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Plasminogen activator inhibitor-1 and the kidney

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Eddy, Allison A. Plasminogen activator inhibitor-1 and the kidney. *Am J Physiol Renal Physiol* 283: F209–F220, 2002; 10.1152/ajprenal.00032.2002.—Plasminogen activator inhibitor-1 (PAI-1) is a serine protease inhibitor that was isolated 20 years ago. First recognized as an inhibitor of intravascular fibrinolysis, it is now evident that PAI-1 is a multifunctional protein with actions that may be dependent on or independent of its protease inhibitory effects. The latter often involve interactions between PAI-1 and vitronectin or the urokinase receptor. The protease-inhibitory actions of PAI-1 extend beyond fibrinolysis and include extracellular matrix turnover and activation of several proenzymes and latent growth factors. PAI-1 has been implicated in several renal pathogenetic processes, including thrombotic microangiopathies and proliferative and/or crescentic glomerulopathies. Most recently, it has become clear that PAI-1 also plays a pivotal role in progressive renal disease, both glomerulosclerosis and tubulointerstitial fibrosis. An active area of present research interest, untold stories are likely to be uncovered soon.

fibrinolysis; fibrosis; thrombotic microangiopathy; cellular adhesion; glomerulonephritis; renal fibrosis

OVERVIEW

AN AMAZING BIOLOGICAL STORY has unfolded since an inhibitor of plasminogen activation was first isolated just a little over 20 years ago (102), and there seems to be little doubt that much remains to be learned (23, 79). Plasminogen activator inhibitor-1 (PAI-1), a member of the SERPIN (for SERine Protease INhibitor) family, is the primary physiological inhibitor of tissue-type and urokinase-type plasminogen activators (tPA and uPA, respectively). Three other molecules with PAI activity are now known: PAI-2, which may inhibit uPA in vivo; PAI-3, more correctly named protein C inhibitor to indicate its true biological action; and protease nexin-1 (156). PAI-1 is a single-chain, 50-kDa glycoprotein that exists in conformationally active and latent forms. After synthesis, active PAI-1 is rapidly secreted from most cells, with platelets the only cell type known to store quantities of latent PAI-1. Within the circulation, active PAI-1 is unstable unless it is bound to vitronectin. The primary source of active plasma PAI-1 is still unclear, but it may be hepatic. PAI-1 may also be synthesized as an acute-phase protein.

Under normal conditions, the only fibrinolytic inhibitor that is detected in significant quantities in the kidney is α_2-antiplasmin (111), although low levels of protease nexin-1 and protein C inhibitor have been reported in mouse mesangial cells and human tubular cells, respectively (116, 140). Not normally expressed in the kidney, PAI-1 is rapidly induced in a variety of acute and chronic renal diseases. On the basis of a series of in vitro and in vivo studies, it appears that PAI-1 may be produced by several different cells within the kidney (142, 149). Several in situ hybridization studies have demonstrated PAI-1 mRNA in diseased glomeruli and tubules and an inflamed interstitium, but counterstaining studies with specific cellular markers have not been performed to clearly establish the specific identity of the PAI-1-transcribing cells. PAI-1 mRNA has been identified in glomerular parietal epithelial cells in several pathological states (11, 63, 88, 105, 122, 182) and in cells presumed to be mesangial (68, 105, 122, 179), visceral epithelial (36), and glomerular endothelial (62, 105, 122, 132, 179). Intrarenal cells thought to be inflammatory leukocytes (38, 62, 68, 88, 172, 182) and renal tubules (36, 38, 39, 105, 122) may also become a source of PAI-1. While not yet subjected to rigorous investigation, the induction of PAI-2 and protein C inhibitor has not been documented in diseases of the kidney. Increased expression of protease nexin-1 has been reported in proliferative glomerulonephritis (116) and obstructive nephropathy (78), the significance of which remains to be established. It has been suggested that protease nexin-1 may not function as a PAI but rather as an inhibitor of thrombin (152).

REGULATION OF PAI-1 EXPRESSION

The synthesis of PAI-1, one of the most highly regulated fibrinolytic components, is rapidly induced by a

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Table 1. *Factors reported to increase PAI-1 expression*

Growth factors	Epidermal growth factor (76), fibroblast growth factor (145), granulocyte-macrophage colony-stimulating factor (69), hepatocyte growth factor (176), insulin-like growth factor (151), interleukin-1 (46), macrophage colony-stimulating factor (69), platelet-derived growth factor (158), transforming growth factor-α (98), transforming growth factor-β (103), tumor necrosis factor-α (150), vascular endothelial growth factor-β (134)
Coagulation factors	Fibrin fragments (133), thrombin (58), tPA (141)
Metabolic factors	Glucose (128), glucosamine (83), insulin (2), oxidized low-density lipoproteins (35), lipoprotein(a) (49)
Hormones	Aldosterone (19), angiotensin (59, 84, 169), erythropoietin (119), renin (126)
Environmental factors	Endothelial stretch (28), hypoxia (138), radiation (188)
Others	Bone morphogenic protein-7 (185), endothelin-1 (190), endotoxin (46, 148), glucocorticoids (110), hyaluronan fragments (77), reactive oxygen metabolites (189), SPARC (97)

PAI-1, plasminogen activator inhibitor-1; SPARC, secreted protein, acidic, and rich in cysteine; tPA, tissue-type plasminogen activator.

variety of factors. Transcriptional regulation is most important, but changes in mRNA stability may be involved in some situations (100). While the list of reported PAI-1 agonists is impressive (Table 1), some of these effects are cell specific, and most of these data derive from in vitro studies. Inhibition of PAI-1 has been less extensively investigated, but suppression has been reported with interferon-γ, nitric oxide, natriuretic factors, and lipid-lowering drugs (18, 47, 56). A topic of considerable present interest originated with the observation that plasma PAI-1 levels could be correlated with variations in the structure of the PAI-1 gene. In particular, higher levels are associated with a polymorphic variance in the number of guanine bases (4G rather than 5G) at *position −675* upstream of the transcription start site (93). The 5G site has been shown to bind a transcription repressor protein, E2F (95). Several recent studies suggest that the homozygosity for the 4G allele may be an independent risk factor for the development of atherosclerosis and cardiovascular disease, although conflicting data exist (93).

PROTEASE INHIBITOR-DEPENDENT ACTIONS OF PAI-1

PAI-1 inhibits uPA and tPA, the two known mammalian plasminogen activators, by forming an irreversible 1:1 molar complex. PAI-1 is consumed by this process. The noncatalytic domains of the two plasminogen activators are very different, which likely accounts for their distinct biological roles (Fig. 1). The nonenzymatic domain of tPA has a high affinity for fibrin and is in fact an inefficient activator of plasminogen in the absence of fibrin. As a consequence, tPA functions almost exclusively as a mediator of intravascular fibrinolysis and clot dissolution. Within normal kidneys, tPA has been identified within glomerular cells and collecting duct epithelial cells (147).

In contrast, uPA does not bind to fibrin, and it is most often found at extravascular sites, where it not only generates active plasmin but also may cleave other substrates, including some extracellular matrix proteins (Table 2). The noncatalytic domain of both single-chain pro-uPA and the two-chain active protease may bind to a specific cellular receptor, the urokinase receptor (uPAR), also known as CD87 (168). Cellular binding concentrates uPA and plasmin protease activity to pericellular regions. In normal kidneys, uPA, most of which is secreted into the urine, is produced in significant quantities by proximal tubules. However, several cells that are recruited or activated in the kidney in response to injury may produce uPA, including monocytes, macrophages, fibroblasts, and myofibroblasts. The pattern of uPAR expression in normal kidneys has not yet been carefully examined.

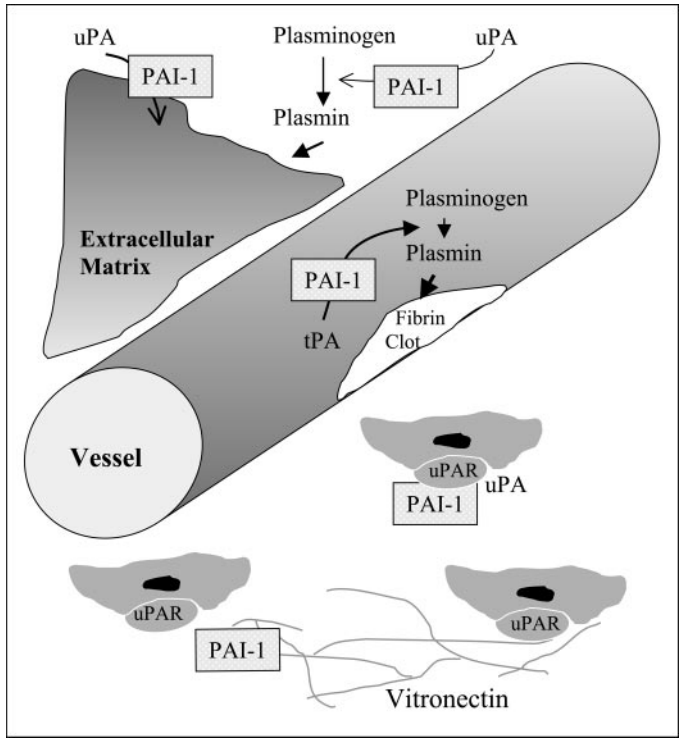

Fig. 1. Schematic summary of some of the biological functions of plasminogen activator inhibitor-1 (PAI-1). Within blood vessels, PAI-1 blocks tissue-type plasminogen activator (tPA)-dependent plasmin generation and degradation of fibrin clots. In extravascular areas, PAI-1 impairs matrix turnover by inhibiting urokinase-type plasminogen activator (uPA)-dependent activation of plasminogen. Plasma is a protease for several substrates that modulate matrix composition (Table 2). PAI-1 itself accumulates within extracellular matrices due to its high affinity for vitronectin. It also interferes with urokinase receptor (uPAR) and uPA-dependent (and by steric hindrance, $\alpha_v\beta_3$-dependent) cellular adhesion to vitronectin. As a consequence, cellular migration to distant sites may actually be facilitated if other chemoattractant or adhesion molecules are nearby. When PAI-1 binds to the uPAR-uPA cellular receptor complex, it is inactivated, internalized (with assistance from the low-density lipoprotein receptor-related protein), and degraded.

Table 2. *Enzymatic substrates*

Enzyme	Substrate/Reference No(s).
tPA	Plasminogen (21)
uPA	Plasminogen (99), fibrin (65), fibronectin (61), latent bFGF (131), latent HGF (124), latent MT-MMP (87)
Plasmin	Fibrin (106)
	Proenzymes (MMPs, prourokinase) (86, 120)
	Latent growth factors (bFGF, TGF-β, VEGF) (104, 136, 175)
	Extracellular matrix proteins (fibronectin, laminin, thrombospondin, entactin, tenascin-C, heparan sulfate proteoglyan, perlecan) (5, 30, 64, 108, 114, 135, 175)

uPA, urokinase-type plasminogen activator; MT-MMP, membrane-type metalloproteinase; bFGF, basic fibroblast growth factor; HGF, hepatocyte growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor.

Tubular uPAR immunoreactivity has been reported in normal human kidneys (170), whereas in another study in situ hybridization failed to detect uPAR mRNA (179). In vitro studies suggest that this receptor may be expressed by glomerular epithelial and mesangial cells as well (127, 144). PAI-1 is often found bound to vitronectin, an interaction that promotes the deposition of PAI-1 within extracellular matrices and facilitates its interaction with uPA and uPAR.

Plasminogen, the preferred substrate of both uPA and tPA, is primarily synthesized in the liver and circulates in a relatively high concentration in the plasma, although as much as 40% of circulating plasminogen migrates to extravascular sites (143). Plasminogen mRNA has been detected in the human kidney (112), a finding we have not been able to confirm in mouse kidneys (Eddy AA, Zhang G, Kim H, Ikeda Y, and Lopez-Guisa J, unpublished observations). Plasmin has several other possible substrates in addition to fibrin, which forms the basis for the consideration that plasmin plays an important role in extracellular matrix remodeling (Table 2).

UNIQUE EFFECTS OF PAI-1

In recent years, it has become evident the PAI-1 may influence the behavior of several cells through activities that are independent of its inhibitory effects on uPA and tPA activities and plasmin generation. In particular, PAI-1 modulates cellular adhesion and migration and appears to play an important role in inflammation, wound healing, angiogenesis, and tumor cell metastasis. These activities involve a complex interplay among PAI-1, vitronectin, uPAR, and certain integrin receptors, with different outcomes observed depending on the cell type and the composition of its immediate microenvironment (Fig. 1) (15, 101, 160). A key finding that appears to underlie these effects was the recognition that PAI-1 and uPAR compete for a common binding domain (somatomedin B) on the NH_2 terminus of vitronectin, near but distinct from the vitronectin RGD site that binds to $\alpha_v\beta_3$-integrins (101). When vitronectin binds to PAI-1 (which it does with much a higher affinity than to uPAR), it not only prevents cellular adhesion between uPAR and vitronectin-rich extracellular matrices but may also inhibit adhesive actions between $\alpha_v\beta_3$-integrins and vitronectin by steric hindrance. In vitro at least, the presence of PAI-1 inhibits vitronectin-dependent cellular adhesion and migration.

However, these interactions may have other consequences. Vitronectin may function as a shuttle to transfer PAI-1 to uPAR-bound uPA, with profound consequences (174). Once transferred, PAI-1 undergoes conformational changes that destroy its affinity for vitronectin and promote its degradation after endocytosis via a process that involves interactions between the uPAR-uPA-PAI-1 complex and the low-density lipoprotein receptor-related protein (LRP) (73, 94). During this latter process, PAI-1 is degraded and uPAR is recycled to the cell membrane.

On the basis of these interactions, it seems paradoxical that under many in vivo situations the presence of PAI-1 facilitates rather than inhibits cell migration. This is particularly true in cancer cell biology, whereby high tumor levels of PAI-1 predict a more aggressive metastatic phenotype (4). Recent studies in PAI-1 null mice have confirmed this association, with significantly more metastases observed in PAI-1 wild-type mice than in mice that are PAI-1 deficient (7). The basis of the promigratory effects of PAI-1 are still not entirely understood. For some cells, it may be that PAI-1 releases them from a vitronectin anchor, allowing more robust responses involving other adhesion reactions (between $\alpha_v\beta_3$-integrins and fibronectin, for example) and chemotactic signals (81). In other situations, the promigratory effects of PAI-1 appear coupled to an angiogenic response (7). Here again, the molecular details have not yet been fully dissected, but studies in genetically engineered mice have documented a dampened angiogenic response in PAI-1-deficient mice and a greater response in PAI-1-overexpressing mice (109). An ex vivo study of angiogenesis also demonstrated the importance of PAI-1, with abolition of angiogenesis in the absence of PAI-1 (33). These recent studies suggest that the angiogenic effects of PAI-1 are dependent on protease-inhibitory effects rather than its interactions with vitronectin and cellular adhesion molecules (6, 33). A question that deserves further evaluation in vivo is whether PAI-1 promotes angiogenesis by decreasing angiostatin generation. Angiostatin is a degradation product of plasminogen, which consists of its five kringle domains and is released in the presence of free sulfhydryl donors (57).

Finally, another cellular process deserving of further investigation is the role of PAI-1 in leukocyte recruitment. Several components of the coagulation cascade have leukocyte chemoattractant activity, including uPA, fibrin, thrombin, and uPAR. Although a specific PAI-1 receptor has never been reported, there is some evidence that PAI-1 may have chemotactic effects for monocytes and fibroblasts (32, 129). Furthermore, uPAR facilitates the migration of lymphohemopoietic cells via interactions that may involve the selectins, β_1-, β_2-, or β_3-integrins (26, 157). Leukocyte recruitment was significantly reduced in uPAR-deficient mice with pulmonary *Pseudomonas aeruginosa* infection (66), and lymphocyte recruitment was depressed in an immunologic model of pulmonary injury (67). Our laboratory recently found that renal interstitial monocyte recruitment in response to ureteral obstruction is also significantly attenuated in uPAR null mice (186). Whether PAI-1 is directly involved in uPAR-dependent recruitment of lymphohemopoietic cells is not yet clear. Given that uPA also has chemotactic effects, PAI-1 may also block leukocyte recruitment (32).

PAI-1 IN ACUTE RENAL INJURY

Thrombotic Microangiopathy

Thrombotic microangiopathy is a specific pathological entity that, within the kidney, typically involves fibrin deposition in glomerular capillaries and extraglomerular arterioles. There is now rather compelling evidence that PAI-1 plays an active role in the generation of the fibrin thrombi that are formed in response to glomerular endothelial cell injury. Glomerular PAI-1 deposition has been demonstrated in the kidneys of patients with thrombotic microangiopathy (179). Elevated plasma PAI-1 levels are reported in most studies of patients with hemolytic uremic syndrome (HUS), and the duration of the elevation has been shown to correlate with disease outcome (13, 107, 125). A recent prospective study documented that elevated plasma PAI-1 levels occur in the subset of children with *Escherichia coli* 0157:H7 enteric infection who develop HUS (~15%) before the onset of clinical renal disease, suggesting that PAI-1 plays an early role in the pathogenesis of the renal damage (25). With the recent characterization of better animal models of HUS, it is hoped that the specific role of PAI-1 in glomerular microvascular damage will soon be elucidated (82, 161, 165).

PAI-1 has also been implicated in renal thrombotic microangiopathy initiated by other causes of microvascular endothelial cell injury, such as preeclampsia, endotoxemia, and radiation exposure. Elevated plasma PAI-1 levels have been reported in women with preeclampsia (48). Inheritance of the 4G PAI-1 allele has been associated with an increased risk of preeclampsia (181) but not with diarrhea-associated HUS (159). Renal PAI-1 gene expression is increased in endotoxin-treated animals (117), and treatment with PAI-1-neutralizing antibodies significantly reduced renal fibrin deposition (118). However, a recent study of LPS-induced renal disease in genetically manipulated mice identified α_2-antiplasmin rather than PAI-1 as the more important regulator of renal fibrinolytic activity. Genetic deficiency of α_2-antiplasmin, but not of PAI-1, significantly reduced renal fibrin deposition (34). In an animal model of radiation nephritis, inhibition of angiotensin II-dependent renal PAI-1 expression significantly decreased glomerular thrombosis and sclerosis (132).

Renal Vasculitis

Perhaps the most frequently observed glomerular pathological finding that characterizes renal vasculitis is a focal necrotizing lesion filled with fibrin. It seems reasonable to speculate that PAI-1 plays a role in the genesis of this lesion as well, although there are few human data and no reliable animal models to verify this hypothesis. PAI-1 protein has been identified together with fibrin deposits in renal biopsy specimens from patients with focal necrotizing glomerulonephritis due to systemic lupus erythematosus (68). While increased plasma levels of PAI-1 have been reported in patients with Henoch-Schonlein purpura, it is not yet clear whether this finding represents a marker of endothelial damage or a pathological feature (14). The PAI-1 4G phenotype may be a predictor of focal necrotizing lesions among patients with diffuse proliferative lupus nephritis (171).

Proliferative Glomerulonephritis

The presence of PAI-1 mRNA and protein has been documented in several studies of both human and animal models of proliferative glomerulonephritis, especially those associated with fibrin deposition and crescent formation (reviewed in Ref. 142). It seems clear that inhibition of glomerular PA activity worsens the severity of glomerular injury. Mice genetically deficient in plasminogen or the combination of uPA and tPA were shown to develop more aggressive crescentic glomerulonephritis after an injection of anti-GBM antiserum, specifically, more inflammation, crescent formation, and necrosis in association with greater fibrin deposition (92). Given that tPA is considerably more abundant than uPA in glomeruli, it is perhaps not surprising that the isolated deficiency of tPA, but not uPA, resulted in glomerular injury intermediate in severity between wild-type mice and double PA-deficient mice. Treatment with recombinant tPA has been reported to decrease the extent of fibrin deposition and mesangial matrix expansion in rats with anti-Thy-1 glomerulonephritis (71).

Thus far most studies infer that PAI-1 participates in the pathogenesis of acute glomerular damage by promoting fibrin accumulation. However, given the potential for PAI-1 to alter the turnover of other uPA and plasmin substrates, together with its more recently recognized protease-independent effects, it is likely that newer roles for PAI-1 in glomerular injury will be identified in the future. Because fibrin accumulation is a significant mediator of acute glomerular injury, strategies designed not only to enhance fibrinolysis, by

blocking PAI-1, for example, but also to prevent fibrin formation might be therapeutic. Several anticoagulant studies performed in the 1960s and 1970s yielded conflicting results in animal models (reviewed in Ref. 44), perhaps further evidence for a multifactorial role for PAI-1. It is noteworthy that thrombin itself also has cellular receptors, protease-activated receptors (PARs). PAR-1 and PAR-2 are expressed in the kidney (16, 62, 63, 180). PAR-1-deficient mice have been shown to develop less severe crescentic glomerulonephritis than wild-type mice (31).

Membranous Nephropathy

Membranous nephropathy, a noninflammatory glomerular disease, deserves special mention even though any comment about the role of PAI-1 in disease pathogenesis is purely speculative at this time. In a PCR-based study of human kidney biopsies, PAI-1 transcripts were found to be abundant in membranous nephropathy (68). PAI-1 protein colocalizes with vitronectin, and also likely with SP40, 40 (or clusterin), within the epimembranous deposits (29, 123). It is also remarkable that the target antigen in the rat model of membranous nephropathy, megalin, is a plasminogen receptor (115). These are curious findings, the functional significance of which remains to be determined.

PAI-1 IN PROGRESSIVE RENAL DISEASE

In recent years, PAI-1 has emerged as a critical mediator of glomerulosclerosis and renal interstitial fibrosis. This has become a particularly exciting story, because PAI-1 could be a possible therapeutic target not only to delay progressive renal disease but also perhaps even for disease regression, if treatment is initiated before matrix accumulation has destroyed cellular structures within the kidney. PAI-1 mediates several effects that may facilitate matrix accumulation through the impairment of matrix turnover. Both uPA and plasmin can degrade several extracellular matrix proteins (Table 2) (reviewed in Ref. 142). While plasmin also activates latent transforming growth factor (TGF)-β in vitro (104), an undesirable effect that would enhance fibrosis, this effect does not appear to be prominent in several in vivo studies. Plasmin also activates several latent matrix-degrading proteases, including single-chain (latent) uPA and certain latent metalloproteinases (especially MMP-1, or collagenase-1, and MMP-3, or stromelysin-1). In addition, uPA activates membrane type-1-MMP, which subsequently activates MMP-2 or 72-kDa gelatinase.

While PAI-1 is essentially undetectable in normal kidneys, PAI-1 mRNA and/or protein have been found to be increased in several renal diseases associated with fibrosis, such as obstructive nephropathy (37, 129), protein-overload proteinuria (42), radiation nephropathy (20, 132), aging (105), hypertensive nephropathy (162), anti-tubular basement membrane nephritis (51, 164), nephrotoxicity (36, 80, 153, 154), lipid-induced renal injury (40), lupus nephritis (89, 167), Thy-1 nephritis (71, 166), focal segmental glomerulosclerosis (68, 184), diabetic nephropathy (183), and allograft nephropathy (155, 163, 172).

The potential importance of PAI-1 in progressive renal disease first gained impetus with the recognition that TGF-β is a critical mediator of renal fibrosis and that TGF-β is a powerful inducer of PAI-1 expression (103). In fact, in some cells induction of PAI-1 may be its most dramatic effect. TGF-β-overexpressing mice develop progressive glomerulosclerosis in conjunction with increased PAI-1 expression (96). Studies by Baricos et al. (10) highlight the importance of the uPA, tPA, and MMP-2 activity for mesangial cell degradation of extracellular matrix proteins and the enhancement of this activity by PAI-1 inhibition (10). In this in vitro experimental system, both PAI-1 production and plasminogen activation were shown to be mediated by TGF-β (9). The case against PAI-1 was strengthened once it became evident that a major feature of the renoprotective effect resulting from the inhibition or absence of angiotensin II activity was a reduction in TGF-β activity. It appears that PAI-1 expression may be induced at several steps along this pathway (to some extent cell dependent) by renin, angiotensin II, angiotensin IV, aldosterone, and shear stress in addition to TGF-β-dependent induction. Several studies based on the use of animal models performed by Border and Noble (17) and Fogo and their respective colleagues (54, 55, 137), as well as several other laboratories, have consolidated the link among the renin-angiotensin-aldosterone cascade, TGF-β, and PAI-1 in the pathogenesis of glomerulosclerosis. In the model of Thy-1 nephritis, TGF-β neutralization decreased glomerular PAI-1 deposition and the severity of glomerulosclerosis (166), whereas recombinant tPA therapy significantly reduced glomerular matrix accumulation (71). Angiotensin II can stimulate PAI-1 production both directly (90) and indirectly via TGF-β induction (3, 177). In vivo infusion of angiotensin II increases renal PAI-1 mRNA levels, a response that can be blocked by a selective angiotensin type I-receptor antagonist (122). Studies in several experimental models demonstrate that the renoprotective effects associated with pharmacological inhibition of angiotensin II are mediated, at least in part, by a reduction in PAI-1 expression. For example, administration of an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker decreased renal PAI-1 production and glomerulosclerosis severity in rats with radiation-induced renal injury (132). Administration of an angiotensin type 1-receptor antagonist to 18-mo-old rats not only slowed the rate of progression of glomerulosclerosis, in association with reduced PAI-1, but also revealed evidence of disease regression (105).

Our laboratory has extended the evidence by investigating the renal response to injury in mice genetically deficient in PAI-1 (Fig. 2). In the model of unilateral ureteral obstruction, the degree of interstitial fibrosis was significantly attenuated in PAI-1 null mice (129). A similar protective outcome was observed in the milder interstitial fibrosis model induced by protein overload (130). These results were impressive given

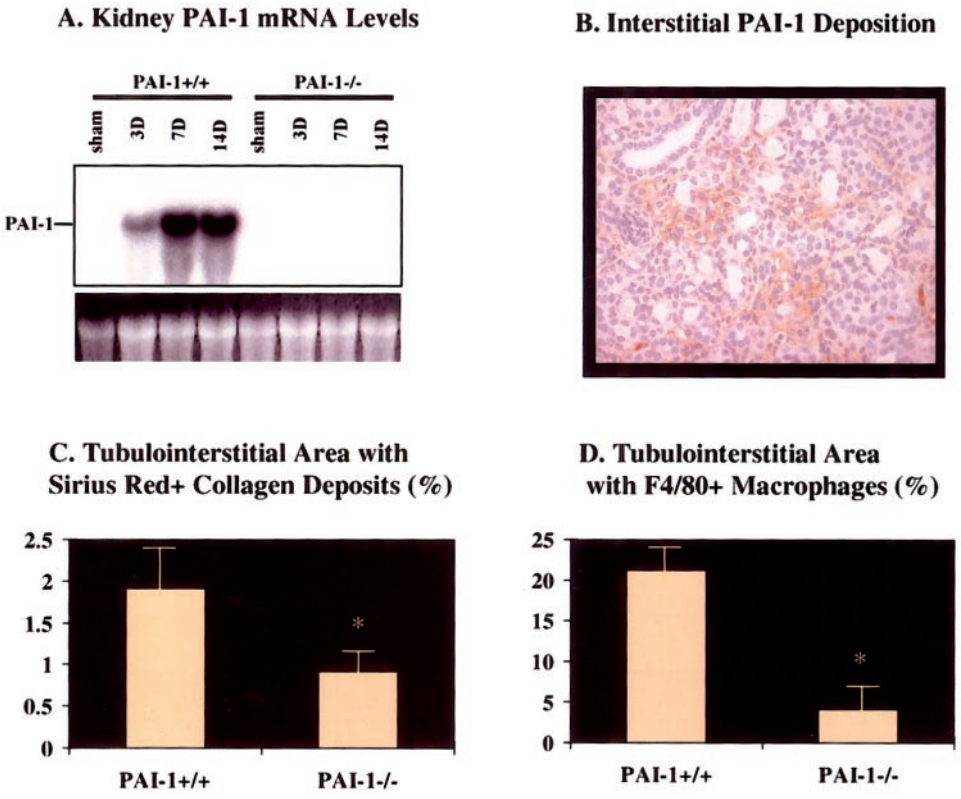

Fig. 2. PAI-1 plays a role in the pathogenesis of renal interstitial fibrosis, as illustrated by studies of the model of unilateral ureteral obstruction (UUO). After ureteral ligation, renal PAI-1 mRNA levels increase rapidly in wild-type mice (PAI-1+/+; *A*) and PAI-1 protein accumulates in the renal interstitium (*B*). This response is absent in PAI-1-deficicient mice (PAI-1−/−). After 7 days of UUO, the severity of interstitial fibrosis is significantly reduced in the PAI-1−/− mice (*C*). Renal macrophage recruitment is also delayed in the PAI-1−/− mice (*D*). *$P <$ 0.05. Data were reproduced from Ref. 129 with permission from Blackwell Science.

our earlier studies suggesting that the single deficiency of another protease inhibitor, the tissue inhibitor of metalloproteinases-1 (TIMP-1), which is also dramatically upregulated in association with interstitial fibrosis, conferred no protection (43, 91). It is likely that high constitutive renal levels of TIMP-2 and/or TIMP-3 compensated for the absence of TIMP-1. These findings suggest that PAI-1 is not only an important profibrotic protease inhibitor but also a unique and nonredundant molecule in the kidney. In our studies, renal expression of protein C inhibitor mRNA was never detected by Northern blot analysis. However, protease nexin-1 mRNA expression rose in parallel with PAI-1 in the wild-type animals and alone in the PAI-1 null mice, yet it did not overcome the protective effects of PAI-1 deficiency (78). These findings are consistent with the prior suggestion that protease nexin-1 normally functions as an inhibitor of thrombin rather than PAs (152). The other main inhibitor of fibrinolysis, α_2-antiplasmin, is produced by normal kidneys; however, in response to ureteral obstruction, its level of expression decreased significantly.

Studies in PAI-1-deficient mice have also documented less severe bleomycin-induced lung fibrosis (45). While the first published study associated the protective effect with decreased pulmonary fibrin deposition, more recent studies indicate that increased fibrin clearance does not account for the antifibrotic effects of PAI-1 deficiency, as bleomycin-induced pulmonary fibrosis is not attenuated by a genetic deficiency of either the Aα- or the γ-chain of fibrinogen (72, 139). Whether significant amounts of fibrin accumulate in the renal interstitium and contribute to progressive interstitial fibrosis is a question that has not yet been carefully investigated.

There do appear to be some fundamental differences between the protective effects of PAI-1 deficiency in the lung and the kidney. While studies in the bleomycin model indicate that increased plasmin activity is linked to the protective effects of PAI-1 deficiency, the critical substrate remains unclear (72). In our studies of ureteral obstruction, a difference in plasmin activity could not be shown between the deficient and the wild-type mice (129). This may be due to inherent limitations of the assay, and studies are in progress in plasminogen-deficient mice to clarify this issue. However, there was one other significant difference in the renal response to obstruction. The recruitment of interstitial monocytes was significantly delayed in the PAI-1-deficient mice. Because monocytes are often implicated in the fibrogenic process through numerous activities, it is quite likely that the blunting of the inflammatory response accounts, at least in part, for the antifibrotic effects of PAI-1 deficiency (41). It is not yet known whether the ability of PAI-1 to facilitate renal interstitial monocyte recruitment is a function of chemotactic or cell adhesion activities. These findings differ from the pulmonary response to bleomycin-induced injury, whereby leukocyte recruitment is apparently unaltered by PAI-1 deficiency (72).

In an effort to further investigate the role of the plasmin-protease cascade in renal fibrosis, our laboratory has recently been examining the role of uPAR. Although it is clear that uPAR is a multifunctional

receptor, one of its important roles is that it is the only known pathway for elimination of PAI-1 from tissues. Despite similar levels of PAI-1 mRNA in response to ureteral obstruction, significantly more PAI-1 protein accumulated in the kidneys of the uPAR null mice, and the degree of fibrosis was more severe (186, 187). Several other differences were noted between the uPAR wild-type and -deficient mice, but it is likely that greater PAI-1 accumulation contributed to the more robust fibrogenic response observed in the absence of uPAR.

Diabetic Nephropathy

Insulin-resistant states, associated with obesity, hypertension, and diabetes, are characterized by elevated plasma PAI-1 levels (12, 93, 121). The source of this excessive PAI-1 production is likely multifactorial, but one known contributor is tumor necrosis factor-α-dependent adipocyte PAI-1 synthesis (146). Perturbations in metabolic balance may also contribute to the PAI-1-excessive state as insulin, glucose, glucosamine, and oxidized low-density lipoproteins have each been reported to stimulate PAI-1 production (8, 22, 27, 35, 53, 83). Beyond the scope of this review, an extensive body of literature implicates PAI-1 in the pathogenesis of atherosclerosis and cardiovascular disease, although the strength of the association remains controversial. PAI-1 has recently been shown to play a central role in the pathogenesis of hypertension-induced vascular damage (85). PAI-1 may also play a role in the vasculopathy associated with hyperhomocysteinemia (113).

An obvious question is whether PAI-1 plays a role in the pathogenesis of diabetic nephropathy. PAI-1 expression is increased in diabetic nephropathic kidneys (184). The renoprotective effects of angiotensin II inhibition have been associated with reductions in renal TGF-β expression (60, 74, 178), and TGF-β has been shown to play a role in the pathogenesis of experimental diabetic nephropathy (70, 191). While it seems reasonable to predict from these data that PAI-1 is involved in the genesis of diabetic nephropathy, definitive proof is not yet available. Studies in progress in our own and other laboratories are investigating whether the genetic deficiency of PAI-1 can alter the natural history of diabetic nephropathy, but the results of these studies are not yet available.

In a Japanese population of patients with non-insulin-dependent diabetes mellitus, the presence of albuminuria has been associated with higher plasma PAI-1 levels (75). However, with one exception (171), studies have failed to identify the 4G PAI-1 allele as a risk factor for the development of diabetic nephropathy. Diabetic nephropathy is the one human disease with documented reversibility of mesangial matrix expansion, if the diabetic milieu is eliminated by successful pancreatic transplantation (52) or inadvertent transplantation of a diabetic kidney into a nondiabetic recipient (1). It would be exciting to demonstrate that turning off PAI-1 activity is involved not only in delaying progressive renal disease but also perhaps even in initiating its regression.

In summary, PAI-1, a simple 379-amino acid peptide, has emerged as an important mediator of several renal diseases, both acute and chronic. Future studies should begin to distinguish fibrinolytic and other protease-dependent and -independent effects, fundamental information that will be invaluable during the quest for new therapeutic agents. Like most biological molecules, PAI-1 likely has important beneficial effects as well. To date, only a single patient has been recognized to have a genetic deficiency of PAI-1 (50). Despite the normal phenotype of PAI-1-deficient mice (24), one has to question whether PAI-1 deficiency is really that rare, or alternatively, whether it is usually incompatible with human survival. For these reasons, as well as several others, further pursuit of PAI-1 physiology and pathophysiology seems to be a worthy endeavor.

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