Diabetic nephropathy, the predominant single cause of ESRD in the developed world (1), is characterized histologically by mesangial matrix expansion and sclerosis, glomerular basement membrane thickening, and hyaline deposits in the glomerular arterioles (2,3). Although the mesangial cells and podocytes are proposed as the major mediators of diabetic nephropathy, diabetic-induced microvasculature injury also plays a key role in the pathogenesis. Similar to diabetic retinopathy, increased density of glomerular capillaries, resulting from glomerular neovascularization, and increased number of efferent arterioles at the glomerular vascular pole have been seen in biopsies of patients with type 1 diabetes (4,5). In addition, there is increased glomerular expression of vascular growth factors, including angiopoietins and vascular endothelial growth factor (VEGF) (5–7), that likely contribute to diabetic nephropathy by promoting vessel leakage and reducing transendothelial electrical resistance (6,8).

At present, the only therapeutic agents that have been shown specifically to retard but not halt the progression of diabetic nephropathy target the renin-angiotensin system. Angiotensin-converting enzyme inhibitors (ACEI) decrease angiotensin II (Ang II) production, whereas Ang receptor blockers (ARB) inhibit the Ang II type I (AT1) receptor (reviewed in references [9,10]). Both of these drug classes decrease systemic and intraglomerular BP primarily by inhibiting the action of Ang II on the AT1 receptor. In addition to their intraglomerular hemodynamic effects, these drugs might diminish proteinuria and ameliorate diabetic nephropathy by other mechanisms. One interesting possibility, currently described in tumor angiogenesis, is that ACEI and ARB have antiangiogenic effects by reducing endothelial cell migration, tube formation, and Ang II–dependent productions of VEGF (11–13).

If neovascularization does indeed contribute significantly to the pathogenesis of diabetic nephropathy, then antiangiogenic therapies, currently applied to tumor angiogenesis, might be used in synergy with ACEI and ARB. One possible antiangiogenic strategy is to target endothelial growth factors (VEGF and angiopoietins) and/or their receptors (FLK-1, FLT-1, and Tie2) (14–17). Administration of anti-VEGF neutralizing antibodies has been shown to decrease hyperfiltration, albuminuria, and glomerular hypertrophy in diabetic rats or mice (8,18,19). Although promising, anti-VEGF therapy has not yet been used in patients with diabetes. Moreover, when this therapy was administered for the treatment of colorectal cancer, frequent adverse effects, including hypertension, bleeding episodes, thrombotic events, and proteinuria, were reported (20). This suggests that these antibodies will be difficult to administer in patients with diabetic nephropathy.

Another exciting antiangiogenic therapy was developed subsequent to the finding that endogenous cleavage products of non–extracellular matrix (angiotatin) and extracellular matrix (tumstatin and endostatin) molecules can prevent tumor neovascularization (21–23). These molecules specifically target endothelial cells and inhibit their proliferation, survival, migration, and sprouting. The potential to target neovascularization in diabetic nephropathy with these endogenously produced antiangiogenic products became evident after the finding that enzymes that are required for the generation of antiangiogenic molecules from their precursors (plasminogen and collagens IV, XV, and XVII) are downregulated in diabetes (24); levels of endogenous angiotatin within diabetic glomeruli are decreased (24); and delivery of tumstatin, endostatin, or angiotatin can ameliorate renal injury in the early stages of type 1 diabetes (24–26).

Administration of tumstatin, a cleavage product of collagen IV, or endostatin, a cleavage product of collagen XVIII, has been shown to reduce glomerular hypertrophy, hyperfiltration, and albuminuria in streptozotocin-induced diabetic mice (25,26). Similarly, glomerular mesangial matrix expansion, extracellular matrix accumulation, endothelial cell proliferation, and monocyte/macrophage infiltration were significantly inhibited by endostatin or tumstatin peptides (25,26). In contrast, nephrin expression was increased in the glomeruli of endostatin- or tumstatin-treated diabetic mice, suggesting that antiangiogenic therapy might be helpful in maintaining the glomerular filtration barrier, resulting in the amelioration of albuminuria (25,26). Although it is not clear whether the endothelium is the only and/or major target for these two antiangiogenic molecules, enhanced expression of integrin α5β1, the major receptor for endostatin (27), has been observed in the glomerular endothelial cells of diabetic mice (26), suggesting that the primary target of endostatin is the glomerular endothelial cells.

The article by Zhang et al. in this issue shows that systemic
adenoviral delivery of angiostatin to diabetic rats results in a significant reduction of albuminuria and glomerular hypertrophy (24). What is particularly interesting about this study is that the target of angiostatin is the mesangium, not the endothelium. This observation seems to agree with the finding that extra-endothelial targets for angiostatin, tumstatin, and endostatin have previously been documented (28–30). Zhang et al. further show that in vitro treatment of mesangial cells with angiostatin inhibited high glucose–induced VEGF, TGF-β, monocyte chemoattractant protein-1, and fibronectin synthesis, whereas it enhanced the levels of pigment epithelium–derived factor, an endogenous antiangiogenic factor (24). This publication brings to light the possibility that targeting glomerular cell components, other than endothelial cells, with classical antiangiogenic factors might be beneficial in the treatment of diabetic nephropathy.

Current rodent models of diabetic nephropathy using antiangiogenic molecules suffer from the limitation that their effects were evaluated primarily in the early stages of the disease. Moreover, no studies to evaluate the efficacy of antiangiogenic agents on patients with diabetic nephropathy have been performed yet. Whether this novel therapy might be beneficial to patients with diabetes is unknown and difficult to predict, as it is unclear whether the diagnosis of diabetic nephropathy can be made early enough to reap the benefits of these drugs. Nevertheless, they do provide hope that targeting neovascularization might be a novel approach to retard the progression of diabetic nephropathy.

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