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Original Article

Tenascin-C expression in renal biopsies from patients with tubulointerstitial nephritis and its relation to disease activity and prognosis

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Abstract: Tenascin-C (TNC) is an extracellular matrix protein that is transiently expressed in close association with tissue remodeling in various organs. Expression of TNC in patients with tubulointerstitial nephritis (TIN) is not well-characterized. Using renal biopsy specimens from 25 patients with TIN and 8 patients with thin basement membrane disease (controls), we assessed immunohistochemical staining for TNC and investigated its relation with clinicopathologic data. TNC was undetectable in the controls, but TNC was observed in the interstitium of specimens from all patients with TIN, and strong TNC staining was detected within active tubulitis lesions. TNC was not principally expressed in glomeruli, and it was also absent from scar tissue. Comparison with Sirius red staining revealed that TNC was present where collagen fibers had not yet formed. The percent area of TNC within the interstitium (% TNC-positive area) showed a significant negative correlation with illness duration and significant positive correlations with the serum CRP level and eGFR aggravation, both of which reflect disease activity. On the other hand, no correlation was found between % TNC-positive area and eGFR recovery during 2 years of follow up. Examination of renal biopsy specimens from TIN patients revealed that TNC appears during the active stage of inflammation and then disappears with healing. This suggests that TNC expression reflects TIN disease activity, but not prognosis.

Keywords: Renal biopsy, tenascin-C, tubulointerstitial nephritis

Introduction

Tenascins are glycoproteins abundant in the extracellular matrix of developing vertebrate embryos. They reappear or are strongly expressed around healing wounds and in the stroma of some tumors. There are four members of the tenascin gene family: tenascin-C (TNC), tenascin-R, tenascin-X and tenascin-W. TNC is the most extensively studied member of the family [1, 2]. One interesting feature of TNC is that it is transiently expressed in specific areas in association with cell migration or motility. Its restricted spatiotemporal distribution suggests not only that it plays a key role during tissue remodeling, but also that its expression may reflect disease activity. As such, attempts have actually been made to use TNC as a prognostic marker for interstitial pneumonia, psoriasis, and myocarditis [3-6].

In the kidney, TNC has been detected in mesangial, periglomerular, and tubulointerstitial areas [7-10]. It is strongly expressed during renal development [11] and is strongly re-expressed in various kidney diseases [12]. Many types of glomerulonephritis reportedly show strong TNC expression in humans [7-10, 13-15]. On the other hand, the dynamics of TNC expression remain elusive in tubulointerstitial nephritis (TIN), which is a frequent cause of acute kidney injury leading to chronic kidney disease. TIN is associated with an immune-mediated infiltration of the kidney interstitium

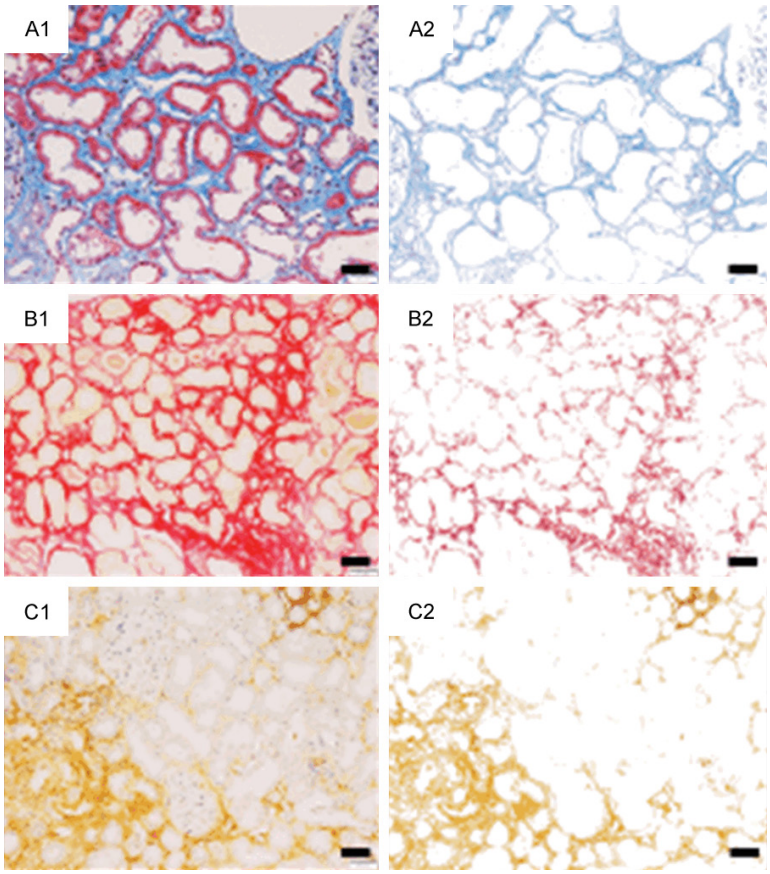

Figure 1. Quantitative assessment of % Interstitium within the total specimen (blue; Masson's trichrome) (A1 and A2), % Fibrosis within the interstitium (red; Sirius red) (B1 and B2), and % TNC-positive area within the interstitium (brown; immunostained) (C1 and C2). Bars, 50 μm.

by inflammatory cells, which may progress to fibrosis [16]. Patients often present with nonspecific symptoms, which can lead to delayed diagnosis and treatment of the disease. The etiology of TIN can be drug-induced, infectious, idiopathic, genetic, or related to a systemic inflammatory condition such as tubulointerstitial nephritis and uveitis syndrome (TINU), inflammatory bowel disease, or immunoglobulin G4-associated immune complex multi-organ autoimmune disease [16, 17]. However, the most common cause of TIN is from medication or drug exposure.

In the present study, we examined the distribution of TNC in renal tissue obtained at biopsy from patients with TIN at various stages, and compared the results with clinical and histologic data to determine the clinical value of TNC expression for assessment of the activity and prognosis of human inflammatory kidney disease.

Materials and methods

Patients

We retrospectively reviewed the medical records of 25 patients (11 males and 14 females; 56±14 years old) with biopsy-proven TIN diagnosed at Gifu University Hospital and Asahi University Hospital between June 2011 and December 2017. A biopsy was performed in patients who primarily presented with acute kidney failure or in patients with suspected TIN. Patients were excluded, who had bleeding tendency, a functionally single kidney, atrophic kidneys, or uncontrolled hypertension. Each attending physician determined the timing of the TIN onset when he/she for the first time noted clinical signs or symptoms suggestive of TIN-e.g., fever, general malaise, urine abnormality, continuous use of drugs and so forth. TIN has two common clinical presentations: sudden onset and rapid decline in renal function-acute TIN-and protracted onset and slow decline in renal function-chronic TIN. Obviously acute TIN, with time, can turn into chronic TIN; therefore, overlaps between these two entities often exist [18]. In this study, we enrolled the patients purely based on the pathologic findings of TIN which actually presented mixture of acute and chronic lesions. Clinical data, including age, gender, history of disease, medication, and blood and urine chemistry were obtained at renal biopsy. We calculated the aggravation of estimated glomerular filtration rate (eGFR) as the difference between the value at biopsy and the value before the onset of the disease, which is presented as DeGFR-a (eGFR aggravation). The patients were followed-up in our hospitals for an average of 23 months (range: 1-84 months), during which the most recent laboratory data were obtained. The recovery of eGFR was calculated as the difference between the most recent follow-up value and the

Table 1. Clinical characteristics of the patients

Patient No.	Age/Gender	Days from Onset	At Biopsy						Follow-up		Therapy
			CRP mg/dl	UP g/day	β2-MG μg/l	Cre mg/dl	eGFR ml/min/1.73 m^2	DeGFR-a ml/min/1.73 m^2	Interval months	ΔeGFR-r ml/min/1.73 m^2	
Tubulointerstitial Nephritis Patients											
1	74 F	30	0.01	0.4	-	2.56	15.1	26.6	1	13.3	PSL
2	68 M	30	-	0.1	1108	3.25	19.2	32.4	66	34.7	PSL
3	50 M	3650	0.2	0.3	-	1.73	38.0	42.6	84	27.8	PSL
4	46 F	1095	-	0.1	-	1.51	30.4	40.2	18	5.6	PSL
5	43 F	180	-	1.2	-	1.54	55.3	11.4	2	7.1	PSL
6	78 M	11	7.77	0.1	>5000	5.73	9.6	44.8	6	47.6	DW, PSL
7	64 M	180	0.13	0.09	-	1.25	46.1	9.1	2	9.1	PSL
8	45 M	14	0.68	0.09	-	2.14	29.8	35.3	6	29.0	PSL
9	60 M	365	0.1	0.05	-	1.99	41.5	18.4	54	0	PSL
10	73 F	7	0.17	0.1	-	1.43	28.3	29.0	48	22.4	-
11	30 F	730	0.02	0.175	-	0.71	78.6	2.9	84	0	PSL
12	55 F	1095	1.29	0.4	299	0.58	82.4	0	12	0	-
13	38 F	730	-	0.1	-	1.3	45.0	0	12	7.6	mPSL
14	50 F	60	2.2	0.35	14	1.35	35.5	16.8	15	15.3	PSL
15	64 F	150	0.65	0.2	-	1.9	29.8	34.4	18	37.2	PSL
16	60 M	60	0.39	0.31	52800	4.5	13.3	51.6	28	2.8	DW, PSL
17	66 F	60	1.88	2.59	2940	5.19	7.1	22.7	5	8.6	PSL
18	63 M	30	1.23	1.22	15800	3.92	14.7	16.4	9	25.2	PSL
19	53 M	30	0.54	0.27	4400	2.1	25.7	28.2	18	0	Anticoagulant
20	24 F	30	0.19	0.4	32700	1.0	58.9	26.2	15	21.7	PSL
21	58 M	90	0.02	0.07	1230	1.89	32.4	17.2	36	-2.3	-
22	72 F	15	12.3	0.4	48.4	10.2	4.5	54.9	4	54.9	DW, tHD, PSL
23	69 M	60	0.26	3.0	30700	3.63	16.0	8.3	3	29	PSL
24	51 F	30	5.28	0.14	7900	2.1	32.8	26.4	12	38.5	DW
25	40 F	180	0.02	0.06	532	1.6	28	0	18	0	-
Mean±SD	56±14 M/F=11/14	233±320	1.7±3.0	1.0±2.5	13754	2.6±2.1	34.2±20.6	23.6±15.2	23.2±24.5	15.2±14.2	
Thin Basement Membrane Disease (Control) 1 to 8											
Mean±SD	37±13 M/F=1/7	-	-	0.1±0.1	-	0.6±0.1	82.1±9.5	-	-	-	-

DW, drug withdrawal; PSL, predonisolone; mPSL, methylpredonisolone; tHD, temporal hemodialysis.

Table 2. Etiologies of tubulointerstitial nephritis and pathologic and immunohistochemical variables of the renal biopsies

Patient No.	Etiology	Inflammatory Cells (/HPF)	% Interstitium Area (%)	% Fibrosis Area in Interstitium (%)	% TNC+Area in Interstitium (%)
Tubulointerstitial Nephritis Patients					
1	Idiopathic	122	14.8	55.6	30.0
2	Idiopathic	53	11.6	58.3	32.9
3	TINU	177	14.0	60.8	77.2
4	Hyperuricemia	111	12.2	58.0	19.2
5	Autoimmune	95	19.3	48.9	35.0
6	Drug-induced	27	9.7	97.8	89.0
7	Autoimmune	84	36.3	22.5	3.7
8	Autoimmune	65	19.9	47.8	33.4
9	Hyperuricemia	106	29.3	86.1	22.3
10	Hyperuricemia	40	6.3	60.4	31.7
11	Autoimmune	18	18.4	82.4	10.9
12	Autoimmune	17	20.6	94.1	13.5
13	TINU	30	26.5	29.2	39.4
14	Idiopathic	96	37.9	59.1	54.9
15	Autoimmune	30	48.4	44.3	61.1
16	Drug-induced	41	21.6	95.8	90.0
17	Idiopathic	134	38.8	45.6	59.5
18	Idiopathic	24	31.4	74.9	69.2
19	Thrombosis	41	27.1	79.6	87.3
20	TINU	50	21.8	78.0	49.5
21	Autoimmune	18	29.0	57.8	25.0
22	Drug-induced	68	6.7	85.6	15.0
23	Autoimmune	60	10.1	72.3	4.0
24	Arug-induced	35	15.7	60.9	99.7
25	Autoimmune	54	8.1	83.0	7.6
Mean±SD		63.8±41.0	21.4±11.0	65.5±19.7	42.4±29.0
Thin Basement Membrane Disease (Control) 1 to 8					
Mean±SD		0±0	15.2±5.0	51.8±11.8	0.9±1.1

value at biopsy and is presented as ΔeGFR-r (eGFR recovery).

As non-TIN control specimens, we used eight renal biopsy specimens from patients with thin basement membrane disease (TBM), which does not present with inflammation, proteinuria, or histologic abnormalities. All of the patients gave informed consent, and the study was performed in accordance with the Declaration of Helsinki. The ethical committees at the two participating universities have approved this study (Gifu University, no. 29-62; Asahi University, no. 28-6-8).

Renal pathology

Three-μm-thick paraffin sections stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS), Masson's trichrome, periodic acid-methenamine-silver (PAM) and Sirius red were examined using a light microscope. Mesangial hypercellularity, increased mesangial matrix, glomerulosclerosis, extracapillary lesions (crescent formation), interstitial fibrosis and inflammation, tubular atrophy, tubulitis, and arterial hyalinosis were evaluated. Two observers blinded to the study protocols graded these features. We also quantitatively assessed inflammatory cell infiltration, the interstitial area, and the fibrotic area in the biopsies. Inflammatory cells were counted in five or more randomly selected 100 μm^2 tissue areas in HPFs (400×). To evaluate interstitial and fibrotic areas, light micrographs of histologic sections stained with Masson's trichrome and Sirius red were processed using Photoshop for color discrimina-

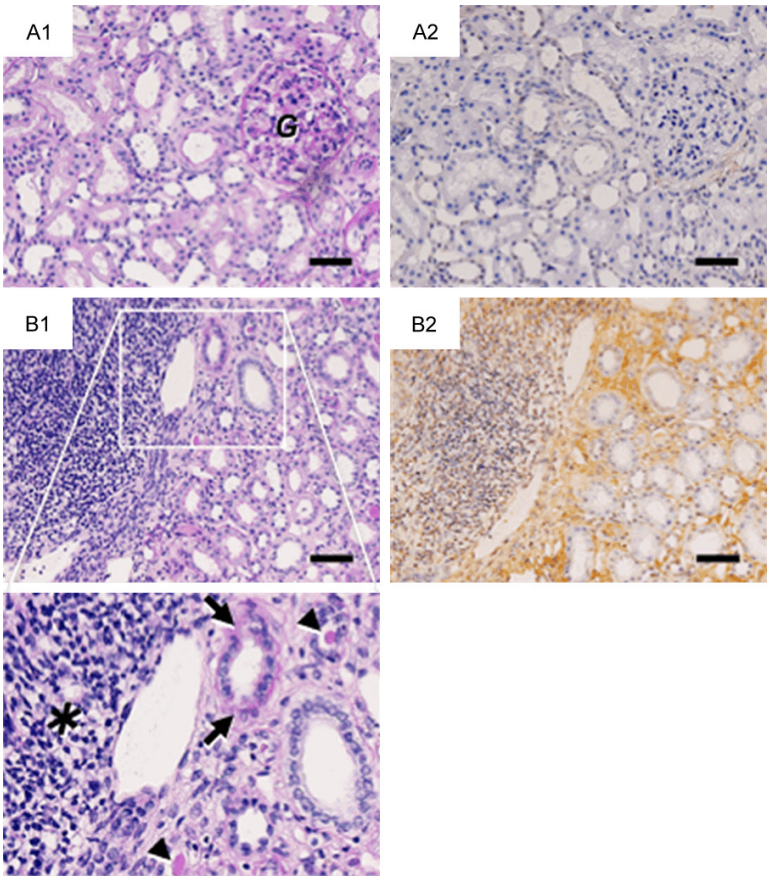

Figure 2. Immunohistochemical detection TNC in renal biopsy specimens. (A1 and A2) Renal biopsy specimens from a patient with TBM patients (non-TIN control). No histologic abnormalities are seen. (A1), PAS stain; (A2), TNC immunostain. No TNC immunopositivity is seen. (B1 and B2) Renal biopsy specimens from a patient with TIN. Active inflammatory lesions are apparent in the interstitium as shown below (B) in the highly magnified photograph of the boxed area of (B1). There is inflammatory cell infiltration in the interstitium, partial tubular destruction (arrows), and Tamm-Horsfall proteins (arrowheads). *, granulomatous accumulation of inflammatory cells. (B1), PAS stain; (B2), TNC immunostain. TNC immunopositivity is present in the interstitium. Bars, 50 μm.

tion, after which the % area of interstitium (percent Masson's trichome stained area (blue) in the cortex area) and % area of fibrosis in the interstitium (percent Sirius red stained area (red) in the interstitium) were calculated for each specimen (**Figure 1**).

Immunohistochemical detection of TNC

Three-μm-thick sections were deparaffinized and rehydrated through a graded alcohol series. The epitopes were then retrieved by heating the sections in sodium citrate buffer 3 times for 5 min each in a microwave. To block peroxidase activity, the sections were incubated in 3% hydrogen peroxide in PBS for 5 min at room temperature, after which they were blocked with normal horse serum. Sections were then incubated with a primary antibody against TNC (clone 4F10TT, diluted 1:500, IBL, Gunma, Japan). A Vectastain Elite ABC system (Vector Laboratories) was used to immunostain the sections, with diaminobenzidine served as the chromogen. The nuclei were counterstained with hematoxylin. Several immunohistochemical preparations were subsequently stained with Sirius red for simultaneous observation of TNC and collagen fibers.

Quantitative assessment of TNC-positive areas was carried out for the entire interstitial areas of biopsy specimens using Photoshop for color discrimination (brown, immunopositive area; white, immunonegative area), after which the % TNC-positive area in the interstitium was calculated for each case (**Figure 1**).

Statistical analysis

Results were analyzed using SPSS version 22, and were expressed as medians (minimum-maximum) for non-normally distributed data and as the mean ± SD for normally distributed data. Group comparisons were made using analysis of variance with post hoc Student's t tests. Spearman's analysis was used to assess the correlation between data. Values of $P<0.05$ were considered significant.

Results

Clinical and pathological characteristics

The clinical characteristics of the study population are presented in **Table 1**. The mean age at the patients at the time of diagnosis was 56±14 years (24-78 years old), and renal biopsy was performed about 233±320 days

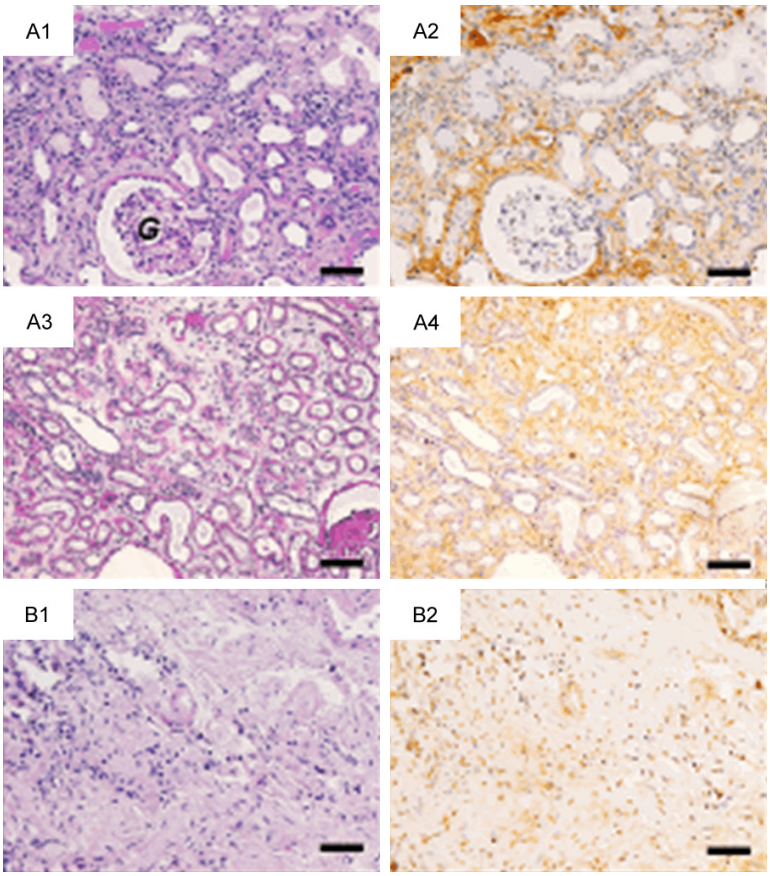

Figure 3. Immunohistochemical detection of TNC in renal biopsies from patients with TIN. A1-A4. Renal biopsy specimens from a patient with TIN in which chronic inflammatory lesions are present, -i.e. tubular atrophy and interstitial fibrosis associated with some degree of interstitial mononuclear cell infiltrates. TNC immunopositivity was detected in the interstitium but not intact glomeruli. Panels A1 and A3, PAS stain; A2 and A4. TNC immunostain. B1 and B2. Renal biopsy specimens from a patient with TIN in which scar tissue was apparent. Immunostaining for TNC is scarce. B1. PAS stain; B2. TNC immunostain. Bars, 50 μm.

(7-3650 days) after the initial symptoms. At the time of the biopsy, 48% of the patients exhibited a systemic inflammatory reaction, with CRP values greater than 0.5 mg/dl, and abnormal serum b2-microglobulin levels were noted in all patients tested for a tubulointerstitial injury marker. Proteinuria >1 g/day was seen in 4 patients (16%). The eGFR value at biopsy was less than 60 ml/min/1.73 m^2 in 92% of the patients, and in all patients was lower than the value before the onset of the disease, -i.e., the DeGFR-a (eGFR aggravation: the difference between the value at biopsy and the value before the onset of the disease) was negative. The responsive drugs were stopped in 4 patients with drug-induced TIN, treated 19 patients with steroids and 1 patient with an anti-coagulant, and observation only in 4 patients. No patients died during the follow-up period. After follow-up for nearly 2 years (23±25 months), the eGFR had recovered at least partially in most patients, -i.e., the ΔeGFR-r (eGFR recovery: the difference between the most recent follow-up value and the value at biopsy) was positive. There was no difference in the degree of renal function recovery (ΔeGFR-r) between patients with and without steroid therapy.

The etiologies of TIN are shown in **Table 2**: autoimmune, 9 cases; idiopathic, 5 cases; drug-induced, 4 cases; TINU, 3 cases; hyperuricemia, 3 cases; and thrombosis, 1 case. The histologic findings were compatible with those of acute and chronic TIN [18]. Microscopically, the cellular infiltration and edema were multifocal and varied in intensity. The predominant cell types were mononuclear cells, including lymphocytes and macrophages, as well as neutrophils. Tubular injury included tubulitis, breaks in the tubular basement membrane, necrosis of tubular cells, and atrophy and loss of tubules. Granulomas and Tamm-Horsfall protein were occasionally seen. The glomeruli were largely spared and arteriolar changes were nearly absent. In addition to those findings, which are consistent with acute interstitial nephritis, tubular atrophy and interstitial fibrosis, the hallmarks of chronic interstitial nephritis were combined in many cases where degenerative changes to the glomeruli and intimal thickening of arterioles were occasionally seen.

Detection of TNC in renal biopsy specimens

Immunostaining for TNC was largely undetectable in renal biopsy specimens from the control TBM patients (**Figure 2A1** and **2A2**). By contrast, TNC was detected in the interstitium

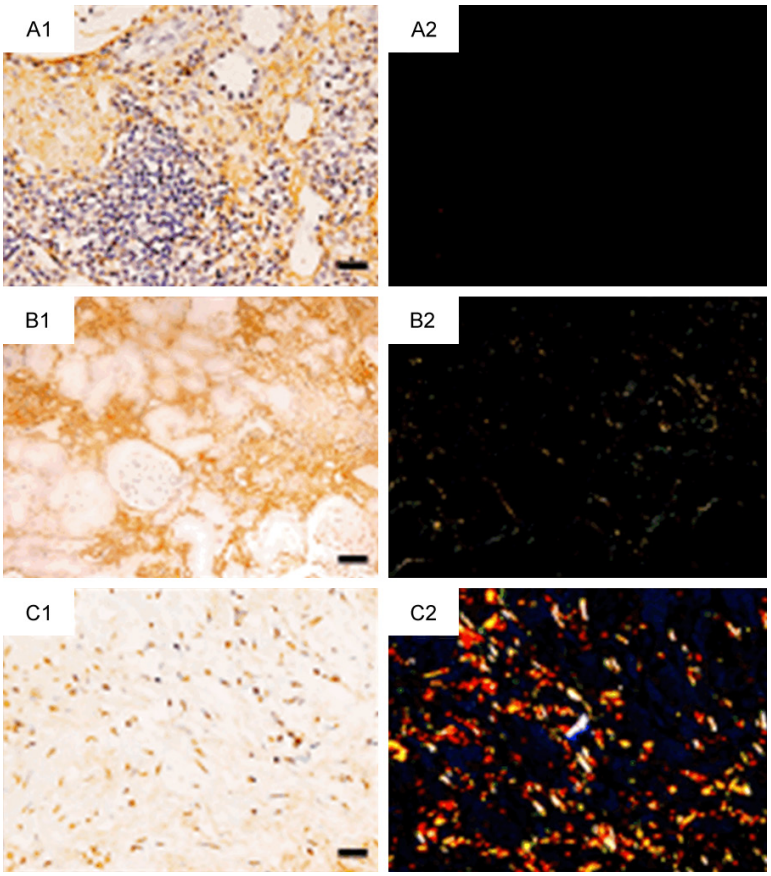

Figure 4. Comparison of disease stage-dependent changes in detection of TNC and collagen fibers. Immunostaining for TNC (A1-C1) in combination with Sirius red staining observed under a polarizing microscope (A2-C2). Shown are renal biopsy specimens from patients with TIN containing acute (A1 and A2), subacute (B1 and B2), and chronic (C1 and C2) lesions. In the preparations stained with Sirius red, types I and type III collagen fibers can be identified as yellow-red and green fibers, respectively. Bars, 20 μm.

of specimens from TIN patients. The immunostaining was strong within active tubulitis lesions (**Figure 2B1** and **2B2**), though much less staining was seen in lesions where acute inflammatory cells had massively accumulated. TNC was observed in areas of the interstitium where chronic inflammatory lesions were present, i.e., tubular atrophy and interstitial fibrosis associated with some degree of interstitial mononuclear cell infiltrate (**Figure 3A1-A4**). TNC was generally not expressed in glomeruli (**Figure 3A2**), though low levels were detected within glomeruli when tissue destruction was severe. TNC was nearly absent within scar tissue (**Figure 3B1** and **3B2**). Color discrimination analysis of the immunohistochemical preparations revealed that the % TNC-positive (brown) area of interstitium was significantly greater in the TIN patients (42±29%) than in the control TBM patients (0.9±1.1%) (**Table 2**).

Sirius red staining under polarized light shows type I and type III collagen as yellow-red and green, respectively [19]. Comparison of TNC immunostaining with Sirius red staining revealed TNC to be present where collagen fibers was absent within TIN specimens (**Figure 4A1** and **4A2**). As fine collagen fibers developed to replace areas of tubule dropout, TNC immunostaining became weaker, but intense staining was observed as long as tissue injury was active (**Figure 4B1** and **4B2**). Within foci where inflammation had ceased and scar tissue had formed, no TNC staining was detected (**Figure 4C1** and **4C2**). No colocalization was detected between TNC and type I and III collagen fibers.

Relation between TNC expression and disease activity and prognosis in patients with TIN

Table 3 shows the coefficients of correlation between the % TNC-positive area of interstitium in the biopsy specimens and the clinicopathologic data measured in the TIN patients from whom the specimens were collected. We found that the % TNC-positive area had a significant negative correlation with illness duration, but was unrelated to age, gender, amount of proteinuria, serum b2-microglobulin, serum creatinine, or eGFR at biopsy (**Table 3** and **Figure 5**). There was also no difference in the % TNC-positive area between males (49±33%) and females (38±25%) or between TIN etiologies (autoimmune, 22±18%; idiopathic, 49±15%; drug-induced, 73±34%; TINU, 55±16%; hyperuricemia, 24±5.3%; thrombosis, 87%). The % TNC-positive area was found to significantly and positively correlate with CRP and DeGFR-a, both of which reflect disease activity (**Table 3** and **Figure 5B**). Among the pathologic variables tested, we detected no correlation between TNC expression and interstitial inflammation, interstitial area or interstitial fibrosis (**Table 3**).

Table 3. Correlation between % TNC and clinicopathologic data in patients with tubulointerstitial nephritis

	% TNC$^+$ Area	
	R Value	*P* Value
Clinical Data		
At Biopsy		
Age, yr	0.080	0.705
Duration of Illness, mo	-0.476	0.016
CRP, mg/dl	0.496	0.022
WBC, /μl	0.233	0.262
Proteinuria, g/day	0.178	0.395
Hematuria, RBC/f	0.183	0.382
Creatinine, mg/dl	0.389	0.055
BUN, mg/dl	0.029	0.890
eGFR, ml/min/1.73 m^2	-0.321	0.118
ΔeGFR-a (eGFR aggravation), ml/min/1.73 m^2	0.479	0.016
At Follow-up		
ΔeGFR-r (eGFR recovery), ml/min/1.73 m^2	0.312	0.129
Pathological Data		
Inflammatory Cells, cells/hpf	-0.096	0.647
% Interstitium, %	0.192	0.358
% Fibrosis in Interstitium, %	0.147	0.484

After following up for an average of approximately 2 years (23±25 months, range: 1 to 84 months), all patients with TIN were alive, and the renal function of most patients had recovered at least partially, as indicated by the positive ΔeGFR-r values (**Table 1**). No correlation was found between % TNC-positive area and ΔeGFR-r (**Table 3** and **Figure 5D**).

Discussion

The renal expression and distribution of TNC have been investigated for nearly 30 years. In a general review, Jahnukainen et al. described the distribution of TNC in human tissue, briefly mentioning that increased TNC staining was detected in glomerulopathies and interstitial nephritis but providing no further details about the pathological process [20]. Renal transplant biopsies showing acute and chronic rejection have also been studied in this context [21]. Truong's group and others subsequently investigated tenascin expression in various kidney diseases [7-15]. However, attention was focused mainly on glomerular diseases, including various types of glomerulonephritis; only 2 studies by that group dealt with TIN [9, 10]. They reported diffuse staining of tenascin in both acute and chronic TIN and they noted positive staining even in areas of mature or organized fibrosis [10], which is inconsistent with the present findings. Our immunohistochemical staining revealed that TNC is expressed during the active stage of inflammation and then disappears with healing. In addition, we did not detect TNC in intact glomeruli in either TIN or TBM patients. This negative finding also appears inconsistent with earlier studies carried out mainly in the 1990's, which describe tenascin positivity in normal glomerular megangial cells [7-14]. This inconsistency may reflect the different conditions of the immunohistochemical staining between the studies. It should be noted, however, that those studies used antibodies against tenascin, which may not have been specific for TNC and therefore detected other tenascin family members. Tenascin-W, for example, is known to be expressed in healthy kidney [22]. As described previously [5], we used a mouse monoclonal antibody against TNC (clone 4F-10TT), which was raised though immunization of a TNC-null mouse [23] using purified human TNC [24]. Recent studies using a specific antibody against TNC reported no expression of TNC in normal glomeruli in mice or zebrafish [25, 26], which is consistent with our present human study.

In the present study, we report the expression and distribution pattern of TNC within renal biopsy specimens from 25 patients with TIN. TNC was expressed during the active stage of inflammation and then disappeared with healing. Consistent with that histologic observation, a time-dependent reduction in TNC expression in TIN was revealed in the present study by the negative correlation between % TNC-positive area and disease interval. We also found positive correlations between % TNC-positive area and the serum CRP level (an inflammatory marker) and eGFR aggravation (indicative of renal dysfunction), both of which reflect TIN activity. Thus, expression of TNC likely reflects TIN disease activity.

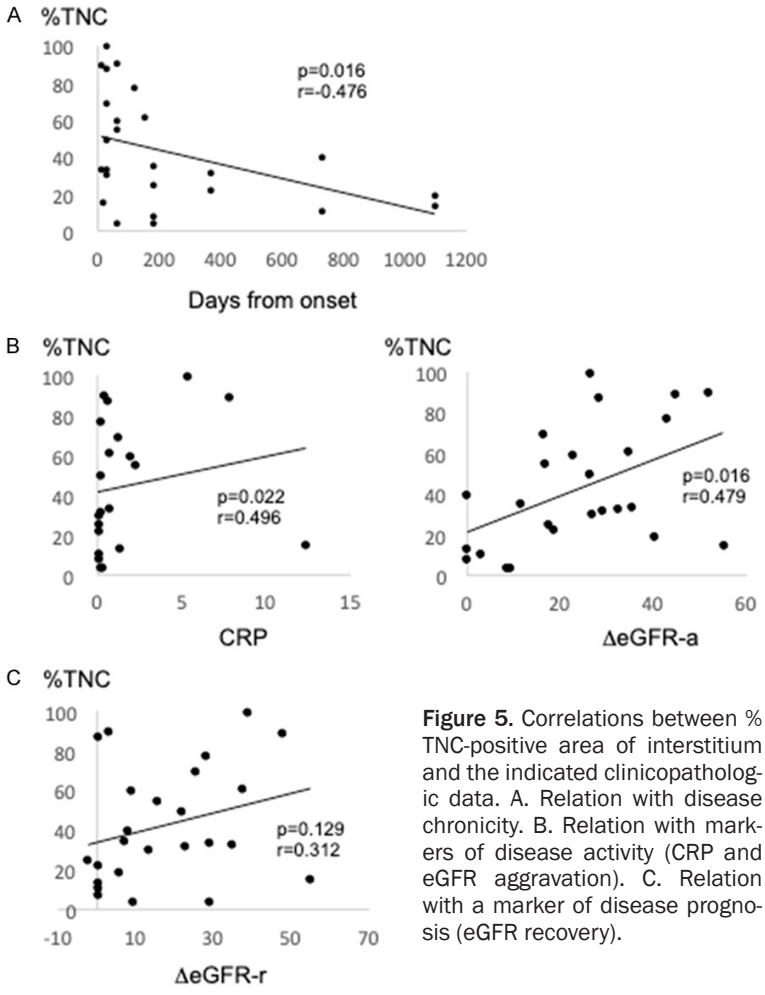

Figure 5. Correlations between % TNC-positive area of interstitium and the indicated clinicopathologic data. A. Relation with disease chronicity. B. Relation with markers of disease activity (CRP and eGFR aggravation). C. Relation with a marker of disease prognosis (eGFR recovery).

We observed that TNC positivity precedes formation of collagen fibers within inflammatory lesions. This finding is consistent with an earlier study using a mouse model of myocarditis [5]. Early expression of TNC after injury has been reported also in various tissues [27, 28]. TNC was previously hypothesized to interact with other extracellular matrix molecules and function as a scaffold for subsequent collagen deposition [29]. A more recent study, however, revealed that TNC is incorporated into the extracellular matrix by periostin, which can bind to collagen and fibronectin [30]. An important feature of TNC may be its detectability at the early stages of tissue injury. Most recently, Chen et al. reported a protective role of TNC against tubular epithelial cell injury through recruiting Wnt ligands in an experimental acute kidney injury model [26].

Prognosis primarily depends upon the cause of the TIN and factors such as therapy administered for systemic diseases, timing of therapy, previous renal function, and removal of any known offending agents. Chronicity portends a poorer outcome, and detection of fibrosis in renal biopsies is a marker of irreversible change. Consequently, early identification of TIN can often improve renal outcomes. Prolonged low molecular weight proteinuria is indicative of a poorer prognosis and decreased GFR [31]. In a review of adults with TIN, 64% made a full recovery, while 23% had partial recovery and 13% remained on renal replacement therapy [17]. In our study, nearly all patients recovered fully or partially during the follow-up, and none received renal replacement therapy. However, we found no correlation between the % TNC-positive area in biopsies and degree of eGFR recovery during follow-up (ΔeGFR-r value). Thus, the presence of TNC in a renal biopsy specimen does not appear to predict prognosis in TIN.

In the present study, we enrolled patients with TIN purely based on the pathologic findings and did not evaluate them separately at the etiological basis because of the relatively small number of the patients studied. However, renal lesions may possibly develop differently with causes of TIN. For example, TIN caused by hyperuricemia usually takes chronic process and occurs insidiously [32]. It would be ideal to analyze the development of renal lesions separately in each cause of TIN.

In human inflammatory tissues, TNC has been reported to be produced by fibroblasts in myocarditis [6] and by myofibroblasts in pleuritis [33]. However, there has been no human study reporting TNC-producing cells in TIN. Further study is warranted on this issue.

Conclusions

The immunohistochemical evidence presented indicates that TNC is present within renal biop-

sy specimens from patients with TIN. TNC was detected during the active stage of inflammation and then disappeared with healing. The expression level of TNC appears to reflect disease activity but not prognosis.

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Disclosure of conflict of interest

None.

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