The Vasculature in Diabetic Nephropathy: All Tied Up?

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Diabetic nephropathy (DN) is the leading cause of ESRD in the United States, and its global occurrence is rising rapidly. As evidenced by the wide spectrum of debilitating macro- and microvascular complications that patients eventually experience, the vascular endothelium is a prominent target of longstanding diabetes. In the hunt for breakthrough discoveries that could someday transform the treatment of DN, signaling pathways that regulate the form and functions of blood vessels have recently garnered significant attention. In this issue of JASN, Dessapt-Baradez et al. have deployed a combination of conditionally transgenic mice and human DN biopsy studies to advance the proposition that therapies targeting the vasculature may ameliorate DN.

In 2001, the National Institutes of Health initiated the Animal Models of Diabetic Complications Consortium to tackle the well known resistance of inbred mouse strains to DN and other diabetic manifestations, a limitation that had severely impeded investigation of the molecular pathogenesis underlying progressive diabetes. The field of vascular research in DN received a substantial boost in 2006 and 2007 when two groups reported in JASN that diabetic mice null for endothelial nitric oxide synthase (eNOS−/−) recapitulated major structural and functional features of advanced human DN. The enzyme eNOS is highly specifically expressed in the endothelium and is responsible for producing the vasodilator nitric oxide, which is thought to contribute to vascular homeostasis. Loss of eNOS-derived nitric oxide activity has been observed in diabetic patients well before the onset of severe end-organ complications (reviewed by De Vriese et al.).

Although the regulation of eNOS is complex, two important growth factors upstream of eNOS have been implicated in DN—vascular endothelial growth factor-A (VEGF-A) and, more recently, angiopoietins-1 and -2 (Angpt-1 and -2). VEGF-A and Angpt-1 are constantly secreted by healthy podocytes and signal distinct receptors expressed on the surface of endothelial cells, VEGFR1/2 and Tie-2, respectively. As a potentially useful oversimplification, VEGF-A signals through VEGFR2 to induce angiogenesis and to attenuate barrier function, the latter activity accounting for VEGF’s original name of “vascular permeability factor.” Angpt-1 activates Tie-2 to stabilize newly sprouted vessels, and, importantly, it prevents vascular leakage and enhances basal microvascular barrier function. Systemic administration of the anti-VEGF antibody bevacizumab can produce glomerular endotheliosis, proteinuria, and thrombotic microangiopathy, indicating an essential role for VEGF in the maintenance of glomerular architecture and health. No comparable clinical data regarding Angpt-1 inhibition exist because drugs targeting this pathway are investigational. But unlike with VEGF-A, conditional knockout mice suggest that Angpt-1 is dispensable in the mature glomerulus.

The available data for VEGF-A in DN appear to be conflicting. For example, VEGF-A has been reported to be upregulated or downregulated in human DN biopsies. Deletion of VEGF from podocytes has been shown to exacerbate DN in the streptozotocin (STZ) model of type 1 diabetes by Sivaskandarajah et al., whereas Veron et al. reported that inducible overexpression of VEGF in the podocyte causes severe nodular glomerulosclerosis in the STZ model. Similar to the results of Veron et al., the Gnudi laboratory showed that podocyte overexpression of a naturally occurring VEGF inhibitor called sFlt-1 improves DN. An attempt to synthesize the VEGF literature in DN is beyond the current scope of this editorial, but in contrast, the current report from Dessapt-Baradez et al. adds to two prior independent experimental studies that collectively demonstrate a renoprotective role for Angpt-1 in DN.

In 2007, a group led by Park used a systemic viral gene therapy approach to achieve excess circulating Angpt-1 for 8 weeks starting during young adulthood in db/db type 2 diabetic mice. They found that renal levels of inflammatory adhesion proteins and profibrotic signaling molecules were reduced by Angpt-1 treatment. Urinary albumin excretion was reduced from approximately 150 μg/d to approximately 100 μg/d, and histopathologic changes, namely mesangial matrix expansion and glomerular basement membrane thickness, were similarly reduced by Angpt-1. The study was somewhat confounded because the Angpt-1 group also exhibited less severe elevation of fasting blood glucose levels and less visceral adiposity. In 2011, the Quaggin laboratory genetically deleted Angpt-1 at the end of in utero development and administered STZ 1–3 weeks after weaning. Unlike Lee et al. they observed no Angpt-1-dependent effect.
on glucose metabolism, as assessed by the percentage glycosylated hemoglobin. Twenty weeks after STZ administration, diabetic Angpt-1 knockouts had a urine albumin-to-creatinine ratio of 0.25 compared with 0.06 in wild-type diabetic controls. Although not scored, mesangial matrix expansion was much more prominent in the diabetic Angpt-1 knockouts than wild-type diabetic controls.

In the current report, the group led by Gnudi used a gain-of-function system (as did Park et al.), and they studied type 1 diabetes as modeled by STZ (as did Quaggin et al.). They overexpressed Angpt-1 in the podocyte beginning shortly after the induction of hyperglycemia, and they studied outcomes after 10 weeks of excess podocyte-expressed Angpt-1. They noted that excess Angpt-1 did not alter baseline renal physiology or structure. They showed that expression of the Angpt-1 receptor, Tie-2, falls in experimental diabetes, and that their “therapy” of locally expressed Angpt-1 enhances Tie-2 activation. Diabetic Angpt-1 transgenic mice had urinary albumin of 508 g/d in diabetic wild-type controls. Unlike in the prior reports, the authors did not observe any appreciable rescue of mesangial matrix expansion or of GBM thickening by Angpt-1, leaving the physical mechanisms by which diabetic proteinuria improved downstream of Angpt-1 unclear. Finally, they note that excess Angpt-1 did not alter baseline renal physiology or structure. They showed that expression of the Angpt-1 receptor, Tie-2, falls in experimental diabetes, and that their “therapy” of locally expressed Angpt-1 enhances Tie-2 activation. Diabetic Angpt-1 transgenic mice had urinary albumin of 508 μg/d compared with 2101 μg/d in diabetic wild-type controls. Unlike in the prior reports, the authors did not observe any appreciable rescue of mesangial matrix expansion or of GBM thickening by Angpt-1, leaving the physical mechanisms by which diabetic proteinuria improved downstream of Angpt-1 unclear. Finally, they note that excess Angpt-1 did not alter baseline renal physiology or structure. They showed that expression of the Angpt-1 receptor, Tie-2, falls in experimental diabetes, and that their “therapy” of locally expressed Angpt-1 enhances Tie-2 activation.

To summarize, experiments from three independent groups that added Angpt-1 to the diabetic milieu or genetically removed it suggest that Angpt-1 confers renoprotection in experimental diabetes. Because the basis of proteinuria in DN is incompletely understood, there is no consensus on how Angpt-1 is attenuating renal damage in diabetes. To wit, Dessapt-Baradez et al. examined glomerular cell proliferation, VEGFR2 phosphorylation, eNOS activation, and nephrin expression in their model. Cross-talk between the VEGF and Angpt-1 signaling axes and, indeed, the larger network of pathways among endothelia and vascular smooth muscle cells may confound efforts to implicate a single linear cascade. It also remains unclear whether Angpt-1 actually “heals” DN because the interventional studies in mice have commenced at an early, preproteiunuria stage of diabetes.

Because only a minority of patients with diabetes develop DN, it will be interesting to test whether polymorphisms in genes comprising vascular pathways or protein levels in the blood or urine can help identify at-risk patients. Conversely, long-term patients with diabetes who do not develop complications may possess a unique vascular-protective profile. If diabetes is fundamentally a metabolic disturbance, we should ask what triggers the dysregulation of vascular pathways and why there is a decades-long delay from hyperglycemia to overt complications. Finally, more studies are needed to explore how blood vessel destabilization may contribute to the final common pathway of fibrosis in diabetes as well as other forms of CKD. The study from Dessapt-Baradez et al. provides new evidence implicating Angpt-1 as a renoprotective factor in DN and, more broadly, reminds us that pathogenic molecular events with persistent functional consequences may be unfolding months to years before standard measures of chronic disease are manifest.

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DISCLOSURES

None.

REFERENCES


