Translocation of dendrin to the podocyte nucleus in acute glomerular injury in patients with IgA nephropathy

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ABSTRACT

Background. It has been reported that podocytopenia has been occurring with increasing disease severity in patients with IgA nephropathy (IgAN). Dendrin is localized at the slit diaphragm (SD) in podocytes. We showed that dendrin translocates to the nucleus of injured podocytes in experimental nephritis and the nuclear dendrin promotes podocyte apoptosis. It is still unknown whether dendrin translocates from the SD to podocyte nucleus in IgAN. We investigated the presence of nuclear dendrin in patients with IgAN and the association between the translocated dendrin to the podocyte nucleus and disease activity.

Methods. Fourteen adult patients with IgAN were enrolled. The pathological parameters were analyzed. Immunostaining of renal biopsy specimens and urinary sediments from IgAN or minimal change nephrotic syndrome (MCNS) as the control was performed.

Results. A positive correlation was observed between an acute extracapillary change and the number of dendrin-positive nuclei. The location of dendrin in the nuclei was found in urinary podocytes of IgAN. The number of dendrin-positive nuclei in urinary podocytes of IgAN was significantly higher than that of MCNS. Urinary podocytes, which expressed the apoptosis marker annexin V, were also detected in IgAN. The translocation of dendrin to the podocyte nucleus as well as strong cathepsin L staining were detected in the glomeruli of IgAN.

Conclusion. An increasing number of dendrin-positive nuclei in the glomeruli suggest acute glomerular injury in IgAN. Apoptotic podocytes were detectable in the urine of IgAN. It
appears that the translocation of dendrin to the podocyte nuclei enhances podocyte apoptosis in acute glomerular injury and leads to podocytopenia in patients with IgAN.

**INTRODUCTION**

IgA nephropathy (IgAN) is the most common primary glomerulonephritis. An often insidious progression to end-stage kidney disease in 25–40% of cases is accompanied by development of glomerulosclerosis [1]. The development of glomerulosclerosis in several human and experimental diseases is associated with podocytopenia [1–6], and the number of podocytes per glomerulus might serve as a parameter of podocyte injury and provide prognostic information on patients with IgAN [7]. Lemely et al. [2] reported that podocytopenia is associated with increasing disease severity in IgAN. The studies of Hara et al. [8] provided evidence that detached podocytes in the urine indicate podocyte injury in glomerulonephritis. They also revealed a potential causative role for prolonged urinary loss of podocytes in disease progression in children with IgAN [9].

There are several causes of podocytopenia, including apoptosis, detachment from the glomerular basement membrane (GBM) and the inability of podocytes to proliferate [10]. Urinary podocytes indicate the degree of podocyte injury in glomerular diseases [9, 11–17]. Vogelmann et al. [11] identified apoptotic podocytes in urinary sediments of patients with focal segmental glomerulosclerosis (FSGS) and lupus nephritis (LN). So far, apoptotic podocytes have not been detected in urine from human IgAN. It is controversial whether apoptosis occurs in the glomeruli or after detachment from the GBM. Several studies have indicated signaling pathways of podocyte apoptosis including the Notch pathway, TGF-β, homocysteine and dendrin [18–23].

Dendrin is a proline-rich protein that was identified in telecephalic dendrites of sleep-deprived rats, and also detected in mouse and human kidney podocytes [23–25]. In the podocytes, dendrin directly binds to nephrin and CD2-associated protein (CD2AP) which is an adaptor molecule involved in podocyte homeostasis that can repress proapoptotic TGF-β signaling [26]. In adult mouse kidney, dendrin was detected in the podocyte foot process at the cytoplasmic insertion of the slit diaphragm (SD). We have reported that dendrin accumulates in the nuclei of injured podocytes in experimental nephritis, and proapoptotic TGF-β induces the nuclear translocation of dendrin [23]. Moreover, the nuclear dendrin has been identified as a modulator of TGF-β-induced apoptosis. Yaddanapudi et al. [27] have recently shown that CD2AP regulates the TGFβ1-dependent translocation of dendrin from the SD to the nucleus. The nuclear dendrin acted as a transcription factor to promote the expression of cytosolic cathepsin L (CatL). CD2AP itself was proteolyzed by CatL, promoting the sustained expression of the protease during podocyte injury, and in turn increasing the apoptotic susceptibility of podocyte to TGF-β1. In humans, dendrin was detected in podocytes of normal kidney and minimal change nephrotic syndrome (MCNS) [25]. However, the nuclear dendrin has not been found in the kidneys of patients with MCNS, which show no podocyte loss or glomerulosclerosis. We have recently reported that the nuclear dendrin was detected in human kidney biopsy specimens from patients with FSGS, LN and membranous nephropathy (MN) [28]. It is still unknown whether dendrin translocates from the SD area to the podocyte nucleus in patients with IgAN.

In the present study, we aimed to evaluate whether the nuclear dendrin is a useful parameter for assessing podocyte injury in patients with IgAN. We also investigated whether dendrin is detected in urinary podocytes.

**MATERIALS AND METHODS**

**Antibodies**

Rabbit polyclonal antisera against human dendrin have been described previously [28]. Mouse monoclonal antibody against human podocalyxin (PCX) and extracellular PCX were

<table>
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<th>Table 1. Clinical findings at the time of renal biopsy</th>
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<td><strong>Histological grade</strong></td>
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<td><strong>I/II</strong></td>
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<td><strong>III/V</strong></td>
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<td>Sex (M/F)</td>
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<td>Age (years)</td>
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<td>s-Cr (mg/dL)</td>
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<td>eGFR(mL/min/1.73 m²)</td>
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<td>Proteinuria (g/day)</td>
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<td>Hematuria (scores 0–4)</td>
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Data are shown as the mean ± SEM. M, male; F, female; S-Cr, serum creatinine; eGFR, estimated glomerular filtration rate. Hematuria score: 0 for 0–5 red blood cell/high-powered field (RBC/HPF), 0.5 for 6–10 RBC/HPF, 1.0 for 11–30 RBC/HPF, 2.0 for 31–100 RBC/HPF, 3.0 for >100 RBC/HPF, 4.0 for numerous RBC/HPF. *P < 0.05 Grade I / II versus III / V.
Patients
Fourteen adult patients, who had been diagnosed with IgAN by renal biopsies performed in the Juntendo University Hospital, were enrolled in this study. Patients with systemic lupus erythematosus, Henoch-Schönlein purpura, liver cirrhosis or other systemic diseases were excluded. The estimated glomerular filtration rate (eGFR) was calculated using the formula established by the Japanese Society of Nephrology for Japanese: $194 \times \text{s-Cr}^{-1.094} \times \text{age}^{-0.287} (\times 0.739 \text{ if female})$ [29]. The degree of hematuria was scored as described previously [12]. All of these patients were untreated prior to this study. Clinical data of the patients is shown in Table 1. Of the 14 patients, 7 were male, 4 were Grade I/II and 10 were Grade III/IV in histological grading [30, 31]. There was a significant difference in all factors (age, s-Cr, eGFR, proteinuria and hematuria) between the two groups: Grade I/II and Grade III/IV.

Renal histological findings
The sections for light microscopy were stained with periodic acid-Schiff. The following pathological parameters were analyzed according to the criteria of Shigematsu et al. [32]. The histological activity was estimated by the occurrence of acute glomerular endocapillary and extracapillary changes and tubulointerstitial changes, and the histological chronicity was estimated by the occurrence of chronic glomerular endocapillary and extracapillary changes and interstitial fibrosis. The extent of tissue injury was evaluated in four grades and scored (0, 1, 2 and 3) (Shigematsu’s classification). This evaluation was applied to all glomeruli in the biopsy sections, and the average scores were calculated. We also evaluated renal biopsy sections using the Oxford classification [33, 34]. Moreover, IgAN patients were divided into four groups at the time of renal biopsy by the predicted prognosis classification as

FIGURE 1: Triple staining with dendrin, PCX and DAPI of renal biopsy specimens from IgAN patients showed the localization of dendrin, which is present in the capillary areas and podocyte nuclei in all grades (Grades I–IV). (A–D) Nuclear dendrin can be found in all grades (asterisks). Original magnifications were ×400 for lower magnification and ×1000 for higher magnification.
follows [30, 31]: Grade I: slight mesangial proliferation and increased matrix were observed. Glomerulosclerosis, crescent formation and/or adhesion to Bowman’s capsule were not observed. Grade II: slight mesangial proliferation and increased matrix were observed. Glomerulosclerosis, crescent formation and/or adhesion to Bowman’s capsule were observed in <10% of all biopsied glomeruli. Grade III: moderate, diffuse mesangial cell proliferation and increased matrix areas were observed. Glomerulosclerosis, crescent formation and/or adhesion to Bowman’s capsule were seen in 10–30% of all glomeruli. Grade IV: glomerulosclerosis, crescent formation and/or adhesion to Bowman’s capsule were seen in >30% of all glomeruli.

Urine samples

Ten milliliters of freshly voided urine from patients with IgAN and MCNS, and healthy individuals, were centrifuged at 700g for 5 min. The sediments were prepared on poly-L-lysine-coated microscope slides at 200g for 5 min (cytospin preparations), then air dried for at least 30 min and fixed in acetone at −20°C for 5 min.

Immunofluorescence of renal biopsy sections and urinary podocytes

The renal sections from patients were snap frozen, and the cryosections (3 μm) were post-fixed with cold acetone (−20°C). The renal sections and urine samples were then blocked using blocking solution [phosphate-buffered saline (PBS), 2% fetal calf serum and 0.2% fish gelatin]. The primary antibodies, i.e. rabbit anti-human dendrin and mouse anti-human PCX antibodies, were incubated at room temperature for 60 min, followed by 30 min of incubation with secondary antisera at 1:300 dilution [Alexa Fluor 488 donkey anti-rabbit IgG and Alexa Fluor 555 goat anti-mouse IgG (Invitrogen, Carlsbad, CA)]. Nuclei were stained with DAPI (4′, 6-diamidine-2-phenylindole) for 15 min. The slides were washed with PBS several times and then mounted as described before [35]. The samples were analyzed under a confocal laser-scanning microscope (Fluoview FV1000, Olympus, Tokyo, Japan). The number of podocytes was counted with DAPI-positive cells enclosed with PCX in each glomerulus. The number of dendrin-positive nuclei, which were detected within the PCX-positive area [28], was counted in each glomerulus. We determined whether the histological scores obtained by Shigematsu’s classification and the Oxford classification are related to the number of dendrin-positive nuclei. Double-staining studies with CatL and dendrin, and post-staining with DAPI were also performed in kidney sections from patients with IgAN, MCNS and minor glomerular injury. In urine samples, the number of DAPI, PCX-positive cells and PCX-positive cells expressing dendrin on the nucleus were counted at a magnification of ×200.

Table 2. Renal biopsy section evaluated with the Oxford classification

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<th>N-dendrin/PCX-positive cells</th>
<th>N-dendrin/DAPI-positive cells</th>
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<tr>
<td></td>
<td>r</td>
<td>P</td>
</tr>
<tr>
<td>M</td>
<td>−0.1094</td>
<td>0.7488</td>
</tr>
<tr>
<td>S</td>
<td>−0.4385</td>
<td>0.1774</td>
</tr>
<tr>
<td>E</td>
<td>0.1535</td>
<td>0.6523</td>
</tr>
<tr>
<td>T</td>
<td>−0.2704</td>
<td>0.4212</td>
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</table>

No significant correlation was detected between the Oxford score and the ratio of dendrin-positive nuclei for each parameter. M, mesangial hypercellularity score; S, segmental glomerulosclerosis score; E, endocapillary hypercellularity score; T, tubular atrophy/interstitial fibrosis score.
Apoptotic cells

To detect urinary apoptotic podocytes, freshly voided urine was centrifuged and cytospun on microscope slides as described above, then fixed in 2% paraformaldehyde at 4°C for 5 min. After washing with PBS, each sample was incubated with 1 μL of TACS AV Biotin (R&D Systems, MN) in 100 μL of buffer at 37°C for 30 min. For double staining, after washing with PBS, each sample was incubated with an anti-extracellular PCX antibody at room temperature for 60 min. After washing with PBS, the slides were incubated with FITC-streptavidin (BD Biosciences, Japan) at 1:200 dilution and secondary antibody (Alexa Fluor 555 goat anti-mouse IgG) at 1:300 dilution at room temperature for 30 min. The slides were examined under a confocal laser-scanning microscope (Fluoview FV1000, Olympus, Tokyo, Japan).

Statistics

All values were expressed as the mean ± SE. Differences between the two groups were evaluated by t-test. Correlation between variables was evaluated by least-squares linear regression. A P-value of <0.05 was considered significant.

RESULTS

Expression and localization of dendrin in IgAN

At all grades, dendrin staining showed both linear and dotted patterns on the glomerular capillary walls (Figure 1A–D). Some dendrin-positive nuclei in the glomeruli were detected in renal biopsy specimens from all grades (Figure 1A–D). The number of dendrin-positive nuclei per glomerulus...
and the number of dendrin-positive nuclei in PCX-positive cells and in DAPI-positive cells in Grade I/II were significantly higher than those in Grade III/IV (Figure 2A–C).

**Histological findings of IgAN and nuclear dendrin**

In the Oxford classification, a significant correlation was not detected between each parameter (M: mesangial score, S: segmental sclerosis, E: endocapillary hypercellularity, T: tubular atrophy/interstitial fibrosis) and the number of dendrin-positive nuclei among PCX-positive cells or among DAPI-positive cells in the glomerulus (Table 2).

In Shigematsu’s classification, a positive correlation was observed between acute endocapillary changes and the number of dendrin-positive nuclei (Figure 3A, \( r = 0.432, P < 0.05 \)), and a marked positive correlation was observed between extracapillary changes and the number of dendrin-positive nuclei per glomerulus (Figure 3B, \( r = 0.728, P < 0.05 \)). An inverse correlation was observed between chronic endocapillary changes, extracapillary changes and the number of dendrin-positive nuclei per glomerulus (Figure 3C, \( r = -0.590, P < 0.05 \); Figure 3D, \( r = -0.491, P < 0.05 \)). No significant correlation was observed between acute and chronic tubulointerstitial changes and the number of dendrin-positive nuclei per glomerulus (Figure 3E and F).

**Clinical parameters and nuclear dendrin in the glomerulus**

There was no significant correlation between proteinuria and number of dendrin-positive nuclei (Figure 4A). A significant inverse correlation was observed between the levels of s-Cr and the ratio of dendrin-positive nuclei in the podocytes (Figure 4B, \( r = -0.617, P < 0.05 \)). A significant positive correlation was observed between the levels of eGFR and the ratio of dendrin-positive nuclei in podocytes (Figure 4C, \( r = 0.548, P < 0.05 \)).

**Expression of dendrin in urinary podocytes**

There were no PCX-positive cells or dendrin-positive cells in the urinary sediments of normal individuals (Figure 5A). In the urinary sediments of MCNS patients, only a few PCX-positive cells expressing dendrin were detected (Figure 5B). In IgAN patients, many PCX-positive cells were detected and some of the PCX-positive cells showed dendrin expression in the nuclei (Figure 5C). The ratio of PCX-positive cells in the urinary DAPI-positive cells from IgAN patients was significantly higher than that from MCNS patients (IgAN \( n = 10 \), MCNS \( n = 4 \), \( P < 0.05 \)) (Figure 5D). There was a significant difference in the ratio of dendrin-positive nuclei in PCX or DAPI-positive cells between IgAN and MCNS patients (IgAN \( n = 10 \), MCNS \( n = 4 \), \( P < 0.05 \)) (Figure 5E and F).
Expression of annexin V in urinary podocytes

In the urine samples of IgAN patients, annexin V was detected on the cell surface of PCX-positive cells (Figure 6A). In the same urine samples, dendrin was also detected in the nuclei of PCX-positive cells (Figure 6B).

Expression of CatL and dendrin in the glomeruli

The expression of CatL was increased in the glomeruli of IgAN patients compared with MCNS and minor glomerular injury. The dendrin-positive nuclei were detected in the glomeruli of IgAN patients (Figure 7).

FIGURE 5: Urine samples from IgAN patients showed urinary podocytes with dendrin-positive nuclei. (A–C) Triple staining with dendrin, PCX and DAPI in urine samples from normal individuals, and MCNS and IgAN patients was performed. Original magnification was ×200. (A) No PCX-positive cells with dendrin-positive nuclei were detected in normal individuals. (B) A few PCX-positive cells with dendrin-positive nuclei were detected in MCNS patients. (C) Some PCX-positive cells showed dendrin staining in the nuclei in IgAN patients. (D) The ratio of PCX-positive cells in urinary DAPI-positive cells in IgAN was higher than that in MCNS. (IgAN: n = 10, MCNS: n = 4, P < 0.05) (E, F) The ratios of dendrin-positive nuclei in PCX-positive cells and DAPI-positive cells in IgAN were significantly higher than that in MCNS (IgAN: n = 10, MCNS: n = 4, P < 0.05).

DISCUSSION

Adriamycin (ADR) induced nephrotic mice, a nephrosis and FSGS model, showed the translocation of dendrin to the podocyte nucleus before urinary albumin excretion, podocyte loss
and glomerulosclerosis [28]. Hill et al. [36] reported that podocytopathy of a type similar to that in primary FSGS occurs frequently in IgAN. Furthermore, Karoui et al. [37] suggested that FSGS plays an important role in the pathogenesis and progression of IgAN. Possibly, podocyte apoptosis leads to podocyte depletion and consequently to glomerulosclerosis in FSGS [5, 38]. In this study, the number of dendrin-positive nuclei was significantly higher in renal biopsy specimens with only a few sclerotic glomeruli. These results suggest that a larger number of dendrin-positive nuclei in renal biopsy specimens in the early stage of IgAN relate to podocyte damage, which might induce podocyte apoptosis, leading to podocyte loss from the GBM. The disease progression to glomerulosclerosis in IgAN is actually accelerated by frequent recurrences of acute inflammation, and the process of sclerosis is enhanced by postinflammatory sclerosis and fibrosis (chronic changes) [9, 32]. In this study, a positive correlation was observed between acute extracapillary changes and number of dendrin-positive podocyte nuclei per glomerulus. On the other hand, an inverse correlation was observed between chronic endocapillary and extracapillary changes and number of the dendrin-positive podocyte nuclei per glomerulus. These results suggest that acute inflammation in the glomeruli causes the translocation of dendrin to the podocyte nucleus in IgAN patients. The initial point of development of extracapillary change in the glomeruli is a rupture or break in the GBM. These are three-dimensional crater-like lesions that occur throughout the GBM followed by the detachment of podocytes [32]. Small epithelial crescents are then formed, and these cellular crescents often result in fibrocellular or fibrous crescents, which are sclerotic elements of the glomeruli. Therefore, it is possible that the nuclear dendrin is the initial point of podocyte damage, which finally develops into glomerulosclerosis.

Hara et al. [12] found a positive correlation between the presence of urinary podocytes and histological features of acute extracapillary changes in children with glomerulopathies such as IgAN, LN and membranoproliferative glomerulonephritis (MPGN). We reported that dendrin relocates to the nuclei of injured podocytes in a murine model of crescentic glomerulonephritis and that relocated nuclear dendrin amplified TGF-β-induced podocyte apoptosis [23]. These results led us to speculate that the translocation of dendrin to the podocyte nucleus as a response to podocyte injury might be related to podocyte apoptosis and the loss of podocytes from the GBM in IgAN patients. We wanted to confirm whether the localization of dendrin on urinary podocytes is in the nuclei. Several factors such as intraglomerular hypertension, immune complexes and mutated proteins in podocytes should promote podocyte apoptosis or detachment from the GBM. Translocation of dendrin should be one of these factors. Several studies reported that podocyte apoptosis in the glomeruli is detected in animal models such as ADR-treated rats [28], puromycin-treated rats [5] and diabetic rats [39]. In humans, the plasma from septic patients with acute kidney injury induced apoptosis in podocytes [40, 41]. So far, apoptotic podocytes have not been detected in IgAN patients. In this study, a large number of urinary podocytes were detected in IgAN patients, while none or a few urinary podocytes were detected in MCNS patients. Furthermore, dendrin that had already accumulated in the nuclei of urinary podocytes was detected in IgAN patients. In FSGS and LN patients, urinary apoptotic podocytes were identified [11]. In this study, annexin V, which is a marker of apoptosis, was detected in some urinary podocytes in IgAN patients. It is unclear whether podocyte apoptosis occurs in the glomeruli before detachment or after detachment from the GBM. Considering that annexin V becomes positive in the early phase of apoptosis [42, 43], injured podocytes in the early phase of apoptosis might be detached from the GBM. Based on these findings, podocytes expressing dendrin in the nuclei are suggestive of apoptotic cells in the acute inflammatory change in IgAN. However, we did not confirm the ratio of dendrin-positive nuclei in the urinary podocytes in each grade of predicted prognosis classification of IgAN patients. Further study will be needed to detect any relation between the number of urinary podocytes with dendrin-positive nuclei and the disease progression of IgAN.
Reiser et al. [44] reported that foot-process (FP) effacement is a migratory event triggered by podocyte injury leading to the activation of CatL. Injured podocytes showed a strong CatL staining throughout the entire cytoplasm compared with the normal control in which CatL was weakly expressed in the perinuclear vesicles. Nuclear dendrin acted as a transcriptional factor to promote the expression of cytosolic CatL. Sever et al. [45] showed that CatL mRNA levels are up-regulated in the glomeruli of MN, FSGS and diabetic nephropathy compared with that in normal control and MCNS, which is characterized by reversible podocyte FP effacement. In this study, several numbers of dendrin-positive nuclei and increasing expression of CatL were detected on the glomeruli of IgAN, but not of MCNS and minor glomerular injury. These results suggest that up-regulated cytosolic CatL in the injured podocytes promotes the translocation of dendrin to the nucleus and enhances podocyte apoptosis in IgAN.

In this study, we did not detect any significant correlation between the number of dendrin-positive nuclei per glomerulus and each parameter in the Oxford classification. A working group of the International IgAN Network reported that extracapillary proliferative lesions were not significantly predictive of the rate of renal function decline [33]. On the other hand, we showed a significant positive correlation between the levels of eGFR and the number of dendrin-positive nuclei per glomerulus, which represents a positive correlation with acute extracapillary changes. This result is compatible with the hypothesis that decreasing eGFR is correlated with the degree of podocytopenia [2]. The reduction in the number of dendrin-positive nuclei might be a supportive marker for

**FIGURE 7**: Renal sections from IgAN patients showed dendrin-positive nuclei with strong CatL staining. (A–D) The triple staining with CatL, dendrin and DAPI of kidney biopsy specimens from IgAN, MCNS and minor glomerular injury was performed. (A and B) The expression of CatL was increased and a large number of dendrin-positive nuclei can be detected in IgAN (case1 and case 2). Asterisks showed dendrin-positive nuclei. (C and D) Kidney biopsy specimens of MCNS and minor glomerular injury showed weak staining of CatL and only a few dendrin-positive nuclei.
estimation of the degree of podocyte injury and to predict detachment of the injured podocytes. Based on our findings, it would be reasonable to propose that urinary podocytes with dendrin-positive nuclei might be a novel marker to determine the extent of glomerulosclerosis in IgAN patients.

In this study, we used an antibody against PCX, but not an antibody against WT-1, as a human podocyte marker. The fact that podocyte nuclei are WT-1 positive [46], whereas the nuclei of mesangial cells and endothelial cells are WT-1 negative, is potentially useful as a marker of podocyte nuclei [47]. However, the mouse monoclonal WT-1 antibody showed not only a nuclear stain but also a cytoplasmic stain in human glomeruli [48]. Therefore, nuclear dendrin expression of human podocytes was confirmed by triple immunostaining with PCX, dendrin and DAPI.

CONCLUSION

The number of dendrin-positive nuclei suggests acute inflammation in patients with IgAN. Apoptotic podocytes were detectable in the urine of IgAN patients. It appears that the large number of nuclear dendrin could be an indication of disease activity and progression to glomerulosclerosis in IgAN.

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CONFLICT OF INTEREST STATEMENT

None declared.

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