Diabetic nephropathy is the single biggest cause of renal failure in industrialized nations [1]. In its early stages diabetic nephropathy is typified by renal hypertrophy, increased glomerular filtration rate (GFR) (i.e., hyperfiltration), and increased urinary albumin excretion [2, 3]. Later, as renal injury progresses, urinary albumin excretion further increases and GFR progressively declines, accompanied by pronounced mesangial expansion, glomerulosclerosis, tubular atrophy, and interstitial fibrosis [2, 3]. It has been presumed that early hypertrophic changes in the mesangium, endothelium [4], and podocytes are integral to the subsequent development of more severe renal histopathologic changes. Nevertheless, the mechanisms initiating and regulating the functional changes in these renal cells remain incompletely characterized, and whether cell hypertrophy is a necessary antecedent to the progression of diabetic nephropathy has not been conclusively demonstrated.

Results from the Diabetes Control and Complications Trial (DCCT) and United Kingdom Prospective Diabetes Study (UKPDS) have clearly demonstrated that the occurrence of diabetic complications, including nephropathy, are critically determined by glucose control [5, 6]. It has also been demonstrated that hyperglycemia, per se, can result in hypertrophy of mesangial cells in vitro [7–11]. Those studies further suggest that hyperglycemia alters the expression of cyclin/cyclin-dependent kinase inhibitors, including p27Kip1 and p21cip1, important regulators of the cell cycle contributing to renal cell hypertrophy in diabetic state [7–11].

Regulation of the cycle occurs via cyclins and their inhibitors at multiple points along the sequential progression of the cell from rest (G0) into G1, S, G2, and M phases [12, 13]. In G1, the cell prepares for DNA duplication by increasing protein synthesis. This phase is accompanied by an increase in cell volume [14]. The cell then enters S phase, duplicating its DNA. After preparing for mitosis in the G2 phase, the cell divides into 2 daughter cells (M phase), completing the cell cycle. Progression through the cell cycle is regulated by a series of protein kinases, including cyclins and cyclin-dependent kinases [15]. In the mature kidney, the majority renal cells remain in the quiescent G0-phase [16, 17]. However, in the diabetic state, renal mesangial cells, podocyte, and tubular epithelial cells are stimulated to actively enter the cell cycle, but arrest in G1 with associated cell hypertrophy [11, 18, 19]. Previous studies using cultured cells demonstrate an increase in cyclin/cyclin-dependent kinase inhibitors, including p27Kip1, p21cip1 contributing to the G1 arrest and renal hypertrophy in hyperglycemia [8, 10, 20, 21].

Does hyperglycemic-dependent renal hypertrophy contribute to diabetic nephropathy? In this issue of Kidney International, Wolf et al reported targeting disruption of the p27Kip1 gene attenuates albuminuria, glomerular sclerosis and mesangial, endothelial and podocyte hypertrophy in a streptozotocin induced diabetic mouse model [22]. Together with previous studies these findings provide an in vivo link between renal hypertrophy and the early changes of diabetic nephropathy. Nevertheless, these short-term studies do not address whether blocking renal hypertrophy can forestall the progression of diabetic nephropathy to end-stage renal disease (ESRD).

It is important to note that only a subset of patients with diabetes mellitus develop nephropathy, and clinical observations linking diabetic renal hypertrophy to ESRD are conflicting. Some clinical observations suggest renal hypertrophy is a predictor of increased creatinine [23], whereas other studies could not distinguish histopathologic correlates of renal hypertrophy in diabetic patients prone to versus resistant to nephropathy [24]. Thus, genetic factors may profoundly influence the progression of diabetic nephropathy in humans [25, 26]. Similarly, recent findings suggest genetic heterogeneity of diabetic nephropathy in inbred mice [27–29]. Further studies of p27kip1 knockouts bred onto mouse strains susceptible to more advanced renal lesions should provide additional insight into the contribution of renal hypertrophy to renal disease in diabetic mellitus and help determine if, in diabetes, big really is bad.

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