Protecting the Microvasculature: A Tight Connection to Ameliorating Chronic Kidney Disease?

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Chronic kidney disease (CKD) results from diverse etiologies, including glomerulonephritis, diabetes, and hypertension (1). The incidence of CKD is increasing worldwide and is predicted to reach epidemic proportions over the next decade (1). Current therapeutic strategies are based on the control, either by lifestyle modification or by pharmacologic intervention, of known risk factors (1), but there is clear need for new approaches and the development of effective therapies presents a major challenge.

A variety of factors have been identified as playing an important role in the progression of CKD to end-stage renal failure (ESRF) (1,2,3). Among these, increasing emphasis has been placed on the role of tissue hypoxia (4,5,6). In extremis hypoxia is a consequence of disruption of the renal microvasculature and there is a direct correlation between loss of the microvasculature and development of glomerular and tubulointerstitial scarring (7). However, a number of other mechanisms may contribute to decreased tissue oxygenation, including anemia, increased vasoconstriction as result of overproduction of vasoconstrictors such as angiotensin II and endothelin-1 or decreased production of vasodilators such as nitric oxide, decreased capillary flow, increased metabolic demand by injured tubular cells, and increased oxygen diffusion distances as extracellular matrix (ECM) accumulates within the tubulointerstitium (5,6). In vitro hypoxia can induce fibrogenic changes in tubular epithelial cells and interstitial fibroblasts (5,8), suggesting a causal role for hypoxia in progression to ESRF. In addition, hypoxia may provide a homing signal for the recruitment of inflammatory cells (9) and also for circulating progenitor cells thought to contribute to the fibrogenic cell population in the injured kidney (10). The importance of hypoxia in the progression to ESRF places the microvasculature and the angiogenic response at the center of the disease process.

In response to microvascular injury, damaged endothelial cells are sloughed off into the circulation and replaced by proliferation of neighboring endothelial cells and/or by recruitment of endothelial progenitor cells from the circulation (11). Where damage is more severe, angiogenesis results in the formation of new capillaries. Angiogenesis is a complex, multistep process coordinated by the interplay of numerous soluble growth factors and inhibitors, cytokines, and proteases as well as ECM proteins and adhesion molecules (12). Regulatory factors include angiogenic molecules such as vascular endothelial growth factor (VEGF), fibroblast growth factors (FGF), angiopoietins (Ang), platelet-derived growth factor, angiogenin, angiotropin, hepatocyte growth factor, CXC chemokines with ELR (Glu-Leu-Arg) motif, platelet endothelial cell adhesion molecule, integrins, and vascular endothelial cadherin, as well as angiostatic factors such as angiotatin, endostatin, thrombospondin, CXC chemokines without ELR motif, and pigment epithelium–derived factor (12). Under homeostatic conditions, the microvasculature is maintained by a delicate balance between these pro- and anti-angiogenic factors. In response to injury the balance tips in favor of pro-angiogenic factors to drive repair. Hypoxia is generally regarded as a potent stimulus for angiogenesis (13); however, for reasons that are not clearly understood, in the hypoxic kidney in CKD the reparative angiogenic response appears to fail and there is no replacement of the damaged microvasculature, resulting in a progressive attrition of the peritubular capillary network.

Therapeutic angiogenesis represents an important approach in the treatment of a variety of ischemic diseases (14) including the kidney (5–7). Among the candidate factors, VEGF and Ang1 are of particular interest as their receptors are expressed specifically on endothelial cells. VEGF, acting through the receptor tyrosine kinases Flt/VEGFR-1 and Flik/VEGFR-2, is a major regulator of blood vessel growth and plays a critical role in promoting endothelial survival and proliferation (15). Ang1, acting predominantly through the tyrosine kinase Tie2 receptor, plays an essential role in regulating vascular growth, development, maturation, and permeability maximizing the interaction between endothelial cells, the surrounding support cells, and the ECM (16).

Both VEGF and Ang1 are expressed in the normal kidney (17,18). In rodent models of CKD, expression of both these pro-angiogenic factors is suppressed (17–19) with a parallel upregulation of anti-angiogenic factors including thrombospondin-1 (18). In the rat remnant kidney model of ESRF,
administration of VEGF ameliorates disease progression (20), illustrating the potential for pro-angiogenic therapy in CKD. However, in experimental systems VEGF has been shown to have a number of side effects and can induce disorganized, leaky, neovessel formation (15,21). On the other hand, angiogenesis induced by Ang1 leads to the formation of nonleaky neovessels.

Park and colleagues recently developed a soluble stable variant of Ang1 (COMP-Ang1) in which the N-terminal portion of the protein was replaced with the short-coiled coil domain of the cartilage oligomeric protein (COMP), which was found to be more potent than Ang1 in phosphorylating the Tie-2 receptor and the downstream signaling molecule, Akt (22). In this issue of JASN, Park et al. show that in the mouse unilateral ureteral obstruction model, intravenous administration of adenoviral COMP-Ang1 both 3 d before and 2 wk after obstruction ameliorated disease (23). Treated kidneys showed reduced inflammation, lower levels of transforming growth factor β (TGF-β) and TGF-β signaling, and a reduction in tubular injury and tubulointerstitial fibrosis, while the renal surface microvasculature and renal blood flow were preserved with a protective effect on both the glomerular and peritubular capillaries. Although a direct comparison between studies is difficult, the efficacy of COMP-Ang1 in retarding disease progression was considered similar to that of two other recognized antifibrotic factors, bone morphogenetic protein-7 (24) and insulin-like growth factor-1 (25), suggesting that COMP-Ang1 may be a important new pro-angiogenic, anti-fibrotic agent.

Whether this novel endothelium-specific therapy might be beneficial to patients with CKD in whom disease is already established remains to be determined and is difficult to predict. Despite encouraging preclinical data, well-controlled clinical trials of pro-angiogenic factors (FGF-2, VEGF) in myocardial and limb ischemia have not yielded clear-cut benefits (14) and it may be that approaches using a master switch such as hypoxia-inducible factor-1 (HIF-1), the key transcriptional regulator of the hypoxic response, may be more effective than single angiogenic factors (5,6,14). However, it is clear that protecting the microvasculature is key to preventing and/or retarding progression of CKD and pro-angiogenic therapies are likely to be an important component of any successful strategy for managing this disease. Indeed, a number established therapies may exert their effects at least in part through previously unrecognized angiogenic effects (26,27). In this context, COMP-Ang1 may prove to be an important addition to the therapeutic armamentarium.

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References


See the related article, “COMP–Angiopoietin-1 Ameliorates Renal Fibrosis in a Unilateral Ureteral Obstruction Model,” on pages 2474–2483.