Apical Proteins Stimulate Complement Synthesis by Cultured Human Proximal Tubular Epithelial Cells

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Abstract. There is increasing evidence to suggest that the renal tubular epithelium is important in the pathogenesis of progressive renal failure resulting from persistent proteinuria. The role of complement in the progression of chronic renal failure is not well defined. The purpose of this study was to characterize the production of complement by human proximal tubular epithelial cells exposed to serum proteins at the apical surface. Complement C3 gene expression was analyzed by reverse transcription and PCR. C3 protein biosynthesis was confirmed by metabolic labeling followed by immunoprecipitation and quantified by enzyme-linked immunosorbent assay. In the quiescent state, proximal tubular epithelial cells grown on permeable membrane supports secreted C3 predominantly into the apical medium. The addition of 5 mg/ml serum proteins led to an 8.9-fold increase in basolateral C3 secretion and a 2.1-fold increase in apical C3 secretion, altering the ratio of basolateral: apical C3 secretion from 0.44 ± 0.16 to 1.87 ± 0.52. C3 mRNA expression was also upregulated in a time- and dose-dependent manner. Serum fractionation demonstrated that the stimulant responsible for these effects was in the molecular weight range 30 to 100 kD. The observed phenomenon was not reproduced when purified human albumin alone was used as the stimulant. These findings could provide a possible mechanism for the link between proteinuria and interstitial fibrosis. This may have potential implications for strategies directed against complement in retarding the progression of chronic renal failure.

Recent evidence suggests that the tubulointerstitium is involved in the progression of various types of glomerulopathy (1–4). It has been shown that in primary glomerular disease, the degree of renal functional impairment correlates better with the extent of tubulointerstitial damage than glomerular damage (5–7). However, little is known about the mechanisms responsible for the spread of tissue injury from the glomerular to the tubular compartment in diseases that are considered primarily glomerular in origin. One possible link is through the development of proteinuria, which could stimulate the production of extracellular matrix proteins or profibrotic cytokines by tubular epithelial cells, as the luminal surface of these cells are exposed to supraphysiologic amounts of serum proteins under proteinuric conditions. Burton et al. (8) demonstrated an increase in fibronectin production and platelet-derived growth factor (PDGF) secretion by cultured human proximal tubular epithelial cells (PTEC) when they were exposed to human serum proteins. This finding suggested a link between proteinuria and interstitial scarring. However, the addition of neutralizing anti-PDGF did not reduce fibronectin synthesis. Moreover, transforming growth factor-β, a major profibrotic cytokine (9), was undetectable in this model. This finding suggests that other mechanisms may be operating in the induction of interstitial changes.

One possible mediator of inflammatory injury in the tubulointerstitium is complement. Complement activation products are deposited on the tubules in a number of glomerular disorders. Recent work by Nomura et al. (10) has shown that inhibition of complement activation after the induction of glomerular proteinuria reduces tubular injury, leading to the suggestion that complement proteins in the glomerular filtrate directly mediate tubular injury. Support for this suggestion comes from cell culture work showing that the membrane attack complex of complement inserts in PTEC and induces arachidonic acid, free radical, and cytokine release as well as cytoskeletal damage (11,12). More recently, work has shown that PTEC themselves have the capacity for synthesis of complement components (13–16), and that enhanced tubular C3 and C4 gene expression is present in a number of glomerular and interstitial disorders (17–20).

We hypothesized that the link between glomerular proteinuria and progressive tubulointerstitial injury might be the hyperinduction of complement synthesis in tubular cells exposed to high protein concentrations. In the study presented here, we tested this hypothesis in a model of cultured human PTEC. The results indicate that complement C3 production by PTEC is polarized and that it is increased at both the mRNA and the biosynthetic levels after exposure to serum proteins. The im-
plications of this phenomenon on the pathogenesis of the progression of chronic renal failure are discussed.

Materials and Methods

Reagents

Cell culture media, defined medium additives, trypsin-ethylenediaminetetraacetate, endotoxin assay kit (Timed Gel Formation), Staphylococcus aureus Protein A, protease inhibitors, and general chemicals were purchased from Sigma Chemicals (Poole, Paisley, United Kingdom). Antibiotics, sera, agarose, and DNA size markers were obtained from Life Technologies BRL. Antibodies for cell characterization were obtained from Sigma, for enzyme-linked immunosorbent assay, from Dako (High Wycombe, United Kingdom) and the Binding Site (Birmingham, United Kingdom). Permeable membrane supports were supplied by Costar (Cambridge, MA). [35S]Methionine and [14C]-labeled protein size markers were obtained from Amersham (Aylesbury, United Kingdom). 125I-human albumin was from ICN (Costa Mesa, CA). Reagents for cDNA synthesis were from Pharmacia (Milton Keynes, United Kingdom) and those for PCR were from Promega (Southampton, United Kingdom). Rabbit anti-human C3 was from Serotec (Oxford, United Kingdom). Microconcentrators were from Flowgen Instruments (Kent, United Kingdom).

Cell Culture

Human PTEC were isolated according to a previously described method (21). Briefly, renal cortical tissue obtained from the normal pole of tumor nephrectomy specimens was cut into small fragments and processed through a series of mesh sieves of diminishing pore size. PTEC were collected on the 53-μm sieve and digested with collagenase (750 U/ml) at 37°C for 15 min. Tubular cells were isolated by centrifugation and grown in Dulbecco’s modified Eagle’s medium/Ham’s F12 (1:1) with 5% fetal calf serum supplemented with insulin and antibiotics. Semipermeable membrane supports were purchased from Costar (Cambridge, MA). [35S]Methionine and [14C]-labeled protein size markers were obtained from Amersham (Aylesbury, United Kingdom). 125I-human albumin was from ICN (Costa Mesa, CA). Reagents for cDNA synthesis were from Pharmacia (Milton Keynes, United Kingdom) and those for PCR were from Promega (Southampton, United Kingdom). Rabbit anti-human C3 was from Serotec (Oxford, United Kingdom). Microconcentrators were from Flowgen Instruments (Kent, United Kingdom).

Growth on Inserts and Permeability Studies

At the second passage, the cells were seeded into 6-well plates on semipermeable membrane supports of 0.4-μm pore size and grown to a confluent monolayer. The apical and basal supernatants were thus separated by the confluent layer of cells and could be sampled independently. To ensure the integrity of this cell monolayer, its permeability to 125I-human albumin was measured. After a confluent cell monolayer was obtained, 5 μl of 125I-human albumin (0.5 μCi/μl) was added to the apical media. After 24 h, 50 μl of apical and basal supernatants were sampled and counted in a gamma counter. To distinguish between leakage of albumin between cells and metabolism with release of amino acids into the basal supernatant, basal samples were precipitated with 10% TCA. All experiments were performed in triplicate.

Serum Preparation

Pooled human sera were obtained from 20 healthy volunteers in the laboratory and stored at −70°C until further use. Endotoxin contamination was excluded by a commercially available endotoxin assay kit. Serum was separated into three different molecular weight fractions by repeated ultracentrifugation in microconcentrators: I, <30 kD; II, 30 to 100 kD; and III, >100 kD. Size separation of the fractions was verified on sodium dodecyl sulfate polyacrylamide gel electrophoresis. Fraction I contained proteins that would be expected to pass through normal glomeruli; fractions II and III contained proteins likely to be filtered in selective and nonselective proteinuria, respectively. All fractions were diluted to a protein concentration of 5 mg/ml in all subsequent experiments. C3-deficient human serum was purchased from Sigma Chemical Co. Its deficiency in C3 was verified by double-ligand enzyme-linked immunosorbent assay as described in the next section.

Assay of C3 in Cell Supernatants

To characterize the direction of C3 synthesis, C3 was measured in the apical and basal supernatants of PTEC grown on cell inserts. To evaluate the effect of serum protein stimulation, C3 in both supernatants was assayed after apical incubation of PTEC in C3-deficient serum for 24 h. An equivalent volume of phosphate-buffered saline (PBS) was added to the controls. A double-ligand enzyme-linked immunosorbent assay was used. Nunc MaxiSorp immunoplates (Nunc, Roskilde, Denmark) were coated overnight at 4°C with 100 μl of sheep antihuman C3c diluted 1/200 in PBS. After washing, they were blocked with PBS, 2% bovine serum albumin (BSA) for 1 h at 37°C. Appropriately diluted supernatant samples were added in duplicates. Rabbit antihuman C3c diluted 1/3000 in sample buffer (PBS, 2% BSA, 0.05% Tween) was then applied, followed by horseradish peroxidase-conjugated goat anti-rabbit IgG diluted 1/5000 in sample buffer, both incubated at 37°C for 1 h. The enzyme activity was read after incubation with o-phenylenediamine by measuring absorbance at 490 nm (MRX 1.1, Dynatech Laboratories, Chantilly, VA). A pooled normal human serum of known C3 concentration was used to generate a standard curve and was included in every reaction. The limit of sensitivity of this assay was 0.3 ng/ml.

RNA Extraction and cDNA Synthesis

Total RNA was extracted from 10⁶ cells by the method of Chomczynski and Sacchi (22) from unstimulated and serum-stimulated cells. Briefly, cells were lysed in 4 M guanidinium thiocyanate, 25 mM sodium citrate, pH 7.0, 0.5% sarcosyl, and 0.1 M 2-mercaptoethanol. This step was followed by phenol/chloroform/isoamyl alcohol extraction and isopropanol precipitation. RNA was quantified by absorbance at 260 nm. Five micrograms total RNA was reverse-transcribed to cDNA in a reaction mixture containing 160 ng of oligo(dT)₁₂₋₁₈, 500 μM of each dNTP, and 200 U Moloney murine leukemia virus reverse transcriptase in 20 μl of solution for 80 min at 37°C. cDNA was stored at −20°C until further use.

PCR Amplification

Primer sequences (Table 1) were based on the known sequence of human C3 (23) and β-actin (24) cDNA. PCR was carried out with cDNA diluted to reflect 0.2 μg of RNA, 3 U of Taq polymerase, and
12.5 pmol each of 3' and 5' primers in 25 μl of a solution containing 10 mM Tris-HCl, pH 9, 50 mM KCl, 2 mM MgCl₂, 0.01% gelatin wt/vol, 0.1% Triton X-100, and 200 μM of each dNTP. The PCR cycle consisted of 1 min of denaturation at 94°C, 1 min of primer annealing at 65°C, and 2 min of extension/synthesis at 72°C. After 30 cycles of amplification, samples were incubated for another 10 min at 72°C. PCR reactions were carried out in a DNA thermal cycler (Perkin-Elmer/Cetus, Buckinghamshire, United Kingdom). The products were separated on 1.2% agarose gels and stained with ethidium bromide.

For quantification, human β-actin primers, 12.5 pmol each, were included in every reaction as an internal control. The number of PCR cycles (30 cycles) was in the linear range of amplification for both sets of primers in accordance with preliminary experiments (data not shown). PCR products in ethidium bromide gels were photographed, and the bands were scanned by using the Qgel 1-D densitometry program. The product yield was expressed as a ratio to β-actin.

**Metabolic Labeling and Immunoprecipitation**

Confluent unstimulated or serum-stimulated PTEC were incubated with methionine-free Dulbecco’s modified Eagle’s medium for 30 min at 37°C, and labeled with [35 S]methionine (500 μCi/ml) for 1 h as described previously (25). Cell lysates and supernatants were collected at this time point or after an additional 6-h incubation with excess (×10) cold methionine. Cell lysates were solubilized in 1% Triton, 0.5% deoxycholic acid, 10 mM ethylenediaminetetraacetate, 2 mM phenylmethylsulfonyl fluoride, 100 μg/ml leupeptin, pepstatin A, and soybean trypsin inhibitor in PBS. Lysates and supernatants were precleared with normal rabbit serum (50 μl/ml) and incubated with a 1/25 dilution of rabbit antihuman C3 for 1 h at 4°C. Immune complexes were precipitated with staphylococcal protein A beads. After repeated washings, immune complexes were released by boiling and separated on 7.5% sodium dodecyl sulfate-polyacrylamide gel electrophoresis gels under reducing conditions as described by Laemmli (26). 14 C-Methylated molecular weight markers were used. Gels were fixed, impregnated with ENHANCE™ (DuPont, United Kingdom), dried, and exposed to x-ray film at −70°C.

**Statistical Analysis**

Data were analyzed using the t test. P values are as stated.

**Results**

**Permeability of Cell Monolayer**

125I-Human serum albumin was used as a marker to measure protein transport and leakage across the PTEC monolayer. In control cultures, 0.81 ± 0.15% of apical counts appeared in the basal media at 24 h. Albumin precipitated by TCA accounted for 22.7 ± 2.51% of these basolateral counts. The cell monolayer, therefore, remained intact with minimal protein leakage. There was no significant change in permeability after incubation with serum apically.

**C3 Secretion by PTEC**

The effect of apical exposure to serum is shown in Figure 1. PTEC grown on permeable cell inserts produced C3 in both the apical and basolateral directions, with apical synthesis predominating. This outcome was not changed after incubation with 1 mg/ml C3-deficient serum protein for 24 h. Both apical and basolateral production increased significantly when PTEC was incubated with 5 mg/ml serum proteins, with basolateral and apical C3 secretion increasing by 8.9-fold and 2.1-fold, respectively.

**Table 1. PCR primer sequences and their location in the cDNA sequence**

<table>
<thead>
<tr>
<th>Primer</th>
<th>Oligonucleotide Sequence</th>
<th>Location in cDNA Sequence</th>
<th>Product Size (bp)</th>
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<tbody>
<tr>
<td>C3-1</td>
<td>GCTGCTCCCTGCTACTAACCCA</td>
<td>87–107</td>
<td>784</td>
</tr>
<tr>
<td>C3-2</td>
<td>AAAGCAGTCCCTCCATACCTTT</td>
<td>850–870</td>
<td></td>
</tr>
<tr>
<td>β-actin-1</td>
<td>ATGTGATATACGGCCGCGTC</td>
<td>46–65</td>
<td>584</td>
</tr>
<tr>
<td>β-actin-2</td>
<td>GCGCTCGGTGAGGATCTTCA</td>
<td>610–629</td>
<td></td>
</tr>
</tbody>
</table>

* Primer-1 is identical to the coding strand; primer-2 is complementary to the coding strand.

Figure 1. C3 concentration in apical (open bars) and basal (hatched bars) supernatants in the resting state and after exposure to apical serum proteins from C3-deficient human serum. The proximal tubular epithelial cell (PTEC) monolayer was washed three times with phosphate-buffered saline and incubated in serum-free medium for 24 h before stimulation. Numbers above each pair of bars represent the ratio of basolateral:apical C3 secretion. Results are obtained from two kidney preparations, each performed in triplicate. Error bars and plus-minus values are standard deviations. *P < 0.01, **P < 0.005 compared with control.
C3 Gene Expression in PTEC

A PCR product, 784 bp in size corresponding to human C3 mRNA, was detected from unstimulated PTEC in the quiescent state. The intensity of this band in relation to that of β-actin as the housekeeping gene remained unchanged after incubation with 1 mg/ml serum protein for 24 h. On addition of 5 mg/ml serum protein, C3 gene expression was significantly upregulated in a time-dependent manner. Maximal response was seen after 24 h of stimulation, with more than a twofold (P < 0.05) increase in the normalized C3/β-actin ratio from gel densitometry compared with control (Figure 2).

To further characterize the response, serum was separated into three molecular weight fractions as described in Materials and Methods. As shown in Figure 3, the upregulation of C3 gene expression was reproduced by fraction II, and to a lesser extent, by fraction III. Because albumin alone is one of the major constituents of fraction II with clinical relevance, the effect of purified human albumin alone, adjusted to 5 mg/ml, was examined. With albumin, there was no effect on C3 gene expression in PTEC compared with control (Figure 3).

Biosynthesis of the C3 Protein

To confirm that the C3 transcript led to C3 biosynthesis, PTEC were metabolically labeled and the C3 protein was precipitated with a specific antiserum. This labeling was carried out in both quiescent and serum-stimulated cells grown to confluence on the bottom of 25-cm² tissue culture flasks.

Figure 2. (A) Time response of C3 gene expression in serum protein-stimulated PTEC. Maximal upregulation of C3 mRNA expression occurred at 24 h. Error bars are standard deviations. (B) A typical gel showing the progressive increase in the intensity of the 784-bp C3 PCR product with the duration of stimulation (numbers above lanes indicate hours of stimulation) compared with the 584-bp β-actin band as the internal control.

Intracellular C3 precipitated from the cell lysates immediately after the pulse period was characterized by a 185-kD band corresponding to the pro-C3 chain. This product diminished from the cell lysates during the 6-h chase period when pro-C3 was processed and secreted from the cell. At the end of the chase period, extracellular C3 precipitated from the supernatants demonstrated two distinct bands of 110 and 75 kD, corresponding to the α and β chains of the final C3 molecule (Figure 4A). In parallel experiments, the amount of pro-C3 and C3 precipitated was greater in serum-stimulated PTEC (Figure 4B). This confirmed that the upregulation in C3 mRNA expression after serum stimulation resulted in an increase in C3 protein biosynthesis.

Discussion

The various cell types of the kidney, including PTEC, have all been shown to be capable of producing complement components (27). However, the polarity of complement synthesis by PTEC has not been characterized before. This study demonstrates that the production of C3 by PTEC grown on membrane supports is polarized, with C3 secreted predominantly...
into the apical medium in the resting state. After stimulation with serum proteins, there is a reversal in this polarity as basolateral C3 synthesis rose much more sharply than apical C3 synthesis (8.9 versus 2.1 times). C3 protein biosynthesis was confirmed by metabolic labeling followed by immunoprecipitation. At the messenger RNA level, constitutive C3 expression occurred at a low level, but was considerably upregulated by stimulation with serum proteins in a time- and dose-dependent manner.

Tubulointerstitial damage is the final common pathologic pathway of many glomerular diseases. However, despite many years of research, the link between glomerular diseases and the subsequent development of tubulointerstitial scarring leading to chronic renal failure has remained obscure. In human glomerular diseases, a correlation between the degree of proteinuria and the extent of interstitial damage has been described by many authors (28–31). In the puromycin aminonucleoside nephrosis model (32) and the protein overload model (33) in rats, there is an intimate temporal relationship between the development of proteinuria and the onset of chronic inflammatory cell infiltrate and accumulation of matrix protein in the interstitium. These observations provide evidence to suggest a role for proteinuria in the progression of chronic renal failure. However, the mechanism through which interstitial fibrosis is induced has not been addressed.

In recent animal studies, complement has been implicated in the pathogenesis of proteinuria-associated tubulointerstitial injury. Complement-depleted rats previously rendered nephrotic displayed a significantly better tubulointerstitial histology and para-aminonipiperate clearance than complement-sufficient rats with the same degree of proteinuria (10). In the latter, there was deposition of C3 and C5b-9 in proximal tubular cells. Similar results were obtained in another study using mononephrectomized rats with mesangial proliferative glomerulonephritis (34). Our finding of increased basolateral secretion of C3 after apical exposure of PTEC to serum proteins provides in vitro evidence to suggest a role for locally synthesized complement in the process of tubulointerstitial damage.

Human PTEC can produce a number of components of the complement system. In fact, it has been demonstrated that PTEC in culture or tissue sections are capable of spontaneously activating complement by the alternative pathway (35,36). This process is by virtue of the presence of a potent C3-convertase activity on the apical surface of PTEC, the activation of which leads to fixation of the C5b-9 neoantigen on the cell surface and the subsequent cytotoxicity (11). In addition to the presence of C3-convertase, there is also a relative lack of complement inhibitors (CD46, CD55, CD59) on the apical surface, predisposing PTEC to complement injury (37). The present study confirms the ability of PTEC to synthesize C3 and in addition demonstrates polarized C3 secretion upon exposure to serum proteins. This mechanism has important pathophysiologic implications, because both the classic and the alternative pathways proceed by means of cleavage of the C3 molecule to result in the formation of other components of the complement cascade, including the terminal attack complex C5b-9.

In progressive renal disease, tubulointerstitial lesions are typically characterized by mononuclear cell infiltrate and the accumulation of extracellular matrix within the interstitial space. The reversal in the predominant direction of C3 synthesis from apical to basal secretion after stimulation

Figure 4. Metabolic labeling and immunoprecipitation of C3. Cells were incubated for 24 h in the absence (A) or presence (B) of serum (5 mg/ml) and then labeled with [35S]methionine for 1 h followed by a chase period of 6 h with cold methionine. The starting cell number was the same in both experiments. Cell lysates (I) and supernatants (E) were precipitated with an antibody against human C3 as described in Materials and Methods. Autoradiographs show the precipitated C3 chains at 0- and 6-h chase. The figure shows the immunoprecipitates of one representative labeling study of three separate experiments.
with serum proteins supports the hypothesis that complement may participate in the process of tubulointerstitial damage. Sublytic concentrations of C5b-9 have been shown to release arachidonic acid products and cytokines such as interleukin-6 and tumor necrosis factor-α (12). Deposition of complement in PTEC brush borders is associated with monocyte/macrophage transmigration from the circulation into the tubulointerstitium and subsequent monocellular cell infiltration and fibroblast proliferation (33). Therefore, persistent local production of C3 in the proximal tubular milieu due to proteinuria, in the presence of other components and enzymes of the complement cascade, might exaggerate and hasten these processes and lead to chronic injury. Furthermore, complement synthesis by PTEC is known to be enhanced by a number of cytokines (13,14), which could be released by leukocytes recruited into the interstitial space, thereby setting up a vicious cycle of local complement activation and transmigration of inflammatory cells.

Another possible link between proteinuria and complement activation is related to the concept of ammoniagenesis within the kidney. Hyperammoniagenesis, which is known to activate complement (40), could result from catabolism of increased amounts of protein reabsorbed by tubular cells (41). Thus, increased ammonia production secondary to proteinuria could result in local complement activation at the level of proximal tubular cells and lead to interstitial scarring. That PTEC can take part in the inflammatory and scarring process is not at all surprising, considering that embryologically, PTEC, like fibroblasts and the cells of the immune system, are of mesenchymal origin (42).

Stimulation with 1.0 mg/ml serum did not result in any appreciable change in C3 production and expression. Significant differences were only observed after addition of 5.0 mg/ml serum proteins. This protein concentration exceeds the range to which proximal tubules are likely to be exposed in nephrotic rats (43). However, it is difficult to know what in vitro concentration is appropriate to mimic the in vivo concentration, in the absence of other costimulants such as cytokines. It is possible that the relatively high protein concentrations used here over a short period simulate more prolonged exposure, as would occur in vivo.

Serum fractionation identified the likely molecular size range of the component responsible for stimulating C3 production. The active component of serum is localized to a fraction of molecular size between 30 and 100 kD, making it unlikely that the active component was a cytokine (unless bound to protein). This fraction contains proteins that pass through the glomerular barrier in proteinuric states, including albumin and transferrin. The addition of albumin alone, however, did not reproduce the effects observed with whole serum, suggesting that either other proteins are responsible or that an agent bound to albumin but removed in the purification of albumin is responsible for the effect. It has been shown that the effect of albumin on interstitial inflammation is mediated through fatty acids bound to albumin (44). For instance, oleate albumin, but not palmitate albumin, causes tubular cell proliferation (45), which is thought to be a maladaptive response to proteinuria in the kidney (46). Although all of these findings agree with the observation by Burton et al. (8) on tubular cell matrix production, others have produced conflicting reports on the effects of albumin on tubular cell function. Rat tubular cells exposed to apical BSA or delipidated BSA demonstrated an upregulation in monocyte chemoattractant peptide-1 mRNA expression and basolateral protein synthesis (47). Exposure of rabbit tubular cells to BSA resulted in an increase in endothelin-1 synthesis (48). In another study published recently, apical BSA induced a predominantly basolateral RANTES secretion in pig tubular cells (49). However, it must be cautioned that in these latter three studies, the stimulatory effect of bovine albumin was obtained from tubular cells originating from other animal species. Their relevance to human, therefore, could only be speculative.

Apart from albumin, transferrin is another important component of proteinuric urine, and is also in the molecular weight range 30 to 100 kD. It has been shown previously that the iron moiety (Fe$^{2+}$) of transferrin is toxic to rat tubular epithelial cells as a result of intracellular iron accumulation, and peroxidative injury after reabsorption of transferrin iron (50). More recently, the protein moiety of transferrin has been implicated in the upregulation of monocyte chemoattractant peptide-1 mRNA expression in rat tubular epithelial cells (47), adding yet another mechanism in addition to iron-driven oxidant stress for the cytotoxic role of transferrin in the causation of tubular injury.

In summary, this study is the first to characterize the polarized nature of human PTEC C3 synthesis and expression in vitro. Our results suggest that complement may be one of the mediators in the development of tubulointerstitial damage in glomerular diseases. Although strategies to reduce proteinuria are not always successful clinically, complement inhibition might eventually be considered as an alternative means of preventing or retarding the progression of chronic renal failure.

References


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