were in conformity with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by local authorities.

Model of anti-thy-1-induced chronic-progressive glomerulosclerosis. Chronic-progressive glomerulosclerosis (cGS) was produced by surgically removing one kidney and intravenously injecting the monoclonal antibody mAb 1-22-3 (5 mg/kg body wt in PBS, pH = 7.4) 3 days later (17, 21, 27). The mAb 1-22-3 antibody binds to a thy-1-like antigen on the surface of mesangial cells of the kidney and causes a fast complement-dependent and NO-dependent mesangial cell lysis within the next 24 h (17, 27). The progression in cGS is linked to the uninephrectomy that is performed before anti-thy-1 antibody injection, since the glomerular disease resolves over ~4 wk in animals with two kidneys (17, 21, 27). Control animals were injected with equal volumes of PBS only.

Treatment with rapamycin. Rapamycin (sirolimus) was given with food at a daily dose of 2.5 mg·kg^{-1}·body wt^{-1}. Rapamycin is a bacterial macrolide widely used as an immunosuppressive drug to prevent rejection in organ transplantation (18). The rapamycin-containing food was produced in our laboratory by using the flour of the standard rat chow (22.5% protein, A1311, Altromin). The drug was mixing the dry food flour in appropriate amounts, water was added to form pellets, and the air-dried pellets were subsequently given to the rapamycin-treated animals.

Experimental groups and design. One week after anti-thy-1 antibody injection, 24-h urine was collected. On the basis of the actual volumes of PBS only.

urine collection in weeks 1, 4, 8, 12, 16, and finally on the day before euthanasia in week 20. Urinary protein was measured using a pyrogallol red microtiter plate technique as previously described (17, 27). Proteinuria is expressed as milligrams protein per 24 hours. Systolic blood pressure was assessed before euthanasia in trained conscious animals by a tail-cuff method as previously described (17, 27).

Blood rapamycin levels. Blood mTOR concentrations were analyzed in weeks 12 and 20 after disease induction. Rapamycin blood levels were determined in whole-blood samples using a rapid, sensitive liquid chromatography–tandem mass spectrometry (LC-MS/MS) method as previously described (25). Eluates from HPLC columns were introduced into a Sciex API 2000 triple-quadrupole mass spectrometer (PerkinElmer Applied Biosystems, Foster City, CA) and calculated (integration of peak areas; calculation of peak area ratios, calibration curve and drug concentration) with PE Sciex TurboQuan (Ver.1.0) software.

Euthanasia. The animals were anesthetized with 0.1 mg ketanes/0.01 mg xylazine per 100 g body wt (ketamine 10%, WDT, Garbsen, Germany; rompun 2%, Bayer Vital, Leverkusen, Germany). Following a midline abdominal incision, 5–10 ml of heparinized blood was drawn from the abdominal aorta, and kidneys were subsequently perfused with 30 ml of ice-cold PBS. Materials and tissues were subsequently processed as described in the following sections.

Renal function. Plasma and urine creatinine and plasma urea were measured spectrophotometrically in enzyme-based assays (17, 27). Creatinine clearance was used to estimate glomerular filtration rate and was calculated on the basis of plasma and urinary creatinine concentrations and the corresponding urine volume and is expressed as milliliters per minute per 100 grams body weight.

Lipid levels. Plasma cholesterol and triglyceride levels were measured by standard enzymatic methods following a 5-h fasting period. Blood lipid concentrations were analyzed by enzymatic photometric assays (CHOD-PAP method for cholesterol and GPO-PAP method for triglyceride) using an Hitachi 917 analyzer (Roche Diagnostics, Basel, Switzerland) (16).

Light and immunohistochemical microscopy. For histological examination, cortical tissue was fixed in Carnoy’s solution. All histological studies were performed in a blinded fashion. Paraffin sections (3 μm) were stained with periodic acid-Schiff reaction (PAS) to determine glomerular and tubulointerstitial fibrosis by computer-based morphometric analysis (17, 28). Renal sections were examined on a Zeiss Axios Imager.A1 light microscope connected to a PL-A662
and TIMP-1 content of the TGF-

supernatants were harvested and stored at 10 mg/ml, respectively. After 48-h incubation at 37°C/5% CO2, glomeruli/ml for 48 h, and minced cortical tissue at a density of g/ml streptomycin. Glomeruli were cultured at a density of 2,000 supplemented with 0.1 U/ml insulin, 100 U/ml penicillin, and 100 a piece of cortical tissue was weighed and minced extensively with a density in the nephritic animals (Con 624 vs. cGS 143 vs. Con 122 ± 3 mmHg, cGS 143 ± 3 g/l in week 12 and 1.86 ± 0.16 µg/l in week 20, confirming the targeted low-dose range.

One week after disease induction, proteinuria (Fig. 1A) was significantly elevated in the nephritic animals, which pointed out the efficacy of the randomization procedure (cGS 148 ± 12 mg/day; cGS+Rapa 147 ± 11 mg/day). Administration of rapamycin started on day 10 after disease induction showed a significant reduction of protein excretion (−38%, cGS+Rapa 183 ± 26 mg/day, P < 0.01) in week 4. In the nephritic control group, a continuous increase in proteinuria was observed, reaching values of 550 ± 46 mg/day at the end of the experiment in week 20. In comparison, final proteinuria was stabilized in the rapamycin-treated group and significantly lower than in the untreated animals (−62%, cGS+Rapa 213 ± 25 mg/day, P < 0.001). Proteinuria of normal control group was constantly low (week 20: 26 ± 3 mg/day).

As shown in Fig. 1B, anti-thy1-induced cGS was characterized by a slight rise in systolic blood pressure 20 wk after disease induction (cGS 143 ± 3 vs. Con 122 ± 3 mmHg).Effects of rapamycin on body weight, drug blood levels, proteinuria, and blood pressure. The animals’ mean body weight at the end of the experiment revealed an advantage for the nonnephritic controls, indicating chronic renal disease and insufficiency in the nephritic animals (Con 624 ± 12 g, cGS 502 ± 14 g, cGS+Rapa 456 ± 10 g; P = not significant).

RESULTS

Fig. 1. Proteinuria (A) and systolic blood pressure (B) 20 wk after induction of anti-thy1 chronic-progressive glomerulosclerosis (cGS). Treatment with rapamycin (+Rapa) was started 10 days after injection of anti-thy1 antibody. Normal animals (Con) received an injection with similar volumes of PBS. ###P < 0.01 and ####P < 0.001 vs. cGS.
Treatment with rapamycin largely prevented systolic blood pressure increase toward normotensive values (cGS + Rapa 127 ± 2 mmHg, \( P < 0.001 \)).

Effects of rapamycin on renal function. The histological photographs in Fig. 2 provide a characteristic overview on the impact of rapamycin administration on renal matrix accumulation in anti-thy1-induced cGS. The most pronounced actions of rapamycin were noted in the tubulointerstitial compartment.

Compared with the normal control animals, anti-thy1-induced cGS was characterized by a marked increase in tubulointerstitial histological matrix protein accumulation (50.1 ± 6.0 vs. 0.4 ± 0.1%), TGF-\( \beta 1 \) protein expression (480 ± 49 vs. 122 ± 10 pg/ml) and TIMP-1 protein expression (2.227 ± 1.063 vs. 901 ± 500 pg/ml) (Fig. 3, \( P < 0.001 \) sGC vs. Con for all parameters). In the chronic anti-thy1 animals treated with rapamycin, significant reductions were observed in tubulointerstitial matrix expansion (–61%, 19.6 ± 4.3%; \( P < 0.001 \)) and expression of TGF-\( \beta 1 \) (–41%, 283 ± 38 pg/ml; \( P < 0.01 \)) and TIMP-1 protein (–58%, 936 ± 236 pg/ml; \( P < 0.05 \)) (Fig. 3).

Antifibrotic, although less pronounced, actions were found at the glomerular level with low-dose rapamycin treatment (Fig. 4). The glomerular matrix score was significantly higher in untreated animals with cGS compared with normal controls (55 ± 4 vs. 21 ± 2%). Correspondingly, glomerular TGF-\( \beta 1 \) protein expression was markedly up-regulated (155 ± 16 vs. 50 ± 4 pg/ml). Low-dose rapamycin led to significant reductions in glomerular matrix protein deposition (–24%, 42 ± 2%; \( P < 0.05 \), vs. cGS) and glomerular TGF-\( \beta 1 \) protein expression (–47%, 97 ± 9 pg/ml; \( P < 0.01 \) vs. cGS). Glomerular TIMP-1 expression was lower in chronic anti-thy1 animals and not further affected by rapamycin.

The changes in tubulointerstitial and glomerular matrix scores were confirmed by analysis of renal collagen I deposition as a valid histological indicator of tissue fibrosis. Representative histological pictures are shown in Fig. 5. In animals with anti-thy1-induced cGS, marked collagen I deposition was found in the interstitial area of the cortex and the mesangial structures of the glomerulus. In histomorphometry, collagen I deposition was 5.0-fold higher in tubulointerstitial and 7.3-fold higher in glomerular sections, respectively, compared with normal controls (Fig. 5, A and B, \( P < 0.001 \) vs. Con for both). Low-dose rapamycin significantly lowered tubulointerstitial and glomerular collagen I deposition by –53 and –65%, respectively (\( P < 0.001 \) vs. cGS for both).

Effects of rapamycin on renal function. To show that decline of renal fibrosis goes along with improved kidney function, indicators of renal function were analyzed at the end of the 20-wk experiment period. As shown in Fig. 6, anti-thy1-induced cGS was characterized by significant increases in plasma creatinine (cGS 1.5 ± 0.4 vs. Con 0.3 ± 0.3 mg/dl) and urea levels (cGS 152 ± 34 vs. Con 42 ± 4 mg/dl) as well as markedly reduced creatinine clearance as indicators of glomerular filtration rate (cGS 0.17 ± 0.03 vs. Con 0.48 ± 0.87 ml·min\(^{-1}\)·100 g body wt\(^{-1}\)). Treatment with low-dose rapamycin significantly improved renal function, as evident in a –47% reduction in plasma creatinine (0.77 ± 0.82 mg/dl; \( P < 0.05 \)), a –44% reduction of plasma urea (84.8 ± 7.78 mg/dl; \( P < 0.01 \)), and an 80% increase in creatinine clearance (0.30 ± 0.04 ml·min\(^{-1}\)·100 g body wt\(^{-1}\); \( P < 0.05 \)).

Effects of rapamycin on blood lipids. Compared with the normal control animals, anti-thy1-induced cGS was characterized by a significant increase in blood triglyceride (2.7 ± 0.3
vs. 1.6 ± 0.2 mmol/l) and cholesterol concentrations (4.2 ± 0.4 mmol/l), respectively. To further explore the molecular and cellular mechanisms underlying the beneficial effects of rapamycin, renal cell proliferation and round cell infiltration (macrophages and lymphocytes) were analyzed in anti-thyl-induced cGS.

Fig. 3. Markers of tubulointerstitial fibrosis 20 wk after induction of anti-thyl cGS. Shown are the tubulointerstitial matrix scores (0–100%) of PAS-stained renal sections obtained by computer-based histomorphometry (A), tubulointerstitial transforming growth factor (TGF)-β1 protein expression (pg/ml; B), and tubulointerstitial tissue inhibitor of metalloproteinases (TIMP)-1 protein expression (pg/ml; C) from extensively minced individual cortical tissues cultured at a density of 10 mg/ml for 48 h. ##P < 0.01 and ###P < 0.001 vs. cGS.

Fig. 4. Markers of glomerular fibrosis 20 wk after induction of anti-thyl cGS. Shown are glomerular matrix scores (0–100%) of PAS-stained renal sections obtained by computer-based histomorphometry (A), glomerular TGF-β1 protein expression (pg/ml; B), and glomerular TIMP-1 protein expression (pg/ml; C) from glomeruli harvested from individual animals and cultured at a density of 2,000/ml for 48 h. #P < 0.05 and ###P < 0.01 vs. cGS.
Effects of rapamycin on renal cell proliferation. As shown in Fig. 7, anti-thy1-induced cGS shows marked tubulointerstitial (271 ± 71 vs. Con 7 ± 4 PCNA-positive cells/tubulointerstitial section) and glomerular proliferation (18 ± 5 vs. Con 2 ± 1 PCNA-positive cells/glomerular section), respectively. In week 20, PCNA-positive renal cell staining in animals treated with rapamycin was reduced by −90% in the tubulointerstitial (27 ± 6 PCNA-positive cells/section; \( P < 0.05 \)) and by −76% in the glomerular compartment (5 ± 1 PCNA-positive cells/section; \( P < 0.05 \)).

Effects of rapamycin on renal mononuclear cell infiltration. The numbers of macrophages and lymphocytes were significantly increased in animals 20 wk after induction of anti-thy1-induced cGS (Fig. 8). In the tubulointerstitial space, 50 ± 9 ED1-positive cells/section, indicating macrophages, and 72 ± 9 CD3-positive cells/section, representing lymphocytes, were
detected. In the glomerular space, 3.4 ± 0.4 ED1-positive cells and 1.9 ± 0.2 CD3-positive cells were counted. Treatment with rapamycin significantly reduced renal cell infiltration. Tubulointerstitial and glomerular macrophage numbers were lowered by 52% (24 ± 4 ED1-positive cells/tubulointerstitial section, \( P < 0.05 \)) and 53% (1.6 ± 0.1 CD3-positive cells/glomerular section, \( P < 0.001 \)) respectively. Renal lymphocyte count was reduced by 58% (35 ± 5 CD3-positive cells/tubulointerstitial section, \( P < 0.001 \)) and 51% (0.8 ± 0.1 CD3-positive cells/glomerular section, \( P < 0.001 \)) respectively.

Taken together, the findings of the present study demonstrate marked renoprotective actions of low-dose rapamycin treatment on the progression of anti-thy1-induced renal disease toward chronic glomerulosclerosis, tubulointerstitial fibrosis, and renal insufficiency. These actions involve joint beneficial effects on proteinuria, renal fibrogenesis, cell proliferation, and leukocyte infiltration, all key pathways of progression in chronic renal disease.

DISCUSSION

Rapamycin, also known as sirolimus or AY-22989, belongs to a novel class of drugs that act through inhibition of the mammalian target of rapamycin (4, 18). Rapamycin was originally derived from the actinomycete Streptomyces hygroscopicus and was first isolated from soil samples from the Easter Islands (Rapa Nui). The mammalian target of rapamycin plays a...
central role in the regulation of cell proliferation, growth, differentiation, migration, and survival (4, 18, 24). mTOR is an intracellular serine/threonine kinase and a central component of a complex signaling network that is highly conserved in evolutionary terms and expressed ubiquitously throughout the cells of the body. Activation of mTOR leads to interaction with downstream effectors such as p70 ribosomal S6 kinase (p70S6K) and eukaryotic initiation factor-4E-binding protein-1. Through these pathways, mTOR controls cellular proliferation, promoting processes such as DNA translation, RNA transcription, ribosomal biogenesis, and cell cycle progression. Inhibitors of mTOR, such as rapamycin or everolimus, bind to an intracellular cytoplasmatic receptor, the FK506-binding protein-12. The complex formed then interacts and disrupts mTOR function and leads to cell cycle arrest in the G1 phase. In addition to blocking cell proliferation, mTOR inhibitors have been found to be anti-inflammatory, antifibrotic, antitumoral, and antifungal, which points to the involvement of mTOR signaling in a wide range of cellular functions (4, 18).

The present study was designed to explore the renoprotective potential of low-dose rapamycin in a chronic model of progressive mesangiproliferative nephropathy, i.e., anti-thy1-induced cGS in the rat. The major findings of the present study are 1) rapamycin remarkably limits the progressive course of chronic anti-thy1 antibody-induced renal disease towards glomerulosclerosis, tubulointerstitial fibrosis, and renal insufficiency; 2) this outcome contrasts to the one previously described in acute, short-term anti-thy1-induced glomerulonephritis in the rat (7, 8); and 3) renoprotection by low-dose rapamycin involved beneficial effects on a number of key pathways of renal disease progression, i.e., proteinuria, renal matrix protein accumulation, cell proliferation, and leukocyte infiltration (15, 17, 23, 28). Both the therapeutic and mechanistic implications of these clinically relevant findings are discussed in the following paragraphs.

The beneficial effects of mTOR inhibition have recently been reported in several rat models of chronic kidney disease, i.e., hypertensive 5/6 nephrectomy, diabetic nephropathy, hypertrophy following unilateral nephrectomy, tubulointerstitial fibrosis due to urethral obstruction or nephrotic syndrome, and polycystic kidney disease (2, 5, 10, 19, 26, 29). These beneficial results are now expanded toward a progressive model of human mesangiproliferative nephropathy as a leading cause of end-stage kidney disease worldwide (13, 14).
The outcome of mTOR inhibition in anti-thy1-induced cGS contrasts with the one previously reported in anti-thy1-induced acute glomerulonephritis (7, 8). In the latter, the mTOR inhibitor everolimus before or during the early marked mesangial cell proliferation turned out to be detrimental, manifesting aggravation of proteinuria, impaired self-healing, increased uremic mortality, and persistent glomerular fibrotic changes. These effects were observed both with high- and low-dose everolimus (7). The studies in anti-thy1 acute and chronic renal disease unanimously indicate that unaffected mTOR signaling is critical for the very early and marked mesangial cell proliferation and subsequent normal glomerular repair of acute anti-thy1 glomerulonephritis (7, 8). In the further course of the disease, inhibition of mTOR even acts beneficially and prevents chronic disease progression. As shown in the present work, this turning point already occurs 10 days after antibody injection, when the mesangial cell proliferation has come to a halt. Furthermore, the consensus on the tandem model of anti-thy1-induced acute and chronic renal disease reveals that findings in acute anti-thy1 glomerulonephritis cannot in all cases be extrapolated toward the chronic anti-thy1 glomerulosclerosis model and vice versa.

The contrasting actions of mTOR inhibition on experimental acute and chronic anti-thy1-induced renal disease mirror in principle the one seen in patients with primary chronic glomerulopathies or renal transplantation. In renal transplant recipients, preventive use of mTOR-based and calcineurin inhibitor-free immunosuppressive strategies has been shown to improve kidney function and transplant histology (12). However, in later stages of chronic allograft nephropathy, the switch to an mTOR inhibitor was associated with adverse effects, such as marked aggravation of proteinuria (9) and eventually deterioration of renal function. Predictors of adverse outcome included preexisting proteinuria >800 mg/day (9). In human primary glomerular disease, mTOR inhibition has been tried in more advanced disease states. In parallel to chronic allograft nephropathy, introduction of mTOR-based treatment was associated with acceleration of proteinuria and decline in renal function in some patients, but was at least to some degree beneficial in others (1, 6, 11). With regard to the relatively early start of mTOR inhibition in this experimental study, the early preventive use of mTOR inhibitors in chronic primary human glomerulopathies has not been determined yet. As in acute and chronic anti-thy1-induced renal disease, the emerging human data indicate that timing, the degree of preexisting disease, and maybe dose appear to be critical for the outcome in rapamycin treatment.

The key action of rapamycin is inhibition of cell proliferation. The present study proves that this pathway was actually operating. Using PCNA staining, low-dose rapamycin treatment went along with significantly lower numbers of both tubulointerstitial and glomerular proliferating cells. Furthermore, this investigation documents that rapamycin interferes with several other key pathways of renal disease progression. This involved reductions in 1) proteinuria, as shown by periodically measured 24-h urinary protein excretion; 2) renal matrix accumulation and fibrosis, as described by tubulointerstitial and glomerular matrix protein and collagen I deposition and the key fibrosis mediator TGF-β; and 3) renal round cell infiltration, as documented by tubulointerstitial and glomerular numbers of infiltrating macrophages and lymphocytes. Thus this study in chronic anti-thy1 glomerulosclerosis indicates that rapamycin directly or indirectly interferes with multiple key pathways in the progression of chronic renal disease, including mesangioproliferative nephropathy.

Systolic blood pressure was significantly lower in the rapamycin-treated animals than in the untreated chronic anti-thy1 animals in week 20 after disease induction. This may have contributed to the renoprotection observed with rapamycin treatment. With regard to their primary mode of pharmacological action (10, 30), mTOR inhibitors pose no direct effect on blood pressure. Therefore, it is likely that the lower blood pressure with rapamycin in this study was mediated indirectly through less renal damage and fibrosis.

mTOR treatment in humans, mainly in patients with solid organ transplantation, has been found to increase markedly blood lipid levels and thereby to adversely affect the cardiovascular risk profile (20). In the present investigation, blood triglyceride and cholesterol concentrations were found to be elevated by the chronic anti-thy1 disease itself. Rapamycin treatment went along with even lower triglyceride levels, while cholesterol levels were unaffected. How this translates into the human situation remains to be defined.

In conclusion, in a model of chronic anti-thy1-induced glomerulosclerosis, low-dose rapamycin significantly slows its progressive course toward chronic renal fibrosis and insufficiency. mTOR inhibition involves joint actions on renal cell proliferation, fibrogenesis, tissue cell infiltration, and proteinuria as key pathways in mediating the progression of chronic renal disease.

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