the interactions with VEGF will be particularly interesting, not least because VEGF inhibitors used clinically can induce proteinuria,12 as will comparisons with the effects of angiopoietin-1 and increased intracellular CAMP, both of which decrease glomerular endothelial cell permeability in vitro.11

The marked reduction of IFN-β1a on proteinuria also raises questions about the nature of the glomerular permeability barrier and the way it is compromised in disease. Until recently, there was a broad consensus that the podocyte slit diaphragm provided the principal barrier to proteins, but there is clear evidence that both the glomerular basement membrane13 and glomerular endothelial cells are also important, although much remains controversial, especially concerning endothelium, as recently debated in JASN.14 In these studies, it is interesting that the rate of passage of FITC-BSA through glomerular endothelial cells was less than half that through podocytes, although possibly a simple in vitro artifact of the experimental conditions. The lack of fenestrae would provide an obvious explanation except that Satchell previously reported11 that permeability to FITC-BSA did not change when fenestrae were induced by VEGF, although electrical resistance decreased rapidly.

There remains the most important question of all: Can the strikingly specific effect of IFN-β1a on proteinuria be applied clinically in patients with nephrotic syndrome? As the authors point out, IFN-α treatment in hepatitis C has been associated with reduced proteinuria in some patients in whom it is complicated by membranoproliferative glomerulonephritis.15 Whether due to IFN-α’s antiviral properties, as was assumed, or a renal effect cannot be discerned without much closer definition between the start of treatment and reduction of proteinuria. Again, the report of Satchell et al. should provoke food for thought and much, much more work.

DISCLOSURES
None.

REFERENCES

See related article, “Interferon-β Reduces Proteinuria in Experimental Glomerulonephritis,” on pages 2875–2884.

Aquaporin 1, Urea Transporters, and Renal Vascular Bundles

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Early theories of urinary concentration focused upon export of sodium by the thick ascending limb of Henle as the “single effect” that, when multiplied along the medullary axis, generates high osmolarity to extract water from the collecting duct. To account for the presence of a urea gradient and absence of

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active transport in the inner medulla, the “solute mixing” or “passive” hypothesis was proposed. By that scheme, osmotic removal of water from a water-permeable, salt-impermeable, descending thin limb of Henle (DTL) concentrates NaCl so that it can be subsequently delivered to the interstitium by diffusive efflux from the thin ascending limb of Henle. Urea, concentrated by water removal from the superficial collecting duct, diffuses to the interstitium in the inner medulla. That ingenious hypothesis was intellectually satisfying, amenable to mathematical simulation, and made predictions of transport properties that could be tested. Difficulties quickly arose, however, because the inner medullary DTL is salt-permeable, and the rate of diffusive solute entry into its lumen is high. Mathematical simulations fell short of predicting urinary osmolarities achieved by rodents. Recently, the NaCl content of the inner medulla was found to be insensitive to knockout of facilitated urea transport in the collecting duct. To date, we remain unable to confidently explain how urine is concentrated in the inner medulla. What is at fault? Are measurements of transport properties incorrect? Is knowledge of a fundamental physiological event missing? Or is failure to account for the grinding complexity of tubular–vascular relationships to blame?

Aquaporins and urea transporters have been identified, and isoform-specific antibodies have been generated to study their distributions. Computing power and software for digitizing serial tissue sections has been combined with immunostaining for nephron- and vascular-specific epitopes to clarify many unknown features and create impressive three-dimensional reconstructions that defy full presentation in two-dimensional journal pages. This detail has provided groundwork for increasingly sophisticated mathematical models that replace primitive notions of a well-mixed interstitium with localized exchanges between nephrons and vessels. Methods for measurement of transport properties of vessels and nephrons have not improved in parallel and paucity of such knowledge remains a brake on the interpretation of this otherwise impressive array of molecular and computational advancements.

In the above context, Zhai et al. provide us with an important revision concerning the distribution of aquaporin 1 (AQP1) and the UT-A2 urea carrier in the outer medulla. Murine immunohistochemistry shows that AQP1 expression is below detection in 90% of thin descending limbs of short looped nephrons (SLN-DTL) with type 1 epithelium. In contrast, SLN-DTL with type 2 epithelia and long-looped nephrons (LLN-DTL) outside vascular bundles express AQP1. SLN-DTL expressed the UT-A2 urea transporter over the last 28% to 44% of their length preceding the inner-outer medullary junction and largely reabsorbed by AQP2-expressing cortical segments. Stated simply, the lack of need to remove water from the SLN-DTL lumen in the outer medulla may account for omission of AQP1 expression.

A few words of interpretational caution are in order. Most importantly, immunohistochemistry cannot fully predict transport properties. The SLN-DTL is notoriously difficult to isolate and study by in vitro micropерfusion. Assuming its correct identification in hamsters, osmotic water permeability was found to be
high.16 Lack of AQP1 expression also does not predict the characteristics of parallel transport pathways; for example, paracellular water transport might be driven by osmotic or hydraulic pressure gradients. The pars recta has been variably described to actively secrete urea.10,17 If that truly occurs, and the rate is sufficiently high, an unlikely possibility is that the transepithelial urea gradient across the SLN-DTL favors export rather than uptake of urea.

One might hypothesize that transendothelial water transport is a bystander of no importance and that transport of nitric oxide is the primary role of AQP1 in vascular bundles. In that case it might serve to control exposure of pericytes in descending vasa recta to nitric oxide and direct nitric oxide from outside vascular bundles to react with its sink, the hemoglobin in red blood cells.

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REFERENCES


See related article, “Aquaporin-1 is Not Expressed in Descending Thin Limbs of Short Loop Nephrons,” on pages 2937–2944.

The Wages of Thin

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Isolated glomerular hematuria associated with a renal biopsy finding of excessively thin glomerular basement membrane (GBM) may occur as a familial or sporadic condition. Neither of the two terms commonly used to describe these patients, benign familial hematuria or thin basement membrane disease, is entirely satisfactory. Familial hematuria is not always benign, and benign hematuria is not always familial. Basement membrane thickening is a descriptive observation, rather than a specific diagnostic finding, and it is clear that several disorders that differ at the molecular level can be associated with this abnormality.1

The finding of thin GBM in a patient with isolated hematuria presents clinical and scientific challenges. The clinical challenges are to accurately forecast the patient’s outcome, to establish an appropriate monitoring plan that will allow early identification of deviation from the predicted disease course, and to provide reliable information for genetic counseling. The scientific challenges are to understand how the mutations in GBM proteins that produce GBM thinning alter glomerular cellular physiology and to elucidate the mechanisms that determine whether GBM thinning ultimately results in glomerulosclerosis.

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