

Progress in Progression?

Matthew D. Breyer
Biotechnology Discovery Research, Eli Lilly and Company, Indianapolis, Indiana

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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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Diabetic nephropathy is the major cause of ESRD in the United States. Unfortunately, only angiotensin-converting enzyme inhibitors or angiotensin type 1 receptor blockers are regis-
It is notable that only 20 to 40% of humans with diabetes develop nephropathy.1,4,8–21 A role for nephropathy-susceptibility genes could explain this heterogeneous outcome.2,22,23 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.

REFERENCES


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