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Review Article

Matrix Metalloproteinases in Renal Diseases: A Critical Appraisal

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Abstract
Matrix metalloproteinases (MMPs) are endopeptidases within the metzincin protein family that not only cleave extracellular matrix (ECM) components, but also process the non-ECM molecules, including various growth factors and their binding proteins. MMPs participate in cell to ECM interactions, and MMPs are known to be involved in cell proliferation mechanisms and most probably apoptosis. These proteinases are grouped into six classes: collagenases, gelatinases, stromelysins, matrilysins, membrane type MMPs, and other MMPs. Various mechanisms regulate the activity of MMPs, inhibition by tissue inhibitors of metalloproteinases being the most important. In the kidney, intrinsic glomerular cells and tubular epithelial cells synthesize several MMPs. The measurement of circulating MMPs can provide valuable information in patients with kidney diseases. They play an important role in many renal diseases, both acute and chronic. This review attempts to summarize the current knowledge of MMPs in the kidney and discusses recent data from patient and animal studies with reference to specific diseases. A better understanding of the MMPs' role in renal remodeling may open the way to new interventions favoring deleterious renal changes in a number of kidney diseases.

Introduction

The matrix metalloproteinases (MMPs) are zinc-dependent endopeptidases within the metzincin subfamily, composed of 25 structurally related peptides [1], classified according to their presynthetic region on chromosomes, their various substrate specificities, and partly to

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their cellular localization. The MMPs share a common functional domain structure. Three common highly conserved domains constitute the general MMP architecture: the pro-domain, the catalytic domain containing the highly conserved zinc-binding site, and a hemopexin C terminal domain [2]. The MMPs are also classified according to fibronectin-like repeats and a flexible hinge region.

Based on their structural features, MMPs can be divided into six major groups, namely: collagenases, gelatinases, stromelysins, matrilysins, membrane-bound MMPs and "other MMPs." Number designations, MMP-1 to MMP-28, are used for classification [3]. MMPs contain the motif His-Glu-X-X-His (X represents any amino acid) that binds zinc in the catalytic site, as well as another zinc molecule and two calcium molecules structurally. The matrixin subfamily are EC designated 3.4.24.x. This group also contains astacin, reprolysin, and serralysin, as well as other more divergent metalloproteinases.

All MMPs are initially synthesized as inactive proenzymes. The pro-domain removal of MMP enables the activation of the proteolytic abilities of these enzymes. The activation of proenzymes occurs either intracellularly by pro-protein convertases, or extracellularly by peptidases such as other MMPs, or plasmin [2, 4]. This tight regulation of MMP activity at the transcriptional and posttranscriptional levels leads to the constitutive expression of some MMPs or to the expression of other MMPs only after transcriptional activation [5].

The processes which lead to the activation of zymogens are crucial for the extracellular matrix (ECM) breakdown. MMPs cleave several ECM components including collagens, gelatins, elastin, glycoproteins, proteoglycans, and casein [6, 7]. Moreover, modern biochemical techniques, e.g. the usage of the degradomic approach, high-throughput and high-resolution analysis, allow the uncovering of not only other ECM substrates, but also novel non-ECM substrates of MMPs that modify cellular functions [2, 7, 8]. MMPs cleave cell surface receptors, process diverse bioactive molecules including chemokines and growth factors [8]. They are also implicated in the release of apoptotic signals and the activation or inactivation of many cytokines [8]. The extracellular MMP activity ranges from changes in cell-to-cell interactions, cell to ECM adhesions, cell survival, and proliferation to tissue composition and cell motility [8, 9].

The proteolytic activities of the MMPs are further controlled mainly by specific endogenous inhibitors comprising tissue inhibitors of metalloproteinases (TIMPs), α_2-macroglobulin, netrins, tissue factor inhibitor 2, type I collagen C-proteinase enhancer protein, cell surface inhibitor, and the reversion-inducing cysteine-rich protein with Kazal motifs (RECK) [2, 10]. In general, all MMPs are inhibited by TIMPs. The mechanism of TIMP inhibition encompasses the binding of N-terminal domain to the catalytic site of the MMPs, where a cysteine-chelating group inactivates the catalytic zinc site with an N-terminal amino and carbonyl group [1, 11] (Fig. 1). TIMPs specifically inhibit MMPs and regulate ECM turnover and tissue remodeling by forming tight-binding inhibitory complexes with MMPs, binding the zinc atom on the MMP active site [12]. Thus, the role of TIMPs involves the maintenance of the balance between ECM formation and ECM breakdown.

MMPs have significant substrate overlap. In general, the collagenases MMP-1, MMP-8, and MMP-13 degrade fibrillar collagen, which is further cleaved by gelatinases MMP-2 and MMP-9. MMP production is tightly regulated, and its expression may be cell specific and depends on signals that are temporarily expressed [13]. MMPs play a pivotal role in embryonic development, tumor growth, and tissue fibrosis in the liver, lung, and kidney [13, 14].

Detailed information on immunohistochemical analysis and subcellular localization of MMP expression in human kidney tissues is available at www.proteinatlas.org [15, 16].

For better orientation in the following text, a short recapitulation of cells present in the kidney is provided.

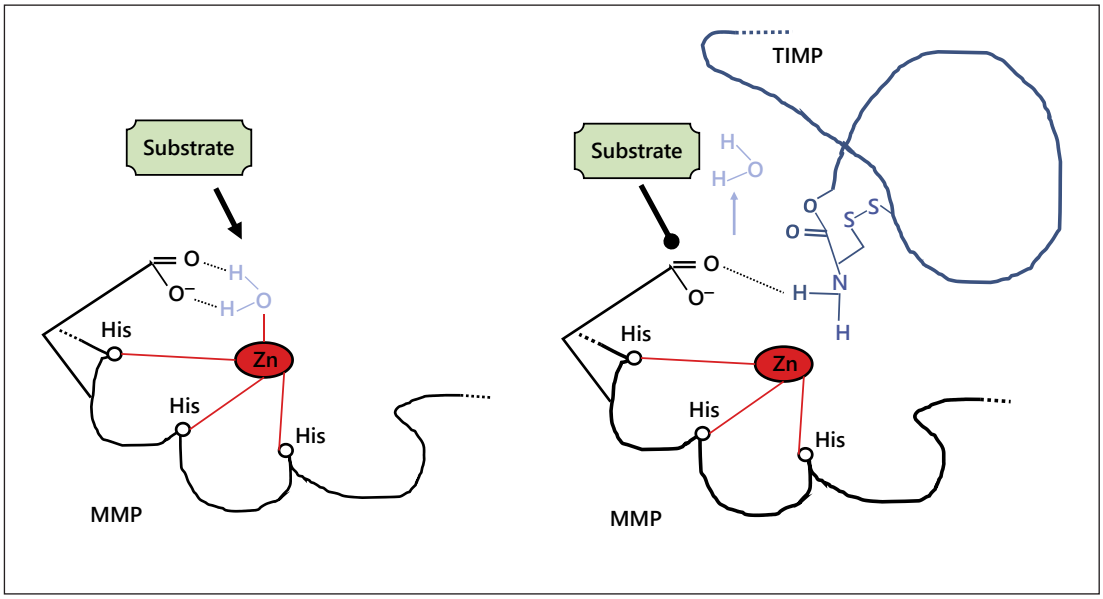

Fig. 1. Schematic structure of the MMP-TIMP interaction. Modified from Gu et al. [301] with permission from ASPET.

In the kidney, the capillaries and the mesangium are covered with epithelial cells (podocytes), constituting the visceral epithelium of Bowman's capsule. Visceral epithelial cells produce the components of the glomerular basement membrane. The parietal epithelium of Bowman's capsule is composed of squamous epithelial cells located on a basement membrane. Mesangial cells are derived from a smooth muscle lineage and are adjacent to the endothelium and thus regulate signaling, recruitment of nonresident cells, and maintenance of the vascular tone in the kidney. There are other mesangial cells nested in the kidney originating from macrophages and monocytes. The mesangial cells are embedded in ECM matrix comprising collagen IV, V, fibronectin, laminin, and proteoglycans. The tubular epithelium contains a single layer of cells anchored to the basement membrane. The collecting duct contains two types of cells: principal cells and intercalated cells, these cells regulate the transport of ions and water. The juxtaglomerular apparatus contains renin-producing juxtaglomerular cells. The interstitium of the kidney is composed of the resident fibroblasts providing a scaffold frame for glomeruli, tubuli, and blood vessels. The interstitium also contains the migrating cells of the immune systems, mainly the dendritic cells. The space between cells is filled by ECM proteins, e.g. proteoglycans, glycoproteins, fibrils, and interstitial fluid.

In the kidney, glomerular intrinsic cells and tubular epithelial cells synthesize MMPs [16, 17]. In addition, macrophages also produce MMPs. Macrophages are cells which play an important role in most human glomerulonephritides [17, 18]. The expression profile of MMPs and TIMPs along the nephron is shown in Figure 2.

MMPs are dominant regulators of ECM formation and breakdown in the glomerulus. Differences in MMP expression or MMP activity determine intrarenal ECM composition [15, 19, 20]. Moreover, MMPs in line with TIMPs influence multiple processes, including: chemokine and cytokine production and release, chemotaxis, the release of apoptotic signals, the activity and proliferation of multiple cell lines [20].

The current knowledge of MMPs in the kidney and recent data from animal and human studies with reference to specific renal disease are further elucidated in this review (Table 1).

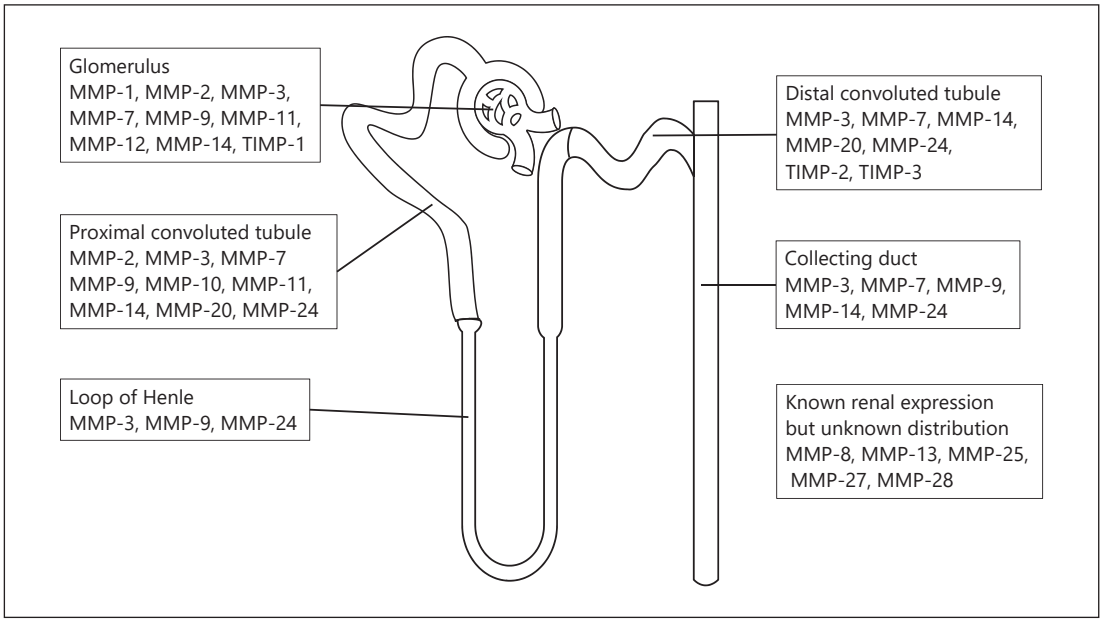

Fig. 2. Known expression profile of MMPs and TIMPs along the nephron in healthy and disease states. Modified from Tan and Liu [20] with permission from The American Physiological Society. Data is accumulated from many original sources.

Collagenases (MMP-1, MMP-8, MMP-13, and MMP-18)

Collagenases: Structure and Function

The collagenases (MMP-1, MMP-8, MMP-13, and MMP-18) cleave fibrillar collagens into 3/4 and 1/4 fragments, which become available for degradation by other MMPs, specifically by the gelatinases MMP-2 and MMP-9 [5]. The other important substrates of collagenases include gelatin, aggrecan, casein, versican, laminin, tenascin [10]. While MMP-1 preferentially degrades collagen III, MMP-8 cleaves collagen I, MMP-13 preferentially cleaves collagen II over collagen I and III [21]. MMP-18 cleaves collagen I. MMP-18 is present in many tissues but is not detected in kidney [22].

Collagenases and Kidney Disease

In glomerular disease, mesangial cells dedifferentiate in reaction to injury, from a mature cell to a myofibroblastic one capable of contraction and proliferation. Mesangial cells are known to be able to produce ECM constituents including type IV collagen. On the other hand, myofibroblastic cells can produce collagens I and III, which normally are not found in glomeruli [23]. In fact, glomerular sclerosis is triggered by the transforming growth factor-β1 (TGF-β1), resulting in an accumulation of type I and III collagen instead of type IV collagen [23, 24].

The known inducers of MMP-1 are ECM MMP inducer [5, 25], oxidized low-density lipoprotein [5, 26], and such cytokines as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) [27]. IL-1, TNF-α and also to some extent IL-6, induce MMP-13 expression [5, 28]. In contrast, inflammatory cytokines IL-1β, TNF-α, or interferon-γ stimulate the MMP-8 production in monocyte-derived human macrophages to a much lesser extent [5, 29].

In an experimental study with adriamycin-induced nephropathy, spontaneously hypertensive rats increased kidney MMP-1 overexpression predominantly in the glomerular

Table 1. Classification of MMPs, their substrates, and their role in kidney diseases

Group of MMPs	MMP	Selected substrates	Kidney detection	Selected renal diseases
Collagenases	MMP-1	Collagen I, II, III, entactin, perlectan, pro-IL-1β, IL-1β, IGF-BP-2, IGF-BP-3, pro-Ilβ, ILβ	Cells in the glomeruli[1]	Diabetic nephropathy, polycystic kidney disease, renal cell carcinoma
	MMP-8	Collagen I, II, III, VII, X, aggrecan, fibronectin, pro-TNF-α, E-cadherin, syndecan, IGF-BP, MCP-1, angiotensin	Cells in the tubules	
	MMP-13	Collagen I, II, III, entactin, aggrecan, tenascin, pro-TNF-α, pro-MMP-9, -13	Expressed in kidney with unknown distribution	
	MMP-18	Collagen I, II, III	Not detected	
Gelatinases	MMP-2	Gelatin, collagen IV, V, XI, laminin, aggrecan, pro-TGF-β, pro-TNF-α, IGFBP-3, IGFBP-5	Cells in both the glomeruli and tubules	Acute kidney injury glomerulosclerosis, tubulointerstitial fibrosis, fibrosis, chronic kidney disease, chronic allograft nephropathy polycystic kidney disease, renal cell carcinoma
	MMP-9	Gelatin, collagen IV, V, XI, pro-IL-8, pro-TNF-α, pro-TGF-β, pro-MMP-2, -9, -13	Cells in both the glomeruli and tubules	Acute kidney injury glomerulosclerosis, tubulointerstitial fibrosis, fibrosis, chronic kidney disease, chronic allograft nephropathy polycystic kidney disease, renal cell carcinoma
Stromelysins	MMP-3	Aggrecan, laminin, fibronectin, fibrinogen, MCP-1, -2, -3, -4, pro-MMP-1, -3, -7, -8, -9, -13	Cells in both the glomeruli and tubules	Renal cell carcinoma, chronic allograft nephropathy, vasculitis
	MMP-10	Gelatins, fibronectin, proteoglycan, pro-MMP-1, -8, -10	Cells in the tubules[2]	Renal cell carcinoma
	MMP-11	Fibronectin, laminin, aggrecan, IGFBP-1	Cells in both the glomeruli and tubules	Glomerulonephritis, vasculitis, renal cell carcinoma
Matrilysins	MMP-7	Plasminogen, pro-α-defensin, FasL, pro-TNF-α, E-cadherin, syndecan, pro-MMPs	Cells in both the glomeruli[2] and tubules	Diabetic nephropathy, hydronephrosis, glomerulonephritis, fibrosis, tubulointerstitial fibrosis, renal cell carcinoma
	MMP-26	Collagen IV, fibronectin, fibrin, fibrinogen, pro-MMP-9	Not detected	
Enamelysin	MMP-20	Enamel matrix proteins, aggrecan	Cells of the proximal and distal tubules	
Membrane-type MMPs	MMP-14	Colagen I, II, III laminin, fibronectin, pro-MMP-2, -13, CD44, tissue transglutaminase	Cells in both the glomeruli and tubules	Glomerulonephritis, diabetic nephropathy, renal cell carcinoma
	MMP-15	Pro-MMP-2, pro-TNF-α, tissue transglutaminase	Cells in both the glomeruli and tubules	
	MMP-16	Collagen III, pro-MMP-2, pro-TNF-α	Low expression in glomeruli, cells and tubules	
	MMP-17	Gelatin, fibronectin, fibrin, pro-MMP-2, ADAMTS-4, TIMPs, pro-TNF-α Pro-MMP-2	Not detected	

Table 1 (continued)

Group of MMPs	MMP	Selected substrates	Kidney detection	Selected renal diseases
	MMP-24		Cells in the tubules[2]	Diabetic nephropathy
	MMP-25	Collagen IV, gelatin, fibrin, fibronectin, pro-MMP-2, pro-MMP-9, TIMPs, uPAR	Cells in the tubules	
Other MMPs	MMP-19	Collagen IV, gelatin, laminin	Low in the tubules	
	MMP-21	Gelatin, α-1-antitrypsin	Low in the cells of glomeruli and tubules	
	MMP-23A	Similar to stromelysins and collagenases	Not detected	
	MMP-23B	Similar to stromelysins and collagenases	Not detected	
	MMP-27	Gelatin, casein	Expressed in kidney	
	MMP-28	Neural cell adhesion molecule, casein	Expressed in kidney	
Inhibitors	TIMP-1	All MMPs, more MMP-9	Cells in both the glomeruli[1] and tubules	Diabetic nephropathy, glomerulosclerosis, tubulointerstitial fibrosis, vasculitis
	TIMP-2	All MMPs, more MMP-2	Cells in the tubules[1]	Diabetic nephropathy, glomerulosclerosis, tubulointerstitial fibrosis, vasculitis
	TIMP-3	All MMPs	Cells in both the glomeruli and tubules[1]	
	TIMP-4	All MMPs	Not detected	

Data was compiled with references from the main text as well as previous reviews [1, 20, 90, 116, 302] and www.proteinatlas.org.
[1] Downregulation in renal pathological conditions. [2] Upregulation in renal pathological conditions.

basement membranes and ECM, and subsequent glomerulosclerosis was most successfully reversed with the use of tempol, most probably due to a blockage of peroxynitrite caused by a combination of oxidative stress and deterioration of matrix proteins [30].

Another experimental study with alloxan-induced diabetes in rodents was associated with low serum MMP-1 levels and increased levels of TIMP-1 expression in promoting kidney damage [31].

The only study of end-stage renal disease (ESRD) patients caused by hypertension failed to detect any differences in circulating MMP-1 levels between the patients with essential hypertension, hypertensive ESRD patients, and normotensive subjects [32]. In patients with polycystic kidney disease (PKD), serum MMP-1 concentrations were elevated compared to the controls [33]. Serum MMP-1 levels were found to be significantly increased in the induced pluripotent stem cell-derived endothelial cells from patients with ADPKD and intracranial aneurysms [34].

MMP-1 cleaves interstitial collagens and participates in the ECM turnover, which is a hallmark of interstitial kidney fibrosis [35]. In acute rejection, the proMMP-1 concentrations increase in response to multiple stimuli of inflammatory cytokines [36]. In contrast to that, another study outlined the role of atorvastatin in the changes of MMP expression and signaling

within abdominal aortic aneurysms. This study showed significantly reduced MMP-13 expression, a tendency toward reduced MMP-8 expression, and also a trend toward diminished TIMP-1 expression within aortic aneurysms [9]. Furthermore, MMP-1 concentrations tend to rise in more advanced coronary lesions, especially in patients with complex lesions [37], including patients with multivessel disease [5, 38]. MMP-8 levels also rise in patients with coronary artery disease (CAD) compared to those without it [5, 39]. Interestingly, MMP-13 levels were not detected in most of both healthy subjects and CAD patients [5, 29]. Corticosteroids were shown to repress the expression of MMP-8 [40]. Corticosteroids decreased MMP-8-positive eosinophils and macrophages and at the same time upregulated TIMP-1 from macrophages protecting the proteolytic effect of MMP-8 in the airways of asthmatic children [40]. Glucocorticoid treatment downregulates the inflammatory genes through the activation of the glucocorticoid receptor, inhibits the cell expression of MMPs and activates the cellular expression of TIMPs. Experimental studies provide evidence that glucocorticoids mediated the transcriptional suppression of cytokine-induced MMP-9 expression in rat mesangial cells [41, 42]. A recent article exploring the effect of biological sealants and adhesive treatments on MMP expression during kidney damage healing found that the expression of collagenases (MMP-1, MMP-8, and MMP-13) and subsequently the expression of gelatinases (MMP-2 and MMP-9) occur at different tested time periods [43]. This overexpression of metalloproteinases at the early healing period obviously does not influence the final kidney repair [43].

Among collagenases with marked glomerular expression, MMP-13 shows a particular propensity towards collagen I, III, and specifically for collagen type II [44–46]. Regarding the role of MMP-13 in kidney injury, the published data is scant. The absence of the MMP-13 in one study resulted in protection from adriamycin-induced kidney injury in mice [47]. The protective role of a decreased MMP-13/TIMP-1 ratio was defined in a study with cardiotrophin 1 infusion in inducing vascular, cardiac, and renal fibrosis [48]. Another murine study suggests that MMP-13, together with MMP-2 and MMP-9, is capable of regulating ECM turnover in hypertension [46]. A specific pattern of changes in the ECM proteolytic system, including decreased MMP-13 values in patients with left ventricular hypertrophy (LVH), was linked to structural, functional, and clinical signs of hypertensive heart disease, with further reduction in patients with LVH and chronic heart failure [49, 50].

The MMP-1 promotor polymorphism 1G/2G together with MMP-3 promotor polymorphisms 5A/6A carries an increased risk of developing renal cell carcinoma as well as various other cancers [51].

Although circulating levels of collagenases in patients with atherosclerosis lesions and hypertensive heart disease have been determined, the situation in patients with renal diseases is vague. Therefore, future studies are needed to define the significance of collagenases in kidney disease, as well as the possible links between renal disease and increased cardiovascular risk in these patients.

Gelatinases (MMP-2, MMP-9)

Gelatinases: Structure and Function

Gelatinases MMP-2 (gelatinase A, 72 kDa) and MMP-9 (gelatinase B, 92 kDa), both abundantly expressed in the kidney, cleave components in the glomerular basement membrane and degrade other ECM structures of the kidney tissue [52]. All TIMPs can inhibit the active forms of MMPs, but the gelatinases in their latent forms are able to organize complexes with TIMPs. TIMP-1 inhibits the latent and active form of MMP-9, but the role of the pro-MMP-9/TIMP-1 complex is not clear. TIMP-2 mostly inhibits pro-MMP-2 [53]. Although TIMP-2 is a

major MMP-2 inhibitor, TIMP-2 also facilitates the activation of proMMP-2 via a cell membrane anchored membrane type 1 metalloproteinase (MT-1-MMP) [11, 54]. Increased expressions of both TIMPs have been associated with glomerulosclerosis [1, 55].

Gelatinases are composed of 3 domains, which are distinguished by the presence of type II additional fibronectin domain inserted into the catalytic domain [5]. The main substrates of gelatinases include: collagen IV and V, aggrecan [56], elastin [57], and denatured collagens (gelatins) [19, 58]. Gelatinases also can degrade collagen types I, VII, X, and XI [59], fibronectin and laminin [60], and vitronectin [61]. Furthermore, MMP-2 has the ability to cleave brevican [62], neurocan [63], and decorin [63, 64].

Both gelatinases MMP-2 and MMP-9 have proinflammatory and anti-inflammatory impacts on numerous tissues [65]. They also process various bioactive molecules significant in kidney diseases, including growth factors such as stromal cell-derived factor-1 (becomes inactive after cleavage) [66], cytokines such as proTGF-β1 [67], proTNF-α [68], and pro IL-1β (activates after cleavage) [68], chemokines (MMP-9 shortens IL-8 at the N-terminus, thus enhancing its potency) [69], and the vasoconstrictor endothelin-1 (ET-1) (MMP-2 participates in the cleavage of big ET-1 into ET-1) [70].

Both MMP-2 and MMP-9 can activate the latent forms of MMPs (pro-MMPs). While proMMP-2, proMMP-9, and proMMP-13 can be cleaved by MMP-9, the proMMP-1, proMMP-2, and proMMP-13 are cleaved by MMP-2 [5].

MMP-2 synthesis and storage occur in the form of a stable, latent pro-enzyme (proMMP-2) form under physiological conditions [5, 71]. Secreted MMP-2 is bound to the tissue inhibitor of MMP 2 (TIMP-2) [72]. This binding occurs between the hemopexin domain of MMP-2 and the noninhibitory C terminal domain of TIMP-2 [11]. Thereafter, the activation of proMMP-2 can be induced by gelatinases MMP-2 or MMP-9 [73, 74]. The inactivation of the enzyme occurs through binding of TIMP-1 (and particularly TIMP-2) to the catalytic site of MMP-2. However, under certain conditions TIMP-2 can positively induce MMP-2 enzymatic activity [5, 75]. TIMPs inhibit all active MMPs, but different TIMPs inhibit different MMPs better than other TIMPs. For example, TIMP-1 inhibits MMP-1, MMP-3, MMP-7, and MMP-9 better than TIMP-2, and TIMP-2 inhibits MMP-2 more effectively than the other TIMPs [76].

The synthesis of MMP-9 also occurs as an inactive proenzyme, which is immediately bound to TIMP-1 [77]. In contrast to MMP-2, MMP-9 can be stored not only in its latent form, but also in an active form [71]. The processes leading to the activation of MMP-9 are rather complex and are finely regulated by other MMPs and TIMPs [5, 78].

The activation of proMMP-9 to the active enzyme form occurs in two major pathways, namely by the exposure to nitric oxide (NO) or proteolytically. The numerous inducers of MMP-9 include MMP-2, MMP-3, collagenase I [78], tissue kallikrein [79], leukocyte elastase, and trypsin [80]. In addition, growth factors, cell surface molecules, cytokines, lipoproteins, and matrix-derived proteins also induce MMP-9 expression [5, 81–83]. Another important novel molecule which can modulate MMP-9 activity is the neutrophil gelatinase associated lipocalin (NGAL), a biomarker of kidney injury. By binding NGAL to MMP-9, the enzyme degradation is inhibited, thereby prolonging MMP-9 peptidase activity [84].

MMP-9 interacts with plasminogen and generates angiostatin. MMP-9 is important for interaction with intracellular adhesion molecule-1 and for the enhanced affinity to collagen. The anti-inflammatory effects of MMP-9 include a change of IL-1β from its precursor and a reduction of IL-2 response. MMP-9 is self-regulated by its own secretion and expression. Furthermore, increased mRNA transcript of MMP-9 is associated with the activation of inflammatory pathways involving nuclear binding of transcription factors nuclear factor-κB (NF-κB) and activator protein-1 complex [83, 85].

TIMPs regulate the effects of MMP-9. The activity of TIMPs facilitates ECM turnover and inflammatory pathways in kidney tissue, thus modifying renal anatomy and physi-

ology [86]. While TIMP-1 inhibits MMP-9, TIMP-2 is the main inhibitor of MMP-2. Enhanced expressions of both TIMPs have been linked with glomerulosclerosis [1, 11, 55]. TIMP-2 in interaction with MT-1-MMP facilitates the activation of pro-MMP-2 [11, 54]. TIMP-2 and TIMP-3 play differential and contrasting roles in renal injury in rodent models: TIMP-3 protects from damage, whereas TIMP-2 promotes injury through MMP-2 activation [87]. TIMP-3, an ECM-bound protein that is expressed ubiquitously, inhibits tumor growth and angiogenesis. TIMP-3 might regulate VEGF-mediated angiogenesis [88]. TIMP-4's structure shows a closer homology to TIMP-2 and TIMP-3, but much less homology to TIMP-1. TIMP-4 expression in tissues is limited, with prevailing tissue expression in the heart, but with little expression in the kidney. TIMP-4 specifically binds to progelatinase A (pro-MMP-2) [89].

MMP-2 and MMP-9 are especially involved in the cross-talk directly between the cells and ECM, through remodeling of the tubular basement membrane. Indeed, MMP-2- and MMP-9-associated proteolytic processes of type IV collagen are crucial for renal basement membrane remodeling, as well as embryonic growth, tissue remodeling and repair, and certain disease states [90, 91].

Furthermore, a number of drug groups including angiotensin II receptor antagonists [92], diuretics [93], calcium channel blockers [94], statins [95, 96], acetylsalicylic acid [97], and thrombin inhibitors [98] have also been linked to modulate gelatinase activity.

Gelatinases and Kidney Disease

In the kidney, MMP expression varies according to their localization across the entire nephron. Mesangial and epithelial cells along with proximal tubular cells are sites where MMP-2, MMP-9, and TIMPs are expressed the most in the kidney [99, 100]. Due to the unique modifying ability of MMP-2 and MMP-9 to cleave plasminogen to angiostatin, MMP-2 can be mapped either near the tubular basement membrane or near the interstitial space. The presence of MMP-9 in tubular and interstitial cells is increased after acute renal failure due to ischemia in rats [101]. MMP-9 is also produced by neutrophils, macrophages, and T-lymphocytes [102]. In addition, the activity of MMP-3, MMP-12, and MMP-7 leads to the generation of angiostatin [103–106].

MMP-2 and MMP-9 are produced at the first stage of kidney embryogenesis in vivo, but only MMP-9 is absolutely required for kidney organogenesis in vitro [107]. MMP-9 protects the mesenchymal cells from apoptosis and stimulates branching morphogenesis during kidney development through the release of stem cell factor (SCF), suggesting the necessity of MMP-9 in normal kidney development [107–109]. The proposed mechanism in the limited proteolysis of ECM proteins includes synthesis of MMP-2 by the activated mesangial cells, with immediate accumulation of MMP-2 at these sites and their involvement in protease cleavage [100]. The subsequent change of mesangial cells to their inflammatory phenotype cells occurs as a consequence of interactions between ECM and integrins, or as a response to ambient growth factors [110].

Diverse glomerular diseases are associated with profound imbalance in ECM turnover. On one hand, increased formation of matrix proteins accompanies scarring processes; on the other, enhanced degradation facilitates glomerular damage in inflammatory disease states [111, 112]. MMP might play a dual role in primary nephropathies: in the early phases, MMP activity contributes to acute damage, while in the later period MMP protects renal parenchyma against excessive matrix deposition [90, 113].

Both the mesangial matrix and glomerular basement membrane are consistently processed via matrix formation and matrix degradation. The main constituent of the mesangial matrix and glomerular basal membrane is type IV collagen, which is the main substrate of the gelatinases MMP-2 and MMP-9, whereas TIMP-1 is the main inhibitor of this degradation

process. Various signals including TGF-β, IL-1, TNF-α, and thrombin influence matrix turnover in the kidney.

These processes are specifically present in chronic kidney disease (CKD). CKD results from a process that causes persistent kidney parenchymal loss or damage. The irreversible reduction in the number of functioning nephrons leads to a gradual inability of renal maintenance of homeostasis over the span of weeks to years. The rate of progression varies according to the underlying pathology, e.g. glomerular disease progresses faster than tubulointerstitial disease, and between individual patients. Progression of CKD is more due to the secondary maladaptive hemodynamic and metabolic changes than due to the underlying disease. In general, CKD comprises complex changes with progressive interstitial scarring, glomerular sclerosis, vessel stiffening, and calcification [114].

The transformation of tubular epithelial cells into profibrotic, mesenchymal scarring cells is linked with fibroblast and cytokine activation leading to ECM remodeling [114]. Indeed, due to the MMPs activities, the imbalanced equilibrium is shifted towards increased matrix synthesis and decreased matrix degradation [115], which promotes the vascular, glomerular, and tubular changes found in CKD [90, 116–118]. An upregulation of MMP-2 and downregulation of MMP-9 activities have been demonstrated in different stages of CKD [58]. In addition, the dysregulation of MMP/TIMP activity and matrix deposition in CKD plays a role in the progressive stages of the disease [20, 114]. Gelatinases impact the initial and progressive changes of CKD in various ways. In children with CKD, MMP-2 levels kept increasing from the beginning of renal failure progression, and the levels of TIMP-1 and TIMP-2 correlated with TGF-β1 [119], suggesting that these markers indicate increased cell damage, inflammation, and aggravation of proteolytic processes in CKD children [119]. A detailed review of MMP-2 and MMP-9 in CKD has already been published, emphasizing the role of the gelatinases in cell structural membrane changes, the activation of various cell signaling pathways, and the processes associated with hypoxia [120].

Moreover, progressive interstitial kidney scarring and tubular atrophy represent the final histological stages of all forms of kidney diseases that develop into ESRD.

Kidney fibrosis accompanies chronic renal diseases. Nowadays, the concept of the progressive glomerular and tubular injury resulting in fibrosis is accepted [121].

Glomerular sclerosis starts with the formation of an adhesion of tuft to Bowman's capsule, which in degenerative conditions leads to focal segmental glomerulosclerosis while in inflammatory processes to crescentic glomerulonephritis. In both conditions, the outcome is similar, leading to the progression of glomerular sclerosis [122]. Both processes of glomerular sclerosis encroach on other lobules and on the glomerular tubular junction resulting in the obstruction of the urinary orifice. This deprives the tubule from filtrate and leads to atrophy. Altogether, these processes result in the degeneration of the corresponding tubule and the loss of the entire nephron [121, 122].

Kidney fibrosis associated with primary tubular disease comes from the regeneration of the tubular cells. Peritubular inflammation and fibrosis support the tubular cells in recovery. When tubular cells fail to fully regenerate and differentiate, the peritubular fibrosis persists. The progressing tubular disease finally involves the glomerulus causing the progression of the CKD [121].

MMPs actively participate in kidney remodeling by altering matrix degradation, specifically changing the glomerular, tubulointerstitial, and vascular spaces of the kidney. The consequences of such ECM alterations include the accumulation of collagens type I and III, and a higher collagen to elastin ratio leading to enhanced volume flow resistance [46, 123–125]. MMPs also cleave bioactive molecules which may therefore stimulate increased ECM protein deposition [67, 126].

The sources of the interstitial collagen deposition are myofibroblastic cells. Interestingly, the organized tubular epithelium is able to transform into the myofibroblastic phenotype under the influence of TGF-β1 [117]. The proteins of the TGF-β subfamily comprise a group of multifunctional cytokines with an impact on the differentiation of the cells, their organization, and proliferation. The role of TGFs in the development of vascular pathologies has already been described [127]. MMP-2, MMP-9, and MMP-13 are capable of releasing latent TGF-β1 [128]. The released TGF-β1 forms tight, large latent protein complexes, and it is only after the proteolytic degradation that the active TGF-β1 becomes available to its receptors TGF-β RI or TGF-β RII and induces signaling. TGF-β1 stimulates the synthesis of MMP-2 through its activator membrane type metalloproteinase MT1-MMP (MMP-14) [117]. Active MMP-2 is necessary for epithelial mesenchymal transformation in the absence of exogenous TGF-β1. Another interesting ability of MMP-2 includes the mediation of the epithelial mesenchymal transformation by the production of TGF-β1 peptide due to proteolysis in a paracrine manner. Another mechanism of importance in kidney fibrosis encompasses the involvement of MMP-9-dependent Notch pathway activation in CKD [129] through TGF-β endothelial-mesenchymal transition in the murine model of kidney scarring [130]. Moreover, MMP-2 alone is responsible for causing the degradation and disruption of the underlying IV collagen-rich basal lamina which is a critical constituent of renal tubular epithelial mesenchymal transformation [117]. Taken together, this data marks that the active MMP-2 is essential to induce the complex downstream genetic changes resulting in tubular epithelial mesenchymal transdifferentiation.

Autophagy is another important process significant for ECM turnover, where cytosolic proteins in autosomes are presented to lysozyme vacuoles for further degradation [131, 132]. Autophagy has been connected to such renal diseases as AKI [133], PKD [134], diabetic nephropathy [135], cisplatin-induced renal injury [136], tubular injury following sepsis [137], and acute ischemic kidney injury [138].

It has been suggested that in a murine model, renovascular fibrosis due to hypertension can be partly dependent on the enhanced expression and activity of MMP-9, MMP-2, and MMP-13 [46]. In addition, autophagy plays a role in hypertension-induced renal remodeling [46]. Although elevated MMP-9 levels correlated with systolic blood pressure, the increase in plasma MMP-2 and MMP-10 correlated better with renal damage induced by hypertension [32]. MMP-2 degrades calponin-1, which leads to vascular smooth muscle cell proliferation and contributes to hypertrophic remodeling in the aorta. In contrast, the MMP-2 induced increased calponin-1 expression in mesenteric arteries in two-kidney, one-clip hypertensive male rats leading to vessel hypercontractility [139]. The divergent effect of calponin 1, regulated by MMP-2, represents one of the possible mechanisms of vessel maladaptation in hypertension [139]. A recent systematic review focused on blood and urine markers found that MMP-2, MCP-1, and TGF-β might identify patients at risk for the finding of renal scarring in biopsy, and subsequent poor renal outcomes [140].

The most common cause of AKI is acute tubular necrosis (ATN), better termed acute tubular injury after ischemia and reperfusion. Endothelial injury together with epithelial cell injury and inflammation are the main pathophysiological mechanisms involved in ATN. An altered expression of cellular adhesion molecules, cytokine and chemokine release, activation of apoptotic stimuli, leucocyte activation, influence of proinflammatory mediators, intracellular calcium influx, reactive oxygen species lead to the dysregulated immune response in ATN [141].

In the kidney, gelatinases MMP-2 and MMP-9 are upregulated after ischemia/reperfusion injury, and the MMP activation modulates renal microvascular permeability and increased microvascular density [103, 142]. MMP-9 has been found coupled in disulphide-linked complexes with NGAL [143]. NGAL has been suggested as an early predictive biomarker

of ischemic AKI in the adult and pediatric population after cardiac surgery [144, 145]. Urinary MMP-9, together with other markers, has also been proposed as a novel biomarker of AKI [146]. A cross-sectional study has demonstrated significantly higher urinary MMP-9 levels in AKI in comparison to urinary MMP-9 concentrations found in CKD patients and healthy control subjects [146]. However, urinary MMP-9 levels in AKI proved to be a poor predictor in distinguishing those patients with urinary tract infection [146].

Moreover, in the rodent model, MMP-9 and SCF have been shown to be important regulators of renal function in AKI. The evidence that MMP-9 protects mice from apoptosis in AKI comes from the ability of MMP-9 to induce the release a soluble form of SCF in kidney tissue. The inhibitory effect of MMP-9 on apoptosis and the rescue by SCF were shown in the ischemia reperfusion model of AKI. This process where MMP-9 facilitated the mobilization of SCF might represent a survival mechanism in AKI [109]. Gelatinases MMP-2 and MMP-9 cleave the tight junction protein zonula occludens-1 in the glomeruli. Moreover, MMP-9 specifically degrades the endothelium-occluding cells, leading to an enhanced vessel permeability [116, 142].

The role of gelatinases in diabetic nephropathy has been illustrated in a number of clinical studies. Indeed, gradual renal remodeling in diabetic nephropathy leads to a deterioration of kidney function, where enhanced storage of ECM plays a crucial role [147, 148]. In diabetic nephropathy, the cardinal histological changes include mesangial expansion, glomerular and tubular membrane thickening and nodular glomerulosclerosis. Further vascular changes, tubular atrophy and interstitial fibrosis appear as diabetic nephropathy progresses.

Among the factors that are involved in ECM breakdown and turnover are reactive oxygen species, plasminogen inhibitor, plasmin, TGF-β1, and MMPs [147–150]. The protein kinase C and hexosamine biochemical pathway activation in diabetic kidney disease leads to the enhanced expression of these profibrotic agents and to induced collagen synthesis and ECM deposition [151].

Mostly, the elevated levels of MMP-2 and MMP-9 in the serum and urine were observed in patients with diabetic nephropathy [152–155]. Elevated MMP-9 levels in plasma even forgo albuminuria development in diabetic nephropathy [154]. Moreover, urinary MMP-9 concentrations correlated with albuminuria as well [156]. Interestingly, an increased MMP-9/TIMP-1 ratio has also been observed in diabetic nephropathy [157]. The enhanced arterial expression of MMP-9 has been noted in diabetic CKD patients, where it is believed to exacerbate the stiffening of the arteries, leading to endothelial dysfunction and impaired angiogenesis in this population [158]. Many factors including MMPs, advanced glycation end products (AGEs), and chemokines contribute to the inflammatory changes in diabetic nephropathy. Using monocyte human renal mesangial cell co-culture system, the complex interconnection between MMP systems and chemokines was identified [159]. Firstly, fractalkine inhibits the mRNA expression and activity of MMP-2, which is important in ECM breakdown. The ECM accumulation is a typical characteristic of diabetic nephropathy, and ECM presence is fundamental for the extravasation of monocytes, and their subsequent migration into the tissues [160]. Secondly, s-fractalkine tempers the intrinsic activity of MMP-2 produced by monocytes and restricts monocyte migration in reaction to MCP-1, illustrating s-fractalkine participation in the regulation of the inflammatory process [161]. Finally, AGEs not only inhibit MMP-2 activity directly, but they also indirectly influence the MMP-2 expression by increasing fractalkine activity [159].

Increased MMP-2 activity and the presence of MMP-2 protein were highly expressed in kidney tissue samples from human diabetic patients [162]. An elevation in urinary MMP-2 levels and MMP-2 enzyme activity has also been observed in type 1 DM patients with albuminuria, in comparison to nonalbuminuric diabetic patients or control subjects [163, 164]. In addition, podocytes were detected in the urinary sediment of albuminuric diabetic patients,

but not in patients with type 1 DM without albuminuria or control subjects [165]. Plasma MMP-9 levels correlated with podocyte number in the urine in this diabetic population [165]. A panel of nine biomarkers including MMP-2, MMP-7, MMP-8, and MMP-13, all involved in collagen metabolic turnover and scarring, were measured in 1,765 type 2 DM and CKD patients of various stages in order to predict the progression of kidney function loss [166]. The encompassing role of matrix gelatinases in CKD, cardiovascular disease, and diabetic nephropathy has been recently emphasized in a detailed review [167]. Taken together, these studies demonstrated deregulated activity of gelatinases and TIMPs in clinical trials of human type 1 or type 2 diabetes, providing a link between MMP-2 and MMP-9 expression and the development of diabetic nephropathy.

Increased MMP activity in glomerulopathies participates in the disease process, and their elevated glomerular expression contributes to the extent of structural glomerular damage. In the animal model of MMP-9 deficient mice, the crescentic proliferative glomerulonephritis and AKI were more pronounced because MMP-9 can degrade fibrin [168] and is capable of releasing soluble SCF from renal cells [109].

Patients with various forms of glomerulonephritis including focal segmental glomerulosclerosis, minimal change disease, human immunodeficiency-associated nephropathy and antineutrophil cytoplasmatic antibody-associated vasculitis each had distinct expression of gelatinases [169–174]. Plasma concentrations of MMP-2, MMP-9, and TIMP-1 are remarkably changed in patients with primary glomerulonephritis including IgA nephropathy, membranous glomerulonephritis, minimal change nephrotic disease, and segmental glomerular sclerosis [169, 171]. Plasma profiles of MMPs and TIMPs differ significantly between various histopathological types of primary glomerulonephritides, thus implying diverse mechanisms in the development of the glomerulus and tubulointerstitial fibrosis [169, 171]. Urinary MMP-9/NGAL ratio has been proposed as a potential distinguishing biomarker between minimal change disease and focal segmental glomerulosclerosis in nephrotic children [175].

Changes in plasma concentrations and glomerular expression of gelatinases were found in lupus nephritis, IgA nephropathy, IgA vasculitis, and the postinfectious nephritides [171, 176, 177].

Some studies [178, 179] reported constitutive and unchanged levels of MMP-2 in the serums of systemic lupus erythematosus (SLE) patients. Conversely, MMP-9 serum levels were increased in SLE patients when compared with healthy subjects [179]. Elevated MMP-9 concentrations were found to be correlated with pneumonitis, Raynaud phenomenon, discoid rash, neurological disorders, and the presence of APLA antibodies [179]. In this study, MMP-9 activity levels were not correlated with SLE disease activity indices (SLEDAI, BILAG) in females, but correlations were found with the SLE activity in the group of male patients [179]. It is possible that the differences between disease activity indices and MMP-9 activity levels might be attributed to the influence of sex hormones. Indeed, progesterone was shown to regulate the MMP-9 generation and activity [180].

However, in other studies, the total concentrations of MMP-9 and active MMP-9 were unexpectedly lower in patients with SLE in comparison with control groups [181, 182]. Moreover, lower levels of total MMP-9 were detected in patients with active disease [182]. Similarly, TIMP-1 concentrations were lower in SLE patients than in healthy volunteers [182]. The levels of these markers did not correlate with the activity of SLE, and the presence of clinical and laboratory symptoms of SLE. Lower levels of MMP-9 and TIMP-1 can result from the accumulation of these enzymes in the inflamed vessels and tissues.

The failure of normal polycystin formation stimulates production of growth factors that lead to the dysregulated cell turnover and uncontrolled proliferation of tubular cells in autosomal PKD in response to the abnormal response to elevated cyclic adenosine monophosphate production. Proliferating tubular cells form tubular cysts that close off the associated

nephron and expand in size over time. Although only 1% of nephrons undergo such cystic change, the associated profibrotic cytokine release and local ischemic surrounding promote epithelial mesenchymal transformation and kidney scarring and progression of CKD. In addition, the enlarging cysts become walled off from the rest of the collecting duct; the cysts might also impinge the normal blood flow to nephrons [183].

PKD has also been associated with MMP dysregulation. Increased levels of MMP-1, MMP-9, TIMP-1, and type IV collagen have been found in the serum of PKD patients when compared with controls [184]. Elevated levels of MMP-2, MMP-3, and MMP-9 have been noted in patients with Alport syndrome [184]. Increased levels of gelatinases, MMP-2, MMP-9, as well as their inhibitors, TIMP-1 and TIMP-2, have also been demonstrated in allograft rejection [185–187]. MMP-2 and MMP-9 gene polymorphisms have been linked with enhanced allograft survival in renal transplant recipients [188], and the immunosuppressive drug rapamycin downregulates MMP-9 expression while upregulating TIMP-1 [189].

To date, multiple studies exploring potential reliable, noninvasive tumor marker for renal cell carcinoma have not been successful. The metzincin family of MMPs and their inhibitors represent feasible marker candidates for diagnosis and surveillance in the follow-up of cancer. The imbalance of MMPs over TIMPs is accompanied by tissue destruction in malignancies. In renal cell carcinoma using a zymography technique, it has been shown that MMP-9 levels were higher in the serums from clear cell carcinoma in comparison to levels from oncocytoma patients. The prevailing enhanced MMP-9 lytic activity was abundantly present in clear cell carcinoma, whereas MMP-2 activity values were detected in far lesser concentrations [190]. These results were further confirmed by the same author in a study where MMP-9 levels were increased in the clear cell carcinoma patients versus the oncocytoma patients. On the contrary, the mean values of MMP-2 and TIMP-1 were comparable in both tumor groups [191]. The results of the discussed studies imply the potential usage of MMP-9, but not MMP-2 in diagnosing renal cancer. Nevertheless, in spite of the findings in these tissues, the measurement of serum and urine MMPs and TIMPs can so far not be used to diagnose kidney cancer.

Gelatinases are immensely important in the development of cardiovascular alterations associated with cardiovascular disease in patients with renal disease [158, 192]. MMP-9 strongly correlated with carotid atherosclerotic burden, irrespectively of other contributing factors in the early, moderate, and advanced stages of CKD [193]. Similarly, the circulating MMP-2 levels were found to be strongly linked to intima thickness in ESRD patients on hemodialysis [194]. MMP upregulation probably results from the activation of NF-κB proinflammatory pathways [195]. Progressive CKD increased the circulating levels of MMP-2, MMP-9, and TIMP-1 expression in the aorta [192]. Moreover, the initiation of higher MMP-2 activity starts at the predialysis CKD stage. Patients with ESRD on peritoneal dialysis and hemodialysis are characterized by further, gradual MMP-2 activation. The increased expression of MMP-2 could represent one of the presumably nontraditional mechanisms that facilitate multiple adverse processes including structural remodeling, vascular dysfunction, and oxidative stress in increased cardiovascular burden in CKD patients receiving dialysis. The TT allele of the C1562T polymorphism in the MMP-9 gene has been linked to the enhanced oxidative stress in patients with nephrolithiasis, in addition to imposing cardiovascular risk in patients with the homozygous TT genotype of MMP-9 [196].

Furthermore, MMP-2 expression associated with the phenotype changes of vascular smooth muscle cells is typical for elastocalcinosis, and even precedes cell loss and the development of arterial medial calcifications in the early stages of CKD [197]. Vascular calcification comprises a number of events beginning with the apoptosis of smooth muscle cells, change in their phenotype and the release of a multitude of proteases, including MMPs [198]. Activation of the Wnt/β-catenin pathway in vascular smooth muscle cells (VSMC) in the precal-

cifying (increased calcium and phosphorus concentrations) culture conditions, associated with further enhanced overexpression of gelatinases (MMP-2 and MMP-9), facilitates the CKD-linked vascular calcification in the process of arteriosclerosis [30, 199–201]. Further reciprocal mechanisms between NO bioavailability and MMP activation [3] strengthens the association between MMP activity and endothelium-dependent relaxation in the dialysis patients [158]. Thus, the proteolytic activity of MMP-2 leads to the loss of arterial structural and functional integrity. The activity of gelatinases, mainly MMP-2, could aid in understanding the pathogenesis of the higher prevalence of vascular disease in CKD.

Most of the reviewed studies demonstrated elevated levels of MMP-2 in ESRD on dialysis in comparison to controls [32, 202], but two studies did not [203, 204]. MMP-9 levels were comparable in two studies [194, 202], increased in two other studies [32, 205], and decreased in a different study [203]. These differences are likely due to multiple factors including the diversities in age, ethnicity, and specificities of dialysis membranes, causes of renal diseases or other clinical states. Moreover, MMP-9 genetic polymorphism influences MMP-9 expression in hemodialysis patients [206]. In addition, a single hemodialysis session does not influence or diminish MMP-2 and MMP-9 levels, or TIMP-1 and TIMP-2 concentrations [204, 207]. While in the previously mentioned study neither MMP-2 serum levels, nor MMP-9 concentrations were shown to be mortality predictors in hemodialysis [208], in a 5-year recent cohort study it was shown that MMP-2 serum concentrations in the fifth year predict mortality in hemodialysis patients [209].

It has been shown that treatment with exogenous MMP-9 demonstrated the protective role of MMP-9 in chronic kidney failure in an animal model [210]. It is feasible that the protective impact of MMP-9 is reached either due to the MMP-9 degradative ability of ECM, or via the inhibitory effect on TIMP-1 and the subsequent proinflammatory response [210].

Interestingly, in the rodent model of renal traumatic injuries, the MMP expression, namely MMP-1, MMP-2, MMP-8, MMP-9, and MMP-13 was different. Different time manner was specifically prominent with maximal MMP-8 and MMP-9 expression after 2 days of injury in healing of the wound. In contrast, the MMP-2 expression peaked after 6 days of kidney traumatic injury [43].

Recently, it has been demonstrated that the astacin proteases meprin-α and -β might serve as targets of treatment in kidney fibrosis and scarring. The acidic modification of meprin-β exhibits a specific selectivity for matrix proteases, such as MMP-2 [211].

Taken together, the measurement of plasma and serum levels of gelatinases may aid in the determination of a variety of renal diseases and also in ESRD patients on dialysis, or patients with a transplanted kidney. To date, ambiguous data exists in relation to the potential ability of blood levels of the gelatinases MMP-2 and MMP-9 to serve as markers for kidney disease. Therefore, to unravel these contradictory issues, the exact determination of the possible transient levels of MMP-2 and MMP-9 (and their inhibitors) in the course of renal disease in prospective studies is required.

Stromelysins (MMP-3, MMP-10, and MMP-11)

Stromelysins: Structure and Function

Stromelysins, namely MMP-3, MMP-10, and MMP-11, are capable of degrading many of the constituents of basement membranes and connective tissues. The inability to degrade type I collagen distinguishes stromelysins from collagenases [5, 212]. MMP-3 degrades such substrates as type II, IV, and IX collagens, as well as fibronectin, laminin, proteoglycans, elastin, and gelatins [5, 213]. MMP-3 and MMP-10 can serve as activators of other MMPs, specifically the precursor pro-forms of MMP-1, MMP-7, MMP-8, and MMP-9

[214], and also other proinflammatory mediators, such as pro-TNF-α [215] and osteopontin [216]. Among other targets, MMP-10 degrades collagen types III, IV and V, gelatin, and elastin in vitro. MMP-10 is best known for enhancing tissue plasminogen activator's fibrinolytic activity [217]. The role of MMP-10 in atherosclerotic vascular remodeling has also been described [218]. In contrast, MMP-11 does not cleave gelatins, collagens, or other major matrix components [219], but is capable of the degradation of serine proteinases like α-1-proteinase inhibitor [220], and also cleaves insulin-like growth factor-binding protein [5, 221].

MMP-11 (stromelysin 3) expression appears to be associated with normal tissue remodeling [17, 222]. MMP-11 is particularly present around a variety of invasive carcinomas, along with stromal fibroblasts [17]. MMP-11, in contrast to other MMPs, presents with a distinct molecular structure, divergent enzyme activity, and different gene arrangement and regulation [17, 223]. The different role of MMP-11 is marked by its weak activity toward matrix substrates, and probably indirect participation in remodeling only through activation of serpins [17].

Stromelysins and Kidney Disease

MMP-3 and TIMP-1 expression are found in the glomerulus (specifically in the mesangial and epithelial cells) and some tubular cells (mostly in the proximal tubular cells) in humans [224]. A diverse group of MMPs, namely MMP-1, MMP-2, and MMP-3, is produced mainly by fibroblasts and smooth muscle cells [225, 226].

Animal studies in rodents highlighted the potential role of stromelysins in the pathogenesis of diabetic nephropathy. The expression of kidney MMP-3 mRNA is diminished in streptozotocin-induced diabetic rats [227]. Kidney tissue analysis from patients with diabetic nephropathy using in situ hybridization techniques revealed that MMP-3mRNA expression was most abundantly present in those with the mildest mesangial expansion, in contrast with the far less mesangial presence in moderate or severe histopathological samples [228]. High MMP-10 levels were associated with nephropathy and proliferative retinopathy in type 1 diabetic patients. The knockout of the *Mmp10* reduces these disorders in a diabetes murine model [229].

Significant progress was reached in evaluating the importance of MMPs including MMP-3 in the dynamic changes of kidney disease in Alport's syndrome, using a mouse model of the disease which is deficient in the α_3-chain of type IV collagen [α_3(IV)] [90, 184]. MMP-3, similar to MMP-2 and MMP-9, appeared in Alport's syndrome in both human and animal models. Gelatinases and stromelysin MMP-3 are able to cleave the components of the basement membrane in Alport's syndrome in vitro [230]. The significance of MMPs in Alport's syndrome differs in relation to the duration of the kidney disease. While in the early stages, the MMPs inhibit the development of kidney lesions, in the later (proteinuric) stage MMPs actually enhance the disease progression [184].

Both MMP-3 and MMP-9 could cause epithelial mesenchymal transition by the degradation of epithelial cell marker E-cadherin in kidney cell cultures of tubular cells, resulting in the activation of β-catenin [20, 231].

Serum MMP-3 concentrations are increased in mesangial proliferative glomerulonephritides such as IgA nephropathy and lupus nephritis [112]. In addition, MMP-3 levels correlate with the clinical parameters of lupus nephritis, including a decreased C4 complement, circulating immune complexes, and decreased creatinine clearance [232]. An enhanced expression of MMP-3 has been observed in IgA vasculitis and ANCA vasculitis [174, 233]. Vasculitis refers to an autoimmune condition with both inflammation and leukocyte infiltration of the blood vessel walls. The damage of the vessel wall encompasses aneurysm formation, vessel occlusion leading to ischemia and infarction.

In comparison to MMP-1 and MMP-9, MMP-3 levels distinguished between active AAV and a disease in remission better than C-reactive protein and erythrocyte sedimentation rate. Furthermore, patients with active ANCA vasculitis at month 6 showed elevated levels of MMP-3 in comparison to those whose disease was in remission [17]. Serum proforms of MMP-2 and MMP-3 illustrate the changes of ECM turnover in the glomeruli and interstitium in chronic transplant nephropathy, and highlight their possible pathogenetic role in the development of this condition [36].

MMP-10 expression has been detected in normal tubular cells [234]. The presence of MMP-10 in cancer cell cytoplasm of conventional renal cell carcinoma was significant and has been independently associated with tumor invasion [234].

MMP-11 can function as a potent mediator of inflammation and demonstrate a chemotactic impact on macrophages, which tend to accumulate in the mesangium and cause early fibrotic changes, participating in the origin of cellular and fibrocellular crescents in the secondary forms of glomerulonephritides [17]. No antifibrotic or mitogenic effects of MMP-11 have been observed within the glomeruli thus far [17].

MMPs influence cell proliferation indirectly. A programmed cell death, or apoptosis, is normally initiated via activation through the Fas receptors or other TNF superfamily receptors the proteolytic cascade of caspases and subsequent cleavage of subcellular structures and nucleus. Kidney tubular cells dispose such receptors [235]. MMPs also display other mechanisms in the regulation of apoptotic signals [236, 237]. Furthermore, the role of MMPs in apoptosis is augmented by TIMPs. The balance between MMPs and TIMPs mediated via various biologically active intracellular or extracellular molecules defines the upregulation or downregulation of apoptosis in relation to tissue characteristics, the levels of biologically active molecules and preservation of cellular homeostasis [238]. Excessive or impaired apoptosis induces tissue scarring and dysfunction [239]. Kidney impairment including ischemia, injury due to nephrotoxicity, radiation, and ureteral obstruction causes apoptosis in the kidney [240].

Cell to ECM adhesion is maintained through direct and indirect bonds to the actin cytoskeleton. Disruption of these connections to ECM has a harmful effect on cell preservation. MMPs induce a specific type of apoptosis known as anoikis altering these cell-to-matrix connections [237, 241]. MMPs promote cellular anoikis through the separation of various cadherins and integrins [242, 243]. The shedding of these adhesion molecules disables the unique assembly of cell-to-cell and cell-to-matrix interconnections in the apoptotically changing cell [244].

MMP-3 stimulates apoptosis by cleaving laminin [245], and MMP-11 suppresses tumor cell apoptosis in the murine model [246]. Furthermore MMP-11 can inhibit apoptosis by releasing IGFs, functioning as survival factors [247]; MMP-11 augments apoptosis in tissue remodeling and crossover [222].

Specifically, MMPs are located and translocated into the nucleus and through proteolytic cleavage control the regulation of cell cycle, nuclear matrix degradation, and apoptosis [248]. MMP-3, for example, stimulates apoptosis by MMP-3 translocation into the nuclei of mammalian cells. This effect on apoptosis is derived from the retention of its enzymatic action [86]. TIMP-1 also binds to the cell surface, and nuclear translocation occurs [249]. MMP-2 and MMP-9 are present in the nuclei and potentially able to cleave nuclear matrix proteins such as protein poly-ADP-ribose-polymerase [250], suggesting functioning of gelatinases similar to those of caspases in the nucleus [237, 251]. Taken together, these observations pinpoint the importance and multiple involvement of MMPs and TIMPs in various apoptotic mechanisms of cell biology. Further research is warranted to investigate the precise mechanisms elicited by stromelysins in the origin and progression of kidney diseases.

Matrilysins (MMP-7 and MMP-26)

Matrilysins: Structure and Function

Matrilysins have the structural peculiarity of lacking a hemopexin domain, having an atypical sixth exon instead [252]. The protease differs from other matrix MMPs by a comparatively smaller size. The enzyme synthesis starts from a 30-kDa inactive preform and continues through a stepwise activation to a definite 18-kDa active form [253, 254]. MMP-7 degrades ECM substrates such as fibronectin, laminin, elastin, entactin, and type IV collagen [5, 253, 254]. In addition, MMP-7 also cleaves proteoglycans, including versican [255]. The full activation of MMP-7 occurs through a series of various enzymes, including trypsin and MMP-3 [256]. MMP-7 could also be activated by aminophenylmercuric acetate in vitro and is partially activated by plasmin and leukocyte elastase [256]. MMP-26 selectively cleaves type I gelatin and α_1-proteinase inhibitor. MMP-26 hydrolyzes the proteinous substrate of matrixins and the TNF-α-converting enzyme. Further selectivity of MMP-26 includes the cleaving of ECM proteins, inactivation of serpins, and the modulation of various cytokine effects [257].

Matrilysins and Kidney Disease

The expression of MMP-7 has been mostly associated with tissue remodeling [254, 258]. An overexpression of MMP-7 has been detected in pathological states such as unilateral ureteral obstruction, PKD, and acute folic nephropathy in mice, but no expression of MMP-7 has been observed in physiological human kidney tubular epithelium [254, 259].

In diabetic nephropathy, hyperglycemia causes alteration of matrix synthesis and degradation by MMP-7, which leads to changes of the physiological microarchitecture of the glomeruli. Moreover, MMPs modulate the enhancement of growth factors. Specifically, in early kidney hypertrophy in streptozotocin-treated diabetic rats, an increase in insulin-like growth factor binding protein (IGFBP)-1, IGFBP-3, and IGFGB-5 has been seen [260]. MMP-7 is capable of cleaving IGFBP-3 [261] and IGFBP-5 [262]. Degradation of IGFBPs by MMP-7 leads to the liberation of IGF-II [263], thus releasing the bioactive IGF, which results in the accumulation of ECM and mesangial expansion. TGF-β, a known profibrotic growth factor, becomes more available through MMP-7 enzymatic decorin processing, which is present in ECM and binds TGF-β [263]. Therefore, MMP-7 renal activity contributes in a direct or indirect way to the process of glomerular basement membrane thickening and the expansion of the mesangium, which constitute the initial changes present in the development of diabetic nephropathy.

An increase in MMP-7 expression (verified by renal biopsy) was found in kidney tissue from patients with hydronephrosis at hemodialysis [259, 264]. MMP-7 seems to act as a novel screening marker for renal disease in lupus nephritis [265], cardiovascular alterations in CKD patients [266], and as a possible predictive marker of kidney transplant rejection [267]. Among potential MMP-7 inhibitors, doxycycline seems to be effective in decreasing the protein loss in urine of patients with glomerulonephritis [268] and diabetic nephropathy [269].

MMP-7 expression has been associated with enhanced renal fibrotic changes [116]. Active MMP-7 was not detected in the rodent aging renal tissue, but the pro-form of the enzyme, pro-MMP-7, has been linked to the increase in collagen expression promoting kidney fibrosis. The enhanced expression of MMP-7 activates the *Col1a2* and *Col3a1* genes through PIK3, p38, ERK, src, and PKA signaling, resulting in the accumulation of collagen in the renal tissue [254]. There is no information on the ability of MMP-7 to cleave Col1a2 and Col3a1. The only collagens that are known to be degradable by MMP-7 are collagen IV [270] and collagen type XVIII [271]. However, MMP-7 activates the gelatinases MMP-2 and MMP-9 [272] and the collagenases MMP-1 and MMP-8, which in turn degrade collagen. Interestingly, the total collagenase activity is decreased and the gelatinase activity is increased in ageing rat kidneys

[270]. Furthermore, MMP-7 gene expression was found to be upregulated in aged kidneys and was associated with the typical histopathological fibrotic changes of old kidneys such as glomerulosclerosis, interstitial fibrosis, and tubular atrophy [273]. In a cohort of 102 CKD patients, high urinary MMP-7 levels were observed [274]. The close association of MMP-7 with kidney fibrosis score supports the potential use of MMP-7 as a biochemical marker of renal scarring [274]. Altogether, these results point out the importance of MMP-7 changes in ECM formation and the breakdown accompanied with either acute or chronic loss of kidney tissue [1]. A recent review evaluated the pivotal effect of MMP-7 in kidney fibrosis on the interaction of three pathways, including epithelial-mesenchymal transition, TGF-β signaling activation, and ECM accumulation, and suggested that MMP-7 not only acts as a target in kidney scarring treatment, but also as a marker of renal fibrosis [275].

The prevalent cause of kidney allograft dysfunction is the fibrosis of interstitium and tubular atrophy. Chronic allograft dysfunction results from both immunological and nonimmunological factors causing slow allograft dysfunction, usually with proteinuria. A key structure that determines the outcome of the transplant is vessels. Nonexistent collateral vasculature accompanying progressive vascular narrowing and occlusion leads to downstream hypoxia and ischemia predominantly in the interstitium [276]. The imbalance in MMP/TIMPs activity plays a leading role in ECM remodeling. Although serum levels of MMPs and TIMPs remained unchanged during subclinical tubulitis linked to existing or newly developing interstitial fibrosis and tubular atrophy, the urinary levels of MMP-1, MMP-7, TIMP-1 were several times higher, and were not found to be elevated in quiescent interstitial fibrosis and tubular atrophy [277].

Apparently, MMP-7 participates in the development and evolution of renal carcinoma [278]. Renal cell carcinomas are adenocarcinomas arising from tubular epithelium. MMPs synthesized by stromal or tumor cell lines are included in tumor advancement. The mechanisms of MMP-7 involvement in tumor progression include modulation of invasion and angiogenesis in renal cell carcinoma, and in multivariate analysis MMP-7 acted as a predictor of poor prognosis in renal carcinoma [279]. In addition, it has been shown that the expression of MMP-7 in clear cell renal cell carcinoma was significantly elevated when compared with controls, and it even correlated with the degree of malignancy and the predicted poor prognosis [280]. On the other hand, the TIMP-2 expression level in the same study in clear cell renal cell carcinoma was clearly lower than in the control group [280]. Therefore, MMP-7 and TIMP-2 can potentially be used as novel biochemical markers for the prognosis evaluation in clear cell renal cell carcinoma patients.

In addition, MMP-7 is able to release the membrane-bound Fas ligand, a transmembrane stimulator of the apoptotic receptor Fas [281]. The released Fas ligand then induces apoptosis of surrounding cells [281] or decreases cancer cell apoptosis [282].

In summary, these discussed studies suggest that both acute and chronic reduction of kidney function may be associated with MMP-7-caused changes in ECM turnover.

Enamelysin (MMP-20)

MMP-20 and Kidney

A recent study has shown that MMP-20, together with dentin sialophosphoprotein, is expressed not only in the ductal epithelial cells of human salivary glands, but it was also found in all sites of the human and monkey nephron exempting the glomeruli, with a high predominance in the proximal and distal tubular cells [283]. The dentin sialoprotein and MMP-20 pairing may actively participate in the restoration and turnover of ECM proteins of the basement membranes in the monkey and human kidney epithelial cells [283].

Membrane-Type MMPs (MMP-14, MMP-15, MMP-16, MMP-17, MMP-24, MMP-25)

Membrane-Type MMPs: Structure and Function

Enzymatic activation of MMPs occurs by the removal of the pro-domain, triggered by other proteases such as plasmin, or by cellular membrane-type MMPs. Four of these belong to type I transmembrane proteins, namely MT1-MMP (MMP-14), MT2-MMP (MMP-15), MT3-MMP (MMP-16), and MT5-MMP (MMP-24), while the remaining two represent glycosylphosphatidylinositol-anchored proteins MT4-MMP (MMP-17) and MT6-MMP (MMP-25). MT-MMPs are a unique class of MMPs bound to the cellular surface by a transmembrane domain. MT-MMPs activities are various, with a leading role in guiding the proteolytic events adjacent to the pericellular microenvironmental processes [258]. All MT-MMPs, excluding MT4-MMP, can activate pro-MMP-2.

MT1-MMP (MMP-14) mainly works as the cell surface activator of MMP-2. MT-1-MMP is capable of cleaving several ECM proteins, namely collagen I, collagen III, fibronectin, and laminin [284, 285]. Additionally, MT1-MMP functions as a "sheddase" for CD44 and syndecan-1 surface proteins [286].

MT-MMPs are capable of activating both pro-MMP-2 and pro-MMP-13 on the cell surface. These enzymes play a leading role in the tissue remodeling which accompanies different physiological and pathological processes. In the presence of MT-1-MMP (MMP-14) situated on the cellular surface, a ternary complex comprised of pro-MMP-2, TIMP-2, and MT1-MMP is formed, resulting in the activation of MMP-2 [1, 287]. The participation of MT1-MMP is essential to this activation.

In general, the aim in the MMP activation or inhibition is the maintenance of matrix homeostasis. For instance, MMP-2 in association with MT1-MMP (MMP-14) is needed for the epithelial mesenchymal transition of NRK-52E cells promoted by TGF-β1 in vitro [117].

Membrane-Type MMPs and Kidney Disease

The role of MT-MMP in the development of kidney injury was investigated in a crescentic glomerulonephritis caused by antiglomerulus basement membrane antibodies in Wistar Kyoto rats. In the invading macrophages in crescent lesions, the activated MT1-MMP (MMP-14) was probably responsible for the pathological breakdown of glomerular ECMs via pro-MMP-2 activation [288].

In the human kidney MMP-24 (MT5-MMP), transcription and production are increased in diabetic kidney disease [162]. Moreover, higher levels of MMP-14 (MT1-MMP) are identified in the urine from patients with diabetic nephropathy [153]. MMP-14 is known to be present as a membrane-bound MMP, or as MMP with various soluble forms. The mechanisms of increased MMP-14 production in urine are not entirely clear, but auto-cleaving is thought to be the most important one [289]. Thus, the increased MMP-14 concentrations in urine could be explained either as a result of the enhanced cleavage of soluble MMP-14 from cells located within the nephron, or as a result of the cellular losses of express-bound MMP-14 cells within the nephron.

"Other MMPs" (MMP-12, MMP-19, MMP-21, MMP-23A, MMP-23B, MMP-27, MMP-28)

Overview of "Other MMPs"

Other MMPs, namely MMP-12, MMP-19, MMP-21, MMP-23A, MMP-23B, MMP-27, MMP-28, do not fit easily into the main groups of MMPs. Their expression is typically bound to a single cell or a tissue type, or they are produced in special circumstances only [86, 290].

MMP-12, also known as macrophage metalloelastase, cleaves both soluble and insoluble elastin. MMP-12 may be implicated in aneurysm formation [291] and in the development of emphysema [292]. MMP-12 produced by macrophages infiltrating the glomeruli modulates high-fat diet-induced glomerular fibrogenesis and inflammation in a mouse model of obesity [293]. MMP-19 (MMP RASI-1) expression is linked to the human epidermis and endothelial cells, and MMP-19 participates in such processes as cellular migration, proliferation, angiogenesis, and adhesion. MMP-19 expression has been found in synovial vascularization in patients with rheumatoid arthritis [294].

MMP-21 degrades ECM proteins in such physiological processes as embryogenesis, reproduction and tissue remodeling, as well as in such pathological disease processes as metastasis development and asthma [295]. The MMP23A gene and the almost identical MMP23B gene can be found in the duplicated region of chromosome 1p36.3. It is most probable that MMP23A functions intracellularly. MMP-23B is strongly expressed in the ovary and the heart [296].

In contrast to the majority of MMPs, MMP-27 is not a secretory protease but is efficiently accumulated in the endoplasmic reticulum in three cellular lines of mammals [297]. Despite its sequence homology with MT-MMPs (the unique C-terminal extension which is necessary and sufficient for endoplasmic reticulum), MMP-27 is not provided with a stable membrane anchorage and therefore does not interact permanently with the cellular membrane. There is sparse information about MMP-27 expression during developmental, physiological or pathological processes. In the adult rat, MMP-27 mRNA is abundantly expressed in antiGG/IgM B-stimulated lymphocytes [298] and in the bone and kidney, with much lower levels found in the heart [299].

The expression of MMP-28, also known as epilysin, is bound to testes and keratinocytes where it is seen as a damage response. MMP-28 is involved in such disease processes as asthma and metastases [300].

Conclusion

In this review, we have discussed the significance of MMPs in multiple processes essential for tissue remodeling, with a special focus on the kidney. MMP expression and activation is orchestrated by various mechanisms including cytokines, growth factors, cell-to-cell and cell-matrix interactions and soluble substances. MMPs are vitally important for kidney development and ECM turnover and intervene in their repair and adaptation. The activity of MMPs facilitates the alterations in ECM components, and thus MMPs are implicated in the development of a number of kidney diseases. Profound knowledge of the impact of MMP actions may grant insight into finding new options to effectively cope with kidney disease. New insights, obtained from numerous studies, imply that at early stages MMPs facilitate glomerular basal membrane breakdown (in relation to a specific background and time frame), while at the later stages MMPs assist to digest ECM components accompanying kidney scarring and fibrosis.

Thorough understanding of MMP actions and different facets of renal physiology and disease relies on both clinical and tissue studies. Further progress in mastering control and regulation of MMP actions depends on the development of certain MMP inhibitors, choice of suitable animal models, and finding specific MMP-targeted therapeutic strategies. These future novel medical strategies regulating and controlling MMP activity may help to elucidate the precise ways for conquering kidney diseases, therefore preventing their detrimental clinical outcome.

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Disclosure Statement

The authors declare they have no conflicts of interest.

References

1 Nagase H, Visse R, Murphy G. Structure and function of matrix metalloproteinases and TIMPs. Cardiovasc Res. 2006 Feb;69(3):562–73.
2 Ohnishi J, Ohnishi E, Shibuya H, Takahashi T. Functions for proteinases in the ovulatory process. Biochim Biophys Acta. 2005 Aug;1751(1):95–109.
3 Puente XS, Sánchez LM, Overall CM, López-Otín C. Human and mouse proteases: a comparative genomic approach. Nat Rev Genet. 2003 Jul;4(7):544–58.
4 Sternlicht MD, Werb Z. How matrix metalloproteinases regulate cell behavior. Annu Rev Cell Dev Biol. 2001; 17(1):463–516.
5 Bäck M, Ketelhuth DF, Agewall S. Matrix metalloproteinases in atherothrombosis. Prog Cardiovasc Dis. 2010 Mar-Apr;52(5):410–28.
6 Page-McCaw A, Ewald AJ, Werb Z. Matrix metalloproteinases and the regulation of tissue remodelling. Nat Rev Mol Cell Biol. 2007 Mar;8(3):221–33.
7 McCawley LJ, Matrisian LM. Matrix metalloproteinases: they're not just for matrix anymore! Curr Opin Cell Biol. 2001 Oct;13(5):534–40.
8 Van Lint P, Libert C. Chemokine and cytokine processing by matrix metalloproteinases and its effect on leukocyte migration and inflammation. J Leukoc Biol. 2007 Dec;82(6):1375–81.
9 Schweitzer M, Mitmaker B, Obrand D, Sheiner N, Abraham C, Dostanic S, et al. Atorvastatin modulates matrix metalloproteinase expression, activity, and signaling in abdominal aortic aneurysms. Vasc Endovascular Surg. 2010 Feb;44(2):116–22.
10 Newby AC. Matrix metalloproteinases regulate migration, proliferation, and death of vascular smooth muscle cells by degrading matrix and non-matrix substrates. Cardiovasc Res. 2006 Feb;69(3):614–24.
11 Pushpakumar S, Kundu S, Pryor T, Givvimani S, Lederer E, Tyagi SC, et al. Angiotensin-II induced hypertension and renovascular remodelling in tissue inhibitor of metalloproteinase 2 knockout mice. J Hypertens. 2013 Nov;31(11):2270–81; discussion 2281.
12 George SJ. Tissue inhibitors of metalloproteinases and metalloproteinases in atherosclerosis. Curr Opin Lipidol. 1998 Oct;9(5):413–23.
13 Préaux AM, Mallat A, Nhieu JT, D'Ortho MP, Hembry RM, Mavier P. Matrix metalloproteinase-2 activation in human hepatic fibrosis regulation by cell-matrix interactions. Hepatology. 1999 Oct;30(4):944–50.
14 Hayashi T, Stetler-Stevenson WG, Fleming MV, Fishback N, Koss MN, Liotta LA, et al. Immunohistochemical study of metalloproteinases and their tissue inhibitors in the lungs of patients with diffuse alveolar damage and idiopathic pulmonary fibrosis. Am J Pathol. 1996 Oct;149(4):1241–56.
15 Hober S, Uhlén M. Human protein atlas and the use of microarray technologies. Curr Opin Biotechnol. 2008 Feb;19(1):30–5.
16 Marti HP. [Role of matrix metalloproteinases in the progression of renal lesions]. Presse Med. 2000 Apr; 29(14):811–7.
17 Nakopoulou L, Lazaris AC, Boletis I, Michail S, Iatrou C, Papadakis G, et al. The expression of matrix metalloproteinase-11 protein in various types of glomerulonephritis. Nephrol Dial Transplant. 2007 Jan;22(1):109–17.
18 Nikolic-Paterson DJ, Atkins RC. The role of macrophages in glomerulonephritis. Nephrol Dial Transplant. 2001;16 Suppl 5:3–7.
19 Lelongt B, Legallicier B, Piedagnel R, Ronco PM. Do matrix metalloproteinases MMP-2 and MMP-9 (gelatinases) play a role in renal development, physiology and glomerular diseases? Curr Opin Nephrol Hypertens. 2001 Jan;10(1):7–12.
20 Tan RJ, Liu Y. Matrix metalloproteinases in kidney homeostasis and diseases. Am J Physiol Renal Physiol. 2012 Jun;302(11):F1351–61.

21 Knäuper V, López-Otin C, Smith B, Knight G, Murphy G. Biochemical characterization of human collagenase-3. J Biol Chem. 1996 Jan;271(3):1544–50.
22 Cossins J, Dudgeon TJ, Catlin G, Gearing AJ, Clements JM. Identification of MMP-18, a putative novel human matrix metalloproteinase. Biochem Biophys Res Commun. 1996 Nov;228(2):494–8.
23 Imai E, Isaka Y, Fujiwara Y, Kaneda Y, Kamada T, Ueda N. Introduction of a foreign gene into the kidney in vivo: development of glomerulosclerosis by the transfection of genes for PDGF and TGF-beta. Contrib Nephrol. 1994;107:205–15.
24 Basile DP. The transforming growth factor beta system in kidney disease and repair: recent progress and future directions. Curr Opin Nephrol Hypertens. 1999 Jan;8(1):21–30.
25 Guo H, Zucker S, Gordon MK, Toole BP, Biswas C. Stimulation of matrix metalloproteinase production by recombinant extracellular matrix metalloproteinase inducer from transfected Chinese hamster ovary cells. J Biol Chem. 1997 Jan;272(1):24–7.
26 Huang Y, Mironova M, Lopes-Virella MF. Oxidized LDL stimulates matrix metalloproteinase-1 expression in human vascular endothelial cells. Arterioscler Thromb Vasc Biol. 1999 Nov;19(11):2640–7.
27 Reunanen N, Westermarck J, Häkkinen L, Holmström TH, Elo I, Eriksson JE, et al. Enhancement of fibroblast collagenase (matrix metalloproteinase-1) gene expression by ceramide is mediated by extracellular signal-regulated and stress-activated protein kinase pathways. J Biol Chem. 1998 Feb;273(9):5137–45.
28 Kusano K, Miyaura C, Inada M, Tamura T, Ito A, Nagase H, et al. Regulation of matrix metalloproteinases (MMP-2, -3, -9, and -13) by interleukin-1 and interleukin-6 in mouse calvaria: association of MMP induction with bone resorption. Endocrinology. 1998 Mar;139(3):1338–45.
29 Dollery CM, Owen CA, Sukhova GK, Krettek A, Shapiro SD, Libby P. Neutrophil elastase in human atherosclerotic plaques: production by macrophages. Circulation. 2003 Jun;107(22):2829–36.
30 Karanovic D, Grujic-Milanovic J, Miloradovic Z, Ivanov M, Jovovic D, Vajic UJ, et al. Effects of Single and Combined Losartan and Tempol Treatments on Oxidative Stress, Kidney Structure and Function in Spontaneously Hypertensive Rats with Early Course of Proteinuric Nephropathy. PLoS One. 2016 Aug;11(8):e0161706.
31 Abdel Aziz MA, Badary DM, Hussein MR. Renal damage following Alloxan-induced diabetes is associated with generation of reactive oxygen species, alterations of p53, TGF-β1, and extracellular matrix metalloproteinases in rats. Cell Biol Int. 2017 May;41(5):525–33.
32 Friese RS, Rao F, Khandrika S, Thomas B, Ziegler MG, Schmid-Schönbein GW, et al. Matrix metalloproteinases: discrete elevations in essential hypertension and hypertensive end-stage renal disease. Clin Exp Hypertens. 2009 Oct;31(7):521–33.
33 Nakamura T, Ushiyama C, Suzuki S, Ebihara I, Shimada N, Koide H. Elevation of serum levels of metalloproteinase-1, tissue inhibitor of metalloproteinase-1 and type IV collagen, and plasma levels of metalloproteinase-9 in polycystic kidney disease. Am J Nephrol. 2000 Jan-Feb;20(1):32–6.
34 Ameku T, Taura D, Sone M, Numata T, Nakamura M, Shiota F, et al. Identification of MMP1 as a novel risk factor for intracranial aneurysms in ADPKD using iPSC models. Sci Rep. 2016 Jul;6(1):30013.
35 Duymelinck C, Deng JT, Dauwe SE, De Broe ME, Verpooten GA. Inhibition of the matrix metalloproteinase system in a rat model of chronic cyclosporine nephropathy. Kidney Int. 1998 Sep;54(3):804–18.
36 Rodrigo E, López-Hoyos M, Escallada R, Fernández-Fresnedo G, Ruiz JC, Piñera C, et al. Circulating levels of matrix metalloproteinases MMP-3 and MMP-2 in renal transplant recipients with chronic transplant nephropathy. Nephrol Dial Transplant. 2000 Dec;15(12):2041–5.
37 Kato R, Momiyama Y, Ohmori R, Taniguchi H, Nakamura H, Ohsuzu F. Levels of matrix metalloproteinase-1 in patients with and without coronary artery disease and relation to complex and noncomplex coronary plaques. Am J Cardiol. 2005 Jan;95(1):90–2.
38 Hwang JJ, Yang WS, Chiang FT, Chen MF, Lin HJ, Huang PJ, et al. Association of circulating matrix metalloproteinase-1, but not adiponectin, with advanced coronary artery disease. Atherosclerosis. 2009 May;204(1):293–7.
39 Kato R, Momiyama Y, Ohmori R, Taniguchi H, Nakamura H, Ohsuzu F. Plasma matrix metalloproteinase-8 concentrations are associated with the presence and severity of coronary artery disease. Circ J. 2005 Sep;69(9):1035–40.
40 Obase Y, Rytilä P, Metso T, Pelkonen AS, Tervahartiala T, Turpeinen M, et al. Effects of inhaled corticosteroids on metalloproteinase-8 and tissue inhibitor of metalloproteinase-1 in the airways of asthmatic children. Int Arch Allergy Immunol. 2010;151(3):247–54.
41 Eberhardt W, Schulze M, Engels C, Klasmeier E, Pfeilschifter J. Glucocorticoid-mediated suppression of cytokine-induced matrix metalloproteinase-9 expression in rat mesangial cells: involvement of nuclear factor-kappaB and Ets transcription factors. Mol Endocrinol. 2002 Aug;16(8):1752–66.
42 Eberhardt W, Kilz T, Akool S, Müller R, Pfeilschifter J. Dissociated glucocorticoids equipotently inhibit cytokine- and cAMP-induced matrix degrading proteases in rat mesangial cells. Biochem Pharmacol. 2005 Aug;70(3):433–45.
43 Lloris-Carsí JM, Barrios C, Prieto-Moure B, Lloris-Cejalvo JM, Cejalvo-Lapeña D. The effect of biological sealants and adhesive treatments on matrix metalloproteinase expression during renal injury healing. PLoS One. 2017 May;12(5):e0177665.
44 Tomita M, Koike H, Han GD, Shimizu F, Kawachi H. Decreased collagen-degrading activity could be a marker of prolonged mesangial matrix expansion. Clin Exp Nephrol. 2004 Mar;8(1):17–26.

45 Ahmed AK, Haylor JL, El Nahas AM, Johnson TS. Localization of matrix metalloproteinases and their inhibitors in experimental progressive kidney scarring. Kidney Int. 2007 Apr;71(8):755–63.
46 Pushpakumar SB, Kundu S, Metreveli N, Tyagi SC, Sen U. Matrix Metalloproteinase Inhibition Mitigates Renovascular Remodeling in Salt-Sensitive Hypertension. Physiol Rep. 2013 Aug;1(3):e00063.
47 Sakamaki Y, Sasamura H, Hayashi K, Ishiguro K, Takaishi H, Okada Y, et al. Absence of gelatinase (MMP-9) or collagenase (MMP-13) attenuates adriamycin-induced albuminuria and glomerulosclerosis. Nephron, Exp Nephrol. 2010;115(2):e22–32.
48 López-Andrés N, Rousseau A, Akhtar R, Calvier L, Iñigo C, Labat C, et al. Cardiotrophin 1 is involved in cardiac, vascular, and renal fibrosis and dysfunction. Hypertension. 2012 Aug;60(2):563–73.
49 Berk BC, Fujiwara K, Lehoux S. ECM remodeling in hypertensive heart disease. J Clin Invest. 2007 Mar;117(3):568–75.
50 Ahmed SH, Clark LL, Pennington WR, Webb CS, Bonnema DD, Leonardi AH, et al. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation. 2006 May;113(17):2089–96.
51 Hirata H, Okayama N, Naito K, Inoue R, Yoshihiro S, Matsuyama H, et al. Association of a haplotype of matrix metalloproteinase (MMP)-1 and MMP-3 polymorphisms with renal cell carcinoma. Carcinogenesis. 2004 Dec;25(12):2379–84.
52 Mandal M, Mandal A, Das S, Chakraborti T, Sajal C. Clinical implications of matrix metalloproteinases. Mol Cell Biochem. 2003 Oct;252(1-2):305–29.
53 Baricos WH. Chronic renal disease: do metalloproteinase inhibitors have a demonstrable role in extracellular matrix accumulation? Curr Opin Nephrol Hypertens. 1995 Jul;4(4):365–8.
54 Hobeika MJ, Thompson RW, Muhs BE, Brooks PC, Gagne PJ. Matrix metalloproteinases in peripheral vascular disease. J Vasc Surg. 2007 Apr;45(4):849–57.
55 Carome MA, Striker LJ, Peten EP, Moore J, Yang CW, Stetler-Stevenson WG, et al. Human glomeruli express TIMP-1 mRNA and TIMP-2 protein and mRNA. Am J Physiol. 1993 Jun;264(6 Pt 2):F923–9.
56 Fosang AJ, Neame PJ, Last K, Hardingham TE, Murphy G, Hamilton JA. The interglobular domain of cartilage aggrecan is cleaved by PUMP, gelatinases, and cathepsin B. J Biol Chem. 1992 Sep;267(27):19470–4.
57 Senior RM, Griffin GL, Fliszar CJ, Shapiro SD, Goldberg GI, Welgus HG. Human 92- and 72-kilodalton type IV collagenases are elastases. J Biol Chem. 1991 Apr;266(12):7870–5.
58 Chang HR, Yang SF, Li ML, Lin CC, Hsieh YS, Lian JD. Relationships between circulating matrix metalloproteinase-2 and -9 and renal function in patients with chronic kidney disease. Clin Chim Acta. 2006 Apr;366(1-2):243–8.
59 Pourmotabbed T. Relation between substrate specificity and domain structure of 92-kDa type IV collagenase. Ann N Y Acad Sci. 1994 Sep;732:372–4.
60 Morodomi T, Ogata Y, Sasaguri Y, Morimatsu M, Nagase H. Purification and characterization of matrix metalloproteinase 9 from U937 monocytic leukaemia and HT1080 fibrosarcoma cells. Biochem J. 1992 Jul;285(Pt 2):603–11.
61 Kenny HA, Kaur S, Coussens LM, Lengyel E. The initial steps of ovarian cancer cell metastasis are mediated by MMP-2 cleavage of vitronectin and fibronectin. J Clin Invest. 2008 Apr;118(4):1367–79.
62 Nakamura H, Fujii Y, Inoki I, Sugimoto K, Tanzawa K, Matsuki H, et al. Brevican is degraded by matrix metalloproteinases and aggrecanase-1 (ADAMTS4) at different sites. J Biol Chem. 2000 Dec;275(49):38885–90.
63 Turk BE, Huang LL, Piro ET, Cantley LC. Determination of protease cleavage site motifs using mixture-based oriented peptide libraries. Nat Biotechnol. 2001 Jul;19(7):661–7.
64 Cauwe B, Van den Steen PE, Opdenakker G. The biochemical, biological, and pathological kaleidoscope of cell surface substrates processed by matrix metalloproteinases. Crit Rev Biochem Mol Biol. 2007 May-Jun;42(3):113–85.
65 Ganea E, Trifan M, Laslo AC, Putina G, Cristescu C. Matrix metalloproteinases: useful and deleterious. Biochem Soc Trans. 2007 Aug;35(Pt 4):689–91.
66 Liu W, Yu WR, Carling T, Juhlin C, Rastad J, Ridefelt P, et al. Regulation of gp330/megalin expression by vitamins A and D. Eur J Clin Invest. 1998 Feb;28(2):100–7.
67 Yu Q, Stamenkovic I. Cell surface-localized matrix metalloproteinase-9 proteolytically activates TGF-beta and promotes tumor invasion and angiogenesis. Genes Dev. 2000 Jan;14(2):163–76.
68 Gearing AJ, Beckett P, Christodoulou M, Churchill M, Clements J, Davidson AH, et al. Processing of tumour necrosis factor-alpha precursor by metalloproteinases. Nature. 1994 Aug;370(6490):555–7.
69 Van den Steen PE, Proost P, Wuyts A, Van Damme J, Opdenakker G. Neutrophil gelatinase B potentiates interleukin-8 tenfold by aminoterminal processing, whereas it degrades CTAP-III, PF-4, and GRO-alpha and leaves RANTES and MCP-2 intact. Blood. 2000 Oct;96(8):2673–81.
70 Schönbeck U, Mach F, Libby P. Generation of biologically active IL-1 beta by matrix metalloproteinases: a novel caspase-1-independent pathway of IL-1 beta processing. J Immunol. 1998 Oct;161(7):3340–6.
71 Nguyen M, Arkell J, Jackson CJ. Human endothelial gelatinases and angiogenesis. Int J Biochem Cell Biol. 2001 Oct;33(10):960–70.
72 Taylor CT, Dzus AL, Colgan SP. Autocrine regulation of epithelial permeability by hypoxia: role for polarized release of tumor necrosis factor alpha. Gastroenterology. 1998 Apr;114(4):657–68.

73 Bergmann U, Tuuttila A, Stetler-Stevenson WG, Tryggvason K. Autolytic activation of recombinant human 72 kilodalton type IV collagenase. Biochemistry. 1995 Mar;34(9):2819–25.
74 Strongin AY, Collier I, Bannikov G, Marmer BL, Grant GA, Goldberg GI. Mechanism of cell surface activation of 72-kDa type IV collagenase. Isolation of the activated form of the membrane metalloprotease. J Biol Chem. 1995 Mar;270(10):5331–8.
75 Pepper MS. Role of the matrix metalloproteinase and plasminogen activator-plasmin systems in angiogenesis. Arterioscler Thromb Vasc Biol. 2001 Jul;21(7):1104–17.
76 Bourboulia D, Stetler-Stevenson WG. Matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs): positive and negative regulators in tumor cell adhesion. Semin Cancer Biol. 2010 Jun;20(3):161–8.
77 Murphy G, Ward R, Hembry RM, Reynolds JJ, Kühn K, Tryggvason K. Characterization of gelatinase from pig polymorphonuclear leucocytes. A metalloproteinase resembling tumour type IV collagenase. Biochem J. 1989 Mar;258(2):463–72.
78 Kolkenbrock H, Hecker-Kia A, Orgel D, Kinawi A, Ulbrich N. Progelatinase B forms from human neutrophils. complex formation of monomer/lipocalin with TIMP-1. Biol Chem. 1996 Jul-Aug;377(7-8):529–33.
79 Menashi S, Fridman R, Desrivieres S, Lu H, Legrand Y, Soria C. Regulation of 92-kDa gelatinase B activity in the extracellular matrix by tissue kallikrein. Ann N Y Acad Sci. 1994 Sep;732:466–8.
80 Bu CH, Pourmotabbed T. Mechanism of activation of human neutrophil gelatinase B. Discriminating between the role of Ca2+ in activation and catalysis. J Biol Chem. 1995 Aug;270(31):18563–9.
81 Leber TM, Balkwill FR. Regulation of monocyte MMP-9 production by TNF-alpha and a tumour-derived soluble factor (MMPSF). Br J Cancer. 1998 Sep;78(6):724–32.
82 Martin J, Eynstone L, Davies M, Steadman R. Induction of metalloproteinases by glomerular mesangial cells stimulated by proteins of the extracellular matrix. J Am Soc Nephrol. 2001 Jan;12(1):88–96.
83 Xu XP, Meisel SR, Ong JM, Kaul S, Cercek B, Rajavashisth TB, et al. Oxidized low-density lipoprotein regulates matrix metalloproteinase-9 and its tissue inhibitor in human monocyte-derived macrophages. Circulation. 1999 Mar;99(8):993–8.
84 Provatopoulou X, Gounaris A, Kalogera E, Zagouri F, Flessas I, Goussetis E, et al. Circulating levels of matrix metalloproteinase-9 (MMP-9), neutrophil gelatinase-associated lipocalin (NGAL) and their complex MMP-9/NGAL in breast cancer disease. BMC Cancer. 2009 Nov;9(1):390.
85 Schmidt R, Bültmann A, Fischel S, Gillitzer A, Cullen P, Walch A, et al. Extracellular matrix metalloproteinase inducer (CD147) is a novel receptor on platelets, activates platelets, and augments nuclear factor kappaB-dependent inflammation in monocytes. Circ Res. 2008 Feb;102(3):302–9.
86 Visse R, Nagase H. Matrix metalloproteinases and tissue inhibitors of metalloproteinases: structure, function, and biochemistry. Circ Res. 2003 May;92(8):827–39.
87 Wang Z, Famulski K, Lee J, Das SK, Wang X, Halloran P, et al. TIMP2 and TIMP3 have divergent roles in early renal tubulointerstitial injury. Kidney Int. 2014 Jan;85(1):82–93.
88 Anand-Apte B, Bao L, Smith R, Iwata K, Olsen BR, Zetter B, et al. A review of tissue inhibitor of metalloproteinases-3 (TIMP-3) and experimental analysis of its effect on primary tumor growth. Biochem Cell Biol. 1996;74(6):853–62.
89 Greene J, Wang M, Liu YE, Raymond LA, Rosen C, Shi YE. Molecular cloning and characterization of human tissue inhibitor of metalloproteinase 4. J Biol Chem. 1996 Nov;271(48):30375–80.
90 Ronco P, Chatziantoniou C. Matrix metalloproteinases and matrix receptors in progression and reversal of kidney disease: therapeutic perspectives. Kidney Int. 2008 Oct;74(7):873–8.
91 Legallicier B, Trugnan G, Murphy G, Lelongt B, Ronco P. Expression of the type IV collagenase system during mouse kidney development and tubule segmentation. J Am Soc Nephrol. 2001 Nov;12(11):2358–69.
92 Cipollone F, Fazia M, Iezzi A, Pini B, Cuccurullo C, Zucchelli M, et al. Blockade of the angiotensin II type 1 receptor stabilizes atherosclerotic plaques in humans by inhibiting prostaglandin E2-dependent matrix metalloproteinase activity. Circulation. 2004 Mar;109(12):1482–8.
93 Ceron CS, Castro MM, Rizzi E, Montenegro MF, Fontana V, Salgado MC, et al. Spironolactone and hydrochlorothiazide exert antioxidant effects and reduce vascular matrix metalloproteinase-2 activity and expression in a model of renovascular hypertension. Br J Pharmacol. 2010 May;160(1):77–87.
94 Marçal DM, Rizzi E, Martins-Oliveira A, Ceron CS, Guimaraes DA, Gerlach RF, et al. Comparative study on antioxidant effects and vascular matrix metalloproteinase-2 downregulation by dihydropyridines in renovascular hypertension. Naunyn Schmiedebergs Arch Pharmacol. 2011 Jan;383(1):35–44.
95 Izidoro-Toledo TC, Guimaraes DA, Belo VA, Gerlach RF, Tanus-Santos JE. Effects of statins on matrix metalloproteinases and their endogenous inhibitors in human endothelial cells. Naunyn Schmiedebergs Arch Pharmacol. 2011 Jun;383(6):547–54.
96 Luan Z, Chase AJ, Newby AC. Statins inhibit secretion of metalloproteinases-1, -2, -3, and -9 from vascular smooth muscle cells and macrophages. Arterioscler Thromb Vasc Biol. 2003 May;23(5):769–75.
97 Hua Y, Xue J, Sun F, Zhu L, Xie M. Aspirin inhibits MMP-2 and MMP-9 expressions and activities through upregulation of PPARalpha/gamma and TIMP gene expressions in ox-LDL-stimulated macrophages derived from human monocytes. Pharmacology. 2009;83(1):18–25.
98 Bea F, Kreuzer J, Preusch M, Schaab S, Isermann B, Rosenfeld ME, et al. Melagatran reduces advanced atherosclerotic lesion size and may promote plaque stability in apolipoprotein E-deficient mice. Arterioscler Thromb Vasc Biol. 2006 Dec;26(12):2787–92.

99 Lenz O, Elliot SJ, Stetler-Stevenson WG. Matrix metalloproteinases in renal development and disease. J Am Soc Nephrol. 2000 Mar;11(3):574–81.
100 Turck J, Pollock AS, Lee LK, Marti HP, Lovett DH. Matrix metalloproteinase 2 (gelatinase A) regulates glomerular mesangial cell proliferation and differentiation. J Biol Chem. 1996 Jun;271(25):15074–83.
101 Basile DP, Fredrich K, Weihrauch D, Hattan N, Chilian WM. Angiostatin and matrix metalloprotease expression following ischemic acute renal failure. Am J Physiol Renal Physiol. 2004 May;286(5):F893–902.
102 Johnatty RN, Taub DD, Reeder SP, Turcovski-Corrales SM, Cottam DW, Stephenson TJ, et al. Cytokine and chemokine regulation of proMMP-9 and TIMP-1 production by human peripheral blood lymphocytes. J Immunol. 1997 Mar;158(5):2327–33.
103 Cornelius LA, Nehring LC, Harding E, Bolanowski M, Welgus HG, Kobayashi DK, et al. Matrix metalloproteinases generate angiostatin: effects on neovascularization. J Immunol. 1998 Dec;161(12):6845–52.
104 Lijnen HR, Ugwu F, Bini A, Collen D. Generation of an angiostatin-like fragment from plasminogen by stromelysin-1 (MMP-3). Biochemistry. 1998 Apr;37(14):4699–702.
105 O'Reilly MS, Wiederschain D, Stetler-Stevenson WG, Folkman J, Moses MA. Regulation of angiostatin production by matrix metalloproteinase-2 in a model of concomitant resistance. J Biol Chem. 1999 Oct;274(41):29568–71.
106 Patterson BC, Sang QA. Angiostatin-converting enzyme activities of human matrilysin (MMP-7) and gelatinase B/type IV collagenase (MMP-9). J Biol Chem. 1997 Nov;272(46):28823–5.
107 Lelongt B, Trugnan G, Murphy G, Ronco PM. Matrix metalloproteinases MMP2 and MMP9 are produced in early stages of kidney morphogenesis but only MMP9 is required for renal organogenesis in vitro. J Cell Biol. 1997 Mar;136(6):1363–73.
108 Arnould C, Lelièvre-Pégorier M, Ronco P, Lelongt B. MMP9 limits apoptosis and stimulates branching morphogenesis during kidney development. J Am Soc Nephrol. 2009 Oct;20(10):2171–80.
109 Bengatta S, Arnould C, Letavernier E, Monge M, de Préneuf HM, Werb Z, et al. MMP9 and SCF protect from apoptosis in acute kidney injury. J Am Soc Nephrol. 2009 Apr;20(4):787–97.
110 Juliano RL, Haskill S. Signal transduction from the extracellular matrix. J Cell Biol. 1993 Feb;120(3):577–85.
111 Singhal PC, Sagar S, Garg P. Simulated glomerular pressure modulates mesangial cell 72 kDa metalloproteinase activity. Connect Tissue Res. 1996;33(4):257–63.
112 Akiyama K, Shikata K, Sugimoto H, Matsuda M, Shikata Y, Fujimoto N, et al. 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. 1997 Feb;95(2):115–28.
113 Lutz J, Yao Y, Song E, Antus B, Hamar P, Liu S, et al. Inhibition of matrix metalloproteinases during chronic allograft nephropathy in rats. Transplantation. 2005 Mar;79(6):655–61.
114 Boor P, Sebeková K, Ostendorf T, Floege J. Treatment targets in renal fibrosis. Nephrol Dial Transplant. 2007 Dec;22(12):3391–407.
115 Aresu L, Benali S, Garbisa S, Gallo E, Castagnaro M. Matrix metalloproteinases and their role in the renal epithelial mesenchymal transition. Histol Histopathol. 2011 Mar;26(3):307–13.
116 Catania JM, Chen G, Parrish AR. Role of matrix metalloproteinases in renal pathophysiologies. Am J Physiol Renal Physiol. 2007 Mar;292(3):F905–11.
117 Cheng S, Lovett DH. Gelatinase A (MMP-2) is necessary and sufficient for renal tubular cell epithelial-mesenchymal transformation. Am J Pathol. 2003 Jun;162(6):1937–49.
118 Chung AW, Yang HH, Kim JM, Sigrist MK, Chum E, Gourlay WA, et al. Upregulation of matrix metalloproteinase-2 in the arterial vasculature contributes to stiffening and vasomotor dysfunction in patients with chronic kidney disease. Circulation. 2009 Sep;120(9):792–801.
119 Musiał K, Zwolińska D. Novel indicators of fibrosis-related complications in children with chronic kidney disease. Clin Chim Acta. 2014 Mar;430:15–9.
120 Cheng Z, Limbu MH, Wang Z, Liu J, Liu L, Zhang X, et al. MMP-2 and 9 in Chronic Kidney Disease. Int J Mol Sci. 2017 Apr;18(4):18.
121 Kaissling B, Lehir M, Kriz W. Renal epithelial injury and fibrosis. Biochim Biophys Acta. 2013 Jul;1832(7):931–9.
122 Kriz W, LeHir M. Pathways to nephron loss starting from glomerular diseases-insights from animal models. Kidney Int. 2005 Feb;67(2):404–19.
123 Funabiki K, Horikoshi S, Tomino Y, Nagai Y, Koide H. Immunohistochemical analysis of extracellular components in the glomerular sclerosis of patients with glomerulonephritis. Clin Nephrol. 1990 Dec;34(6):239–46.
124 Intengan HD, Schiffrin EL. Vascular remodeling in hypertension: roles of apoptosis, inflammation, and fibrosis. Hypertension. 2001 Sep;38(3 Pt 2):581–7.
125 Zhao W, Chen SS, Chen Y, Ahokas RA, Sun Y. Kidney fibrosis in hypertensive rats: role of oxidative stress. Am J Nephrol. 2008;28(4):548–54.
126 Taipale J, Saharinen J, Keski-Oja J. Extracellular matrix-associated transforming growth factor-beta: role in cancer cell growth and invasion. Adv Cancer Res. 1998;75:87–134.
127 ten Dijke P, Arthur HM. Extracellular control of TGFbeta signalling in vascular development and disease. Nat Rev Mol Cell Biol. 2007 Nov;8(11):857–69.
128 Karsdal MA, Larsen L, Engsig MT, Lou H, Ferreras M, Lochter A, et al. Matrix metalloproteinase-dependent activation of latent transforming growth factor-beta controls the conversion of osteoblasts into osteocytes by blocking osteoblast apoptosis. J Biol Chem. 2002 Nov;277(46):44061–7.

129 Sirin Y, Susztak K. Notch in the kidney: development and disease. J Pathol. 2012 Jan;226(2):394–403.
130 Zhao Y, Qiao X, Tan TK, Zhao H, Zhang Y, Liu L, et al. Matrix metalloproteinase 9-dependent Notch signaling contributes to kidney fibrosis through peritubular endothelial-mesenchymal transition. Nephrol Dial Transplant. 2017 May;32(5):781–91.
131 Yang Z, Klionsky DJ. An overview of the molecular mechanism of autophagy. Curr Top Microbiol Immunol. 2009;335:1–32.
132 Glick D, Barth S, Macleod KF. Autophagy: cellular and molecular mechanisms. J Pathol. 2010 May;221(1):3–12.
133 Jiang M, Liu K, Luo J, Dong Z. Autophagy is a renoprotective mechanism during in vitro hypoxia and in vivo ischemia-reperfusion injury. Am J Pathol. 2010 Mar;176(3):1181–92.
134 Belibi F, Zafar I, Ravichandran K, Segvic AB, Jani A, Ljubanovic DG, et al. Hypoxia-inducible factor-1α (HIF-1α) and autophagy in polycystic kidney disease (PKD). Am J Physiol Renal Physiol. 2011 May;300(5):F1235–43.
135 Tanaka Y, Kume S, Kitada M, Kanasaki K, Uzu T, Maegawa H, et al. Autophagy as a therapeutic target in diabetic nephropathy. Exp Diabetes Res. 2012;2012:628978.
136 Yang C, Kaushal V, Shah SV, Kaushal GP. Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. Am J Physiol Renal Physiol. 2008 Apr;294(4):F777–87.
137 Hsiao HW, Tsai KL, Wang LF, Chen YH, Chiang PC, Chuang SM, et al. The decline of autophagy contributes to proximal tubular dysfunction during sepsis. Shock. 2012 Mar;37(3):289–96.
138 Kimura T, Takahashi A, Takabatake Y, Namba T, Yamamoto T, Kaimori JY, et al. Autophagy protects kidney proximal tubule epithelial cells from mitochondrial metabolic stress. Autophagy. 2013 Nov;9(11):1876–86.
139 Parente JM, Pereira CA, Oliveira-Paula GH, Tanus-Santos JE, Tostes RC, Castro MM. Matrix Metalloproteinase-2 Activity is Associated with Divergent Regulation of Calponin-1 in Conductance and Resistance Arteries in Hypertension-induced Early Vascular Dysfunction and Remodelling. Basic Clin Pharmacol Toxicol. 2017 Oct;121(4):246–56.
140 Mansour SG, Puthumana J, Coca SG, Gentry M, Parikh CR. Biomarkers for the detection of renal fibrosis and prediction of renal outcomes: a systematic review. BMC Nephrol. 2017 Feb;18(1):72.
141 Sharfuddin AA, Molitoris BA. Pathophysiology of ischemic acute kidney injury. Nat Rev Nephrol. 2011 Apr;7(4):189–200.
142 Caron A, Desrosiers RR, Béliveau R. Ischemia injury alters endothelial cell properties of kidney cortex: stimulation of MMP-9. Exp Cell Res. 2005 Oct;310(1):105–16.
143 Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, et al.; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature. 2001 Feb;409(6822):860–921.
144 Mishra J, Dent C, Tarabishi R, Mitsnefes MM, Ma Q, Kelly C, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a biomarker for acute renal injury after cardiac surgery. Lancet. 2005 Apr;365(9466):1231–8.
145 Wagener G, Jan M, Kim M, Mori K, Barasch JM, Sladen RN, et al. Association between increases in urinary neutrophil gelatinase-associated lipocalin and acute renal dysfunction after adult cardiac surgery. Anesthesiology. 2006 Sep;105(3):485–91.
146 Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, et al. Urinary biomarkers in the early diagnosis of acute kidney injury. Kidney Int. 2008 Apr;73(7):863–9.
147 Ha H, Lee HB. Reactive oxygen species and matrix remodeling in diabetic kidney. J Am Soc Nephrol. 2003 Aug;14(8 Suppl 3):S246–9.
148 Qian Y, Feldman E, Pennathur S, Kretzler M, Brosius FC 3rd. From fibrosis to sclerosis: mechanisms of glomerulosclerosis in diabetic nephropathy. Diabetes. 2008 Jun;57(6):1439–45.
149 Lassila M, Fukami K, Jandeleit-Dahm K, Semple T, Carmeliet P, Cooper ME, et al. Plasminogen activator inhibitor-1 production is pathogenetic in experimental murine diabetic renal disease. Diabetologia. 2007 Jun;50(6):1315–26.
150 McLennan SV, Kelly DJ, Cox AJ, Cao Z, Lyons JG, Yue DK, et al. Decreased matrix degradation in diabetic nephropathy: effects of ACE inhibition on the expression and activities of matrix metalloproteinases. Diabetologia. 2002 Feb;45(2):268–75.
151 Wolf G, Ziyadeh FN. Molecular mechanisms of diabetic renal hypertrophy. Kidney Int. 1999 Aug;56(2):393–405.
152 Gharagozlian S, Svennevig K, Bangstad HJ, Winberg JO, Kolset SO. Matrix metalloproteinases in subjects with type 1 diabetes. BMC Clin Pathol. 2009 Sep;9(1):7.
153 Lauhio A, Sorsa T, Srinivas R, Stenman M, Tervahartiala T, Stenman UH, et al. Urinary matrix metalloproteinase -8, -9, -14 and their regulators (TRY-1, TRY-2, TATI) in patients with diabetic nephropathy. Ann Med. 2008;40(4):312–20.
154 Tashiro K, Koyanagi I, Ohara I, Ito T, Saitoh A, Horikoshi S, et al. Levels of urinary matrix metalloproteinase-9 (MMP-9) and renal injuries in patients with type 2 diabetic nephropathy. J Clin Lab Anal. 2004;18(3):206–10.
155 Thrailkill KM, Clay Bunn R, Fowlkes JL. Matrix metalloproteinases: their potential role in the pathogenesis of diabetic nephropathy. Endocrine. 2009 Feb;35(1):1–10.
156 Ebihara I, Nakamura T, Shimada N, Koide H. Increased plasma metalloproteinase-9 concentrations precede development of microalbuminuria in non-insulin-dependent diabetes mellitus. Am J Kidney Dis. 1998 Oct;32(4):544–50.
157 Rysz J, Banach M, Stolarek RA, Pasnik J, Cialkowska-Rysz A, Koktysz R, et al. Serum matrix metalloproteinases MMP-2 and MMP-9 and metalloproteinase tissue inhibitors TIMP-1 and TIMP-2 in diabetic nephropathy. J Nephrol. 2007 Jul-Aug;20(4):444–52.

158 Chung AW, Yang HH, Sigrist MK, Brin G, Chum E, Gourlay WA, et al. Matrix metalloproteinase-2 and -9 exacerbate arterial stiffening and angiogenesis in diabetes and chronic kidney disease. Cardiovasc Res. 2009 Dec;84(3):494–504.
159 Wang Y, Wei Q, Liu Q, Li Z, Zhou L, Zou F, et al. Crosstalk between monocytes and renal mesangial cells via interaction of metalloproteinases and fractalkine in diabetic nephropathy. Mol Med Rep. 2013 Dec;8(6):1817–23.
160 Klier CM, Nelson EL, Cohen CD, Horuk R, Schlöndorff D, Nelson PJ. Chemokine-Induced secretion of gelatinase B in primary human monocytes. Biol Chem. 2001 Sep;382(9):1405–10.
161 Vitale S, Schmid-Alliana A, Breuil V, Pomeranz M, Millet MA, Rossi B, et al. Soluble fractalkine prevents monocyte chemoattractant protein-1-induced monocyte migration via inhibition of stress-activated protein kinase 2/p38 and matrix metalloproteinase activities. J Immunol. 2004 Jan;172(1):585–92.
162 Romanic AM, Burns-Kurtis CL, Ao Z, Arleth AJ, Ohlstein EH. Upregulated expression of human membrane type-5 matrix metalloproteinase in kidneys from diabetic patients. Am J Physiol Renal Physiol. 2001 Aug;281(2):F309–17.
163 Thrailkill KM, Bunn RC, Moreau CS, Cockrell GE, Simpson PM, Coleman HN, et al. Matrix metalloproteinase-2 dysregulation in type 1 diabetes. Diabetes Care. 2007 Sep;30(9):2321–6.
164 Diamant M, Hanemaaijer R, Verheijen JH, Smit JW, Radder JK, Lemkes HH. Elevated matrix metalloproteinase-2 and -9 in urine, but not in serum, are markers of type 1 diabetic nephropathy. Diabet Med. 2001 May;18(5):423–4.
165 Nakamura T, Ushiyama C, Suzuki S, Hara M, Shimada N, Ebihara I, et al. Urinary excretion of podocytes in patients with diabetic nephropathy. Nephrol Dial Transplant. 2000 Sep;15(9):1379–83.
166 Mayer G, Heerspink HJ, Aschauer C, Heinzel A, Heinze G, Kainz A, et al.; SYSKID Consortium. Systems Biology-Derived Biomarkers to Predict Progression of Renal Function Decline in Type 2 Diabetes. Diabetes Care. 2017 Mar;40(3):391–7.
167 Dimas GG, Didangelos TP, Grekas DM. Matrix Gelatinases in Atherosclerosis and Diabetic Nephropathy: progress and Challenges. Curr Vasc Pharmacol. 2017;15(6):557–65.
168 Lelongt B, Bengatta S, Delauche M, Lund LR, Werb Z, Ronco PM. Matrix metalloproteinase 9 protects mice from anti-glomerular basement membrane nephritis through its fibrinolytic activity. J Exp Med. 2001 Apr;193(7):793–802.
169 Bauvois B, Mothu N, Nguyen J, Nguyen-Khoa T, Nöel LH, Jungers P. Specific changes in plasma concentrations of matrix metalloproteinase-2 and -9, TIMP-1 and TGF-beta1 in patients with distinct types of primary glomerulonephritis. Nephrol Dial Transplant. 2007 Apr;22(4):1115–22.
170 Ahuja TS, Gopalani A, Davies P, Ahuja H. Matrix metalloproteinase-9 expression in renal biopsies of patients with HIV-associated nephropathy. Nephron Clin Pract. 2003;95(3):c100–4.
171 Zakiyanov O, Kalousová M, Kratochvilová M, Kríha V, Zima T, Tesar V: Changes in levels of matrix metalloproteinase-2 and -9, pregnancy-associated plasma protein-A in patients with various nephropathies. J Nephrol 2013 May-Jun;26(3):502-9.
172 Czech KA, Bennett M, Devarajan P. Distinct metalloproteinase excretion patterns in focal segmental glomerulosclerosis. Pediatr Nephrol. 2011 Dec;26(12):2179–84.
173 Sanders JS, van Goor H, Hanemaaijer R, Kallenberg CG, Stegeman CA. Renal expression of matrix metalloproteinases in human ANCA-associated glomerulonephritis. Nephrol Dial Transplant. 2004 Jun;19(6):1412–9.
174 Sanders JS, Huitema MG, Hanemaaijer R, van Goor H, Kallenberg CG, Stegeman CA. Urinary matrix metalloproteinases reflect renal damage in anti-neutrophil cytoplasm autoantibody-associated vasculitis. Am J Physiol Renal Physiol. 2007 Dec;293(6):F1927–34.
175 Korzeniecka-Kozerska A, Wasilewska A, Tenderenda E, Sulik A, Cybulski K. Urinary MMP-9/NGAL ratio as a potential marker of FSGS in nephrotic children. Dis Markers. 2013;34(5):357–62.
176 Danilewicz M, Wagrowska-Danilewicz M. Differential glomerular immunoexpression of matrix metalloproteinases MMP-2 and MMP-9 in idiopathic IgA nephropathy and Schoenlein-Henoch nephritis. Folia Histochem Cytobiol. 2010 Jan;48(1):63–7.
177 Urushihara M, Kagami S, Kuhara T, Tamaki T, Kuroda Y. Glomerular distribution and gelatinolytic activity of matrix metalloproteinases in human glomerulonephritis. Nephrol Dial Transplant. 2002 Jul;17(7):1189–96.
178 Zucker S, Mian N, Drews M, Conner C, Davidson A, Miller F, et al. Increased serum stromelysin-1 levels in systemic lupus erythematosus: lack of correlation with disease activity. J Rheumatol. 1999 Jan;26(1):78–80.
179 Faber-Elmann A, Sthoeger Z, Tcherniack A, Dayan M, Mozes E. Activity of matrix metalloproteinase-9 is elevated in sera of patients with systemic lupus erythematosus. Clin Exp Immunol. 2002 Feb;127(2):393–8.
180 Nakamura T, Ebihara I, Osada S, Takahashi T, Yamamoto M, Tomino Y, et al. Gene expression of metalloproteinases and their inhibitor in renal tissue of New Zealand black/white F1 mice. Clin Sci (Lond). 1993 Sep;85(3):295–301.
181 Robak E, Wierzbowska A, Chmiela M, Kulczycka L, Sysa-Jedrejowska A, Robak T. Circulating total and active metalloproteinase-9 and tissue inhibitor of metalloproteinases-1 in patients with systemic lupus erythomatosus. Mediators Inflamm. 2006;2006(1):17898.
182 Liu Y, Zheng M, Yin WH, Zhang B. [Relationship of serum levels of HGF and MMP-9 with disease activity of patients with systemic lupus erythematosus]. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2004 Jul;33(4):340–3, 348.
183 Grantham JJ, Torres VE, Chapman AB, Guay-Woodford LM, Bae KT, King BF Jr, et al.; CRISP Investigators. Volume progression in polycystic kidney disease. N Engl J Med. 2006 May;354(20):2122–30.

184 Zeisberg M, Khurana M, Rao VH, Cosgrove D, Rougier JP, Werner MC, et al. Stage-specific action of matrix metalloproteinases influences progressive hereditary kidney disease. PLoS Med. 2006 Apr;3(4):e100.
185 Chang HR, Kuo WH, Hsieh YS, Yang SF, Lin CC, Lee ML, et al. Circulating matrix metalloproteinase-2 is associated with cystatin C level, posttransplant duration, and diabetes mellitus in kidney transplant recipients. Transl Res. 2008 Apr;151(4):217–23.
186 Rödder S, Scherer A, Körner M, Eisenberger U, Hertig A, Raulf F, et al. Meta-analyses qualify metzincins and related genes as acute rejection markers in renal transplant patients. Am J Transplant. 2010 Feb;10(2):286–97.
187 Wong W, DeVito J, Nguyen H, Sarracino D, Porcheray F, Dargon I, et al. Chronic humoral rejection of human kidney allografts is associated with MMP-2 accumulation in podocytes and its release in the urine. Am J Transplant. 2010 Nov;10(11):2463–71.
188 Singh R, Srivastava P, Srivastava A, Mittal RD. Matrix metalloproteinase (MMP-9 and MMP-2) gene polymorphisms influence allograft survival in renal transplant recipients. Nephrol Dial Transplant. 2010 Oct;25(10):3393–401.
189 Osman B, Doller A, Akool S, Holdener M, Hintermann E, Pfeilschifter J, et al. Rapamycin induces the TGFbeta1/Smad signaling cascade in renal mesangial cells upstream of mTOR. Cell Signal. 2009 Dec;21(12):1806–17.
190 Di Carlo A. Matrix metalloproteinase-2 and -9 in the sera and in the urine of human oncocytoma and renal cell carcinoma. Oncol Rep. 2012 Sep;28(3):1051–6.
191 DI Carlo A. Matrix metalloproteinase-2 and -9 and tissue inhibitor of metalloproteinase-1 and -2 in sera and urine of patients with renal carcinoma. Oncol Lett. 2014 Mar;7(3):621–6.
192 Chen NX, O'Neill KD, Chen X, Kiattisunthorn K, Gattone VH, Moe SM. Activation of arterial matrix metalloproteinases leads to vascular calcification in chronic kidney disease. Am J Nephrol. 2011;34(3):211–9.
193 Addabbo F, Mallamaci F, Leonardis D, Tripepi R, Tripepi G, Goligorsky MS, et al. Searching for biomarker patterns characterizing carotid atherosclerotic burden in patients with reduced renal function. Nephrol Dial Transplant. 2007 Dec;22(12):3521–6.
194 Pawlak K, Pawlak D, Mysliwiec M. Serum matrix metalloproteinase-2 and increased oxidative stress are associated with carotid atherosclerosis in hemodialyzed patients. Atherosclerosis. 2007 Jan;190(1):199–204.
195 Newby AC. Metalloproteinase expression in monocytes and macrophages and its relationship to atherosclerotic plaque instability. Arterioscler Thromb Vasc Biol. 2008 Dec;28(12):2108–14.
196 Mehde AA, Mehdi WA, Yusof F, Raus RA, Zainal Abidin ZA, Ghazali H, et al. Association of MMP-9 gene polymorphisms with nephrolithiasis patients. J Clin Lab Anal. 2018 Jan;32(1).
197 Pai A, Leaf EM, El-Abbadi M, Giachelli CM. Elastin degradation and vascular smooth muscle cell phenotype change precede cell loss and arterial medial calcification in a uremic mouse model of chronic kidney disease. Am J Pathol. 2011 Feb;178(2):764–73.
198 Giachelli CM, Speer MY, Li X, Rajachar RM, Yang H. Regulation of vascular calcification: roles of phosphate and osteopontin. Circ Res. 2005 Apr;96(7):717–22.
199 Freise C, Querfeld U. Inhibition of vascular calcification by block of intermediate conductance calcium-activated potassium channels with TRAM-34. Pharmacol Res. 2014 Jul;85:6–14.
200 Hecht E, Freise C, Websky KV, Nasser H, Kretzschmar N, Stawowy P, et al. The matrix metalloproteinases 2 and 9 initiate uraemic vascular calcifications. Nephrol Dial Transplant. 2016 May;31(5):789–97.
201 Freise C, Kretzschmar N, Querfeld U. Wnt signaling contributes to vascular calcification by induction of matrix metalloproteinases. BMC Cardiovasc Disord. 2016 Sep;16(1):185.
202 Pawlak K, Mysliwiec M, Pawlak D. Peripheral blood level alterations of MMP-2 and MMP-9 in patients with chronic kidney disease on conservative treatment and on hemodialysis. Clin Biochem. 2011 Jul;44(10-11):838–43.
203 Rysz J, Banach M, Stolarek RA, Mikhailidis DP, Cialkowska-Rysz A, Pokoca L, et al. Serum metalloproteinases MMP-2, MMP-9 and metalloproteinase tissue inhibitors TIMP-1 and TIMP-2 in patients on hemodialysis. Int Urol Nephrol. 2011 Jun;43(2):491–8.
204 Preston GA, Barrett CV, Alcorta DA, Hogan SL, Dinwiddie L, Jennette JC, et al. Serum matrix metalloproteinases MMP-2 and MMP-3 levels in dialysis patients vary independently of CRP and IL-6 levels. Nephron. 2002 Dec;92(4):817–23.
205 Musiał K, Zwolińska D. Matrix metalloproteinases and soluble Fas/FasL system as novel regulators of apoptosis in children and young adults on chronic dialysis. Apoptosis. 2011 Jul;16(7):653–9.
206 Galal A, Fadel FI, Mokhtar E, Elshamaa MF, Elghoroury EA, Kamel S, et al. Matrix Metalloproteinase (MMP)-9 Levels in Children on Hemodialysis: Association with MMP-9 C-1562T Gene Polymorphism and Vitamin D Levels. Int J Biomed Sci. 2016 Sep;12(3):95–104.
207 Chou FP, Chu SC, Cheng MC, Yang SF, Cheung WN, Chiou HL, et al. Effect of hemodialysis on the plasma level of type IV collagenases and their inhibitors. Clin Biochem. 2002 Jul;35(5):383–8.
208 Kalousová M, Benáková H, Kuběna AA, Dusilová-Sulková S, Tesař V, Zima T. Pregnancy-associated plasma protein A as an independent mortality predictor in long-term hemodialysis patients. Kidney Blood Press Res. 2012;35(3):192–201.
209 Hsiao KC, Tsai JP, Yang SF, Lee WC, Huang JY, Chang SC, et al. MMP-2 serum concentrations predict mortality in hemodialysis patients: a 5-year cohort study. Clin Chim Acta. 2016 Jan;452:161–6.
210 Wang L, Wang J, Wang Y, Fu Q, Lei YH, Nie ZY, et al. Protective effect of exogenous matrix metalloproteinase-9 on chronic renal failure. Exp Ther Med. 2014 Feb;7(2):329–34.

211 Ramsbeck D, Hamann A, Schlenzig D, Schilling S, Buchholz M. First insight into structure-activity relationships of selective meprin β inhibitors. Bioorg Med Chem Lett. 2017 Jun;27(11):2428–31.
212 Chin JR, Murphy G, Werb Z. Stromelysin, a connective tissue-degrading metalloendopeptidase secreted by stimulated rabbit synovial fibroblasts in parallel with collagenase. Biosynthesis, isolation, characterization, and substrates. J Biol Chem. 1985 Oct;260(22):12367–76.
213 Okada Y, Nagase H, Harris ED Jr. A metalloproteinase from human rheumatoid synovial fibroblasts that digests connective tissue matrix components. Purification and characterization. J Biol Chem. 1986 Oct;261(30): 14245–55.
214 Nakamura H, Fujii Y, Ohuchi E, Yamamoto E, Okada Y. Activation of the precursor of human stromelysin 2 and its interactions with other matrix metalloproteinases. Eur J Biochem. 1998 Apr;253(1):67–75.
215 Gearing AJ, Beckett P, Christodoulou M, Churchill M, Clements JM, Crimmin M, et al. Matrix metalloproteinases and processing of pro-TNF-alpha. J Leukoc Biol. 1995 May;57(5):774–7.
216 Agnihotri R, Crawford HC, Haro H, Matrisian LM, Havrda MC, Liaw L. Osteopontin, a novel substrate for matrix metalloproteinase-3 (stromelysin-1) and matrix metalloproteinase-7 (matrilysin). J Biol Chem. 2001 Jul; 276(30):28261–7.
217 Orbe J, Barrenetxe J, Rodriguez JA, Vivien D, Orset C, Parks WC, et al. Matrix metalloproteinase-10 effectively reduces infarct size in experimental stroke by enhancing fibrinolysis via a thrombin-activatable fibrinolysis inhibitor-mediated mechanism. Circulation. 2011 Dec;124(25):2909–19.
218 Rodriguez JA, Orbe J, Martinez de Lizarrondo S, Calvayrac O, Rodriguez C, Martinez-Gonzalez J, et al. Metalloproteinases and atherothrombosis: MMP-10 mediates vascular remodeling promoted by inflammatory stimuli. Front Biosci. 2008 Jan;13(13):2916–21.
219 Noël A, Santavicca M, Stoll I, L'Hoir C, Staub A, Murphy G, et al. Identification of structural determinants controlling human and mouse stromelysin-3 proteolytic activities. J Biol Chem. 1995 Sep;270(39):22866–72.
220 Potempa J, Korzus E, Travis J. The serpin superfamily of proteinase inhibitors: structure, function, and regulation. J Biol Chem. 1994 Jun;269(23):15957–60.
221 Mañes S, Mira E, Barbacid MM, Ciprés A, Fernández-Resa P, Buesa JM, et al. Identification of insulin-like growth factor-binding protein-1 as a potential physiological substrate for human stromelysin-3. J Biol Chem. 1997 Oct;272(41):25706–12.
222 Ishizuya-Oka A, Li Q, Amano T, Damjanovski S, Ueda S, Shi YB. Requirement for matrix metalloproteinase stromelysin-3 in cell migration and apoptosis during tissue remodeling in Xenopus laevis. J Cell Biol. 2000 Sep; 150(5):1177–88.
223 Lijnen HR, Van Hoef B, Vanlinthout I, Verstreken M, Rio MC, Collen D. Accelerated neointima formation after vascular injury in mice with stromelysin-3 (MMP-11) gene inactivation. Arterioscler Thromb Vasc Biol. 1999 Dec;19(12):2863–70.
224 Suzuki D, Miyazaki M, Jinde K, Koji T, Yagame M, Endoh M, et al. In situ hybridization studies of matrix metalloproteinase-3, tissue inhibitor of metalloproteinase-1 and type IV collagen in diabetic nephropathy. Kidney Int. 1997 Jul;52(1):111–9.
225 Seo JY, Park J, Yu MR, Kim YS, Ha H, Lee HB. Positive feedback loop between plasminogen activator inhibitor-1 and transforming growth factor-beta1 during renal fibrosis in diabetes. Am J Nephrol. 2009;30(6):481–90.
226 Crowther M, Goodall S, Jones JL, Bell PR, Thompson MM. Increased matrix metalloproteinase 2 expression in vascular smooth muscle cells cultured from abdominal aortic aneurysms. J Vasc Surg. 2000 Sep;32(3):575–83.
227 Yang Q, Xie RJ, Yang T, Fang L, Han B, Zhang GZ, et al. Transforming growth factor-beta1 and Smad4 signaling pathway down-regulates renal extracellular matrix degradation in diabetic rats. Chin Med Sci J. 2007 Dec; 22(4):243–9.
228 Qi Z, Fujita H, Jin J, Davis LS, Wang Y, Fogo AB, et al. Characterization of susceptibility of inbred mouse strains to diabetic nephropathy. Diabetes. 2005 Sep;54(9):2628–37.
229 Toni M, Hermida J, Goñi MJ, Fernández P, Parks WC, Toledo E, et al. Matrix metalloproteinase-10 plays an active role in microvascular complications in type 1 diabetic patients. Diabetologia. 2013 Dec;56(12):2743–52.
230 Rao VH, Meehan DT, Delimont D, Nakajima M, Wada T, Gratton MA, et al. Role for macrophage metalloelastase in glomerular basement membrane damage associated with alport syndrome. Am J Pathol. 2006 Jul;169(1): 32–46.
231 Zheng G, Lyons JG, Tan TK, Wang Y, Hsu TT, Min D, et al. Disruption of E-cadherin by matrix metalloproteinase directly mediates epithelial-mesenchymal transition downstream of transforming growth factor-beta1 in renal tubular epithelial cells. Am J Pathol. 2009 Aug;175(2):580–91.
232 Kotajima L, Aotsuka S, Fujimani M, Okawa-Takatsuji M, Kinoshita M, Sumiya M, et al. Increased levels of matrix metalloproteinase-3 in sera from patients with active lupus nephritis. Clin Exp Rheumatol. 1998 Jul-Aug; 16(4):409–15.
233 Shin JI, Song KS, Kim H, Cho NH, Kim J, Kim HS, et al. The gene expression profile of matrix metalloproteinases and their inhibitors in children with Henoch-Schönlein purpura. Br J Dermatol. 2011 Jun;164(6):1348–55.
234 Miyata Y, Iwata T, Maruta S, Kanda S, Nishikido M, Koga S, et al. Expression of matrix metalloproteinase-10 in renal cell carcinoma and its prognostic role. Eur Urol. 2007 Sep;52(3):791–7.
235 Feldenberg LR, Thevananther S, del Rio M, de Leon M, Devarajan P. Partial ATP depletion induces Fas- and caspase-mediated apoptosis in MDCK cells. Am J Physiol. 1999 Jun;276(6):F837–46.
236 Lockshin RA, Zakeri Z. Caspase-independent cell death? Oncogene. 2004 Apr;23(16):2766–73.

237 Mannello F, Luchetti F, Falcieri E, Papa S. Multiple roles of matrix metalloproteinases during apoptosis. Apoptosis. 2005 Jan;10(1):19–24.
238 Mannello F, Gazzanelli G. Tissue inhibitors of metalloproteinases and programmed cell death: conundrums, controversies and potential implications. Apoptosis. 2001 Dec;6(6):479–82.
239 Mao H, Li Z, Zhou Y, Li Z, Zhuang S, An X, et al. HSP72 attenuates renal tubular cell apoptosis and interstitial fibrosis in obstructive nephropathy. Am J Physiol Renal Physiol. 2008 Jul;295(1):F202–14.
240 Havasi A, Borkan SC. Apoptosis and acute kidney injury. Kidney Int. 2011 Jul;80(1):29–40.
241 Reddig PJ, Juliano RL. Clinging to life: cell to matrix adhesion and cell survival. Cancer Metastasis Rev. 2005 Sep;24(3):425–39.
242 Herren B, Levkau B, Raines EW, Ross R. Cleavage of beta-catenin and plakoglobin and shedding of VE-cadherin during endothelial apoptosis: evidence for a role for caspases and metalloproteinases. Mol Biol Cell. 1998 Jun;9(6):1589–601.
243 Luchetti F, Mannello F, Canonico B, Battistelli M, Burattini S, Falcieri E, et al. Integrin and cytoskeleton behaviour in human neuroblastoma cells during hyperthermia-related apoptosis. Apoptosis. 2004 Sep;9(5):635–48.
244 Levkau B, Kenagy RD, Karsan A, Weitkamp B, Clowes AW, Ross R, et al. Activation of metalloproteinases and their association with integrins: an auxiliary apoptotic pathway in human endothelial cells. Cell Death Differ. 2002 Dec;9(12):1360–7.
245 Sympson CJ, Talhouk RS, Alexander CM, Chin JR, Clift SM, Bissell MJ, et al. Targeted expression of stromelysin-1 in mammary gland provides evidence for a role of proteinases in branching morphogenesis and the requirement for an intact basement membrane for tissue-specific gene expression. J Cell Biol. 1994 May;125(3):681–93.
246 Wu E, Mari BP, Wang F, Anderson IC, Sunday ME, Shipp MA. Stromelysin-3 suppresses tumor cell apoptosis in a murine model. J Cell Biochem. 2001;82(4):549–55.
247 Baserga R. The contradictions of the insulin-like growth factor 1 receptor. Oncogene. 2000 Nov;19(49):5574–81.
248 Martelli AM, Falcieri E, Zweyer M, Bortul R, Tabellini G, Cappellini A, et al. The controversial nuclear matrix: a balanced point of view. Histol Histopathol. 2002 Oct;17(4):1193–205.
249 Ritter LM, Garfield SH, Thorgeirsson UP. Tissue inhibitor of metalloproteinases-1 (TIMP-1) binds to the cell surface and translocates to the nucleus of human MCF-7 breast carcinoma cells. Biochem Biophys Res Commun. 1999 Apr;257(2):494–9.
250 Kwan JA, Schulze CJ, Wang W, Leon H, Sariahmetoglu M, Sung M, et al. Matrix metalloproteinase-2 (MMP-2) is present in the nucleus of cardiac myocytes and is capable of cleaving poly (ADP-ribose) polymerase (PARP) in vitro. FASEB J. 2004 Apr;18(6):690–2.
251 Soldani C, Scovassi AI. Poly(ADP-ribose) polymerase-1 cleavage during apoptosis: an update. Apoptosis. 2002 Aug;7(4):321–8.
252 Gaire M, Magbanua Z, McDonnell S, McNeil L, Lovett DH, Matrisian LM. Structure and expression of the human gene for the matrix metalloproteinase matrilysin. J Biol Chem. 1994 Jan;269(3):2032–40.
253 Murphy G, Cockett MI, Ward RV, Docherty AJ. Matrix metalloproteinase degradation of elastin, type IV collagen and proteoglycan. A quantitative comparison of the activities of 95 kDa and 72 kDa gelatinases, stromelysins-1 and -2 and punctuated metalloproteinase (PUMP). Biochem J. 1991 Jul;277(Pt 1):277–9.
254 Oelusarz A, Nichols LA, Grunz-Borgmann EA, Chen G, Akintola AD, Catania JM, et al. Overexpression of MMP-7 Increases Collagen 1A2 in the Aging Kidney. Physiol Rep. 2013 Oct;1(5):1.
255 Halpert I, Sires UI, Roby JD, Potter-Perigo S, Wight TN, Shapiro SD, et al. Matrilysin is expressed by lipid-laden macrophages at sites of potential rupture in atherosclerotic lesions and localizes to areas of versican deposition, a proteoglycan substrate for the enzyme. Proc Natl Acad Sci USA. 1996 Sep;93(18):9748–53.
256 Imai K, Yokohama Y, Nakanishi I, Ohuchi E, Fujii Y, Nakai N, et al. Matrix metalloproteinase 7 (matrilysin) from human rectal carcinoma cells. Activation of the precursor, interaction with other matrix metalloproteinases and enzymic properties. J Biol Chem. 1995 Mar;270(12):6691–7.
257 Park HI, Ni J, Gerkema FE, Liu D, Belozerov VE, Sang QX. Identification and characterization of human endometase (Matrix metalloproteinase-26) from endometrial tumor. J Biol Chem. 2000 Jul;275(27):20540–4.
258 Nagase H, Woessner JF Jr. Matrix metalloproteinases. J Biol Chem. 1999 Jul;274(31):21491–4.
259 Surendran K, Simon TC, Liapis H, McGuire JK. Matrilysin (MMP-7) expression in renal tubular damage: association with Wnt4. Kidney Int. 2004 Jun;65(6):2212–22.
260 Park IS, Kiyomoto H, Alvarez F, Xu YC, Abboud HE, Abboud SL. Preferential expression of insulin-like growth factor binding proteins-1, -3, and -5 during early diabetic renal hypertrophy in rats. Am J Kidney Dis. 1998 Dec;32(6):1000–10.
261 Miyamoto S, Yano K, Sugimoto S, Ishii G, Hasebe T, Endoh Y, et al. Matrix metalloproteinase-7 facilitates insulin-like growth factor bioavailability through its proteinase activity on insulin-like growth factor binding protein 3. Cancer Res. 2004 Jan;64(2):665–71.
262 Hemers E, Duval C, McCaig C, Handley M, Dockray GJ, Varro A. Insulin-like growth factor binding protein-5 is a target of matrix metalloproteinase-7: implications for epithelial-mesenchymal signaling. Cancer Res. 2005 Aug;65(16):7363–9.
263 McCaig C, Duval C, Hemers E, Steele I, Pritchard DM, Przemeck S, et al. The role of matrix metalloproteinase-7 in redefining the gastric microenvironment in response to Helicobacter pylori. Gastroenterology. 2006 May;130(6):1754–63.

264 Henger A, Kretzler M, Doran P, Bonrouhi M, Schmid H, Kiss E, et al. Gene expression fingerprints in human tubulointerstitial inflammation and fibrosis as prognostic markers of disease progression. Kidney Int. 2004 Mar;65(3):904–17.
265 Reich HN, Landolt-Marticorena C, Boutros PC, John R, Wither J, Fortin PR, et al. Molecular markers of injury in kidney biopsy specimens of patients with lupus nephritis. J Mol Diagn. 2011 Mar;13(2):143–51.
266 Musiał K, Zwolińska D. MMP-7 as a potential marker of cardiovascular complications in patients with chronic kidney disease (CKD). Basic Clin Pharmacol Toxicol. 2012 Aug;111(2):73–4.
267 Jovanovic V, Dugast AS, Heslan JM, Ashton-Chess J, Giral M, Degauque N, et al. Implication of matrix metalloproteinase 7 and the noncanonical wingless-type signaling pathway in a model of kidney allograft tolerance induced by the administration of anti-donor class II antibodies. J Immunol. 2008 Feb;180(3):1317–25.
268 Ahuja TS. Doxycycline decreases proteinuria in glomerulonephritis. Am J Kidney Dis. 2003 Aug;42(2):376–80.
269 Aggarwal HK, Jain D, Talapatra P, Yadav RK, Gupta T, Kathuria KL. Evaluation of role of doxycycline (a matrix metalloproteinase inhibitor) on renal functions in patients of diabetic nephropathy. Ren Fail. 2010;32(8):941–6.
270 Kraft PJ, Haynes-Johnson DE, Patel L, Lenhart JA, Zivin RA, Palmer SS. Fluorescence polarization assay and SDS-PAGE confirms matrilysin degrades fibronectin and collagen IV whereas gelatinase A degrades collagen IV but not fibronectin. Connect Tissue Res. 2001 Oct;42(2):149–63.
271 Lin HC, Chang JH, Jain S, Gabison EE, Kure T, Kato T, et al. Matrilysin cleavage of corneal collagen type XVIII NC1 domain and generation of a 28-kDa fragment. Invest Ophthalmol Vis Sci. 2001 Oct;42(11):2517–24.
272 Parks WC, Wilson CL, López-Boado YS. Matrix metalloproteinases as modulators of inflammation and innate immunity. Nat Rev Immunol. 2004 Aug;4(8):617–29.
273 Melk A, Mansfield ES, Hsieh SC, Hernandez-Boussard T, Grimm P, Rayner DC, et al. Transcriptional analysis of the molecular basis of human kidney aging using cDNA microarray profiling. Kidney Int. 2005 Dec;68(6):2667–79.
274 Zhou D, Tian Y, Sun L, Zhou L, Xiao L, Tan RJ, et al. Matrix Metalloproteinase-7 Is a Urinary Biomarker and Pathogenic Mediator of Kidney Fibrosis. J Am Soc Nephrol. 2017 Feb;28(2):598–611.
275 Ke B, Fan C, Yang L, Fang X. Matrix Metalloproteinases-7 and Kidney Fibrosis. Front Physiol. 2017 Feb;8:21.
276 Najafian B, Kasiske BL. Chronic allograft nephropathy. Curr Opin Nephrol Hypertens. 2008 Mar;17(2):149–55.
277 Hirt-Minkowski P, Marti HP, Hönger G, Grandgirard D, Leib SL, Amico P, et al. Correlation of serum and urinary matrix metalloproteases/tissue inhibitors of metalloproteases with subclinical allograft fibrosis in renal transplantation. Transpl Immunol. 2014 Jan;30(1):1–6.
278 Sarkissian G, Fergelot P, Lamy PJ, Patard JJ, Culine S, Jouin P, et al. Identification of pro-MMP-7 as a serum marker for renal cell carcinoma by use of proteomic analysis. Clin Chem. 2008 Mar;54(3):574–81.
279 Miyata Y, Iwata T, Ohba K, Kanda S, Nishikido M, Kanetake H. Expression of matrix metalloproteinase-7 on cancer cells and tissue endothelial cells in renal cell carcinoma: prognostic implications and clinical significance for invasion and metastasis. Clin Cancer Res. 2006 Dec;12(23):6998–7003.
280 Lu H, Yang Z, Zhang H, Gan M, Zhou T, Wang S. The expression and clinical significance of matrix metalloproteinase 7 and tissue inhibitor of matrix metalloproteinases 2 in clear cell renal cell carcinoma. Exp Ther Med. 2013 Mar;5(3):890–6.
281 Powell WC, Fingleton B, Wilson CL, Boothby M, Matrisian LM. The metalloproteinase matrilysin proteolytically generates active soluble Fas ligand and potentiates epithelial cell apoptosis. Curr Biol. 1999 Dec;9(24):1441–7.
282 Mitsiades N, Yu WH, Poulaki V, Tsokos M, Stamenkovic I. Matrix metalloproteinase-7-mediated cleavage of Fas ligand protects tumor cells from chemotherapeutic drug cytotoxicity. Cancer Res. 2001 Jan;61(2):577–81.
283 Ogbureke KU, Koli K, Saxena G. Matrix Metalloproteinase 20 Co-expression With Dentin Sialophosphoprotein in Human and Monkey Kidneys. J Histochem Cytochem. 2016 Oct;64(10):623–36.
284 Sato H, Takino T, Kinoshita T, Imai K, Okada Y, Stetler Stevenson WG, et al. Cell surface binding and activation of gelatinase A induced by expression of membrane-type-1-matrix metalloproteinase (MT1-MMP). FEBS Lett. 1996 May;385(3):238–40.
285 Ohuchi E, Imai K, Fujii Y, Sato H, Seiki M, Okada Y. Membrane type 1 matrix metalloproteinase digests interstitial collagens and other extracellular matrix macromolecules. J Biol Chem. 1997 Jan;272(4):2446–51.
286 Itoh Y, Seiki M. MT1-MMP: a potent modifier of pericellular microenvironment. J Cell Physiol. 2006 Jan;206(1):1–8.
287 Fernandez-Catalan C, Bode W, Huber R, Turk D, Calvete JJ, Lichte A, et al. Crystal structure of the complex formed by the membrane type 1-matrix metalloproteinase with the tissue inhibitor of metalloproteinases-2, the soluble progelatinase A receptor. EMBO J. 1998 Sep;17(17):5238–48.
288 Hayashi K, Horikoshi S, Osada S, Shofuda K, Shirato I, Tomino Y. Macrophage-derived MT1-MMP and increased MMP-2 activity are associated with glomerular damage in crescentic glomerulonephritis. J Pathol. 2000 Jul;191(3):299–305.
289 Osenkowski P, Toth M, Fridman R. Processing, shedding, and endocytosis of membrane type 1-matrix metalloproteinase (MT1-MMP). J Cell Physiol. 2004 Jul;200(1):2–10.
290 Lemaître V, D'Armiento J. Matrix metalloproteinases in development and disease. Birth Defects Res C Embryo Today. 2006 Mar;78(1):1–10.
291 Curci JA, Liao S, Huffman MD, Shapiro SD, Thompson RW. Expression and localization of macrophage elastase (matrix metalloproteinase-12) in abdominal aortic aneurysms. J Clin Invest. 1998 Dec;102(11):1900–10.

292 Woodruff PG, Koth LL, Yang YH, Rodriguez MW, Favoreto S, Dolganov GM, et al. A distinctive alveolar macrophage activation state induced by cigarette smoking. Am J Respir Crit Care Med. 2005 Dec;172(11):1383–92.
293 Niu H, Li Y, Li H, Chi Y, Zhuang M, Zhang T, et al. Matrix metalloproteinase 12 modulates high-fat-diet induced glomerular fibrogenesis and inflammation in a mouse model of obesity. Sci Rep. 2016 Jan;6(1):20171.
294 Kolb C, Mauch S, Peter HH, Krawinkel U, Sedlacek R. The matrix metalloproteinase RASI-1 is expressed in synovial blood vessels of a rheumatoid arthritis patient. Immunol Lett. 1997 Jun;57(1-3):83–8.
295 Ahokas K, Lohi J, Lohi H, Elomaa O, Karjalainen-Lindsberg ML, Kere J, et al. Matrix metalloproteinase-21, the human orthologue for XMMP, is expressed during fetal development and in cancer. Gene. 2002 Nov;301(1-2):31–41.
296 Zhao S, Zhao Y, Niu P, Wang N, Tang Z, Zan L, et al. Molecular characterization of porcine MMP19 and MMP23B genes and its association with immune traits. Int J Biol Sci. 2011;7(8):1101–13.
297 Cominelli A, Halbout M, N'Kuli F, Lemoine P, Courtoy PJ, Marbaix E, et al. A unique C-terminal domain allows retention of matrix metalloproteinase-27 in the endoplasmic reticulum. Traffic. 2014 Apr;15(4):401–17.
298 Bar-Or A, Nuttall RK, Duddy M, Alter A, Kim HJ, Ifergan I, et al. Analyses of all matrix metalloproteinase members in leukocytes emphasize monocytes as major inflammatory mediators in multiple sclerosis. Brain. 2003 Dec;126(Pt 12):2738–49.
299 Bernal F, Hartung HP, Kieseier BC. Tissue mRNA expression in rat of newly described matrix metalloproteinases. Biol Res. 2005;38(2-3):267–71.
300 Lohi J, Wilson CL, Roby JD, Parks WC. Epilysin, a novel human matrix metalloproteinase (MMP-28) expressed in testis and keratinocytes and in response to injury. J Biol Chem. 2001 Mar;276(13):10134–44.
301 Gu JW, Tian N, Shparago M, Tan W, Bailey AP, Manning RD Jr. Renal NF-kappaB activation and TNF-alpha upregulation correlate with salt-sensitive hypertension in Dahl salt-sensitive rats. Am J Physiol Regul Integr Comp Physiol. 2006 Dec;291(6):R1817–24.
302 Nestel PJ, Fidge NH, Tan MH. Increased lipoprotein-remnant formation in chronic renal failure. N Engl J Med. 1982 Aug;307(6):329–33.