How Much VEGF Do You Need?

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Vascular endothelial growth factor (VEGF) is a protein that all renal scientists and clinicians need to know about. There are recent comprehensive reviews of the complex biology of VEGF and its receptors (1) and of its role in the kidney (2). In summary, VEGF is a potent mediator of angiogenesis and of vascular permeability. This edition of JASN includes two new contributions on VEGF, one concerning the role of VEGF in the glomerulus, where it is abundantly and exclusively expressed by the podocyte (3), and the other addressing the importance of polymorphisms of the VEGF gene in the progression of chronic kidney disease (4).

The paper by Eremina et al. (3) reports the latest in an elegant series of experiments by Dr. Susan Quaggin’s group in Toronto exploiting podocyte-specific gene promoters to define the precise role of podocyte-derived VEGF in mice. They have shown previously that VEGF deletion from the podocyte causes perinatal death with complete failure of glomerular development, that podocyte-specific overexpression of VEGF results in podocyte proliferation and a collapsing glomerulopathy analogous to that seen in HIV infection, and that intermediate levels of VEGF (50% of normal) lead to proteinuria with endotheliosis similar to that seen in pre-eclampsia (5). The relevance of these findings to human disease is emphasized by the association of pre-eclampsia with high levels of a circulating inhibitor of VEGF (6) and by the occurrence of proteinuria in 64% of patients treated with high-dose anti-VEGF antibody for renal cancer (7). Now the Quaggin group shows that mesangial cells also require podocyte-derived VEGF: when the “dose” of podocyte-derived VEGF is further reduced (to around 25% of normal), mice die at 3 wk of age from renal failure and their glomeruli show a striking loss of mesangial cells (3). This “mesangiolysis” was preceded by loss of glomerular endothelial cells. We can conclude from this and previous work that the level of podocyte-derived VEGF influences all cell types in the glomerulus and that its disruption results in proteinuria. This suggests that restoration of podocyte-derived VEGF to normal should be a therapeutic aim in diverse forms of glomerular disease.

Doi et al. report (4) that gene polymorphisms that are associated with higher circulating levels of VEGF (due to an effect on RNA stability) are significantly more common in males with end-stage renal disease than in matched healthy controls. This implies that having too much circulating VEGF is bad for the kidneys, at least in males, and could support the observations regarding glomerular VEGF, where too much VEGF is also bad. However, as discussed above, in the glomerulus too little VEGF is also bad, and precise control to “normal” levels is desirable. Gene polymorphisms will affect VEGF production by all cells, not just locally in the kidney, and measurement of circulating levels is a crude way of assessing local renal or glomerular levels. In discussing their results, Doi et al. cite the paper by Kang et al. (8), which discusses apparent protection from progressive renal disease in females. However, far from supporting Doi et al.’s conclusions, the Kang paper actually suggested that VEGF induction by estrogen was responsible for the protection, i.e., more VEGF is good for the kidney! Data from animal models of glomerular injury are conflicting. For example, inhibition of VEGF by a specific RNA aptamer was associated with impaired glomerular repair in anti-Thy1.1 nephritis (9) and administration of exogenous VEGF enhanced endothelial repair in two rat models of glomerulonephritis (10); both these papers implied that VEGF is an important beneficial factor for glomerular repair. In contrast, another group reported (11) that, in experimental diabetic nephropathy, blockade of VEGF was beneficial, indicating that VEGF is deleterious.

Simplistic ideas of too much or too little VEGF may be misleading. VEGF exists in multiple isoforms produced by differential splicing of the same gene, and these isoforms have differing functions so that changes in isoform pattern, perhaps without change in total VEGF, could have complex effects. Furthermore, there is a recently described family of “inhibitory” isoforms that differ by only six amino acids from the “active” isoforms (12). These inhibitory isoforms are widely expressed, including in human podocytes (13), and most of the previous VEGF literature uses reagents that will not distinguish between active and inactive isoforms. The influence of VEGF could also be affected by changes in the expression of the various receptors through which it acts, as has been shown in one model of glomerular disease (14). VEGF acts in concert with the angiopoietins (15), with angiopoietin 1 being an apparent endogenous VEGF inhibitor, which is also abundantly expressed by human podocytes in vitro and in vivo (16,17), so that a change in the level of the inhibitor could influence VEGF action even if VEGF itself is not altered. Angiopoietin 2 synergizes with VEGF and is up-regulated in diabetic microvascular complications (18); this could account for the paradox mentioned above (11) that VEGF seems deleterious in diabetic glomerulopathy but beneficial in other forms of glomerular injury. Regarding therapeutic relevance, the concept of inappropriate angiogenesis as a feature of diabetic microvascular complications is supported by the exciting data of Yamamoto et al. (19), showing that the angiogenesis inhibitor tumstatin has impressive beneficial effects in experimental diabetic nephropathy.

VEGF is clearly essential in renal development, particularly in the assembly of the glomerulus. Its role in the physiology of the mature
kidney remains incompletely understood and there is controversy about its importance in kidney disease as a mediator of injury and/or of repair. In health, it is held in balance by tight control of its level of expression, by regulation of patterns of functionally-different isoforms, and by the co-expression of inhibitors. Identifying methods of restoring VEGF control, particularly in the podocyte, poses a major therapeutic challenge that could benefit patients with diverse forms of renal disease. Watch this space!

References


