EDITORIAL

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Urokinase-type plasminogen activator receptor in IgA nephropathy

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IgA nephropathy (IgAN) is the most common pathologic form of primary glomerulonephritis and accounts for up to 50% of cases of this condition diagnosed using renal biopsy in Korea [1]. The most common pathologic findings related to the development of end-stage renal disease were global sclerosis, segmental sclerosis, tubulointerstitial fibrosis, interstitial inflammation, and vascular atherosclerotic changes [2], although the impact of these pathologic factors on renal prognosis is usually reduced when clinical parameters such as glomerular filtration rate (GFR), proteinuria, and blood pressure are considered. However, glomerular sclerosis is among the most meaningful contributors to renal prognosis after adjustment for clinical factors [2]. The podocyte injury in IgAN has been correlated with GFR, the permeability selectivity of the glomerular basement membrane, and glomerular global sclerosis [3] and plays a major role in the progression of IgAN [4,5].

Although mesangial cells are the primary target cells injured in IgAN, podocyte injury also occurs and is manifested by proteinuria, foot-process effacement, and glomerular segmental sclerosis [4,6]. Because polymeric hypogalactosylated IgA1 (pIgA1) cannot directly bind with podocyte, the fundamental mechanism of podocyte injury in IgAN is known as mesangial–podocyte crosstalk [6]. A series of studies of the pathophysiologic mechanism underlying podocyte injury has been published [6]. Briefly, there are three major mediators of podocyte injury. First, the pIgA1 from patients with IgAN upregulated transforming growth factor-ß (TGF-ß) synthesis in a culture medium of mesangial cells, thereby suppressing podocyte differentiation markers such as nephrin, ezrin, and podocin [7,8]. Podocyte dedifferentiation was reversed by anti TGF-ß antibodies and also reproduced by direct stimulation of TGF-ß alone [8,9].

The second important mediator of glomerulotubular crosstalk is tumor necrosis factor-α (TNF-α), which was produced by the podocytes exposed to a pIgA1-conditioned culture medium obtained from patients with IgAN (IgAN–pIgA1 culture medium) [6]. TNF-α enhanced the expression of TNF receptors and interleukin-6 on podocytes in an autocrine fashion [6]. Anti-TNF-α antibodies had a synergistic effect with anti-TGF-ß antibodies in inhibiting the podocyte dedifferentiation induced by the IgAN–pIgA1 medium, suggesting that TGF-ß and TNF-α contribute to mesangial cell-dependent podocyte injury [6].

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The third mediator for this injury may be angiotensin II. Angiotensin II production was increased by mesangial cells in the IgAN–pIgA1 culture medium and reversed by angiotensin II type-I receptor blockers (ARB) or angiotensin-converting enzyme inhibitors [7,10]. Podocyte attachment requires interaction with the glomerular basement membrane, and integrins, such as α3ß1 integrin, have an important role in this process. In a pIgA1-conditioned culture medium for podocyte, integrin-linked kinase was upregulated, and the adhesiveness of podocyte was reduced; these changes were correlated with angiotensin II levels in the medium and were partially reversed by ARB [9].

The urokinase-type plasminogen activator receptor (uPAR) is a multidomain glycoprotein tethered to the cell membrane with a glycosylphosphatidylinositol anchor as the binding site for the extracellular protease urokinase-type plasminogen activator (uPA; urokinase) on the cell surface [11]. However, uPAR interacts with many other proteins, such as integrins, and has pleomorphic functions [12]. The complex molecular interactions between uPAR and uPA or other ligands regulate key events during cell adhesion, migration, proliferation, and survival [12]. The plasminogen activation system is important for reorganizing tissues through proteinolysis [11]. uPAR restricts uPA activation to the immediate vicinity of the cell membrane and coordinates the proteinolysis of the extracellular matrix and cell signaling [11]. uPAR may also function independently from ligands and engages in lateral interactions with other transmembrane cellular receptors [12]. uPAR domains may be shed from the cell membrane as a soluble peptide (soluble uPAR [suPAR]), which has significant chemotactic properties [12].

Recent research has shown that uPAR is an important signaling pathway for kidney disease. uPAR protein was expressed in human glomerular cells in humans, mice, and rats [13]. The glomerular *PLAUR* mRNA expression, which encodes the uPAR protein, was reduced in humans without renal disease and increased in focal segmental glomerulosclerosis (FSGS) and diabetic nephropathy [13], in which podocyte injury is the dominant pathology. This finding was also observed in rodent models with podocytopathy [13]. uPAR had a direct role in regulating podocyte foot-process effacement and podocyte function in an animal model with lipopolysaccharide (LPS)-induced nephropathy [13]. The induction of uPAR in podocytes led to foot-process effacement and urinary protein loss via a mechanism that included activation of α5ß3 integrin [13]. Blockade of the *plaur* gene or α5ß3 integrin in podocytes reduced podocyte motility and reduced proteinuria in mice with LPS [13]. Moreover, suPAR was elevated in two-thirds of subjects with primary FSGS but not in individuals with other glomerular diseases, and higher levels of suPAR before transplantation were associated with an increased risk for the recurrence of FSGS [14]. In an animal model, circulating suPAR activated podocyte ß3 integrin, causing foot-process effacement, proteinuria, and FSGS-like glomerulopathy [14]. The role of uPAR in kidney diseases has been investigated in other animal models, such as ischemia-reperfusion injury and acute kidney allograft rejection [15], nephrotoxic kidney injury [16], and obstructive nephropathy [17]. Enhanced expression of uPAR in intrinsic glomerular cells was related to increases in glomerular sclerosis, ischemia-reperfusion injuries, and transplantation rejection. However, activation of uPAR in a unilateral ureteral obstruction (UUO) model attenuated the fibrogenic responses to injury.

In terms of the therapeutic relevance of the uPAR–podocyte interaction, two studies have investigated amiloride. They found that cyclosporin, a calcineurin inhibitor commonly used in the treatment of FSGS, interfered with the nuclear factor of activated T-cell signaling (NFAT), which was also expressed in podocytes [11]. Inducing podocyte-specific NFATc1 increased podocyte uPAR expression and affected cell motility via activation of the ß3 integrin in rodent models of glomerular disease (LPS; 5/6 nephrectomized rats) [18]. The cyclosporin, NFAT-siRNA, or cell-permeable NFAT inhibitor can block this activation. Amiloride had a significant role in the reduction of podocyte motility *in vitro* and in proteinuria in mice [19]. It inhibited the induction of the uPAR protein and *plaur* mRNA and thereby reduced uPAR-mediated ß3 integrin activation in LPS-treated podocytes, LPS-treated animals, and 5/6 nephrectomized animals in a FSGS model [19]. Thus, amiloride inhibited podocyte uPAR induction and reduced proteinuria in animal glomerular disease models [19]. A recent small clinical study showed that uPA (urokinase) combined with benazepril was more effective than was benazepril alone in reducing proteinuria

and protecting renal function in patients with severe IgAN [20], although endogenous uPA had no effect on preventing fibrosis in a UUO animal model [21].

In this context, "Urokinase, urokinase receptor, and plasminogen activator inhibitor-1 expression on podocytes in immunoglobulin A glomerulonephritis" [22] is an interesting article that provides clues about uPAR signaling pathways and podocyte injury in IgAN. The intensity of uPAR expression in podocytes varies among patients with IgAN and has been associated with tubulointerstitial changes, although the positivity of uPAR in podocytes has not been related to the clinical parameters of blood pressure, proteinuria, GFR, or glomerular scores on the Oxford classification. Research is needed whether podocyte injury or glomerular sclerosis in IgAN is related to the uPAR, integrins, other ligands, or lateral signals in cell membranes and on the usefulness of uPA or treatment of the uPAR signaling pathway.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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