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Review

Pathogenesis of diabetic kidney disease: Review of cellular aspects of renal lesions

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Diabetic kidney disease (diabetic nephropathy) is the most common cause of end-stage renal failure disease in some parts of the world, and is associated with increased cardiovascular mortality and morbidity. This review, based on database resources, was undertaken to review the extracellular and intracellular mechanisms involved in the progression of this disease. Growth factors and, signaling pathways, in addition to, hemodynamic and cellular changes play an important role in the pathogenesis of nephropathy from high glucose level to more complicated biochemical abnormalities. As a conclusion, the understanding of the pathophysiology of diabetic kidney is very complex and heterogeneous and remains poorly understood. But it is important to consider oxygen reactive species and glucose level as the key elements to terminal renal failure or to arrest the progression of this serious disease

Key words: Diabetic, nephropathy, cellular and hemodynamic changes.

INTRODUCTION

Diabetes is a disease in which insulin deficiency leads to elevated blood glucose. It is commonly accompanied by hypertension, which places patients with diabetes at high risk for developing long-term complications such as diabetic nephropathy and which leads to a chronic, progressive deterioration in renal function. Diabetic nephropathy is the most common cause of chronic renal failure and end-stage kidney disease in the United States and is linked with increased cardiovascular mortality and morbidity (Valmadrid et al., 2000). Diabetic nephropathy has been classically diagnosed on the basis of proteinuria in excess of 0.3 g per 24 h. This phase has been referred to as overt nephropathy or macro-albuminuria. However, pioneering studies carried out in Europe have shown that, prior to this stage, tiny amounts of albumin in the urine, undetectable by routine methods, appear and are prognostic of the later progress of proteinuria in both type 1 (Mogensen and Christensen, 1984; Viberti et al., 1982) and type 2 (Mogensen, 1984) diabetic patients, a stage called microalbuminuria or incipient nephropathy. Albuminuria could be a result of many factors like, structural abnormalities.

It is generally believed that elevated urine albumin in diabetic nephropathy is chiefly glomerular in source. For albumin to appear in the urine, it must cross the glomerular filtration barrier. Elevated intraglomerular pressure, loss of negatively charged glycosaminoglycans in the cellular basement membrane and the subsequent enlargement of basement membrane pore size, all lead to albuminuria (Figure 1). Other microscopic abnormal-lities include thickening of the glomerular cell membrane, accumulation of mesangial matrix material and an increase in the number of mesangial cells. As the disease progresses, there is an inverse relationship between the degree of mesangial enlargement and glomerular filtration (Osterby et al., 1990).

Mesangial enlargement is accompanied by a decrease in the surface area available for capillary filtration, which determines glomerular filtration rate. Changes in tubulo-interstitial cells, including thickening of tubular cellar membranes, tubular atrophy, interstitial fibrosis and arteriosclerosis, have also been described. Interstitial expansion is accompanied by an increase in glomerular filtration, albuminuria and mesangial enlargement. It has been hypothesized that the accumulation of protein in the cytoplasm of proximal tubular cells triggers an inflammatory response, thereby leading to the observed

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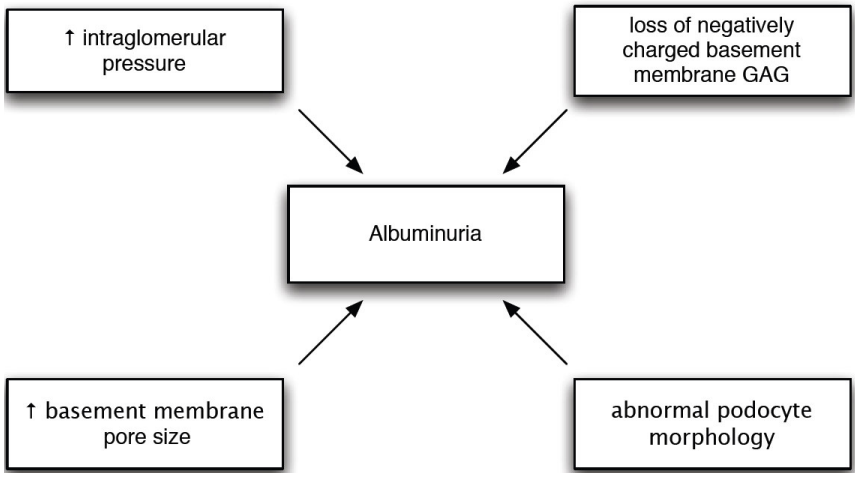

Figure 1. Structural abnormalities have an effect on albuminuria.

tubulointerstitial lesions (Gilbert and Cooper, 1999).

Recent studies have indicated that podocytes may also participate in increasing the degree of proteinuria and the development of glomerulosclerosis (Pavenstadt et al., 2003). Podocytes are terminally differentiated epithelial cells consisting of a cell body from which numerous processes extend and branch. These processes divide sequentially until the terminal foot process lies on the glomerular basement membrane. The podocyte, via the foot processes, supplies structural support for glomerular capillaries, buffers intraglomerular pressure and is the last obstacle in the barrier to protein movement across the glomerulus into the urinary space. Like the basement membrane, the podocyte is shrouded by negatively charged molecules, which repulse anionic proteins such as albumin.

The negative charges also help to keep open the slit diaphragm, which is the structure that bridges the gap between adjacent foot processes. The slit diaphragm is necessary to prevent proteinuria and slit diaphragm proteins like nephrin play critical roles in preventing the escape of protein into Bowman's space. In both human and experimental diabetic animals, podocyte morphology is abnormal (White et al., 2002). It is therefore very likely that abnormalities in podocytes in diabetic patients contribute to proteinuria and ultimately, to glomerulosclerosis. Whether these represent primary lesions in the initiation of diabetic proteinuria or occur as a secondary response to other aspects of the disease process is unclear.

Important cellular events in the development of nephropathy

Irregularities in many cellular processes have been described in the kidney cells of experimental animals and diabetic patients (Figure 2). Most research has focused on glomerular endothelial and mesangial cells. Direct effects of hyperglycemia itself, glycation processes, formation of advanced glycation products and increased modification through the polyol and hexosamine pathways have all been implicated in the pathogenesis of diabetic nephropathy. Recently, it has been proposed that the main abnormality linking all of these pathways is oxidative stress, which represents a disorder in the mitochondrial electron transport chain resulting in the elevated production of reactive oxidative stress molecules

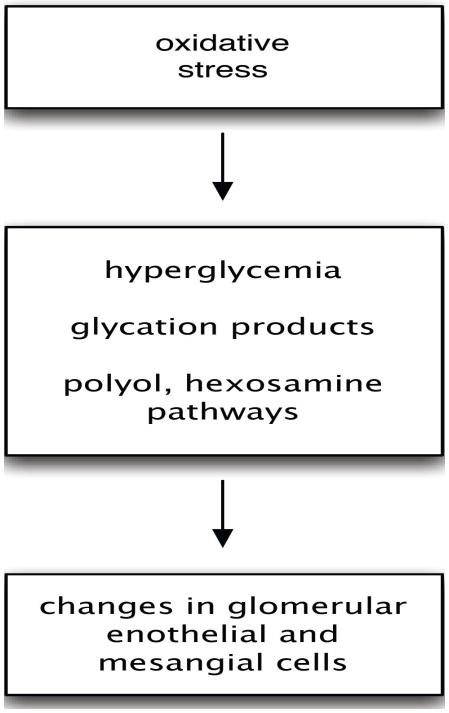

Figure 2. Effect of cellular factors in the development of nephropathy.

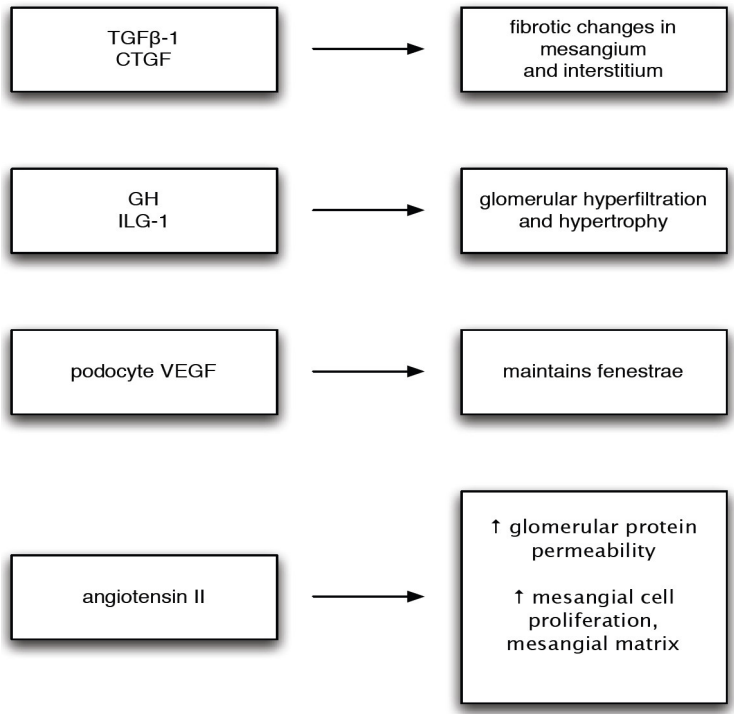

Figure 3. Elevated levels of growth hormone related to glomerular hyperfiltration and hypertrophy.

that stimulate each of the above pathways (Brownlee, 2001).

The increased activity of a wide variety of growth factors (Figure 3) has also been observed in diabetes (Gnudi et al., 2003). Growth factors like transforming growth factor ß-1 and connective tissue growth factor may cause fibrotic changes in the mesangium and interstitium. Similarly, elevated levels of growth hormone and insulin like growth factor-1 appear to be related to glomerular hyper filtration and hypertrophy. A vascular endothelial growth factor, which is synthesized by the podocyte, has a major role in maintaining the fenestrae in glomerular endothelial cells (fenestrae; are specialized plasma membrane microdomains in endothelial cells that are involved in vascular permeability). In addition to its pressor role, which leads to specific constriction of the efferent glomerular arterioles, angiotensin II increases glomerular capillary permeability to proteins and its growth effects stimulate mesangial cell proliferation and accumulation of the mesangial matrix. A number of isoforms of protein kinase C, diacyl glycerol, mitogenic kinases and transcription factors are all stimulated in diabetic nephropathy (Gnudi et al., 2003) by elevated glucose levels and increases in intraglomerular pressure.

Hemodynamic in diabetic nephropathy

Data from experimental models of diabetes show that intraglomerular pressure is elevated, due to constriction of efferent glomerular arterioles (Zatz et al., 1986). This increased pressure leads to glomerular injury by both direct pressure effects and indirectly by increasing proteinuria (Figure 4). Recently, *in vitro* studies have shown that stretching of human mesangial cells stimulates p38 mitogen-activated protein kinase via a protein-kinase-C-dependent pathway, which in turn activates transforming growth factor-ß1 and fibronectin expression (Gruden, 2000). Accordingly, elevated intraglomerular pressure may also intensify cellular and biochemical alterations.

Genetic influences

Only subsets of patients with diabetes develop nephropathy, suggesting that this disease has a genetic component. This is supported by findings from twin and family studies in type 1 diabetes. Numerous studies have shown that individuals with diabetic nephropathy have higher rates of hypertension, dyslipidemia, insulin resistance and premature cardiovascular disease than diabetics with normal albumin excretion. A greater tendency toward these disorders has also been found among first-degree relatives of patients with diabetic nephropathy, compared to first-degree relatives of diabetic patients without nephropathy (Fogarty et al., 2000).

Thus, the genetic factors contributing to the develop-

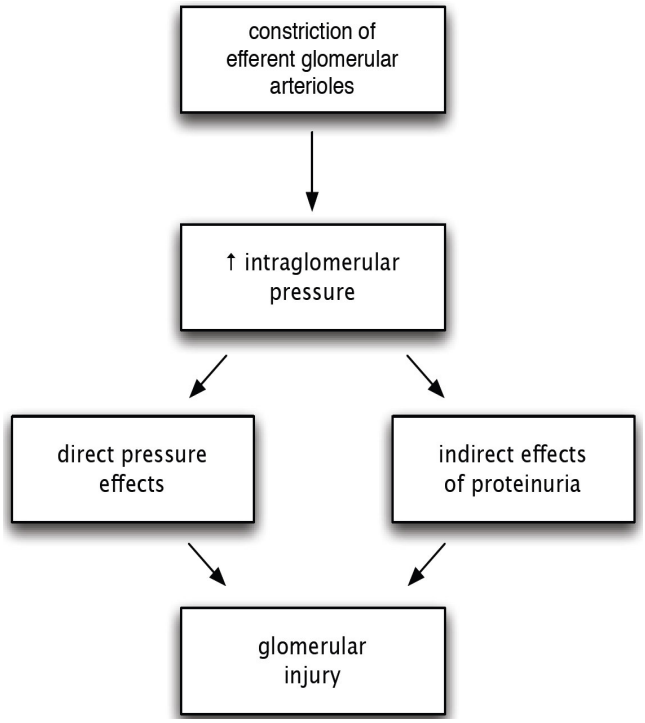

Figure 4. Hemodynamic effect on glomerular unit.

ment of nephropathy also appear to confer a vulnerability to cardiovascular risk factors and premature cardiovascular events. Unfortunately, many of the studies seeking genes responsible for diabetic nephropathy have been limited by inadequate power of the study and the failure to carefully characterize the control, non-nephropathic groups. Thus, much current literature in this area is contradictory (Merta, 2003).

RENAL CHANGES AND PRIMARY PATHWAYS IN THE DEVELOPMENT OF DIABETIC NEPHROPATHY

Alterations in renal extracellular matrices in DN

Similar changes in glomerular ultrastructure are seen in type 1 and 2 diabetes (Osterby, 1992; Osterby et al., 1993). The glomerular basement membrane increases in density, while the extracellular matrix of the mesangium broadens. These basement membrane changes, together with glomerular hyperfiltration, which raises glomerular hydrostatic pressure, induces microalbuminuria. It is the mesangial alterations that play the primary role in decreasing renal function in DN (Steffes et al., 1989).

As the mesangial matrix broadens, it impinges on glomerular capillaries, decreasing the surface available for filtration and restricting or occluding the lumen. Decreasing glomerular function is highly correlated with the extent of these transformations in both types of diabetes, even though they appears to be more heterogeneity in type 2 diabetes (Dalla et al., 2000). In type 2 diabetic patients, there is a strong fact (but not type 1) that concomitant nondiabetic renal disease which influences the GFR by nephron mass reduction and compensatory increase in the size of remnant nephrons. As a result some of the normoalbuminuric patients have advanced lesions whereas some microalbuminuric patients have mild lesions (Nosadini et al., 2000; Gambara et al., 1993).

Tubulointerstitial fibrosis takes place in DN, as well as glomerulosclerosis, but these have been much less thoroughly studied. However, there is a strong correlation between diminished creatinine clearance and both interstitial and mesangial expansion (White and Bilous, 2000), and the mortality rate is increased if interstitial fibrosis is present (Bohle et al., 1991). In this regard, diabetic nephropathy is similar to other renal disorders in which advanced loss of renal function correlates with an increase in interstitial fibrosis (Risdon et al., 1968). Interstitial fibrosis in DN may be triggered by the same factors causing glomerular fibrosis, but may also be influenced by events originating in the glomerulus (Gilbert and Cooper, 1999).

Increases in the mesangial matrix and thickening of the glomerular basement membrane (GBM) in DN may arise due to increases in the levels of proteins that are normally present in these structures and/or accumulation of proteins not normally present. It is evident that some mesangial proteins, such as collagen I and III, are expressed only in the late phases of glomerulosclerosis. They are more closely related to the progression of Kimmelstiel-Wilson nodules than with the diffuse expansion of the mesangial matrix, which takes place primarily in the early phases of the disease. Other proteins, such as fibronectin, are present in the normal mesangium but increase in the expanding mesangium. The principal components of the normal GBM are type IV collagen, the most prominent component, as well as laminin, entactin, and proteoglycans (Zeisbert et al., 2002).

The decrease in heparin sulfate proteoglycans that is observed as the disease progresses contributes to the development of proteinuria (Vernier et al., 1992), as the glycosaminoglycan chains normally create an anionic charge border to protein diffusion across the GBM (Kanwar et al., 1980). Genetically caused diabetes mellitus occurs in db/db mice (a model for type 2) and type 1 diabetes can be induced in mice and rats using streptozotocin (STZ).

These models create nephropathy with alterations in glomerular extracellular proteins that are similar to those seen in human DN, including increased glomerular expression and accumulation of a type IV collagen and fibronectin, while the corresponding heparan sulfate proteoglycan content is decreased (Park, 1997; Koya et al., 2000). As in human DN, hyperglycemia is believed to be the principal factor for initiating these alterations.

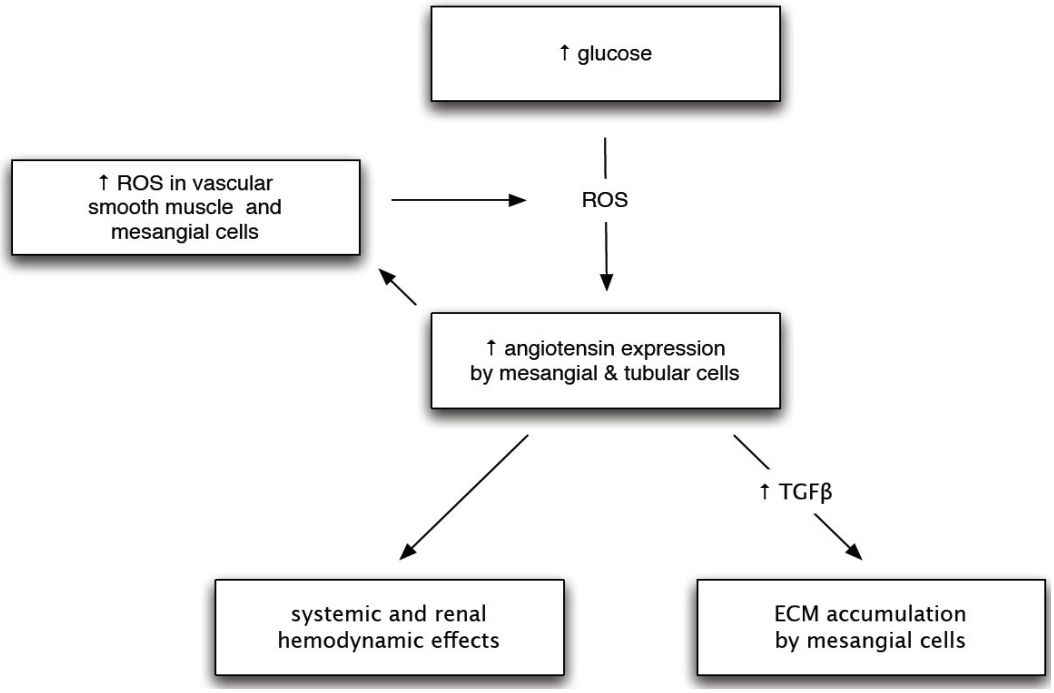

Figure 5. Effect of angiotensin in the pathogenesis of diabetic nephropathy.

THE PRINCIPAL FACTORS AFFECTING MATRIX PROTEIN EXPRESSION IN DN

Angiotensin II

That stimulation of the renal renin-angiotensin system (RAS) may play a role in the pathogenesis of DN has been suggested by the results of several studies that found that both angiotensin- converting enzyme (ACE) inhibitors and angiotensin-receptor- I antagonists can attenuate DN (Ritz and Orth, 1999; Remuzzi et al., 1993). The entire RAS is available in the kidney (Wolf and Ziyadeh, 1997). *In vitro* investigations show that angiotensin expression in mesangial and tubular cells is increased as a feedback response to elevated glucose (Singh et al., 1999). This response appears to be mediated, at some level, by reactive oxygen species (ROS) and later by activation of p38 MAPK in tubular cells (Figure 5) (Hsieh et al., 2002). AngII, the functioning octapeptide derived from angiotensinogen, also stimulates the generation of ROS in vascular smooth muscle cells (Ushio-Fukai-M et al., 1996) and MC (Jaimes et al., 1998).

Because the ROS pathway activates NF-αB, which stimulates further angiotensinogen expression, ROS generation could participate in forming a positive feedback loop (Brasier et al., 2000), maintaining elevated activity of the RAS in DN. Elevated AngII is also generated in hypertension, a disturbance that frequently accompanies diabetes and accelerates the progression of DN (Jandeleit-Dahm and Cooper, 2002). Despite the fact that AngII is connected with both systemic and renal hemodynamic effects, it also has nonhemodynamic effects on glomerular cells, particularly MCs. AngII has been proven to increase ECM accumulation by MCs, primarily by stimulating TGF-β expression (Wolf, 1998).

The mechanism by which AngII transactivates TGF-β has been shown to be similar to that for hyperglycemia. Both transactivate the growth factor gene via two AP-1 regulatory elements. This activation appears to be PKC- and p38 MAPK-dependent (Weigert et al., 2002).

Transforming growth factor (TGF-β)

Many studies have shown that hyperglycemia causes an increase in TGF-β expression at both the mRNA and protein levels in experimental and human diabetes (Weigert C et al., 2002, Park IS, 1997), as well as in cultured MCs (Kolm V et al., 1996, Kolm-Litty V et al., 1998). TGF-β is involved in both the early and later phases of DN. All TGF-β isoforms, including TGF-β1, β2, and β3, as well as the TGF-β type II receptor, have been shown to be increased in diabetic rat models (Isono M et al., 2000). Increased production of TGF-β in patients with diabetes and DN has also been documented (Sharma K et al., 1997). In addition, numerous *in vitro* studies have indicated that expression of TGF-β is elevated in various renal cell types cultured under high-glucose conditions or with advanced glycation end products (AGE) (Ziyadeh FN

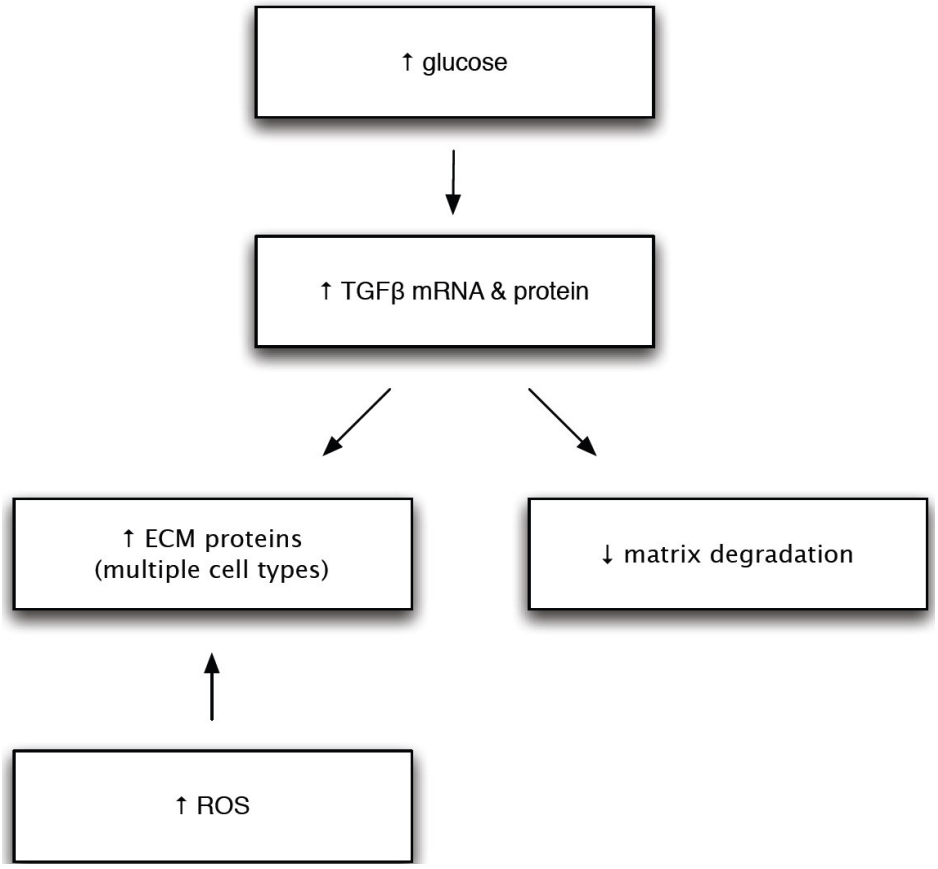

Figure 6. The role of transforming growth factor-β in albuminuria.

et al., 1998, Chen S et al., 2001). At the present time, it is clear that TGF-β is the essential cytokine mediating the synthesis of different ECM proteins in MCs, epithelial cells, renal interstitial cells, and fibroblasts (Figure 6) (Kolm V et al., 1996, Nakamura T et al., 1992, Border WA and Noble NA, 1994). Furthermore, TGF-β affects matrix-degrading enzymes by repressing the synthesis of collagenases and increasing the production of TIMP and plasminogen activator inhibitor 1(PAI-1) (Border WA andNoble NA, 1994). In addition, TGF-β affects local matrix accumulation by upregulating a variety of ECM receptors (80, 85). The main signaling pathway of TGF-β is the Smad pathway (Böttinger EP and Bitzer M, 2002), which is activated in the STZ-diabetic mouse model. TGF-β also activates other pathways, such as MAPK (ERK, SAPK/JNK, and p38 MAPK) (Chin BY et al., 2001). TGF-β also brings about PKA activation in MC by a mechanism that includes the degradation of the inhibitory peptide of PKA (PKI)(Wang L et al., 1998).

ROS pathways stimulating matrix accumulation

Although further *in vitro* and *in vivo* confirmatory studies are required, present data strongly suggest that intracellular ROS, derived either from an AGE-RAGE interaction or glucose metabolism (Brownlee, 2001; Ha and Lee, 2000), have a direct role in the overproduction of ECM proteins and that this can be neutralized by antioxidants (Catherwood et al., 2002). It has been shown that ROS activate the PKC, MAPK and JAK-STAT pathways (Suzuki et al., 1997; Scivittaro et al., 2000), which induce the activation of redox-sensitive transcription factors, including NF-αB, AP-1, STAT, and Egr-1 (Ohba et al., 1994). These increase the transactivation of genes coding for cytokines such as TGF-β and CTGF, which upregulate ECM protein expression (Park et al., 2001).

Conclusion

The principal factors underlying the metabolic, biochemical and structural changes described here to occur in diabetic nephropathy patients are elevated glycemic levels and disordered intrarenal hemodynamics. These factors, influenced by local stimulation of RAS, can modulate renal function and affect downstream signaling pathways involved in diabetic nephropathy. This review will give a comprehensive understanding of mechanisms underlying diabetic nephropathy and will potentially trans-

slate into more refined treatment and prevention of albuminuria.

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