VEGF Receptors and Glomerular Function

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In this issue of *JASN*, Sison *et al.*1 build on previous work from their group demonstrating the necessity of intact podocyte expression of vascular endothelial growth factor (VEGF) in preventing progressive glomerular endothelial damage and proteinuria in mice.2,3 This study adds to these findings by using compound transgenic mice to ask which glomerular cell and which VEGF receptors (VEGFRs) mediate this critical role of VEGF in maintaining normal glomerular function.1

With two major VEGFRs (R1 and R2) and three glomerular cell types (endothelium, mesangium, and podocyte), six possible combinations exist for creating tissue-specific knockouts of single VEGFRs. The authors narrow this considerable experimental complexity by observing no thrombotic microangiopathy in whole-body, VEGFR1-null mice. By contrast, whole-body, VEGFR2-null mice show renal changes mimicking thrombotic microangiopathy after excision of VEGF in the adult podocyte. The two most likely hypotheses to align these findings are (1) a paracrine effect of podocyte-secreted VEGF on mesangium or glomerular endothelium or (2) an autocrine effect whereby the podocyte secretes VEGF, which then activates VEGFR2 expressed by itself or nearby podocytes. Observing a lack of glomerular pathology in the podocyte-VEGFR2-null mouse, the authors then conclude, by process of elimination, that glomerular derangements arising from systemic VEGFR2 deletion are attributable to VEGFR2 expression in the glomerular endothelium (or possibly the mesangium) but not the podocyte. Although this line of reasoning leaves some room for dissent—for example, what role do the thyroid and liver derangements in the total-body VEGFR2 knockout play in the renal changes—the authors use two sensitive tools, a VEGFR2-reporter mouse and quantitative PCR, to assert further that VEGFR2 is not even expressed at appreciable levels in murine podocytes *in vivo*.

Examples of autocrine VEGF action exist in endothelium and hematopoietic stem cells,4,5 but the more conventional observation is that VEGF is produced by perivascular mural cells (vascular smooth muscle cells and pericytes) and provides a local trophic signal for nearby endothelial cells expressing VEGFR2. In this context, VEGFR1 is considered a modulatory receptor because it avidly binds VEGF but is phosphorylated only weakly.6,7 Endothelial cells, in turn, secrete pro-survival mitogens, such as PDGF, to recruit support cells and aid their survival. Indeed, global deletion of either PDGF-β or its receptor results in rudimentary glomeruli lacking mesangial cells.8,9 Although the identity of endothelium-derived, podocyte-supportive factors remains a mystery, this model posits a remarkable symbiosis in which glomerular endothelia and their support cells are engaged in a tonic molecular dialogue to maintain the unique microanatomy necessary for efficient filtration.

Evidence against an autocrine VEGF signaling loop in podocytes *in vivo* is at odds with previous data from independent groups that used cultured human and mouse podocytes.10–12 Of those reports, only one identified VEGFR2,10 whereas the other two implicated VEGFR1 as the critical receptor for VEGF responsiveness.11,12 Sison *et al.*1 note unpublished data that their total-body VEGFR1-null mouse did not copy the phenotype of podocyte-VEGFR1 knockouts and use this observation to support the idea that VEGFR2, not VEGFR1, is essential for VEGF signaling in the glomerulus.

The authors next show that excess podocyte-derived VEGF is also injurious to the filtration barrier, repriming their previous findings2 but with more detailed kinetics. These data are also consistent with a more recent report from a different group.13 Thus, it is probably safe to conclude that either deficient or excess podocyte-derived VEGF is bad for the filtration barrier. Both perturbations lead to proteinuria but by dichotomous pathobiological routes. Loss of VEGF leads to endothelial swelling and formation of microthrombi, hallmarks of endothelial injury. Conversely, excess glomerular VEGF induces a hypertrophic phenotype characterized by glomerular basement membrane thickening, accumulation of mesangial matrix, and, possibly, inflammatory infiltrates. Just as the proteinuria after bevacizumab therapy14 or soluble VEGF receptor 1 elevation15 seems to recapitulate intraglomerular VEGF depletion, it is attractive to speculate that sclerotic renal diseases characterized by high matrix deposition may, too, have roots in local VEGF imbalance.16,17

Numerous questions remain for further investigation. First, the chief finding of this study—that podocytes expressing VEGFR2 did not contribute to VEGF-mediated glomerular pathologies—was reached by using sophisticated mouse genetics to excise the first exon of this gene. Complete excision was confirmed by PCR. Nonetheless, other groups have detected VEGFR2 and phosphorylated VEGFR in podocytes in vivo by immunohistochemistry and by using VEGFR2-reporter mice.13,18 This disparity will need to be resolved. Second, the high expression of VEGFR1 reported in primary mouse podocytes will stimulate further study and may well lead to an appreciation of an autocrine role for podocyte-secreted VEGF in vivo. Third, other members of the VEGF signaling family—VEGF-B, VEGF-C, VEGF-D, placental growth factor, and the co-receptor neuropilin-1—may also modulate the glomerular biology of VEGF-A.

In summary, Sison et al.1 provide convincing evidence that mouse podocytes in vivo express scant, if any, VEGFR2 and that podocyte-derived VEGFR2 does not contribute to the pathologies observed when there is too much or too little glomerular VEGF. In doing so, they have further clarified the nature of intrarenal VEGF mechanisms and opened new avenues for investigation.

DISCLOSURES

None.

REFERENCES


HO-1 in Control of a Self-Eating Kidney

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Autophagy, from Greek meaning self-eating, refers to the degradation of macromolecules and organelles by the lyso-