Matrix metalloproteinases in kidney homeostasis and diseases

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Tan RJ, Liu Y. Matrix metalloproteinases in kidney homeostasis and diseases. Am J Physiol Renal Physiol 302: F1351–F1361, 2012. First published April 4, 2012; doi:10.1152/ajprenal.00037.2012.—Matrix metalloproteinases (MMPs) are a family of zinc-dependent endopeptidases that have been increasingly linked to both normal physiology and abnormal pathology in the kidney. Collectively able to degrade all components of the extracellular matrix, MMPs were originally thought to antagonize the development of fibrotic diseases solely through digestion of excessive matrix. However, increasing evidence has shown that MMPs play a wide variety of roles in regulating inflammation, epithelial-mesenchymal transition, cell proliferation, angiogenesis, and apoptosis. We now have robust evidence for MMP dysregulation in a multitude of renal diseases including acute kidney injury, diabetic nephropathy, glomerulonephritis, inherited kidney disease, and chronic allograft nephropathy. The goal of this review is to summarize current findings regarding the role of MMPs in kidney diseases as well as the mechanisms of action of this family of proteases.

MMP; fibrosis; epithelial-mesenchymal transition; inflammation; apoptosis

THE MATRIX METALLOPROTEINASES (MMPs) are a large family of zinc-dependent endopeptidases that are collectively capable of proteolyzing all components of the extracellular matrix (ECM) (15, 99). The first discovery of MMPs was originally reported by Gross and Lapiere (38) when they described collagenase activity in metamorphosing tadpoles. Since then, the number of known MMPs as well as their characterized functions have risen dramatically (83, 139). It is now accepted that MMPs play a multitude of roles in regulating a diverse array of biological processes such as embryonic development, tissue homeostasis, tumorigenesis, and organ fibrogenesis (15, 97).

Initially thought to degrade only ECM proteins, MMPs are increasingly known to be able to cleave a wide variety of substrates, which range from cell surface receptors and adhesion molecules to growth factors and cytokines. This broad spectrum of substrates enables MMPs to be a critical player not only in regulating ECM remodeling but also in controlling many cell behaviors such as cell proliferation, migration, differentiation, angiogenesis, and apoptosis (37, 83). Over the last decade, thanks to the availability of many genetically modified mice (both knockout and transgenic) and specific pharmacological inhibitors, our understanding of the biology of MMPs in vivo has substantially evolved and improved. Many studies have provided significant insights into the exact roles of specific MMPs in regulating physiological homeostasis and pathological disorders.

MMPs are expressed in both developing and adult kidneys, and they are implicated in regulating nephron formation and the pathogenesis of kidney diseases, as nicely summarized previously in a comprehensive review (15). In light of their proteolytic potential, MMPs are traditionally conceived as antifibrotic players in the development and progression of chronic kidney diseases (CKD), in which tissue fibrosis is the common outcome. This assumption, however, has been challenged recently, and a new paradigm is emerging that MMPs actually play a critical role in the initiation of fibrotic kidney disorders. Here, we review the biology of MMPs, with emphasis on their role and potential mechanisms in the development of kidney diseases.

Biology of MMPs

Structure and classification. All MMPs, with some modifications, share a core set of basic structural domains. As shown in Fig. 1, the prototype MMP consists of a prodomain, a catalytic domain, a hinge region, and a hemopexin-like domain (15, 87). As secreted proteins, MMPs are synthesized with a signal peptide responsible for directing secretion out of the cell. The prodomain consists of a conserved cysteine residue that prevents binding and cleavage of the substrate, while the catalytic domain contains a binding site comprised of three histidines that coordinate with a single zinc and is responsible for the enzymatic activity of the protease. MMP-2 and -9 have a series of fibronectin repeats in this domain as well. A flexible hinge region then separates the catalytic domain from a four-bladed propeller-shaped hemopexin domain. It is felt that substrate specificity as well as endogenous inhibitor binding are influenced by specificities of each MMP’s catalytic and hemopexin domains (37, 139). Some MMPs remain tethered to the cell via transmembrane and cytoplasmic domains at the C terminus. At least one MMP (MMP-23) has a type II transmembrane domain near the N terminus and also possesses a cysteine-rich region and immunoglobulin-like domain (87, 139). The crystal structure of active human MMP-1 containing many of the domains described above is shown in Fig. 2.
MMPs are traditionally classified according to their structure and/or ECM substrate specificity. The collagenases (MMP-1, MMP-8, and MMP-13) can degrade native collagen and are often hypothesized to be antifibrotic. Stromelysins (MMP-3, MMP-10, and MMP-11) share structural similarity with the collagenases but are unable to degrade native collagen. As their name implies, the gelatinases (MMP-2, MMP-9) cleave denatured collagen (gelatin) as well as type IV collagen in basement membranes. Matrilysins (MMP-7, MMP-26) degrade ECM components such as laminin and entactin. The membrane-type MMPs (MT-MMPs) are embedded in the plasma membrane of the cells via type I or II domains or glycosylphosphatidylinositol (GPI)-anchors. Other MMPs do not conform easily to classification and include macrophage elastase (MMP-12) and epilysin (MMP-28) (83, 95). Substrate specificities are summarized in Table 1.

Transcriptional regulation. Regulation of MMPs at the level of gene expression has been reviewed elsewhere (29, 74), and it involves activating protein (AP)-1 and AP-2, PEA3, NF-κB, Smad, and STAT transcription factors and their cognate binding sites. Of note, some of the MMPs, including MMP-7 and MMP-9, are regulated through canonical Wnt/β-catenin signaling (45, 140), a pathway that has been demonstrated to be associated with kidney development and injury (41, 44). Studies from our laboratory have also demonstrated that tissue plasminogen activator (tPA) leads to an enhanced transcription of MMP-9 in renal interstitial fibroblasts, through a pathway dependent on cell-surface LDL receptor-related protein-1 (LRP-1) and on Erk-1/2 activation. This activation is independent of the enzymatic activity of tPA (49, 148).

Posttranslational activation. The MMPs are synthesized as inactive zymogens maintained by a conserved cysteine residue that interacts with the zinc in the active site and prevents a catalytic water molecule from associating with the metal ion, rendering the protease inactive (87). Activation requires disruption of this so-called “cysteine switch,” which can be accomplished through proteolytic cleavage of the propeptide by trypsin, plasmin, or even other MMPs (137). In addition, several MMPs contain a furin-sensitive cleavage site for the propeptide, indicating intracellular activation of these enzymes (87). MMP-9 has a unique relationship with neutrophil gelatinase-associated lipocalin (NGAL), as they are coexpressed by neutrophils and can interact with each other. This interaction prevents the degradation of MMP-9, potentially prolonging its lifespan and effects. As NGAL has long been recognized as a potential biomarker for kidney injury, detectable in the urine of affected individuals, it is conceivable that the interaction of MMP-9 and NGAL could play a specific role in prolonging MMP action in renal pathology (130), and this hypothesis deserves further attention in the future.

An interesting story of MMPs with nitrosative and oxidative stress has also emerged. The cysteine switch contains a thiol residue that can be altered by reactive oxygen species (ROS) and reactive nitrogen species (RNS), causing dissociation from the catalytic site, leading to enzyme activation (96, 137). Such regulation is tightly controlled, as it is shown that at lower concentrations, MMP-7 is activated by hypochlorous acid (from myeloperoxidase), whereas at higher concentrations MMP-7 is inactivated, apparently through oxidative cross-linking of amino acids affecting the active site (31, 32). These
findings suggest that although the cysteine switch thiol is the preferred site of oxidative alteration, at times of greater oxidant production, the enzyme is inactivated, possibly preventing overactivity. Such fine-tuning of MMP activity by oxidative stress underscores the complexity of MMP regulation. Whether such mechanisms play a role in renal pathology remains to be determined.

Natural inhibitors. MMP activity is regulated by a family of naturally occurring, endogenous inhibitors known as tissue inhibitors of metalloproteinases (TIMPs). The four known TIMPs have varying specificities for different MMPs but collectively can inhibit all of them. Generally, TIMPs combine in 1:1 stoichiometry with MMPs and associate with the catalytic and hemopexin domains to cause inhibition (87). However, TIMPs also participate in metalloproteinase activation, as in the case of TIMP-2-associated activation of MMP-2 in the presence of MT1-MMP. There is now evidence that TIMPs can participate in other non-traditional functions such as cell proliferation, apoptosis, and angiogenesis, and that a role of MMPs is to modulate TIMP signaling via sequestering a limited pool of TIMPs (82, 87).

<table>
<thead>
<tr>
<th>MMP</th>
<th>Alternate Names</th>
<th>Selected Substrates</th>
<th>Selected Reference(s)</th>
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<tbody>
<tr>
<td>MMP-1</td>
<td>Collagenase-1</td>
<td>Collagen I, II, III, entactin, perlecant, IGF-BP-2 and -3, pro-IL-1β, IL-1β</td>
<td>38</td>
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<tr>
<td>MMP-2</td>
<td>Gelatinase A</td>
<td>Gelatin, collagen IV, V, XI, laminin, aggrecan, pro-TGF-β, pro-TNF-α, IGFBP-3 and -5</td>
<td>18, 131</td>
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<tr>
<td>MMP-3</td>
<td>Stromelysin-1</td>
<td>Aggrecan, laminin, fibronectin, fibrinogen, MCP-1 to -4, pro-MMP-1, -3, -7, -8, -9, -13</td>
<td>56, 126</td>
</tr>
<tr>
<td>MMP-7</td>
<td>Matriplasin</td>
<td>Plasminogen, pro-α-defensin, Fasl, pro-TNF-α, E-cadherin, syndecan, pro-MMPs</td>
<td>45, 78, 99, 140</td>
</tr>
<tr>
<td>MMP-8</td>
<td>Collagenase-2</td>
<td>Collagen I-III, VII, X, aggrecan, fibronectin, pro-TNF-α, IGF-BP, MCP-1, angiogenin</td>
<td>136</td>
</tr>
<tr>
<td>MMP-9</td>
<td>Gelatinase B</td>
<td>Gelatin, collagen IV, V, XI, pro-IL-8, Pro-TNF-α, pro-TGF-β, pro-MMP-2, -3, -7, -13</td>
<td>49, 146, 153</td>
</tr>
<tr>
<td>MMP-10</td>
<td>Stromelysin-2</td>
<td>Gelatins, fibronectin, proteoglycan, pro-MMP-1, -8, -10</td>
<td>93, 106</td>
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<tr>
<td>MMP-11</td>
<td>Stromelysin-3</td>
<td>Fibronectin, laminin, aggrecan, IGFBP-1</td>
<td>84</td>
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<td>MMP-12</td>
<td>Metalloelastase</td>
<td>Elastin, fibronectin, laminin, plasminogen, pro-TNF-α</td>
<td>46</td>
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<tr>
<td>MMP-13</td>
<td>Collagenase-3</td>
<td>Collagen I, II, III, entactin, aggrecan, tenascin, pro-TNF-α, pro-MMP-9, -13</td>
<td>62, 63</td>
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<tr>
<td>MMP-14</td>
<td>MT1-MMP</td>
<td>Collagen I, II, III, laminin, fibronectin, pro-MMP-2, -13, CD44, tissue transglutaminase</td>
<td>87</td>
</tr>
<tr>
<td>MMP-15</td>
<td>MT2-MMP</td>
<td>Pro-MMP-2, pro-TNF-α, tissue transglutaminase</td>
<td>1</td>
</tr>
<tr>
<td>MMP-16</td>
<td>MT3-MMP</td>
<td>Collagen III, pro-MMP-2, pro-TNF-α, tissue transglutaminase</td>
<td>118</td>
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<tr>
<td>MMP-17</td>
<td>MT4-MMP</td>
<td>Gelatin, fibronectin, fibrin, pro-MMP-2, ADAMTS-4, TIMPs, pro-TNF-α</td>
<td>129</td>
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<tr>
<td>MMP-18</td>
<td>Collagenase-4</td>
<td>Collagen I, II, III</td>
<td>10, 85</td>
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<tr>
<td>MMP-19</td>
<td>Stromelysin-4</td>
<td>Collagen IV, gelatin, laminin</td>
<td>73</td>
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<tr>
<td>MMP-20</td>
<td>Enamelysin</td>
<td>Amelogenin, aggrecan, cartilage oligomeric matrix protein (COMP)</td>
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<td>MMP-21</td>
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<td>Gelatin, α-1-antitrypsin</td>
<td>138</td>
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<tr>
<td>MMP-23</td>
<td></td>
<td>May be similar to stromelysins and collagenases</td>
<td>18</td>
</tr>
<tr>
<td>MMP-24</td>
<td>MT5-MMP</td>
<td>Pro-MMP-2</td>
<td>118</td>
</tr>
<tr>
<td>MMP-25</td>
<td>MT6-MMP</td>
<td>Collagen IV, gelatin, fibrin, fironectin, pro-MMP-2 and -9, TIMPs, uPAR</td>
<td>98, 115</td>
</tr>
<tr>
<td>MMP-26</td>
<td>Matriplasin-2</td>
<td>Collagen IV, fibronectin, fibrin, fibrinogen, pro-MMP-9</td>
<td>35</td>
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<tr>
<td>MMP-27</td>
<td></td>
<td>Gelatin, casein</td>
<td>53</td>
</tr>
<tr>
<td>MMP-28</td>
<td>Epilysin</td>
<td>Neural cell adhesion molecule (NCAM), casein</td>
<td>53</td>
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MMP, matrix metalloproteinase. Data were compiled with the noted references as well as previous reviews (37, 95). uPAR, urokinase plasminogen activator receptor; IGF-BP, insulin-like growth factor binding protein.
is induced in human kidney biopsies from patients with diabetic nephropathy, and its level is closely correlated with β-catenin abundance (45). Observations have also described downregulation of MMP-1 and TIMPs, with upregulation of membrane-type MMPs (21, 60, 108, 109).

The role of MMPs in the pathogenesis of diabetic nephropathy is controversial and inconsistent. In addition, experimental models do not always recapitulate clinical findings, as recently reviewed (126). These contradictions could be caused by differences in animal strains, samples obtained, and cell types examined, as well as the fact that diabetes treatment affects MMP expression (126). Some models show that decreased MMP activity, particularly of MMP-2 and MMP-9, ameliorate kidney lesions (107, 114, 144, 150), whereas in other models maintenance of MMPs, namely, MMP-1 and in some cases even MMP-9, is associated with improvement (see Table 2) (4, 34). Similarly contradictory, TIMP-3 was elevated in diabetes, but TIMP-3 null mice actually had worsened fibrosis and increased activation of MMP-2 (55, 57). Collectively, these data highlight the complexities of MMP pathobiology and the continued need for mechanistic studies.

Nondiabetic glomerular disease. MMP levels are altered in other nondiabetic glomerular diseases. Single nucleotide polymorphisms in MMP-14 confer risk for developing focal segmental glomerulosclerosis (FSGS) (101, 108), whereas in diabetes, MMP-14 transcription is increased (112). MMP levels are also altered in other renal diseases, as summarized in Table 2 and reviewed elsewhere (75).

Table 2. Effect of MMP manipulations in kidney diseases

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Model System</th>
<th>Overall Effect</th>
<th>Specific Findings</th>
<th>Reference(s)</th>
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<td>Acute kidney injury</td>
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<td></td>
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<tr>
<td>MMP-2 null</td>
<td>Mouse, I/R</td>
<td>Improved</td>
<td>Reduced incidence of AKI</td>
<td>59, 61</td>
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<tr>
<td>MMP-9 null</td>
<td>Mouse, I/R</td>
<td>Improved</td>
<td>Prevented loss of microvascular density</td>
<td>61</td>
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<tr>
<td>MMP-9 null</td>
<td>Mouse, I/R</td>
<td>Worsened</td>
<td>Tubular apoptosis, delayed recovery</td>
<td>11</td>
</tr>
<tr>
<td>MMP inhibition</td>
<td>Rat, I/R</td>
<td>Improved</td>
<td>Decreased AKI, apoptosis, and cytokine release</td>
<td>51</td>
</tr>
<tr>
<td>MMP inhibition</td>
<td>Mouse, I/R</td>
<td>Improved</td>
<td>Decreased histological damage</td>
<td>91</td>
</tr>
<tr>
<td>Diabetic nephropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP inhibition</td>
<td>Human, diabetes</td>
<td>Improved</td>
<td>Decreased proteinuria at 3 mo</td>
<td>2</td>
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<tr>
<td>MMP-1 transgenic</td>
<td>Mouse, diabetes</td>
<td>Improved</td>
<td>Decreased fibrosis</td>
<td>4</td>
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<tr>
<td>MMP inhibition</td>
<td>Rat, diabetes</td>
<td>Improved</td>
<td>Reduced proteinuria/glomerulosclerosis/fibrosis</td>
<td>144</td>
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<tr>
<td>Interstitial fibrosis</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>TIMP-1 null</td>
<td>Mouse, UUO</td>
<td>No change</td>
<td>Compensatory TIMP-3 upregulation</td>
<td>57</td>
</tr>
<tr>
<td>TIMP-1 overexpression</td>
<td>Mouse, UUO</td>
<td>Worsened</td>
<td>Increased fibrosis and inflammation</td>
<td>13</td>
</tr>
<tr>
<td>MMP-9 null</td>
<td>Mouse, aging, UUO</td>
<td>Worsened</td>
<td>Increased fibrosis</td>
<td>55</td>
</tr>
<tr>
<td>MMP-9 null</td>
<td>Mouse, UUO</td>
<td>Improved</td>
<td>Reduced fibrosis and EMT</td>
<td>141</td>
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<tr>
<td>MMP-2 inhibition</td>
<td>Mouse, UUO</td>
<td>Worsened</td>
<td>Reduced inflammation, accelerated fibrosis</td>
<td>90</td>
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<tr>
<td>Inherited diseases</td>
<td></td>
<td></td>
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<tr>
<td>MMP inhibition</td>
<td>Rat, PKD</td>
<td>Improved</td>
<td>Decreased cyst number</td>
<td>92</td>
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<td>MMP gene deletion or inhibition</td>
<td>Mouse, Alport’s</td>
<td>Stage-specific</td>
<td>Early inhibition attenuated disease, late inhibition worsened disease</td>
<td>153</td>
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<tr>
<td>Glomerulonephritis</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>Rat, IC nephritis</td>
<td>Improved</td>
<td>Decreased proliferative lesions, IgG/C3 deposits</td>
<td>110</td>
</tr>
<tr>
<td>MMP inhibition</td>
<td>Rats, MPG</td>
<td>Improved</td>
<td>Decreased mesangial proliferation, fibrosis</td>
<td>119</td>
</tr>
<tr>
<td>MMP inhibition</td>
<td>Rats, MPG</td>
<td>Improved</td>
<td>Decreased collagen, α-SMA expression</td>
<td>81</td>
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<tr>
<td>MMP-9 or -13 null</td>
<td>FSGS</td>
<td>Improved</td>
<td>Decreased collagen IV and proteinuria</td>
<td>111</td>
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</table>

TIMP, tissue inhibitor of metalloproteinase; I/R, ischemia-reperfusion injury; AKI, acute kidney injury; UUO, unilateral ureteral obstruction; PKD, polycystic kidney disease; EMT, epithelial-mesenchymal transition; MPG, membranoproliferative glomerulonephritis; FSGS, focal segmental glomerulosclerosis; α-SMA, α-smooth muscle actin.
enceptual glomerulosclerosis (FSGS), although the underlying mechanism is unknown (86). Patients with FSGS, minimal change disease, membranous nephropathy, human immunodeficiency virus (HIV)-associated nephropathy, as well as anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, each had unique expression patterns of MMP-2 and MMP-9 (3, 9, 24, 112, 113). Increased glomerular MMP-9 was found in lupus nephritis, IgA nephropathy, Henoch-Schoenlein Purpura (HSP), and postinfectious glomerulonephritis (134). MMP-7 is induced in renal tubular epithelium of the kidneys in FSGS and IgA nephropathy (45). MMP-3 is upregulated in HSP and ANCA vasculitis (113, 115).

Experimentally, MMP-9 is upregulated in models of FSGS, lupus nephritis, and Thy1.1 nephritis, a model for membranoproliferative glomerulonephritis (MPGN) (69, 81, 128, 132). However, impaired resolution of disease appears to be associated with a paradoxical decrease in MMP-9 late in the course of Thy1.1 nephritis (128). Meanwhile, MMP-2 is increased in both lupus and MPGN (81, 119, 133). A few studies utilizing both selective and nonselective MMP inhibitors in these models appear to ameliorate renal injury (Table 2).

Inherited kidney disease. Polycystic kidney disease (PKD) is the most common inherited kidney disorder and has been associated with MMP dysregulation. In serum of PKD patients, there is an increase in TIMP-1, MMP-1, MMP-9, and type IV collagen (a target of MMP-9) compared with controls (88). There is also dramatic upregulation of MMP-7 associated with expression of Wnt in PKD (120). As Wnt/β-catenin signaling is activated in tubular injury, it now appears that MMP-7 is a target of this pathological signaling. MMP-14 is also noted in cyst-lining epithelia in experimental PKD, and MMP inhibitor therapy decreases cyst formation (92).

Alport syndrome (AS) is characterized by a mutation in collagen IV, which may lead to altered basement membrane proteolysis. Upregulation of MMP-2, -3, and -9 occurred in both human AS and in animal models, and each MMP could digest AS-derived basement membrane in vitro. Interestingly, early MMP inhibition before onset of proteinuria attenuates renal lesions while inhibition after proteinuria accelerates disease progression (153). Numerous other MMPs are upregulated in AS, but their roles have yet to be determined (22, 79, 103).

Chronic allograft nephropathy. Chronic rejection remains the major limitation of renal transplantation, and circumstantial evidence may indicate a role for MMPs. Numerous studies have collectively identified increases in MMP-2, MMP-7, MMP-8, and MMP-9, as well as TIMP-1 and -2 in cases of allograft rejection (16, 27, 68, 80, 104, 105, 145). Interestingly, polymorphisms in MMP-2 and -9 have been associated with increased allograft survival (116), and the immunosuppressive drug rapamycin inhibits MMP-9 expression while increasing TIMP-1 (94). The potential mechanism of MMPs in rejection remains an area of active investigation.

Mechanisms of MMP Action in Kidney Disease

As renal fibrosis is the common final outcome of CKD, it was initially thought that MMPs may be globally protective through antagonism of ECM accumulation. With an increasingly expanding list of new MMP substrates, one has to concede that MMP roles are not limited to digestion of matrix. We have recently proposed that renal fibrosis appears to progress through a series of phases including inflammation, fibroblast/myofibroblast activation, matrix deposition, and fibrosis (70). It is conceivable that MMPs act at all levels of this pathologic process, as well as in regulation of apoptosis and angiogenesis (Figs. 4 and 5).

Inflammation. MMPs have critical roles in inflammatory cell recruitment and chemotaxis, thereby regulating the inflammatory response (Fig. 4). ICAM-1, a cell surface molecule promoting leukocyte transmigration into tissues, is cleaved by MMP-13 and MMP-14, suggesting an anti-inflammatory effect (28, 124). Consistent with this, transgenic TIMP-1 overexpression does increase ICAM-1 in proximal tubular epithelium (13). MMP-9 appears to play a role in self-propagating inflammation by creating collagen fragments which are both chemotactic for neutrophils and stimulate them to release more MMP-9 (146). Furthermore, MMP-9 mediates dendritic cell (DC) migratory capacity and may also bind to cell surface costimulatory molecules (50, 151). MMP-14 similarly appears to have stimulatory roles in DC migration (35, 149). MMP-7 cleaves syndecans and their attached neutrophilic chemokines, increasing inflammation by generating a chemotactic gradient (64, 122). In addition, MMP-7 may promote inflammation by facilitating the release of TNF-α from macrophages (43). This MMP also cleaves E-cadherin and can regulate migration of DCs containing the E-cadherin receptor, CD103 (αEβ7-integrin) (75).
After chemotaxis, MMPs also regulate inflammatory cell function. Gelatinase inhibition depresses lymphocyte proliferation in vitro and in vivo in experimental lung disease (12). MMP-8 and -9 promote neutrophil survival (23, 58). Although unproven, it has been proposed that MMPs could play a role in exposing immunoreactive epitopes through cleavage of substrates, leading to immune complex deposition (132). Regulation can occur in both ways, as inflammatory cytokines modulate MMP production (89).

Inflammation mediates transplant rejection, but we can only infer from nonrenal organ transplants the role of MMPs in the kidney allografts. MMP-2 null mice have decreased T cell alloreactivity and inflammatory cytokine release, while MMP-9 null mice have increased alloreactivity and cytokine release (14). Broad-spectrum inhibition of MMPs leads to decreased inflammatory cell chemotaxis and improves cardiac graft survival (26). However, these results may be tissue specific, as MMP-9 null mice have improvement in survival of tracheal allografts (30).

Epithelial-mesenchymal transition. Epithelial-mesenchymal transition (EMT) is the conversion of epithelium to a fibroblastic or myofibroblastic phenotype (71). Although the role of EMT in renal fibrosis is controversial (102, 152), it is clear that MMPs are a part of its regulation under experimental conditions. MMP-2 localizes to areas of purported EMT, and, when added to epithelial cultures, is sufficient to induce the expression of α-smooth muscle actin (α-SMA), a marker of myofibroblasts (17). Furthermore, mice overexpressing MMP-2 in proximal tubular epithelium induces EMT in a process characterized by basement membrane disruption, leading to spontaneous tubular atrophy consistent with chronic kidney injury (18). MMP-3 induces EMT in lung fibroblasts and promotes fibrosis in vivo (147). MMP-9 could mediate EMT and increase the migratory capacity of kidney epithelial cells (52, 123). Both MMP-3 and MMP-9 could individually induce EMT in renal tubular cell cultures through cleavage of the epithelial cell marker E-cadherin, which leads to activation of β-catenin (Fig. 5) (154). Consistent with these results, MMP-9 null mice have decreased EMT as measured by α-SMA and decreased fibrosis after abusive injury (141).

Cell proliferation and apoptosis. One of the interesting roles discovered for MMPs is their involvement in the regulation of cell proliferation and apoptosis (Fig. 5) (72, 100). MMPs modulate cell proliferation primarily by indirect mechanisms. For instance, MMP-9 is known to cleave membrane-bound precursor proteins and release EGF-like ligands that subsequently bind to the EGF receptor (100). Similarly, MMPs may sequester TIMP-1, which could lead to inhibition of TIMP-1-mediated fibroblast proliferation (72).

General MMP inhibition induces cell cycle arrest and apoptosis in mesangial cells in anti-Thy1.1 nephritis, while TIMP-1 similarly reduces apoptosis in mesangial cells under stress in vitro (25, 67). MMP-7 can stimulate apoptosis through cleaving and generating active soluble Fas ligand (101). On the other hand, MMP-9 protects against apoptosis in acute kidney injury through release of soluble stem cell factor (SCF), which is the ligand for the c-kit tyrosine kinase receptor (11).

MMPs also modulate apoptosis via surprising mechanisms separate from ectodomain shedding. MMP-8 null mice have reduced neutrophil apoptosis via downregulation of caspases (23). Interestingly, MMP-3 could actually translocate into the nucleus of mammalian cells and stimulate apoptosis, and this effect is dependent on retention of its catalytic activity (117). Similarly, MMP-1 can localize to mitochondria and the nucleus of various cell types, and knockdown of MMP-1 by small interfering RNA (siRNA) sensitizes cells to apoptosis (66). Further investigation is necessary to determine whether these mechanisms impact the development of renal diseases.

ECM accumulation. Mesangial cell activation is believed to be responsible for glomerulosclerosis development, and evidence supports a pathogenic role for MMP-2, which is upregulated in kidney fibrosis (18). MMP-2 production is increased in mesangial cell cultures when exposed to components of the ECM, including collagen I, vitronectin, and fibronectin (77). Cultured mesangial cells with high expression of MMP-2 have greater proliferative capacity, are more motile, and produce more α-SMA and collagen. This phenotype is reversed with MMP-2-silencing RNA (131). Therefore, somewhat surprisingly, MMP-2 can promote ECM production and accumulation in kidney cells. Whether MMP-2 exerts its action via a direct mechanism or an indirect one, such as promoting the release of fibrogenic cytokines, remains to be determined.

ECM degradation. The excessive accumulation of ECM in CKD is likely to involve aberrant levels of MMPs/TIMPs. MMP-1 is downregulated in aging kidneys that have collagen deposition (33). TIMP-1 overexpression occurs in fibrosis and can promote fibroblast proliferation independently of MMP inhibition (72). TIMP-1 deficiency does not prevent fibrosis, perhaps due to the compensatory upregulation of other TIMPs (57).

While the degradation of ECM proteins by MMPs is beneficial in that it reduces matrix accumulation, products of the degraded
ECM components may be capable of exerting some biological actions. In this regard, a recent study shows that MMP-9 induced EMT in vitro only when tubular cells were cultured on Matrigel (141), suggesting that the proteolytic products of Matrigel by MMP-9 are instrumental in promoting EMT. Therefore, increased ECM degradation by MMPs, per se, may not necessarily translate into a reduced fibrosis in CKD.

Degradation of the basement membrane, which is mainly composed of type IV collagen and laminin, by MMPs such as MMP-2, -7 and -9 could have a detrimental effect on the integrity of renal parenchyma, thereby promoting the progression of CKD (Fig. 5). We have shown that although tPA can lead to myofibroblast activation, serve as a mitogen for renal fibroblasts, and promote their survival (42, 47, 48), its ability to induce MMP-9, which in turn impairs tubular basement membrane, probably plays a critical role in renal fibrogenesis (148).

Taken together, it is conceivable that the impact of ECM degradation by MMPs in CKD is very complex and could be either positive or negative to disease progression, depending on MMP substrate specificities, disease models, and stages.

Vascular remodeling. MMPs also play an important role in regulating endothelial cell behavior and vascular wall stiffness/elastcity, thereby affecting vascular physiology and pathology. It is well known that the proteolytic products of collagens by MMPs, such as endostatin, are critical mediators in regulating endothelial cell biology and angiogenesis (39, 143) (Fig. 5). Angiostatin, generated by MMP-mediated degradation of collagens, is antiangiogenic and is increased in ischemic injury (8), consistent with a finding of reduced peritubular capillary density in the outer medulla after acute renal failure (6). This is accompanied by persistent hypoxia that can be detected up to 5 wk after ischemia-reperfusion injury (7). These changes in renal vasculature could portend worsened renal prognosis and increased vulnerability to future injuries.

More recent studies confirm increased perivascular MMP-2 and -9 after acute ischemic injury, and MMP-9 null mice display reduced microvascular losses after ischemia, associated with preserved VEGF levels (61). Vascular permeability is reduced with inhibition of MMPs (121). Systemic effects are also present, as CKD and dialysis patients have higher MMP-2 and -9 levels in extrarenal arteries, associated with calcification and loss of elasticity. MMP inhibitors are capable of improving vessel relaxation (19, 20).

Conclusion and Perspectives

Numerous inherited and acquired kidney diseases are characterized by dysregulation of MMPs. In disorders ranging from PKD to diabetic nephropathy to glomerulonephritis, MMPs are upregulated (MMP-2, -7, and -9) as well as downregulated (MMP-1). With the availability of MMP null animal models as well as MMP-specific pharmacological inhibitors, we now have the tools to carry out sophisticated mechanistic studies that promise to provide greater insights into their exact roles in renal pathophysiology.

Far from being simple enzymes whose only role is to maintain ECM homeostasis, MMPs and their associated TIMPs are now implicated in a diverse array of biological processes and cellular events. MMPs can both promote and inhibit inflammation, acting on events from chemotaxis to lymphocyte proliferation. Some MMPs such as MMP-2, MMP-7, and MMP-9 seem necessary and sufficient to induce EMT, a potentially significant step in fibrosis. Surprising intracellular localization of MMPs and their roles in regulating various cellular activities are just beginning to emerge.

The discovery of the specific roles for various MMPs does suggest possible therapeutic options for patients with renal diseases. However, as described in this review, the roles of MMPs in kidney diseases are extremely complex, necessitating that specific inhibitors target a single pathological MMP, delivered at a particular point in time when that MMP is active, without affecting MMPs important for normal tissue homeostasis and function. Such therapy is challenging, even conceptually, and suggests that clinically useful MMP inhibitors are still a distant reality.

Nonetheless, continued research is needed to further refine our understanding of MMPs in specific renal pathologies. Identification of the varying mechanisms of action of MMPs will undoubtedly aid in our basic understanding of the pathogenesis of various kidney disorders. Utilizing this knowledge should renew the hope for targeted therapies that can be beneficial for patients with kidney diseases in the future.

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