

Matrix Remodeling in Diabetic Nephropathy

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Diabetic nephropathy (DN) remains the leading cause of vascular morbidity and mortality in diabetes patients. Despite the progress in understanding the diabetic disease process and advanced management of nephropathy, a number of patients still progress to end-stage renal disease (ESRD). The underlying mechanism still needs to be clarified. Gaseous signaling molecules, so-called gasotransmitters, such as nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H₂S), have been shown to play an essential role in the development, progression, and ramification of DN depending on their availability and physiological actions. Although the studies on gasotransmitter regulations of DN are still emerging, the evidence revealed an aberrant level of gasotransmitters in patients with diabetes.

diabetic nephropathy

nitric oxide

carbon monoxide

1. Structural Protein (Collagen and Elastin) Regulation by Gaseous Molecules in Diabetic Nephropathy (DN)

During the development and progression of DN, glycation of the extracellular matrix (ECM) leads to the deposition of the ECM proteins in the mesangium, renal tubulointerstitium, and glomerular basement membranes (GBMs) ^[1]. Increased expression of ECM causes thickening of the GBM as well as the tubular basement membrane (TBM) and expanded mesangial matrix, leading to glomerulosclerosis and tubulointerstitial fibrosis ^[1]. Therefore, the accumulation of ECM proteins plays an important role in the development of DN.

The ECM glycoproteins that are increased in DN include collagen, laminin, fibronectin, and proteoglycans. Initially, glycation affects the interactions of collagen with the cells and other matrix components, but the most damaging effects are caused by the formation of glucose-mediated intermolecular cross-links, which greatly hampers the critical flexibility and permeability of the tissues and reduces turnover. The principal perturbations of ECM components in the GBM include upregulation of collagen IV ($\alpha 3$ and $\alpha 4$ chains), V, VI, laminin, and fibronectin, while there is a downregulation in heparan sulfate proteoglycans ^{[1][2][3]}. In addition, the changes in the ECM proteins of the tubulointerstitial compartment include elevated expression of collagen I and small leucine-rich (SLR) proteoglycans, viz., decorin and biglycans ^[4]. On the other hand, mesangial matrix changes comprise increased expression of collagen I, III, IV ($\alpha 1$ and $\alpha 2$ chains), V, VI, laminin, fibronectin, and SLR proteoglycans ^{[1][2]}. As collagen and elastin are the two major structural protein components in the ECM, the changes in these proteins and the role of gaseous molecules in DN are discussed below.

1.1. Collagen and Gaseous Molecules in DN

The collagen family of proteins is the most abundant in humans and provides the framework for the most vulnerable tissues in the kidney, such as the renal basement membrane. The optimal functioning of the kidney tissues is dependent on the integrity of their supporting framework of collagen.

An earlier study demonstrated that the exogenous application of a low dose (250 ppm) of CO in a glass exposure chamber inhibits the development of renal fibrosis in obstructive nephropathy by attenuating the induction of key ECM proteins, such as type 1 collagen, in mice [5]. Moreover, it has also been demonstrated that the low dose of CO treatment inhibits progressive chronic allograft nephropathy by reducing collagen 1 in rats [6].

Previous reports showed that arginine increases plasma levels of nitrate/nitrite in diabetic patients [7]. Arginine has been shown to increase nitrates and exhale NO in both control as well as insulin-dependent diabetes mellitus (IDDM) patients [8]. Moreover, it was also indicated that L-arginine inhibits collagen accumulation in the kidney [9], heart [10], and GBM [11] of diabetic mice and also in advanced-stage glycosylation end products (AGEs) [11][12]. As the AGEs are reported to quench NO [13], arginine supplementation may appear to be beneficial to improve endothelium-dependent vasodilation by inhibiting AGE-mediated mitigation of NO-dependent relaxation [7].

A previous study revealed that H₂S donors, such as sodium hydrosulfide (NaHS), inhibit the renal fibrosis of obstructive nephropathy by attenuating the accumulation of collagen fibrils in the renal interstitium in rats [14]. Supplementation with H₂S has been shown to mitigate renal damage in hypertensive models by reducing blood pressure, proteinuria, and oxidative stress and inhibiting excessive collagen type I and collagen type III deposition [15][16][17]. In a murine model, H₂S supplementation has also been reported to prevent HHcy-induced glomerulosclerosis by regulating collagen [18]. Recently, H₂S has been demonstrated to ameliorate renal tissue fibrosis and the development of DN by inhibiting excessive collagen deposition in STZ-induced diabetic rats [19].

1.2. Elastin and Gaseous Molecules in DN

Elastin is a 70 kDa glycoprotein, and it constitutes the central core of elastic fibers. Elastin provides support and elasticity, which are important for many tissues and organs, such as the blood vessels, heart, skin, lungs, and uterus. The cross-linked and random-coiled structure of elastin renders the capacity of the elastic network to stretch and recoil. A unique glycoprotein microfibril, Fibrillin, has been recently identified to be associated with elastic fibers in compliant tissues [20]. Elastin is not considered to be a primary component of the capillary BM. Notably, the capillary tuft of the glomerulus is devoid of elastin, and it is present only in the mesangial stalk as well as in afferent and efferent arterioles [21]. This may be one of the reasons why the capillary BM of the glomerular tuft undergoes remodeling expansion and causes thickening of its BM when exposed to intra-glomerular hypertension, which occurs early in the natural history of T2D.

It has been reported that NO donors, such as S-nitrosoglutathione, facilitate a multi-fold increase in the synthesis and deposition of ECM protein elastin in a dose-dependent manner [22]. Another study exhibited that NO delivery dose-dependently stimulates tropoelastin synthesis to increase vascular elasticity [23]. These studies indicate that NO supplementation may ameliorate the adverse effect of renovascular remodeling during DN.

A recent study demonstrated that H₂S might attenuate vascular calcification by upregulating elastin levels through inhibition of the Stat3/CAS signaling cascade during hyperglycemia [24]. Homocysteine (Hcy), which induces elastolytic proteinase in VSMCs [25], has been reported to cause arterial stiffness by modulating the elastin/collagen ratio, resulting in hypertension [26] and diabetes [27]. Moreover, HHcy has been shown to decrease H₂S [28] and increase MMPs, which induce the degradation of elastin [29][30][31]. In the hypertensive and diabetic mouse models, HHcy-induced activation of MMPs was shown to be normalized by oral or intraperitoneal H₂S supplementation, leading to the prevention of renal damage [32][33][34][35]. Therefore, H₂S treatment could be a promising therapeutic approach to prevent renovascular damage by attenuating the MMP-mediated degradation of elastin.

2. Proteinases and Their Inhibitors' (MMPs and TIMPs) Regulation by Gaseous Molecules in DN

Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that are involved in the breakdown and remodeling of ECM components [36]. The abnormal activity of these endopeptidases is associated with a variety of vascular diseases, including cardio-pulmonary and renovascular [37][38]. Research findings suggest that hyperglycemia abnormally affects the expression and activity of MMPs in diabetic kidneys [39].

Currently, 28 different types of MMPs have been discovered in vertebrates [40]. Of these, at least 23 mammalian MMPs have been recognized, and these MMPs were further subdivided into different groups [41][42]. Structural analysis revealed that MMPs are multi-domain proteins that generally consist of a prodomain, a catalytic domain, a hinge region, and a hemopexin domain in the case of collagenases, gelatinases, and membrane-type MMPs (MT-MMPs). MMPs are generally secreted as nonfunctional pro-MMPs, which are activated either by cleavage of the prodomain by different proteinases, such as plasmin and MT-MMPs, or by oxidation of reactive cysteine within the prodomain [43][44]. MT-MMPs are a typical class of MMPs with a broad spectrum of activities and remain anchored to the cell surface by the transmembrane domains. MT-MMPs are believed to predominantly regulate proteolytic activities within the pericellular microenvironment due to their presence on the cell surface [45].

The expression of several MMPs and tissue inhibitors of metalloproteinases (TIMPs) in the nephron of various species has already been discussed elsewhere [1][46]. Sub-cellular localization of protein expression of several MMPs, including MMP-2, -3, -9, -10, -11, -14 (MT1-MMP), -15 (MT2-MMP), TIMP-2, and TIMP-4, have been reported and summarized in human kidney tissues [47][48]. As the MMPs play a major role in the glomerular ECM degradation and turnover, the alteration in expression and activity of the MMPs influences the intra-renal extracellular matrix composition [49][50]. Renal hypertrophy, which is developed early in T1D, predominantly occurs in individuals who develop DN later and is implicated in poor renal prognosis [51][52][53]. As the unusual ECM accumulation is one of the hallmarks of DN, it is plausible that changes in MMP expression and activation may contribute to DN, especially to the advent of renal hypertrophy. It is noteworthy that, apart from the direct role in ECM turnover, MMPs secrete or activate numerous growth factors, viz., tumor necrosis factor- α , pro-transforming growth factor- β , insulin-like growth factors, and heparin-binding-epidermal growth factor, which are involved in renal hypertrophy, tubular cell proliferation, renal scarring, and kidney fibrosis [54][55][56][57].

The role of MMPs in DN is critical in the earlier phases of the disease progression when increased matrix accumulation, the release of pro-fibrotic growth factors, and altered cell motility disrupt the glomerular and tubular architectures. Therefore, an in-depth understanding of the role of MMPs in the pathogenesis of DN is essential for the therapeutic intervention of MMPs in preventing and mitigating diabetic kidney disease.

2.1. Gelatinases (MMP-2 and MMP-9)

In numerous studies, it has been shown that dysregulation in intra-renal gelatinase plays an important role in kidney diseases. For example, it has been demonstrated that intra-renal MMP-2 expression is increased in AL-amyloidosis [58] and human renal carcinoma [59]. It has also been shown that MMP-2 is essential for instigating the transformation of renal tubular cell epithelium–mesenchymal transformation, which is a critical step in forwarding the progression of renal interstitial fibrosis in several kidney diseases, including DN [60][61]. In reality, over-expression of MMP-2 in renal proximal tubular epithelial cells was demonstrated to develop the characteristic pathologic changes of chronic kidney disease [62].

A contrasting relationship between MMP-2 dysregulation and DN was revealed. The decreased expression and/or proteolytic activity of MMP-2 and increased activity of the MMP-2 inhibitor, TIMP-2, were observed in renal tissues of the rodent diabetic models [63][64][65]. On the other hand, both the increase as well as a decrease in MMP-2 production or activity have been observed in rodent mesangial cells cultured under hypoglycemic conditions [66]. However, in human studies, an increase in MMP-2 association and activity was evidenced in DN [67][68]. In addition, the upregulation of MT5-MMP, which contributes to the activation of MMP-2, was observed in diabetic kidney tissue in humans [69]. An elevation in urinary MMP-2 concentrations and/or MMP-2 activity was shown in albuminuric patients having T1D compared to that of controls as well as non-albuminuric patients [70][71].

In a murine model of T2D, MMP-9 expression in the kidneys of mice that developed nephropathy was increased compared to controls [72]. In addition, an elevated level of MMP-9 has been observed in the urine of patients with T2D and DN, and the level of MMP-9 was found to be increased in congruence with the extent of albuminuria [73][74]. Injury or apoptosis in the podocyte has been identified as a part of renal disease processes characterized by the failure of the filtration barrier [75][76]. Cultured podocytes have been shown to produce MMP-2 and MMP-9, which can be influenced by various cytokines, growth factors, and hyperglycemic conditions [77]. Recently, hyperglycemia-induced apoptosis and depletion of podocytes have been demonstrated in murine T1D and T2D models [78].

Interestingly, podocytopenia occurs early in diabetic patients with T1D and T2D [79][80][81]. A hypothetical reduction in podocyte density could be achieved by glomerular basement membrane expansion, secondary to MMP-induced alterations of the ECM turnover. While coupled with hyperglycemia-induced podocyte injury and increased apoptosis of the podocytes, a distinct increment in membrane permeability would result, leading to diabetic albuminuria. The appearance of podocytes in the urinary sediment of diabetic patients having albuminuria compared to the absence of podocytes in the normoalbuminuric T1D patients corroborates this hypothesis [82]. These patients' plasma MMP-9 levels were significantly correlated with the number of urinary podocytes.

Therefore, these findings indicate that diabetes-associated gelatinase dysregulation may perturb podocyte integrity and permeability of the glomerular basement membrane [82].

It is noteworthy to mention that the CO-releasing molecule CORM-2 was found to inhibit MMP-2 activities in the alveolar epithelial cells [83]. NO has been shown to modulate the cytokine (IL-1 β)-induced expression of MMP-9 and also regulate the enzymatic activity of MMP-9 in a rat mesangial cell culture [84]. It has also been demonstrated that NO regulates MMP-9 expression in rat mesangial cells through a post-transcriptional mechanism [85]. NO-mediated post-transcriptional regulation of MMP-9 was also evidenced in rat mesangial cells [86]. In addition, an increased NO level has been shown to modulate MMP-2 and -9 activation in the diabetic fetoplacental unit [87].

2.2. Tissue Inhibitors of Metalloproteinases (TIMPs)

Decreased serum levels of TIMP-1 and TIMP-2 have been observed in patients with T2D and DN compared to diabetes alone or non-diabetes chronic renal failure [88]. On the contrary, in the younger T1D patients with normal kidney function, TIMP-1 or TIMP-2 concentrations remained unchanged compared to that of age-matched non-diabetic controls [70]. Differences in the disease severity and duration or differences in the pathophysiology of T1D and T2D may explain these contrasting clinical observations.

Elevated plasma levels of HO-1 and TIMP-4 have been demonstrated as potential markers of pathogenesis in T2DM with tuberculosis [89]. It has been demonstrated that NO regulates TIMP-1 in rat mesangial cells [84]. Moreover, H₂S supplementation by GYY4137 has been shown to regulate TIMP-1 expression in mouse kidney mesangial and glomerular endothelial cells [90]. A recent study showed that H₂S intervention alleviates renal fibrosis and may play a protective role against the development of DN by regulating TIMP-1 in STZ-induced diabetic rats [19].

3. Gap Junction Regulation by Gaseous Molecules in DN

Gap junctions are formed by the members of the connexins (Cxs) protein family [91]. The association between two Cxs in the plasma membrane of adjoining cells gives rise to a functional gap junction channel facilitating cell-to-cell communication [92]. Among twenty distinct types of connexins, human and mouse kidneys have been reported to express eight isoforms of Cxs, viz., Cx26, 30, 32, 37, 40, 43, 45, and 46 [93]. A recent study revealed that H₂S ameliorates the expression of Cx40, Cx43, and Cx45 in diabetic animal models [93][94]. Differential regulations of connexins, i.e., upregulation of Cx40 and downregulation of Cx37 and Cx43, have been reported to act in conjunction with eNOS to modulate vascular function in diabetes [95][96]. Le Gal and colleagues showed a distinct role of the CX40-mediated regulation of NO production in a hypertensive mouse model [97]. On the other hand, the role of NO in the regulation of gap-junction-mediated intercellular communication has also been reported in the mesangium. Yao et al. (2005) demonstrated that elevated NO augments CX43-mediated gap junctional intracellular communication in mesangial cells via protein kinase A and that decreased NO may cause loss of CX43-mediated cell communication in the mesangium in DN [98].

4. Other Integral Membrane Proteins' (Caveolin and eNOS) Regulation by Gaseous Molecules

Caveolin is crucial for the formation of caveolae membranes, which act as scaffolding domains. The caveolin family consists of three caveolins, i.e., caveolin-1, -2, and -3 [99][100]. Caveolin-1 and -2 co-express as well as form a hetero-oligomeric complex in the many cell types [101][102], while caveolin-3 is muscle-specific [103]. Generally, caveolin-1 and -3 have higher regulatory activity than caveolin-2.

Caveolin-1 can induce caveolae formation, while caveolin-2 cannot induce the formation of caveolae. Therefore, generally, caveolin-1 is considered the principal structural protein of caveolae [104]. In recent years, the presence of caveolae and caveolin-1 and their roles in the kidney have been demonstrated in several studies [104][105][106][107][108][109]. Thus, controlling the proliferation ability of the mesangial cells could be an effective therapy for kidney diseases [109]. In fact, exogenous CO administration, as well as adenoviral-mediated HO-1 expression, enhanced the association between caveolin-1 and toll-like receptor-4 (TLR4), leading to the generation of anti-inflammatory response [110]. These findings identify the HO-1-mediated interaction between caveolin-1 and TLR4 as the potential therapeutic targets for inflammatory diseases [111].

In a mouse model of DN in T1D, caveolin-1 deficiency has been reported to render protection against mesangial matrix expansion [112]. Caveolin-1 expression was found to be upregulated in the glomeruli of patients with glomerular disease, including DN [104]. Elevated caveolin-1 plays a critical role in the suppression of eNOS-mediated renal NO production, which is presumably responsible for the progression of DN [113]. However, treatment with a NO donor, such as sodium nitrite, or NO precursor, such as L-arginine, ameliorated the adverse effects of DN [113].

In endothelial cells, caveolin-1 is the principal structural component of caveolae. Caveolin-1 acts as a scaffolding protein and is involved in the modulation of receptor signaling and the function of the caveolar enzymes [114][115]. eNOS is inhibited by its protein–protein interaction with caveolin-1 in the unstimulated endothelial cells. The course of eNOS activation by the stimulation of an agonist involves intracellular Ca^{2+} mobilization and a subsequent interaction between calmodulin and eNOS. The eNOS/calmodulin interaction allows the release of eNOS from the inhibitory complex with caveolin-1 [116][117]. Thus, changes in caveolin-1 abundance and eNOS interactions may influence eNOS activity and, subsequently, vascular function and modeling. A comprehensive knowledge and understanding of the role of caveolin-1 in mediating the cellular functions in diabetes are requisite for the interpretation of NO pathophysiology in the diabetic kidney. In diabetes, although ROS-mediated inactivation of NO has been suggested as the key mechanism behind the decreased bioavailability of eNOS-derived NO [118][119], other relevant mechanisms involved in the direct changes in eNOS function and molecular integrity have also been proposed [120]. Moreover, the expression of renal cortical eNOS regarding some of its functional determinants, such as cellular localization, phosphorylation status, and dimer/monomer formation, has been explored in normal and diabetic rats [121]. Furthermore, renal cortical expressions, as well as localization of the endogenous eNOS inhibitor caveolin-1 and its colocalization with eNOS, have been revealed.

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