Cellular and Molecular Basis of Epithelial-Mesenchymal Transition in Renal Fibrosis

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Abstract
Regardless of the underlying etiology, tubulointerstitial fibrosis is a common mechanism in the progression of chronic kidney disease (CKD) to end-stage renal disease. Epithelial-mesenchymal transition (EMT) of renal tubular cells plays an important role in tubulointerstitial fibrosis. Transforming growth factor-β (TGF-β)/Smad and Mad protein (TGF-β/Mad) is thought to be a main signaling pathway for EMT of renal tubular cells. Progressive renal disease is also characterized histologically by an interstitial infiltrate of mononuclear cells. The chemokines secreted from renal tubular cells can trigger integrin-dependent adhesion of circulating mononuclear cells that leads to infiltration at tubulointerstitial space. The direct interaction of integrin lymphocyte function-associated antigen 1 (LFA-1; αβ, integrin) on mononuclear cells and its ligand, intracellular adhesion molecule-1 (ICAM-1) on renal tubular epithelial cells, contributes to a part of the EMT of renal tubular cells.

Introduction
Regardless of the underlying etiology, tubulointerstitial fibrosis is a common mechanism in the progression of chronic kidney disease (CKD) to end-stage renal disease [1,2]. Epithelial-mesenchymal transition (EMT) of renal tubular cells, a process in which differentiated epithelial cells undergo transition to a fibroblast phenotype, plays an important role in renal fibrosis [3,4]. The cellular and molecular mechanism behind EMT has been increasingly understood as a result of basic and clinical studies in this field.

Characterization of EMT

EMT was originally described as an event for dispersing cells in vertebrate embryos [5]. EMT also has pivotal roles in cancer cells as a molecular mechanism for tumor invasion and metastasis [6-8]. EMT is a biological process in which an epithelial cell that interacts with basement membrane with its basal surface undergoes transition to a mesenchymal cell phenotype, which has enhanced migratory capacity and invasiveness and increased production of extracellular matrix [9]. This transition is characterized by loss of epithelial cell marker proteins such as E-cadherin, occludin and cytokeratin and acquisition of mesenchymal cell marker proteins such as α-smooth muscle actin (α-SAM), vimentin, fibroblast-specific protein 1 (FSP1) and fibronectin (Figure 1) [9-11].

EMT in renal fibrosis

Evidence for the role of EMT of tubular cells in renal fibrosis is emerging. Fibroblasts are not abundant in normal kidney. Iwano et al. [12] reported the convincing evidence for EMT in vivo as a source of interstitial fibroblast. They showed 36% of all FSP1-positive fibroblasts in interstitial space originated from renal proximal tubules after unilateral ureteral obstruction using genetically tagged proximal tubular cells [12]. In addition, several studies using a similar cell lineagetracing technique reported a substantial number of fibroblasts were derived from capillary endothelia which is a specialized type of epithelia by endothelial-to-mesenchymal transition [13,14]. These results strongly suggested that renal tubular epithelial cells and capillary endothelia migrated into interstitial space during EMT. In addition, the activation of originally resident fibroblasts and the accumulation of perivascular smooth muscle cells, pericytes and circulated fibrocytes were speculated to be associated with some portions of fibroblasts [15].

Several clinical studies utilizing human kidney biopsies suggested that EMT of tubular cells plays a role in the pathogenesis of renal fibrosis [16-18]. Nishitani et al. [17] reported that FSP1 was detected in some tubular epithelial cells undergoing EMT as well as fibroblasts in areas showing severe interstitial fibrosis in renal biopsy specimens of IgA nephropathy patients [17]. Furthermore, FSP1 expression is directly correlated with serum creatinine and inversely correlated with estimated creatinine clearance [17]. Rastidi et al. [18] reported the...
expression of α-SMA and vimentin on tubular epithelial cells in various renal diseases; however, they were not detected in tubular epithelial cells of normal kidney [18]. They also reported that about 10% of tubular cells lost epithelial proteins and these EMT feature changes were associated with serum creatinine and the degree of interstitial damage [18]. Hertig et al. [16] reported that de novo expression of vimentin of tubular epithelial cells in allograft kidney was significantly correlated with the progression of fibrosis.

There are rooms to discuss the extent of contribution of EMT for renal fibrosis. Although loss of epithelial markers and acquired mesenchymal markers are a feature of EMT, fibroblastic transition has been more difficult to define because most of these markers change are not specific for fibroblast because they are expressed in other cells as inflammatory cells and endothelial [19]. Furthermore, tubular epithelial cells and endothelial cells after stimulations may undergo partial EMT in which these cells only changed one or two phenotypic markers but not leave their local microenvironment [11,16]. Further studies will be required to investigate the EMT for renal fibrosis.

**Fibrogenic and antifibrogenic factors for EMT of renal tubular cells**

Accumulated evidence has revealed that EMT of renal tubular cells can be induced by a variety of molecules (Table 1).

**Transforming growth factor-β**

In CKD, transforming growth factor-β/Sma and Mad protein (TGF-β/Smad) is thought to be a main signaling pathway for EMT of renal tubular cells [20-22]. Three TGF-β isoforms (TGF-β 1, 2 and 3) were identified in mammals [23-25]. Although it depends on the tissue, all three isoforms may be involved in EMT. TGF-β3, is the most extensively studied in EMT of renal tubular cells [26]. TGF-β, mainly induces phosphorylation and activation of Smad2 and Smad3 via transmembrane TGF-β receptor. Then, phosphorylated Smad2 and Smad3 heterooligomerize with Smad4 and translocate into the nucleus, where they regulate the various genes that mediate EMT [27,28]. TGF-β, also activates Smad-independent signaling, which plays a role for EMT, such as through extracellular signal-regulated kinase (ERK) 1/2, p-38 mitogen-activated protein kinase (p38 MAPK) and phosphatidylinositol-3-kinase/Akt [11]. The activation of ERK pathway is required for TGF-β-induced EMT of renal tubular cells and long-term ERK1/2 activation is an important mechanism involved in the EMT of renal tubular cells [29,30].

**Other fibrogenic and antifibrogenic factors**

Integrin-linked kinase (ILK) is a serine/threonine protein kinase that interacts with cytoplasmic domains of β-integrins and regulates the integrin signals. ILK regulates EMT by its protein kinase activity [31,32]. Wnt induces dephosphorylation of β-catenin as a result of activation of its downstream signaling pathway. This stabilizes β-catenin translocation into the nucleus, where it binds to T cell factor/lymphoid enhancer-binding factor-1 (LEF1) to regulate the various genes that mediate EMT [33,34]. Connective tissue growth factor (CTFG) is a downstream mediator of TGF-β signaling. CTFG binds to its receptor. CTFG induces fibroblast proliferation and matrix protein synthesis [35,36]. Angiotensin II is reported to increase TGF-β, in renal tubular cells. Several studies demonstrated that the block of angiotensin II by angiotensin converting enzyme inhibitor attenuated tubulointerstitial fibrosis with reduced TGF-β production [37,38]. In addition, several studies demonstrated that angiotensin II might have a direct effect on collagen gene expression [39,40]. These results suggested that angiotensin II may have fibrogenic effects independent of the TGF-β, pathway. Endothelin-1 (ET-1) is most abundant in kidney among the three isoforms that have been identified in mammals. ET-1 up-regulates TGF-β expression [26]. In addition, ET-1 may have a direct effect to promote renal fibrosis by stimulating matrix synthesis and decreasing collagenase activity [26,41,42]. Interleukin-1 (IL-1) is a proinflammatory cytokine that has the potential to increase proliferation of fibroblasts and matrix production [43].

**Antifibrogenic factors**

Hepatocyte growth factor (HGF) has been reported to attenuate tubulointerstitial fibrosis associated with reduction of platelet-derived growth factor and TGF-β, in nephritic mouse model [44,45]. Bone morphogenic protein-7 (BMP-7) directly attenuates TGF-β, Smad signaling and prevents EMT of renal tubular cells [46,47]. Insulin-like growth factor-1 (IGF-1) has been reported to reduce tubulointerstitial collagen accumulation in obstructive uropathy mouse model [48]. Vitamin D analogue and statin contribute to suppress EMT of renal tubular cells at least to some extent [49,50].

**Role of mononuclear cells for EMT on renal tubular cells**

Progressive renal disease is characterized histologically by an interstitial infiltrate of mononuclear cells. Most of these infiltrated cells have migrated from the circulation through peritubular capillary endothelium into the interstitial space. The locally secreted chemokines can trigger integrin-dependent adhesion of circulating leukocytes that leads to infiltration [51-54]. The stimulus for this migration is thought to be chemotactic cytokines that are secreted from tubular cells. Several studies have characterized the expression pattern of chemokines in animal models of tubulointerstitial disease [55-57]. They demonstrated that various chemokine such as chemokine ligand 2 (CCL2), chemokine ligand 3 (CCL3), chemokine ligand 4 (CCL4) and chemokine ligand 5 (CCL5) are expressed only in the diseased compartment of the kidney and renal chemokine expression has been found to correlate with the leukocyte accumulation area and renal damage [55-58]. The blocking of CCL2 activity by antibodies or antisense against CCL2 reduced the infiltration of mononuclear cells in several murine nephrotic nephritis models [59,60]. CCL2 null mice given nephrotoxic serum showed reduced tubulointerstitial injury [61]. CCL5 antagonist reduced proteinuria, T cell and macrophage infiltration in nephrotoxic serum-induced nephritis mouse model [62]. These studies strongly suggest that infiltrated mononuclear cells have pivotal roles in the progression of renal tubular damage leading to renal fibrosis; however, the mechanism of how those infiltrated mononuclear cells contribute to renal fibrosis remains to be elucidated. Recently, we reported that the interaction of integrin lymphocyte function-associated antigen 1 (LFA-1; αβ, integrin) on peripheral blood mononuclear cells (PBMCs) and intracellular adhesion molecules-1 (ICAM-1) on renal tubular epithelial cells accelerated TGF-β, induced EMT of renal tubular epithelial cells [63]. LFA-1 is the predominant integrin on leukocytes and an important molecule in firm adhesion and migration.
of leukocytes to inflammatory sites [64,65]. LFA-1 also plays pivotal roles as a signal transduction molecule by binding its ligand, ICAM-1 [66,67]. Normally, LFA-1 is expressed in a low-affinity state for its ligand and, thus, cells do not make unnecessary adhesive contacts while in circulation [68,69]. The affinity of LFA-1 for ICAM-1 is mediated by a conformational change of LFA-1 [68,69]. They play essential roles in most inflammatory reactions [68,69]. ICAM-1 has been reported to be expressed on renal tubular epithelial cells and its expression was found to be associated with the infiltration of leukocytes in CKD [70,71]. We reported that renal tubular epithelial cells stimulated with TGF-β1, induced conformational activation of LFA-1 on PBMCs by increasing CXCL12, which was reported to activate LFA-1 on both monocytes and lymphocytes [63,72-76]. Then, the direct interaction of LFA-1 on PBMCs and ICAM-1 on renal tubular epithelial cells activated ERK1/2 signaling to accelerate the part of EMT of renal tubular epithelial cells induced by TGF-β1 [63].

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