

1)

### Cytokine

### ACE Inhibitor

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< >

Angiotensin (ANG) 가  
 . ANG 가 ANG 가  
 cytokine . cytokine  
 transforming growth factor(TGF)- ANG 가 TGF-  
 , angiotensin converting enzyme(ACE) inhibitor  
 , TGF-  
 cytokine ACE inhibitor  
 cytokine ACE inhibitor . ACE inhibitor 11  
 RT-PCR TGF- 1, interleukin  
 (IL)-6, IL-10, tumor necrosis factor(TNF)- mRNA  
 cytokine - actin . ACE inhibitor TGF- 1 mRNA  
 11 5 6 가 . IL-6 mRNA  
 11 . IL-10 4 , 3  
 가 4 IL-10 mRNA . TNF- 1  
 mRNA 8 가 2 ACE inhibitor  
 가 IL-6 ACE  
 inhibitor , ACE inhibitor가  
 IL-6가 ACE inhibitor  
 TGF- 1 , ANG II가 TGF-  
 TNF- 가 ACE inhibitor가 IL-6 2

, ANG

Angiotensin ( ANG )가

2,

1,

: 5  
Tel : 0331)219- 5133, Fax : 0331)219- 5109

. ANG cytokine 가

—Seung-Jung Kim, et al.: The Effect of ACE Inhibitors on the Gene Expression of Various Cytokines in Peripheral Blood Mononuclear Cells from Patients with Glomerular Diseases: TGF- $\beta$ , IL-6, IL-10 and TNF- $\alpha$  —

cytokine Tumor necrosis factor- ( TNF- ) cytokine 24)  
가 가 . cytokine  
가 IgA ,  
가 가  
cytokine (he- TNF- 가 가  
modynamic) 가 3), ANG 가 25-27). Interleukin- 10( IL- 10)  
cytokine cytokine  
(non- hemodynamic) 가 . 28),  
ANG 가 29),  
angiotensin converting enzyme(ACE) in- 가  
hibitor가 ACE inhibitor  
가 RNA reverse transcrip-  
가 tion- polymerase chain reaction( RT- PCR)  
4). ACE inhibitor cytokine  
cytokine 가 transforming cytokine  
growth factor- ( TGF- ) . TGF- ACE inhibitor ACE  
가 inhibitor가  
cytokine  
5-10). TGF- ANG  
ACE inhibitor  
8, 17-20), ACE 1.  
inhibitor가 TGF- ACE inhibitor 11  
, 2). . 11  
ACE inhibitor TGF- 6  
5 . 6  
. IgA 2 ,  
TGF- cytokine , 1 , B  
Interleukin- 6( IL- 6) 1 , 1 , 1  
, Ranieri IgA . 11 44.2  $\pm$  15.1  
가 IL- 6가 IgA IL- 6 4 : 7  
1.1  $\pm$  0.4mg/dl . ACE inhibitor  
가 ANG 22). IL- 6 TGF- Fosinopril  
가 , 10- 20mg . ACE  
Moriyama 23) inhibitor  
ANG IL- 6 가 ANG ACE inhibitor  
28.3  $\pm$  31.2(4- 118)  
. ANG IL- 6 (Table 1).

2. 75mM KCl, 3mM MgCl<sub>2</sub>, 10mM DTT, 0.5 mM deoxynucleoside triphosphate(dNTP; dATP, dCTP, dGTP, dTTP), 200Unit M-MLV(Moloney murine leukemia virus) reverse transcriptase, 100ng random hexanucleotide primer 20 μl 37 60

1) **Total RNA** Ficoll-Paque gradient (peripheral blood mononuclear cell, PBMC) Trizol<sup>®</sup>(GibcoBRL, USA) 1ml 가 100 μl 65 10

- 70 chloroform 가 12,000x g 10 TE buffer(pH 8.0) 가 50 μl cDNA - 20 isopropyl alcohol 가 RNA RNA spec- 3) **PCR** TGF- 1, IL- 6, TNF- , IL- 10 house keeping gene - actin cytokine primer PCR (Table 2). 1.5mM MgCl<sub>2</sub>, 50mM KCl, 10mM Tris-HCl (pH 8.3), 0.01% gelatin, 40 μM dNTP,

2) **RT** 1 μg RNA 50mM Tris-HCl(pH 8.3),

**Table 1. Clinical and Laboratory Characteristics of 11 Patients**

Patient	Age(years)	Sex	Diagnosis(Renal biopsy)	Sampling Interval(days)	Initial Cr(mg/dl)
1	27	F	FSGS	31	2.0
2	53	F	IgA nephropathy	17	0.8
3	65	M		4	0.9
4	30	F		118	1.0
5	21	F		32	0.8
6	50	F	IgA nephropathy	24	0.6
7	41	M	HBV associated MGN	16	1.0
8	48	F		15	1.3
9	52	M	Amyloidosis	7	0.9
10	33	F		30	0.7
11	66	M	Diabetic nephropathy	17	1.5
mean ± SD	44.2 ± 15.1			28.3 ± 31.2	1.1 ± 0.4

**Table 2. Sequences and Sizes of the Primers Which were Used in PCR**

Cytokines	Primers	Sizes of PCR products(bp)
- actin	sense 5' -GGT CAC CCA CAC TGT GCC CAT- 3' antisense 5' -GGA TGC CAC AGG ACT CCA TGC- 3'	350
TGF- 1	sense 5' -CTG CGG ATC TCT GTG TCA TT- 3' antisense 5' -CTC AGA GTG TTG CTA TGG TG- 3'	246
IL- 6	sense 5' -ATG TGT GAA AGC AGC AAA GAG- 3' antisense 5' -TCC AAA AGA CCA GTG ATG ATT- 3'	134
IL- 10	sense 5' -TAA GGG TTA CCT GGG TTG CCA A- 3' antisense 5' -CAC TCA TGG CTT TGT AGA TGC C- 3'	257
TNF-	sense 5' - TGG CGT GGA GCT GAG AGA TAA- 3' antisense 5' - GAT GGC AGA GAG GAG GTT GAC- 3'	175

0.4 μM primer, 1U Taq DNA polymerase  
 - actin cDNA 1 μl, cy-  
 tokine cDNA 2 μl 25 μl  
 PCR . PCR Perkin Elmer  
 9600 thermocycler(Gene Amp PCR system  
 9600, Perkin Elmer, CA, USA) 94  
 20 denaturation, 57 30 pri-  
 mer annealing, 72 20 primer extension  
 - actin, IL- 6, IL- 10 32 cycle,  
 TGF- , TNF- 40 cycle . PCR  
 94 30 가  
 72 5 extension . PCR  
 2% NuSieve®(FMC Bioproducts USA)  
 1% Ultrapure®(Gibco BRL USA) agarose gel  
 electrophoresis negative  
 film densitometer .  
 4가 cytokine - actin  
 ACE inhibitor .  
 4) ± . ACE  
 inhibitor ,  
 , cytokine  
 paired t-test P- value 0.05

**1. ACE inhibitor**  
 (Table 3)  
 ACE inhibitor  
 107.9 ± 16.0mmHg 100.2 ± 12.3mmHg  
 (P<0.01). 24  
 ACE inhibitor 3.0 ± 2.2g/24hours  
 2.0 ± 2.1g/24hours (P<  
 0.001).  
**2. ACE inhibitor cytokine**  
 TGF- 1 ACE inhibitor  
 6 가 5  
 (Fig. 1). IL- 6  
 11 ACE inhibitor  
 (P<0.05, Fig. 2). IL- 10  
 ACE inhibitor 3  
 가 4 4  
 IL- 10 가  
 (Fig. 3). TNF-  
 2 ACE inhibitor 가  
 1 8  
 가 가  
 (Fig. 4).

**Table 3. Changes in Mean BP and Urinary Protein Excretion after Start of ACE Inhibitor Therapy**

Patient	Mean BP(pre ACEI*) (mmHg)	Mean BP(post ACEI) (mmHg)	Urine protein(pre ACEI) (g/24 hours)	Urine protein(post ACEI) (g/24 hours)
1	106.7	100.0	1.3	0.7
2	100.0	100.0	6.0	4.7
3	113.3	100.0	7.9	7.2
4	104.7	95.0	2.4	1.0
5	73.3	75.0	1.5	1.0
6	133.3	113.3	1.9	0.9
7	95.0	83.3	2.7	1.6
8	116.1	113.3	1.6	1.0
9	106.6	100.6	4.8	3.2
10	111.3	102.0	1.3	0.6
11	127.0	113.3	1.8	0.7
mean ± SD	107.9 ± 16.0	100.2 ± 12.3	3.0 ± 2.2	2.0 ± 2.1
paired T- test	P<0.01			

\*ACEI : angiotensin converting enzyme inhibitor

**Fig. 1.** Change in TGF- mRNA expression after ACE inhibitor therapy.

**Fig. 3.** Change in IL-10 mRNA expression after ACE inhibitor therapy.

**Fig. 2.** Change in IL-6 mRNA expression after ACE inhibitor therapy.

**Fig. 4.** Change in TNF- mRNA expression after ACE inhibitor therapy.

cytokine TGF-  
ACE inhibitor

가  
ACE inhibitor  
cytokine mRNA  
가 cytokine  
cytokine

, ACE inhibitor가 cytokine , IgA  
 cytokine TGF- $\beta$ 가 isoform  
 , 가 ACE inhibitor 가  
 cyto- fibronectin EDA +  
 kine plasminogen activator inhibitor-1 TGF- $\beta$   
 가 isoform TGF- $\beta$  1 가  
 cytokine 가 45).  
 가 TGF- $\beta$  ANG  
 ANG 가 , Gibbons  
 ANG TGF- $\beta$   
 30-33). ANG 가 17),  
 가 1 ANG ( ANG  
 AT-1 ) , 가 TGF- $\beta$   
 ANG 가 18, 19). Kagami  
 34). ANG II TGF- $\beta$   
 가 35) 가 , ANG 가 TGF- $\beta$   
 가 8).  
 가 36, 37). ACE inhibitor가 cytokine  
 가 38), (mononu- clear phagocyte)가 ACE inhibitor TGF- $\beta$   
 39). Ichinose cytokine 20).  
 IgA IgA TGF- $\beta$  1  
 IL-4, IL-5, IL-6 cytokine mRNA ACE inhibitor 11  
 40). cytokine 가 5  
 cytokine 가 TGF- $\beta$  ACE inhibitor  
 cytokine 가 . ANG 가 TGF- $\beta$   
 41-44). cytokine 가  
 cytokine TGF- $\beta$  가  
 , 7, TGF- $\beta$  가  
 45, 46) 45, 47), TGF- $\beta$  가 .  
 48) TGF- $\beta$  가 Wolf 가 49).  
 . Yamamoto  
 가 TGF- $\beta$  isoform, TGF- $\beta$  1  
 TGF- $\beta$  1, TGF- $\beta$  2, TGF- $\beta$  3가 가 . 가 AT-1  
 , losartan hydrala-

zine, reserpine, hydrochlorothiazide 3 54).  
 , ANG ACE inhibitor ANG  
 가 TGF- TNF- 가  
 TGF- ACE inhibitor가 TNF-  
 Wolf 가 ACE inhibitor가 TNF-  
 8 17-19), ACE inhibitor 가 IL-6  
 가 TNF- 가 TNF-  
 TGF- TNF- 가 25-27),  
 TNF- 가  
 TGF- ACE inhibitor Sporn TNF- 가  
 ACE inhibitor IL-6 24).  
 11 IL-10 T helper cell 2 subset  
 Moriyama monocyte macrophage  
 23) ANG IL-6 가  
 ANG 가 IL-6 mRNA 55, 56).  
 AT-1 CV-11974 IL-10 가 29).  
 , ANG 가 AT-1 ACE  
 IL-6 mRNA 가 inhibitor  
 ANG IL-6 ACE inhibitor가  
 IL-10  
 가 , ACE inhibitor가  
 , ACE inhibitor가 IL-6  
 cytokine  
 IL-6가 30) ACE inhibitor 가  
 51) TNF- IL-6 ACE inhibitor 가 , IL-6 ACE  
 가 inhibitor ACE inhibitor  
 Fukuzawa 가 IL-6가  
 ACE inhibitor TNF- ACE inhibi-  
 10-3mol/l lipopolysaccharide tor IL-6  
 TNF- , 10 가  
 ACE inhibitor TNF- 가 TGF-  
 52) TNF- IL-10 ACE inhibitor  
 IL-6 , IL-10 ACE inhibitor  
 Schindler , TGF-  
 IL-6  
 TNF- , ACE in-  
 53) De Caestecker IgA hibitor가 TGF-  
 TNF- 가 IL-6 ANG 가 TGF-

ACE inhibitor  
가  
cytokine

= *Abstract* =

**The Effect of ACE Inhibitors on the Gene Expression of Various Cytokines in Peripheral Blood Mononuclear Cells from Patients with Glomerular Diseases : TGF- $\beta$ 1, IL-6, IL-10 and TNF- $\alpha$**

Seung- Jung Kim, M.D., Gyu- Tae Shin, M.D.  
Kyoung- Ai Ma, M.D., Sang- Don Kim, M.D.  
Han- Min Lee, M.D., Seog- Bae Ji, M.D.  
Heung- Soo Kim M.D. and Do- Hun Kim, M.D.

*Department of Nephrology, School of Medicine,  
Ajou University, Suwon, Korea*

Angiotensin (ANG) has been known to induce systemic and glomerular hypertension, which leads to renal tissue injury and progressive fibrosis of kidney. Some effects of ANG may be mediated by its effect on the cytokine synthesis. In the present study, we investigated the effect of ANG inhibition on the expression of various cytokines implicated in the pathogenesis and progression of the kidney disease. Blood samples of 11 patients with glomerulonephritis were obtained before the ACE inhibitor therapy and then while they were taking ACE inhibitors. Using peripheral blood mononuclear cells(PBMC) harvested from the samples, RT-PCR was performed to evaluate the changes in mRNA expression of TGF- $\beta$ 1, IL-6, TNF- $\alpha$  and IL-10. The ratios of target cytokines and  $\beta$ -actin were calculated. TGF- $\beta$ 1 mRNA expression was decreased in five patients after ANG inhibition with ACE inhibitors, while it was increased in the remaining six patients. ACE inhibitors consistently decreased IL-6 mRNA expression in all 11 patients. IL-10 expression was decreased in 4 patients, and increased in 3 patients after ANG inhibition. It was not expressed in 4 patients. TNF- $\alpha$  expression was increased in 8 patients, and decreased in only 1 patient. In two patients, it was not changed while on

ACE inhibitors.

**Conclusion :** ACE inhibitors attenuate IL-6 expression consistently in all 11 patients. This is the first-time demonstration of the in vivo inhibitory effect of ACE inhibitors on IL-6 mRNA expression in humans. The lack of significant suppression of TGF- $\beta$ 1 in PBMC suggests that the in vivo attenuating effect of ACE inhibitors on TGF- $\beta$ 1 may be derived from renal hemodynamic changes. The tendency of heightened expression of TNF- $\alpha$  confirms the previous investigations in which IL-6 was shown to down regulate TNF- $\alpha$  expression.

**Key Words :** Angiotensin, ACE inhibitor, TGF- $\beta$ 1, IL-6, IL-10, TNF- $\alpha$

- 1) Johnson RJ, Alpers CE, Yoshimura A, Lombardi D, Pritzl P, Floege J, Schwartz SM : *Renal injury from angiotensin II-mediated hypertension. Hypertension* **19**:464-474, 1992
- 2) Miller PL, Rennke HG, Meyer TW : *Glomerular hypertrophy accelerates hypertensive glomerular injury in rats. Am J Physiol* **261**:F459-F465, 1991
- 3) Shankland SJ, Ly H, Thai K, Scholey JW : *Increased glomerular capillary pressure alters glomerular cytokine expression. Circ Res* **75**: 844-853, 1994
- 4) Hollenberg NK, Raij L : *Angiotensin-converting enzyme inhibition and renal protection. An assessment of implications for therapy. Arch Intern Med* **153**:2426-2435, 1993
- 5) Okuda S, Languino LR, Ruoslahti E, Border WA : *Elevated expression of transforming growth factor-beta and proteoglycan production in experimental glomerulonephritis: Possible role in expansion of the mesangial extracellular matrix. J Clin Invest* **86**:453-462, 1990
- 6) Kopp JB, Klotman ME, Adler SH, Bruggeman LA, Dickie P, Marinos NJ, Eckhaus M, Bryant JL, Notkins AL, Klotman PE : *Progressive glomerulosclerosis and enhanced renal accumulation of basement membrane components in mice transgenic for human immunodeficiency virus type I genes. Proc Natl Acad Sci USA* **89**:1577-1581, 1992
- 7) Yamamoto T, Nakamura T, Noble NA, Ruoslahti E, Border WA : *Expression of transforming growth factor- $\beta$  is elevated in human and experimental diabetic nephropathy. Proc Natl Acad Sci USA* **90**:1814-1818, 1993

- 8) Kagami S, Border WA, Miller DE, Noble NA : *Angiotensin stimulates extracellular matrix protein synthesis through induction of transforming growth factor- $\beta$  expression in rat glomerular mesangial cells.* *J Clin Invest* **93**:2431-2437, 1994
- 9) Lee LK, Meyer TW, Pollock AS, Lovett DH : *Endothelial cell injury initiates glomerular sclerosis in the rat remnant kidney.* *J Clin Invest* **96**:953-964, 1995
- 10) Esposito C, Liu Z-H, Striker GE, Phillips C, Chen N-Y, Chen WY, Kopchick JJ, Striker LJ : *Inhibition of diabetic nephropathy by a GH antagonist : A molecular analysis.* *Kidney Int* **50**:506-514, 1996
- 11) Kopp JB, Factor VM, Mozes M, Nagy P, Sanderson N, Bottinger EP, Klotman PE, Thorgerirsson SS : *Transgenic mice with increased plasma levels of TGF- $\beta$  1 develop progressive renal disease.* *Lab Invest* **74**:991-1003, 1996
- 12) Shankland SJ, Pippin J, Pichler RH, Gordon KL, Friedman S, Gold LI, Johnson RJ, Couser WG : *Differential expression of transforming growth factor- $\beta$  isoforms and receptors in experimental membranous nephropathy.* *Kidney Int* **50**:116-124, 1996
- 13) Shihab FS, Andoh TF, Tanner AM, Noble NA, Border WA, Franceschini N, Bennett WM : *Role of transforming growth factor- $\beta$  1 in experimental chronic cyclosporine nephropathy.* *Kidney Int* **49**:1141-1151, 1996
- 14) Shihab FS, Tanner AM, Shao Y, Weffer MI : *Expression of TGF- $\beta$  1 and matrix proteins is elevated in rats with chronic rejection.* *Kidney Int* **50**:1904-1913, 1996
- 15) Tamaki K, Okuda S, Nakayama M, Yanagida T, Fujishima M : *Transforming growth factor- $\beta$  1 in hypertensive renal injury in Dahl salt-sensitive rats.* *J Am Soc Nephrol* **7**:2578-2589, 1996
- 16) Oikawa T, Freeman M, Lo W, Vaughan DE, Fogo A : *Modulation of plasminogen activator inhibitor-1 in vivo : A new mechanism for the anti-fibrotic effect of renin-angiotensin inhibition.* *Kidney Int* **51**:164-172, 1997
- 17) Gibbons GH, Pratt RE, Dzau VJ : *Vascular smooth muscle cell hypertrophy vs. hyperplasia.* *J Clin Invest* **90**:456-461, 1992
- 18) Anderson PW, Do YS, Hsueh WA : *Angiotensin causes mesangial cell hypertrophy.* *Hypertension* **21**:29-35, 1993
- 19) Wolf G, Mueller E, Stahl RA, Ziyadeh FN : *Angiotensin -induced hypertrophy of cultured murine proximal tubular cells is mediated by endogenous transforming growth factor- $\beta$ .* *J Clin Invest* **92**:1366-1372, 1993
- 20) Zoja C, BiolSciD, Donadelli R, Corna D, Testa D, Facchinetti D, Maffi R, Luzzana E, Colosio V, ChempharmD, Bertani T, Remuzzi G : *The renoprotective properties of angiotensin-converting enzyme inhibitors in a chronic model of membranous nephropathy are solely due to the inhibition of angiotensin : Evidence based on comparative studies with a receptor antagonist.* *Am J Kidney Dis* **29**:254-264, 1997
- 21) Noble NA, Border WA : *Angiotensin in Renal fibrosis : Should TGF- $\beta$  rather than blood pressure be the therapeutic target?* *Semin in Nephrol* **17**:455-466, 1997
- 22) Ranieri E, Gesualdo L, Petrarulo F, Schena FP : *Urinary IL-6/EGF ratio : A useful prognostic marker for the progression of renal damage in IgA nephropathy.* *Kidney Int* **50**:1990-2001, 1996
- 23) Moriyama T, Fujibayashi M, Fujiwara Y, Kaneko T, Xia C, Imai E, Kamada T, Ando A, Ueda N : *Angiotensin stimulates interleukin-6 release from cultured mouse mesangial cells.* *J Am Soc Nephrol* **6**:95-101, 1995
- 24) Sporn MB : *The importance of context in cytokine action.* *Kidney Int* **51**:1352-1354, 1997
- 25) Matsumoto K : *Increased release of tumor necrosis factor- $\alpha$  by monocytes from patients with glomerulonephritis.* *Clin Nephrol* **40**:148-154, 1993
- 26) Suranyi MG, Guasch A, Hall BM, Myers BD : *Elevated levels of tumor necrosis factor- $\alpha$  in the nephrotic syndrome in humans.* *Am J Kidney Dis* **21**:251-259, 1993
- 27) Wu TH, Wu SC, Huang TP, Yu CL, Tsai CY : *Increased excretion of tumor necrosis factor  $\alpha$  and interleukin 1 beta in urine from patients with IgA nephropathy and Schonlein-Henoch purpura.* *Nephron* **74**:79-88, 1996
- 28) Chernoff AE, Granowitz EV, Shapiro L, Vannier E, Lonnemann G, Angel JB, Kennedy JS, Rabson AR, Wolff SM, Dinarello CA : *A randomized, controlled trial of IL-10 in humans. Inhibition of inflammatory cytokine production and immune responses.* *J Immunol* **154**:5492-5499, 1995
- 29) Matsumoto K : *Decreased release of IL-10 by monocytes from patients with lipoid nephrosis.* *Clin Exp Immunol* **102**:603-607, 1995
- 30) Shibata H, Suzuki H, Murakami M, Sato A, Saruta T : *Angiotensin type 1 receptor messenger RNA levels in human blood cells of*

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- patients with primary and secondary hypertension: reference to renin profile. *J Hyperten* **12**: 1275-1284, 1994
- 31) Suzuki H, Shibata H, Murakami M, Sato A, Naito M, Ichihara A, Matsumoto A, Tsujimoto G, Hirasawa A, Horie K, Saruta T: *Modulation of angiotensin type 1 receptor mRNA expression in human blood cells: Comparison of platelets and mononuclear leukocytes.* *Endocrine J* **42**:15-22, 1995
  - 32) Dieguez-Lucena JL, Aranda-Lara P, Ruiz-Galdon M, Garcia-Villanova J, Morell-Ocana M, Reyes-Engel A: *Angiotensin-converting enzyme genotypes and angiotensin receptors: Response to therapy.* *Hypertension* **28**:98-103, 1996
  - 33) Kitazono T, Padgett RC, Armstrong ML, Tompkins PK, Heistad DD: *Evidence that angiotensin is present in human monocytes.* *Circulation* **91**:1129-1134, 1995
  - 34) Lijnen P, Fagard R, Petrov V: *Cytosolic calcium changes induced by angiotensin in human peripheral blood mononuclear cells are mediated via angiotensin subtype 1 receptors.* *J Hyperten* **15**:871-878, 1997
  - 35) Schreiner GF, Cotran RS, Pardo V, Unanue ER: *A mononuclear cell component in experimental immunological glomerulonephritis.* *J Exp Med* **147**:369-384, 1978
  - 36) Monga G, Mazzucco G, Castello R: *Glomerular monocyte infiltration in human nephropathies: Prevalence and correlation with clinical and morphological variables.* *Virchows Arch* **405**:483-496, 1985
  - 37) Ferrario F, Castiglione A, Colasanti G, Barbiano di Belgioioso G, Bertoli S, D'Amico G: *The detection monocytes in human glomerulonephritis.* *Kidney Int* **28**:513-519, 1985
  - 38) Kobayashi M, Koyama A, Narita M, Shigematsu H: *Intraglomerular monocytes in human glomerulonephritis.* *Nephron* **59**:580-585, 1991
  - 39) Arima S, Nakayama M, Naito M, Sato T, Takahashi K: *Significance of mononuclear phagocytes in IgA nephropathy.* *Kidney Int* **39**:684-692, 1991
  - 40) Ichinose H, Miyazaki M, Koji T, Furusu A, Ozono Y, Harada T, Shin M, Nakane PK, Hara K: *Detection of cytokine mRNA-expressing cells in peripheral blood of patients with IgA nephropathy using non-radioactive in situ hybridization.* *Clin Exp Immunol* **103**:125-132, 1996
  - 41) Feldmann M, Brennan FM, Chantry D, Haworth C, Turner M, Katsiki P, Londei M, Abney E, Buchan G, Barrett K, Concovan A, Kissanerghis M, Zeng R, Grubeck-Lueben-Stein B, Barkley D, Chu CQ, Field M, Maini RN: *Cytokine assays: Role in the evaluation of the pathogenesis of autoimmunity.* *Immunol Rev* **119**:105-123, 1991
  - 42) Firestein GS, Alvaro-Gracia JM, Maki R: *Quantitative analysis of cytokine gene expression in rheumatoid arthritis.* *J Immunol* **144**:3447-3453, 1990
  - 43) Linker-Israeli M, Deans RJ, Wallace DJ, Prehn J, Ozeri-Chen T, Klineberg JR: *Elevated levels of endogenous interleukin-6 in SLE.* *J Immunol* **147**:117-123, 1990
  - 44) Kitani A, Hara M, Hirose T, Harigai M, Suzuki K, Kawakami M, Kawaguchi Y, Hidaka T, Kanagoe M, Nakamura H: *Autostimulatory effects of interleukin-6 on excessive B cell differentiation in patients with SLE: Analysis of interleukin-6 production and interleukin-6 receptor expression.* *Clin Exp Immunol* **88**:75-83, 1992
  - 45) Yamamoto T, Noble NA, Cohen AH, Nast CC, Hishida A, Gold LI, Border WA: *Expression of transforming growth factor- $\beta$  isoforms in human glomerular diseases.* *Kidney Int* **49**:461-469, 1996
  - 46) Iwano M, Kubo A, Nishino T, Sato H, Nishioka H, Akai Y, Kurioka H, Fujii Y, Kanauchi M, Shiiki H, Dohi K: *Quantification of glomerular TGF- $\beta$  1 mRNA in patients with diabetes mellitus.* *Kidney Int* **49**:1120-1126, 1996
  - 47) Yoshioka K, Takemura T, Murakami K, Okada M, Hino S, Miyamoto H, Maki S: *Transforming growth factor- $\beta$  protein and mRNA in glomeruli in normal and diseased human kidneys.* *Lab Invest* **68**:154-163, 1993
  - 48) Sharma VK, Bologa RM, Xu G-P, Li B, Mouradian J, Wang J, Serur D, Rao V, Suthanthiran M: *Intragraft TGF- $\beta$  1 mRNA: A correlate of interstitial fibrosis and chronic allograft nephropathy.* *Kidney Int* **49**:1297-1303, 1996
  - 49) Wolf G, Schneider A, Wenzel U, Helmchen U, Stahl RAK: *Regulation of glomerular TGF- $\beta$  expression in the contralateral kidney of two-kidney, one-clip hypertensive rats.* *J Am Soc Nephrol* **9**:763-772, 1998
  - 50) Simeonova PP, Toriumi W, Kommineni C, Erkan M, Munson AE, Rom WN, Luster MI: *Molecular regulation of IL-6 activation by asbestos in lung epithelial cells: role of reactive oxygen species.* *J Immunol* **159**:3921-3928, 1997
  - 51) Duncan MR, Berman B: *Stimulation of collagen*

- and glycosaminoglycan production in cultured human adult dermal fibroblasts by recombinant human interleukin 6. J Invest Dermatol* **97**:686-692, 1991
- 52) Fukuzawa M, Satoh J, Sagara M, Muto G, Muto Y, Nishimura S, Miyaguchi S, Qiang XL, Sakata Y, Nakazawa T, Ikehata F, Ohta S, Toyota T : *Angiotensin converting enzyme inhibitors suppress production of tumor necrosis factor- in vitro and in vivo. Immunopharmacology* **36**:49-55, 1997
- 53) Schindler R, Mancilla J, Endres S, Ghorbani R, Clark SC, Dinarello CA : *Correlations and interactions in the production of interleukin-6(IL-6), IL-1, and tumor necrosis factor(TNF) in human blood mononuclear cells: IL-6 suppresses IL-1 and TNF. Blood* **75**:40-47, 1990
- 54) De Caestecker MP, Bottomley M, Telfer BA, Hutchinson IV, Vose BM, Ballardie FW : *Detection of abnormal peripheral blood mononuclear cell cytokine networks in human IgA nephropathy. Kidney Int* **44**:1298-1308, 1993
- 55) Tipping PG, Kitching AR, Huang XR, Mutch DA, Holdsworth SR : *Immune modulation with interleukin-4 and interleukin-10 prevents crescent formation and glomerular injury in experimental glomerulonephritis. Eur J Immunol* **27**:530-537, 1997
- 56) Kitching AR, Tipping PG, Huang XR, Mutch DA, Holdsworth SR : *Interleukin-4 and interleukin-10 attenuate established crescentic glomerulonephritis in mice. Kidney Int* **52**:52-59, 1997
-