Mesangial Cell Responses to High Glucose Levels and the Development of Diabetic Glomerulosclerosis

N. S. Nahman, jr.
The Ohio State University. Columbus OH 43210, USA

Type I diabetes results in the development of diabetic glomerulosclerosis in approximately 50 % of patients [1]. From 1986-1989, the US Renal Data System reported that 33 % (44,672 patients) of all patients with end-stage renal disease had diabetes, making diabetic glomerulosclerosis the most common cause of end-stage renal disease in the United States [1,2]. Although therapeutic approaches to the management of diabetic nephropathy, such as control of hypertension[3], dietary protein restriction [4,5] and the use of angiotensin converting enzyme inhibitors [6,7] may have a favorable effect on the course of the disease, the basic pathophysiologic mechanisms that underlie the development of diabetic glomerulosclerosis remain unclear. The purpose of this review is to examine one aspect in the pathophysiologic development of diabetic glomerulosclerosis, specifically the effects of elevated glucose levels on mesangial cell function and how such alterations may contribute to mesangial expansion and the development of glomerulosclerosis.

The pathology and pathophysiology of diabetic glomerulosclerosis

Diabetic glomerulosclerosis is characterized by mesangial expansion secondary to the accumulation of extracellular matrix protein [1]. The development of mesangial expansion in type I diabetics represents a very advanced histologic lesion [8,9] and correlates with significant clinical nephropathy [8]. In one of the most important reports to delineate the correlation between the histopathology of diabetic glomerulosclerosis and clinical nephropathy, Mauer showed that in renal biopsy specimens from 45 patients with type I diabetes, mesangial expansion correlated strongly with albuminuria, hypertension and a decrease in the glomerular filtration rate [8]

Histopathologically, the extracellular matrix proteins reported to accumulate in the glomerular mesangium from humans with diabetic nephropathy include fibronectin, laminin and collagen types IV and V [10,11]. In the mesangium of diabetic rats,an increase in collagen and fibronectin have been demonstrated [12]. In addition, the accumulation of extracellular matrix protein in diabetes is not restricted to the kidney, but appears to be a systemic process [13-16]

The pathophysiologic mechanisms that lead to the accumulation of mesangial matrix protein in diabetes are unclear, but several possible pathways have been suggested. Hostetter proposed that hyperglycemia, with its associated volume expansion and glomerular hyperperfusion, results in glomerular capillary hypertension and the subsequent development of glomerulosclerosis [17]. In support of this contention is the demonstration that diabetic rats with glomerular hypertension develop glomerulosclerosis, and that this process can be prevented when glomerular capillary hypertension is ameliorated by treatment with a converting enzyme inhibitor [18].

In addition to glomerular hyperperfusion, hyperglycemia may induce alterations in mesangial cell function either directly, or via non-enzymatic glycosylation of the proteins of the mesangium with subsequent effects on mesangial cell function. Both processes can result in changes in mesangial cell proliferation and matrix protein homeostasis. These processes are considered in the following discussion.

Correspondencia: Dr. N. S. Nahman, Jr.
Division of Nephrology.
Department of Internal Medicine.
N 210 Means Hall.
1654 Upham Dr.
The Ohio State University.
Columbus, OH 43210.
USA.

Mesangial cell proliferation and matrix protein synthesis under elevated glucose conditions

Elevated glucose levels inhibit cultured mesangial cell proliferation [19-21] .This effect is specific for gluco-

se and does not appear to be the result of hypertonicity [19]. The mechanism by which elevated glucose inhibits mesangial cell proliferation is unclear, although glucose-induced stimulation of antiproliferative cytokines [21] or the attenuation of cellular responses to proliferative cytokines [20] may play a role.

In addition to inhibiting cellular proliferation, elevated glucose levels also stimulate extracellular matrix protein synthesis in both mesangial and endothelial cells [19,22,26]. The induction of matrix protein synthesis by glucose appears to be specific for glucose and, in rodent mesangial cells, could not be induced with osmotic controls [24]. Using human mesangial cells, we demonstrated both an increase in mesangial cell fibronectin and fibronectin mRNA after exposure to hypertonic mannitol[19], however, the levels of both mRNA and protein were less than those observed from cells exposed to high glucose conditions. The reasons for the differences in cellular responses to osmotic stimuli observed in these two studies is unclear, but may in part be due to known differences between cultured rat and human mesangial cells [10, 12 27].

The mechanisms by which elevated glucose increases matrix protein synthesis could include a direct stimulatory effect of glucose or its metabolites on intracellular messengers or cytokines known to regulate matrix protein production. This could include a glucose-induced increase in the absolute rate in which cells synthesize a protein, as shown in a diabetic mouse model [28]. Alternatively, specific mediators of matrix protein synthesis may be induced by high glucose levels. Delineating all of the compounds that regulate matrix protein synthesis is beyond the scope of this review, however, the results of studies examining the synthesis of the matrix glycoprotein fibronectin, can serve as examples of this approach.

Demonstrating that elevated glucose levels regulate a known mediator or mediators of fibronectin synthesis could provide a model for how high glucose ultimately increases fibronectin synthesis in a given system. For example, rat mesangial cells exposed to high glucose levels have been shown to up-regulate the expression and activity of the intracellular messenger enzyme, protein kinase C. These observations were associated with an increase in mesangial cell fibronectin production [24] and are consistent with our own data demonstrating that stimulating protein kinase C activity with phorbol ester results in an increase in fibronectin gene expression and fibronectin protein levels [29]. Thus these studies suggest that high glucose stimulates the intracellular synthesis of protein kinase C, which in turn up-regulates fibronectin synthesis.

In a similar approach, dissecting the mediators of glucose induced matrix protein synthesis could include a more detailed examination of the specific response elements present in the promoter region on the gene of each matrix protein. Again, using fibronectin as an example, the fibronectin gene promoter is known to contain a TGF response element, suggesting that stimuli that increase TGF may induce fibronectin gene expression. In addition, the cyclic AMP response element, also present in the promoter region of the fibronectin gene, bears striking homology to the phorbol ester response element [30]. This observation suggests a putative role for protein kinase C in mediating mesangial cell fibronectin expression and is compatible with the work demonstrating the stimulatory effect of high glucose on protein kinase C activity and fibronectin synthesis [24].

The above studies provide a crucial link between environmental stimuli (such as hyperglycemia) and matrix protein gene expression, by demonstrating the induction by glucose, of intracellular mediators known to interact with specific response elements present on matrix protein genes. This approach may prove to be a useful tool for further dissection of mechanisms of glucose-induced increases in matrix protein synthesis.

Elevated glucose levels and mesangial cell matrix remodelling mechanisms

Alterations in extracellular matrix remodelling mechanisms could also account for the accumulation of glomerular matrix proteins observed in diabetic glomerulosclerosis. In this regard, mesangial cells have been shown to synthesize enzymes capable of degrading the proteins of the extracellular matrix [31-33], including a neutral proteinase[33] and matrix metalloproteinases 1, 2 and 3 [34, 35].

These enrymes are secreted in a latent form[36] and may be regulated by soluble inhibitors [33,36,37]. The tissue inhibitor of metalloproteinase is produced and secreted by mesangial cells [33,38] and appears to beup-regulated under high glucose conditions [38]. no period providing evidence that elevated ambient glucose concentrations may slow the degradation of matrix protein components by stimulating the production of degradative enzyme inhibitors.

Elevated glucose concentrations also lead to non-enzymatic glycosylation of matrix proteins and the formation of stable advanced glycosylation end products (AGEs) [39]. In patients with diabetes, AGEs accumulate systemically [39] and their accumulation appears to parallel the loss of renal function in patients with diabetic nephropathy [40]. Mesangial cells may contribute to maintaining the integrity of the extracellular matrix by regulating the accumulation of AGEs [41].

Mesangial cells have been shown to express receptors for AGEs and bind, internalize and metabolize AGE modified protein [41]. In addition, AGE modified matrix protein induces functional changes in mesangial cells, including a decrease in proliferation and an increase in fibronectin production [41].

In summary, diabetic nephropathy is characterized by mesangial accumulation of extracellular matrix protein, resulting in anatomic disarray and renal functional impairment. The accumulation of matrix proteins in diabetic nephropathy may, in part, be mediated by mesangial cell dysfunction induced by elevated ambient glucose conditions. High glucose levels may alter mesangial cell function by directly inducing matrix protein synthesis or inhibiting matrix protein degradation. In addition, the formation of advanced glycosylation end products may alter mesangial cell function and contribute to the development of diabetic nephropathy.

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