Transforming growth factor β1 and diabetic nephropathy

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Abstract
Transforming growth factor β1 (TGFβ1) is established to be involved in the pathogenesis of diabetic nephropathy. The diabetic milieu enhances oxidative stress and induces the expression of TGFβ1. TGFβ1 promotes cell hypertrophy and extracellular matrix accumulation in the mesangium, which decreases glomerular filtration rate and leads to chronic renal failure. Recently, TGFβ1 has been demonstrated to regulate urinary albumin excretion by both increasing glomerular permeability and decreasing reabsorption in the proximal tubules. TGFβ1 also increases urinary excretion of water, electrolytes and glucose by suppressing tubular reabsorption in both normal and diabetic conditions. Although TGFβ1 exerts hypertrophic and fibrogenic effects in diabetic nephropathy, whether suppression of the function of TGFβ1 can be an option to prevent or treat the complication is still controversial. This is partly because adrenal production of mineralocorticoids could be augmented by the suppression of TGFβ1. However, differentiating the molecular mechanisms for glomerulosclerosis from those for the suppression of the effects of mineralocorticoids by TGFβ1 may assist to develop novel therapeutic strategies for diabetic nephropathy. In this review we discuss recent findings on the role of TGFβ1 in diabetic nephropathy.
**Introduction**

Transforming growth factor β1 (TGFβ1) is a multifunctional cytokine that controls numerous biological processes including immunity(92), differentiation(29), tumor suppression(2), tumor metastasis(107), senescence(68), migration(17), wound healing(105), apoptosis(108), cell division(2), adipogenesis(76), and osteogenesis(27). In addition, the renal expression of TGFβ1 mRNA and protein are increased in patients with diabetes mellitus(110), and it enhances the synthesis and crosslinking of extracellular matrix (ECM)(3, 81).

In the U.S. population, the most frequent cause of chronic renal failure is diabetes mellitus (~44 %). No more than 20~40 % of diabetic subjects, however, develop nephropathy despite having similar blood glucose levels, suggesting the presence of genetic predisposition to the complication. The T869C polymorphism in the human TGFβ1 gene, leading to the L10P variant of the coding protein, is associated with an increased risk of diabetic nephropathy(71, 77, 109), but how the functional change of TGFβ1 protein increases the incidence of diabetic nephropathy remains elusive.

In incipient diabetic nephropathy, the glomerular filtration rate (GFR) increases by 25~50 % (glomerular hyperfiltration)(1) by the reduction of tubuloglomerular feedback, which is caused by the increase in sodium/glucose reabsorption and hence the reduced sodium delivery in the macula densa(101). However, in the late stage of diabetic nephropathy, the GFR eventually declines as the number of functional nephrons decreases, which leads to the insufficiency of renal excretory function. The decline in GFR is associated with the expansion of mesangial area, which is caused by cell proliferation and accumulation of ECM.

Although the increase in urinary excretion of albumin is considered to be the early indicator of diabetic nephropathy, the mechanisms whereby hyperalbuminuria occurs in diabetic subjects are not fully understood. However, impairment of barrier function at the slit diaphragm between podocytes and the decrease in reabsorption of filtered albumin by proximal tubules have recently been identified as pivotal in the development of diabetic albuminuria.

Mice having the heterozygous Akita diabetogenic mutation expressing ~10%, 50%, 100%, 200%, and 300% normal Tgif1 mRNA levels have recently been generated. In these mice, the severity of glomerulosclerosis and albuminuria is enhanced as the expression of TGFβ1 is increased, despite blood pressure being negatively correlated with TGFβ1 expression(31). It is noteworthy that the diabetic mice with 10% normal TGFβ1 expression exhibit near-normal glomerular histology, GFR and urinary albumin excretion, in spite of the presence of primary aldosteronism and hypertension. Additionally, the markedly increased urinary excretion of water, electrolytes and glucose in Akita type 1 diabetes was diminished to levels comparable to those in non diabetic wildtype mice by the genetic insufficiency of TGFβ1.

These previous findings suggest that TGFβ1 plays a pathophysiological role not only in promoting glomerulosclerosis, interstitial fibrosis and the decline in GFR, but also in increasing
urinary excretion of albumin, water, electrolytes and glucose in diabetes. In the current review, we will discuss the mechanisms whereby TGFβ1 causes renal morphological and functional changes in diabetes mellitus. As such, therapeutic strategies targeting TGFβ signaling may be developed to effectively treat chronic excretory insufficiency in patients with diabetes.

**TGFβ1 facilitates accumulation of extracellular matrix (ECM) in diabetic nephropathy**

Previous studies show that neutralizing anti-TGFβ antibodies prevented glomerulosclerosis and interstitial fibrosis, and reduced expression of ECM genes including fibronectin and type IV collagen in mice with type 1 and type 2 diabetes(90, 116), suggesting that TGFβ signaling plays a critical role in ECM accumulation in diabetic nephropathy. Both canonical and alternative signaling of TGFβ1 have been suggested to be involved in the development of diabetic nephropathy(15, 19).

Since glucose availability is impaired in diabetes, the metabolic shift occurs from glycolysis towards oxidative phosphorylation by using more fatty acids as an energy source (Figure). As a result, the mitochondrial electron transport chain increases superoxide production and stimulates three major pathways of hyperglycemic damage (activation of the polyol pathway, advanced glycation end-products generation and protein kinase C activation)(72). Furthermore, high glucose induces reactive oxygen species (ROS) via NAD(P)H oxidase, mitochondrial electron transport chain and protein kinase C(57).

Hydrogen peroxide upregulates TGFβ1 and its downstream ECM-related genes including integrin-linked kinase, fibronectin and collagen types I, III and IV(25, 48). In the reverse direction, pharmacological inhibition of different ROS sources including NAD(P)H oxidase and mitochondrial respiratory chain decreases the transcription of TGFβ1 via reduced activity of activated protein-1(26), indicating that ROS-induced enhancement of the transcription of TGFβ1 may at least in part account for the increase in TGFβ1 expression in diabetes.

Previous studies have demonstrated that TGFβ1 stimulates the transcription of the components of ECM, including collagen, fibronectin and laminin(5, 41). It has been demonstrated that TGFβ1 also increases the expression of lysyl oxidase, that forms crosslinks between collagen and elastin fibers which stabilizes their structure(3). TGFβ1 also stimulates the transcription of procollagen lysyl hydroxylase 2, which hydroxylates lysyl residues of collagen telopeptides and is essential for collagen crosslinking(24). In addition, TGFβ1 augments the expression of plasminogen activator inhibitor-1(39) and tissue inhibitor of metalloproteinases-1(100), both of which inhibit the activity of ECM-degradating matrix metalloproteinases.

The effect of TGFβ1 on the expression of matrix metalloproteinase 9 (MMP9) is controversial. TGFβ1 increases the expression of MMP9 in cultured cells and in isolated perfused kidney(13, 82), whereas transgenic overexpression of TGFβ1 decreases MMP9
expression in mice(100, 112). The exact reason for this discrepancy is unclear, but the suppressive effect of TGFβ1 on mineralocorticoid production may be related. Previous studies have demonstrated that aldosterone increases the transcription of MMP9 via phosphoinositide-3-kinase (PI3K), p38 mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK)(23) and oxidized Ca++/calmodulin-dependent protein kinase II (oxCaMKII)(32), suggesting that TGFβ1 decreases tissue MMP9 expression via suppressing circulating aldosterone produced in adrenocortical cells.

Recently, TGFβ type 1 receptor antagonists and aldosterone have also been found to increase the expression of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS)-1, which also degrades ECM(16, 54).

Thus, TGFβ1 facilitates ECM accumulation by increasing production and stabilization of ECM and by suppressing its degradation, which plays a causative role in developing glomerulosclerosis and interstitial fibrosis in diabetic nephropathy.

TGFβ1 facilitates dedifferentiation of renal cells

Previous studies suggest that TGFβ1 induces epithelial-mesenchymal transition/transdifferentiation (EMT), a dedifferentiation process by which the epithelial cellis transformed into the myofibroblast, a type of the mesenchymal stem cell(96). In the kidney, tubular cells are normally lining the tubular basement membrane and have a highly polarized structure for efficient reabsorption of solutes and proteins from urinary space into peritubular capillaries, but through the EMT process they lose cell polarity and gain migratory and fibrogenic properties of myofibroblasts(35). Indeed, TGFβ1 has been demonstrated to induce EMT in proximal tubules(115), collecting duct cells(43), glomerular podocytes(33, 88), and glomerular parietal epithelial cells(93).

It has been demonstrated that hypoxia inducible factor 1α (HIF-1α) enhances EMT in murine proximal tubular epithelial cells(34). Since the effect of hypoxia on EMT is only partially inhibited by anti-TGFβ antibodies, TGFβ signaling is unlikely to be the only mechanism to induce EMT(34). Prolyl hydroxylase domain-containing proteins (PHDs) hydroxylates HIF-1α(42). Hydroxylated HIF-1α binds to von Hippel-Lindau tumor suppressor protein, and is subject to polyubiquitination and degradation by proteasomes(44). TGFβ1 has been shown to decrease both mRNA and protein levels of PHD2 and hence stabilizes HIF-1α protein(66). Overexpression of the HIF-1α PHD2 transgene, which enhances degradation of HIF-1α, completely prevents TGFβ1-induced changes in the expression of HIF-1α and marker genes for EMT, suggesting that HIF-1α mediates TGFβ1-induced EMT(30).

It has also been shown that TGFβ1 activates Jagged/Notch signaling pathway and that the activated Notch triggered EMT(74). These results suggest that TGFβ1-induced EMT is also mediated at least in part by Jagged/Notch signaling.
Previous studies suggest that endothelial-mesenchymal transition/transdifferentiation (EndMT), a process by which endothelial cells are transformed into myofibroblasts, also contributes to renal fibrosis in streptozotocin (STZ)-induced type 1 diabetic mice(113). TGFβ1 has been demonstrated to induce EndMT(114). Overexpression of Snail induced EndMT, but suppression of Snail expression abrogated TGFβ2-induced EndMT in mouse endothelial cells, suggesting that Snail mediates TGFβ signaling-induced EndMT(50).

Thus, TGFβ1 may be involved in the process of EMT and EndMT in diabetic nephropathy, which decreases the number of functional cells and increase the accumulation of ECM leading to impairment of renal excretory and reabsorptive function. However, controversy remains over the contribution of each of these processes to renal fibrosis(18).

TGFβ1 enhances diabetic albuminuria via both glomerular and post-glomerular mechanisms

A number of previous studies have demonstrated that TGFβ1 promotes the development of diabetic albuminuria. Several transgenic animal models overexpressing TGFβ1 exhibited increased urinary excretion of albumin(51, 100). Chronic treatment with the soluble human TGFβ type II receptor reduced albuminuria without changing blood glucose levels in STZ-induced diabetic mice(84). However, several studies did not show a significant effect of the suppression of TGFβ signaling on albuminuria in diabetic animals. For instance, chronic peritoneal infusion of neutralizing anti-TGFβ antibodies did not alter urinary albumin excretion in db/db type 2 diabetic mice(116). Furthermore, genetic deficiency of Smad3, an intracellular signaling molecule which is downstream of TGFβ receptors, did not affect albuminuria in STZ-induced diabetic mice(104).

Microalbuminuria is low-grade albuminuria, which is ranged from 30 to 300 mg/day in humans, and is widely established as an early indicator of diabetic nephropathy. However, whether the elevated urinary excretions of albumin plays a causative role in diabetic tubular damage or it is merely a consequence of diabetic nephropathy is still controversial(45).

The paradigm that the sieving of albumin at the slit diaphragm is the predominant mechanism to prevent albuminuria has been questionable because of the lack of a clearing mechanism of the sieved albumin(91). Indeed, the concentration of albumin at the Bowman’s capsule estimated with two-photon microscopy has been demonstrated to be within the nephrotic range (1-10 mg/ml) even in normal conditions(86). In contrast, others using micropuncture technique have reported less concentrations of albumin (20-30 μg/ml) than the nephrotic-range in Bowman's capsule(53, 97). Nevertheless, these results indicate that both incomplete glomerular barrier and subsequent tubular reabsorption/degradation are important in preventing albuminuria(10).

Nephrin is abundantly expressed in the slit diaphragm and considered to exert a barrier
function against glomerular filtration of albumin(37, 106). The mutations in the nephrin gene lead to urinary overexcretion of high molecular weight proteins and albumin and congenital nephrotic syndromes(47, 79). Yet, tubular handling of protein is important as well. Megalin and cubilin in the brush border of proximal tubular cells, contribute to the endocytosis of albumin and low molecular weight proteins(9, 22, 59, 67, 111).

The expression of nephrin is decreased in diabetes(12). TGFβ1 decreases renal mRNA levels of nephrin(31), and increases the permeability of albumin in the podocyte(56). Additionally, the presence of diabetes attenuates the expression of megalin(98). TGFβ1 decreases renal megalin mRNA levels in Akita type 1 diabetic mice(31), which might attenuate the albumin endocytosis mediated by megalin(22).

Therefore, it is likely that diabetic albuminuria is the result of a double insult in the kidney’s ability to process albumin, increased permeability at the slit diaphragm and reduced tubular reabsorption. However, in what proportion the diabetic albuminuria is caused by tubular dysfunction and/or to podocyte dysfunction is controversial(75, 85, 98, 99).

Albuminuria in Akita mice expressing 10% TGFβ1 mRNA was markedly reduced as compared with that in Akita mice, and was comparable to non-diabetic wildtype mice, despite similar glucose levels and increased systolic blood pressure in the 10% hypomorphic Akita mice(31). In the reverse direction, genetic overexpression of TGFβ1 markedly increased urinary albumin excretion despite no significant changes in blood glucose or blood pressure(31). The amount of urinary albumin excretion in the 10% hypomorphic Akita mice was found to be increased by 20 fold by overexpressing Tgfb1 expression in the proximal tubular cells, but only by 4 fold by overexpressing Tgfb1 in the podocytes.

Thus, TGFβ1 plays a critical role in developing hyperalbuminuria. These findings demonstrate that attenuated tubular reabsorption of albumin appears to be the predominant factor leading to diabetic albuminuria, rather than enhanced glomerular filtration.

TGFβ1 inhibits the production and function of mineralocorticoids

Plasma levels of aldosterone are increased in diabetic patients(36), and aldosterone has been shown to increase ROS by stimulating NAD(P)H oxidase(83). These findings suggest that the increased action of mineralocorticoids partly contributes to the development of diabetic complications. Indeed, chronic administration of spironolactone, a mineralocorticoid receptor antagonist, decreased albuminuria in patients with diabetes(89).

It has been shown that TGFβ1 potently inhibits the synthesis of aldosterone in vitro(28, 38, 61). TGFβ1 also suppresses the production of androstenedione, corticosterone and cortisol(38). This broad suppressive effect of TGFβ1 on steroidogenesis may be partly because TGFβ1 decreases the expression of cytochrome P450 side-chain cleavage (P450scc), adrenodoxin reductase and adrenodoxin, which controls the initial step of steroidogenesis(69).
The mRNA levels for steroidogenic acute regulatory protein (StAR), which supplies cholesterol to P450scc by transporting it from the outer to the inner mitochondrial membrane, is also decreased by TGFβ1(4). In the bovine adrenocortical cells, TGFβ1 also reduced the transcript levels of hydroxyl-delta-5-steroid dehydrogenase, 3 β- and steroid delta-isomerase 1 (Hsd3b1) and steroid 17-alpha-monoxygenase (Cyp17a1)(55).

It has recently been reported that TGFβ1 decreases cortisol and 11-hydroxyandrostenedione production induced by forskolin by 85% and production of aldosterone induced by angiotensin II by 80%. The activity of steroid 11β-hydroxylase (Cyp11b1) and the transcript levels for Cyp11b1 induced by forskolin, as well as the activity of aldosterone synthase (Cyp11b2) and the transcript levels for Cyp11b2 induced by angiotensin II were strongly inhibited by TGFβ1 in the NCI-H295R cell line(61). TGFβ1 suppressed the Cyp11b1 promoter activity, but the Smads-binding sequence was not responsible for the transcriptional inhibition. This result suggests that TGFβ1 indirectly represses Cyp11b1 promoter activity(61). Intriguingly, the mRNA levels of steroidogenic factor 1, the genetic deficiency of which causes the absence of gonadal and adrenal steroidogenic cells(64), were inhibited by TGFβ1(60). Steroidogenic factor 1 binds to a shared promoter element of steroidogenic enzymes including Cyp11b1, Cyp11b2, steroid 21-hydroxylase (Cyp21a1) and Cyp11a1(80), and enhances their expression(52). Thus, numerous steroidogenic steps that are upstream of the synthesis of aldosterone are suppressed by TGFβ1.

Indeed, it has been shown that plasma levels of aldosterone and the adrenal expression of several steroidogenic enzymes involved in the production of aldosterone including Cyp11b1, Cyp11b2, Star, Hsd3b1 and Cyp21a1 is decreased as TGFβ1 expression is increased in mice having graded expression of TGFβ1(46). The suppressive effect of overexpression of TGFβ1 on plasma levels of aldosterone was also observed in Akita diabetic mice(31).

Although TGFβ1 exerts a suppressive effect on adrenocortical production of aldosterone, the stimulatory effect of aldosterone on the activity of epithelial sodium channel (ENaC) is also inhibited by TGFβ1. Aldosterone expands the volume of extracellular fluid by increasing ENaC activity. ENaC is expressed in the “aldosterone-sensitive distal nephron” which is comprised of collecting ducts, connecting tubules, and late distal convoluted tubules(21, 62). The aldosterone-sensitive distal nephron also expresses two other components required for sodium reabsorption in response to aldosterone: Na⁺/K⁺-ATPase and mineralocorticoid receptors. Although aldosterone is the major regulator of ENaC activity, TGFβ1 also regulates ENaC activity either in combination with aldosterone or independently(6, 62). The aldosterone-induced increase in sodium transport via the ENaC is inhibited by TGFβ1 (40). TGFβ1 enhances βENaC internalization which facilitates destabilization of the cell surface ENaC complex(78). It has also been found that the total activity, functional expression and open probability of ENaC in mice underexpressing TGFβ1 are all greater than those in wild type(46).
Protease nexin-1 (PN-1) has recently been found to inhibit prostasin, which augments the activity of ENaC(8, 103). Intriguingly, aldosterone and TGFβ1 reciprocally regulate the expressions of PN-1 and prostasin. Thus, prostasin expression is increased by aldosterone and decreased by TGFβ1, whereas PN-1 expression is decreased by aldosterone and increased by TGFβ1(103).

Aldosterone and TGFβ1 differentially control the reabsorption of sodium in proximal tubular cells. Na+/K+-ATPase alpha1 subunits and mineralocorticoid receptors are expressed in the proximal tubules of the mouse, rat and human(87). The activity of sodium/proton exchange is stimulated and the expression of sodium/proton exchanger 3 on the cell surface is increased by aldosterone in cultured proximal tubular cells(14). By contrast, the Na+/K+-ATPase α and β subunits expression and the Na+/K+-ATPase activity are dose dependently decreased by TGFβ1(73, 94).

Thus, TGFβ1 has been suggested to inhibit both aldosterone production in the adrenal cortex and aldosterone actions in the kidney. Although TGFβ1 has been shown to directly increase ROS in cultured cells(95), it counteracts against production and action of aldosterone, which enhances ROS generation and tissue fibrosis(7, 65). Inhibition of aldosterone by TGFβ1 may be a negative feedback mechanism in diabetic nephropathy.

**TGFβ1 suppresses reabsorption of water and glucose in proximal tubules**

Notably, the urine volume in TGFβ1 hypomorphic Akita diabetic mice was comparable to that in non-diabetic wild type mice(31). In addition, the urinary output of glucose in diabetes was substantially decreased by genetic insufficiency of TGFβ1, despite unchanged plasma concentrations of insulin and glucose. The marked reduction in urinary water and glucose excretion by genetic insufficiency of TGFβ1 was also observed in their non-diabetic counterparts(31, 46). In addition, genetic disruption of small mothers against decapentaplegic homolog (Smad) 3, which is the intracellular signaling molecule downstream of TGFβ receptors, also reduced urine volume despite little change in plasma levels of glucose in STZ-induced diabetic mice(19). These findings indicate that TGFβ1 mediates hyperglycemia-induced polyuria and glucosuria, which has been attributed to osmotic diuresis.

The marked decrease in urinary water excretion in TGFβ1 hypomorphic mice cannot be explained merely by enhanced aldosterone function, because chronically high aldosterone levels have been demonstrated to increase urine volume due to impaired urine concentration ability(11). The diminished diuresis of the 10% hypomorphs was found to be fully reversed by overexpressing Tgfb1 in the proximal tubule(31), and partially restored by overexpressing Tgfb1 in the collecting duct cells (our unpublished observation), indicating that TGFβ1 suppresses the reabsorption of water in both proximal tubular cells and collecting ducts.

The finding that glucosuria and polyuria are both absent in the TGFβ1 hypomorphic diabetic mice may be related to the previous observation that the sodium/glucose co-transporters
(SGLTs), which the proximal tubule highly expresses, co-transport each sugar molecule with more than 200 water molecules(63). In concordance with this inference, the urinary output of glucose was partially restored in Akita mice with the expression of Tgfb1 augmented in proximal tubules(31). Furthermore, high glucose, hydrogen peroxide and TGFβ1 have been shown to decrease the SGLT activity measured with α-methyl-D-glucopyranoside, a metabolically inert analogue of D-glucose, and the expression of SGLT 1 and 2 and sodium-hydrogen exchanger (NHE) 1 and 3 in primary cultured rabbit proximal tubule cells, which is associated with genetic expression profile of EMT(58).

Although the chronic efficacy of the inhibitors of SGLT 1 and 2, which are being used for the purpose of controlling blood glucose, on diabetic nephropathy is still controversial(20, 102), several studies suggest that SGLT inhibitors prevent cardiovascular and renal complications via reducing blood glucose levels(49, 70). Thus, the facts that both diabetes by itself and TGFβ1 decrease the reabsorption of glucose in proximal tubular cells may be the compensatory mechanism preventing further tissue damage.

**Conclusion**

A number of features of diabetic nephropathy were absent in the TGFβ1 hypomorphic Akita mice, indicating that decreasing the expression of TGFβ1 may have therapeutic benefits in diabetics. However, the globally low expression of TGFβ1 resulted in primary aldosteronism(31, 46). Consequently, lowering the expression of TGFβ1 throughout the body could be deleterious in patients with diabetes. Nevertheless, these problems by TGFβ1 insufficiency might be circumvented if kidney-specific reduction of the expression of TGFβ1 was achieved.

Experimental results with tissue-specific TGFβ1 overexpression suggest that suppressing TGFβ1 expression in the proximal tubule is more likely to decrease albuminuria and interstitial fibrosis than to prevent the decrease in renal excretory function. In contrast, reducing expression of TGFβ1 in the podocyte may be more effective in avoiding the GFR decrease than in decreasing albuminuria and interstitial fibrosis. Thus, manipulations which lead to the decreased TGFβ1 expression in the podocyte may be useful for preventing/treating the decline in renal function in diabetic nephropathy.

Further studies are needed to unravel the mechanisms for the TGFβ1-induced accumulation of ECM and for the suppression of the effects of mineralocorticoids by TGFβ1, and this understanding might be useful for developing new therapeutic options for preventing and/or treating diabetic nephropathy.

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Conflicts of Interest
The authors have no conflicts of interest.

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Figure legend

Figure. A diagram depicting the proposed effects of transforming growth factor-β1 (TGFβ1) on the features of diabetic nephropathy. ROS, reactive oxygen species; EMT, epithelial-mesenchymal transition; EndMT, endothelial-mesenchymal transition.
Diabetes Mellitus

Glucotoxicity  
Fatty acid oxidation

Mineralocorticoids

ROS

TGFβ1

Tubular dysfunction  
EMT, EndMT  
ECM accumulation

Albuminuria, Polyuria, Glucosuria  
Glomerulosclerosis,  
Tubulointerstitial fibrosis