NEPHRON

Original Paper

Nephron 1996;72:579–586

Tenascin Is an Ubiquitous Extracellular Matrix Protein of Human Renal Interstitium in Normal and Pathologic Conditions

Luan D. Truong[a]
Stephen V. Foster[a]
Roberto Barrios[a]
Vivette D'Agati[d]
Regina R. Verani[c]
Juan M. Gonzalez[b]
Wadi N. Suki[b]

[a] Departments of Pathology and [b] Medicine, Methodist Hospital and Baylor College of Medicine, and [c] Department of Pathology, University of Texas Health Science Center, Houston, Tex., [d] Department of Pathology, Columbia University, New York, N.Y., USA

Abstract

Tenascin, a large oligomeric glycoprotein, is a recent addition to a list of increasing extracellular matrix proteins. Previous studies have documented the strong expression of tenascin in embryonic kidney and in both normal and abnormal mature glomeruli implicating an important role of this extracellular matrix protein in nephrogenesis and glomerular scarring. Whether tenascin plays any role in interstitial fibrosis, a common final pathway of tubulointerstitial nephritis, is not known; on the other hand, a detailed knowledge of the structural components of interstitial fibrosis is essential for further studies on other fundamental aspects of this biologically and clinically important process. In this study, the expression of tenascin in the renal interstitium was immunohistochemically evaluated in 208 renal specimens including normal kidney (23 cases), acute tubular necrosis (8), acute tubulointerstitial nephritis (8), chronic primary tubulointerstitial nephritis (30), tubulointerstitial nephritis secondary to glomerular diseases of mild (46) and severe (55) degree, ischemic damage (24), and rejection (14). It was found that in normal kidney tenascin expression was limited to the medullary interstitium. In kidney with tubulointerstitial nephritis, tenascin was ubiquitously and constantly expressed in any areas with tubulointerstitial damage regardless of diagnosis, etiology, the cortical vs. medullary location of the lesions, stage of the fibrogenetic process, density of fibroblasts, or severity of interstitial inflammation in the affected areas. Indeed, strong tenascin expression was seen in areas where there was only interstitial edema or inflammation as judged by routine light microscopic preparations. In summary, this study systematically documents tenascin as a novel extracellular matrix protein selectively expressed in the medullary interstitium in normal kidney, and ubiquitously present in areas with interstitial fibrosis.

Key Words
Immunohistochemistry
Tubulointerstitial nephritis
Interstitial fibrosis

Introduction

Tenascin (TN), an extracellular matrix (ECM) protein independently described by many laboratories between 1983 and 1985, is a large oligomeric glycoprotein composed of six identical subunits connected at their amino terminus by disulfide bonds to a central globular domain. Each subunit with a molecular weight ranging from 180 to 320 kD is composed of a proximal domain of 13 epidermal growth factor-like homologous repeats, a middle do-

KARGER
E-Mail karger@karger.ch
Fax + 41 61 306 12 34

0028–2766/96/0724–0579$10.00/0

Luan D. Truong, MD
Department of Pathology MS-205
6565 Fannin
The Methodist Hospital
Houston, TX 77030 (USA)

Accepted:
April 24, 1995

Table 1. Cases used for the staining of tenascin

Normal kidney		23
Adjacent to renal cell carcinoma	20	
From autopsy	3	
Acute tubular necrosis		8
Acute TIN		8
Drug-induced	4	
Associated with uveitis	1	
Idiopathic	3	
Chronic primary TIN		30
Idiopathic	10	
Congenital	1	
Chronic pyelonephritis	4	
Chronic cyclosporin toxicity	3	
Lithium toxicity	4	
Cast nephropathy associated with myeloma	1	
Analgesic abuse	2	
Sarcoid	4	
Mitochondrial DNA deletion	1	
Chronic secondary TIN, secondary to glomerular or vascular diseases		101
Mild[1]	46	
Moderate-severe[2]	55	
Ischemic damage		24
Renal artery stenosis	3	
Arterio/arteriolonephrosclerosis	11	
Kidney tissue adjacent to renal tumor	10	
Rejection		14
Acute	9	
Chronic	5	
Total		208

[1] Involvement of less than 30% of the tissue surface area.
[2] Involvement of more than 30% of the tissue surface area.

main of 8–15 fibronectin type III homologous repeats, and a distal domain with homology to the β- and γ-chains of fibrinogen [1–3].

Tubulointerstitial nephritis (TIN) is characterized morphologically by various degrees of tubular atrophy, interstitial fibrosis, edema and inflammation. TIN may be secondary to a preceding vascular or glomerular lesion (secondary TIN) or may occur as a primary process, in which there is no significant alteration of glomeruli and blood vessels, at least early in the disease process (primary TIN) [4]. Interstitial fibrosis, an integral component of advanced TIN regardless of etiology, is characterized by expansion of ECM, traditionally thought to be composed of various types of collagens including collagen types I and III, fibronectin and proteoglycans [5–8]. More recently, several new ECM proteins have been described including undulin, osteonectin, thrombospondin and TN [9–11]. Although there is some work on the distribution of these ECM proteins in kidney tissue [9–11], to the best of our knowledge, no study has focused specifically on their expression and roles in renal interstitial fibrosis. A detailed knowledge of the structural components of interstitial fibrosis would be essential for further understanding of this frequent and clinically important process.

We, therefore, undertook a systematic evaluation of the distribution of TN in the interstitium of normal kidney with various types of TIN. Our findings demonstrate that TN is ubiquitously expressed in renal interstitial fibrosis.

Materials and Methods

Materials

208 cases (167 renal biopsies and 41 nephrectomy specimens) from the Departments of Pathology, The Methodist Hospital, Baylor College of Medicine, Houston; University of Texas, Houston and Columbia University, New York, were selected for the study. The diagnoses of the cases are summarized in table 1.

Tissue Preparation

Tissue used for this study was either fresh frozen or fixed. For frozen tissue, fresh tissue blocks were embedded in OCT mounting medium and snap-frozen at −70 °C. For fixation, tissue was fixed in either 10% buffered formalin, Zamboni fluid (containing picric acid and formaldehyde), or B5 fixative (containing 1.0 *M* formaldehyde, 0.3 *M* glyoxal and 6% methanol) for up to 10 h, and embedded in paraffin. In all cases, 4-μm sections were cut and submitted to staining.

Antibodies

The anti-TN antibody is a mouse monoclonal antibody directed against purified human TN obtained from cultured U251 glioma cells (Dako Corporation, Carpinteria, Calif., USA). The specificity of this antibody for TN has been confirmed by immunoblotting and absorption studies as previously described [12]. Briefly, the immunoblotting study showed that the antibody selectively reacted with TN extracted from normal human kidney and aortic wall, but did not detect either fibronectin or laminin. The absorption study showed that immunoreactivity was lost when the antibody was absorbed with 25 μg/ml of purified TN (Chemicon, Temecula, Calif., USA) before staining.

Staining Techniques

Staining was performed on frozen tissue only (13 cases), fixed tissue only (66 cases) and both fresh and frozen tissue (129 cases). Simultaneous staining for both frozen and fixed tissue was done since although satisfactory immunolocalization of TN was observed for both types of tissue in most cases, unequivocal positive staining for TN was occasionally obtained only in frozen tissue. In contrast, a precise localization of staining was sometimes only possible in fixed tissue. The standard avidin-biotin-peroxidase complex technique was used [13]. Briefly, the staining procedure included: (a) rehydration; (b) suppression of endogenous peroxidase activity with 1.5% H_2O_2 in methanol for 15 min; (c) digestion with type XIV protease

(Sigma, St. Louis, Mo., USA), (0.02% protease in 0.05 *M* Tris buffer, pH 7.6, 0.025% $CaCl_2$, 7 min at 37°C); (d) treatment with 10% normal horse serum in PBS for 30 min to prevent nonspecific staining; (e) incubation with primary antibody diluted to 1/100 in PBS for 1 h at room temperature; (f) incubation with secondary antibody directed against mouse immunoglobulins (Vector Laboratories, Burlingame, Calif., USA) at 1/100 dilution for 1 h at room temperature; (g) incubation with avidin-biotin-peroxidase complex (Vector Laboratories) at 1/100 dilution for 1 h at room temperature; (h) color development with diaminobenzidine (Sigma), 50 mg% for 6 min at room temperature; (i) counterstaining with 4% methyl green for 15 min at room temperature.

Tissue sections from a decubitus ulcer were used as a positive control. The negative controls included replacement of the primary antibody with an irrelevant antibody from the same species.

Methods of Evaluation

Correlation of the staining characteristics of TN with other parameters of TIN including diagnostic categories, severity of interstitial inflammation, the density of interstitial fibroblasts, and the histologic types of interstitial fibrosis (which may be classified as predominantly edema, or 'young' cellular connective tissue, or 'mature' poorly cellular connective tissue) was done.

Results

Expression of TN in Renal Interstitium

Normal Kidney. Most of the cortical interstitium was not stained. However, even in 'normal kidney', rare microscopic foci of tubular atrophy and interstitial fibrosis, probably representing age-related changes, were seen especially in the superficial portion of the cortex; the interstitium in these areas showed strong staining (fig. 1). The medullary interstitium displayed strong, diffuse staining (fig. 1).

Acute Tubular Necrosis (ATN). The diffusely widened, edematous interstitium characteristically seen in ATN displayed strong, diffuse staining (fig. 2).

Acute TIN. Regardless of etiology, foci of interstitial edema/early fibrosis showed diffuse staining; this staining was intense regardless of variations in the degree of interstitial inflammation between specimens or in different areas of the same specimen. The TN staining highlighted the extensively connecting network of fine fibers, even in areas where light microscopic examination of routine-stained sections showed only edema (fig. 3).

Chronic Primary TIN. In each case, all the areas with interstitial damage displayed strong staining, whereas the adjacent or distant areas with intact interstitium showed no staining. Thus, this differential expression of TN not only faithfully reflected the topography of interstitial changes seen by light microscopy but also represented a sensitive marker for these changes (fig. 4a, b). Although TN staining was noted in all phases of interstitial fibrosis,

Fig. 1. Normal kidney. Diffuse staining for tenascin is noted in the medullary interstitium. The intact cortical interstitium shows no staining; but some subcapsular scars (arrowheads), usually seen in 'normal' kidney tissue especially in old age, strongly express tenascin. Marked differential expression of tenascin is also noted for medulla and the column of Bertin (b). There is diffuse, global staining of glomeruli, which, on higher magnification, is limited to the mesangium. Smooth muscle of an arcuate artery (a) and an arcuate vein (v) as well as smaller cortical vessels also express tenascin. Immunoperoxidase. ×8.5.

staining patterns differed as follows: in areas of interstitial edema/early fibrosis, the pattern was similar to that seen in the case of acute TIN; in areas of mature or organized fibrosis, the staining was somewhat weaker but recapitulated the coarse, fibrillary pattern of interstitial fibrosis seen by light microscopy (fig. 4a). There was no correlation between the degree of staining and the density of interstitial fibroblasts, or the severity or type of interstitial inflammation (fig. 4a,b). An exception was a peculiar pattern of TN expression in areas of severe chronic interstitial inflammation, where strongly stained fine fibers were seen insinuated between the inflammatory cells; these

Fig. 2. Acute tubular necrosis. In this case, although the interstitium shows diffuse edema with inconspicuous fibrosis as judged by routine light-microscopic preparations, a distinctive network of fibers stained strongly for tenascin is noted. Diffuse mesangial staining is also present. Immunoperoxidase. × 800.

Fig. 3. Acute tubulointerstitial nephritis. A network of fibers strongly stained for TN is noted diffusely in the interstitium, ensheathing interstitial inflammatory cells. Immunoperoxidase. × 1,600.

Fig. 4. Primary, chronic tubulointerstitial nephritis. **a** Coarse, compact fibers strongly stained for tenascin are noted in the lower field, which displays features of mature fibrosis as judged by routine light microscopic preparation. Noted in the upper field is an interconnecting fiber network, which stains strongly for tenascin and ensheathes many interstitial inflammatory cells. **b** Diffuse interstitial deposition of tenascin, with sparing of the granulomas (G) in this case of sarcoidal chronic tubulointerstitial nephritis. Immunoperoxidase. × 800.

fibers were not apparent by routine light microscopy (fig. 4a).

Chronic, Secondary TIN. Secondary tubulointerstitial damage is frequently seen in a large variety of glomerular or renal vascular diseases and, in general, quantitatively correlates with the severity of the primary lesions. Regardless of diagnostic categories, each area of interstitial damage, even mild or focal, displayed interstitial accumulation of TN; moreover, this accumulation showed an exquisite correlation with the topography of the interstitial damage (fig. 5). Other features of TN staining were similar to those seen in cases of primary chronic TIN.

Ischemic Damage. The tubulointerstitium with ischemic damage as seen in renal artery stenosis, arterio/arte-

Fig. 5. Chronic secondary tubulointerstitial nephritis in a case of IgA nephropathy. Strong interstitial expression of tenascin is limited to the areas with tubular atrophy and interstitial widening. Incidentally, there is global mesangial staining of a glomerulus. Immunoperoxidase. × 800.

Fig. 6. Ischemic damage in a case of segmental renal artery stenosis. Only the area with ischemic damage (left) displays tenascin accumulation, contrasting with absence of interstitial expression of tenascin in the adjacent intact area. Incidentally, there is mesangial staining of an intact glomerulus and global staining for the two globally sclerotic glomeruli (s). Immunoperoxidase. × 800.

Fig. 7. Rejection. **a** In this field, the interstitium displays mature interstitial fibrosis with scanty mononuclear inflammatory cell infiltrate (upper), merging into an area of severe inflammation (lower). HE. × 800. **b** A consecutive section shows that although tenascin accumulates in both areas, remarkably different staining patterns are noted. Incidentally, a glomerulus with features of chronic transplant glomerulopathy expresses peripheral staining for tenascin. Immunoperoxidase. × 800.

nolonephrosclerosis and in kidney tissue adjacent to renal tumors showed characteristic changes including uniformly atrophic, simplified tubules with disproportionately mild interstitial fibrosis and inflammation. The interstitium in these areas displayed strong TN expression, contrasting sharply with absence of TN staining in adjacent but histologically normal areas (fig. 6).

Rejection. TN expression in the interstitium of these cases was even more pronounced than that seen in other diagnostic categories. Kidney with either acute or chronic rejection diffusely expressed interstitial TN in areas of either interstitial edema, mature interstitial fibrosis or organized interstitial fibrosis (fig. 7a, b). However, the expression was more marked in acute rejection and corre-

lated roughly with the degree of interstitial inflammation. Indeed, in the most severe cases, staining was seen in renal capsular or peripelvic soft tissue, where inflammation was noted.

Expression of TN in Renal Tubules

Staining was not seen in cytoplasm or basement membrane of either normal or affected tubules in any cases.

Discussion

To the best of our knowledge, the distribution of TN in human kidney tissue was previously addressed in six articles and three abstracts, none of which systematically evaluated the participation of TN in interstitial fibrosis [12, 14–21].

Ventimiglia et al. [14] used Western and Northern blotting, respectively, to study normal kidney tissue obtained from two autopsies. Koukoulis et al. [15], in a general review of TN distribution in a wide variety of abnormal human tissues, briefly mentioned an increased TN staining in 'glomerulopathies' and 'interstitial nephritides'. Gould et al. [16], in an immunohistochemical study of 26 renal transplant biopsies described 'strong diffuse vs. uneven' staining of the interstitium in acute or chronic rejection; mesangial and vascular staining was also noted. Bourdon et al. [17] immunostained two normal autopsy kidneys and noted 'strong fibrous medullary interstitial staining', with variable mesangial staining and no staining of the cortical interstitium. Two other studies by Assad et al. [18], and by our group [12], respectively, were more comprehensive but limited to the glomerular changes. Among the three abstracts referenced above, one focused on glomeruli in crescentic GN and the other two, on the interstitium in various forms of cystic disease [19–21].

Our study clearly establishes for the first time that TN is an ECM protein consistently present in human renal interstitium in both normal and pathologic conditions. We found that in normal adult kidney, although TN was strongly and diffusely expressed in medulla, it was not found in cortical interstitium. This intriguing pattern of differential expression, has not been noted for any other normal ECM protein component of the renal interstitium [7, 8]. This finding supports the concept that there is structural heterogeneity within the renal interstitium [22] and that the medullary and cortical interstitial fibroblasts are morphologically and functionally distinct [23]. We also noted a marked immunolocalization of TN in the medulla, which contrasted sharply with a negative staining of the contiguous peripelvic soft tissue, indicating an exquisitely site-specific expression of TN with possible functional implications.

In kidney with TIN, we found that TN is ubiquitously and constantly expressed in any areas with tubulointerstitial damage regardless of diagnosis, etiology, location of the lesions, stage of the fibrogenetic process, density of the fibroblasts, or severity of the interstitial inflammation in the affected areas. We and others have established that TN synthesis is increased in glomeruli affected with a wide variety of diseases [12, 15, 18]; the interstitial accumulation of TN in areas of tubulointerstitial damage is even more pronounced than that seen in glomeruli, since in several cases, where glomerular staining was totally or partially lost by fixation, TN in interstitium is still readily detectable (fig. 3). Whether this difference is related to the amount of TN accumulated or to a site-specific differential expression of TN isoforms [2, 3] with variable resistance to fixation and sensitivity to the utilized anti-TN antibody remains unsettled.

The findings from our study are of significance, since they may potentially facilitate better understanding of TIN, a common and functionally important component of most renal diseases [4]. Tubulointerstitial damage is not only the predominant lesion of primary TIN but is also a nearly constant accompaniment of any renal disease, with the possible exception of minimal change disease [4]. Moreover, repeated studies have established that regardless of the types of primary renal diseases, it is the tubulointerstitial damage that correlates best with the decreased renal function, and most accurately predicts renal outcome [23–25]. On the other hand, it is obvious that a detailed knowledge of the structural basis of interstitial fibrosis, a common final pathway of TIN of any type, is essential for further studies on other fundamental aspects of this process. Up until recently, the paradigm for studying TIN includes the complex interaction of inflammatory cells, tubular epithelium, interstitial fibroblasts, biologically active hormones and growth factors synthesized by these cells, and interstitial ECM proteins including collagen types I, III, V, fibronectin and glycoproteins [5–8]. Findings from our study suggest that any future work on the pathogenesis and evolution of TIN must take the ubiquitous expression of TN in renal interstitum into consideration.

The cell types responsible for the synthesis of interstitial TN in normal or pathologic conditions are not known but are probably interstitial fibroblasts. Fibroblasts cultured from chicken embryo and nonrenal human tissue

were shown to synthesize and secrete TN [13], whereas epithelial cells have not been known as a source of TN [1–3]. In normal kidney, the remarkable divergence of cortical and medullary expression of TN supports the role of interstitial fibroblasts to synthesize TN, since it has been well established that interstitial fibroblasts in normal cortex and medulla, respectively, are morphologically, and probably, functionally distinct [22]. It has also been shown that interstitial fibroblasts cultured from renal tissue with interstitial fibrosis differentiate into several phenotypes with various response to cytokines as well as diversity in their capability to synthesize ECM proteins [8, 26, 27]. It is, therefore, conceivable that renal interstitial fibroblasts, regardless of location, acquire a new capability to synthesize TN in response to diverse tubulointerstitial damage, accounting for the marked TN accumulation in any areas with interstitial fibrosis.

Mechanisms controlling the expression of TN in the renal interstitium in both normal and pathologic conditions have not been elucidated. Interstitial fibroblasts cultured from human or murine kidney with interstitial fibrosis have been shown to synthesize and secrete several ECM proteins, a process influenced by various hormones and growth factors, most prominent among which is TGF-β1 [8, 26, 27]. In two models of interstitial fibrosis in rat and rabbit, respectively, interstitial accumulation of ECM proteins was associated with increased mRNA for TGF-β [28, 29]. Although TN, being emphasized only recently, was not included in the ECM proteins evaluated in these studies [8, 28, 29], its synthesis is probably similarly influenced by TGF-β. Indeed, cultured chicken embryo fibroblasts respond to exogenously administered TGF-β by a dramatic increase in TN synthesis at both the mRNA and protein levels [30]. Although TGF-β has been repeatedly identified in normal and pathologic glomeruli [31–34], its presence in renal interstitium and its role in intestinal fibrosis have just been recently recognized [35].

In summary, this study systematically documents TN as a novel ECM protein selectively expressed in the medullary interstitium in normal kidney. Furthermore, TN is shown to be a constant constituent of interstitial fibrosis throughout its various phase of development and regardless of its etiology. The functional significance of this ubiquitous expression remains to be evaluated.

Acknowledgement

This study was supported in part by a generous gift from the Moran Foundation, Houston, Tex., USA.

References

1 Cliquet M: Tenascin: An extracellular matrix protein involved in the morphogenesis of epithelial organs. Kidney Int 1992;41:629–639.
2 Chiquet-Ehrismann R: What distinguishes tenascin from fibronectin. FASEB J 1990;4:2598–2604.
3 Erickson HP, Bourdon MA: Tenascin: An extracellular matrix protein prominent in specialized embryonic tissue and tumors. Ann Rev Cell Biol 1989;5:71–92.
4 Eknoyan G, McDonald MA, Appel D, Truong LD: Chronic tubulointerstitial nephritis: Correlation between structural and functional findings. Kidney Int 1990;38:736–743.
5 Kuncio GS, Neilson EG, Haverty T: Mechanism of tubulointerstitial fibrosis. Kidney Int 1991;39:550–556.
6 Downer G, Phan SH, Wiggins RC: Analysis of renal fibrosis in a rabbit model of crescentic nephritis. J Clin Invest 1988;82:998–1006.
7 Jones CL, Buch S, Post M, McCulloch L, Liu E, Eddy AA: Renal extracellular matrix accumulation in acute puromycin aminonucleoside nephrosis in rats. Am J Pathol 1992;141:1381–1396.
8 Rodemann HP, Muller GA: Characterization of human renal fibroblasts in health and disease. II. In vitro growth, differentiation and collagen synthesis of fibroblasts from kidneys with interstitial fibrosis. Am J Kid Dis 1991;17:684–686.
9 Just M, Herbst H, Hummel M, Durkop H, Tripier D, Stein H, Schuppan D: Undulin is a novel member of the fibronectin-tenascin family of extracellular matrix glycoproteins. J Biol Chem 1991;266:17326–17332.
10 Sage EH, Bornstein P: Extracellular proteins that modulate cell-matrix interactions. J Biol Chem 1991;266:14831–14834.
11 Tarboletti G, Morigi M, Figliuzzi M, Giavazzi R, Zoja C, Remuzzi G: Thrombospondin induces glomerular mesangial cell adhesion and migration. Lab Invest 1992;67:566–571.
12 Truong LD, Pindur J, Barrios R, D'Agati V, Lechago J, Suki W, Majesky M: Tenascin is an important component of the glomerular extracellular matrix in normal and pathologic conditions. Kidney Int 1994;45:201–210.
13 Hsu SM, Raine L, Fanger H: A comparative study of the peroxidase-antiperoxidase method and an avidin-biotin complex method for studying polypeptide hormones with radioimmunoassay antibodies. Am J Clin Pathol 1981;75:734.
14 Ventimiglia B, Wikstrand CJ, Ostrowski LE, Bourdon MA, Lightner VA, Bigner DD: Tenascin expression in human glioma cell lines and normal tissues. J Neuroimmunol 1992;36:41–55.
15 Koukoulis GK, Gould VE, Bhattacharyya A, Gould JE, Howeedy AA, Virtanen I: Tenascin in normal, reactive, hyperplastic and neoplastic tissues: Biologic and pathologic implications. Hum Pathol 1991;22:636–643.
16 Gould VE, Martinez-Lacabe V, Virtanen I, Sahlin KM, Schwartz MM: Differential distribution of tenascin and cellular fibronectins in acute and chronic renal allograft rejection. Lab Invest 1992;67:71–79.
17 Bourdon MA, Wikstrand CJ, Furthmayr H, Matthews TJ, Bigner DD: Human glioma-mesenchymal extracellular matrix antigen defined by monoclonal antibody. Cancer Res 1983;43:2796–2805.

18 Assad L, Schwartz MM, Virtanen I, Gould VE: Immunolocalization of tenascin and cellular fibronectins in diverse glomerulopathies. Virchows Arch [B] 1993;63:307–316.
19 Nakao N, Kusakabe M, Nihei H, Sakakura T, Natori Y: Parietal epithelial cells produce tenascin (TN) in crescentic glomerulonephritis (abstract). J Am Soc Nephrol 1993;4:660.
20 Dahmane F, Narcy F, Dumez Y, Gubler M-C: Distribution and ontogenesis of tenascin in normal and cystic human fetal kidneys (abstract). J Am Soc Nephrol 1993;4:648.
21 Klingel R, Ramadori G, Schuppan D, Meyer zum Büschenfelde K-H, Kohler H: Co-expression of extracellular matrix glycoproteins undulin and tenascin in human autosomal dominant polycystic kidney disease (abstract). J Am Soc Nephrol 1992;3:636.
22 Lemley KV, Kriz W: Anatomy of the renal interstitium. Kidney Int 1991;39:370–381.
23 Bohle A, Mackensen-Haen S, Gise HV, et al: The consequences of tubulo-interstitial changes for renal function in glomerulopathies: A morphometric and cytologic analysis. Pathol Res Pract 1990;186:135–144.
24 Bohle A, Mackensen-Haen S, Gise HV: Significance of tubulointerstitial changes in the renal cortex for the excretory function and concentration ability of the kidney: A morphometric contribution. Am J Nephrol 1987;7:421–433.
25 Bohle A, Kressel G, Muller CA, Muller GA: The pathogenesis of chronic renal failure. Pathol Res Pract 1989;185:421–440.
26 Alvarez RJ, Sun MJ, Haverty TP, Iozzo RV, Myers JC, Neilson EG: Biosynthetic and proliferative characteristics of tubulointerstitial fibroblasts probed with paracrine cytokines. Kidney Int 1992;41:14–23.
27 Muller GA, Markovic-Lipkovski J, Frank J, Rodemann HP: The role of interstitial cells in the progression of renal diseases. J Am Soc Nephrol 1992;2:5198–5205.
28 Coimbra T, Wiggins R, Noh JW, Merritt S, Phan SH: Transforming growth factor-β production in anti-glomerular basement membrane disease in the rabbit. Am J Pathol 1991; 138:223–234.
29 Jones CL, Buch S, Post M, McCulloch L, Liu E, Eddy AA: Pathogenesis of interstitial fibrosis in chronic purine aminonucleoside nephrosis. Kidney Int 1991;40:1020–1031.
30 Pearson CA, Pearson D, Shibahara S, Hofsteenge J, Chiquet-Ehrismann R: Tenascin: cDNA cloning and induction by TGFB. EMBO J 1988;7:2677–2981.
31 Kaname S, Uchida S, Ogata E, Kurokawa K: Autocrine secretion of transforming growth factor-β in cultured rat mesangial cells. Kidney Int 1992;42:1319–1327.
32 MacKay K, Kondaiah P, Danielpour D, Austin HA III, Brown PD: Expression of transforming growth factor-β1 and β2 in rat glomeruli. Kidney Int 1990;38:1095–1100.
33 Yoshioka K, Takemura T, Murakami K, Okada M, Hino S, Miyamoto H, Maki S: Transforming grown factor-β protein and mRNA in glomeruli in normal and diseased human kidneys. Lab Invest 1993;68:154–163.
34 Border WA, Noble NA: Cytokines in kidney disease: The role of transforming growth factor-β. Am J Kid Dis 1993;22:105–113.
35 Yamamoto T, Noble NA, Miller DE, Border WA: Sustained expression of TGF-β1 underlies development of progressive kidney fibrosis. Kidney Int 1994;45:916–927.