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Mini Review

Contribution of inflammation-associated bone-marrow-derived cells to kidney fibrosis

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Chronic inflammation-associated kidney fibrosis leads to progressive kidney dysfunction. Cell sources of matrix-producing cells in diseased kidneys include activated resident stromal cells (e.g., fibroblasts and pericytes), cells derived from epithelial-mesenchymal transition/endothelial-mesenchymal transition, and infiltrating bone-marrow-derived cells (e.g., fibrocytes, T cells, and monocytes/macrophages). Recent studies show that bone-marrow-derived cells are recruited to diseased kidneys, interact with renal resident cells, and produce chemokines/cytokines, growth factors, and collagens, thereby promoting and escalating chronic inflammatory processes and eventually leading to kidney fibrosis.

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Introduction

The number of dialysis patients due to chronic kidney diseases (CKD) is on the rise. In addition, CKD is an independent risk factor for cardiovascular diseases and has a large influence on all-cause mortality. Thus, improving the prognosis of CKD is an important issue based on medical, social, and health economical aspects[1)]. Kidney fibrosis is a common process of progressive kidney diseases that lead to renal failure, regardless of its etiologies. The histological characteristics of kidney interstitial fibrosis include tu-

bular atrophy and dilation, interstitial leukocyte infiltration, fibroblast accumulation, and increased interstitial matrix deposition[2]. Among these characteristic changes, interstitial matrix deposition is key step. Cell sources of matrix-producing cells in diseased kidneys include activated resident stromal cells (e.g., fibroblasts and pericytes), cells derived from epithelial-mesenchymal transition (EMT), and endothelial-mesenchymal transition (EndMT), and infiltrating bone-marrow-derived fibrocytes[3-5].

In 1994, Bucala et al. identified fibrocytes as a circulating bone-marrow—derived $CD34^+$ cell population of fibroblast-like cells that infiltrate from inflammatory exudates into subcutaneously implanted wound chambers[6]. Accumulating evidence proposes that fibrocytes occupy 0.1-0.5% of peripheral blood leukocytes and that these cells are candidate participants in organ fibrosis in the lungs, skin, heart, liver, and kidneys[7, 8]. Originally, fibrocytes were identified by the coexpression of CD34 and type 1 collagen. In addition, fibrocytes were identified by dual positivity of CD34 or CD45 and type 1 collagen or type 1 procollagen[6, 7]. A recent study revealed that other marker (e.g., CD45RO, 25F9, or S100A8/A9) can distinguish fibrocytes from monocytes/macrophages or fibroblasts[9]. In this review, we focus on the involvement of bone-marrow-derived cells and their interaction to renal resident cells in the process of kidney fibrosis.

Involvement of T cells and monocytes/macrophages in kidney fibrosis

Tapmeier et al. investigated the role of different T-cell populations in kidney fibrosis in a mouse model of UUO and found that $CD4^+$ T cells are critical in the pathogenesis of kidney fibrosis[10]. Nikolic-Paterson speculated three functions of T cells during kidney fibrosis: 1) T cells may operate directly on fibroblasts and pericytes to promote their migration, proliferation, and differentiation, resulting in myofibroblasts accumulation; 2) T cells may induce a profibrotic phenotype in the infiltrating macrophage population, which secretes profibrotic and pro-proliferative cytokines and growth factors; 3) T cells may affect directly tubular epithelial cells to induce secretion of cytokines and growth factors that, in turn, act on fibroblasts[11]. However, precise functions of T cells during kidney fibrosis are unclear so far.

Recent studies show a diverse range of macrophage responses to the microenvironment, suggesting their role in kidney injury[12]. Colony-stimulating factor-1 promotes renal repair in mice after ischemia-reperfusion injury by recruiting and resulting macrophage function[13]. Thus, macrophages mediate tissue repair rather than drive inflammation. On the other hand, we observed that human peripheral CD14-positive monocytes/macrophages directly make a contribution to producing type 1 collagen, which is dependent on MCP-1/CCL2-CCR2 signaling[12]. Additionally, the presence of MCP-1/CCL2 expression is suggestive of a chronic stage of disease. Moreover, the measurement of urinary MCP-1/CCL2 expression is a useful clinical tool for monitoring disease activity and progression of kidney fibrosis in inflammatory kidney diseases, including diabetic nephropathy[14-18]. These findings were supported by the fact that blockade of MCP-1/CCL2 prevents leukocyte migration to the kidney, urinary protein excretion, and TGF-β expression, thereby preventing glomerulosclerosis and interstitial fibrosis[16, 19-21]. Besides MCP-1/CCL2, blockade of fractalkine-CX3CR1 also reduced kidney fibrosis, along with reduction in macrophage infiltration[22, 23]. Glomerular podocytes express CCR2 receptor, suggesting that MCP-1/CCL2 activation of CCR2 on podocytes may underlie induction of MMP-12, leading to glomerular basement membrane damage and urinary protein excretion[24]. Furthermore, there were significant interrelation between the numbers of $CD45^+$/$proCol1^+$ cells and macrophages in human kidneys, as well as urinary levels of MCP-1/CCL2, indicating the close relationship between $CD45^+$/$proCol1^+$ cells and macrophages. Based on these results, we consider that the MCP-1/CCL2-CCR2 signaling recruits and activates bone-marrow — derived cells, especially macrophages, and mediates kidney fibrosis, regardless renal etiologies.

Identification of cells positive for CD34 or CD45 and type 1 collagen in kidney fibrosis

The signification of fibrocytes in kidney fibrosis remains to be established. Using immunostaining and flow cytometry, we observed CD45 and type 1 collagen dual-positive ($CD45^+$/$Col1^+$) cells infiltrating the kidney interstitium, especially the corticomedullary regions, in a mouse model of progressive kidney fibrosis induced by unilateral ureteral obstruction (UUO)[25]. Additionally, the number of infiltrating $CD45^+$/$Col1^+$ cells increased with fibrotic progression after UUO, peaking on day 7. These findings prompted us

next to investigate the presence of CD45 and type 1 procollagen dual-positive (CD45$^+$/proCol1$^+$) cells infiltrating human diseased kidneys, particularly in patients with diabetic nephropathy. The number of infiltrating CD45$^+$/proCol1$^+$ cells in the interstitium positively correlated with the severity of interstitial fibrosis, the number of CD68-positive macrophages, and the levels of urinary monocyte chemoattractant protein 1 (MCP-1)/chemokine (C-C motif) ligand 2 (CCL2) in patients with CKD. On the other hand, a negative correlation was observed between the estimated glomerular filtration rate and 24 hour creatinine clearance. Consistent with the reduction of disease activity after glucocorticoid therapy, the number of interstitial CD45$^+$/proCol1$^+$ cells and macrophages, as well as urinary MCP-1/CCL2 levels, significantly decreased[26]. These findings suggest that CD45$^+$/proCol1$^+$ cells could be involved in the pathogenesis of kidney fibrosis through interaction with macrophages and MCP-1/CCL2.

CD45$^+$/Col1$^+$ cells and renin-angiotensin-aldosterone system in kidney fibrosis

The renin-angiotensin-aldosterone system (RAAS) is a major pathway in the pathogenesis of fibrosis and depends on two major receptors, designated angiotensin II receptor type 1 (AT1R) and receptor type 2 (AT2R). Upregulation of RAAS was observed in UUO mice, in which plasma and intrarenal angiotensin II content were elevated[27]. Renal AT1 mRNA and receptor binding also increased in this model[28]. Aldosterone increased plasminogen activator inhibitor type 1 (PAI-1), a major inhibitor of extra cellular matrix (ECM) degradation in rat fibroblasts. Aldosterone and TGF-β together produced dramatic synergistic effects on PAI-1 production and subsequent ECM accumulation[29]. We hypothesized that CD45$^+$/Col1$^+$ cells may depend on the RAAS for their contribution to kidney fibrosis. In a mouse model, the extent of kidney fibrosis in AT2R-KO mice was more evident, concomitant with the larger number of infiltrating CD45$^+$/Col1$^+$ cells in fibrotic kidneys[30]. CD45$^+$/Col1$^+$ cell numbers in bone marrow also increased in mice with UUO, especially in AT2R-KO mice. Pharmacologic inhibition of AT1R reduced the degree of kidney fibrosis, along with the decreased number of CD45$^+$/Col1$^+$ cells in the kidney and bone marrow. AT1R inhibition also decreased the angiotensin-II—stimulated expression of type 1 procollagen α1 mRNA in isolated human CD45$^+$/proCol1$^+$ cells, whereas an AT2R inhibitor augmented the expression of type 1 procollagen α1 mRNA. These results suggest that AT1R/AT2R signaling contributes to the pathogenesis of kidney fibrosis[30].

Stromal cell activation and kidney fibrosis

Activation of local stromal cells (e.g., fibroblasts and pericytes) and generation of myofibroblasts from epithelial cells (via EMT) and endothelial cells (via EndMT) are associated with tubulointerstitial fibrosis[31]. Among these cells, tubular epithelial cells, glomerular podocytes and endothelial cells undergo transition after injury, and are involved in kidney fibrosis[32-34].

In contrast to the cell transition, Duffield et al. reported that pericytes and perivascular fibroblasts were major sources of collagen-producing cells in the pathogenesis of kidney fibrosis[35, 36]. In addition to this finding, platelet-derived growth factor receptor activates pericytes in a mouse model of kidney fibrosis[37]. Pericytes were also reported as collagen-producing cell in hepatic fibrosis and spinal cord injury[38, 39]. These findings suggest that fibrosis by fibroblasts and pericytes would be principal and common pathways of organ fibrosis. In addition, Asada et al. reported that EPO-producing cells in healthy kidney and scar-producing myofibroblasts during fibrosis originate from the same P0-Cre lineage-labeled extrarenal cells, which enter the embryonic kidney at E13.5 to become renal fibroblasts and transit from one another depending on the condition of the kidney. They also demonstrated that almost all cortical fibroblasts in the kidney arise from P0-Cre—expressing precursors[40]. These findings are important to speculate different lineage of fibroblasts. However, the recent lineage tracing studies have excluded the role of EMT in experimental kidney and liver fibrosis[35, 41]. Moreover, Roufosse et al. revealed a minimal contribution of bone-marrow-derived cells to collagen production in experimental kidney fibrosis, using collagen promoter reporter mice[42]. Further studies are required to determine the origin and contribution of stromal cells in kidney fibrosis.

Phospholipid mediators in kidney fibrosis

There are a number of pro-fibrotic mediators. TGF-β could be a principal mediator, which stimulates the differentiation of fibroblasts into myofibroblasts and promotes extra cellular matrix deposition. Lysophosphatidic acid (LPA) is

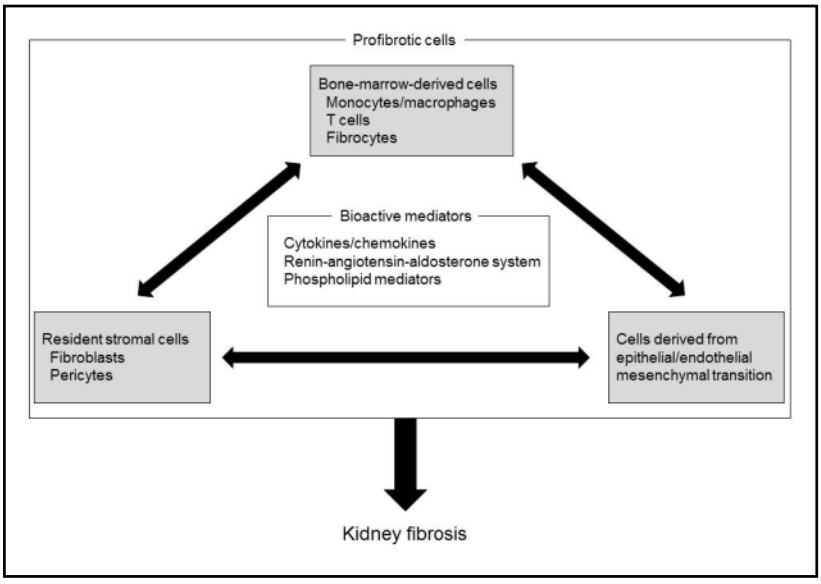

Fig.1 Possible cellular mechanisms and bioactive mediators in kidney fibrosis

a growth factor-like phospholipid, which is known to regulate several cellular processes including motility, proliferation, survival, and differentiation by acting LPA_{1-4} receptors. UUO induced tubulointerstitial fibrosis was significantly attenuated in LPA_1-KO mice and, in LPA_1 antagonist treated WT mice[43]. Further, LPA induced proximal tubular cell secretion of platelet-derived growth factor-β and connective tissue growth factor through LPA_2[44]. Additionally, some studies revealed the interaction between bone-marrow-derived cells and phospholipid mediators. Maeda et al. investigated the involvement of sphingosine 1-phosphate (S1P) receptor subtypes in S1P-induced migration of CD4 T cells and bone marrow-derived dendritic cells in mice[45]. However, further studies needed to understand the precise contribution of phospholipid mediators in kidney fibrosis.

Conclusion and future directions

Kidney fibrosis is caused by a complex network, consisting of various cell sources including infiltrating bone-marrow-derived cells, activated resident stromal cells, and cells derived from EMT/EndMT, and bioactive mediators, such as cytokines/chemokines, RAAS, and phospholipid mediators (Fig.1). The interaction among fibrogenetic cells and mediators promote inflammatory processes, resulting in kidney fibrosis. Further studies are needed to clarify the contribution of cell types in bone-marrow-derived cells for kidney fibrosis.

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Conflict of Interest

None

Referances

1) Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G: Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005; 67: 2089-2100.
2) Strutz F, Zeisberg M: Renal fibroblasts and myofibroblasts in chronic kidney disease. J Am Soc Nephrol. 2006; 17: 2992-2998.
3) Guarino M, Tosoni A, Nebuloni M: Direct contribution of epithelium to organ fibrosis: epithelial-mesenchymal transition. Hum Pathol. 2009; 40: 1365-1376.
4) Vernon MA, Mylonas KJ, Hughes J: Macrophages and renal fibrosis. Semin Nephrol. 2010; 30: 302-317.
5) Tapmeier TT, Fearn A, Brown K, Chowdhury P, Sacks SH, Sheerin NS, Wong W: Pivotal role of CD4+ T cells in renal fibrosis following ureteric obstruction. Kidney Int. 2010; 78: 351-362.
6) Bucala R, Spiegel LA, Chesney J, Hogan M, Cerami A: Circulating fibrocytes define a new leukocyte subpopulation that mediates tissue repair. Mol Med. 1994; 1: 71-81.

7) Herzog EL, Bucala R: Fibrocytes in health and disease. Exp Hematol. 2010; 38: 548-556.
8) Delprat B, Ruel J, Guitton MJ, Hamard G, Lenoir M, Pujol R, Puel JL, Brabet P, Hamel CP: Deafness and cochlear fibrocyte alterations in mice deficient for the inner ear protein otospiralin. Mol Cell Biol. 2005; 25: 847-853.
9) Pilling D, Fan T, Huang D, Kaul B, Gomer RH: Identification of markers that distinguish monocyte-derived fibrocytes from monocytes, macrophages, and fibroblasts. Plos one. 2009; 16: e7475.
10) Tapmeier TT, Fearn A, Brown K, Chowdhury P, Sacks SH, Sheerin NS, Wong W: Pivotal role of CD4+ T cells in renal fibrosis following ureteric obstruction. Kidney Int. 2010; 78: 351-352.
11) Nikolic-Paterson DJ: CD4+ T cells: a potential player in renal fibrosis. Kidney Int. 2010; 78: 333-335.
12) Ricardo SD, van Goor H, Eddy AA: Macrophage diversity in renal injury and repair. J Clin Invest. 2008; 118: 3522-3530.
13) Alikhan MA, Jones CV, Williams TM, Beckhouse AG, Fletcher AL, Kett MM, Sakkal S, Samuel CS, Ramsay RG, Deane JA, Wells CA, Little MH, Hume DA, Ricardo SD: Colony-stimulating factor-1 promotes kidney growth and repair via alteration of macrophage responses. Am J Pathol. 2011; 179: 1243-1256.
14) Sakai N, Wada T, Furuichi K, Shimizu K, Kokubo S, Hara A, Yamahana J, Okumura T, Matsushima K, Yokoyama H, Kaneko S: MCP-1/CCR2-dependent loop for fibrogenesis in human peripheral CD14-positive monocytes. J Leukoc Biol. 2006; 79: 555-563.
15) Wada T, Yokoyama H, Su SB, Mukaida N, Iwano M, Dohi K, Takahashi Y, Sasaki T, Furuichi K, Segawa C, Hisada Y, Ohta S, Takasawa K, Kobayashi K, Matsushima K: Monitoring urinary levels of monocyte chemotactic and activating factor reflects disease activity of lupus nephritis. Kidney Int. 1996; 49: 761-767.
16) Wada T, Yokoyama H, Furuichi K, Kobayashi KI, Harada K, Naruto M, Su SB, Akiyama M, Mukaida N, Matsushima K: Intervention of crescentic glomerulonephritis by antibodies to monocyte chemotactic and activating factor (MCAF/MCP-1). FASEB J. 1996; 10: 1418-1425.
17) Wada T, Furuichi K, Segawa-Takaeda C, Shimizu M, Sakai N, Takeda SI, Takasawa K, Kida H, Kobayashi KI, Mukaida N, Ohmoto Y, Matsushima K, Yokoyama H: MIP-1alpha and MCP-1 contribute to crescents and interstitial lesions in human crescentic glomerulonephritis. Kidney Int. 1999; 56: 995-1003.
18) Wada T, Furuichi K, Sakai N, Iwata Y, Yoshimoto K, Shimizu M, Takeda SI, Takasawa K, Yoshimura M, Kida H, Kobayashi KI, Mukaida N, Naito T, Matsushima K, Yokoyama H: Up-regulation of monocyte chemoattractant protein-1 in tubulointerstitial lesions of human diabetic nephropathy. Kidney Int. 2000; 58: 1492-1499.
19) Wu X, Dolecki GJ, Sherry B, Zagorski J, Lefkowith JB: Chemokines are expressed in a myeloid cell-dependent fashion and mediate distinct functions in immune complex glomerulonephritis in rat. J Immunol. 1997; 158: 3917-3924.
20) Wada T, Furuichi K, Sakai N, Iwata Y, Kitagawa K, Ishida Y, Kondo T, Hashimoto H, Ishiwata Y, Mukaida N, Tomosugi N, Matsushima K, Egashira K, Yokoyama H: Gene therapy via blockade of monocyte chemoattractant protein-1 for renal fibrosis. J Am Soc Nephrol. 2004; 15: 940-948.
21) Kitagawa K, Wada T, Furuichi K, Hashimoto H, Ishiwata Y, Asano M, Takeya M, Kuziel WA, Matsushima K, Mukaida N, Yokoyama H: Blockade of CCR2 ameliorates progressive fibrosis in kidney. Am J Pathol. 2004; 165: 237-246.
22) Furuichi K, Gao JL, Murphy PM: Chemokine receptor CX3CR1 regulates renal interstitial fibrosis after ischemia-reperfusion injury. Am J Pathol. 2006; 169: 372-387.
23) Shimizu K, Furuichi K, Sakai N, Kitagawa K, Matsushima K, Mukaida N, Kaneko S, Wada T: Fractalkine and its receptor, CX3CR1, promote hypertensive interstitial fibrosis in the kidney. Hypertens Res. 2011; 34: 747-752.
24) Rao VH, Meehan DT, Delimont D, Nakajima M, Wada T, Gratton MA, Cosgrove D: Role for macrophage metalloelastase in glomerular basement membrane damage associated with alport syndrome. Am J Pathol. 2006; 169: 32-46.
25) Sakai N, Wada T, Yokoyama H, Lipp M, Ueha S, Matsushima K, Kaneko S: Secondary lymphoid tissue chemokine (SLC/CCL21)/CCR7 signaling regulates fibrocytes in renal fibrosis. Proc Natl Acad Sci U S A. 2006; 103: 14098-14103.
26) Sakai N, Furuichi K, Shinozaki Y, Yamauchi H, Toyama

T, Kitajima S, Okumura T, Kokubo S, Kobayashi M, Takasawa K, Takeda S, Yoshimura M, Kaneko S, Wada T: Fibrocytes are involved in the pathogenesis of human chronic kidney disease. Hum Pathol. 2010; 41: 672-678.

27) el-Dahr SS, Gee J, Dipp S, Hanss BG, Vari RC, Chao J: Upregulation of renin-angiotensin system and downregulation of kallikrein in obstructive nephropathy. Am J Physiol. 1993; 264: F874-F881.

28) Yoo KH, Norwood VF, el-Dahr SS, Yosipiv I, Chevalier RL: Regulation of angiotensin II AT1 and AT2 receptors in neonatal ureteral obstruction. Am J Physiol. 1997; 273: R503-R509.

29) Huang W, Xu C, Kahng KW, Noble NA, Border WA, Huang Y: Aldosterone and TGF-beta1 synergistically increase PAI-1 and decrease matrix degradation in rat renal mesangial and fibroblast cells. Am J Physiol Renal Physiol. 2008; 294: F1287-F1295.

30) Sakai N, Wada T, Matsushima K, Bucala R, Iwai M, Horiuchi M, Kaneko S: The renin-angiotensin system contributes to renal fibrosis through regulation of fibrocytes. J Hypertens. 2008; 26: 780-790.

31) Liu Y: Cellular and molecular mechanisms of renal fibrosis. Nat Rev Nephrol. 2011; 7: 684-696.

32) Liu Y: New insights into epithelial-mesenchymal transition in kidney fibrosis. J Am Soc Nephrol. 2010; 21: 212-222.

33) Li J, Qu X, Bertram JF: Endothelial-myofibroblast transition contributes to the early development of diabetic renal interstitial fibrosis in streptozotocin-induced diabetic mice. Am J Pathol. 2009; 175: 1380-1388.

34) Kizu A, Medici D, Kalluri R: Endothelial-mesenchymal transition as a novel mechanism for generating myofibroblasts during diabetic nephropathy. Am J Pathol. 2009; 175: 1371-1373.

35) Humphreys BD, Lin SL, Kobayashi A, Hudson TE, Nowlin BT, Bonventre JV, Valerius MT, McMahon AP, Duffield JS: Fate tracing reveals the pericyte and not epithelial origin of myofibroblasts in kidney fibrosis. Am J Pathol. 2010; 176: 85-97.

36) Lin SL, Kisseleva T, Brenner DA, Duffield JS: Pericytes and perivascular fibroblasts are the primary source of collagen-producing cells in obstructive fibrosis of the kidney. Am J Pathol. 2008; 173: 1617-1627.

37) Chen YT, Chang FC, Wu CF, Chou YH, Hsu HL, Chiang WC, Shen J, Chen YM, Wu KD, Tsai TJ, Duffield JS, Lin SL: Platelet-derived growth factor receptor signaling activates pericyte-myofibroblast transition in obstructive and post-ischemic kidney fibrosis. Kidney Int. 2011; 80: 1170-1181.

38) Friedman SL: Hepatic stellate cells: protean, multifunctional, and enigmatic cells of the liver. Physiol Rev. 2008; 88: 125-172.

39) Göritz C, Dias DO, Tomilin N, Barbacid M, Shupliakov O, Frisén J: A pericyte origin of spinal cord scar tissue. Science. 2011; 333: 238-242.

40) Asada N, Takase M, Nakamura J, Oguchi A, Asada M, Suzuki N, Yamamura K, Nagoshi N, Shibata S, Rao TN, Fehling HJ, Fukatsu A, Minegishi N, Kita T, Kimura T, Okano H, Yamamoto M, Yanagita M: Dysfunction of fibroblasts of extrarenal origin underlies renal fibrosis and renal anemia in mice. J Clin Invest. 2011; 121: 3981-3990.

41) Chu AS, Diaz R, Hui JJ, Yanger K, Zong Y, Alpini G, Stanger BZ, Wells RG: Lineage tracing demonstrates no evidence of cholangiocyte epithelial-to-mesenchymal transition in murine models of hepatic fibrosis. Hepatology. 2011; 53: 1685-1695.

42) Roufosse C, Bou-Gharios G, Prodromidi E, Alexakis C, Jeffery R, Khan S, Otto WR, Alter J, Poulsom R, Cook HT: Bone marrow-derived cells do not contribute significantly to collagen I synthesis in a murine model of renal fibrosis. J Am Soc Nephrol. 2006; 17: 775-782.

43) Pradère JP, Klein J, Grès S, Guigné C, Neau E, Valet P, Calise D, Chun J, Bascands JL, Saulnier-Blache JS, Schanstra JP: LPA1 receptor activation promotes renal interstitial fibrosis. J Am Soc Nephrol. 2007; 18: 3110-3118.

44) Geng H, Lan R, Singha PK, Gilchrist A, Weinreb PH, Violette SM, Weinberg JM, Saikumar P, Venkatachalam MA: Lysophosphatidic Acid Increases Proximal Tubule Cell Secretion of Profibrotic Cytokines PDGF-B and CTGF through LPA2- and Gαq-Mediated Rho and αvβ6 Integrin-Dependent Activation of TGF-β. Am J Pathol. 2012; 181: 1236-1249.

45) Maeda Y, Matsuyuki H, Shimano K, Kataoka H, Sugahara K, Chiba K: Migration of CD4 T cells and dendritic cells toward sphingosine 1-phosphate (S1P) is mediated by different receptor subtypes: S1P regulates the functions of murine mature dendritic cells via S1P receptor type 3. J Immunol. 2007; 178: 3437-3446.