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Role of TGF- β in Mesangial Matrix Accumulation in Chronic Progressive Glomerular Disease

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1. Introduction

Lesions of focal segmental glomerulosclerosis (FSGS) are a pathological hallmark of progressive glomerular injury. Glomerulosclerosis frequently complicates most renal diseases, and is characterized by the collapse of the glomerular tuft with the accumulation of mesangial matrix. Transforming growth factor- β (TGF- β) is a key regulator of extracellular matrix (ECM) protein synthesis in renal cells. TGF- β is secreted as latent complexes, which are stored in the ECM to provide stability to the active molecule and a readily activable source of it (Lawrence 2001). Overexpression of active TGF- β 1 in transgenic mice causes mesangial expansion and thickened capillary loops in the glomeruli (Kopp et al. 1996), while monoclonal antibody to TGF- β reduces the glomerulosclerosis in experimental proliferative glomerulonephritis (GN) (Yu et al. 2004) and diabetic nephropathy (Benigni et al. 2003; Ziyadeh et al. 2000).

Cultured mesangial cells secrete TGF- β and ECM proteins in response to various fibrogenic stimuli (Kim et al. 2001; Lee et al. 2004; Lee and Song 2009a; Ziyadeh et al. 1994, 1998). In chronic mesangial diseases, such as IgA nephropathy (IgAN) and diabetic nephropathy, TGF- β 1 mRNA expression by mesangial cells is increased, yet mesangial immunostaining for active TGF- β 1 is frequently negative (Kim et al. 2002; Stein-Oakley et al. 1997; Wahab et al. 2005). Only podocytes covering the sclerotic segments exhibit increased expression of TGF- β 1 protein (Kim et al. 2002; Wahab et al. 2005). These findings suggest that mesangial cells secrete latent TGF- β in chronic mesangial disease, which may be localized to the podocyte surface to be activated (Lee and Song 2009b).

Podocytes are the target of injury in most glomerular diseases. Expression of TGF- β mRNA and/or protein by podocytes is increased in progressive podocyte diseases, such as primary FSGS, membranous nephropathy, Alport syndrome and Denys-Drash syndrome (Kim et al. 2003; Kim et al. 1999; Patek et al. 2003; Sayers et al. 1999; Shankland et al. 1996). In addition, mesangial matrix is frequently increased in association with glomerulosclerosis (Gregory et al. 1996; Lee and Koh 1993; Lee and Lim 1995; Kim et al. 1995; Patek et al. 2003). Thus, TGF- β , that is expressed and/or activated by podocytes, may contribute to mesangial matrix oversynthesis in both chronic mesangial disease and podocyte disease (Lee 2011).

This review will discuss the recent findings on the mechanisms and consequences of latent TGF- β activation and TGF- β -induced mesangial matrix accumulation in chronic progressive glomerular disease.

2. Structure of mesangial cells

Glomerular mesangial cells together with their surrounding matrix constitute the mesangium, a structure that is separated from the capillary lumen by the endothelium. The mesangial cells are surrounded by mesangial matrix, that is similar but not identical to the peripheral glomerular basement membrane (GBM). The mesangial matrix contains type IV collagen, sulfated glycosaminoglycans, fibronectin and laminin. The mesangial cells are often compared with vascular smooth muscle cells, and are able to proliferate and produce excessive matrix proteins when stimulated.

3. Chronic progressive glomerular diseases with TGF- β overexpression in podocytes

3.1 IgAN

The diagnosis of IgAN is based on the demonstration of predominant or codominant IgA deposition in the mesangium. The glomerular histopathology mainly represents the mesangial lesions showing cell proliferation and/or matrix expansion. In addition, focal abnormalities of the GBM are sometimes present, with reticulation, thinning and thickening, as well as subepithelial deposits (Lee et al. 1987, 1989). Up to 30% of patients with IgAN eventually progress to end-stage renal disease (ESRD) after a follow-up of 25 years (Ibels and Györy 1994). The more severe glomerular lesions, which have higher percentage of glomerulosclerosis and crescents, are significantly related to progressive IgAN (El Karoui et al. 2011; Lee et al. 2005). Other glomerular lesions, such as mesangial hyperplasia and endocapillary lesions, also contribute to worse prognosis (Working Group of the International IgA Nephropathy Network 2010).

The intensity of immunostaining for platelet-derived growth factor, type IV collagen, laminin, and fibronectin is increased in the mesangium in renal biopsies with IgAN (Kim et al. 2002). In the early stage of IgAN with mesangial cell proliferation, some mesangial cells show immunoreactivity for TGF- β 1 (Stein-Oakley et al. 1997). Mesangial immunostaining for active TGF- β 1, however, is very weak or almost negligible in most human IgAN, despite increased mesangial TGF- β 1 mRNA levels. Instead, hyperplastic podocytes covering the sclerotic segments exhibit increased expression of TGF- β 1 protein (Kim et al. 2002).

Mesangial expression of TGF- β isoforms is transiently upregulated in acute anti-Thy1.1 nephritis, a rodent model of mesangial proliferative GN (Hartner et al. 2003; Ito et al. 2001; Liu et al. 2004), in which TGF- β 1 expression is only segmentally and weakly distributed (Ito et al. 2001).

3.2 Primary FSGS

Primary FSGS is a clinicopathologic entity characterized by nephrotic syndrome and progression to ESRD. Intrarenal transcription of TGF- β 1 is increased in children with FSGS compared to those with minimal lesion, suggesting that TGF- β 1 gene transcription is indicative of progressive renal damage typical of FSGS (Strehlau et al. 2002). Expression of TGF- β 1 is increased in patients with primary FSGS, particularly in podocytes of sclerotic segments (Kim et al. 2003). Volume density of mesangial matrix is significantly greater in the FSGS patients than in minimal lesion cases. In patients with FSGS, the percent glomerulosclerosis correlates directly with mesangial volume per glomerulus (Lee and Lim 1995).

3.3 The significance of FSGS formation in chronic glomerular disease

Some authors regarded FSGS as a nonspecific heterogeneous form of renal injury (Whitworth et al. 1978). The lesions of FSGS following primary glomerular diseases, such as IgAN and membranous nephropathy, have often been excluded in the category of secondary FSGS, because they were regarded as the nonspecific chronic scarred phase of the disease (D'Agati et al. 2004). Nonetheless, the lesions of FSGS in IgAN show immunohistochemical changes, which are basically identical to those described in primary FSGS, with loss of podocyte markers (Hill et al. 2011). Furthermore, podocytes covering the sclerotic segments exhibit enhanced expression of TGF- β 1 in IgAN and advanced diabetic nephropathy similar to those observed in primary FSGS. Thus, common podocyte lesions may contribute to the development of FSGS in both primary FSGS and other chronic glomerular diseases.

3.4 Membranous nephropathy

Membranous nephropathy is a well-characterized histological entity with a highly variable clinical course. Overall, approximately 30-40% of patients develop significant renal failure 10-15 years after the diagnosis of nephropathy (Perna et al. 2004). New genomewide association study suggests that sequence variations within HLA and receptor for phospholipase A2 are responsible in part for the development of idiopathic membranous nephropathy (Stanescu et al. 2011). The hallmark of membranous nephropathy is the presence of glomerular subepithelial deposits that typically contain immunoglobulin and complement component. Between and around these deposits, the GBM is thickened due to the accumulation of GBM material, forming subepithelial projections or spikes. Complement membrane attack complex (C5b-C9) plays an important role in the development of podocyte injury and proteinuria in passive Heymann nephritis (PHN), an experimental model of human membranous nephropathy (Couser and Nangaku 2006). Upregulation of TGF- β 1 and GBM protein mRNAs by podocytes is shown in patients with membranous nephropathy (Kim et al. 1999). Expression of TGF- β 2 is also markedly increased in podocytes in experimental membranous nephropathy, together with upregulation of TGF- β receptors (Shankland et al. 1996).

Lesions of FSGS are observed in 43% of the membranous nephropathy patients, in whom the degree of mesangial expansion and GBM thickening is significantly greater than the remaining cases without FSGS (Lee and Koh 1993). In PHN, mesangial volume was also significantly elevated, together with GBM thickening (Remuzzi et al. 1999).

3.5 Diabetic nephropathy

Diabetic nephropathy remains the most common cause for ESRD as the burden of diabetes increases worldwide. Nearly one-third of patients with diabetes develop nephropathy (Choudhury et al. 2010). Mesangial matrix expansion and thickening of the GBM are hallmarks of diabetic nephropathy, which occur even within a few years after the onset of type 1 diabetes (Drummond and Mauer 2002). If left untreated, 20-40% of patients with type 2 diabetes show progression to renal failure (Adler et al. 2003; Remuzzi et al. 2002).

In the early stage of human diabetic nephropathy, some mesangial cells show immunoreactivity for TGF- β 1. Yet mesangial immunostaining for active TGF- β 1 is very weak or almost negligible in most human diabetic nodular glomerulosclerosis, despite increased mesangial TGF- β 1 mRNA levels. Rather, podocytes covering the sclerotic

segments show increased expression of TGF- β 1 mRNA and protein (Wahab et al. 2005). In the glomeruli of experimental diabetic nephropathy, only a few cells show positive immunostaining for TGF- β 1 (Hill et al. 2000). Enhanced expression of glomerular TGF- β 1 is observed mainly in podocytes of diabetic animals (Baba et al. 2005; Okada et al. 2006).

3.6 Alport renal disease

Collagen type IV is the main component of the GBM, which includes six genetically distinct isoforms named α 1(IV) to α 6(IV). The α 3- α 5(IV) chains originate solely from podocytes in both the developing and mature glomerulus (Abrahamson et al. 2009). The α 1/ α 2(IV) collagen network, by contrast, seems to originate mainly from glomerular endothelial cells (Lee et al. 1993), and is localized predominantly at the endothelial aspect of human GBM (Zhang and Lee 1997).

Alport syndrome is primary genetic disease of the basement membrane. In the kidney, this disorder is characterized by an absence of collagen α 3 α 4 α 5(IV) in the GBM, progressive thickening and multilamination of the GBM, proteinuria, and renal failure. Yet collagen α 1/ α 2(IV) is retained throughout the GBM (Abrahamson et al. 2003; Kashtan et al. 2001). In podocytes of α 3(IV) collagen-knockout mice with Alport renal disease, mRNA expression of TGF- β 1 is increased (Sayers et al. 1999). With disease progression, mesangial matrix and cells are increased, followed by the development of glomerulosclerosis (Gregory et al. 1996; Kim et al. 1995).

3.7 Denys-Drash syndrome

Wilms' tumour suppressor gene, WT1, is essential for normal podocyte function. Mutations of WT1 induce Denys-Drash syndrome (DDS) characterized by diffuse mesangial sclerosis. In DDS mice, the development of glomerulosclerosis is preceded by de novo TGF- β 1 expression in podocytes, while TGF- β 1 expression is absent in the mesangium (Patek et al. 2003).

In summary, expression of TGF- β 1 by podocytes is increased not only in progressive podocyte disease but also in chronic mesangial disease. Despite mesangial matrix expansion in association with glomerulosclerosis in both types of disease, immunohistochemical antigen detection for mesangial TGF- β 1 seems to be difficult even in chronic mesangial disease.

4. Activation of latent TGF- β

TGF- β is secreted as latent complexes associated with a latency-associated peptide (LAP). TGF- β /LAP complex is referred to as the small latent complex. Most cells secrete TGF- β as part of a large latent complex, in which latent TGF- β binding protein (LTBP) is linked to the small latent complex. LTBP has a role in targeting the transport of latent TGF- β complex into the ECM (Hyytiäinen et al. 2004; Koli et al. 2008).

The large latent complex is susceptible to proteolysis, within which LTBP is first cleaved at the protease sensitive hinge region. The soluble large latent complex is then released from the ECM and is activated by another proteolytic event that releases TGF- β from LAP (Koli et al. 2001). The TGF- β released then binds to its receptor and exerts its cellular functions.

Under in vitro conditions, latent TGF- β is activated by heating, acid or alkaline treatment, irradiation, reactive oxygen species (ROS), proteases including plasmin, cathepsin, calpain, matrix metalloproteinase (MMP)-2 and MMP-9, some integrins, or thrombospondin-1 (TSP-1) (for review, see Koli et al. 2001).

Several activation mechanisms may exist in vivo as reviewed below (Table 1).

4.1 TGF- β activation by proteolysis

Plasmin could function as an *in vivo* activator of TGF- β (Lyons et al. 1990; Edgton et al. 2004). Plasmin can release the large latent TGF- β complex from the ECM by cleaving LTBP at the amino terminal hinge region (Taipale et al. 1992). Furthermore, it can cleave LAP that releases active TGF- β dimer from the large latent TGF- β 1 complex (Annes et al. 2003; George et al. 2005; Lyons et al. 1990).

MMP-2 and MMP-9 have also been implicated in the cleavage of LAP and the release of mature TGF- β at the cell surface (Yu and Stamenkovic 2000).

4.2 TSP-1-mediated activation of TGF- β

TSP-1 is known to be a major physiologic activator of latent TGF- β (Crawford et al. 1998). A specific peptide sequence within TSP-1, KRFLK, binds to the LSKL sequence in LAP, and releases mature TGF- β by inducing conformational changes in the protein (Crawford et al. 1998; Lawrence 2001; Koli et al. 2008). However, it is not clear whether TSP-1 alone could directly activate latent TGF- β (Abdelouahed et al. 2000; Grainger and Frow 2000; Otsuka et al. 2007).

Overexpression of both TSP-1 and active TGF- β occurs in podocytes in patients with FSGS (Kim et al. 2003) and diabetic nephropathy (Wahab et al. 2005). In various experimental renal disease models, TSP-1 is co-localized with TGF- β and predicts the development of tissue fibrosis (Hugo et al. 1998).

4.3 ROS-mediated activation of TGF- β

ROS produced by ionizing radiation was found to induce rapid TGF- β activation *in vivo* (Barcellos-Hoff and Dix 1996). ROS can activate TGF- β directly through oxidation-induced conformational change in LAP, in which the unique methionine residue in the TGF- β 1/LAP functions as a redox switch center (Jobling et al. 2006), or indirectly through the activation of proteolytic enzymes (Koli et al. 2008).

4.4 Integrins in TGF- β binding and activation

Integrins can bind to the RGD recognition domain in the LAP of TGF- β 1 and TGF- β 3. Particularly, α v β 6 and α v β 8 are known to activate the TGF- β complex (Munger et al. 1999; Mu et al. 2002), leading to release of TGF- β either by tractional force (α v β 6) or by membrane type-1 MMP (MT1-MMP)-dependent proteolytic activity (α v β 8) (Koli et al. 2008). By cell movement, an α v β 6-integrin-expressing cell causes sufficient traction for the release of mature TGF- β from the ECM-anchored large latent complex (Annes et al. 2004).

Activators	Mechanisms of action	1 st author
Plasmin	- Proteolytic nicking of LTBP releasing large latent TGF- β complex from the ECM	Taipale (1992); Lyons (1990); Annes (2003); George (2005)
	- Proteolytic nicking of the LAP	
TSP-1	- Induction of conformational changes in LAP	Crawford(1998); Lawrence (2001); Koli (2008)
ROS	- Induction of conformational changes in LAP	Jobling (2006); Koli (2008)
	- Inducing activation of proteolytic enzymes	
Integrin, α v β 6	- Release of TGF- β from LAP by tractional force	Annes (2004)

TGF- β , transforming growth factor- β ; LTBP, latent TGF- β binding protein; ECM, extracellular matrix; TSP-1, thrombospondin-1; LAP, latency-associated peptide; ROS, reactive oxygen species.

Table 1. Proposed mechanisms for latent TGF- β activation in chronic glomerular disease

$\alpha\beta 6$ integrin is expressed in the diseased kidneys confined to the distal tubules and collecting ducts (Trevillian et al. 2004). Deleting TGF- β type II receptor in collecting duct cells in vitro resulted in increased integrin $\alpha\beta 6$ -dependent TGF- β activation, that increased collagen synthesis in co-cultured renal interstitial fibroblasts (Gewin et al. 2010).

5. Mechanism of TGF- β overexpression by podocytes in chronic glomerular disease

5.1 Incomplete activation of mesangial TGF- β in chronic mesangial disease

Intense mesangial immunostaining for LTBP-1 is observed in anti-Thy1.1 nephritis associated with severe but transient mesangial matrix accumulation (Porst et al. 2006). In rats with anti-Thy1.1 nephritis, active TGF- $\beta 1$ -positive area/glomerulus was 18%, while treatment with antisense TSP-1 oligodeoxynucleotides reduced it to 9% (Daniel et al. 2003). In wild-type and TSP-1 deficient diabetic mice, the TGF- $\beta 1$ -positive area in the glomerulus was 5% and 3%, respectively (Daniel et al. 2007). Thus, TSP-1 seems to activate mesangial TGF- $\beta 1$ more actively in acute mesangial proliferative GN than in chronic mesangial disease.

Plasmin can release the large latent TGF- β complex from the mesangial matrix by cleaving LTBP at the amino terminal hinge region (Taipale et al. 1992) (Fig. 1). The plasmin-mediated

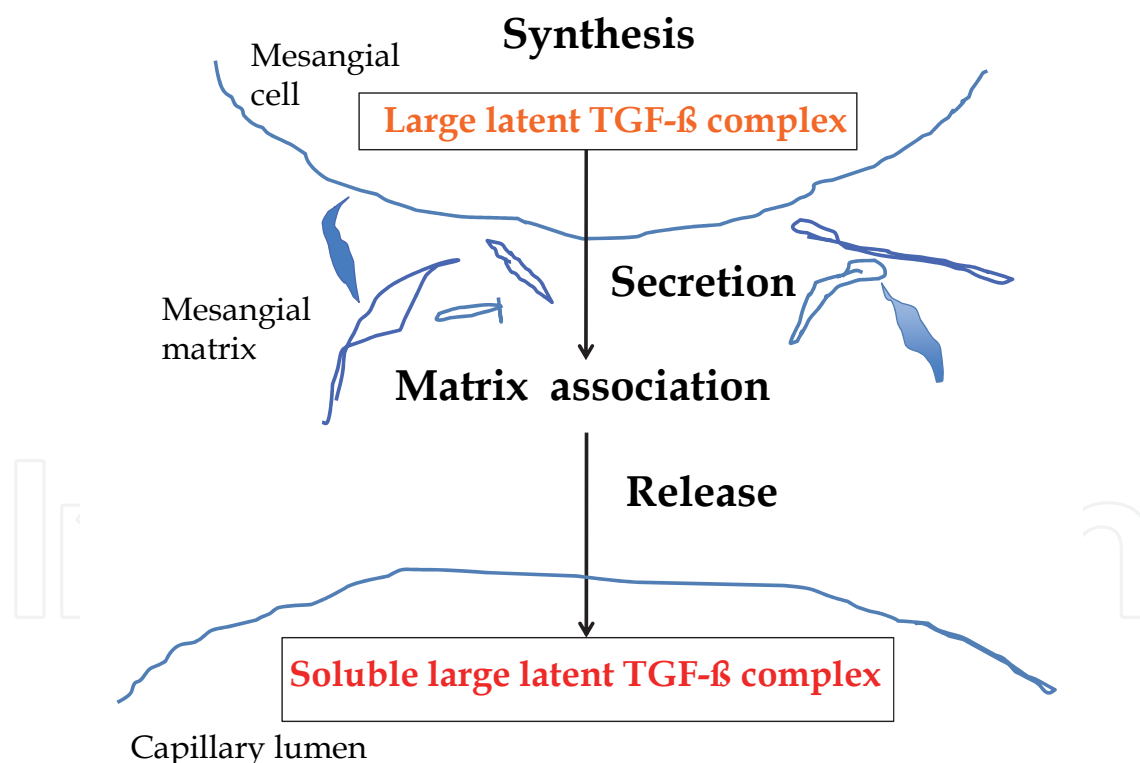


Fig. 1. Incomplete activation of mesangial TGF- β in chronic mesangial disease. Upon fibrogenic stimuli, large latent TGF- β complex in association with latent TGF- β binding protein (LTBP) is synthesized and secreted from mesangial cells. It is then associated with mesangial matrix via N-terminus of LTBP. In protease-mediated activation of TGF- β , LTBP is first cleaved at the protease sensitive amino terminal hinge region, and soluble large latent complex is released.

TGF- β activation, however, may be neutralized via feedback inhibition, since TGF- β -induced production of plasminogen activator inhibitor-1 decreases the active plasmin formation in mesangial cells (Baricos et al. 2003). Furthermore, accumulation of mesangial matrix progressed in association with enhanced mesangial fibrin deposition in rats with anti-Thy 1.1 nephritis (Liu et al. 2004). Thus, the mesangial cell surface surrounded by an enlarged matrix may not express sufficient plasmin to further cleave LAP that liberates active TGF- β dimer from the large latent TGF- β 1 complex.

In view of the enhanced expression of TGF- β 1 in podocytes in human IgAN (Kim et al. 2002) and end-stage diabetic nephropathy (Wahab et al. 2005), podocytes seem to respond to paracrine TGF- β coming from the mesangium. Even though free active TGF- β is liberated from the mesangium, it has a very short half-life in plasma (2-3 min) (Coffey et al. 1987), in contrast to the latent TGF- β complex with a significantly longer half-life (>100 min) (Wakefield et al. 1990). Thus, soluble forms of large latent TGF- β complex, rather than active TGF- β , may be localized to the podocyte surface after its release from the mesangial matrix (Fig. 1 and 2).

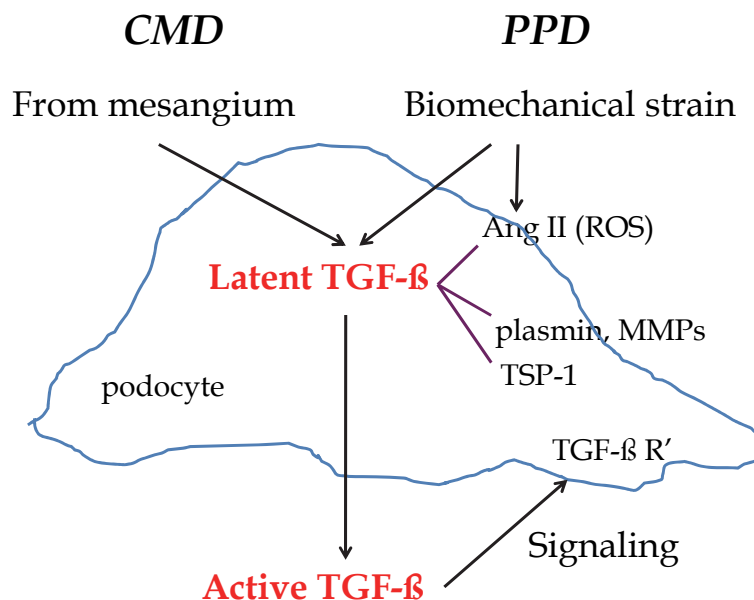


Fig. 2. Hypothetical pathway for TGF- β activation by podocytes in the diseased glomeruli. Soluble large latent TGF- β complex coming from the mesangium in chronic mesangial disease (CMD) and biomechanical strain-induced TGF- β in progressive podocyte disease (PPD) may be the source of latent TGF- β complex in podocytes. It is then activated by angiotensin II (Ang II)/reactive oxygen species (ROS), plasmin, matrix metalloproteinases (MMPs) and thrombospondin-1 (TSP-1). Active TGF- β , which is released from latency-associated peptide, is able to associate with the signaling receptors (TGF- β R'), and signal transduction pathway is activated.

5.2 Induction of podocyte TGF- β by glomerular hypertension or biomechanical strain in progressive podocyte disease

In progressive podocyte diseases, TGF- β expression is increased in podocytes (Kim et al. 1999, 2003; Patek et al. 2003; Sayers et al. 1999; Shankland et al. 1996; Wahab et al. 2005). Unlike mesangial cells, podocytes do not overexpress TGF- β 1 in response to common in

vitro metabolic stimuli, such as high glucose (Iglesias-de la Cruz et al. 2002) and angiotensin II (Ang II) (Chen et al. 2005). Yet albumin load or mechanical strain increases the levels of TGF- β 1 and Ang II, as well as TGF- β type I, II and III receptors in cultured podocytes (Abbate et al. 2002; Dessapt et al. 2009; Durvasula et al. 2004).

Increased intraglomerular pressure results in cellular strain and perpetuates further damage to the podocytes in progressive glomerular disease, eventually leading to glomerulosclerosis (Kriz et al. 1998). The less cross-linked and possibly more elastic physical properties of the GBM in some podocyte diseases may subject the podocytes to elevated biomechanical strain even under normal glomerular blood pressure. As the disease progresses and nephron mass is lost, glomerular hypertension develops, further exacerbating the biomechanical strain and the effector functions influenced by it (Meehan et al. 2009). In the remnant kidney model of glomerular capillary hypertension, TGF- β 1 (Abbate et al. 2002) and Ang II type I receptor (Durvasula et al. 2004) are upregulated by podocytes.

Together, an increase in glomerular capillary pressure may stimulate Ang II and TGF- β 1 expression in podocytes through mechanical force injury in progressive podocyte diseases (Lee 2011) (Fig. 2).

5.3 Activation of latent TGF- β by podocytes in chronic glomerular disease

In podocyte diseases, Ang II-induced oxidative stress may activate the latent TGF- β and, subsequently, the TGF- β signaling system in podocytes (Lee 2011) (Fig. 2). Indeed, diabetic podocytopathy seems to be mediated by Ang II (Ziyadeh and Wolf 2008) and oxidative damage (Zheng et al. 2008).

Osteopontin expression strongly correlates with glomerular disease, and is increased specifically in podocytes. Treatment of podocytes with recombinant osteopontin activated the NF- κ B pathway, increased the expression of urokinase-type plasminogen activator (uPA) and MMP-2 and -9, and increased podocyte motility (Lorenzen et al. 2008). Strong expression of uPA protein and mRNA is sometimes observed within crescents (Lee et al. 2001). These observations suggest that damaged podocytes in the diseased glomeruli may release plasmin, MMP-2 and -9 to activate latent TGF- β (Fig. 2).

In human FSGS, expression levels of TGF- β 1, TSP-1 and TGF- β type II receptor mRNAs and proteins as with phosphorylated Smad2/Smad3 are increased by podocytes (Kim et al. 2003), suggesting that TSP-1 may activate TGF- β in podocytes (Fig. 2). In addition, diabetic mediators upregulate the TGF- β type II receptor that both binds the ligand and initiates the signaling cascade, suggesting that the podocyte is primed to respond to TGF- β (Iglesias-de la Cruz et al. 2002; Wolf et al. 2005).

Altogether, podocyte-derived plasmin, MMPs and TSP-1, and particularly Ang II-induced oxidative stress may activate the latent TGF- β in podocytes in diseased glomeruli. The activated TGF- β may bind to its receptor on podocytes, activating the TGF- β /Smad signaling pathway to induce the expression of its target genes, such as connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF) (Fig. 2 and 3).

6. Paracrine effector mechanism of CTGF and VEGF for TGF- β to act on mesangial cells

The podocyte TGF- β , the active form of which has a very short half-life in plasma, is unlikely to traverse the GBM to promote sclerosis in the adjacent mesangium. Instead, some TGF- β -induced humoral factors produced by podocytes seem to have fibrogenic effects on mesangial cells (Lee and Song 2009b).

CTGF is a major autocrine growth factor induced by TGF- β . TGF- β 1 induces CTGF mRNA and protein expression in podocytes (Ito et al. 2001) and mesangial cells (Riser et al. 2000). Expression of CTGF mRNA and/or protein in the mesangium and podocytes is upregulated in human chronic glomerular disease (Ito et al. 1998; Wahab et al. 2005). It is increased particularly in the glomeruli of patients with mesangial matrix expansion (Suzuki et al. 2003). Treatment with the CTGF antisense oligonucleotides significantly reduced the mesangial matrix expansion in diabetic mice (Guha et al. 2007). Furthermore, induction of diabetes in podocyte-specific CTGF-transgenic mice results in an increased mesangial CTGF expression with more severe mesangial expansion than diabetic wild-type mice (Yokoi et al. 2008). TGF- β 1 stimulates VEGF expression in podocytes (Iglesias-de la Cruz et al. 2002). VEGF is a potent angiogenic molecule and is detected predominantly in podocytes (Bailey et al. 1999; Wendt et al. 2003). Yet glomeruli are not sites of angiogenesis, possibly because podocytes mainly express VEGF_{165b} protein, which inhibits VEGF₁₆₅-mediated angiogenesis (Cui et al. 2004). VEGF may play an important role in TGF- β 1-induced glomerular fibrosis (Chen et al. 2004, 2005). VEGF overexpression by podocytes led to mesangial expansion (Veron et al. 2010; Zhang et al. 2010). Furthermore, anti-VEGF attenuates the mesangial matrix expansion in diabetic mice (Flyvbjerg et al. 2002).

The dominant production of VEGF-A by podocytes and the localization of its receptor, VEGFR-2, on glomerular endothelial cells suggest that VEGF-A moves across the GBM, opposing the ultrafiltration gradient to move water and solutes from the capillaries into the Bowman's space (Satchell et al. 2006). In fact, about one third of VEGF secreted from

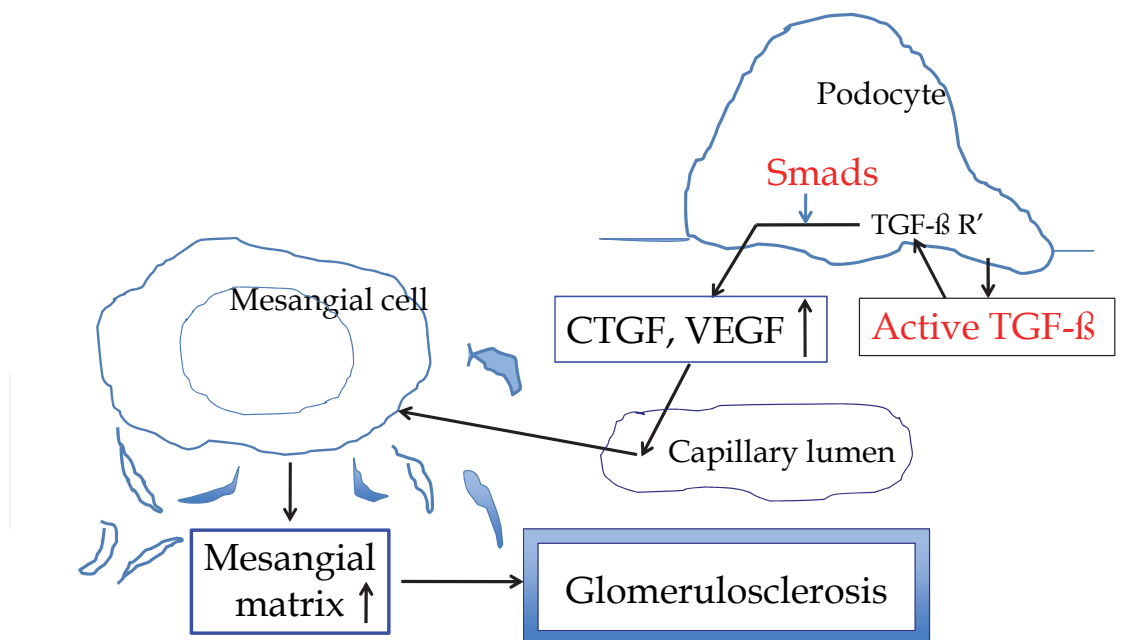


Fig. 3. Hypothetical pathway for mesangial matrix accumulation via activation of TGF- β by podocytes in chronic glomerular disease. The activated TGF- β may bind to its receptor (TGF- β R') on podocytes, activating TGF- β /Smad signaling pathway to induce the overexpression of its target genes, connective tissue growth factor (CTGF) and vascular endothelial growth factor (VEGF). The CTGF and VEGF secreted from podocytes may reach the capillary lumen and stimulate mesangial cells to produce excessive matrix proteins, culminating in the development of glomerulosclerosis.

podocytes would reach the capillary lumen and accumulate there, supporting the view that VEGF can move against the flow of glomerular filtration (Katavetin and Katavetin 2008). Although it is not clear whether this is also the case for CTGF, the experiments performed by Yokoi et al. (2008) support that possibility.

In summary, TGF- β -induced CTGF and VEGF secretion by podocytes may act as an effector mechanism, necessary for mesangial matrix accumulation in chronic glomerular disease, culminating in the development of glomerulosclerosis (Fig. 3).

7. Conclusions

In chronic mesangial disease, large latent TGF- β complexes secreted by mesangial cells may be stored in the mesangial matrix, from which soluble large latent TGF- β complexes may be released and localized to the podocyte surface. In progressive podocyte disease, by contrast, mechanical pressure or biomechanical strain may upregulate Ang II and TGF- β expression in podocytes. In both chronic mesangial disease and progressive podocyte disease, podocyte-derived plasmin, TSP-1 and ROS, particularly Ang II-induced oxidative stress, seem to be involved in TGF- β activation. Active TGF- β may induce CTGF and VEGF overexpression in podocytes, which may act as a paracrine effector mechanism on mesangial cells to stimulate mesangial matrix synthesis culminating in the development of glomerulosclerosis. In summary, this review provides new mechanistic insights into the role of TGF- β in mesangial matrix synthesis in chronic progressive glomerular disease. Better understanding of the activation of TGF- β signaling and its downstream effectors, CTGF and VEGF, may provide novel tools for the prevention of glomerulosclerosis.

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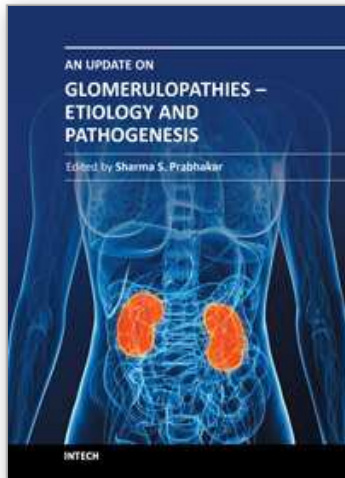
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