Linking Metabolism and Immunology: Diabetic Nephropathy Is an Inflammatory Disease

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Diabetic nephropathy is one of the most important concerns in nephrology, as well as in medicine at large. Rapidly increasing rates of diabetes throughout the developed world represent an emerging epidemic with profound consequences. This epidemic is likely to drive previously unforeseen rates of vascular target organ complications. As survival from acute cardiovascular complications continues to improve, management of chronic complications such as kidney disease assume ever-larger roles. Diabetes is the leading cause of end-stage renal disease in the United States, accounting for approximately 45% of incident cases and 55% of prevalent cases in the present decade (1,2). End-stage renal disease in diabetes, particularly type 2, has been described as a medical catastrophe of worldwide dimensions (3). So what can be done to reduce the burden of diabetic nephropathy? Available therapies shown to prevent or slow progression should be broadly applied. These therapies include strict glycemic control and treatment of hypertension with inhibitors of the renin-angiotensin system (4–10). However, in recent clinical trials in which care was presumably optimized, renoprotection was far from complete. And, in reality, controlling hyperglycemia and hypertension in usual care settings is often more challenging than in clinical trials. Hence, even more effective therapies that interrupt mechanisms of kidney damage induced by hyperglycemia and/or hypertension are urgently needed.

The bench-to-bedside paradigm of translational research is that two-way street where the clinic and the laboratory meet. For clinicians and patients, this is an opportunity to obtain more effective therapies. For scientists, discovery and technology can be applied to a meaningful clinical problem. Two elegant papers in this issue of the journal illustrate the hope of translational research (11,12). The paper by Kelly and colleagues utilized a model of diabetes and hypertension produced by administration of streptozotocin to a rat transgenic for the renin gene (11). Groups of diabetic and control rats were treated, or not, with an inhibitor of protein kinase C–

PKC–

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ruboxistaurin. Moreover, tubulointerstitial macrophage accumulation, osteopontin expression, and pro-fibrotic injury markers were returned to control levels by this treatment.

These observations have important translational implications. First, ruboxistaurin has already moved into clinical trials for diabetic nephropathy, as well as for other microvascular complications (16). The data reported by Kelly and colleagues provide further scientific rationale and biologic plausibility for how this drug may ameliorate kidney disease even when hyperglycemia and hypertension are not well controlled, a situation all too common in the clinical realm (11). Second, on the scientific side, mechanisms of PKC–

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activation and its actions provide insight into how a classic metabolic disease, diabetes, is linked to an immunological signature, inflammation. PKC is composed of at least 12 isoforms which signal a number of cellular responses, including oxidative stress, activation and/or expression of inflammatory mediators, cellular proliferation, and tissue fibrosis (16). Various PKC isoforms, particularly PKC–

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, are activated in diabetes. Hyperglycemia, acting through generation of cellular diacylglycerol, is a predominant PKC activator, but advanced glycation end products (AGE) and other metabolic products may also participate in activation (16).

Intracellular adhesion molecule (ICAM)-1 is expressed on the surface of a number of cell types in response to PKC activation (17–19). ICAM-1 promotes inflammation by enhancing leukocyte infiltration and adherence. In a complementary paper, Chow and colleagues illustrate yet another dimension of the link between diabetes and inflammation by examining the role of ICAM-1 in glomerular and tubulointerstitial disease in db/db mice (12). These mice spontaneously develop hallmarks of type 2 diabetes, including hyperglycemia, hyperinsulinemia, and obesity. Their kidney disease is manifest by albuminuria, decreased GFR, glomerular hypertrophy and cellularity, and tubular atrophy and fibrosis. The conventional db/db mice were compared with a
strain deficient in ICAM-1 using a gene knockout strategy, as well as to lean heterozygote controls. In db/db mice, ICAM-1 expression was increased in glomeruli and tubules, along with a marked increase in macrophage infiltration. ICAM-1 deficiency decreased most manifestations of kidney disease and macrophage accumulation in db/db mice. Further in vitro studies showed that rat macrophages cultured with either a high level of glucose or an AGE-modified protein produced increased amounts of active TGF-β. Conditioned media from AGE-stimulated macrophages caused cultured rat proximal tubular epithelial cells to produce ICAM-1. These data suggest that macrophage stimulation by hyperglycemia or AGE may augment pro-fibrotic responses of resident kidney cells and enhance their expression of ICAM-1. Thus, the paper by Chow and colleagues strongly implicates ICAM-1–induced inflammation in the pathogenesis of glomerular and tubulointerstitial disease in a model of type 2 diabetes and provides evidence that cellular responses are directly induced by metabolic disturbances.

In conclusion, diabetic nephropathy can be viewed as an inflammatory disease triggered by disordered metabolism. PKC-β, a cellular signaling mediator activated by hyperglycemia and associated metabolic disturbances, has been targeted for a novel therapeutic class that has moved into clinical trials for diabetic nephropathy. The rationale for targeting an inflammatory mechanism, ICAM-1, is emerging and may lead to yet another therapeutic class. If findings such as these can be fully translated into clinical treatments, hopes for better strategies to reduce the burden of diabetic nephropathy may be realized.

References