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See the related article, "Partial Rescue of Glomerular Laminin α5 Mutation by Wild-Type Endothelial Cells Produce Hybrid Glomeruli," on pages 2285–2293.

Angiopoietin-2 and Glomerular Proteinuria

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The close spatial apposition between podocytes, fenestrated endothelia, and mesangial cells within the glomerulus has led to speculation that paracrine growth factors secreted by these cells are required to maintain structural and functional integrity of glomerular permselectivity in adults. This line of thinking has advanced the concept that disruption in the normal balance of these paracrine growth factors might give rise to proteinuric renal disease.

Angiopoietin-2 is an antiangiogenic growth factor that is secreted by endothelial cells during periods of active vascular remodeling and opposes the proangiogenic effects of angiopoietin-1 mediated through activation of the endothelial tyrosine kinase receptor Tie-2.[1,2] Previous studies have shown that angiopoietin-2 is expressed in developing glomeruli, where it is normally downregulated after birth[3] but is upregulated in a variety of experimental models of glomerular disease, including diabetes.[4–6] As such, angiopoietin-2 is a candidate growth factor that might play a role in destabilizing glomerular endothelia, causing a breakdown of glomerular permselectivity in proteinuric renal diseases.

In this issue of *JASN*, Davis *et al.*[7] address this question using an inducible transgenic strategy to promote prolonged (5 to 10 wk) ectopic expression of angiopoietin-2 in adult mouse podocytes. These mice develop low levels of nonselective proteinuria, indicating that angiopoietin-2 has the capacity to modify glomerular permselectivity. These observations raise two important questions that warrant further discussion: How does angiopoietin-2 cause proteinuria, and what is the significance of these findings for pathogenesis of glomerular disease?

Electron microscopic studies in these angiopoietin-2–overexpressing mice demonstrate glomerular endothelial apoptosis, but there is no evidence of glomerular capillary collapse or foot process effacement. These findings are consistent with the role of angiopoietin-2 in destabilizing endothelial cell integrity[8] but raise questions about the mechanism of proteinuria.

The authors provide evidence that the slit diaphragm protein nephrin, an essential component of the glomerular permselectivity barrier,[9] is downregulated in angiopoietin-2–overexpressing mice. On the basis of the observation that proteinuria has been described in the absence of foot process effacement, the authors argue that these changes in the expression of nephrin may give rise to a defect in slit diaphragm function without inducing a structural abnormality in podocytes. This is certainly a possibility that might be confirmed by more detailed ultrastructural analysis of the slit diaphragm. However, an alternative possibility is that the primary defect in these mice results from loss of glomerular endothelial integrity.

This speculation is consistent with Davis's observations of endothelial cell apoptosis and that expression of the angiopoietin-1/2 receptor Tie-2 is generally restricted to endothelial cells.[10] Furthermore, despite the important focus on podocyte biology in the pathogenesis of proteinuric renal disease,[9] there is emerging evidence that the specialized, fenestrated endothelia along the glomerular capillary also play a significant role in maintaining the charge selective barrier to proteinuria.[11,12] In addition, it could be argued that the low levels of proteinuria observed in the angiopoietin-2–overexpressing mice are more consistent with human microalbuminuria that is thought to reflect a primary defect in endothelial as opposed to glomerular epithelial function.[13]

The functional significance of these changes in angiopoietin-2–overexpressing mice for glomerular pathology is even less clear cut. For example, it is uncertain whether mild proteinuria without evidence of structural abnormalities in glomerular architecture will give rise to progressive renal disease. Long-term studies using this mouse model would establish whether this is the case. More important, however, is that it is unclear whether persistent, isolated expression of angiopoietin-2 in podocytes reflects the more complex environment of

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the glomerulus in disease states. There is evidence, for example, that glomerular expression of a key regulator of angiopoietin-2 function, vascular endothelial growth factor A (VEGF-A), is upregulated in some glomerular diseases (notably diabetic nephropathy) and downregulated in others.[14]

This is a critical issue because angiopoietin-2 has different effects on vascular remodeling and endothelial integrity depending on the coincident levels of VEGF-A.[10] On this basis, we might expect increased levels of angiopoietin-2 and VEGF-A in diabetic glomeruli to have different effects from those of angiopoietin-2 overexpression in other glomerular diseases. These issues can be addressed only by evaluating the impact of decreasing angiopoietin-2 expression in appropriate experimental models. However, these studies cannot be performed using germline *angiopoietin-2* null mice, because these mice die within the first 2 weeks of life with severe defects in the lymphatic system.[15] Studies in *angiopoietin-2* heterozygous null mice might be informative if gene dosage has an impact on angiopoietin-2 expression and function. Otherwise, we will have to wait for definitive studies in which the effect of temporally controlled, cell-specific deletion of *angiopoietin-2* is evaluated experimentally. It may be some time before we obtain a definitive answer to these questions, as the necessary floxed *Ang-2* mutants have yet to be generated.

DISCLOSURES

None.

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Hemoglobin Variability in Dialysis Patients

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Hemoglobin variability is the extent to which multiple measured hemoglobin values differ from each other. Variability may be assessed within the same patient or between patients in a group; in the context of clinical practice, it is generally the variability within a patient that is important, whereas for quality assurance purposes, both variability within patients (an index of individual stability) and between patients (an index of the extent to which values differ between patients) may be relevant. As West *et al.* observe in the current issue of *JASN*,[1] the adjustment of epoetins in the management of anemia in renal disease, whether done by clinical judgment, the use of simple clinical decision rules, or a more complex computer program essentially follows the principles of a negative-feed-

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