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EDITORIAL

Diabetic nephropathy: It's in the numbers

Progressive renal disease is characterized by glomerulosclerosis, tubulointerstitial fibrosis and vascular sclerosis. Tubulointerstitial fibrosis is assumed to be merely secondary to glomerular sclerosis with resulting ischemia to the remaining nephron segment. Regardless of its etiology, interstitial fibrosis is recognized as an accurate marker of progressive decline in glomerular filtration rate (GFR) in chronic renal diseases, including diabetic nephropathy [1, 2]. This may relate in part to the larger sample of nephrons examined by assessing the tubulointerstitium, compared to the relatively smaller number of glomeruli in human renal biopsies. Previous studies of the pathology of human diabetic nephropathy from the Minnesota group and others have largely focused on the glomerular lesions. These important studies have defined key functional-structural relationships of mesangial matrix expansion and decreased capillary filtration surface area with renal dysfunction [3, 4].

New data also have emerged to demonstrate the pliability of sclerosing kidney tissue. Cure of patients' diabetes mellitus by pancreas transplant has even demonstrated, by repeat renal biopsies, the possible regression of early glomerular as well as tubulointerstitial lesions [5]. Sclerosis is not an end-stage static condition; rather it is a dynamic process with ongoing cell turnover and remodeling of extracellular matrix. The responsiveness of glomerular lesions to various experimental interventions has been intensively investigated. However, these approaches have been limited by the lack of optimal rodent models. Diabetic mice and rats do develop mesangial expansion, but true Kimmelstiel-Wilson nodules or interstitial fibrosis and progressive renal failure are lacking. A recently launched NIDDK-funded consortium has as its primary objective the development of a better mouse model of diabetic nephropathy. In this issue of *Kidney International*, Katz et al show exciting new data emphasizing the importance of the interstitial lesion [6]. These findings underscore the urgent need for better tools to study the pathogenesis of interstitial lesions in diabetic nephropathy.

These timely new data expand our insights into the dynamics of the tubulointerstitial injury mechanisms in type I diabetes. Diabetes is broadly considered a microvascular disease. Indeed, these morphometric studies demonstrated a decrease in abundance of peritubular capillaries. Recent studies have pointed to a primary importance of peritubular capillary density, possibly modulated by vascular endothelial derived growth factor (VEGF) or other angiogenic factors in various progressive renal diseases [7]. Future studies may demonstrate whether these interstital microvascular lesions are causal or consequential in the development of interstitial injury in diabetic nephropathy.

In the study by Katz et al, lymphocytes and macrophages were increased in late stages of interstitial fibrosis, as expected. Macrophages have diverse roles in tissue injury, mediating repair and remodeling after injury. Persistence of activated macrophages is tightly correlated with progressive fibrosis in the kidney. However, macrophage infiltration is dissociated from fibrosis in the absence of $\alpha_v\beta_6$ integrin, an epithelial-expressed local activator of transforming growth factor-β (TGF-β), supporting that a parenchymal cell profibrotic response may be necessary to effect fibrosis [8]. Thus, macrophages and tubular epithelial cells together may contribute to these later stages of fibrosis. The balance of extracellular matrix (ECM) synthesis versus degradation is influenced by matrix metalloproteases and their inhibitors, the tissue inhibitors of matrix metalloproteases (TIMPs), and the plasmin/plasminogen activator system and its inhibitor, plasminogen activator inhibitor-1 (PAI-1). The net effect may be remodeling and repair or interstitial fibrosis [9]. The potential role of these modulators of ECM metabolism in established diabetic interstitial lesions is yet to be determined.

An unexpected and interesting finding is the qualitative difference observed in the earliest interstitial lesion versus more established lesions. The elegant, detailed morphometric analyses indicate an increase in interstitial cell fractional volume at early stages, preceding the accumulation of interstitial collagen. This is in stark contrast to the time course of the diabetic mesangial lesion, where the expanded mesangial area is largely due to increased matrix accumulation rather than hypercellularity. The increased cell component of the interstitium was not explained by infiltrating lymphocytes and macrophages, which were rare in the early lesion. The precise nature of the interstitial cells in the early lesion has not been identified in the current study, but will provide much interesting fuel for further studies. These cells could possibly represent myofibroblasts. In addition to infiltrating macrophages, interstitial myofibroblasts are postulated to play a key role in interstitial fibrosis. These activated

interstitial cells are a major source of collagen synthesis, and increased expression of α-smooth muscle actin (SMA), a marker of myofibroblasts, predicts progressive renal dysfunction both in human and experimental renal disease. The source of myofibroblasts is a topic of controversy. Bone marrow-derived or potential renal stem cells may give rise not only to interstitial cells but also to regenerating parenchymal cells.

Epithelial-mesenchymal transformation (EMT) is another possible mechanism for generation of interstitial myofibroblasts [10]. This seamless plasticity of cells changing from epithelial to mesenchymal phenotypes exists during early development. Data indicate that EMT also may occur in the adult after injury. Injured tubular epithelial cells can change phenotype both in vivo and in vitro, with de novo expression of a fibroblast-specific protein (FSP1), and possibly migrate into the interstitium as myofibroblasts. The components of the surrounding matrix regulate this process [11]. If indeed these early infiltrating cells are myofibroblasts, the process of their emergence may be a key target for early interventions to thwart progressive structural injury in the interstitium.

In summary, these detailed studies employ sophisticated morphometric analyses in a well-characterized population of diabetic patients. The exciting results indicate varying pathogenic mechanisms at different stages of diabetic nephropathy, pointing to potential new targets for the interstitial damage that is an important component of progressive disease in diabetic patients. The studies further suggest the possibility of different mechanisms in early stages of interstitial versus glomerular scarring processes, with potential alternate therapeutic strategies to be considered for the early interstitial events.

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REFERENCES

1. Schainuck LI, Striker GE, Cutler RE, Benditt EP: Structural-functional correlations in renal disease. II. The correlations. *Hum Pathol* 1:631–41, 1970
2. Taft JL, Nolan CJ, Yeung SP, *et al*: Clinical and histologic correlations of decline in renal function in diabetic patients with proteinuria. *Diabetes* 43:1046–1051, 1994
3. Osterby R, Gundersen HJG, Horlyck A, *et al*: Diabetic glomerulopathy: Structural characteristics of the early and advanced stages. *Diabetes* 32 (Suppl 2):79–82, 1983
4. Mauer SM, Steffes MW, Ellis EN, *et al*: Structural-functional relationships in diabetic nephropathy. *J Clin Invest* 74:1143–1155, 1984
5. Fioretto P, Steffes MW, Sutherland DE, *et al*: Reversal of lesions of diabetic nephropathy after pancreas transplantation. *N Engl J Med* 339:69–75, 1998
6. Katz A, Caramori MLA, Sisson-Ross S, *et al*: An increase in the cell component of the cortical interstitium antedates interstitial fibrosis in type 1 diabetic patients. *Kidney Int* 61:2058–2066, 2002
7. Kang DH, Kanellis J, Hugo C, *et al*: Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol* 13: 806–816, 2002
8. Munger JS, Huang X, Kawakatsu H, *et al*: The integrin alpha v beta 6 binds and activates latent TGF beta 1: A mechanism for regulating pulmonary inflammation and fibrosis. *Cell* 96:319–328, 1999
9. Eddy AA: Molecular basis of renal fibrosis. *Pediatr Nephrol* 15: 290–301, 2000
10. Al-Awqati Q, Oliver JA: Stem cells in the kidney. *Kidney Int* 61:387–395, 2002
11. Okada H, Inoue T, Suzuki H, *et al*: Epithelial-mesenchymal transformation of renal tubular epithelial cells in vitro and in vivo. *Nephrol Dial Transplant* 15 (Suppl 6):44–46, 2000