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See related article, “Aberrant Regulation of Planar Cell Polarity in Polycystic Kidney Disease,” on pages 1521–1532.

Progress in Progression?

Matthew D. Breyer

Biotechnology Discovery Research, Eli Lilly and Company, Indianapolis, Indiana

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Diabetic nephropathy is the major cause of ESRD in the United States.¹ Unfortunately, only angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers are regis-

tered for slowing the progression of diabetic nephropathy—but they do not halt progression.^{2–5} Given that diabetic nephropathy costs the health care system close to \$30 billion per year,⁶ one would hope to see a flurry of active clinical trials aimed at registering new therapies to slow progression. Instead, the sad truth is that only 31 interventional phase 2 or 3 trials are currently listed on ClinicalTrials.gov and most only study various angiotensin-converting enzyme inhibitor/angiotensin type 1 receptor blocker and renin inhibitor combinations. In striking contrast, there are 757 breast cancer and 989 lung cancer interventional survival trials and 175 interventional major adverse cardiac event outcomes trials in the same database.⁷

Numerous hurdles exist to closing this gap for diabetic nephropathy, including the identification of dynamic biomarkers that reflect not just the presence of disease but also the rate of loss of kidney function.^{8,9} Discovery of these biomarkers and novel therapies will require a deeper understanding of the pathophysiology of diabetic nephropathy. Because of limited access to diseased human kidney tissues, validated and clinically relevant animal models of diabetic nephropathy would significantly facilitate these efforts.

The laboratory mouse represents a unique experimental platform offering unprecedented genetic characterization and capability for genetic engineering.^{10–15} Characterization of diabetes and its associated renal phenotype in mice provides hope that the right mouse model will elucidate the pathophysiology of human diabetic nephropathy. The National Institutes of Health–sponsored Animal Models of Diabetic Complications Consortium (AMDCC) recently outlined three major phenotypes needed for a robust mouse model of diabetic nephropathy¹⁶: More than 50% decline in GFR over the lifetime of the animal; >10-fold increase in albuminuria compared with controls for that strain at the same age and gender; and pathology in kidneys showing advanced mesangial matrix expansion with or without nodular sclerosis and mesangiolysis, any degree of arteriolar hyalinosis, glomerular basement membrane (GBM) thickening by >50% over baseline, and tubulointerstitial fibrosis.

Of these criteria, only decline in GFR translates to a clinical end point successfully used in trials to register a drug for diabetic nephropathy—that being a doubling of the serum creatinine. Reductions in proteinuria have yet to be accepted as a surrogate end point for registration by regulatory agencies,¹⁷ and it is not practical to run a phase 3 trial on the basis of pathology, because this would require serial kidney biopsies to monitor an unproven therapy. Unfortunately, no mouse model of diabetic nephropathy thus far exhibits a progressive halving of the GFR. In fact, few mouse models exhibit convincing histopathologic changes of diabetic nephropathy or progressively increasing albuminuria. These deficiencies have significantly impeded our ability to link changes in histopathology to biomarker discovery and limit confidence that preclinical efficacy in mice will translate into meaningful clinical effects in humans.

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Correspondence: Dr. Matthew D. Breyer, Lead Generation Biology, Biotechnology Discovery Research, Eli Lilly and Company, 355 E. Merrill Street, Indianapolis, IN 46285. Phone: 317-655-6783; Fax: 317-277-2934; E-mail: breyer_matthew@lilly.com

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It is notable that only 20 to 40% of humans with diabetes develop nephropathy.^{18–21} A role for nephropathy-susceptibility genes could explain this heterogeneous outcome.^{22,23} Similar to human disease, comparison of diabetic nephropathy in different strains of inbred mice shows that some strains develop more robust nephropathy than others.^{24–26} Individuals within an inbred mouse strain are genetically identical, and the genetic differences between strains can be used to model human genetic diversity,^{11,27} so the differential susceptibility to nephropathy seen in various strains of diabetic mice supports the existence of genetic modifiers of susceptibility to nephropathy, including maternal health.²⁸

In this issue of *JASN*, Hudkins *et al.*²⁹ report the histopathologic picture of nephropathy in the diabetic black and tan and brachyuric (BTBR) ob/ob mouse is dramatically more severe than in the widely studied db/db C57BLKS mouse.³⁰ BTBR ob/ob mice exhibit impressive lesions, including nodular glomerulosclerosis and arteriolar hyalinosis—features of diabetic nephropathy rarely observed in other mouse models. Albuminuria is also of early onset and achieves robust levels >10-fold those observed in nondiabetic mice.

Unfortunately, several key features of human diabetic nephropathy are not present in this model. At the top of the list is the failure to detect an increased serum creatinine or a consistent increased blood urea nitrogen level. Measurement of creatinine and GFR in mice is notoriously difficult and complicated by high rates of endogenous creatinine secretion³¹ or altered creatinine production.³² Measurement of inulin clearance is technically feasible, but laborious serial measurements are difficult to implement.^{31,33} Still, the disconnect between the histopathologic picture in the BTBR ob/ob mouse and the largely unchanged blood urea nitrogen or creatinine level is puzzling. These mice also remained normotensive—a nearly invariant companion of progressive renal failure in humans.³⁴

It is also noteworthy that the GBM is only 18% thicker in diabetic BTBR ob/ob mice compared with nondiabetic BTBR mice despite that ob/ob mice are markedly hyperglycemic. Introggression of the mutant obese leptin allele (*Lep^{ob}*) from C57BL/6 mouse onto the BTBR background was originally shown to confer more severe insulin resistance and hyperglycemia,^{35,36} possibly contributing to worsening nephropathy in BTBR *versus* C57BL/6 ob/ob mice. In contrast, the hyperglycemia in the C57BLKS db/db strain is greater than in BTBR ob/ob mice, yet the renal histopathology of the BTBR ob/ob mice is more severe. This, together with the modest increase in GBM thickening in the BTBR ob/ob kidney, suggests that factors other than hyperglycemia contribute to renal disease in this strain of mouse; pertinently, there was no evidence an autoimmune process.³⁷

The BTBR ob/ob mouse represents a significant addition to the models of murine diabetic nephropathy; however, it remains unclear how closely the pathogenesis of kidney disease in this model mirrors that of human diabetic nephropathy. Were we to have better understanding of the pathogenesis of human diabetic nephropathy, generation of authentic mouse

models could be accelerated dramatically. Although yet to be forthcoming, identification of human genetic variants that confer major risk for diabetic nephropathy would also allow construction of a better mouse. In the absence of this information, the development of clinically translatable mouse models of this disease will continue to be an iterative process relying on careful empiric observations and development of better tools to define progression of kidney failure.

DISCLOSURES

None.

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See related article, "BTBR Ob/Ob Mutant Mice Model Progressive Diabetic Nephropathy," on pages 1533–1542.

Dietary Fructose and Elevated Levels of Blood Pressure

Matthew R. Weir

Division of Nephrology, University of Maryland School of Medicine, Baltimore, Maryland

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Hypertension is a multifactorial disease in which both genetic and environmental factors play a role in the slope of changing

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Correspondence: Dr. Matthew R. Weir, Division of Nephrology, University of Maryland School of Medicine Medical Center, 22 S. Greene Street, Room N3W143, Baltimore, MD 21201. Phone: 410-328-5720; Fax: 410-328-5685; E-mail: mweir@medicine.umaryland.edu

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