Review Article

Transforming growth factor-beta and the glomerular filtration barrier

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A B S T R A C T

The increasing burden of chronic kidney disease worldwide and recent advancements in the understanding of pathologic events leading to kidney injury have opened up new potential avenues for therapies to further diminish progression of kidney disease by targeting the glomerular filtration barrier and reducing proteinuria. The glomerular filtration barrier is affected by many different metabolic and immune-mediated injuries. Glomerular endothelial cells, the glomerular basement membrane, and podocytes—the three components of the filtration barrier—work together to prevent the loss of protein and at the same time allow passage of water and smaller molecules. Damage to any of the components of the filtration barrier can initiate proteinuria and renal fibrosis. Transforming growth factor-beta (TGF-β) is a pleiotropic cytokine strongly associated with the fibrogenic response. It has a known role in tubulointerstitial fibrosis. In this review we will highlight what is known about TGF-β and how it interacts with the components of glomerular filtration barrier and causes loss of function and proteinuria.

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Introduction

Proteinuria is a common finding in many kidney diseases such as diabetic nephropathy and chronic glomerulonephritis. Elevated urine protein is strongly associated with glomerulosclerosis, interstitial fibrosis, and progression of chronic kidney disease [1], and independently predicts worse clinical outcomes [2]. Most agents that reduce proteinuria have beneficial effects on long-term renal function [3]. Despite widespread use of drugs that decrease proteinuria, progression to end-stage kidney disease remains all too common.

Traditionally, our understanding of the pathogenesis of proteinuria focused on glomerular hypertension. Effective treatment has been aimed at the renin–angiotensin system, which reduces intraglomerular pressure [4]. Over the past decade, interest has shifted from this mechanical view to a cellular and molecular perspective. The glomerular filtration barrier consists of endothelial cells, a basement membrane, and a specialized epithelial cell—the podocyte (Fig. 1). Dysfunction in any component of the glomerular filtration barrier can lead to proteinuria. Increasingly, it has been recognized that there is a basal cross-talk between the endothelium and the podocytes, mainly involving angiogenic molecules such as vascular endothelial growth factor (VEGF) that maintain the health of the filtration barrier [5]. Perturbation of this signaling can lead to endothelial cell or podocyte injury. Podocyte injury manifests as retraction of the podocyte foot processes leading to effacement, loss of slit diaphragm proteins [6], dedifferentiation, detachment, and apoptosis [7]. Podocyte de-differentiation has been described as a process similar to epithelial to mesenchymal transition (EMT) and has been shown to occur in response to transforming growth factor-beta (TGF-β) [8].

Causes and consequences of proteinuria

Many common kidney diseases such as diabetes and chronic glomerulonephritis first manifest with structural glomerular injury and proteinuria [9] followed by tubulointerstitial
fibrosis [10]. Proteinuria is a prognostic indicator in a variety of kidney diseases. In a large cohort study, Hemmelgarn et al. [2] demonstrated that the presence of even mild proteinuria (trace to 1+ on urine dipstick or 30–300 mg/g albumin to creatinine ratio) increased the risk of mortality and progressive renal failure independently of baseline renal function and other prognostic markers. Proteinuria is a common condition with significant implications with respect to population health. In the National Health and Nutrition Examination Survey study, 8.2% of the general US population have mild proteinuria, and 1.1% have overt proteinuria [11].

Although proteinuria is strongly linked epidemiologically to progressive chronic kidney disease, there is ongoing debate as to whether proteinuria is causally linked to tubulointerstitial fibrosis. When renal tubular cells are grown in culture and exposed to high levels of protein, the cells express inflammatory and fibrogenic cytokines [12]. These in vitro findings are supported by evidence from animal models where protein overload alone induces chronic renal injury [13]. Other hypothesized mechanisms to explain progressive interstitial fibrosis after glomerular injury include loss of peritubular capillaries and tubular hypoxia [14,15], filtered cytokines [13], misdirected filtrate from sclerosed glomeruli [14], and interstitial inflammation [15].

Although there is some disagreement [16], the prevalent paradigm is that proteinuria is primarily a result of dysfunction of the glomerular filtration apparatus with a special focus on the podocyte. The podocyte is a terminally differentiated epithelial cell with a highly specialized structure that consists of foot processes that wrap around the glomerular capillaries. A series of transmembrane proteins link the foot processes, and comprise the ‘slit diaphragm’ structure that is crucial to proper function of this barrier [6].

If podocytes are injured, the expression of the slit diaphragm proteins decreases. For example, in diabetic nephropathy, the expression of nephrin decreases [17] and nephrin appears in the urine [18]. Later in the course of glomerular disease, podocytes detach from the basement membrane and also are found in the urine [19,20]. Podocyte apoptosis is also a common finding in advanced glomerular injury [21].

Communication between components of the filtration barrier

It is increasingly clear that components of the glomerular filtration barrier interact with each other directly or through paracrine mediators (Fig. 2). For example, podocytes secrete vascular growth factors that maintain glomerular endothelial health [22]. Elevated levels of podocyte derived VEGF leads to a collapsing glomerulopathy, whereas decreased VEGF leads to endotheliosis (endothelial swelling and fibrin deposition) [22]. An anti-VEGF antibody used commonly in bowel and renal cancer has been shown to increase the risk for proteinuria and hypertension [23], suggesting a direct clinical effect of altering the podocyte/endothelial cell interaction.

Glomerular endothelial cells show evidence of dysfunction at an early stage of glomerular injury [24] and secrete TGF-β in response to VEGF stimulation [25]. Paracrine interaction between endothelium and podocytes involves other angiogenic factors such as angiopoietin-1 (ANGPT-1) [26] and ANGPT-2 [27]. These are secreted by podocytes and impact on endothelial cells.

Although not directly part of the glomerular filtration apparatus, mesangial cells play an important role in paracrine signaling. Mesangial cells respond to high glucose [28] and pathogenic immunoglobulin A (IgA) [29] by secreting TGF-β. Khan et al. [30] have shown that mesangial cells can have a protective effect. TGF-β bound to the integrin αvβ3 is sequestered on mesangial cell membrane. When β3 integrin was knocked out, they observed decreased levels of bioactive TGF-β, which resulted in endothelial cell apoptosis and proteinuria [30]. Mesangial cells also produce other paracrine signals such as stromal-derived factor-1, which affects podocyte function [31].

Integrins play a role in the interaction between podocytes and the glomerular basement membrane (GBM). Integrin α3β1 on podocytes allows adhesion with β2 laminin of the