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Past, Present, and Future Perspectives of Plasminogen Activator Inhibitor 1 (PAI-1)

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Abstract

Plasminogen activator inhibitor 1 (PAI-1), a SERPIN inhibitor, is primarily known for its regulation of fibrinolysis. However, it is now known that this inhibitor functions and contributes to many (patho)physiological processes including inflammation, wound healing, cell adhesion, and tumor progression. This review discusses the past, present, and future roles of PAI-1, with a particular focus on the discovery of this inhibitor in the 1970s and subsequent characterization in health and disease. Throughout the past few decades diverse functions of this serpin have unraveled and it is now considered an important player in many disease processes. PAI-1 is expressed by numerous cell types, including megakaryocytes and platelets, adipocytes, endothelial cells, hepatocytes, and smooth muscle cells. In the circulation PAI-1 exists in two pools, within plasma itself and in platelet α-granules. Platelet PAI-1 is secreted following activation with retention of the inhibitor on the activated platelet membrane. Furthermore, these anucleate cells contain PAI-1 messenger ribonucleic acid to allow de novo synthesis. Outside of the traditional role of PAI-1 in fibrinolysis, this serpin has also been identified to play important roles in metabolic syndrome, obesity, diabetes, and most recently, acute respiratory distress syndrome, including coronavirus disease 2019 disease. This review highlights the complexity of PAI-1 and the requirement to ascertain a better understanding on how this complexserpin functions in (patho)physiological processes.

Keywords

PAI-1; Thrombosis; ARDS; Obesity; Metabolic syndrome

Plasminogen activator inhibitor 1 (PAI-1) belongs to the serine protease family (SERPIN), originally recognized for its role in regulating the fibrinolytic system. However, it is now known to play important roles in many other (patho) physiological processes including inflammation, wound healing, cell adhesion, and tumor progression. PAI-1 regulates the fibrinolytic system via inhibition of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) thereby attenuating plasminogen activation and subsequent fibrin degradation.

The crucial role for PAI-1 in hemostasis is underscored by the fact that a homozygous deficiency in this serpin gives rise to a mild-moderate bleeding diathesis.[1] Conversely, increased levels of PAI-1 are associated with thrombotic complications.[2–6] A strong relationship between PAI-1 obesity, diabetes, and metabolic syndrome has identified a key role for this serpin in these pathophysiological processes.[7] This review will focus on the discovery of PAI-1 and its emerging recognition as a potential biomarker and predictor of thrombosis and acute respiratory distress syndrome (ARDS).

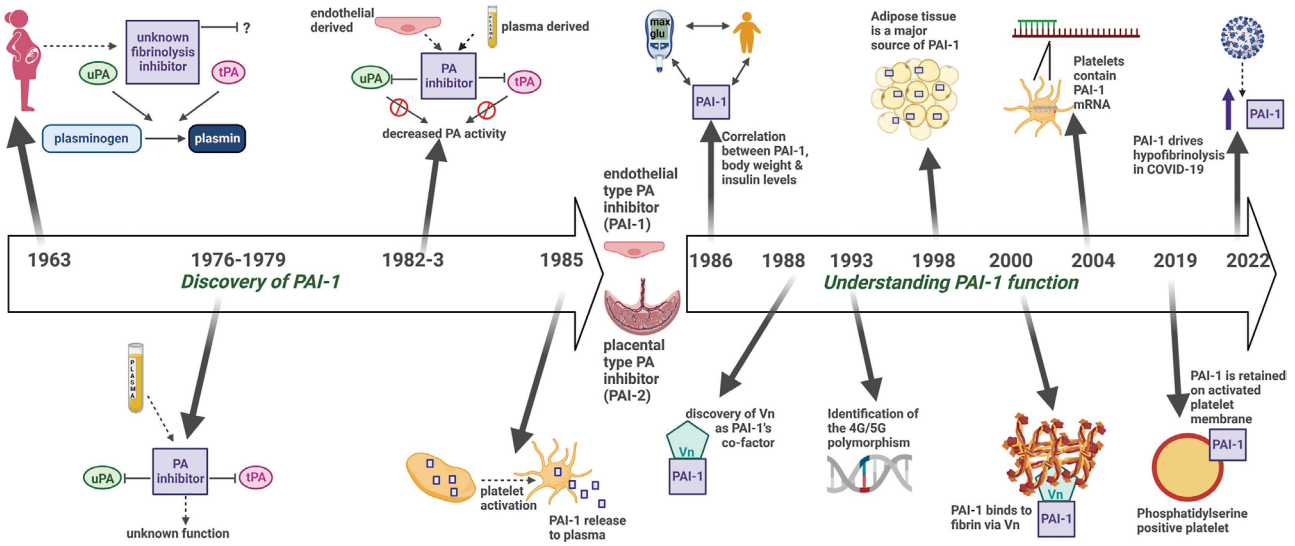

Fig. 1 Timeline of plasminogen activator inhibitor 1 (PAI-1) discovery. Briefly, a fibrinolysis inhibitor not directed to plasmin was first identified in 1963 in pregnant women. Reports of a specific plasminogen activator (PA) inhibitor followed, but its function and origin remained elusive. In 1982 a plasma-derived PA inhibitor and in 1983 an endothelial-derived PA inhibitor were found to decrease PA activity. In 1985, the nomenclature was updated and endothelial type PA inhibitor became PAI-1, and the placental type PA inhibitor, PAI-2. In the same year, the main source of plasma PAI-1 was identified within platelets and found to be released upon platelet activation. In 1986, a correlation between plasma PAI-1 levels, body weight, and insulin levels was revealed. A few years later (1988) vitronectin (Vn) was identified to stabilize PAI-1 in its active form and became known as PAI-1's cofactor. In 1993, a 4G/5G polymorphism in the PAI-1 gene was discovered that influenced PAI-1 plasma levels. Five years later (1998), adipose tissue was found to be a major source of PAI-1 and in the millennium, it was shown that PAI-1 binds to fibrin via Vn. In 2004, studies revealed that platelets contain PAI-1 messenger ribonucleic acid (mRNA) and in 2019 we showed that PAI-1 is retained on the surface of activated platelets. During the coronavirus disease 2019 (COVID-19) pandemic, PAI-1 was identified as a key driver of the hypofibrinolytic state observed in patients with severe COVID-19.

Discovery

Reports of a specific plasminogen activator (PA) inhibitor were first reported in 1963, when Brakman and Astrup identified a fibrinolytic inhibitor in pregnant women that did not directly inhibit plasmin but instead seemed specific for urokinase[8] (Fig. 1). Additional reports of a specific PA inhibitor present in human plasma followed[9,10]; however, there was uncertainty as to whether specific PA inhibitors had any necessary function,[8] as the abundance of circulating α_2-antiplasmin, the inhibitor of plasmin, was thought to be sufficient for regulation of the fibrinolytic system.[11–13] Kinetic data to support the notion of PA inhibition was lacking and the then current dogma was that activity was regulated by release from the vessel wall, hepatic clearance, specific interactions with fibrin, or proteolytic activation.

The existence and importance of specific PA inhibitors in plasma was revealed in 1982 when it was found that addition of tPA to plasma significantly attenuated its functional activity[14,15] (Fig. 1). Subsequently, synthesis of a highly stable PA inhibitor of M_r 55,000 was described to be released from bovine aortic endothelial cells.[16] In 1985, our mentors and predecessors at the University of Aberdeen, Professors' Booth and Bennett, identified a PA inhibitor housed within platelets that was present in negligible amounts in platelet-free plasma.[17] This inhibitor was secreted following platelet activation and formed a 1:1 complex with tPA.[17]

These observations collectively led to the classification of PA inhibitors by the Subcommittee on Fibrinolysis at the International Committee on Thrombosis and Haemostasis in Jerusalem, Israel in 1985.[18] They initially identified three groups: the endothelial type PA inhibitor, the placental type PA inhibitor, and protease nexin.[18] The ensuing advancement in laboratory techniques permitted differentiation between PA and plasmin inhibitors, purification of PAI-1,[19] development of specific antisera to PAI-1, and cloning of PAI-1 deoxyribonucleic acid.[20,21] This allowed demonstration that this serpin was the principal physiological inhibitor of tPA and uPA that is capable of inhibiting cell-associated proteolysis as well as intravascular fibrinolysis.[22]

Mechanism of Action

Like other members of the SERPIN superfamily, PAI-1 inhibits its target serine proteases, tPA and uPA, by mimicking the substrate of the target protease on the exposed reactive center loop (RCL) to which the enzyme binds forming a reversible Michaelis–Menten complex.[23–25] The RCL is cleaved by PA, allowing PAI-1 to "trap" its substrate in a stable covalent acyl-enzyme complex.[26] Cleavage is coupled with rapid insertion of the RCL into the PAI-1 β-sheet A,[27] translocating the PA to the opposite side of PAI-1 molecule, thereby resulting in distortion and inactivation.[28,29] PAI-1 is a more potent inhibitor of tPA than uPA, as demonstrated by their second-order rate constants which differ by an order of magnitude (12.6×10^7 $M^{-1}s^{-1}$ vs. 4.8×10^6 $M^{-1}s^{-1}$).[30] These differences arise due to an increased contact area between tPA and PAI-1.[23,31]

Circulating PAI-1 exists largely in complex with tPA.[32] The complex is cleared from the circulation by the low-density lipoprotein receptor family leading to endocytosis and deg- radation.[33] In an uncomplexed state PAI-1 can exist in either an active or latent state.[34–36] The latent form of PAI-1 occurs due to spontaneous insertion of its RCL in to the central body of the PAI-1 molecule, producing an additional strand of β- sheet A.[35] The active form of PAI-1 is very unstable, with a short half-life of < 10 minutes, before it is rapidly converted to its inactive, latent form.[34,37] PAI-1 is stabilized in its active form by binding to its cofactor, the adhesive glycoprotein vitronectin (Vn),[38–40] which delays conversion of PAI-1 to its latent conformation and endows capacity to bind to fibrin.

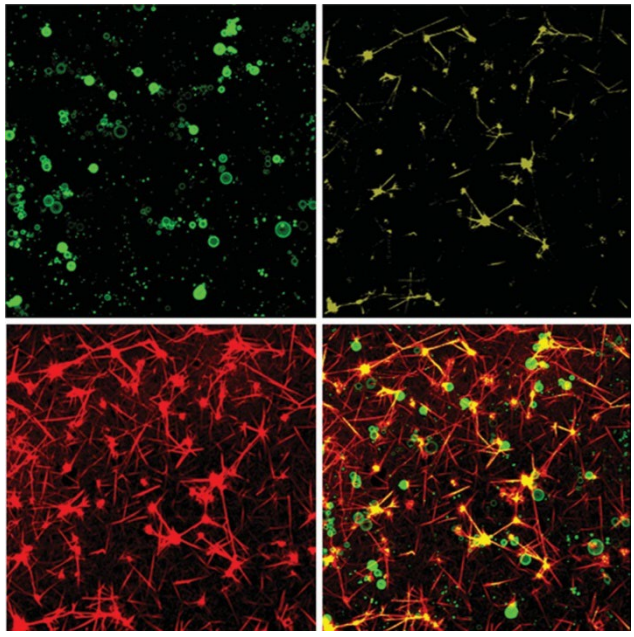

Fig. 2 Plasminogen activator inhibitor 1 (PAI-1) is secreted from activated platelets and colocalizes on platelet-associated fibrin fibers to stabilize the thrombus from premature degradation. Platelet-rich plasma (PRP) clots (30%) were formed in the presence of annexin V-fluorescein isothiocyanate (FITC) to label platelets (green), a DyLight 550 fluorescently labeled antibody to PAI-1 (yellow) and Alexa Fluor 647 labeled fibrin(ogen) (red). Clotting was initiated with 0.125 U/mL thrombin and clots were formed at 37°C for 2 hours. Clots were imaged using a Zeiss LSM710 confocal microscope.
Scale bar represents 10 μm. Figures from Morrow et al, 2019.[148]

Source of PAI-1

Plasma PAI-1 is present at a low concentration of 5 to 20 ng/mL[41] (0.4 nM[41]) and is an important determinant of fibrinolytic potential in plasma.[42] It is cleared by the liver with a half-life of approximately 5 minutes indicating a high basal rate of synthesis. The major circulating pool of PAI-1, accounting for approximately 90%, is located within platelet α-granules.[36,43,44] Our work has shown that following de-granulation of platelets a proportion of the inhibitor remains associated with the activated platelet membrane and is associated with platelet-bound fibrin, as well as forming part of the secretome (Fig. 2).[45] PAI-1 is known

to be synthesized and packaged into α-granules within megakaryocytes, the precursor cells that produce and release plate- lets into the circulation.[46]

However, other studies indicate de novo synthesis of functional PAI-1 within platelets,[47–49] from translationally active messenger ribonucleic acid (mRNA).[47] The synthesis of PAI-1 increased when platelets were activated with thrombin, suggesting that de novo PAI-1 synthesis could be a mechanism for platelets to contribute to thrombus stabilization.[47] Other cell types, including hepatocytes, adipocytes, endothelial, and smooth muscle cells, also produce PAI-1.[36,50–52] Circulating PAI-1 levels are under genetic control that is directly related to an insertion/deletion (5G/ 4G) polymorphism at position –675 of the promoter.[53] The 4G/5G polymorphism in PAI-1 differs according to the ethnic group and has a direct impact on circulating levels of the serpin, with the 4G allele giving rise to elevated plasma PAI-1.[54–58] Furthermore, levels of PAI-1 vary according to gender and show a positive correlation with increasing age.[59] The cellular origin of plasma PAI-1 remains unknown,[60] as the forms of PAI-1 secreted by various cells do not differ structurally or via glycosylation. Studies have suggested that the liver may be the primary plasma source of PAI-1, as PAI-1 gene expression is upregulated by endotoxins and several inflammatory mediators, namely, tumor necrosis factor al- pha (TNF-α) and transforming growth factor beta (TGF-β).[61–63] PAI-1 is highly expressed in the vasculature, within endothelial cells and smooth muscle cells[64,65] and while the contribution of these cells to the circulating pool is unclear, its synthesis is clearly driven by cytokine regulation.[66] PAI-1 is also synthesized by adipocytes with increased expression in adipose tissue derived from obese humans and mice.[67] Several human ex vivo studies have shown that PAI-1 repleased from visceral adipose tissues contribute to plasma PAI-1 levels.[43,68,69] However, the relationship is complex, as an increase in adipocyte PAI-1 mRNA does not always translate to an increase in the plasma concentration. For example, PAI-1 gene expression in subcutaneous adipose tissue was increased in obese patients on a low-calorie diet, while plasma PAI-1 levels decreased.[70]

PAI-1 as a Risk Factor for Thrombosis

Inhibition of fibrinolysis by PAI-1 promotes a prothrombotic state by reducing fibrin degradation. PAI-1 is a key protein in the progression of vascular events and is linked to both arterial (myocardial infarction [MI],[2,3,5] stroke[4]) and venous thrombosis (deep vein thrombosis [DVT][6] and microvascular thrombosis[71]). Plasma PAI-1 concentration has been shown to increase prior to MI[5] with levels persistently elevated in survivors.[2] Additionally, plasma PAI-1 levels are associated with heart failure, death, and a strong independent predictor of mortality at 30 days in patients with acute ST-elevated MI (STEMI).[72] Hypofibrinolysis has recently been recognized as a risk factor for patients with STEMI and our recent work has shown that shear-induced platelet reactivity was associated with an increased rate of thrombin generation and is correlated with reduced endogenous fibrinolysis.[73] As platelets harbor high concentrations of PAI-1, it is hypothesized that platelet-derived PAI-1 is driving hypofibrinolysis in STEMI patients. Following acute MI, the renin-angiotensin II system (RAS) is strongly activated, triggering PAI-1 synthesis via angiotensin II.[74] PAI-1 displays circadian rhythm with a peak in early morning, that coincides with the time of onset of MI.[75] Both the clock system and RAS have been linked to circadian variation of PAI-1 with the angiotensin type 1 receptor linked to tissue-specific circadian oscillations in this inhibitor. To this degree it has been suggested that angiotensin-converting enzyme inhibitors targeted to the RAS system may decrease PAI-1 levels and reduce the risk of "early morning" MI.[76]

Increased serum levels of PAI-1 are evident in patients with atherosclerotic disease, including coronary artery disease[77] and stroke.[78] Dysregulation of the fibrinolytic system in atherosclerotic plaque development has been attributed to reduced vascular smooth muscle cell migration, via inhibition of Vn binding to the integrin $\alpha v\beta_3$.[79] A large meta-analysis has indicated that PAI-1 is implicated in the pathogenesis of atherosclerotic disease[80] with elevated levels of PAI-1 detected within atherosclerotic plaques.[81–83] Schneiderman et al found significantly elevated levels of PAI-1 mRNA in severely dis- eased arteries in patients undergoing aortic occlusion surgery compared to normal vessles.[81] Further analysis revealed that PAI-1 mRNAwas abundant in the base of the plaque, within the intima of the atherosclerotic arteries, and in cells contained within the necrotic core and in endothelial cells of the adventitial vessels.[81] PAI-1 may also contribute to the developing atherosclerotic plaque by exerting a stabilizing effect on the surrounding fibrin matrix and allowing fibrin to act as a scaffold for migrating cells.[84]

A higher incidence of DVT[85] and venous thrombosis[86] has been noted in Asian Indian patients harboring the 4G poly-morphism.[85,86] Similar studies in white Caucasian populations have described association of the 4G polymorphism with idiopathic DVT and inherited thrombophilia.[87] Generally, perioperative DVT has been linked to increased levels of circulating PAI-1[6] and interestingly preoperative plasma PAI- 1 levels have been identified as an independent risk factor for the onset of DVT in patients undergoing total hip arthroplasty.[88] Furthermore, elevated levels of plasma PAI-1 were identified as an independent risk factor for venous thrombosis in a study comparing the clot lysis times of 770 thrombosis with 743 healthy controls.[89]

PAI-1 as a Biomarker for Obesity, Diabetes, and Metabolic Syndrome

Plasma PAI-1 is associated with obesity and significantly correlates with a variety of adiposity measures, including body mass index (BMI), waist-to-hip ratio, total fat mass, and visceral and subcutaneous adipose tissue.[90–92] The Insulin Resistance Atherosclerosis Study was the first to report that PAI-1 antigen and activity positively correlate with BMI (r ¼ 0.314/0.425, respectively).[93]

Adipocytes from obese humans harbor twice as much PAI-1 mRNA resulting in an approximate sixfold increase in secretion of PAI-1 and plasma PAI-1 activity compared to lean individuals.[54] Weight loss in obese subjects reduces plasma PAI-,[91,94,95] indicating that circulating levels are directly related to the degree of adipose tissue. In line with this, pharmacological inhibition of plasma PAI-1 in animal models results in weight loss, as well as a reduction in adipose tissue and adipocyte volume.[62,67,96,97]

Metabolic syndrome encompasses several conditions that considerably elevate the risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (T2DM). Diagnosis of metabolic syndrome includes at least three of the following criteria[98,99]: abdominal obesity, dyslipidemia, hypertension, hyperglycemia, or insulin resistance. A correlation between metabolic syndrome and PAI-1 levels was established in the late 1980s.[100] Elevated levels of PAI-1 in individuals with metabolic syndrome has been demonstrated using criteria defined by both the World Health Organisation[101] and the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults.[102] Elevated levels of PAI-1 in humans predicted the incidence of metabolic syndrome in two prospective studies.[103,104] It is well established that PAI-1 correlates with risk of CVD[105] and onset of T2DM.[106] Together, these data have led to the interpretation that PAI-1 is a true component of metabolic syndrome[107] and could be an important clinical criterion for development of future CVD.[108]

There is accumulating evidence implicating PAI-1 in the development of hypertension,[109] and plasma PAI-1 is associated with several risk factors for hypertension, including obesity,[110,111] insulin resistance,[111,112] and inflammation.[113] Studies reveal a direct correlation between plasma PAI-1 and hypertension as well as its associated conditions,[114–120] namely, arterial stiffness[121] and atherosclerosis.[122] Interestingly, the 4G allele for PAI-1 is associated with increased systolic, diastolic, and mean arterial blood pressure,[123] disclosing a direct link between plasma PAI-1 and blood pressure. Despite plasma PAI-1 correctly predicting the risk of hypertension in human studies, it did not provide a significant advantage over conventional risk factors, such as fasting glucose, alcohol consumption, BMI, cigarette smoking, or C-reactive protein (CRP).[124]

PAI-1 as a Biomarker for Respiratory Disease

ARDS develops due to the increased alveolar-capillary permeability associated with the secretion of a fluid rich in cells and plasma proteins that results in the recruitment of inflammatory leukocytes and platelets which elevate the local inflammatory response.[125,126] Elevated PAI-1 has previously been associated with ARDS, including in severe acute respiratory syndrome coronavirus (SARS-CoV) and acute lung injury (ALI).[127,128] In ARDS, CRP promotes local release of PAI-1 from endothelial cells,[129,130] and infiltration of platelets and subsequent activation may result in local release. Attenuation of the plasminogen activation system leads to abnormal turnover of fibrin in the alveolar space. In ALI, a significant increase in PAI-1 antigen and activity levels in plasma and edema fluid have been reported, with plasma PAI-1 identified as an independent risk factor for poor prognosis and mortality.[129–135] One study concluded that PAI-1 levels > 640 ng/mL in edema were a 100% positive predictor of mortality.[129]

Thrombosis, both venous and arterial, is associated with severe coronavirus disease 2019 (COVID-19).[136–140] Large vessel thrombi are present in almost half of critically ill COVID-19 patients and microthrombi are

observed in more than 80% of cases.[141] These thrombotic complications are observed despite prophylactic and full-dose anticoagulation.[139] Importantly, a hypofibrinolytic state and elevated PAI-1 was previously observed in the SARS-CoV epidemic in 2002 and 2003.[127] Studies have shown that fibrin persistence was mediated by overexpression of PAI-1 which inhibits local uPA and tPA.[127] SARS-CoV infected cells contain high levels of TGF-β1, which in turn stimulates expression of extracellular matrix protease inhibitors, including PAI-1.[142] Our recent work has shown that a hypofibrinolytic state driven by elevated PAI-1 is also present in COVID-19.[143]

Several studies align with observations of increased PAI-1 in COVID-19, which is associated with platelet activation, thereby exacerbating the hypercoagulable and hypofibrinolytic state in severely ill patients.[143–145] An increase in Vn, the stabilizing cofactor of PAI-1, and its substrate, tPA, have also been observed.[143–145] Interestingly, inflammatory cytokines, including interleukin 6 (IL-6), IL-8, TGF-β, and TNF-α, were significantly increased and strongly correlated with PAI-1 antigen and activity levels in COVID-19 patients.[143,146] The source of plasma PAI-1 in COVID-19 is currently unknown but it has been suggested to correlate with obesity in severely ill patients.[147]

These studies illustrate a clear role for PAI-1 in the etiology of ARDS and suggest this inhibitor is a key driver in the abnormal turnover of fibrin in the alveolar space.

Conclusion and Perspectives

Since the early discovery of an alternative fibrinolytic inhibitor in the 1960s[8] and subsequent elucidation of PAI-1 synthesis, secretion, and function in the 1980s,[14,15,17] the understanding of this complex serpin has significantly evolved. It is now evident that PAI-1 harbors many additional functions, peripheral to its role in fibrinolysis, of which our understanding is still in its infancy. The source of plasma PAI-1 remains an enigma, as are the effector molecules and inflammatory stimulus that may influence the source and the pathophysiological function of this serpin. A large number of factors are proposed to interact and modify PAI-1 function, including, Vn, fibrin, and heparin. Further study of these interactions will develop a better understanding of their importance and how they alter the pathophysiology of thrombosis, ARDS, and metabolic syndrome and its associated pathologies, in which PAI-1 is now understood to play a crucial role.

Authors′ Contributions

G.B.M. researched, wrote, and edited the manuscript. N.J.
M. conceived the idea and wrote/edited the manuscript.

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Conflict of Interest

G.B.M. and N.J.M. have no relevant conflict of interest to declare in relation to the material discussed in this manuscript. N.J.M. reports personal fees from STAGO, grants and personal fees from LFB, grants from Alveron, from null, outside the submitted work.

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