high.\textsuperscript{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.\textsuperscript{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 via UT-A2 in the inner stripe. Finally, AQP1 may conduct nitric oxide.\textsuperscript{18} 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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DISCLOSURES

None.

REFERENCES


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.\textsuperscript{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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The article by Voskarides et al. in this issue of JASN highlights these clinical and scientific challenges. The study was undertaken to investigate the concurrence of thin GBM and FSGS in 20 members of 13 Cypriot families. The authors excluded mutations at the known FSGS loci ACTN4, TRPC6, and CD2AP; however, they were able to identify heterozygous mutations in COL4A3, the gene encoding the α3 chain of type IV collagen, in nine families and a mutation in COL4A4, which encodes the α4(IV) chain, in one family. Seven apparently unrelated families share a missense mutation in α3(IV) that changes glycine 1334 to glutamate, suggesting an ancestral founder effect. Three families were found to have a missense mutation in α3(IV) converting glycine 871 to cysteine. One of these 10 families carries both mutations; in this family, two children of heterozygous parents are compound heterozygotes for autosomal recessive Alport syndrome. The COL4A4 mutation consisted of a single-nucleotide deletion, creating a frameshift and consequent premature stop codon.

Barker et al. demonstrated in 1990 that mutations in COL4A5, the locus for the α5 chain of type IV collagen, cause the X-linked form of Alport syndrome, and Mochizuki et al. showed in 1994 that mutations in both alleles of COL4A3 or COL4A4 result in autosomal recessive Alport syndrome. In 1996, Lemmink et al. described a heterozygous COL4A4 mutation segregating with hematuria in a large family in which no affected member had developed ESRD. Since then, several dozen heterozygous mutations in COL4A3 and COL4A4 have been identified in individuals with familial hematuria associated with thin GBM (see references 11 to 18 of the article by Voskarides et al.2). The great majority of these subjects had normal renal function and normal urine protein excretion and negative family histories for ESRD. In approximately 60% of kindreds with autosomal dominant hematuria and thin GBM, the disease gene is not linked to COL4A3 or COL4A4. Some heterozygous mutations in COL4A3 and COL4A4 cause autosomal dominant Alport syndrome, with characteristic GBM thickening and lamellation.

The study by Voskarides et al. is not the first to describe the association of thin GBM and FSGS. Among 92 patients with hematuria and thin GBM, van Paassen et al. found FSGS in 11 (12%); all 11 patients had proteinuria in addition to hematuria. A striking finding of the study by Voskarides et al., however, was the high incidence of ESRD: 16 (19.5%) of 82 patients with adequate follow-up information. Such a high rate of renal failure has not been previously reported in patients with thin GBM. ESRD was a late event, occurring after age 50. In fact, almost half of the patients who were older than 51 yr had progressed to renal failure (16 of 35). In contrast, only two of 11 patients with thin GBM and FSGS reported by van Paassen et al. had elevated serum creatinine levels, and none had progressed to ESRD.

The report by Voskarides et al. is also not the first to document the coexistence of thin GBM, FSGS, and a COL4A3 mutation. Longo et al. found a nine-nucleotide deletion in COL4A3, resulting in loss of a Ser-Pro-Gly tripeptide in the collagenous domain of α3(IV) in a female patient with hematuria, proteinuria, thin GBM, and FSGS.

These observations suggest that when thin GBM due to COL4A3 and COL4A4 mutations is associated with FSGS, the renal outcome is more likely to resemble FSGS than thin base- ment membrane nephropathy. Hemizygous mutations in COL4A5 (X-linked Alport syndrome) and mutations affecting both alleles of COL4A3 or COL4A4 (autosomal recessive Alport syndrome) lead inevitably to glomerulosclerosis, although modifier genes (quantitative trait loci) may influence the rapidity with which glomerulosclerosis occurs. Are heterozygous mutations in COL4A3 and COL4A4 capable of producing glomerulosclerosis independent of the influence of modifier genes? Mice heterozygous for a COL4A3 deletion exhibit thin GBM and late development of proteinuria and glomerulosclerosis, so it seems that mutation in one COL4A3 allele can create conditions favoring glomerular scarring; however, this model was generated on the renal disease–prone SvJ/129 genetic background and may represent a better model for the disease occurring in the Cypriot families than for typical thin basement membrane nephropathy.

An intriguing ultrastructural finding of the study by Voskarides et al. was the presence of podocyte foot process effacement. Although this is a characteristic feature of FSGS, it is an unexpected finding in patients with hematuria associated with thin GBM, in which foot processes are typically well preserved. Perhaps heterozygous COL4A3 and COL4A4 mutations, coexisting with certain polymorphisms that influence foot process integrity, can produce foot process effacement, proteinuria, and eventual FSGS. For example, Tonna et al., in abstract form, described two patients who had hematuria, thin GBM, and proteinuria and carried the R229Q polymorphism in podocin, which has been proposed as a risk factor for development of proteinuria and FSGS. The R229Q polymorphism was not examined in the study by Voskarides et al.

The report by Voskarides et al. should not overturn the conventional notion that thin GBM, in patients with isolated hematuria and family histories that are negative for kidney failure, is usually associated with good renal outcomes. It is clear, however, that offering a benign prognosis is not appropriate when thin GBM is associated with proteinuria, foot process effacement, or a positive family history of kidney failure. Even those expected to have good outcomes deserve reexamination for development of proteinuria every 1 to 2 yr.

DISCLOSURES
None.

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