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A Glimpse of Matrix Metalloproteinases in Diabetic Nephropathy

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Abstract

Matrix metalloproteinases (MMPs) are proteolytic enzymes belonging to the family of zinc-dependent endopeptidases that are capable of degrading almost all the proteinaceous components of the extracellular matrix (ECM). It is known that MMPs play a role in a number of renal diseases, such as, various forms of glomerulonephritis and tubular diseases, including some of the inherited kidney diseases. In this regard, ECM accumulation is considered to be a hallmark morphologic finding of diabetic nephropathy, which not only is related to the excessive synthesis of matrix proteins, but also to their decreased degradation by the MMPs. In recent years, increasing evidence suggest that there is a good correlation between the activity or expression of MMPs and progression of renal disease in patients with diabetic nephropathy in humans and in various experimental animal models. In such a diabetic *milieu*, the expression of MMPs is modulated by high glucose, advanced glycation end products (AGEs), TGF-β, reactive oxygen species (ROS), transcription factors and some of the microRNAs. In this review, we focused on the structure and functions of MMPs, and their role in the pathogenesis of diabetic nephropathy.

Keywords

Diabetic nephropathy; extracellular matrix; metalloproteinases; TGF-β

INTRODUCTION

Diabetic nephropathy (DN) is one of the severe forms of microangiopathies in patients with diabetes mellitus, and this reno-vascular complication is the most prevalent cause of end-stage renal failure (ESRD) in the Western world. Only 20% of the diabetic patients with ESRD have a survival rate up to five years [1, 2]. A better understanding of the pathogenesis of DN is needed to facilitate the development of more effective and early therapeutic

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CONFLICT OF INTEREST

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strategies to prevent ominous pathologic changes in kidney, which if not dealt with at an early stage would have an irreversible outcome. In addition, there are several other risk factors which further contribute to the progression of DN with worsening outcome, and they include glomerular hypertension, hyperglycemia, proteinuria, hyperlipidemia and heredity [3–8]. Although, abundant research has been carried out over a period of three decades to delineate the pathogenesis of DN a well-defined underlying unifying mechanism has yet to be emerged.

Morphological changes in the kidney seen in patients with type 1 and 2 diabetes are quite similar and they are confined to all the three compartments of the kidney, *i.e.*, glomerulus, tubulo-interstitium and intrarenal vasculature [9–11]. The classical changes are seen in the glomerular compartment, and they include glomerular hypertrophy, thickening of glomerular basement membrane (GBM) and mesangial expansion with the formation of Kimmelstiel-Wilson nodules [12–14]. The changes usually accompanied with glomerular lesions include tubulo-interstitium undergoing fibrosis while there is also arteriolar thickening and hyalinization in the vascular compartment of the kidney. Basically, there is an imbalance of extracellular matrix (ECM) synthesis and degradation, which most likely is responsible for accumulation for excessive matrices in various compartments of the kidney [13, 15]. Thus, the genesis of Kimmelstiel-Wilson lesion, a diagnostic feature of DN, is not only due to the excessive synthesis of ECM glycoproteins but also to a decreased degradation by matrix metallo-proteinases (MMP) [16]. In this regard, numerous studies have been carried out since the discovery of MMPs to address their intra-renal dysregulation, *i.e.*, perturbation in their expression and activity, in the progression of DN. In this article, we review the structure and function of MMPs and their relevance in the pathogenesis of DN, while also focusing on the role of their interactive partners, *i.e.*, **T**issue **I**nhibitor of **M**etallo-**P**roteinases (TIMPs) in the progression of DN.

MATRIX METALLOPROTEINASES

Structure, Classification and Functions

In general, Matrix Metallo-proteinases (MMPs) include a Zn^{++} ion binding site that is essential for their zinc-dependent proteolytic activities. These proteinases constitute a much larger superfamily of zinc peptidases having topological similarities among its members or groups and they are globally known as “metzincins” [17]. Within the superfamily, there is a category of MMPs with more than 28 members and 6 subgroups. Overall their domain structure is comprised of a propeptide, Zn^{++} binding catalytic domain, four hemopexin-like domains, transmembrane domain and a cytoplasmic domain. Tridimensional structural analyses of the MMPs indicate that topologically they share the catalytic domain consisting of an orderly sequential arrangement of twisted five-stranded β-sheets and three α-helices. Among these include certain metzincins, such as, MMP-8, adamlysin II, astacin and bacterial alkaline protease [18]. Another characteristic of the metzincins include a highly conserved motif containing three histidines (HEXXHXXGXXH) that bind zinc at the catalytic site and a methionine turn following the active catalytic site [10]. This catalytic site motif has essential histidine (H), glutamic acid (E) and glycine (G) residues, while X is a variable amino acid residue [19, 20]. Based on this amino acid sequence of the catalytic

motifs, the family of metzincins has been further extended to include certain other proteases, such as, astacins, reprolysins (ADAMs) and serralysins, besides the MMPs, thus making the classification and functionalities of metzincins highly complex and at times confusing [21–23]. Certainly, under the broad category of metzincins, the MMPs, a multigene family with shared domain structure, are believed to play an essential role in the breakdown of extracellular matrix (ECM) in order to maintain a proper balance in its synthesis and degradation [24]. This process of turnover is essential for morphogenesis, embryonic development, reproduction, remodeling of tissues under normal and pathologic states, the prototype of latter being neoplastic and inflammatory diseases [24, 25]. As indicated above that for the large part MMPs share a core structure made up of a prodomain, a catalytic domain, a hinge region and a hemopexin-like domain (Hpx); however, a few variations do exist. For instance, MMP2 (gelatinases A) and MMP9 (gelatinases B) have three repeats of a fibronectin type II-like motif in the metalloproteinase domain [26–28]. MMP7, MMP26 and MMP23 lack the linker peptide and the Hpx domain [29]. MMP-23 has a distinct cysteine-rich domain and an IL-1 receptor-like domain following the metalloproteinase domain instead of the Hpx domain [30]. MT4-MMP (membrane-Type 4 matrix metalloproteinases) is endowed with unique hydrophobicity properties at its C-terminus that are akin to some of the GPIanchored proteins, such as human uPAR, NCAM120 and Thy-1 [31].

On the basis of substrate specificity and sequence homology, MMPs have been subclassified into six groups (see Table 1): Collagenases (MMP1, MMP8, MMP13 and MMP18) [32–35], Gelatinases (MMP2 and MMP9) [36, 37], Stromelysins (MMP3, MMP10 and MMP11) [38–40], Matrilysins (MMP7 and MMP26) [39, 41, 42], Membrane-type matrix metalloproteinases (MT-MMP14, -MMP15, -MMP16, -MMP17, -MMP24 and –MMP25) [43–49] and other MMPs (MMP12, MMP19, MMP20, MMP21, MMP23, MMP27 and MMP28) [25, 50–58]. Except for the MT-MMPs most of the MMPs are secreted out and have extracellular distribution; however, recent evidence suggest that MMP1, MMP2 and MMP11 also have intracellular expression where they may interact with cytosolic proteins to modulate various biological processes [59–61]. Whether cellular or extracellular or transmembrane localization it is now well accepted that MMPs regulate a variety of physiological and pathological processes, including embryonic development, tissue homeostasis, inflammatory, vascular and autoimmune disorders, carcinogenesis and fibrogenesis in various organ systems [26, 62–85].

Regulation of MMPs

Under physiological conditions, in order for MMPs to exert their full effect following transcriptional induction and translation and biochemical activation, they need to be expressed in a coordinated manner with a highly restricted spatiotemporal distribution, suggesting they do not target their cellular or extracellular substrates indiscriminately, although they can act synergistically to degrade a broad spectrum of ECM glycoproteins. Besides, cell and time specific transcriptional, translation and post-translation modulation of MMPs followed by secretion at specific target sites their enzymatic activities are also regulated by some of the known endogenous metalloproteinase inhibitors known as TIMPs while they may be other additional MMP inhibitors that are yet to be discovered. Normally, the activities of most of the matrixins are negligible or they have very low expression in

healthy intact tissues, and this general biologic characteristic may be related to the sharing of common *cis*-elements in the promoters regions of MMPs, meaning thereby that their expression is tightly controlled at the transcriptional level depending upon the biologic state of a given cell type. Furthermore the literature information indicate that a multitude of signaling intermediates are involved in the activation of transcription factors, such as, NF-KB, Ap-1, AP-2, MAPK, STAT, SMAD and PEA3 in order for MMPs to exert their effects [29, 63, 86, 87]. In this regard, Wnt/β-catenin signaling controlling MMP7 and MMP9 expression has been described in rodent animal models, and this regulatory mechanism among many others may be relevant to the pathobiology of kidney injury [88, 89]. Interestingly, among humans there are also genetic variations which influence the level of MMP gene expression that ultimately may dictate the progression of a given disease process. In fact, the relationship between some of the diseases and single nucleotide polymorphisms (SNPs) of MMPs' promoters has been described. For instance, recently it has been shown that rs3025058 at position-1612 in MMP3 and rs2276109 at position −82 in MMP12 are associated with an increased susceptibility to cardiovascular disease [90]. In addition, Kure *et al.* demonstrated that the variants at the MMP3/MMP12 locus are associated with a reduced risk of diabetic nephropathy in patients with type 1 diabetes [91].

Although MMPs expression seems to be heavily modulated at the transcriptional level, a series of post-translation regulation mechanisms have also been identified in recent years. Miriam *et al.* reported that there are transcripts that harbor specific sequences in their 5′- or 3′-untranslated regions (UTRs) of MMPs to which UTR-binding proteins can associate to regulate their corresponding mRNAs levels [92]. For instance, AU-rich elements present in 3'-UTR of MMP1 and MMP9 heavily determine their mRNA stability and ultimately the biological effects [93, 94]. Rydziel *et al.* reported that cortisol modulates mRNA stability *via* AU-rich sequences of 3'-UTR region in MMP13 in osteoblasts [95].

An additional gene regulation of MMPs' expression and subsequent activation of various signaling pathways and targeting other genes and organ system by microRNAs (miRNAs) has recently attracted the attention of many investigators. Zhihong Yang *et al.* found that the miR-127 inhibits the expression of MMP13 protein both by repressing the 3'-UTR activity and inhibiting MMP13/TGF-β signaling in human hepatocellular carcinoma [96]. Similarly, miR-133a was found to down-regulate MMP14 protein expression with decreased frequency of lung cancer metastasis. Likewise, Lin SY *et al.* [97] demonstrated that over-expression of miR-92a could repress the expression of RECK, a MMP inhibitor, by post-transcriptional regulation in H1299 cells.

Since the discovery of MMPs, the investigators over the last 2–3 decades have been exploring to develop inhibitors that could directly neutralize the activities of MMPs at the intra- or extra-cellular target sites, although several endogenous inhibitors of MMP, known as TIMPs, that are capable of modulating cellular homeostasis have been identified [98, 99]. The TIMPs family includes at least four 20 – 29 kDa secreted proteins (TIMP1 - 4) that exhibit specificities for different MMPs [26, 29]. Allison *et al.* found that TIMP1 mRNA expression is quite low in mouse kidney, while TIMP2 and TIMP3 mRNA are expressed at high levels, while TIMP4 is undetectable [100]. Interestingly, almost all the known MMPs can be inhibited by TIMP1, 2 and 3 [101]. However, recent studies show that although

TIMP1 is a poor inhibitor of MT1-MMP, MMP19 and ADAM17, it can be transformed to an active inhibitor of ADAM17 when substitution of threonine is made at residue 98 with leucine (T98L) [99, 102]. Additionally, TIMP4 is involved in suppressing the activity of MMP1, MMP2, MMP3, MMP7 and MMP9 [103]. Furthermore, besides having inhibitory effect on MMPs, the TIMPs are endowed with other biological activities, including cell growth, migration, invasion, antiangiogenesis, anti- and pro-apoptosis and synaptic plasticity [104–109]. TIMPs as a major MMPs inhibitor was considered increasing ECM accumulation and renal fibrosis as it can reduce the degradation of matrix proteins [110–112]. However, Allison A *et al.* found that the degree of renal interstitial fibrosis did not diminish in TIMP1 deficiency mice [100]. Furthermore, TIMP3 prevented glomerular and tubulointerstitial from age-depended renal injury [113]. Recent study has also shown that aggravated renal damage in response to lack of TIMP3 but not TIMP2 in UUO model, which accompanyed by the increase expression of collagen type I/III and activites of capase-3 [114]. Microarray analysis suggested that significant difference gene expression in TIMP3−/− mice compared to TIMP2−/− mice after UUO. Moreover, TIMP3 is a pivotal negative modulator of renal TNFα which induced renal fibrosis and injury in UUO [113]. Conceivably, several other proteins also have inhibitory activity targeting the MMPs, such as, RECK, TFPI-2, PCPE and α2-Macroglobulin, however, still much more research is needed to characterize their biological properties and functions [115].

MMPs AND DIABETIC NEPHROPATHY

The spatial-temporal localization and delineation of functions of MMPs in the kidney is quite complex, and that to some extent may be related to a given MMP involved in a particular disease process and animal specie. Certainly, the balance of ECM synthesis and degradation/turnover is one of the most significant processes for maintaining the glomerular structural and functional integrity [116, 117]. The MMPs may affect ECM turnover *via* several different mechanisms. Abnormal MMP expression or activity will directly render into an altered ECM turnover, and such an abnormal matrix is likely to influence heavily the behavior of glomerular cells [118]. Besides the ECM degradation or turnover, MMP2 can modulate the biology of the glomerular mesangial cells upon exogenous reconstitution of active MMP2 to antisense MMP RNA-induced quiescent cells, and in doing so they rapidly reverted to a pro-inflammatory phenotype [119]. MMPs also can activate or release some of the growth factors, such as insulin like growth factors, tumor necrosis factor (TNF-α) and heparin-binding-epidermal growth factor, and such a modulation is associated with profound pathologic changes that adversely affect cellular homeostasis in various diseases [120–123]. During the past few years, extensive investigatory efforts have delineated the role of MMPs in a variety of kidney diseases, including acute kidney injury, diabetic nephropathy, tubulo-interstitial fibrosis and various forms of glomerulonephritis [26]. The MMPs have long been identified as critical mediators of ECM degradation and turnover, but increasing evidence support that they in conjunction with TIMPs play an important role in the progression of diabetic nephropathy.

The Expression of MMPs in Patients with Diabetic Nephropathy

Traditional thinking is that hyperglycemia down-regulates the expression and activity of MMPs in patients with diabetic nephropathy (DN), as a result there is a decreased ECM degradation and accumulation in the matrices leading to mesangial expansion with the evolution of Kimmelstiel-Wilson lesions. It is well established that high glucose ambience adversely affects ECM degradation or turnover and enzymatic activities of MMPs and TIMPs in patients with DN. Surprisingly, circulating TIMP1, TIMP2 and MMP2 have also been found to be decreased in patients with DN [124]. However, there are conflicting reports suggesting that MMP2, MMP9, MMP7, MMP8, MMP14 as well as TIMP1 are increased in the serum or urine from diabetic patients [125–128]. Similarly, there are variations in the renal tissue expression of MMP2 in the biopsy specimen of patients with DN. Sekiuchi *et al.* reported that MMP2 is weakly expressed in the glomerular capillary loops and Bowman's capsules along with TIMP2 in the mesangial area, suggesting that MMP-2 most likely is involved in the turnover of glomerular basement membrane [129]. Del Prete *et al.* demonstrated a dramatic decrease in MMP2 gene expression in glomeruli of patients with type 2 diabetes [130]. However, another study showed that MMP2 protein and related enzyme activity were up-regulated in kidneys of patients with diabetes, as assessed by Western blot analysis and ELISA methods [126]. Similarly, MMP7 mRNA expression was reduced in renal tissues from patients with DN compared with control [131], while by immuno- histochemical staining methods they were found to be up-regulated [89]. In addition, these unique changes in the MMP7 expression in renal tubular epithelia may be in some ways related to Wnt/β-catenin signaling in the kidney [89]. Furthermore, by *in situ* hybridization, a significantly down-regulated expression of MMP3 and TIMP1 mRNA in intrinsic glomerular cells and tubular epithelia was observed in patients with DN. Tubular expression was found to correlate with the extent of interstitial injury, while it was inversely proportional to the glomerular mesangial expansion [132]. MT5-MMP expression was detected only in the kidney by Western blot analyses and it was noted to be significantly increased in patients with DN [126]. Romanic *et al.* reported that MT5-MMP was highly expressed in epithelia of proximal and distal convoluted tubules in diabetic patients. Furthermore, the expression of MT5-MMP was associated with tubular atrophy, which incidentally worsens the progression of DN [126]. In another study MMP10 levels were reported to be high in diabetic patients and positively correlated with the degree of damage related to nephropathy in diabetic patients [133]. Taken together, MMPs and TIMPs expression in DN patients is somewhat variable, and their role in kidney pathology seems to be still very much confounding. But one can safely assume that the imbalance in MMP-TIMP expression or activation could lead to abnormal ECM deposition which decidedly remains as one of the hallmark of DN.

Albuminuria or microalbuminuria as a clinical biomarker of DN is matter that has been a critical issue for several years [134, 135]. Numerous studies demonstrated a strong correlation between the MMPs expression and the degree of albuminuria or the severity of clinical symptoms. It has also been reported that urinary TIMP1 levels remarkably increase in diabetic patients, and they are associated with the severity of diffuse glomerulosclerosis and urinary N-acetyl-β-glucoaminidase (NAG) excretion [136]. Another study demonstrated that circulating MMP7 levels were up-regulated in the micro- as well as macro-albuminuric

groups and had negative correlation with glomerular filtration rate in patients with diabetes [137]. Interestingly, Sekiuchi *et al.* reported that MMP9 expression was concentrated in the stalk mesangial of the glomerulus in patients with DN, as delineated by the immuno-histochemical studies, suggesting that MMP9 may play a critical role in the turnover of the mesangial matrix in DN [129]. In another recent study, Szu-Yuan Li *et al.* observed that MMP-9 was dramatically increased in the glomeruli of diabetic mice, and MMP-9 deficiency attenuates diabetic nephropathy by modulation of podocyte functions and dedifferentiation. Moreover, they found, in diabetic patients, the upregulation of urinary MMP-9 concentrations occurred earlier than the onset of microalbuminuria. Collectively, these results suggest MMP-9 play a role in the development of diabetic nephropathy [138]. In addition, the presence of MMP9 in urine of DN patients was detected where they were seen as high molecular weight complexes that were significantly higher than healthy adults [125]. Moreover, a positive correlation has been well documented between the urinary excretion of MMP9 and the magnitude of albuminuria and renal lesions in patients with type 2 diabetes mellitus [139, 140]. Ebihara *et al.* [139] discovered that the plasma MMP9 levels were elevated before the onset of albuminuria, and they were dramatically decreased following treatment with angiotensin-converting enzyme inhibitor in patients with type 2 diabetes patients with high risk for development of diabetic nephropathy. In addition, a recent study has shown that elevated MMP9 levels in T2DM patients had strongest association with age, BMI, hyperglycaemia, blood pressure, HbA1c and progression of diabetes [127]. Furthermore, plasma concentration of MMP9 in diabetic patients has been significantly correlated with the aberrant shedding of podocytes in the urine, which is reduced by treating with Trandolapril [141]. These findings are in accord with other studies [125, 139, 140"], and the literature data suggest that urinary MMP9 may be a useful marker for diagnosing the degree of renal damage in early phases of DN. On the other hand, Toni *et al.* demonstrated that serum MMP-9 concentration correlates with the incidence of DN [141], and they hypothesized that the patients with A21 allele of the MMP9 gene may be protective with respect to the occurrence and progression of DN [142]. Importantly, findings of another recent study suggested that MMPs could serve as a potential target for the therapeutic intervention in DN. Aggarwal *et al.* demonstrated that compared with angiotensin-converting enzyme inhibitors (ACEIs) and or angiotensin receptor blockers (ARBs), doxycycline (an inhibitor of MMP) can effectively reduce proteinuria in adult patients with DN, but unfortunately it is effective only for a short duration, *i.e.*, less than 12 weeks [143].

The Expression of MMPs in Animal Model of Diabetes

Rodent studies have provided further insights into the potential contribution of MMPs and TIMPs in animal models of diabetic nephropathy (DN). Interestingly, an altered expression and enzyme activity of MMPs and TIMPs have been reported in DN models. But the quandary is that both up- and down-regulation has been described for MMP-2 expression or enzyme activity in renal tissues in rodent models of diabetes [111, 144, 145"]. Fornoni *et al.* investigated the MMP2 mRNA expression and activity in mesangial cells derived from kidneys of ROP mouse (reduced nephron number) that rapidly develop glomerulosclerosis and from parental B6 mouse strain that are resistant to develop glomerulosclerosis [144]. Exposure of cells to high glucose (HG) ambience led to a comparable increase in the MMP2

mRNA expression and activity in both the ROP and B6 mice mesangial cells, but this altered expression was reversible when glucose concentration was reduced from 25 mmol/L to 6 mmol/L in B6 mice cells only. These intriguing observations suggested that there is a potential role of MMP2 in the progression of DN in the model of sclerosing phenotype ROP mice under HG ambience [144]. Similarly, renal MMP2 expression and activity have been observed to be increased mainly after 16 weeks STZ induced mice when the sclerosing process is overtly seen. In addition, transgenic studies by Takamiya *et al.* indicate that MMP2-KO mice have relatively high serum levels of BUN and Creatinine and increased urinary excretion of albumin and NAG compared to their wild-type littermates [146]. Their studies also highlighted that changes in MMP-2 in diabetic mice may be time dependent, and the increased renal expression and activity of MMP2 may be a protective compensatory mechanism during the early phases of DN, while it may be operationally ineffective in later sclerosing phases. MMP9 is another protease which has been investigated with respect to its role in the DN with mixed variable results and contradictions. It is of interest to note that non-specific pharmacological inhibition of MMP9 with doxycycline were found to be associated with amelioration of renal injury [143]. In addition, it is also reported that Simvastatin protects kidney damage of diabetic rat through the suppression of MMP9 expression [147]. Along these lines, the expression of MMP9 mRNA and protein were found to be up-regulated compared with the control group in 16 weeks of Kkay mice with glomerular sclerosing lesions [148]. Similarly, Szu li *et al.* reported reduced glomerular hyperfiltration and glomerular basement membrane thickening in diabetic $MMP9^{-/-}$ mice than diabetic WT mice [138]. *In vitro*, overexpression of MMP9 upregulated the expression of mesenchymal markers protein and induced podocyte dedifferentiation and increased the ECM synthesis [138]. Conflicting results were reported in another study with 24 weeks of STZ rat where increased collagens IV in the glomerulus and tubulo-interstitium was noted to be associated with decreased matrix degradation activity and reduced MMP9 mRNA expression in the kidney. Furthermore, the changes in MMPs and type IV collagen accumulation were attenuated by ACE inhibitor, Perindopril [149]. Taken together, these observations suggest that the MMPs expression level were inconformity at different phases of DN. It was reported that MMP-9 directly processed TGF-β into an active ligand [150] and it also regulated the release of growth factors like VEGF [151]. Furthermore, MMP9 may act on pro-inflammatory pathway through induction of TNF-α [152, 153] and IL-1β [72, 154] in an early phase of diabetic rat or mouse. These data indicates that expression of MMP9 was increased in early phase of DN, which directly promoted the degradation of basal membrane protein of kidney and stimulated secretion of activate growth factors as well, culminating in renal lesion. However, in later phase of DN, the expression of MMP9 was negatively regulated by feedback mechanism leading to decreased degradation of ECM and renal tissue fibrosis under DN condition eventually. On the other hand, Most likely, in DN it is the high glucose ambience or hyperglycemic environment that down-regulate MMP3, MMP7, MMP14 and TIMP3 in various diabetic animal models [131, 155–157]. The direct relevance of MMPs in DN is provided by the studies showing suppression of excessive type 1 collagen accumulation and renal fibrosis following MMP1 plasmid DNA gene delivery via microspheres implanted in the DN mouse model [158]. Along these lines conceivably gene disruption of another protease, i.e., MMP-10, may prevent renal damage in diabetic mice since reduced expansion of mesangial matrix and interstitial macrophage

accumulation were observed in MMP10−/− mice [133]. Taken all together the above observations, it seems that the altered expression and dysfunction of MMPs and TIMPs may be related to the development of DN, however, as to how the differential expression of various MMPs and TIMPs influence the renal disease progression in diabetic patients remains somewhat enigmatic. High glucose, AGEs, ROS, hypoxia, TGF-β and miRNA *et al.* probably be involved in regulating the expression and activity of MMPs. We would depict them one by one in the following text.

High Glucose and MMPs

A large body of data focusing on the role of MMPs in the DN is available in the literature, however, the specific mechanism(s) in regard to their modulation are not clear rather they are somewhat complex. There are several mechanisms by which dysregulation in renal MMPs and TIMPs expression or activity in kidney could contribute to the development of progressive DN. As previously mentioned, MMPs expression is tightly regulated by various mechanisms that include transcription and post-transcription. Evidence indicates that HG may regulate MMP gene expression *via* various transcription factors, such as, AP-1 and NF-κB [159, 160] or depending upon the tissue levels of growth factor cytokines, such as, TGF-β and CTGF [161, 162]. Since AP-1 is made up of Fos and Jun families of transcription factors its role may be dependent upon the dimeric composition that most likely would influence the downstream signaling pathways [163]. There are two AP-1 sites in the promoters of MMP1 and MMP3 and the consensus AP-1 sequences at the second site is variable, which may explain why the differential effects by these MMPs following the induction by HG are observed [164]. Differential regulation was also observed following HG induced increased levels of PDGF which exclusively and negatively regulate the MMP3 expression while sparing the MMP1 [164]. Similarly, although MMPs expression is increased in human mesangial cells under prolonged HG ambience associated high MMP2 activity while that of MMP9 decrease under such an environment. These opposite catalytic effects are interesting and may be related to the compositional differences in the promoter sequences of these two gelatinases [165]. In addition, MMP2 does not have a TGF-β inhibitor element (TIE) and AP-1 sites, whereas they are included in the MMP9 promoter [166]. In this regard, Alison K *et al.* study suggested that the increased MMP9 mRNA level induced by hyperglycemia might mediated by AP-1 and NF-κB transcription factors [164]. Recently, Bai Y *et al.* investigated the ERK1/2 MAPK signaling pathway and its role in MMPs expression in murine podocytes exposed to HG ambience [167]. HG-induced increase in MMP9 activity in earlier phases of culture required activation of ERK1/2 MAPK signaling and that is associated with downstream decreased collagen IV collagen expression, suggesting blocking of the ERK pathway is critical in the modulation of MMP9 expression and thereby the ECM turnover.

AGEs and MMPs

Advanced glycation or glycol-oxidation end products, known as AGEs, are aberrantly synthesized molecules that can be one of the major factors influencing the progression of DN. Hyperglycemia leads to the generation of AGEs which is basically as a result of condensation of sugar and free amino group with the formation of a labile Schiff base which undergoes further complex intra-molecular modification to generate complex toxic AGEs.

Such derivatization can occur between sugar and lipids as well, and their formation can be initiated in both intra- and extracellular compartments [168–170]. Several forms of AGEs derivatives have been described in renal injury related to diabetes, and morphologic changes that are often associated with it include glomerular and tubular basement membrane thickening, capillary aneurysmal dilatation, mesangial expansion with formation of Kimmelstiel-Wilson nodules and arteriolar thickening and hyalinosis [171–173]. Biologically active AGEs can be highly reactive in the intra- and extra-celluar compartments and their downstream injurious effects include increased oxidative stress, alterations in the molecular conformations of the molecules and aberrant expression of cytokines and growth factors [171, 174, 175]. As a result the AGE formation can alter the functionalities of several important extracellular matrix molecules, such as, type I collagen, type III collagen, type IV collagen and fibronectin and laminin [176–179]. Furthermore, AGEs can modulate the intracellular signaling pathways and gene and protein expression by interacting with their receptors, *i.e.*, RAGE [180]. In this regard, a significant reduction in the gene and protein expression of MMP7 was observed in patients with DN and STZ-animal model system and in mesangial cells *in vitro* subjected to HG ambience, and these effects were blocked by neutralizing TGF-β antibodies and Aminoguanidine, an inhibitor AGEs formation [131]. Interestingly, AGEs can modulate the expression of certain growth factors belonging to CNN family. Broadly speaking the latter include six members: CYR61 (Cysteine-Rich61, CYR61/CCN1), CTGF (Connective Tissue Growth Factor, CTGF/CCN2), NOV (Nephroblastoma Over-expressed, NOV/CCN3), WNT1-Inducible Signalling Pathway proteins 1, 2 and 3 (WISP1, -2 and -3 or CCN4, -5 and -6) [181]. They have been shown to regulate various biological processes, such as, cellular activity, fibrosis, inflammation and angiogenesis. Hughes *et al.* reported that AGEs increase the CCNs mRNA and protein levels in retina of rats with STZ induced rat and that were reduced following the treatment with Aminoguanidine [181]. Recently, Wang X *et al.* described that CCN-2 mRNA and protein expression were increased by glycated ECM, which in turn can up-regulate the expression of fibronectin and TIMP-1 in human renal mesangial cells, and this circuitous cycle may play a role in evolution of phenotypic changes seen in the glomerulus in DN [182]. Additionally, the AGEs *via* AGE:RAGE interaction can activate PKC, MAPK and NF-κB, which can in turn modulate the expression of TGF-β and subsequently of MMPs. Such ligand: receptor interactions can also generate reactive oxygen species (ROS), which then can regulate the MMPs' expression *via* modulation of various transcription factors [16]. Interestingly, Mclennan SV *et al.* demonstrated that glycation of ECM certainly increases the gene expression of MMP-2, but decreases TGF-β mRNA and activity in human fetal mesangial cells, suggesting that glycation of matrix affects MMP2 is independent of TGF-β initiated signaling pathway [183].

ROS, Hypoxia and MMPs

The excessive generation of ROS and the development of oxidative stress (OS) are regarded as the key events influencing the pathogenesis of DN [184, 185]. The ROS are known to modulate various biological processes, such as, cell proliferation and cell adhesion, as well as certain pathobiologic processes, such as, atherosclerosis and immunologically-mediated inflammatory disorders [186–188]. The activation of AGEs and ROS are intricately interwoven and thus may amplify the signaling cellular events in a hyperglycemic

environment. It is known that over-production of ROS by HG in renal cells though AGE:RAGE interaction or glucose auto-oxidation or metabolism modulate the activation of PKC, NF-κB and AP-1, as well as increase the TGF-β activity, thereby promoting a further increase in the expression of ECM proteins [189]. Moreover, this increase in the activity of these signaling molecules and expression of cytokines and ECM can be effectively reduced with the treatment by antioxidants [189–192]. Uemura S *et al.* suggested that MMPs activity is tightly correlated with the cellular redox balance. They indicated that the expression of MMP9 in the vasculature is redox-sensitive since it can be reduced by various antioxidants, such as, N-acetyl-L-cysteine (NAC) [193]. On one hand, excessive generation of ROS could increase the expression of some of the key transcription factors, such as, AP-1 or NF-κB, that are important for the gene activation of MMPs in a vast number of disease processes [194], while on the other hand, oxidant stress also may regulate MMPs by direct oxidation of crucial cysteine residues within the DNA-binding domain [194, 195]. Masash *et al.* demonstrated that MT1-MMP plays a vital role in NADPH oxidase-dependent signaling pathways that are initiated following AGE:RAGE interaction [196]. They demonstrated that the gene disruption of MT1-MMP remarkably blocks the NADPH oxidase activity and ROS generation in smooth muscle cells [196]. Furthermore, mitochondrial-derived ROS may also regulate MMP-9 activation or expression *via* activation of ERK-1/2 signal cascade in vascular endothelial cells in hyper- homocysteinemic (HHCY) state [197]. Although HHCY state induces MMP-9 in myocytes it negatively regulates their contractile functions, apparently related to the perturbation in the mitochondrial homeostasis [198]. In line with this contention, other MMPs, *i.e.*, MMP2, has been shown to negatively regulate mitochnodrial functions in states of oxidant stress [199]. Similarly, gene disruption of MMP-9 in mice led to the amelioration of mitochondrial dysfunctions and development of retinopathy in diabetic *milieu* [200]. Like the evidence that increased MMP-9 activity *in vitro* in bovine carotid artery endothelial cells (BAECs) induced by HG can be inhibited by antioxidants there is also evidence that insulin infusion *in vivo* has an inhibitory effect on the increased expression of MMP9 in patients with hyperglycemia, which in part may be related to the insulin capacity to exert antioxidant and anti-inflammatory effects besides lowering the blood sugar levels [201].

In recent years the notion that in DN increases oxidative stress is commonly associated with hypoxia has attracted the attention of many investigators [16, 202]. The hypoxic injury seems to be an overwhelming feature of several other renal diseases beside DN [203–206]. Kidneys from diabetic animals have increased renal oxygen consumption [207]. Conceivably, it is related to the increased metabolic rate and oxygen demand in various target tissues which will inevitably lead to kidney tissue hypoxia and potentially contribute to the progression of diabetic nephropathy [208]. The tubule-interstitial hypoxia is a most significant early event in diabetes [206]. Recent studies have delineated that the tubule-interstitial damage, including tubular cells apoptosis in patients with DN, is related to hypoxia-induced injury or at least it would certainly contribute to the onset of the development of DN [16, 206, 209]. There are literature reports which suggest that hypoxic stimuli boost the ECM synthesis and deceleration of its turnover with up-regulation of α1 chain of type 1 collagen as well as that of the tissue inhibitor of TIMP-1, and down-regulation of collagenase in human renal cortical fibroblasts when subjected to relative

anoxic ambience [210]. Furthermore, they found that the increased expression of TIMP1 induced by hypoxia was associated with activation of transcription factor known as hypoxia-inducible factor 1(HIF-1)[210]]. Moreover, HIF-1-mediated hypoxic injury in tubular epithelial cells involves CTGF since the promoter of this growth factor includes hypoxia response elements [211]. Hypoxia also decreases the expression of MMP-9 and MMP-2 activity in human cortical fibroblasts under normal as well as HG ambience [212]. However, the cells derived from 2/3 of patients only had increased MMP9 and MMP2 expression under HG ambience, suggesting that effects of hypoxia and HG may be independent from each other with respect to MMP activities, and hypoxia may be a better predictable parameter with respect to kidney injury [212].

TGF-β and MMPs

Numerous studies have demonstrated a vital role of TGF-β in aberrant accumulation of ECM in glomerular and tubulo-interstitial compartments in DN [116, 213, 214]. The overexpression of TGF-β mRNA and protein in diabetic kidney in both experimental models and human has been observed [215]. By in situ hybridization and immunehistochemistry, besides TGF-β, an increased mRNA and protein expression of type IV collagen in both glomeruli and tubulo-interstitium of diabetic rats has been seen [216]. Furthermore, expression of specific matrix proteins induced by TGF-β was seen to be increased in glomeruli of diabetic rat as well of patients with DN [215]. TGF-β initiates its fibrogenic effects by stimulating matrix synthesis of various integral ECM proteins, such as, fibronectin, collagens and proteoglycans [217, 218]. At the same time there is inhibition of matrix degradation by dampening the synthesis of proteases and boosting the levels of TIMPs [219] while modulating the cellular matrix receptor (integrin) expression to strengthen cell-matrix connections [220].

Experimental data support that HG regulates MMP and TIMP expression, possibly through TGF-b axis [221]. Singh R *et al.* found a decrease of MMP2 activity that was conceivably regulated by TGF-β1 in rat mesangial cells under HG ambience [161]. They also reported that TIMP2 and TGF-β1 levels were increased following HG stimulation, while secreted MMP2 protein capable of degrading type IV collagen was decreased, and this effect was blocked partially by neutralizing anti-TGF-β1 antibody. Baricos *et al.* found that these effects were conceivably due to the blocking of the conversion of latent MMP-2 to active form in human mesangial by cells TGF-β1 [222]. In addition, studies by McLennan *et al.* suggested MMP2 and TIMP1 gene expression were increased, while MMP-9 mRNA was decreased in diabetic rat kidney and these events are associated with altered transcriptional activities of TGF-β [149]. Furthermore, TGF-β1 stimulates the synthesis of MMP14 and MMP2, which is required for epithelial-mesenchymal transformation (EMT) in the rat remnant kidney model of progressive renal fibrosis [223]. Cheng and Lovett *et al.* also found that active MMP2 could induce EMT alone *in vitro* and amplify the transformation course by proteolytic generation of TGF-β1 thought paracrine way [223]. In addition, transgenic mice highly expressing active MMP2 in renal proximal tubular epithelial cells exhibited glomerulosclerosis, extensive mononuclear cell infiltration, tubular interstitial fibrosis and developing renal fuction dysregulation compared with control [224]. This proteolytic gelatinase cleaves type IV collagen, a major component of basement membranes

and maintenance the epithelial phenotype of proximal tubular eptihelial cells [225], leading to TBM destruction which is significant to trigger EMT. Nuclear run-off analyses suggest that the TGF-β regulates MMP2 expression at both transcriptional and post transcriptional levels by early increase in MMP2 transcription while at the same time increasing the half-life of the MMP2 mRNA in human fibroblasts [226] or through increased stability of the MMP2 proenzyme [227]. In addition, TGF-β has also been found to increase MMP-9 mRNA stability [227]. On the other hand CM *et al.* reported that the TGF-β decreased the synthesis of collagenase in fetal rat calvarial bone cells and human fibroblasts, whereas the TIMP mRNA levels were found to be increased [228]. Similarly, TGF-β1 also was found to suppress the transcriptional activity of stromelysin [229, 230]. Moreover, TGF-β inhibits ECM related gene expression by associating Fos- containing protein complex with the TGF-β1 inhibitory elements (TIE) localized in the promoter regions of stromelysin [231]. This is in accord with other studies which suggest that TGF-β could affect several MMPs that contain AP-1 sites in their promoter regions that are intricately involved in the regulation of MMPs expression [163].

TGF-β also reduces MMP-7 gene and protein expression and also the activity in mesangial cells cultured under high glucose ambience as indicated above, and the effect is abolished with TGF-β neutralizing antibody in STZ-induced diabetic rats *in vivo* as well [131]. A recent *in vitro* study reported that TGF-β induced Wnt1 expression, activated β-catenin and up-regulated Wnt target genes, such as, MMP7 and MMP9 [88]. In addition, TGF-β and Smad4 signaling pathway down-regulated renal ECM degradation in DN in rats with STZ induced diabetes, and this was accompanied by diminished MMP3 mRNA expression but increased both TIMP-1 and collagen III mRNA [155]. Another intriguing observation reported by MClennan SV and Martell SK indicated that glycation of matrix perturbs the balance between MMP2 and its inhibitors and may not be related to TGF-β activity in the accumulation of ECM at the target sites [183]. Overall, it seems that the effect of TGF-β on the MMPs' and TIMPs' expression is differential depending upon their regulation during different pathobiological processes.

MiRNA and MMPs

MiRNAs are a family of a small non-protein-encoding RNAs which control gene expression by inhibiting target mRNAs [232]. Several miRNAs, such as, miR-216A, miR-217, miR-192, miR-377, miR-21 and miR-29c are believed to play a significant role in the progression of DN [233]. Almost all of these miRNA are increased by HG or TGF-β in mouse or human mesangial cells [234–238]. MiRNA has also been found to take part in some of the biological processes, such as, ECM accumulation, resulting in aberrant tissue phenotype. Recently, Alvarez *et al.* demonstrated that an increase in miR-1207-5p, under hyperglycemia conditions, contributes to ECM accumulation in the kidney [233]. Under *in vitro* conditions, expression of miRNA1207-5p is markedly up-regulated in kidney cells with HG, while TGF-β stimulation enhanced the protein levels of major ECM glycoproteins [233]. Recently, Wang *et al.* elucidated that hyperglycemia-induced over-expression of miR-21 conceivably perturbs the balance between MMP and TIMP activities in DN [239]. Interestingly, in their studies they noted that the expression of miR-21 was significantly increased in KK-ay mice compared with control mice, which positively correlated with the

expression of collagen IV, TIMP1 and FN; however, it negatively correlated with MMP9 protein levels. Furthermore, the antagmir-21 up-regulated the MMP9 protein levels, which suggests that miR-21 directly influence MMP9 expression. There is evidence that hyperglycemia induces an increase of TGF-β/Smad 2, which could promote miR-21 overexpression [240, 241]. Likewise, TIMP3 expression is also regulated by numerous of miRNAs including miR-21, miR-181b, miR-182, miR-216 and miR-221/2 [242]. Among various miRNAs, the miR-217 has been shown to modulate TIMP3 expression indirectly *via* SirT1 small interference RNA inhibition [242]. In addition, miR-21 was found to be increased both in human kidney biopsies from diabetic patients and in mesangial cells under HG conditions. Interestingly, miR-21 levels increase and TIMP3 level decrease were detected almost at the same time point under HG ambience [242]. Taken together, these data indicate that miRNA can directly or indirectly regulate MMP:TIMP balance, the perturbations in which would likely contribute to the aberrant ECM synthesis and renal fibrosis in DN.

CONCLUSIONS AND PERSPECTIVE

DN reflects a pathological hallmark of overproduction and expansion ECM in the kidney [117]. Therefore, the MMP family which can influence the balance between synthesis and degradation of ECM proteins may play a significant role in the progression of DN. The MMP superfamily includes of various proteases, including collagenases, gelatinases, stromelysins, matrilysins and membrane type- collagenases [25]. The research efforts are ongoing in discovering a detailed understanding of regulation of the MMPs/TIMP in hyperglycemic *milieu*. Experimental and clinical studies revealed that expression of MMPs/TIMPs *in vitro* or *in vivo* is somewhat discordant and inconsistent; importantly, the regulatory mechanism(s) that how hyperglycemia modulates MMPs and TIMPs have not yet been completely understood. These contradictions may be explained by the difference in samples obtained, cell types and the effect of varying therapies given to humans for the treatment of diabetes, as well as the duration of DN that impact MMPs expression [243]. Certainly, the influence of hyperglycemia on MMP and TIMP expression effectively reinforce the degradation arm of MMP/TIMP system that ultimately lead to increase ECM accumulation and pathological disorders, resulting in reno-vascular complications of diabetes [243]. As shown in (Fig. 1), under diabetic condition, HG and AGE induce hypoxia, cellular ROS level, activation of PKC and TGF-β signaling pathway, leading to dysregulation of MMT/TIMPs expression via various transcription factor(s). In addition, HG can also regulate MMT/TIMPs expression through ERK1/2 MAPK and miRNA, which results in imbalance of ECM synthesis and degradation, leading to the progression of DN. However, as discussed in this review, the role of MMPs in DN is intriguingly complex and the mechanisms are still elusive. Continued research may be required to fully understand the underlying genetic and molecular regulation of MMPs in DN, and undoubtedly it will help us further expound the pathogenesis of DN.

Consensus of recent studies suggest that MMPs may serve as sensitive and clinically useful biomarkers for predicting pathological changes seen in DN. In future, MMP9 may become a new biomarker of renal injury like Neutrophil gelatinase- associated lipocalin (NGAL). A research study with Type 1 diabetic patients has indicated that the changes in urine NGAL

and MMP9 are concomitant, and both of them were positively correlated with albuminuria [244]. Urine MMP2 concentrations of type 1 diabetic subjects were correlated with several clinic parameters which predict increased risk for DN (renal hyperfiltration, microalbuminuria, duration of disease, and higher hemoglobin A1c levels) [245]. Furthermore, another study suggested the use of MMP-inhibitors as preventive therapeutic agents for patients with Alport syndrome before the onset of kidney disease could be advantageous, but if delayed from this early time frame the inhibition may result in detrimental progression of kidney injury [246]. If similar mechanisms are operative in the development of DN, then very early intervention with anti-MMP treatment in DN patients before the onset of microalbuminuria could prevent or retard the progression of DN [243]. Certainly, further studies are needed to define the redundancies and specificities of MMP regulators along with robust research efforts to fully comprehend the mechanism(s) involved in MMPs' regulation under hyperglycemia ambience in concert with a major effort to search for the drugs that could ultimately lead to potentially effective, and efficient therapeutic measures.

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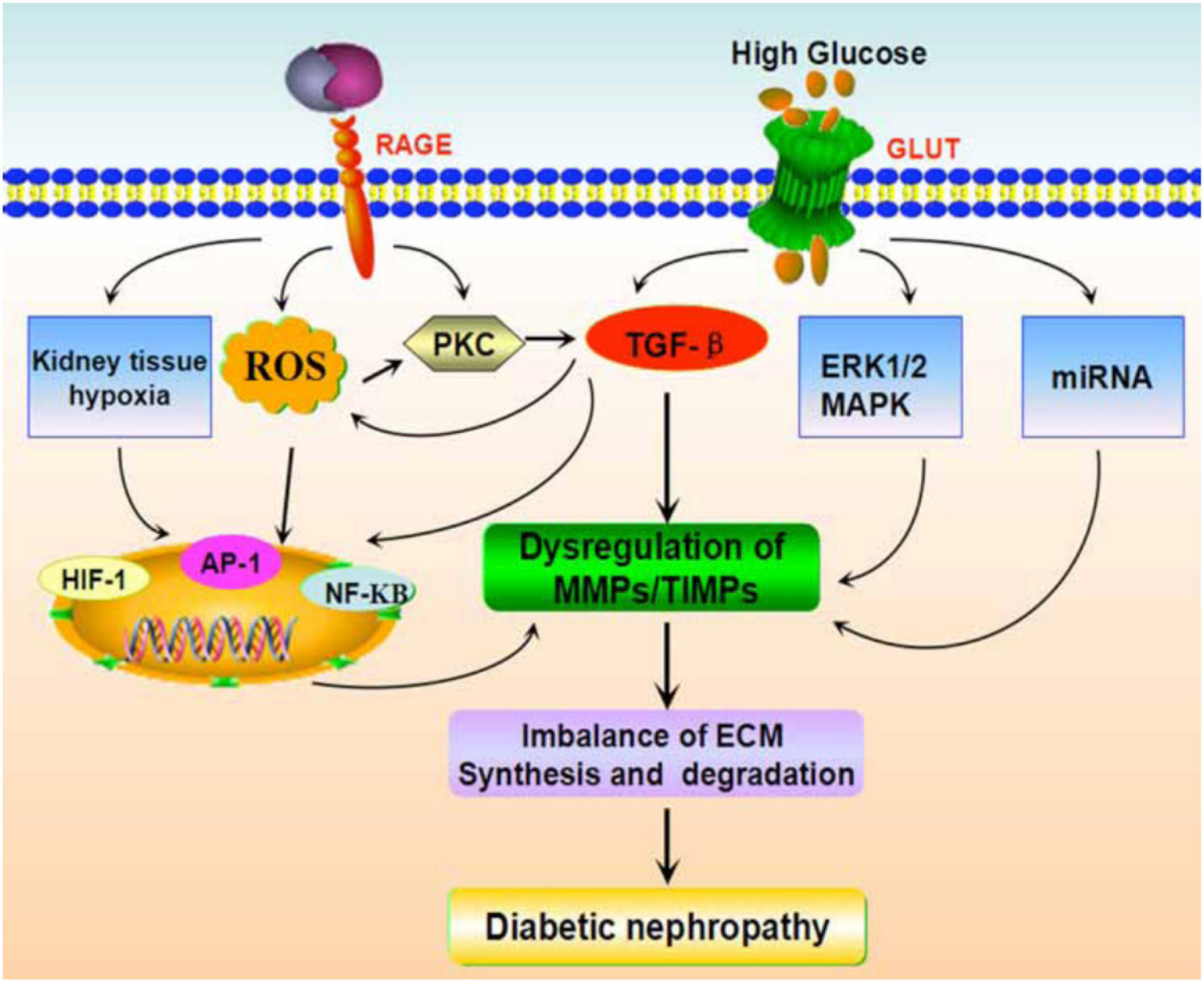

Fig. (1). Regulatory mechanism involving MMPs in the diabetic nephropathy

Schematic drawing depicting the conceivable regulatory mechanism(s) in MMPs/TIMPs regulation by high glucose and advanced glycation end products (AGEs). Hyperglycemia and AGEs may induce ROS and TGF-β as well kidney tissue hypoxia. The ROS, hypoxia and high glucose lead to the activation of NF-κB, AP-1 and HIF-1 and thereby transcription of some of the MMPs. Inside the cells, the AGEs and ROS can activate PKC, which in turn can modulate the expression of TGF-β. TGF-β stimulates synthesis of matrix glycoproteins and modulation of MMPs/TIMPS *via* transcriptional mechanisms. High glucose also can active ERK1/2MAPK signaling and miRNAs, leading to alter MMPs expression. In addition, the mechanical stretch, besides dysregulation of MMPs and TIMPs, lead to increased extracellular matrix synthesis and its accumulation and decreased degradation, the hallmark features of diabetic nephropathy.

Abbreviations: MMP, matrix metalloproteinase; TIMP, tissue inhibitor of metalloproteinase; ECM, extracellular matrix; AP-1, activator protein 1; NF-κB, nuclear factor kappa B; ROS, reactive oxygen species; TGF-β, transforming growth factor β;

ERK1/2, extracellular-signal-regulated kinases1/2; MAPKs, mitogen-activated protein kinases.

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Table 1

The Matrix Metalloproteinase (MMP) and Substrate As Well As Action

Group	MMPs	Enzyme	Substrate(s)	Activated by	Action(s) Pro-fibrotic Anti-fibrotic
Collagenases	MMP1	Collagenase-1	Collagen (I–III, VII, X); entactin, IL-1β; IGFBP-2,3; perlectan; pro-IL-1β; aggrecan; versican; perlecan; serpins	MMP-3,10; PDGF; plasmin; hyperglycemia; inflammatory cytokines; kallikrein; chymase	Yes [158]
	MMP8	Collagenase-2	Collagen (I–III, VII, X); aggrecan; fibronectin; pro-TNF-α; IGF-BP,	hyperglycemia; MMP-3,10; plasmin	Yes [79]
	MMP13	Collagenase-3	Collagens (I, II, III); gelatin; aggrecan; tenascin	MMP-2,3,10,14,15; plasmin, TGF-β	Yes [74] Yes [85]
	MMP18 (Xenopus)	Collagenase-4	not determined	not determined	
Gelatinase	MMP2	Gelatinase A	Collagen type (I, II, III, IV, V, VII, X, XI, XIV); gelatin; aggrecan; laminin; fibronectin; elastin; MMP-9; MMP-13	hyperglycemia; MMP-1,7,13,14,15,16,24,25; NF-KB; plasmin; TGF-β tryptase; CTGF thrombin	Yes [224] Yes [77]
	MMP9	Gelatinase B	Collagen (IV, V, VII, XI, XIV); gelatin; fibronectin; elastin; pro-IL-8; pro-TNF-α	hyperglycemia; MMP-2,3,13; TGF-β; TNF-α; VEGF; AP-1; NF-KB; plasmin	Yes [75] Yes [77]
Stromelysins	MMP3	Stromelysins-1	Collagens (III, IV, V, IX, X), proteoglycans, fibronectin, elastin	plasmin; kallikrein; chymase; tryptase	Yes [78]
	MMP10	Stromelysins-2	Collagens (III, IV, V); fibronectin, proteoglycan; aggrecan, gelatin	Elastase; hyperglycemia; cathepsin; plasmin;	Yes [133]
	MMP11	Stromelysins-3	Collagen IV; fibronectin; proteoglycans; laminin; IGFBP-1	Furin	Not determined
Matrilysins	MMP7	Matrilysins-1	Collagens (IV, X); fibronectin; E-cadherin; entactin	hyperglycemia; Wnt/β catenin MMP-3; plasmin	Yes [80] Yes [81]
	MMP26	Matrilysins-2	Collagen IV; fibronectin; fibrinogen; gelatin	Pro-MMP9	Not determined
Membrane-type	MMP14	MT1-MMP	Collagen (I, II, III), casein; laminin; fibronectin; nidogen; aggreca; tenascin; perlecan	TGF-β; hyperglycemia; Plasmin; furin; E-cadherin	Yes [62] Yes [77]
	MMP15	MT2-MMP	MMP2; fibronectin, laminin; tissue transglutaminase	not determined	Not determined
	MMP16	MT3-MMP	Collagen III; fibronectin; MMP2; tissue transglutaminase	furin	Not determined
	MMP17	MT4-MMP	Gelatin; fibronectin; proMMP2; fibrillin	not determined	Not determined
	MMP24	MT5-MMP	Collagen I; fibronectin; gelatin	hyperglycemia;	Not determined
	MMP25	MT6-MMP	Collagen IV; gelatin; fibrin; laminin; proMMP9	not determined	Not determined
Other MMPs	MMP12	Macrophase metalloelastase	Collagen IV; elastin; gelatin; plasminogen; fibronectin	Plasmin	Yes [82]

Group	MMPs	Enzyme	Substrate(s)	Activated by	Action(s) Pro-fibrotic Anti-fibrotic
	MMP19		Aggrecan; fibronectin; gelatin; nidogen; cartilage oligomeric matrix protein	Trypsin	Yes [83]
	MMP20	Enamelysin	Aggrecan; amelogenin; cartilage oligomeric matrix protein	not determined	Not determined
	MMP21		Gelatin; α-1-antitrypsin	not determined	Not determined
	MMP23		not determined	not determined	
	MMP27		not determined	not determined	
	MMP28	Epilysin	Neural cell adhesion molecule (NCAM); casein	not determined	Yes [84]

Adapted from references (26, 51, 52, 53) and from articles referred to in the text.