MINIREVIEW

Plasminogen Activator Inhibitor-1 in the Pathogenesis of Asthma

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Plasminogen activator inhibitor (PAI)-1 is the main inhibitor of the fibrinolytic system and is known to play an essential role in tissue remodeling. Recent evidence indicates that chronic asthma may lead to tissue remodeling such as subepithelial fibrosis and extracellular matrix (ECM) deposition in the airways. However, the role of PAI-1 in asthma is unknown. Recently the mast cell (MC), which plays a major role in asthma, was found as a novel source of PAI-1, and a large number of MCs expressing PAI-1 are infiltrated in the airways of patients with severe asthma. Furthermore, PAI-1–deficient mice show reduced ECM deposition in the airways of a murine model of chronic asthma by inhibiting MMP-9 activity and fibrinolysis. In a human study, the 4G allele frequency was significantly higher in the asthmatic patients than in the control group. In view of the findings that the 4G allele is associated with elevated plasma PAI-1 level, elevated PAI-1 level in the lung may contribute to the development of asthma. In summary, PAI-1 may play an important role in the pathogenesis of asthma and further studies evaluating the mechanisms of PAI-1 action may lead to the development of a novel therapeutic target for the treatment and prevention of asthma. Exp Biol Med 229:138–146, 2004

Key words: mast cells; plasminogen activator inhibitor-1; asthma

Chronic asthma may lead to irreversible airway structural changes characterized by subepithelial fibrosis, extracellular matrix (ECM) deposition, smooth muscle hypertrophy, and goblet cell hyperplasia in the airways (1–4). Inflammatory cells such as T cells, eosinophils, and mast cell (MCs) are believed to cause irreversible airway structural changes by releasing proinflammatory cytokines and growth factors (5, 6). This suggests that chronic inflammation causes injury to the airways and modulates fibrogenesis, leading to end-stage fibrotic scarring. However, whether suppressing airway inflammation effectively prevents or reverses airway structural changes is controversial (6, 7).

Recent studies demonstrated the inefficacy of anti-inflammatory therapy in some patients with asthma, suggesting that an unregulated pathologic tissue remodeling process occurs in spite of adequate anti-inflammatory therapy (8, 9). Tissue remodeling usually involves two distinct processes: physiologic remodeling or regeneration, which is the replacement of injured tissue by parenchymal cells of the same type, and pathologic remodeling, which is the replacement by ECM. Pathologic remodeling eventually leads to altered restitution of airway structure such as subepithelial fibrosis and increase in smooth muscle and mucus gland mass (5).

Plasminogen activator inhibitor (PAI)-1 is the key inhibitor of the plasminogen activation system (PAS), which comprises an inactive proenzyme, plasminogen, that can be converted to the active enzyme, plasmin. Plasmin degrades fibrin into soluble fibrin degradation products. Two physiologic plasminogen activators (PAs) have been identified; the tissue-type PA (tPA) and the urokinase-type PA (uPA). The tPA-mediated plasminogen activation has a main role in the dissolution of fibrin in the circulation. On the other hand, uPA binds to a specific cellular receptor (uPAR), resulting in enhanced activation of cell-bound plasminogen. The main function of uPA is known to be in the induction of pericellular proteolysis via the degradation of matrix components or via activation of latent proteinases

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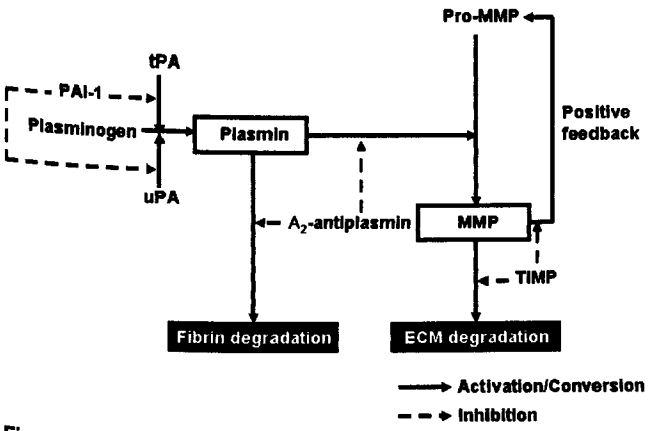

Figure 1. Plasminogen activation system and its interaction with the MMP system. Plasmin degrades fibrin and can also convert latent MMPs into the active forms, which degrade ECM. PAI-1 is the major inhibitor in PAS by inhibiting the activities of PAs. α-2 antiplasmin is another important inhibitor of PAS at the level of plasmin.

or growth factors. Inhibition of the PAS may occur either at the level of the PA, by specific PAIs such as PAI-1, PAI-2, and PAI-3 or at the level of plasmin, mainly by α-2 antiplasmin (10). The PAS and its interaction with the matrix metalloproteinase (MMP) system are schematically represented in Figure 1.

The PAIs belong to the SERPIN family, named after the serine protease inhibitor. PAI-1, a 50-kDa glycoprotein, is the main PAI secreted *in vivo* and is a potent fast-acting and irreversible inhibitor of tPA and uPA. It forms stoichiometric complexes with active PAs, which are subsequently endocytosed and degraded. The role of PAI-1 in asthma is poorly understood, although PAI-1 is known to play an important role in other tissue repair processes such as pulmonary fibrosis and renal fibrosis (11, 12). We and others recently demonstrated the possible role of PAI-1 in asthma (13–15). The implicated mechanisms of PAI-1 action in these studies involve inhibiting fibrinolysis and the MMP system, which are crucial in the tissue remodeling process (13). In this review, we will approach the possible role of PAI-1 in asthma based on the recent data demonstrating that MCs are a novel source of PAI-1 and a large number of MCs expressing PAI-1 are infiltrated in the airways of patients with severe asthma.

Mast Cells and Their Mediators in Asthma

Mast Cells in Asthma. Asthma is known as a chronic inflammatory disorder of the airways. T cells, eosinophils, and MCs are the three major cell types implicated in airway inflammation (16). T cells are activated in patients with asthma (17, 18) and orchestrate the bronchial inflammatory response through the release of multifunctional cytokines (19–21). Eosinophils are abundant in asthma, and their numbers correlate with the degree of airway hyperresponsiveness (AHR; Refs. 22, 23). The accumulation of MCs in the airways and increased levels of specific MC-derived mediators in bronchoalveolar lavage fluid (BALF) of patients with asthma indicate the role of MCs in the pathogenesis of this disease.

Animal models using MC-deficient or MC-reconstituted mice show the critical role of MCs in the pathophysiology of asthma. One such model is a mouse with a mutation of the W locus (W/W^v) that encodes for the c-kit receptor (24). These mice have virtually no tissue MCs because of their inability to respond to stem cell factor, which is essential in MC growth and differentiation from the hematopoietic progenitor cells. Using MC reconstitution technique, Williams and Galli (25) demonstrated that MCs are essential in recruitment of eosinophils into BALF and lung tissues and in the development of AHR after allergen stimulation. In contrast, Masuda *et al.* (26) reported that MCs play a role in the development of allergen-induced subepithelial fibrosis although airway inflammation, epithelial remodeling, and AHR caused by repeated allergen challenge are independent of MCs, at least in their model.

Mast Cell Mediators in Asthma. MCs initiate acute bronchoconstriction through IgE-mediated release of preformed and newly formed mediators from granules within the cell. Many of these mediators have direct spasmogenic activity on the smooth muscle of the airways (27). This immediate reaction accounts for acute symptoms and signs in asthma.

Histamine. Histamine is one of the most abundant preformed mediators in MCs and is released on exocytosis of the granule (28). Histamine causes bronchoconstriction, increased mucus secretion, vasodilation, and increased vascular permeability of the airways.

Eicosanoids. MCs also produce considerable amounts of newly formed eicosanoid mediators, the cysteinyl leukotrienes (LTs) and prostanoids, as well as platelet-activating factor (PAF; Refs. 29, 30). The levels of histamine, prostaglandin (PG)D_2, and its metabolite PGD9α, and 11β-PGF_2 are elevated in the BALF of sensitized individuals after allergen challenge (31, 32). PGD_2 causes bronchoconstriction, vasodilation, and increased vascular permeability. PGD_2 also directly activates eosinophils, causes neutrophil chemotaxis, and inhibits platelet aggregation (33).

LTC_4 is converted to LTD_4, which is a potent mediator of asthma (34, 35). Levels of LTs are increased in the BALF of patients with asthma. The level of LTC_4 is also increased in bronchial biopsies of patients with aspirin-sensitive asthma (36). When agents that either inhibit the synthesis of LTs or block the LT receptor were administered to patients with asthma, these agents produced a rapid improvement in pulmonary function in some of these patients, demonstrating that LTs play an important role in asthma (37).

PAF is a potent chemoattractant of other inflammatory cells such as eosinophils, neutrophils, monocytes, and macrophages. A combination of PAF and interleukin (IL)-5 may have synergistic effect in eosinophil chemotaxis (38). PAF acetyl hydrolase degrades PAF, and deficiency of this enzyme may be associated with severe asthma (39). On

the other hand, PAF antagonists improve AHR in some asthmatics (40). Taken together, these findings suggest that MC-derived mediators play an important role in AHR and airway inflammation in patients with asthma.

Cytokines. MCs produce a variety of cytokines (41–44). The range of cytokines originated by MCs is similar to that produced by T-helper 2 (TH2) cells, which play a central role in atopic asthma (19). MC-derived tumor necrosis factor (TNF)-α in mice has an important role in neutrophil recruitment and a critical protective role in a murine endotoxic shock model (45, 46). In murine models, TNF-α upregulates the expression of E-selectin and intracellular adhesion molecule (ICAM)-1 on endothelial cells that may facilitate the trafficking of both eosinophils and neutrophils to the inflammatory site (47). Bradding *et al.* (48) showed that MC-associated TNF-α was significantly increased in asthmatics in immunohistochemical analysis of endobronchial biopsy specimens. However, no TNF-α immunoreactivity was present in either T cells or eosinophils. This shows that MCs are a major source of TNF-α in bronchial asthma.

MCs produce chemoattractants, including the C-X-C chemokine IL-8, a potent neutrophil chemoattractant (49). Stimulated human MC lines express mRNA for IL-1, IL-3, and platelet-derived growth factor (50). A lymphocyte-specific chemokine, lymphotactin, is released from activated MCs (51), suggesting that MCs contribute to the recruitment of lymphocytes to areas of allergic inflammation. Furthermore, MCs produce C-C chemokines, I-309 and TCA3, respectively, after FcεRI cross-linking or cell-to-cell contact with T lymphocytes (52–54). Murine MCs also produce IL-1, IL-2, IL-3, and nerve growth factor and contain transcripts for IL-10, IL-12, RANTES (regulated upon activation, normal T cell expressed and secreted), and the macrophage inflammatory protein (MIP) family of chemokines.

Cytokines and growth factors that are relevant to the proliferation and activation of fibroblasts, cells implicated in the structural changes in the asthmatic airway, have also been identified in MCs. Murine MC-derived transforming growth factor (TGF)-β1, as well as TNF-α, induce a transient and marked increase of type I collagen mRNA in dermal fibroblasts after IgE-dependent activation (55). Basic fibroblast growth factor, which promotes fibroblast differentiation and angiogenesis, is found in the majority of MCs from normal skin and lung and in tissue samples characterized by fibrosis, hyperplasia, and neovascularization. Although MCs generate a series of cytokines and chemokines, the question still remains as to the relative contributions of MC-produced cytokines in the airways of asthmatics in comparison with those produced by eosinophils or T lymphocytes.

Proteases. MC-derived chymases and tryptases are activated by a heparin-dependent pathway (56). These enzymes degrade a variety of extracellular peptides and proteins, including vasoactive intestinal peptide (VIP), a bronchodilating neuropeptide (57). Tryptases inactivate procoagulant proteins, prevent the deposition of fibrin, and activate uPA. Tryptases also activate MMPs, which are crucial in the tissue remodeling process (58); stimulate the growth and differentiation of fibroblasts (59); and induce airway smooth muscle cell hyperplasia (60). Furthermore, tryptases promote the influx of circulating inflammatory cells into inflamed tissues (58). The mitogenic activity of tryptases on fibroblasts and smooth muscle cells could promote the subepithelial deposition of collagen types III and V as well as increase airway wall thickness (61). In addition to the chymase and tryptases, MCs are an important source of MMPs such as MMP-2 and MMP-9 and their specific inhibitor, tissue inhibitor of metalloproteinase (TIMP)-1 (62–64).

Mast Cell–Derived PAI-1

Induction of PAI-1 mRNA in Mast Cell DNA Microarray. The development of molecular biology and genetic technology opened the way to screen at-risk individuals for asthma (65). Identifying the differentially regulated genes from the inflammatory cells involved in asthma provides a clue as to which genes play a key role in this disease. We and others (66–69) have reported differentially expressed MC-derived genes by using cDNA microarray or subtraction library. We screened 7075 genes to identify those that were upregulated in stimulated MCs. Human mast cell line (HMC)-1 cells were exposed to a combination of phorbol myristate acetate (PMA) and calcium ionophore (A23187) to achieve maximal stimulation (70). Among the inducible genes that were identified, PAI-1 mRNA was induced at the highest level followed by uPAR mRNA (Table 1). Other PA genes such as tPA and uPA were not significantly induced.

PAI-1 Production and Secretion by MCs. We performed Northern blot analysis to confirm the results from the DNA microarray. The PAI-1 mRNA was undetectable in unstimulated HMC-1 cells, whereas PAI-1 mRNA was expressed at a high level in HMC-1 cells after stimulation (70). We also cultured primary cultured human MCs (PCHMCs) from the human cord blood and stimulated by IgE receptor cross-linking. The PAI-1 message was undetectable in unstimulated cells and was induced in cells stimulated by IgE receptor cross-linking. Furthermore, a considerable amount of PAI-1 was secreted by HMC-1 cells and PCHMCs after stimulation, whereas virtually no PAI-1 was secreted by either group of unstimulated cells.

Mast Cell-Derived PAI-1 on Fibrosis. We examined MC-derived PAI-1's ability to neutralize tPA activity by measuring net tPA activity (70). The tPA activity in the supernatants of unstimulated HMC-1 cells was very high. The activity was almost completely absent in the supernatants of HMC-1 cells after stimulation. Restored tPA activity by neutralizing PAI-1 show that this reduction in tPA activity was due to inhibition by PAI-1.

The total effect of PAI-1 secretion in the fibrinolytic system of human MCs was determined by performing a clot lysis assay (70). Supernatants from unstimulated HMC-1 cells induced clot lysis. No clot dissolution was seen with

Table 1. Differential Expression of Genes Participating in MMP and PA Systems in HMC-1 Cells*

Gene name	Differential expression
Plasminogen activator inhibitor, type I	−34.2
Plasminogen activator, urokinase receptor	−4.2
Metalloproteinase domain 17	−3.2
Tissue inhibitor of metalloproteinase 1	−2.7
Plasminogen activator, tissue-type	−1.2
Plasminogen activator, urokinase-type	−1.1
Plasminogen activator inhibitor, type II	+1.8

* Differential expression; absolute numbers correlates to the degree of differential expression between resting and activated cells. – or +, upregulation or downregulation of the gene after activation, respectively.

supernatants from stimulated HMC-1 cells. When the cells were pretreated with neutralizing antibody against PAI-1 before stimulation and the supernatants were added to a synthetic fibrin meshwork, the clot lysis effect was fully recovered in the supernatants from the MCs pretreated with the neutralizing antibody, suggesting MC-derived PAI-1 completely suppresses tPA activity and converts a fibrinolytic environment to a fibrosis dominant condition.

Mechanisms of PAI-1 Action

PAI-1 Inhibits Fibrinolysis and MMP Activation. PAI-1 inhibits fibrinolysis by blocking the conversion of plasminogen to plasmin. PAI-1 also plays a role in the control of MMP activation. The MMP system is comprised of the MMPs and their inhibitors (TIMPs) that contain several conserved motifs and a zinc-binding site. The MMP family contains at least 28 known members, which are grouped according to their substrate specificity (71–73). The collagenases (MMP-1, -8, -13) degrade fibrillar forms of interstitial collagen. The gelatinases (MMP-2 and -9) are specific for denatured collagens and collagen-IV of the basement membrane. Stromelysins (MMP-3, -10, -11) cleave noncollagen components such as fibronectin, laminin, and vitronectin. Metalloelastase (MMP-12) cleaves elastin and membrane type (MT)-MMP (MMP-14) cleaves various collagens and noncollagen components.

The MMPs are secreted in the extracellular space in catalytically latent forms because of the binding of the active site zinc atom to an unpaired cysteine of the propeptide domain. Disruption of the cysteine-zinc bond by conformational change or limited proteolysis leads to the opening of the switch. Then the autocatalytic cleavage of the propeptide yields the active enzyme (74). The activation of MMPs may also occur through the cleavage by MT-MMPs. The activation of MMP-2 at the cell surface is due to MT1-MMP. Active MMP-2 is then released into the extracellular space but may also remain at the cell surface, in which it has been shown to bind to the integrin $\alpha_v \beta_3$ (75).

In vitro, plasmin directly activates pro–MMP-1, -3, -9, -10, and -13 (76–80), whereas proMMP-2 is indirectly activated by plasmin (81). Several active MMPs are also able to activate other pro-MMPs, indicating positive feedback mechanisms. For instance, MMP-3 can activate pro–MMP-9 (82), and MMP-3 and -10 can superactivate procollagenase, generating collagenase with higher specific activity (77, 79).

PAI-1 Promotes Cell Migration. Homologous recombinant mice lacking uPA are deficient in recruitment of T cells and macrophages and succumb to bacterial (Cryptococcus neoformans) infection (83). They are also deficient in supporting the growth and malignant development of chemically induced melanomas (84). Furthermore, uPAR-deficient mice exhibit a reduced ability to recruit neutrophils to the peritoneum upon inflammatory stimuli (85). Although PAI-1 generally inhibits cell adhesion and migration by blocking the action of uPA, endothelial cell recruitment to tumor sites is totally abolished in PAI-1–deficient mice (86). However, little is known about the mechanism by which the PAS regulates cell adhesion and migration.

The proteolytic and nonproteolytic effects of uPA are interconnected through PAI-1. The PAI-1 binds to uPA not only in solution but also when uPA is receptor bound and therefore inhibits cell surface plasminogen activation, plasmin formation, and proteolytic stimulation of cell migration (87, 88). PAI-1 is located in the ECM in a vitronectin (VN)-bound form, and VN binding also influences its structure, preventing its conversion into a latent form. The aminoterminal region of VN (the somatomedin domain) contains the PAI-1–binding site close to the RGD sequence mediating binding to integrins (89). Binding of VN to PAI-1 and integrins is mutually exclusive. Cell adhesion onto VN is inhibited by PAI-1 in a process that does not require its active site. Through this mechanism, PAI-1 inhibits the migration of cells on VN substrate (90,91).

Regulation of PAI-1 Expression

The PAI-1 gene contains at its 5′ regulatory end several known consensus *cis* regulatory elements, which bind *trans* activating factors such as Sp1, activated protein-1 (AP-1), nuclear factor-κB (NF-κB), Smad3 and Smad4, and others (92–96). The PAI-1 gene transcription is activated by inflammatory cytokines, especially IL-1β (97), TNF-α (98), and TGF-β (99), and nonspecific protein kinase C activators such as PMA (70, 100). Inhibition of PAI-1 has been less extensively studied, but suppression has been reported with interferon-γ, nitric oxide, natriuretic factors, and lipid-lowering drugs (101–103).

The plasma level of circulating PAI-1 has been shown to be genetically controlled, and a polymorphism in the 5′ gene promoter has been described. Two alleles, 4G and 5G at position -674 in the promoter region, are encountered, and the plasma level of PAI-1 has been shown to be higher in patients with the 4G/4G genotype than in those with the 5G/5G genotype, whereas the 4G/5G genotype has intermediate

values (94). The 4G/4G genotype is reported to be associated with an increased risk of myocardial infarction in adult male patients. The molecular mechanisms involved in the increased synthesis of PAI-1 by the 4G allele as compared with the 5G allele appears to be related to the binding of NF-κB to the *cis* regulatory region, which is partially inhibited by a regulatory protein, binding to the 5G sequence but not, or to a lesser extent, to the 4G sequence. Under IL-1 stimulation of the cells, the PAI-1 gene transcription rate is higher with the 4G allele than with the 5G allele (104).

PAI-1 in Lung Diseases

PAI-1 in Pulmonary Fibrosis. Fibrosis is due to the abnormal accumulation of ECM in basement membranes and interstitial tissues (105). The abnormal ECM in fibrosis is made of an excess of normal components of ECM such as fibronectin, laminin, proteoglycans, and collagen type IV but also an accumulation of proteins that is not found in the normal ECM such as collagen types I and III (106). These latter proteins characterize the scarring process and are usually irreversibly deposited in the fibrotic tissues.

The lung parenchymal cells themselves may undergo a fibroblastic *trans* differentiation and overproduce the ECM components. Proliferation of fibroblasts and myofibroblasts within the lung are also involved in the fibrogenic process. On the other hand, the ECM can be degraded, and it is likely that the fibrogenic process may also result from a deficit in ECM degradation. However, the relationship between ECM degradation and fibrogenesis is more complex than initially suspected because abnormal ECM accumulation is often preceded or combined with an increased expression of ECM-degrading enzymes (107). This increased proteolytic activity is presumably required for degradation of the normal ECM by infiltrating inflammatory and fibroblastic cells and its replacement by abnormal ECM. The PAS and MMP systems are two main systems involved in degrading ECM in the lung (108).

Damaged alveoli during inflammatory lung diseases can be repaired by replacement of injured alveolar cells, restoration of damaged ECM, and clearance of plasma proteins that have leaked into the alveolar space. Plasmin plays an important role in this repair process by being involved in cell migration, modulation of inflammatory activity, and breakdown of fibrin and other ECM. This latter function of plasmin may be important for limiting scar formation by dissolving the provisional matrix on which fibroblasts invade and secrete interstitial collagens. The normal alveolar space has net fibrinolytic activity because of the presence of uPA (109, 110). However, during many acute and chronic inflammatory lung disorders, fibrin accumulates in lung tissue (111). The fibrinolytic activity is decreased in BALF from patients with the adult respiratory distress syndrome (109, 110), idiopathic pulmonary fibrosis (112), sarcoidosis (112, 113), and bronchopulmonary dysplasia (114). All of the above diseases have been associated with the development of pulmonary fibrosis.

PAI-1 is the major inhibitor of PAs not only in plasma (10) but also in the alveolar space (110). Elevated levels of PAI-1 have been observed in BAL specimens obtained from patients with adult respiratory distress syndrome and have been shown to reduce the fibrinolytic capacity of the fluid (109, 110). A similar pattern of depressed fibrinolysis can be seen in a variety of animal models of lung injury (115). Bleomycin-induced lung injury is an established murine model of human pulmonary fibrosis. PAI-1–deficient mice were resistant to pulmonary fibrosis after bleomycin-induced lung injury, presumably because of accelerated fibrinolysis (11). On the other hand, PAI-1 transgenic mice suffered a severe lung injury and ECM deposition after bleomycin challenge. Furthermore, the level of PAI-1 gene expression strongly correlates with the amount of collagen deposition in lung tissues, suggesting that the balance of fibrinolytic activity within the lung is an important determinant of the pulmonary response to inflammatory injury.

PAI-1 in Asthma. We demonstrated that PAI-1 promotes ECM deposition in the airways of a murine model of chronic asthma (116). When the mice were challenged with OVA for 4 weeks, PAI-1 production was increased by 4-fold in lung tissue and by 5-fold in BALF of wild-type (WT) mice. Both PAI-1–deficient and WT mice showed similarly increased numbers of peribronchial eosinophils (20-fold) and goblet cells (4-fold) and OVA-specific IgE levels (7-fold) after OVA challenge, compared with saline challenge. When hydroxyproline assay was performed, the levels of collagen deposition were 2-fold less in lung tissue from PAI-1–deficient mice than WT mice after OVA challenge (116).

We also determined whether PAI-1 promotes collagen deposition in the airways of OVA-challenged mice by inhibiting the activity of MMP-9 by measuring MMP-9 activity in lung homogenates and BALF of PAI-1–deficient and WT mice. After OVA challenge, MMP-9 activity was approximately 3-fold higher in lung tissue and BALF from PAI-1–deficient mice than WT mice. This suggests that PAI-1 may promote ECM deposition by inhibiting MMP-9 activity.

We also demonstrated that PAI-1 promotes irreversible fibrin deposition by comparing the amounts of water-insoluble fibrin in PAI-1–deficient and WT mice (116). The amounts of total lung water-insoluble fibrin were minimal in PAI-1–deficient and WT mice after saline challenge. The amounts of water-insoluble fibrin were 4-fold less in lung tissue from PAI-1-deficient mice than in WT mice after OVA challenge. Taken together, these data suggest that PAI-1 may promote ECM deposition by inhibiting fibrinolysis and MMP-9 activity.

With regard to human asthma, we recently reported increased expression of PAI-1 in lung MCs from fatal asthmatics by double immunofluorescence colocalization (70). We then demonstrated that the 4G allele is preferentially

Table 2. Transmission Disequilibrium Test for the 4G and 5G Alleles in Asthma and Atopy

	Transmitted	Not transmitted	χ^2	*P* value
Asthma				
4G	44	23	6.6	0.0139
5G	23	44		
Atopy				
4G	28	20	1.3	0.3123
5G	20	28		

transmitted to asthmatic children (Table 2). Later Buckova *et al.* (15) also demonstrated that the 4G allele is associated with asthma. These data suggest that elevated PAI-1 levels in the lung may be associated with the development of asthma.

Conclusion

PAI-1 is the main inhibitor of the fibrinolytic system and is known to play an essential role in tissue remodeling. Recent evidence indicates that chronic asthma may lead to tissue remodeling. We demonstrated that MCs are a major source of PAI-1, and a large number of MCs expressing PAI-1 are infiltrated in the airways of patient with fatal asthma. Furthermore, PAI-1–deficient mice show reduced ECM deposition in the airways of a murine model of chronic asthma by enhancing MMP-9 activity and fibrinolysis. Genotyping studies suggested that elevated PAI-1 levels in the lung may contribute to the development of asthma. In summary, PAI-1 may play an important role in the pathogenesis of asthma and further studies evaluating the mechanisms of PAI-1 action in asthma may lead to the development of a novel therapeutic target for the treatment and prevention of asthma.

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