Article

Valsartan Inhibited the Accumulation of Dendritic Cells in Rat Fibrotic Renal Tissue

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To observe the accumulation of dendritic cells (DCs) in rat remnant kidney and its contribution to tubulointerstitial fibrosis, under influence of valsartan on DCs, a rat remnant kidney model was established by subtotal nephrectomy. Four experimental groups were included: normal, sham, model (SNx) and the group treated with Valsartan (SNxV). Rats were killed at week 1, 4 and 12, respectively. $CD1a^+CD80^+$ DCs were assayed by double immunostaining method and the images were analyzed with Axioplan 2 microscopy. The expressions of P-selectin, TGF-β1, α-SMA, collagen III and fibronectin was analyzed by immunohistochemistry or semi-quantitative RT-PCR, and the level of tubulointerstitial firosis (TIF) was scored. $CD1a^+CD80^+$ DCs were gradually increased among renal tubules, interstitium and vessels, especially in interstitium, and the number of DCs in model group at week 12 was much more than that in model groups at week 1 or 4. The expressions of P-selectin, TGF-β1, α-SMA, collagen III and fibronectin in tubulointerstitial areas and the degree of TIF was increased substantially in model group at week 12. The accumulation of DCs in interstitium was well associated with the loss of renal function and the progression of tubulointerstitial fibrosis. Valsartan treatment inhibited the local accumulation of DCs and attenuated renal tubulointerstitial damage. The local DCs accumulation was related to tubulointerstitial fibrosis and renal dysfunction following renal ablation. Blockade to angiotensin II might be a potent way to attenuate renal immuno-inflammatory injury. *Cellular & Molecular Immunology*. 2006;3(3):213-220.

Key Words: dendritic cell, tubulointerstitial fibrosis, nephrectomy, valsartan

Introduction

The deterioration of renal function is well correlated with the progressive tubulointerstitial damage, rather than glomerular lesions, and the mechanisms that initiate tubulointerstitial injury in the context of early hemodynamic alterations remain to be elucidated (1). Tubulointerstitial infiltration of inflammatory cells is a common feature in nonimmune renal diseases, those cells not only secrete various proinflammatory cytokines (IL-1, TNF-α) and profibrotic cytokines (TGF-β1, CTGF), but also induce the activation of fibroblast (α-SMA^+ myofibroblast), as well as enhance the synthesis of extracellular matrix (fibronectin, collagen III) (2). Dendritic cells (DCs) are highly specialized antigen-presenting cells with a unique ability for inflammation defence and immune modulation (3-5). Our previous researches have indicated DCs moving into renal tissue were mainly mediated by P-selectin, and the number of DCs aggregated in tubulo-interstitial area had a close relationship with early stage of renal tubulointerstitial damage (6, 7). It has been shown that cultured DCs expressed angiotensinogen, angiotensin converting enzyme (ACE) and angiotensin II receptors (ATR1, ATR2) (8). Angiotensin II (AngII) is an octapeptide that is involved in several steps of the inflammatory process, which may promote the accumulation of immunocompetent cells, induces the expression of adhesion molecules and the secretion of chemokines. ATR1 antagonists could markedly inhibit DC maturation and ability for presenting antigen (9). To address the role of DCs on the immune renal tubulo-interstitial injury, we established a chronic fibrotic kidney model and treated the rats with ATR1 blockade (valsartan). We observed the distribution of DC in renal tubulo-interstitium, and detected the role of valsartan on DC

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accumulation and renal lesions.

Materials and Methods

Setting up renal subtotal ablation animals model and in vivo measurement

The remnant kidney is a representative model in the study of progressive renal disease. Seventy-two Sprague-Dawley rats were involved in this experiment. Subtotal nephrectomy in 3-week-old rats was operated by two-step method as previous study described (10). Rats were randomly divided into four groups: normal (n = 18); sham (n = 18), renal decapsulation alone was performed as control; SNx (n = 18), undergone 5/6 nephrectomy; SNxV (n = 18), treated with valsartan after nephrectomy, 30 mg/day/kg. Systolic blood pressure (SBP) was measured every 4 weeks in awake animals by the tail-cuff method. At week 1, 4 and 12 after surgery, six rats from each group were respectively anesthetized with ether and euthanized by decapitation; blood samples were harvested. Urine collection was performed the day before euthanasia by housing the animals in metabolic cages, to measure the urinary protein excretion (biuret assay). The sera separated from blood samples were tested for serum cretinine (Scr) and blood urea nitrogen (BUN). Therefore, the creatinine clean-out rate (Ccr) could be calculated. The rats in normal and sham groups were also examined to observe baseline expression. Kidneys were quickly removed and fixed in 4% buffered formaldehyde and processed routinely.

Renal morphologic analysis

Paraffin-embedded kidney sections from the rats were prepared at 2 μm thickness by a routine procedure. Sections were stained with hematoxylin/eosin or masson for general histology. Tubulointerstitial injury (defined as focal tubular atrophy, tubular dilatation with cast formation, interstitial expansion with perivascular inflammation, or thickening of the tubular membrane), was scored in a blind fashion semiquantitively on the basis of a scale of 0 (absent), 1 (mild), 2 (moderate), and 3 (severe). Five random, non-overlapping fields at high magnification (×400) were selected for scoring in the cortical region from each animal. The overall injury index was calculated on the basis of individual values determined per rat and expressed as mean ± SEM of six animals per group.

Immunohistochemistry assay

Indirect immunoperoxidase staining of 4 μm sections was performed using the following primary antibodies: a mouse polyclonal antibody against P-selectin (raised in our laboratory, working concentration 1:100), a rabbit polyclonal antibody against fibronectin (FN) (Gibco, working concentration 1:100), a rabbit polyclonal antibody against TGF-β1 (Santa Cruz, working concentration 1:100), a rabbit polyclonal antibody against collagen III (Sigma, working concentration 1:100), a mouse monoclonal antibody against α-SMA (Dako, working concentration 1:100). Controls included omitting the primary antibody. The expressions of P-selectin, TGF-β1, α-SMA, collagen III and FN among tubulointerstitium were graded semiquantitively and reflected changes in the area by the intensity of immunostaining. Twelve to twenty-five cortical fields (in each section) were evaluated in blinded fashion using a grid in the eyepiece of the microscope at a 200 magnification. A semiquantitive scoring system (0-4) was developed: score 0, 0-5%; score 1, 6-25%; score 2, 26-50%; score 3, 51-75%; score 4, 76-100% area of tubulointerstisium are positive or surrounded by positive staining within the grid.

Dual-label immunofluorescence staining analysis

Distribution of DCs in renal tissues was assayed by dual-label staining immunofluorescence image analysis method (8). Renal tissue sections were blocked with 0.3% BSA for 20 min, then incubated with goat anti-human CD1a polyclonal antibody (Santa Cruz, working concentration 1:100) and mouse anti-human CD80 polyclonal antibody (BD Biotech, working concentration 1:100) overnight at 4°C. Subsequently, the sections were added with FITC conjugated anti-mouse IgG and RPE conjugated anti-goat IgG (Jackson, working concentration 1:200), respectively. The sections were incubated for 1 h at 37°C, washed with PBS and then mounted. The first antibody was replaced by PBS to be a negative control. The sections were observed by a multifunctional automatic microscopy (Axioplan 2, ZEISS Co.) and the images were captured by digital camera (AxioCam, picture elemen 3,900 × 3,090). CD1a was positively stained by red-fluorescence, and CD80 by green-fluorescence. Cells with dual staining as shown by yellow-fluorescence represented DCs ($CD1a^{+}CD80^{+}$). All data were analyzed by the KS400 imaging process system and software (Ver 3.0),

Table 1. Primers of P-selectin, TGF-β1, α-SMA, collagen III, FN and GAPDH

	Size	Sense	Antisense
P-selectin	348 bp	5'-TGTATCCAGCCTCTTGGGCATTCC-3'	5'-TGGGACAGGAAGTGATGTTACACC-3'
TGF-β1	294 bp	5'-GGACTACTACGCCAAAGAAG-3'	5'-TCAAAAGACAGCCACTCAGG-3'
α-SMA	288 bp	5'-GATCACCATCGGGAATGAACGC-3'	5'-CTTAGAAGCATTTGCGGTGGAC-3'
Collagen III	560 bp	5'-CTGGACCAAAAGGTGATGCTG-3'	5'-TGCCAGGGAATCCTCGATGTC-3'
FN	295 bp	5'-TTATGACGATGGGAAGACCTA-3'	5'-GTGGGGCTGGAAAGATTACTC-3'
GAPDH	500 bp	5'-GACAAGATGGTGAAGGTCGG-3'	5'-CACGGAAGGCCATGCCAGTGA-3'

Table 2. The changes of BP, UP, BUN, SCr, Ccr in different groups at week 12

Group	BP (mmHg)	UP (mg/24h)	BUN (mM)	SCr (μM)	Ccr (ml/min·kg)
Normal	114.7 ± 5.19	9.40 ± 3.16	6.63 ± 1.05	31.67 ± 5.39	4.01 ± 1.02
Sham	127.5 ± 5.35	10.39 ± 4.84	6.87 ± 1.11	34.0 ± 5.63	5.08 ± 1.71
SNx	195.5 ± 12.24*	101.95 ± 47.45*	26.46 ± 12.74*	97.0 ± 34.05*	1.59 ± 0.41*
SNxV	126.2 ± 13.04$^{\triangle}$	54.65 ± 26.81$^{\triangle}$	15.74 ± 5.48$^{\triangle}$	59.2 ± 22.35$^{\triangle}$	3.29 ± 1.08$^{\triangle}$

*$p < 0.01$, *vs* sham group; $^{\triangle}p < 0.05$, *vs* SNx group; n = 6.

and the area, number and density of DC yellow-fluorescence were measured.

Semi-quantitative RT-PCR analysis

Total RNA was isolated from renal cortex as previously described (15). RT-PCR analysis was performed using a ThermoScrip RT-PCR Kit following the manufacturer's instruction (Shanghai Sangon). The first-strand cDNA was synthesized by using oligonucleotide primers and M-MLV reverse transcriptase (Promega), PCR amplification (35 cycles) used primers specific for rat P-Selectin, TGF-β1, collagen III, α-SMA and FN (the primer sequences showed in Table 1). All samples were subjected to RT-PCR for housekeeping gene GAPDH as a positive control and as an internal standard. PCR products were resolved on 1.5% agarose gels in 1× Tris-borate-EDTA (TBE) buffer, visualized by ethidium bromide, photographed using a gel 1000 ultraviolet documentation system (Bio-Rad), and analyzed by densitometry.

Statistical analysis

SPSS software version 11.0 was used for statistical analyses. Data presented as means ± SD, were evaluated by one-way ANOVA tests, *t*-test and Pearson bivariate correlation tests. A difference was considered significant when *p* value was less than 0.05.

Results

Changes of blood pressure, proteinuria and renal function in four groups at week 12

Table 2 summarized values for balance and blood data in all rats studied. Twelve weeks after nephrectomy, renal hypertrophy was evident in the SNx rats, systolic BP was significantly different from that in Sham animals; proteinuria increased gradually reaching a mean value of 101.95 ± 47.45 g/24 h at week 12. Scr and BUN concentrations were also significantly increased in SNx group rats, therefore Ccr in SNx group significantly decreased compared with Sham group, which indicated development of renal insufficiency. BP levels of valsartan treated group rats were significantly lower than those of SNx rats during the whole experimental period after induction of nephrectomy. Concentrations of Scr and BUN in SNxV rats were slightly higher than those in sham rats and were significantly lower than SNx rats at week 12 (Table 2).

Pathological changes

In SNx group, typical interstitial fibrosis could be observed, which was characteristic with narrowing and the obstruction of the capillary vessel lumen, the degeneration of renal tubular epithelial cells, the poly-focal atrophy, renal interstitial fibrosis, significant increase of extracellular matrix and diffusive infiltration of inflammatory cells. From the the semiquantitive data of Table 3, it was apparent that the degree of tubulointerstitial fibrosis (TIF) was significantly severer in SNx rats than that in Sham rats ($p < 0.01$). Treatment with valsartan ameliorated the damage in tubularinterstitium and TIF was attenuated compared with SNx group (Figure 1).

Expression of P-selectin, TGF-β1, Col III, α-SMA and FN in renal tubulointerstitium

In normal or sham rats, P-selectin and TGF-β1 were either absent or only weakly expressed by some tubular epithelial

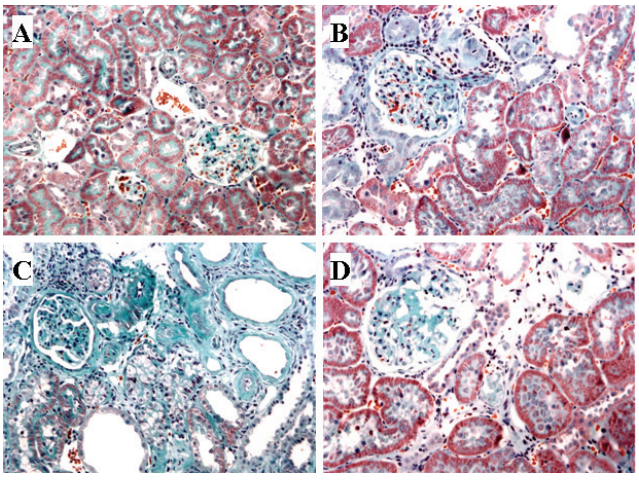

Figure 1. Histopathological changes in four groups at week 12 (×200). (A) Normal renal tubulointerstitial structure in normal group; (B) Normal renal tubulointerstitial structure in sham group; (C) Fibrosis renal tubulointerstitial structure with degeneration of renal tubular epithelial cells, deposition of extracellular matrix and infiltration of widespread inflammatory cells in SNx group; (D) The pathological changes in SNxV group were alleviated remarkably.

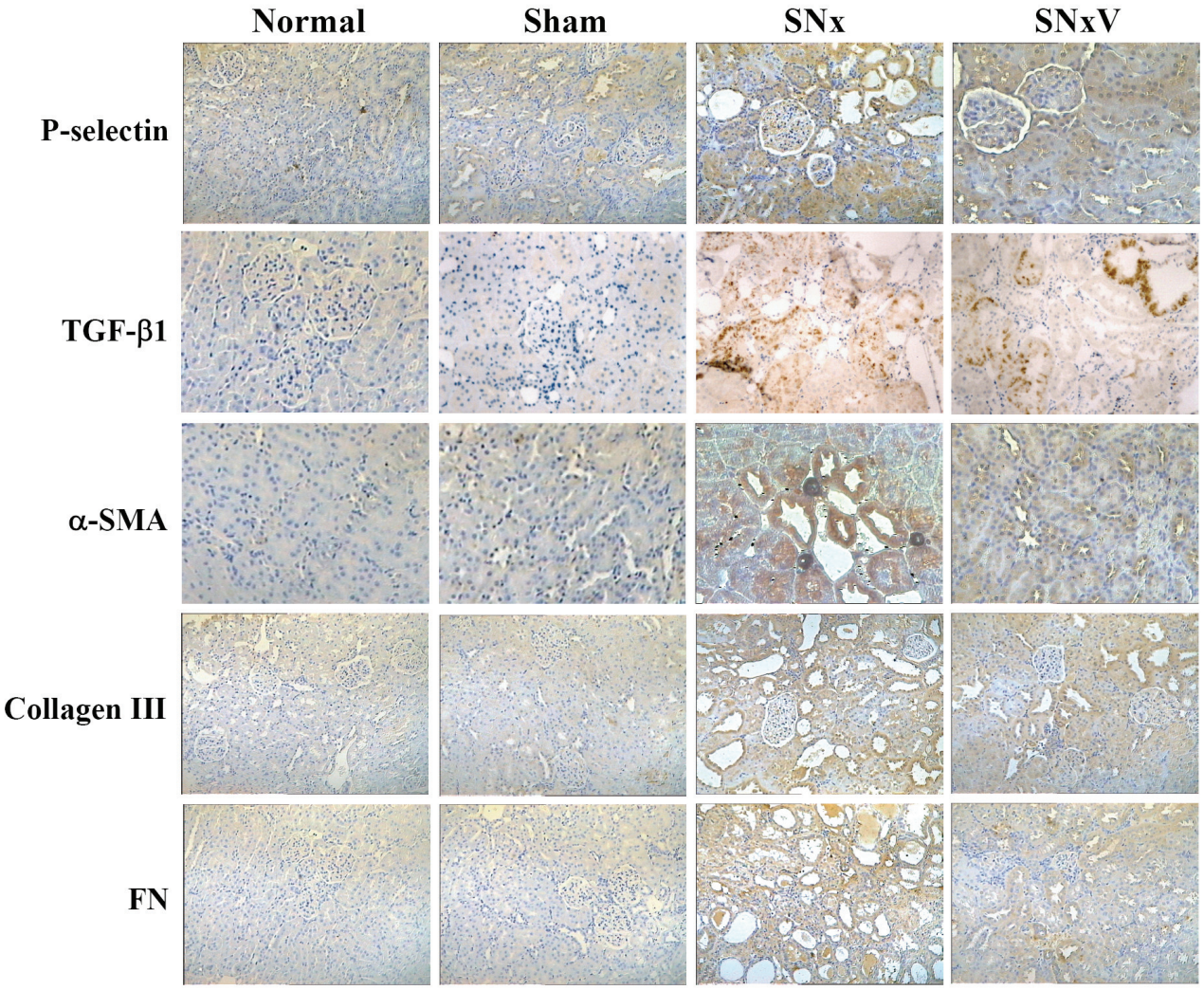

Figure 2. The distribution of P-selectin, TGF-β1, α-SMA, collagen III and FN in four groups at week 12 (immunohistochemistry, ×200). Almost no or weak staining was observed in normal group; weak staining was observed in sham group, similar to normal group; positive staining was enhanced significantly in SNx group; the level of positive staining in SNxV group was attenuated prominently compared with SNx group.

cells among tubulointerstitium. The presences of above proteins were up-regulated remarkedly among renal tubulointerstitium while TILs being severe. At the first week after renal ablation, their expression was weak, focal and appeared to be intracellular but dramatically increased at week 4, and up to 12, P-selectin and TGF-β1 staining were maximal and part of the staining appeared to be extracellular. Similar with P-selectin, at week 12, the expression of collagen III, α-SMA and FN remained at a very high level and predominantly localized in sclerotic lesions (Figure 2, Table 3). There was strong correlation between the expression of P-selectin and the presence of TGF-β1, Col III, α-SMA and FN (Table 4). However, in rats administrated with valsartan, the level of P-selectin, TGF-β1, collagen III, α-SMA and FN was much less prominent in its intensity than that of rats in SNx group at week 12 (Table 3).

P-selectin, TGF-β1, α-SMA, Col III and FN mRNA expressions

The mRNA levels of P-selectin, TGF-β1, α-SMA, collagen III and FN were measured by RT-PCR at week 12. Few cortical P-selectin, TGF-β1, α-SMA, collagen III and FN were detected in normal and sham group. But the mRNA levels of P-selectin, TGF-β1, α-SMA, collagen III and FN in SNx rats were increased markedly compared with the Sham group ($p < 0.05$). In contrary, the mRNA levels of P-selectin TGF-β1, α-SMA, collagen III and FN in SNxV group were increased to a lesser extent than those of SNx group ($p < 0.05$) (Figures 3 and 4).

Distribution of DCs in renal tubulointerstitium

$CD1a^+CD80^+$ DCs mainly distributed in tubulointerstitium in the early stage of the disease, rarely appeared in normal renal tissues and abnormal glomeruli. The number of $CD1a^+$

Table 3. The alteration of P-selectin, TGF-β1, α-SMA, collagen III and FN in four groups at week 12

Group	P-selectin	TGF-β1	α-SMA	Col III	FN
Normal	0.07 ± 0.03	0.24 ± 0.10	0.05 ± 0.02	0.83 ± 0.41	0.67 ± 0.41
Sham	0.09 ± 0.05	0.27 ± 0.15	0.07 ± 0.04	0.95 ± 0.62	0.83 ± 0.52
SNx	2.65 ± 0.12**	1.62 ± 0.45*	132.57 ± 26.74**	2.14 ± 0.56*	1.79 ± 0.49*
SNxV	1.32 ± 0.09$^{\triangle}$	1.10 ± 0.32$^{\triangle}$	83.00 ± 15.24$^{\triangle}$	1.35 ± 0.34$^{\triangle}$	1.15 ± 0.24$^{\triangle}$

*$p < 0.05$, *vs* Sham group; **$p < 0.01$, *vs* Sham group; $^{\triangle}p < 0.05$, *vs* SNx group; n = 6.

Table 4. Relationship between the degree of renal interstitial fibrosis and P-selectin, TGF-β1, α-SMA, collagen III, FN (*r*)

	P-selectin	TGF-β1	α-SMA	Collagen III	FN
Degree of renal interstitial fibrosis (*r* value)	0.667**	0.824***	0.364*	0.636**	0.516**

*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

$CD80^+$ DCs also increased in renal tubulointerstitium while TIL being severe. The distribution was prominently greater in SNx group at week 12 than that of at week 1 or 4. Valsartan also reduced the accumulation of DCs to a lesser extent compared with SNx group (Table 5, Figure 5).

Relationship between DC distribution in renal tissue and renal function

There was strong correlation between distribution number of $CD1a^+CD80^+$ DCs and the degree of tubulointerstitial lesions as well as creatinin clear-out rate (r = 0.823, r = -0.367, respectively, $p < 0.01$). Furthermore, their tubulointerstitial distribution also correlated with the expression of P-selectin, TGF-β1, α-SMA, collagen III and FN (all $p < 0.01$) (Table 6).

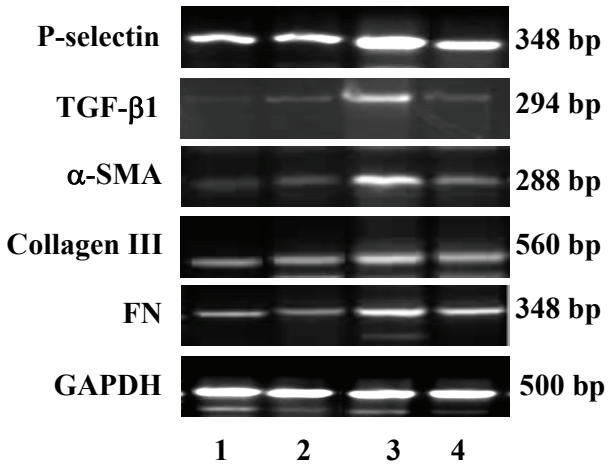

Figure 3. Electrophoresis images of P-selectin, TGF-β1, α-SMA, collagen III and FN mRNA expression of renal cortex in four groups at week 12. Lane 1, normal; Lane 2, sham; Lane 3, SNx; Lane 4, SNxV.

Discussion

Recent researches have demonstrated the degree of renal tubulointerstitial damage correlate more closely to renal failure than glomerular sclerosis (11). Infiltration of inflammatory cells and immunological response synergized to induce the early stage injury of renal interstitium, the latter was also pathogenic to renal interstitial fibrosis (2). DCs are the most potent antigen presenting cells in the immune system and critically involved in the initiation of primary immune responses, autoimmune diseases, graft rejection,

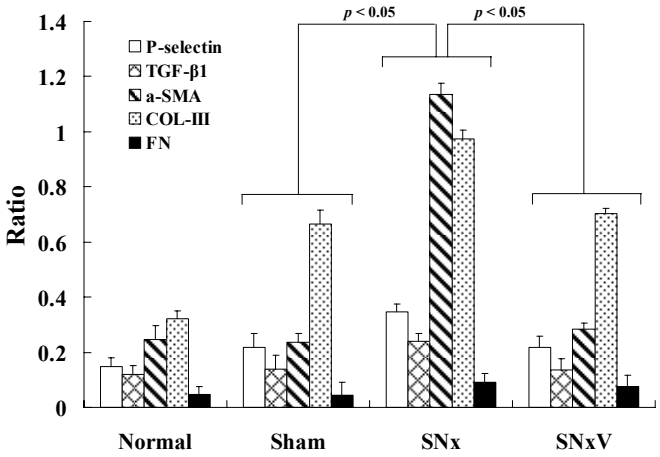

Figure 4. Comparison of P-selectin, TGF-β1, α-SMA, collagen III and FN mRNA expression in four groups at week 12. After 12 weeks of subtotal nephrectomy and treatment with valsartan, the mRNA levels of P-selectin, TGF-β1, α-SMA, collagen III and FN in renal cortex were detected by RT-PCR. There were significant differences by the variance analysis in P-selectin, TGF-β1, α-SMA, collagen III and FN mRNA expressions among four groups ($p < 0.05$).

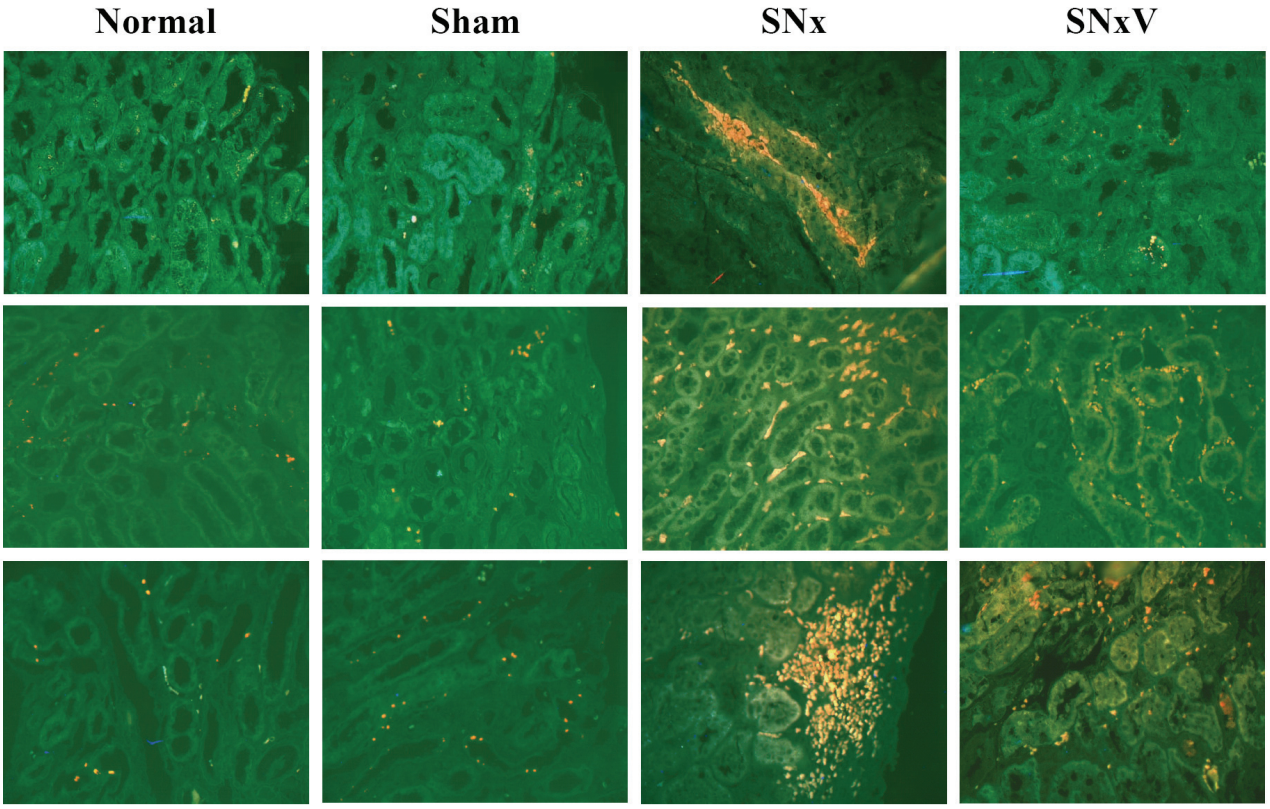

Figure 5. The distribution of dendritic cells in rat renal tissue of different groups (dual label stain, ×1,200). Almost no or few $CD1a^+CD80^+$ DCs distributed in normal group; few $CD1a^+CD80^+$ DCs were observed among renal tubule, interstitium and vessel in Sham group, mainly distributed in interstitial area; abundant $CD1a^+CD80^+$ DCs were aggregated in renal interstitium in SNx group, and the infiltration of DC at week 12 had significant difference with that at week 1 and 4 in SNx group; the accumulation of $CD1a^+CD80^+$ DCs in SNxV group was attenuated prominently comparing with SNx groop.

human immunodeficiency virus infection, and the triggering of adaptive immunity. Recently, more and more researches focused on the effects of DCs on renal inflammatory diseases. We have found P-selectin mediated the aggregation of DC in renal interstitium, and played a critical role on initiating the early stage renal interstitial damage (12, 13). In addition, maturation of DCs is crucial for the initiation of immunity and it can be influenced by various factors, particularly by microbial and inflammatory products, but molecular biological events that occur during the DC maturation are still poorly described (14, 15). Historically, AngII was regarded only as important in the regulation of blood volume, peripheral vascular tone, and blood pressure. However, recent studies showed that AngII was also related to other biological processes, such as apoptosis, vascularr emodeling, and inflammation. AngII is a vasoactive octapeptide involved in several steps of the inflammatory process and is considered as a true cytokine. The AngII receptor type I antagonist could not only inhibit the maturation of DC induced by AngII, reduce the expression of CD1a, but also weaken the activity of DCs to present antigen. Our study provided additional evidence on the role of immuno-competent cells in a nonimmune, Ang II-induced, renal disease.

Table 5. The distribution of DCs among renal interstitium on different phrases (number/mm^2)

Group	1 week	4 weeks	12 weeks
Normal	399.5 ± 150.5	434.5 ± 161.9	425.1 ± 157.8
Sham	435.1 ± 175.5	527.7 ± 291.4	550.3 ± 224.0
SNx	1868.5 ± 837.5*	2435.8 ± 1218.1*	3807.2 ± 1742.1*$^{\triangle}$
SNxV	753.4 ± 270.8$^{\triangle}$	1253.2 ± 596.7$^{\triangle}$	1720.6 ± 916.2$^{\triangle}$

*$p < 0.01$, *vs* sham group; $^{\triangle}p < 0.01$, *vs* SNx group at 1 week and 4 weeks; $^{\triangle}p < 0.01$, *vs* SNx group; n = 6.

Table 6. Relationship between the number of DCs and BUN, Scr, Ccr, P-selectin, TGF-β1, α-SMA, collagen III, FN

	BUN	SCr	Ccr	P-selectin	TGF-β1	α-SMA	Collagen III	FN	TIF
Number of DCs (*r* value)	0.254*	0.263*	-0.367**	0.566**	0.477**	0.288*	0.408**	0.495**	0.823*

*$p < 0.05$, **$p < 0.01$, *** $p < 0.001$.

In this study, chronic interstitial fibrosis was induced by renal subtotal ablation. After induction, residue nephron displayed some changes on structure and function due to compensable hyperperfusion, hyperfiltration and hyperpressure. While the injury persisted, various pathological changes occurred, which involved the deposition of extracellular matrix, so as to result in renal tubulointerstitial fibrosis and glomerular sclerosis, finally the patient entered the uremia stage. The rats in SNx group showed obvious physiological changes, which included hypertension, proteinuria, renal indecificience, reduction in Ccr and pathological changes, which is characteristic with thicken of tubular base membrane, dilation or atrophy of renal tubule, interstitial fibrosis and infiltration of abundant inflammatory cells. We performed CD1a and CD80 dual-label immunofluorescence staining for analyzing DC distribution and found paralleling with the expression of P-selectin, $CD1a^+CD80^+$ DCs mainly distributed in tubulointerstitium from 1 week after renal ablation, the accumulation was up-regulated while the disease was severer and peaked at week 12. In addition, within dilated or atrophy tubule and fibrosis interstitium where DCs mainly distributed, more expression of TGF-β1 and α-SMA was observed, and more collagen III, FN deposited. Moreover, the number of $CD1a^+CD80^+$ DCs among tubulointerstitium associated with the degree of TILs and renal insufficiency. Since inflammation was main course to mediate and initiate the renal tubulointerstitial damages, and cellular immune was thought as the main mechanism to induce renal tubulointerstitial fibrosis, we hypothesized at the early stage of renal tubulointerstitial injury, more and more DCs, performed as inflammatory cells and main antigen presenting cells, migrated into renal tubulointerstitium with P-selectin mediation, then participated and initiated the interstitial injury. DCs promoted the secretion of TGF-β1, which stimulated the transdifferentiation of tubular epithelial cells and interstitial fibroblasts, increased the synthesis of extracellular matrix, such as collagen III and FN, finally enhanced the progression of fibrosis and remodeling of renal tissue at the end stage of disease.

Treating with valsartan could not only reduce systolic BP and urinary protein, but also antagonize the expression of P-selectin, TGF-β1, α-SMA, collagen III and FN. As results, the extent of tubulointerstitial fibrosis was alleviated, as well as the renal function was ameliorated. In addition, valsartan inhibited the accumulation of $CD1a^+CD80^+$ DCs among rat renal interstitium. Such inhibitory effects might relate to the expression of AngII and its receptors. We suggested that the local secretion of AngII was up-regulated through autocrine or paracrine pathway after renal ablation, and AngII played an important role in modulating DC function and immune reaction. For instance, AngII increased the expression of P-selectin, chemokines, induced and mediated DC migrating to inflammatory reaction areas in renal interstitium (16-18), then DCs seized, processed and presented antigen, stimulated T lymphocyte and initiated the immune reaction. On the other hand, both AngII and valsartan were recognized and captured by DCs as exogenous antigens. Thus, they might cause nonspecific up- and down-regulations of the expression of genes that played important roles in a network integrating cellular responses (enhancing antigen presentation, cell metabolism, rearrangements in cytoskeleton) to a number of stimuli. Furthermore, valsartan blocked AngII binding to AT1 receptor, reduced the expression of P-selectin, then antagonized DC migration and proinflammatory cytokine secretion, finally ameliorated the immuno-inflammatory response and attenuated the renal injury (19, 20).

In conclusion, DCs infiltrated among renal tubulo-interstitium under the P-selectin mediation, were correlated closely with progression of renal interstitial fibrosis. Valsartan inhibited the activation of renal local RAS, reduced DC intrarenal migration and maturation, down-regulated the profibrotic cytokine synthesis, ameliorated renal inflammatory damage. However, the mechanism still need be elucidated by further study.

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