Medical students are taught that endothelial dysfunction is relevant to the pathophysiology of diabetic microvascular disease, especially the glomerular defects that are characteristic of diabetic nephropathy. The facts, however, belie a paucity of knowledge about the molecular biology of the glomeruli of humans with type 1 or type 2 diabetes. Which genes are activated in the glomerular endothelial cells of patients with long-term diabetes? Which genes are abnormally suppressed? The extent of our ignorance is impressive. Fortunately, a study recently reported by Isermann et al. remedies, at least in small part, this deficit.

As a consequence of their unique position between two sets of arterioles, glomerular endothelial cells are exposed to very high hydraulic pressures, especially as compared with those of typical capillary beds. The strong frictional force of the circulation, the large ultrafiltration coefficient, and the high oxygen tension in the lumen also affect this vascular bed. These stresses may be exacerbated by a range of changes that include transmission of systemic hypertension into the glomerulus and augmented production of noxious stimuli — such as angiotensin II, reactive oxygen and nitrogen species, and advanced glycation end products — all of which are characteristic of the diabetic milieu.

However, the glomerular endothelial cell is not without allies. For example, vascular endothelial growth factor (VEGF), produced constitutively and in abundance by podocytes, somehow traverses the glomerular basement membrane and protects endothelial cells against apoptosis. Diminution of this protection is associated with disease; soluble VEGF receptor 1 (also called soluble fms-like tyrosine-kinase 1) has been observed in patients with preeclampsia. Activated protein C also protects the glomerular endothelial cell against apoptosis. Protein C is activated by the binding of thrombin (a product of the coagulation cascade) to its receptor — thrombomodulin — on the surface of the glomerular endothelial cell (Fig. 1). Because this complex catalyzes the activation of protein C, it has a key role at the interface between the endothelium and blood constituents. Activated protein C has potent antithrombotic effects and pleiotropic, cytoprotective, fibrinolytic, and antiinflammatory properties. The study by Isermann et al. suggests that diabetic nephropathy is associated with the reduced glomerular production and action of activated protein C.

Recombinant activated protein C reduces mortality among adults with severe sepsis; its pharmacologic administration possibly compensates for functionally deficient, endogenous, activated protein C. Given the anticoagulant effect of activated protein C, it is not surprising that the associated risk is bleeding, although a key role for this protein in the microvasculature of patients with sepsis was not expected by many researchers.

Isermann et al. report that although thrombomodulin is strongly expressed in the glomeruli of wild-type mice, its messenger RNA and protein levels — in addition to the production of activated protein C — are chronically depleted in the glomeruli of mice with streptozotocin-induced diabetes mellitus. This finding is reminiscent of blood vessels in acute sepsis. Using genetically engineered mice, Isermann et al. dissected pathways that involved activated protein C and that were pertinent to diabetic nephropathy. They studied mice in which thrombomodulin-dependent activation of protein C was impaired. After 26 weeks, these mice had significantly worse proteinuria and glomerular extracellular matrix accumulation than did wild-type mice with diabetes. In contrast, the structural and functional manifestations of diabetic nephropathy did not develop in transgenic mice with a potent form of activated protein C. Moreover, their glomerular endothelial cells and podocytes underwent apoptosis at a slower rate than those in mice with blunted activation of protein C.
A reduced capacity to generate activated protein C in the glomeruli of animals with diabetes could be predicted to augment the local accumulation of thrombin and fibrin. Fibrin deposition in the glomerular microvasculature results in inflammation and coagulation. Isermann et al. observed that treatment with low-molecular-weight heparin (enoxaparin) augmented the diabetic nephropathy in their models. This is surprising, given that heparin would be predicted to decrease the
local production of thrombin, and it suggests that the anticoagulant properties of activated protein C are not pivotal to its protective effect on the glomerulus. Encouraging, therefore, is the production of recombinant variants of activated protein C with cytoprotective actions, clinical efficacy in mouse models of sepsis, but less than 10% anticoagulant activity of the wild-type protein.4

The extent to which the action of activated protein C in the mouse model described by Isermann et al. relates to the human setting remains to be determined. Regardless, the study inspires a review of our current understanding of how diabetic nephropathy develops. In humans with diabetes, expansion of the mesangium and loss of capillary-filtering surface correlate closely with a declining glomerular filtration rate, leading to speculation that the progressively expanding mesangium squashes the glomerular capillaries. The findings of Isermann et al. indicate another scenario: loss of glomerular endothelial cells, which is partly caused by reduced levels of activated protein C, initiates injury, and mesangial expansion is a response to that injury. Moreover, apoptosis may also cause the loss of glomerular epithelial cells that occurs, pari passu, with worsening proteinuria in patients with diabetic nephropathy.

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