Matrix Metalloproteases: Potential Role in Type 2 Diabetic Nephropathy

Gantala Srilatha Reddy and Hanumanth Surekha Rani

Abstract

Type 2 diabetes mellitus is the most common form and constitutes a major diabetic population in all countries. The complications of diabetes mellitus (DM) include nephropathy, neuropathy, retinopathy, and cardiovascular disease. Type 2 diabetic nephropathy (DN) is a devastating complication of DM and a main cause of end-stage renal failure. Evidences show that susceptibility to Type 2 DN has a significant genetic component in addition to environmental factors. In Type 2 DN, hyperglycemia-induced changes include extracellular matrix (ECM) deposition, basement membrane (BM) thickening, as well as vascular smooth muscle and mesangial cell growth. ECM proteins are degraded by zinc-dependent endopeptidases called matrix metalloproteases (MMPs) which in turn are regulated by tissue inhibitors of metalloproteases (TIMPs). The proteases (MMPs) and antiproteases (TIMP) offer the opportunity to identify the determinants of the disease that are very likely to be causative and might lead to new therapeutics with strong molecular underpinning.

Keywords

Diabetes mellitus · Type 2 diabetic nephropathy · Glomerular basement membrane · Matrix metalloproteases · Tissue inhibitors of metalloproteases Polymorphism

G. Srilatha Reddy · H. Surekha Rani (✉)
Department of Genetics & Biotechnology, Osmania University,
Hyderabad 500007, Telangana, India
e-mail: surekharanih@gmail.com

S. Chakraborti and N.S. Dhalla (eds.), *Pathophysiological Aspects of Proteases*,
DOI 10.1007/978-981-10-6141-7_25

1 Introduction

1.1 Diabetes Mellitus

Diabetes Mellitus (DM) is a chronic multifactorial disorder associated with a relative or absolute deficiency of insulin or its function and presently reconciles as the twenty-first century's most common chronic disease worldwide. Globally the incidence of DM is increasing in all age-groups and the prevalence was estimated to be 2.8% (175 million people) in 2000 while recent trends show that it might increase to 4.4% (366 million people) in 2030 [1, 2].

DM is the most incessant disease and is the cause of death throughout the world and now ranks the fifth, succeeding communicable diseases, cancer, cardiovascular disease, and chronic respiratory diseases [3]. The long-term effects of DM include gradual development of specific complications of retinopathy (potential blindness), nephropathy (leading to kidney failure), and/or neuropathy, etc. Renal failure in diabetes, particularly in Type 2 DM, has become "a medical catastrophe of worldwide dimension."

1.2 Diabetic Nephropathy

One of the extreme complications of DM is diabetic nephropathy (DN) and develops in 25–40% of patients with Type 1 or Type 2 DM and an essential cause of increased morbidity and mortality in these patients [4]. It is the common cause of end-stage renal disease (ESRD) requiring dialysis. The classical definition of Type 2 DN is a progressive rise in urine albumin excretion, copulates with increasing blood pressure, and leads to declining glomerular filtration and eventually ESRD.

The risk factors for Type 2 DN include reduced glycemic control, prolonged duration of diabetes, insulin resistance, high blood pressure (BP), advanced age, smoking, race, genetic propensity, etc.

The existence of microalbuminuria is the earliest clinical evidence of nephropathy. Microalbuminuria progresses result in proteinuria. Once overt proteinuria develops, renal function progressively declines and ESRD attains [5]. Both environmental and genetic factors accord to the development and outcome of Type 2 DN.

The functional unit of the kidney is the glomerulus and glomerular mesangial cells together with resident monocytes/macrophages, and surrounding matrix material constitutes the mesangium. It is involved in regulation of glomerular circulation and filtration [6]. In addition to regulating glomerular filtration, it is also involved in basement membrane (BM) remodeling. Hyperglycemia induces hemodynamic and metabolic stimuli mediators for kidney injury. These activate ischemic, pro-oxidant, fibrotic, and inflammatory pathways leading to mesangial matrix accumulation.

Prolonged duration of hyperglycemia in Type 2 DN leads to noticeable changes like: diffuse glomerulosclerosis, thickened glomerular basement membrane (GBM), nodular glomerulosclerosis, podocyte loss, exudative lesions in the Bowman's capsule, glomerular hyperperfusion, and hyperfiltration. Many factors have been divulged to be involved in this defective regulation, including vascular endothelial growth factor (VEGF), nitric oxide, and the renin-angiotensin system, especially angiotensin II [7].

Alteration in the morphology occurs in mesangial cells due to continuous cycle of stretch/relaxation and leads to enhanced proliferation and increased production of extra cellular matrix (ECM) components. The effect of stretch occurs partially as a result of increase in expression of ECM components, fibronectin, collagen I, III, and IV, and laminin. The hemodynamic changes increase the production of mesangial cell matrix, promotes the leakage of albumin from the glomerular capillaries, expands the GBM, and causes injury to podocytes. It can also induce the release of localized growth factors and cytokines which in turn activates some of the matrix metalloproteases (MMPs) which further degrade the ECM present on GBM.

2 Matrix-Metalloproteases: General Aspects

MMPs are tightly regulated enzymes having the ability to degrade the ECM and BM constituents. They are a family of endopeptidases that share structural domains but diverge in cellular sources, substrate specificity, and inducibility. All MMPs have several prevailing characteristics which are as follows:

1. MMP family members within their organization have a conserved domain pattern.
2. They contain Zn^{2+} at their active site and require calcium a cofactor for their stability.
3. They are secreted as inactive zymogens and require activation for further ECM degradation.
4. The proteins which build up the BM and the ECM are the common substrates for all MMPs.
5. The MMP's enzymatic activity is optimal at physiological pH.
6. The MMP's proteolytic activity is inhibited by TIMPs.

The MMPs have been classified into six subgroups, based on the sequence homology and substrate specificity, Collagenases (MMP-1, 8, 13 and 18), Gelatinases (MMP-2 and 9), Stromelysins (MMP-3, 10 and 11), Matrilysins (MMP-7 and 26), Membrane-type matrix metalloproteases (MT-MMP-14, 15, 16, 17, 24 and 25), and other MMPs (MMP-12, 19, 20, 21, 23, 27 and 28). Except for the MT-MMPs, most of the MMPs are secreted out and have extracellular distribution; however, recent

evidence suggests that some MMPs like MMP-1, 2 and 11 have intracellular expression where they may merge with cytosolic proteins to modulate various biological processes [8].

3 The Biological Roles of the MMPs

Numerous physiological and developmental events are regulated by ECM. MMPs degrade ECM, and the main function is assumed to be the remodeling of the ECM. Morphogenesis and tissue growth is a critical process of remodeling of ECM and MMPs control angiogenesis by releasing pro-angiogenic factors such as basic fibroblast growth factor (bFGF) or VEGF [9]. MMPs uphold cell proliferation by augmenting the release of insulin-like growth factor (IGF) and the transforming growth factor α (TGF-α). Regulation of apoptosis is the main biological role of MMPs as an increase in apoptotic cell death is substantiated by the over expression of certain MMPs like MMP-3, 7, 9, and 11.

4 Regulation of MMPs

MMPs are neutral proteases maintain the equity between synthesis and degradation of matrix proteins. The MMP proteolytic actions are controlled at three levels involving, proenzyme activation, transcription, and inhibition by the TIMPs. The MMPs are synthesized as pro-MMPs (latent zymogens), and their enzymatic activation requires prodomain removal. The serine proteases or the other active MMPs also extracellularly activate most MMPs, for example, MMP-2 requires active MT1-MMP and TIMP-2 which binds to C-terminus of pro-MMP-2 which further undergoes a complex activation pathway.

The MMP transcriptional regulation mechanism in kidney disease is quite complex and in turn induced by various signals, such as cytokines, oncogene products, growth factors and also the activation of many other signal transduction pathways [10]. Metabolic pathways are the major arbitrators of Type 2 DN involving the activation of the immune system and chronic inflammation. Several studies suggest that the meager raise in monocytes/macrophages noticed in glomeruli contributes significantly to the development of Type 2 DN. Inherent renal cells, in conjunction with mesangial, glomerular endothelial, dendritic, and renal tubular cells, are able to upregulate the inflammatory factors and cytokines, mainly interleukin 1 (IL-1), IL-6, and IL-18, VEGF, tumor necrosis factor a (TNF-a), and TGF-β, which all have been implicated in transcription regulation of MMPs in Type 2 DN progression.

Lastly, the MMP's activity is controlled tightly by the action of endogenous inhibitors (TIMPs). They have an N-terminal and C-terminal domain of 125 and 65 amino acids with each comprising three conserved disulfide bonds. The N-terminal

domain folds as a separate unit and is capable of inhibiting most of the MMPs. In addition to TIMPs, another important inhibitor of MMPs is α-2 macroglobulin which binds to MMP receptors generating an MMP-macroglobulin complex which is inactive.

5 High Glucose (HG) and MMPs

There are several mechanisms by which dysregulation in renal MMPs and TIMPs ratio or activity in kidney could commit to the development of progressive Type 2 DN. As previously mentioned, MMP's expression is firmly controlled by diverse mechanisms that include transcription and posttranscription. Evidence illustrates that increase in glucose levels may also regulate MMP gene expression via varied transcription factors NF-κB and AP-1 or relies upon growth factors like connective tissue growth factor (CTGF) and transforming growth factor (TGF-β) [11, 12].

6 AGEs and MMPs

Glycol-oxidation end products or advanced glycation end products are known as AGEs are one of the major aberrantly synthesized molecules that can influence the progression of Type 2 DN. Hyperglycemia leads to the generation of AGEs which is primarily as a consequence of a condensation of free amino group and sugar with the development of a labile Schiff base which undergoes complicated intramolecular modification to generate complex toxic AGEs. Such derivatization can occur between sugar and lipids as well, and their production can be initiated in both intra and extracellular compartments [13, 14].

Several forms of AGE derivatives have been described in renal injury related to diabetes, and morphologic changes that are often related with it encompass glomerular and tubular BM thickening, capillary aneurismal delay, mesangial expansion with production of Kimmelstiel-Wilson nodules, arteriolar thickening, and hyalinosis. AGE formation can modify the function of certain important ECM molecules, such as collagen Type 1, 3, 4, fibronectin, laminin, etc. Furthermore, AGEs can modulate the intracellular signaling pathways, gene and protein expression by interacting with their receptors, i.e., RAGE.

The AGEs via AGE: RAGE synergy can stimulate PKC, MAPK, and NF-kB, which can, in turn, modulate the expression of TGF-β and subsequently MMPs. Such ligand: receptor synergy can also generate reactive oxygen species (ROS), which then can regulate the MMPs expression via articulation of various transcription factors [15].

7 MMPs in Type 2 Diabetic Nephropathy

Type 2 diabetic nephropathy is a feature of renal and interstitial fibrosis, which ultimately progresses toward ESRD. Normal growth and development is the main physiologic feature of ECM remodeling. At several levels of ECM turnover MMPs are involved, playing a crucial role in glomerular ECM synthesis and degradation [16]. MMPs are redox sensitive, as high levels of oxidative stress and inflammatory markers activate them from their inactive latent form to active form. The amount and durational activity of MMPs determine the extent of glomerular structural damage as demonstrated by higher MMP levels in various glomerulonephritis forms [17].

The observations of Johnson et al. [18] could relate redox stress, inflammation, and MMP in glomerular failure. The presence of elevated levels of MMPs within inflammatory glomeruloscelerosis has led to the indication that increased inflammatory response coupled with increased MMP levels may cause the glomerular damage in Type 2 DN [19].

With a robust activation of MMPs, the BM and supporting ECM could be degraded allowing a complete detachment of the renal cells (mesangial cell, podocyte, and endothelial cell) within the glomerulus and the proximal renal tubule ensuing in ECM remodeling, apoptosis, atrophy, dysfunction, and cytoskeleton rearrangement. MMPs produced in various cell types in the kidney suggest their involvement in ECM degradation in glomerulus, renal morphogenesis, and remodeling [20, 21]. The dysregulated remodeling and accumulation of ECM in renal fibrosis affect all main compartments of the kidney being termed glomerulosclerosis in the glomeruli, tubulointerstitial fibrosis in the tubulointerstitium, and arterio- and arteriolosclerosis in the vasculature, where all renal cells are involved in fibrosis [22].

8 Polymorphic Studies of MMPs in Type 2 DN

Single nucleotide polymorphism (SNPs) can be used to identify the DNA sequence variation, susceptibility to disease and to understand an individual response to certain drugs.

8.1 Collagenases

Collagenases are enzymes that cleave the peptide bonds of collagen, the main component of ECM, includes collagenase-1, 8 and 13. MMP-1 (Interstitial Collagenase) which is localized on chromosome 11q22 is the most ubiquitously considered interstitial collagenase and it's over expression is associated with several diseases. MMP-1 having collagen as the main substrate is a key determinant of

ECM degradation, degrades the interstitial collagens, collagen Type 1, 2, and 3 [23]. A SNP at −1607 bp promoter region in human MMP-1 gene has been found to be associated with elevated risk of various diseases including Type 2 DN. The MMP-1 promoter region contains consensus sequences for DNA-binding proteins such as Ets/PEA-3, AP-1, and AP-2 [24].

The transcription is augmented by creating an Ets binding site at SNP (−1607) promoter region. The transcriptional start site of the MMP-1 gene at −1607 position is proportionate by two alleles (1G) or (2G) guanine nucleotides [25]. A 20 fold higher transcriptional activity seen in 2G allelic promoter of MMP-1 gene than 1G allele and is associated with higher MMP-1 levels.

MMP-8 (Matrix metalloproteinase-8) plays a major role in degradation of ECM components, collagens Type 1, 2 and 3, modifies the immune responses and regulates the cytokine activity. The gene coding for MMP-8 is located on chromosome 11q22.3. The three polymorphisms at −381A/G, −799 C > T and +17C/G in the MMP-8 gene are known to modify the gene transcription [26].

Human collagenase-3 (MMP-13), a protease, plays a role in ECM degradation and cleaves collagen Type 1, 2, 3, 4, 14 and Type 10 and also activates or degrades key regulatory proteins such as CTGF and TGFB1. The gene coding for MMP-13 is located on chromosome 11q22.2. A SNP at 77A → G in the promoter region of the MMP-13 gene has been detected. The SNP at this position leads to alterations in the gene expression and plays a modulatory role on transcriptional activity in the pathogenesis of various diseases [27].

8.2 Gelatinases

Gelatinases are proteolytic enzymes that hydrolyze gelatin into polypeptides, peptides, and amino acids. In humans, gelatinases are MMP-2 and MMP-9. MMP-2 is notably interesting because of its multiple functions and ubiquitous expression [28]. MMP-2, also known as gelatinase A, is a 72 kDa that degrades Type 4 collagen and is located on chromosome 16q12.2. It is a fundamental component of the BM. Increased expression of MMP-2 may accelerate the degeneration of gap junction protein and Type 4 collagen, leading to the vascular complications of diabetes and Type 2 DN.

Several SNPs have been described in the promoter region of MMP-2 and of these two SNPs C-1306T and C-735T prevailing upstream from the transcriptional start site effect MMP-2 transcriptional activity. MMP-2 is likely to be regulated by transcription factors; among these controlling elements, Sp1 binding site is important.

Price et al. [29] suggested that the MMP-2 transition at promoter region C-1306T could remarkably alter the promoter activity, due to disruption of the Sp1 binding site (CCACC box). MMP-2 is expressed in mesangial cells, and as a result of proinflammatory signaling, the dramatical expression of MMP-2 is elevated in various glomerulopathies [30].

MMP-9 (gelatinase B) degrades the ECM components exclusively Type 4 collagen, gelatin, and laminin, and the gene coding for MMP-9 is located on chromosome 20q11.2-q13.1 [31]. A number of SNPs found in the promoter region particularly an SNP at −1562C > T has distinct implication and has an allele-specific effect on MMP-9 transcription suggesting that MMP-9 may play a critical role in the turnover of the mesangial matrix in Type 2 DN [32]. This promoter contains the 9-bp sequence (GCGCAC/TGCC) an important gene expression regulatory element. The increased levels of MMP-9 results are due to the loss of DNA–protein interaction due to a C to T substitution.

In addition, a recent study has shown that Type 2 DN patients has elevated levels of MMP-9 and had a substantial association with age, hyperglycemia, blood pressure, body mass index, glycated hemoglobin (HbA1c), and progression of diabetes [33].

8.3 Stromelysins

Stromelysin, the enzymes of MMP family, plays a major role in the degradation of proteoglycans, gelatin, and other ECM constituents. It includes MMP-3 (stromelysin-1), MMP-10 (stromelysin-2) and MMP-11 (stromelysin-3). MMP-3 (stromelysin-1), a member of MMP-family degrades collagen Types 3, 4, 9 and 10, proteoglycans, elastin, fibronectin and laminin, and also involved in the activation of other MMPs (e.g. pro-MMP-1, -8, -9 and -13), and auto activation of pro-MMP-3. The gene is located on the chromosome 11q22.2-22.3, and the expression level of this gene was found to be altered by SNPs.

At the upstream of the MMP-3 transcription start site, the SNP identified in the promoter region at −1171 bp has one allele having five adenosines (5A) and other having run of six adenosines (6A) and was found the allele having five adenosines has higher transcriptional activity [34]. MMP-3 elevated levels have been observed in sera from patients with a number of diseases like active lupus nephritis, mesangial proliferative glomerulonephritis, IgA nephropathy, etc.

Stromelysin-2 (MMP-10) is another important Zn-dependent endopeptidase cleaves laminin, fibronectin, proteoglycan core protein, elastin, gelatins of Type 1, 3, 4, and 5. MMP-10 also activates pro-MMP-1, -7, -8 and -9, which degrades extracellular collagen in different pathological conditions along with other MMPs. The gene is part of a cluster of MMP genes and located on chromosome 11q22.3. The two polymorphisms rs17435959 (G > C) at position 102780582 and rs17293607 (C > T) at position 102779658 are identified. These two polymorphisms lead to the substitution of specific amino acids and may have functional effects. MMP-10 serum levels have a close relationship with some risk factors for ischemic stroke, such as carotid intima-media thickness, presence of carotid plaques, inflammatory markers and smoking and its role in the pathogenesis of Type 2 DN are still unexplored.

Stromelysin-3 (MMP-11), the enzyme encoded by this gene is intracellularly activated by furin, in contrast to other MMP's, and cleaves alpha 1-proteinase

inhibitor but weakly degrades structural proteins of the ECM. The gene for MMP-11 is located on chromosome 22q11.23. MMP-11 associated diseases mostly include ophthalmomyiasis and colorectal cancer.

8.4 Tissue Inhibitors Metalloproteases (TIMPs)

MMPs are inhibited by TIMPs consisting of 184–194 amino acids. Four structurally related TIMP family members include TIMP-1, -2, -3 and -4. Inhibition is accomplished by their ability to interact with the zinc-binding site within the catalytic domain of active MMPs [35]. TIMPs have a certain degree of specificity toward MMP family members. To maintain the sustainability of healthy tissues, the balance between MMPs and TIMPs is important. The balance disrupted by the polymorphic variants within TIMP gene is associated with development of various diseases.

The biological activities of TIMPs involve anti-angiogenesis, cell migration, effects on cell growth and differentiation, synaptic plasticity, anti- and pro-apoptosis. Type 2 DN certainly associate with altered activity of the MMP and TIMP which in turn leads to glomerulosclerosis [36].

8.4.1 Metallopeptidase Inhibitor 1/TIMP-1

The best-identified gene is the TIMP-1, present on X chromosome (Xp11.3-p11.23). TIMPs bind with active MMPs with high affinity and have complicated roles in pathological and physiological tissue remodeling. TIMPs inhibit all MMPs, but TIMP-1 is an indigent inhibitor of MT1-MMP, MT3-MMP, MT5-MMP, MMP-19 and, ADAM-10. At exon 6 of TIMP-1 gene located 536C/T polymorphism capable of binding and preventing the activation of most MMPs [37].

8.4.2 Metallopeptidase Inhibitor 2/TIMP-2

TIMP-2 is a secretory protein located at 17q25, inhibits the proteolytic activity of MMP-2 involved in the ECM degradation. Additionally, Apoptosis and cell growth are regulated by TIMPs [38]. An SNP identified at G > C −418 position in the promoter region of TIMP-2 may influence the binding of Sp1 transcription factor and downregulates the TIMP-2 transcriptional activity [39].

8.4.3 Metallopeptidase Inhibitor 3/TIMP-3

TIMP-3, a member of the TIMP family, inhibits the action of MMPs which are involved in ECM degradation. It has also been shown to have inhibitory effects on angiogenesis and tumor growth [12, 13]. ADAM-10, 12, 17 and ADAMTS-1, 4 and 5 are inhibited by TIMP-3, and the gene is located on chromosome 22q12.3. Recently, three novel polymorphisms in the promoter region of TIMP-3 gene (−899T/A, −915A/G and −1296T/C) have been identified. TIMP-3 polymorphism has an impact on various complex diseases such as spontaneous abortion, cancer, diabetic nephropathy, macular degeneration, and hypertension [40].

8.4.4 Metallopeptidase Inhibitor 4/TIMP-4

TIMP-4 belongs to the TIMP gene family and is expressed predominantly in the heart, which inhibits the action of MMP-2 by binding strongly to MMP-2 carboxyl hemopexin domain. The gene is located on chromosome 3p25.2. Two SNPs (rs3755724, −55C/T, promoter; rs17035945, 3′-untranslated region) were genotyped in TIMP-4 gene [41].

9 Conclusion

Type 2 end-stage renal disease is a devastating condition, MMPs are the major regulators of ECM degradation in Type 2 DN pathology and progression. The proteases (MMPs) and antiproteases (TIMP) offer the opportunity to identify the determinants of the disease that are very likely to be causative and may also lead to new therapeutics with strong molecular underpinning.

References

1. Amos AF, McCarty DJ, Zimmet P (1997) The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 19:S1–S85
2. Chan JC, Malik V, Jia W et al (2009) Diabetes in Asia: epidemiology, risk factors, and pathophysiology. JAMA 301:2129–2140
3. King GL (2008) The role of inflammatory cytokines in diabetes and its complications. J Periodontol 79:1527–1534
4. Murphy M, Crean J, Brazil DP, Sadlier D, Martin F, Godson C (2008) Regulation and consequences of differential gene expression in diabetic kidney disease. Biochem Soc Trans 36:941–1005
5. Hemanth KN, Prashanth S, VidyaSagar J (2011) Diabetic nephropathy pathogenesis and newer targets in treatment. Int J Pharm Sci Rev Res 6:91–101
6. Kimberly R, Hyun Mi K, Thomas H, Katalin S (2014) Molecular mechanisms of diabetic kidney disease. J Clin Investig 124(6):2333–2340
7. Ziyadeh FN, Wolf G (2008) Pathogenesis of the podocytopathy and proteinuria in diabetic glomerulopathy. Curr Diab Rev 4:39–45
8. Xu X, Xiao L, Xiao P et al (2014) A glimpse of matrix metalloproteinases in diabetic nephropathy. Curr Med Chem 21(28):3244–3260
9. Bergers G, Brekken R, McMahon G et al (2000) Matrix metalloproteinase-9 triggers the angiogenic switch during carcinogenesis. Nat Cell Biol 2:737–744
10. Egeblad M, Werb Z (2002) New functions for the matrix metalloproteinase in cancer progression. Nature 2:161–174
11. Hsieh HL, Chi PL, Lin CC, Yang CC, Yang CM (2014) Up-regulation of ROS-dependent matrix metalloproteinase-9 from high-glucose-challenged astrocytes contributes to the neuronal apoptosis. Mol Neurobiol 50:520–533
12. Kanwar YS, Sun L, Xie P, Liu FY, Chen S (2011) A glimpse of various pathogenetic mechanisms of diabetic nephropathy. Annu Rev Pathol 6:395–423
13. Busch M, Franke S, Ruster C, Wolf G (2010) Advanced glycation end-products and the kidney. Eur J Clin Invest 40(8):742–755

14. Schrijvers BF, De Vriese AS, Flyvbjerg A (2004) From hyperglycemia to diabetic kidney disease: the role of metabolic, hemodynamic, intracellular factors and growth factors/cytokines. Endocr Rev 25(6):971–1010
15. Wendt T, Tanji N, Guo J et al (2003) Glucose, glycation, and RAGE: implications for amplification of cellular dysfunction in diabetic nephropathy. J Am Soc Nephrol 14 (5):1383–1395
16. Engelmyer E, van Goor H, Edwards DR, Diamond JR (1995) Differential mRNA expression of renal cortical tissue inhibitor of metalloproteinase-1, -2, and -3 in experimental hydronephrosis. J Am Soc Nephrol 5(9):1675–1683
17. Akiyama K, Shikata K, Sugimoto H et al (1997) Changes in serum concentrations of matrix metalloproteinases, tissue inhibitors of metalloproteinases and type IV collagen in patients with various types of glomerulonephritis. Res Commun Mol Pathol Pharmacol 95:115–128
18. Johnson PJ, Tyagi SC, Katwa LC et al (1998) Activation of extracellular matrix metalloproteinases in equine laminitis. Vet Rec 142:392–396
19. Catania JM, Chen G, Parrish AR (2007) Role of matrix metalloproteinases in renal pathophysiologies. Am J Physiol Renal Physiol 292:F905–F911
20. Dimas G, Iliadis F, Grekas D (2013) Matrix metalloproteinases, atherosclerosis, proteinuria and kidney disease: link-age–based approaches. Hippokratia 17:292–297
21. Keeling J, Herrera GA (2008) Human matrix metalloproteinases: characteristics and pathologic role in altering mesangial homeostasis. Microsc Res Tech 71:371–379
22. Matthew G, William CP (2014) Diverse functions of matrix metalloproteinases during fibrosis. Dis Model Mech 7:193–203
23. Saffarian S, Collier IE, Marmer BL, Elson EL (2004) Goldberg G. Interstitial collagenase is a brownian ratchet driven by proteolysis of collagen. Science 306:108–111
24. Rutter JL, Mitchell TI, Buttice G et al (1998) A single nucleotide polymorphism in the matrix metalloproteinase-1 promoter creates an Ets binding site and augments transcription. Cancer Res 58:5321–5325
25. Arakaki PA, Marques MR, Santos MCLG (2009) MMP-1 polymorphism and its relationship to pathological processes. J Biosci 34:313–320
26. Izakovicova HL, Hrdlickova B, Vokurka J, Fassmann A (2012) Matrix metalloproteinase 8 (MMP8) gene polymorphisms in chronic periodontitis. Arch Oral Biol 57:188–196
27. Leeman MF, Curran S, Murray GI (2003) The structure, regulation, and function of human matrix metalloproteinase-13. Crit Rev Biochem Mol Biol 37(3):149–166
28. Aimes RT, Quigley JP (1995) Matrix metalloproteinase-2 is an interstitial collagenase. Inhibitor-free enzyme catalyzes the cleavage of collagen fibrils and soluble native type I collagen generating the specific 3/4- and 1/4-length fragments. J Biol Chem 270:5872–5876
29. Price SJ, Greaves DR, Watkins H (2000) Identification of novel, functional genetic variants in the human matrix metalloproteinase-2 gene: role of Sp1 in allele-specific transcriptional regulation. J Biol Chem 276(10):7549–7558
30. Pan MR, Hung WC (2002) Nonsteroidal anti-inflammatory drugs inhibit matrix metalloproteinase-2 via suppression of the ERK/Sp1-mediated transcription. J Biol Chem 277(36):32775–32780
31. Eberhardt W, Huwiler A, Beck KF, Walpen S, Pfeilschifter J (2000) Amplification of IL-1ß-induced matrix metalloproteinase-9 expression by superoxide in rat glomerular mesangial cells is mediated by increased activities of NF-kB and activating protein-1 and involves activation of the mitogen-activated protein kinase pathways. J Immunol 165:5788–5797
32. Zhang B, Ye S, Herrmann SM et al (1999) Functional polymorphism in the regulatory region of gelatinase B gene in relation to severity of coronary atherosclerosis. Circulation 99:1788–1794
33. Tadahide K, Yutaka Y, Junichi KPK et al (2004) Expression of MMP-9 in mesangial cells and its changes in anti-GBM glomerulonephritis in WKY rats. Clin Exp Nephrol 8:206–215

34. Humphries S, Bauters C, Meirhaeghe A, Luong L, Bertrand M, Amouyel P (2002) The 5A6A polymorphism in the promoter of the stromelysin-1 (MMP3) gene as a risk factor for restenosis. Eur Heart J 23:721–725
35. Keith B, Hideaki N (2010) The tissue inhibitors of metalloproteinases (TIMPs): an ancient family with structural and functional diversity. Biochim Biophys Acta 1803:55–71
36. Kanauchi M, Nishioka H, Nakashima Y, Hashimoto T, Dohi K (1996) Role of tissue inhibitors of metalloproteinase in diabetic nephropathy. Nihon Jinzo Gakkai Shi 38:124–128
37. Lambert E, Boudot C, Kadri Z et al (2003) Tissue inhibitor of metalloproteinases-1 signalling pathway leading to erythroid cell survival. Biochem J 372:767–774
38. Hoegy SE, Oh HR, Corcoran ML, Stetler-Stevenson WG (2001) Tissue inhibitor of metalloproteinases-2 (TIMP-2) suppresses TKR-growth factor signaling independent of metalloproteinase inhibition. J Biol Chem 276:3203–3214
39. Jaworski DM, Perez-Martinez L (2006) Tissue inhibitor of metalloproteinase-2 (TIMP-2) expression is regulated by multiple neural differentiation signals. J Neuro chem 98:234–247
40. Beranek M et al (2003) Three novel polymorphisms in the promoter region of the TIMP-3 gene are not associated with proliferative diabetic retinopathy in Type 2 diabetes mellitus. Curr Eye Res 27(2):91–93
41. Olson TM, Hirohata S, Ye J, Leco K, Seldin MF, Apte SS (1998) Cloning of the human tissue inhibitor of metalloproteinase-4 gene (TIMP4) and localization of the TIMP4 and Timp4 genes to human chromosome 3p25 and mouse chromosome 6, respectively. Genomics 51 (1):148–151