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The plasminogen activator inhibitor-1 paradox in cancer: a mechanistic understanding

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Abstract
The paradoxical pro-tumorigenic function of plasminogen activator inhibitor 1 (PAI-1, aka Serpin E1) in cancer progression and metastasis has been the subject of an abundant scientific literature that has pointed to a pro-angiogenic role, a growth and migration stimulatory function, and an anti-apoptotic activity, all directed toward promoting tumor growth, cancer cell survival, and metastasis. With uPA, PAI-1 is among the most reliable biomarkers and prognosticators in many cancer types. More recently, a novel pro-tumorigenic function of PAI-1 in cancer-related inflammation has been demonstrated. These multifaceted activities of PAI-1 in cancer progression are explained by the complex structure of PAI-1 and its multiple functions that go beyond its anti-fibrinolytic and anti-plasminogen activation activities. However, despite the multiple evidences supporting a pro-tumorigenic role of PAI-1 in cancer, and the development of several inhibitors, targeting PAI-1, has remained elusive. In this article, the various mechanisms responsible for the pro-tumorigenic functions of PAI-1 are reviewed with emphasis on its more recently described contribution to cancer inflammation. The challenges of targeting PAI-1 in cancer therapy are then discussed.

Keywords Plasminogen activator inhibitor 1 · PAI-1 · Protease inhibitor · SerpinE1 · Tumor microenvironment · Inflammation

1 Introduction: the PAI-1 paradox

The seminal observation made by Riech's laboratory in 1973 that urokinase plasminogen activator (uPA) was the most robustly induced enzymatic activity in Rous Sarcoma Virus-transformed chicken cells [1] brought significant attention to the potential pro-tumorigenic role of plasminogen activation in cancer. Its importance was further underlined when multiple clinical studies revealed that cancer patients whose tumors have a high content of uPA and its receptor uPAR have worse clinical outcomes [2–4].

It was thus expected that because of its primary inhibitory activity on uPA, plasminogen activator inhibitor 1 (PAI-1), a member of the serine protease inhibitor (Serpin) family, would have an anti-tumor effect, and it came as a surprise when these same studies and others reported high levels of PAI-1 in tumors that were associated with a poor rather than a favorable clinical outcome and that were less responsive to chemotherapy [5–11].

2 Complex and dynamic structure of PAI-1

Central to discovering the mechanisms supporting the pro-tumorigenic role of PAI-1 is the understanding of its complex and dynamic structure that explains its pleiotropic biological function (Fig. 1). PAI-1 is a 45 kDa single-chain glycoprotein of 379–381 residues with 9 α helices and 3 β sheets [12]. A unique structural aspect of PAI-1 and other members of the Serpin family is the presence of a 26 (Ser 343-Arg 368) amino acid reactive center loop (RCL) in the C-terminal region of the molecule that contains a proteolytic cleavage (P1-P1′, Arg 346-Met 347) for uPA. Depending on the state of the RCL, PAI-1 exists in three forms. An active form that has the RCL in an helical configuration exposed at the surface of the molecule, a latent form unable to interact with uPA with the intact RCL as a strand internalized (analogy to the blade of a jack-knife) in the β-sheet A, and a cleaved form where the P1′ Met residue of the RCL is exposed and the N-terminal portion of

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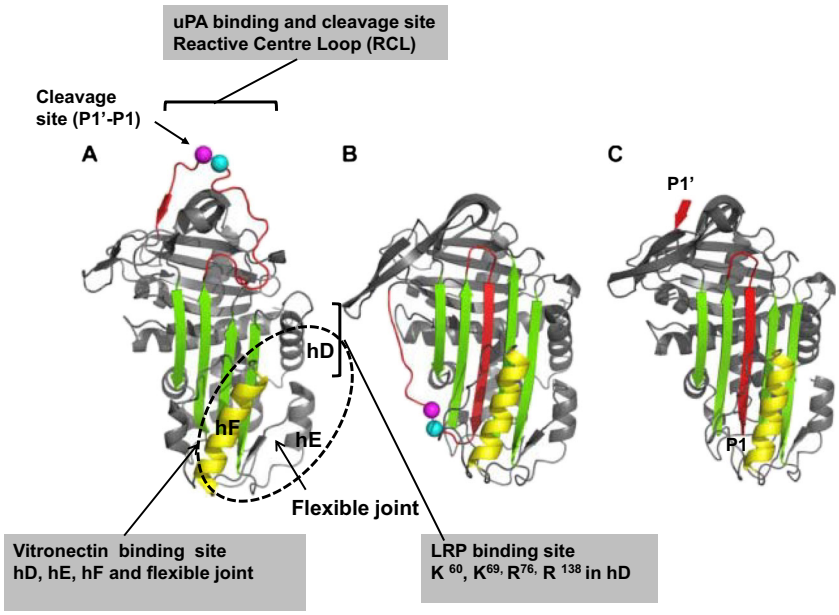

Fig. 1 Structure and function of PAI-1. The reactive center loop (RCL) binds to uPA and blocks uPA-generated plasmin. It is "internalized" as an additional strand (s4A in red) in the β-sheet A (in purple) upon latency and cleaved at P1-P1′ by uPA. In blue, βsheet B whose position is modified upon latency. The helix D (hD) contains basic aa, which are involved in binding to LRP1. The region containing helices hD, hE, and hF (flexible joint) binds to the somatomedin B (SMB) domain in the N-terminal domain of vitronectin, preventing interaction with integrin. Adapted from [12]

the RCL containing the P1 residue remains inside the β sheet A.

Three domains binding to distinct proteins have been identified in PAI-1. The uPA binding domain is located in the RCL and binding of uPA to the RCL triggers its cleavage at the P1-P1′ site, followed by the internalization of the N-terminal portion of the RCL containing the P1 site and uPA being translocated to the opposite pole of the molecule [13]. A second domain located in a flexible joint region between helix hD and hF spanning from residue 13 to 147, binds to the somatomedin B domain of vitronectin [14, 15]. Binding of PAI-1 to the somatomedin B domain of vitronectin stabilizes PAI-1, delaying its internalization in a latent form and increasing its anti-uPA ability. The binding of PAI-1 to vitronectin also masks the adjacent RGD binding site for αv integrins and inhibits cell adhesion to vitronectin [16, 17]. A third domain located in the N-terminal helix hD with a critical Lys 69 residue binds PAI-1 alone or complexed with uPA and tissue (t)PA to the endocytosis lipoprotein receptor proteins (LRP)-1 and (LRP)-2. Binding of PAI-1 to uPA at the cell surface *via* the attachment of uPA to its receptor (uPAR) triggers an interaction with LRP1 which leads to the intracellular internalization of the entire complex [18, 19]. A: Active PAI-1. B; Latent PAI-1. C; Cleaved PAI-1. Adapted from [20].

3 PAI-1 as a biomarker guiding cancer therapy

Numerous studies published in the late 1990s and early 2000s reported that PAI-1 is overexpressed by most human cancer cell lines—in particular, those derived from solid tumors—and in most human neoplasms. Its expression positively correlates with poor clinical outcome in patients with breast, ovarian, bladder, colon, and non-small cell lung cancers [8, 21–28].

As a result of these observations, the prognostic value of the tissue levels of uPA and PAI-1 was tested in a large multinational (European Organisation for Research and Treatment of Cancer [EORTC], American Society of Clinical Oncology [ASCO], and Arbeitsgemeinschaft Gynäkologische Onkologie [AGO]) prospective clinical trial in 8377 patients with breast cancer without node involvement. This study, in which patients with high tumor tissue levels of uPA and/or PAI-1 determined by ELISA were randomized to 6 courses of chemotherapy or to observation, not only validated the long-term prognostic impact of uPA/PAI-1 levels but also demonstrated the benefit from adjuvant chemotherapy in the high-uPA/PAI-1 group [24].

4 PAI-1 polymorphism and cancer prediction

The PAI-1 (SERPINE1) gene is located on chromosome 7 (7q21.3-q22) and a polymorphism in the promoter of the gene has been described at position −675. This polymorphism known as 4G consists of deletion of a guanosine nucleotide. The 4G/4G homozygous polymorphism has a stronger binding for transcription factors whereas the 5G polymorphism allows the binding of repressor elements. As a result, higher levels of PAI-1 and a slight increase in deep venous thrombosis are observed in individuals with the 4G genotype [29]. These discoveries led to a series of clinical studies examining whether the 4G/5G polymorphism in patients with cancer could predict a more severe outcome in association with higher levels of PAI-1. Whereas several studies in breast, hepatocellular carcinoma, testicular, endometrial, and oral

cancer indicated a correlation between 4G/5G polymorphism, higher levels of PAI-1, and overall poor clinical outcome [30–35], other studies in breast, renal cell, prostate, and colorectal cancers have failed to show such correlation [31, 36–40]. A meta-analysis of 10 publications on 4G/5G polymorphism in breast cancer revealed a 39% increase in the incidence of breast cancer in populations with the 4G/4G homozygous phenotype. The study also revealed an association between the 5G/5G genotype and the presence of lymph node metastasis. No differences between genotype and histological grade and overall survival were identified [41]. The issue of the role of PAI-1 gene polymorphism in cancer is thus not entirely clear.

5 PAI-1 and the hallmarks of cancer

Using the text mining Cancer Hallmark Analytical Tool (http://chat.lionproject.net) [42], 3739 articles and abstracts with PAI-1 were assigned to one of the 10 Hallmarks of Cancer [43] with a pre-eminent role in five hallmarks, sustaining proliferative signals, resisting cell death, angiogenesis, invasion and metastasis, and tumor-promoting inflammation (Fig. 2). We discuss here the role of PAI-1 in these five hallmarks with an emphasis on the PAI-1 interactive domain involved and the mechanisms identified (Table 1).

6 Role of PAI-1 in sustaining proliferative signals

Some studies have shown that PAI-1 has a growth stimulatory activity leading to G1-phase to S phase cell-cycle progression through cyclin D3/cdk4/6 upregulation in cancer cells [44]. However, other studies in human breast cancer cell lines have indicated an inhibitory function of PAI-1 on anchorage-dependent and independent proliferation [77]. Whether PAI-1 directly affects tumor cell cycle remains controversial as long as no precise molecular mechanism is identified.

PAI-1 also has an indirect modulatory effect on cancer cell growth *via* its anti-fibrinolytic activity and modulatory activity on cell adhesion and uPA/uPAR activity. By inhibiting fibrinolysis, PAI-1 maintains the activity of thrombin which interacts with protease-activated receptors (PAR) in tumor cells and enhances proliferation *via* PAR activation [48]. Thrombin interacting with PAR also transcriptionally upregulates PAI-1 [49]. By promoting detachment from vitronectin and adhesion to fibronectin, PAI-1 stimulates fibronectin-dependent cell growth [45] and by downregulating uPA/uPAR interaction with EGFR, PAI-1 inhibits EGF-dependent cell growth [50]. Studies have also shown that PAI-1 plays a role in senescence [46]. PAI-1, a target of p53 and TGF-β, is upregulated in aging fibroblasts and inhibits the release and bioavailability of many growth factors. Suppression of PAI-1 in aging fibroblasts stimulates proliferation and allows them to bypass senescence. PAI-1 may also stimulate dormancy through uPAR and uPA inhibition. In breast, prostate, melanoma, and fibrosarcoma cell lines, the ERK/p38 activity ratio determines whether *in vivo* cells will proliferate or go into dormancy. A high ERK/p38 ratio favors tumor growth, whereas a low ERK/p38 ratio induces dormancy. The ERK/p38 ratio is affected by pericellular uPA activity. A high-uPA and uPAR activity stimulates α5β1-integrin and activates ERK1/2 resulting in a high ERK/p38 ratio. By contrast, the inhibition of uPA/uPAR activity by PAI-1 reverses the ratio inhibiting growth and promoting cell dormancy [47]. PAI-1 is therefore more a modulator of cancer cell proliferation, having complex activities involving multiple interactions with uPA, uPAR, integrins, extracellular matrix (ECM) proteins that have indirect effects on the signaling activity of thrombin, growth factor receptors, and integrins.

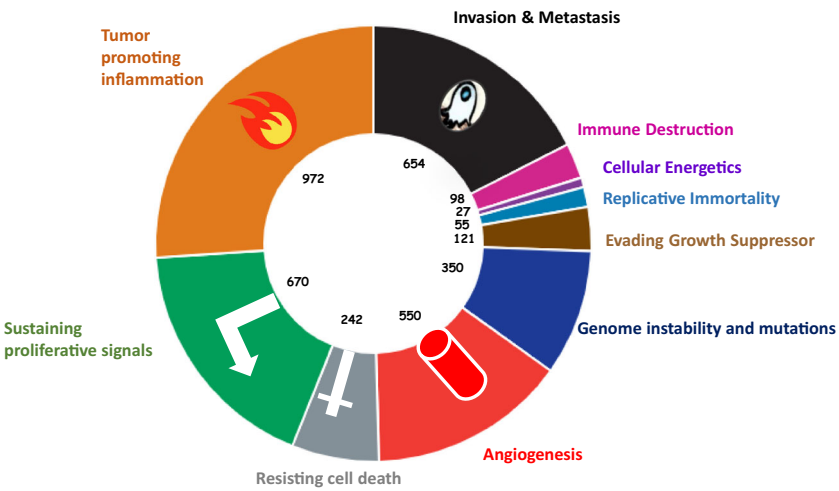

Fig. 2 Role of PAI-1 in cancer progression. The doughnut diagram represents the proportion of publications assigned to each indicated hallmark and was obtained using the Cancer Hallmarks Analytics Tool [42] (http://chat.lionproject.net/). The numbers inside the doughnut represent the number of publications

Table 1 Multifaceted activities of PAI-1 in human cancer

Hallmark	Effect	PAI-1 domain	Mechanism
Sustaining proliferative signals	Increases transition from G0/G1 to S phase	Unknown	Upregulation of cyclin E and cyclin E complexes with CDK with decrease in p53, p21, and p27 [44]
	Modulates cell adhesion	Vitronectin binding	Increases adhesion/proliferation to fibronectin [45]
	Promotes senescence and dormancy	uPA binding (RCL)	Altering ERK/p38 ratio *via* inhibition of uPA/uPAR [46, 47]
	Inhibition of fibrinolysis	uPA binding (RCL)	Increase in PAR stimulation by thrombin; PAR activation upregulates PAI-1 [48, 49]
	Inhibits EGFR signaling	uPA/uPAR/PAI-1 complex	Inhibits uPA/uPAR interaction with EGFR [50]
Resisting cell death	Decreases intrinsic apoptosis	uPA binding (RCL)	Intracellular inhibition of caspase 3 [51]
	Induces anoikis	Vitronectin binding domain	Inhibition of cell adhesion to vitronectin, increases cell migration and adhesion to fibronectin (double edge) [52]
	Decreases apoptosis	uPA binding (RCL)	Decrease in FasL cleavage and shedding by plasmin, inhibition of FasL-mediated apoptosis in tumor cells [53, 54]
	Protects from apoptosis	LRP-1 binding	Stimulates c-Jun/ERK and increases expression of Bcl-2 and Bcl-XL [52]
Angiogenesis	Increases EC survival	uPA binding (RCL)	Decrease in FasL cleavage and shedding by plasmin, inhibition of FasL-mediated apoptosis in EC [55]
	Inhibits EC adhesion to vitronectin	Vitronectin binding domain	Stimulation of EC migration from vitronectin toward fibronectin [56]
	Increases EC organization in fibrin matrix	uPA binding (RCL)	Increase in EC adhesion to fibrin and IL-8 production [57, 58]
Invasion and metastasis	Modulates tumor cell migration	uPA binding and vitronectin binding	Promotes cell detachment from vitronectin and prevents excessive degradation of ECM proteins [59]
	Increases *in vivo* metastasis	Unknown	Not clearly defined [60–67]
	Decreases *in vivo* metastasis	Unknown	Not clearly defined [68–70]
	Inhibition of fibrinolysis	uPA binding (RCL)	Promotes NET [71, 72]
Tumor promoting inflammation	Increases monocyte/macrophage migration	LRP binding	Recruits monocytes to tumor site [73–75]
	Promotes macrophage M2 polarization	uPA binding (RCL)	Activates p38/NFkB/Il-6/STAT3 [76]

7 Role of PAI-1 in resisting tumor cell death

The anti-apoptotic activity of PAI-1 has been extensively described and the mechanisms have been well characterized [78]. By inhibiting cell adhesion to vitronectin, PAI-1 can have a pro- and anti-apoptotic effect. By promoting cell detachment, it stimulates anoikis, but as cells detach from vitronectin and migrate toward other ECM proteins, they can resist apoptosis [52]. As a serpin, PAI-1 inhibits intracellular caspase 3, protecting tumor cells from chemotherapy-induced apoptosis [51]. Extracellular PAI-1 also inhibits the cleavage and shedding of FasL by plasmin at the surface of tumor cells protecting them from FasL-mediated and chemotherapy-induced cell death [53, 54]. By interacting with LRP-1, PAI-1 induces c-Jun/ERK signaling driving an increase in the production of anti-apoptotic proteins like Bcl 2 and Bcl-X_L [52].

8 Role of PAI-1 in angiogenesis

PAI-1 is a stimulator of angiogenesis by promoting migration, survival, and proliferation in endothelial cells (EC). This pro-angiogenic activity stems from its protease-inhibiting and vitronectin-binding functions [55, 79]. As an inhibitor of plasminogen activation, PAI-1 protects EC from FasL-dependent extrinsic apoptosis [55]. Through its ability to bind to the somatomedin B domain of vitronectin, PAI-1 interferes with the binding of EC to vitronectin promoting EC detachment from vitronectin and migration toward a fibronectin-rich but less vascularized tumor stroma [56]. Through its anti-fibrinolytic activity, PAI-1 increases fibrin deposition which promotes EC organization [57] and the release of angiogenic proteins like interleukin (IL)-8 [58].

9 Role of PAI-1 in invasion and metastasis

Many *in vitro* experiments have demonstrated that PAI-1 promotes tumor cell migration. By preventing the adhesion of tumor cells to vitronectin, PAI-1 stimulates their migration toward other ECM substrates like fibronectin [80]. By inhibiting uPAR-bound uPA, PAI-1 also prevents excessive pericellular degradation of ECM proteins necessary for cell adhesion and migration [59]. PAI-1 thus plays a role of the modulator of cell migration by both promoting cell detachment from some ECM proteins like vitronectin and by preventing excessive pericellular ECM degradation. By contrast, *in vivo* studies in metastasis have reported conflicting results, with some experiments suggesting a pro-metastatic effect [60–67] and others either an inhibitory effect [68–70] or an absence of effect [81] on metastasis [82]. The discordance in these data is still not well understood and illustrates the complexity of studies related to metastasis in mice [20]. A major problem in the interpretation of these studies is the fact that they are based on a variety of routes of tumor cell administration (experimental, subcutaneous, and orthotopic implantation), different mouse background (immunocompetent, immunodeficient, or transgenic mice), and different experimental approaches (pharmacological and genetic knock-down, genetic knock-out, overexpression). Whereas some studies use the macroscopic evaluation of metastasis, others have relied on a more precise microscopic detection of micrometastases. The amount of PAI-1 produced and its source (tumor cells vs. host cells) also play a critical role, with host-derived PAI-1 having a more critical role [83]. The discordance among the data reported also needs to take into consideration the differences between human and mouse PAI-1 and their plasminogen activation system [84]. Thus, although clinical and preclinical studies suggest that PAI-1 stimulates the formation of metastasis, in the absence of more mechanistic experiments, the precise contribution of PAI-1 to metastasis remains elusive.

One potential novel mechanism by which PAI-1 could stimulate the extravasation of circulating tumor cells (CTC) at the site of metastasis is *via* neutrophil extracellular traps (NET). These recently described structures made of DNA and proteolytic enzymes formed during infection could support the formation of metastasis [71]. By activating the formation of microthrombi through its anti-fibrinolytic activity, PAI-1 may stimulate the extravasation of CTC to metastatic sites in NET [72].

10 Role of PAI-1 in cancer inflammation

PAI-1 levels are elevated in non-malignant inflammatory conditions such as sepsis, metabolic syndromes (MetS), and arthritis [85–88]. Experimental *in vivo* studies performed in animal models as well as in humans have shown that inflammatory cytokines like tumor necrosis factor-α (TNF-α) and IL-6 stimulate PAI-1 expression [89, 90], corroborating previously reported correlation between PAI-1 expression and inflammation [91]. These observations indicated that PAI-1 is a downstream consequence of inflammation and a contributor to the thrombotic and anti-fibrinolytic syndromes associated with inflammation and cancer as initially observed by Armand Trousseau in 1865 [92]. Adipocytokines like insulin, insulin-like growth factor-1, TNF-α, IL-6 and leptin/adiponectin, and other by-products of MetS such as glucose and cholesterol alter PAI-1 expression, not only in stromal cells but also in cancer cells to potentially favor invasion and metastasis [77]. However, more recent studies suggest that PAI-1 is not only a consequence of but also a contributor to inflammation. PAI-1 increases the production of IL-8 and leukotriene B4 in alveolar epithelial cells and promotes the migration of inflammatory cells [93]. PAI-1 stimulates the recruitment of fibrosis-inducing cells and macrophages [73–75] and the survival of T lymphocytes [94]. The contributory role of PAI-1 in cancer-related inflammation has only recently been explored. Our laboratory has recently demonstrated that through its interaction with LRP-1, tumor-derived PAI-1 promotes the migration of monocytes [76]. PAI-1 also influences the polarization of monocytes/macrophages toward an M2 pro-tumorigenic function through the activation of p38MAPK and NFκB in macrophages and the transcriptional upregulation of IL-6. *Via* an autocrine loop, IL-6 activates signal transduction and activator of transcription (STAT) in monocytes leading toward an increase in the expression of arginase, IL-10, and CD163. Mutational analysis demonstrated that this latter function requires the C-terminal uPA-interacting domain and is independent of the N-terminal LRP-1 binding domain required for the stimulation of monocyte migration [76].

11 Targeting PAI-1

Considering the abundant scientific literature supporting a pro-tumorigenic role of PAI-1 in human cancer, it is surprising that there is still no definitive evidence that inhibition of PAI-1 could have any therapeutic effect in cancer patients. Numerous small molecule and antibody inhibitors of PAI-1 have been developed over the last 10 years [95] and several have been tested in preclinical animal models. Whereas they have shown efficacy in models of acute thrombosis, promoting rapid thrombus re-permeabilization, their activity in models of cancer progression and metastasis is less clear, with the demonstration of an inhibitory effect on tumor growth and metastasis in some cases and an absence of significant effect in other cases [20].

The first group of small inhibitors, SK-116 and SK-216, were shown to cause an almost 2-fold reduction in the number

Table 2 Roles of PAI-1 in cancer

Pro-tumorigenic activity	Established
Biomarkers of poor outcome	Established
Biomarker guiding therapy	Established
Prognostic value of G4/G5 polymorphism	Controversial
Role in carcinogenesis	Controversial
Role in cancer cell proliferation	Not fully understood
Role in dormancy	Suggested
Protective role in apoptosis	Established
Role in angiogenesis	Established
Role in cell migration	Established
Role in metastasis	Controversial
Role in cancer inflammation	Emerging

of small intestinal polyps in Min mice [96] and a 2-fold reduction in the growth of subcutaneous primary B16 melanoma tumors and metastasis in mice [67]. They were also shown to have preclinical activity in malignant pleural mesothelioma [97]. PAI-039, Tiplaxtinin, an indol-oxoacetic acid-based inhibitor extensively tested in acute thrombosis, has been shown to have anti-tumor activity in T47 bladder cancer and HeLa cell tumors in mice [98]. TM 5275 and 554, N-acylanthranilic acid derivatives were found active in some preclinical cancer models but not in others [99, 100]. However, none of these inhibitors have been tested in therapeutic clinical trials in cancer. The effectiveness of PAI-1 inhibitors has been limited by their lack of activity against the stable, vitronectin-bound form of PAI-1, their insufficient pharmacokinetic properties with a half-life of less than 2 h, and high therapeutic concentrations in the μM range [101] and their testing as a single agent. The need for a high therapeutic index is another important consideration since PAI-1 inhibition will require a chronic administration to prevent cancer metastasis or induce dormancy. The use of these inhibitors should be re-evaluated within the context of combination therapies, including immunotherapy, considering their recently identified role on macrophage recruitment and polarization in the TME.

12 Conclusion

More than 30 years have passed since the first reports of the expression of PAI-1 in cancer cells by Kretzmer and Vassali's laboratories [102, 103]. There is now an extensive literature that supports the pro-tumorigenic activity of PAI-1. The role and use of PAI-1 as a biomarker of cancer prognosis and response to therapy are well established. The mechanisms explaining most of the pro-tumorigenic activities of PAI-1 are well understood (Table 2). Targeting PAI-1 in cancer remains challenging, in part because of difficulties in the design of more effective inhibitors against active PAI-1 suitable for chronic administration. Considering the important role of PAI-1 in the TME and in cancer-related inflammation, PAI-1 could have a function in immune escape and targeting PAI-1 in combination with immunotherapy should be an important aspect to investigate.

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References

1. Unkeless, J. C., Tobia, A., Ossowski, L., Quigley, J. P., Rifkin, D. B., & Reich, E. (1973). Enzymatic function associated with transformation of fibroblasts by oncogenic viruses. 1. Chick-embryo fibroblast cultures transformed by avian rna tumor-viruses. Journal of Experimental Medicine, 137(1), 85–111.
2. Duffy, M. J., Reilly, D., McDermott, E., O'Higgins, N., Fennelly, J. J., & Andreasen, P. A. (1994). Urokinase plasminogen activator as a prognostic marker in different subgroups of patients with breast cancer. *Cancer, 74*(8), 2276–2280. https://doi.org/10.1002/1097-0142(19941015)74:8<2276::aid-cncr2820740811>3.0.co;2-7.
3. Duggan, C., Maguire, T., McDermott, E., OHiggins, N., Fennelly, J. J., & Duffy, M. J. (1995). Urokinase plasminogen activator and urokinase plasminogen activator receptor in breast cancer. *Int.J.Cancer, 61*, 597–600.
4. Grondahl-Hansen, J., Peters, H. A., van Putten, W. L., Look, M. P., Pappot, H., Ronne, E., et al. (1995). Prognostic significance of the receptor for urokinase plasminogen activator in breast cancer. *Clinical Cancer Research, 1*(10), 1079–1087.
5. Annecke, K., Schmitt, M., Euler, U., Zerm, M., Paepke, D., Paepke, S., et al. (2008). uPA and PAI-1 in breast cancer: review of their clinical utility and current validation in the prospective NNBC-3 trial. *Advances in Clinical Chemistry, 45*(45), 31–45.
6. Janicke, F., Prechtl, A., Thomssen, C., Harbeck, N., Meisner, C., Untch, M., Sweep, C. G. J. F., Selbmann, H. K., Graeff, H., & Schmitt, M. (2001). Randomized adjuvant chemotherapy trial in high-risk, lymph node-negative breast cancer patients identified by urokinase-type plasminogen activator and plasminogen activator inhibitor type 1. *Journal of the National Cancer Institute, 93*(12), 913–920.
7. Binder, B. R., & Mihaly, J. (2008). The plasminogen activator inhibitor "paradox" in cancer. *Immunology Letters, 118*(2), 116–124.
8. Schmitt, M., Harbeck, N., Brunner, N., Janicke, F., Meisner, C., Muhlenweg, B., et al. (2011). Cancer therapy trials employing level-of-evidence-1 disease forecast cancer biomarkers uPA and its inhibitor PAI-1. *Expert Review of Molecular Diagnostics, 11*(6), 617–634.
9. Kwaan, H. C., Mazar, A. P., & McMahon, B. J. (2013). The apparent uPA/PAI-1 paradox in cancer: more than meets the eye. *Seminars in Thrombosis and Hemostasis, 39*(4), 382–391. https://doi.org/10.1055/s-0033-1338127.
10. Foekens, J. A., Schmitt, M., van Putten, W. L., Peters, H. A., Kramer, M. D., Janicke, F., et al. (1994). Plasminogen activator inhibitor-1 and prognosis in primary breast cancer. *J.Clin.Oncol., 12*, 1648–1658.
11. Foekens, J. A., Look, M. P., Peters, H. A., van Putten, W. L., Portengen, H., & Klijn, J. G. (1995). Urokinase-type plasminogen

activator and its inhibitor PAI-1: predictors of poor response to tamoxifen therapy in recurrent breast cancer. *J.Natl.Cancer Inst., 87*(10), 751–756.

12. Wind, T., Hansen, M., Jensen, J. K., & Andreasen, P. A. (2002). The molecular basis for anti-proteolytic and non-proteolytic functions of plasminogen activator inhibitor type-1: roles of the reactive centre loop, the shutter region, the flexible joint region and the small serpin fragment. *Biol.Chem, 383*(1), 21–36. https://doi.org/10.1515/BC.2002.003.
13. Mottonen, J., Strand, A., Symersky, J., Sweet, R. M., Danley, D. E., Geoghegan, K. F., Gerard, R. D., & Goldsmith, E. J. (1992). Structural basis of latency in plasminogen activator inhibitor-1. *Nature, 355*(6357), 270–273. https://doi.org/10.1038/355270a0.
14. Seiffert, D., & Loskutoff, D. J. (1991). Evidence that type 1 plasminogen activator inhibitor binds to the somatomedin B domain of vitronectin. *The Journal of Biological Chemistry, 266*(5), 2824–2830.
15. Lawrence, D. A., Berkenpas, M. B., Palaniappan, S., & Ginsburg, D. (1994). Localization of vitronectin binding domain in plasminogen activator inhibitor-1. *J.Biol.Chem., 269*(21), 15223–15228.
16. Mimuro, J., & Loskutoff, D. J. (1989). Purification of a protein from bovine plasma that binds to type 1 plasminogen activator inhibitor and prevents its interaction with extracellular matrix. Evidence that the protein is vitronectin. *The Journal of Biological Chemistry, 264*(2), 936–939.
17. Madsen, C. D., Ferraris, G. M., Andolfo, A., Cunningham, O., & Sidenius, N. (2007). uPAR-induced cell adhesion and migration: vitronectin provides the key. *The Journal of Cell Biology, 177*(5), 927–939. https://doi.org/10.1083/jcb.200612058.
18. Jensen, J. K., Malmendal, A., Schiott, B., Skeldal, S., Pedersen, K. E., Celik, L., et al. (2006). Inhibition of plasminogen activator inhibitor-1 binding to endocytosis receptors of the low-density-lipoprotein receptor family by a peptide isolated from a phage display library. *The Biochemical Journal, 399*(3), 387–396. https://doi.org/10.1042/bj20060533.
19. Webb, D. J., Nguyen, D. H., Sankovic, M., & Gonias, S. L. (1999). The very low density lipoprotein receptor regulates urokinase receptor catabolism and breast cancer cell motility in vitro. *The Journal of Biological Chemistry, 274*(11), 7412–7420. https://doi.org/10.1074/jbc.274.11.7412.
20. Placencio, V. R., & DeClerck, Y. A. (2015). Plasminogen activator inhibitor-1 in cancer: rationale and insight for future therapeutic testing. *Cancer Research, 75*(15), 2969–2974. https://doi.org/10.1158/0008-5472.can-15-0876.
21. Look, M. P., van Putten, W. L., Duffy, M. J., Harbeck, N., Christensen, I. J., Thomssen, C., et al. (2002). Pooled analysis of prognostic impact of urokinase-type plasminogen activator and its inhibitor PAI-1 in 8377 breast cancer patients. *J Natl.Cancer Inst., 94*(2), 116–128.
22. Knoop, A., Andreasen, P. A., Andersen, J. A., Hansen, S., Lænkholm, A. V., Simonsen, A. C. W., Andersen, J., Overgaard, J., & Rose, C. (1998). Prognostic significance of urokinase-type plasminogen activator and plasminogen activator inhibitor-1 in primary breast cancer. *Br.J.Cancer, 77*(6), 932–940.
23. Niki, M., Yokoi, T., Kurata, T., & Nomura, S. (2017). New prognostic biomarkers and therapeutic effect of bevacizumab for patients with non-small-cell lung cancer. *Lung Cancer (Auckl), 8*, 91–99. https://doi.org/10.2147/lctt.s138887.
24. Harbeck, N., Schmitt, M., Meisner, C., Friedel, C., Untch, M., Schmidt, M., Sweep, C. G. J., Lisboa, B. W., Lux, M. P., Beck, T., Hasmüller, S., Kiechle, M., Jänicke, F., & Thomssen, C. (2013). Ten-year analysis of the prospective multicentre Chemo-N0 trial validates American Society of Clinical Oncology (ASCO)-recommended biomarkers uPA and PAI-1 for therapy decision making in node-negative breast cancer patients. *European Journal of Cancer, 49*(8), 1825–1835. https://doi.org/10.1016/j.ejca.2013.01.007.
25. Mazzoccoli, G., Pazienza, V., Panza, A., Valvano, M. R., Benegiamo, G., Vinciguerra, M., Andriulli, A., & Piepoli, A. (2012). ARNTL2 and SERPINE1: potential biomarkers for tumor aggressiveness in colorectal cancer. *Journal of Cancer Research and Clinical Oncology, 138*(3), 501–511. https://doi.org/10.1007/s00432-011-1126-6.
26. Robert, C., Bolon, I., Gazzeri, S., Veyrenc, S., Brambilla, C., & Brambilla, E. (1999). Expression of plasminogen activator inhibitors 1 and 2 in lung cancer and their role in tumor progression. *Clin.Cancer Res., 5*(8), 2094–2102.
27. Fujii, T., Obara, T., Tanno, S., Ura, H., & Kohgo, Y. (1999). Urokinase-type plasminogen activator and plasminogen activator inhibitor-1 as a prognostic factor in human colorectal carcinomas. *Hepatogastroenterology, 46*(28), 2299–2308.
28. Chambers, S. K., Ivins, C. M., & Carcangiu, M. L. (1998). Plasminogen activator inhibitor-1 is an independent poor prognostic factor for survival in advanced stage epithelial ovarian cancer patients. *Int.J.Cancer, 79*(5), 449–454.
29. Dossenbach-Glaninger, A., van Trotsenburg, M., Dossenbach, M., Oberkanins, C., Moritz, A., Krugluger, W., et al. (2003). Plasminogen activator inhibitor 1 4G/5G polymorphism and coagulation factor XIII Val34Leu polymorphism: impaired fibrinolysis and early pregnancy loss. *Clinical Chemistry, 49*(7), 1081–1086.
30. Yildirim, M. E., Karakus, S., Kurtulgan, H. K., Kilicgun, H., Ersan, S., & Bakir, S. (2017). The Association of Plasminogen Activator Inhibitor Type 1 (PAI-1) level and PAI-1 4G/5G gene polymorphism with the formation and the grade of endometrial cancer. *Biochemical Genetics, 55*(4), 314–321. https://doi.org/10.1007/s10528-017-9796-7.
31. Castello, R., Espana, F., Vazquez, C., Fuster, C., Almenar, S. M., Aznar, J., et al. (2006). Plasminogen activator inhibitor-1 4G/5G polymorphism in breast cancer patients and its association with tissue PAI-1 levels and tumor severity. *Thrombosis Research, 117*(5), 487–492. https://doi.org/10.1016/j.thromres.2005.03.025.
32. Jevric, M., Matic, I. Z., Krivokuca, A., Dordic Crnogorac, M., Besu, I., Damjanovic, A., et al. (2019). Association of uPA and PAI-1 tumor levels and 4G/5G variants of PAI-1 gene with disease outcome in luminal HER2-negative node-negative breast cancer patients treated with adjuvant endocrine therapy. *BMC Cancer, 19*(1), 71. https://doi.org/10.1186/s12885-018-5255-z.
33. Divella, R., Daniele, A., Abbate, I., Savino, E., Casamassima, P., Sciortino, G., Simone, G., Gadaleta-Caldarola, G., Fazio, V., Gadaleta, C. D., Sabbà, C., & Mazzocca, A. (2015). Circulating levels of PAI-1 and SERPINE1 4G/4G polymorphism are predictive of poor prognosis in HCC patients undergoing TACE. *Translational Oncology, 8*(4), 273–278. https://doi.org/10.1016/j.tranon.2015.05.002.
34. Gilabert-Estelles, J., Ramon, L. A., Braza-Boils, A., Gilabert, J., Chirivella, M., Espana, F., et al. (2012). Plasminogen activator inhibitor-1 (PAI-1) 4 G/5 G polymorphism and endometrial cancer. Influence of PAI-1 polymorphism on tissue PAI-1 antigen and mRNA expression and tumor severity. *Thrombosis Research, 130*(2), 242–247. https://doi.org/10.1016/j.thromres.2011.10.007.
35. Vairaktaris, E., Yapijakis, C., Serefoglou, Z., Vylliotis, A., Ries, J., Nkenke, E., Wiltfang, J., Derka, S., Vassiliou, S., Springer, I., Kessler, P., & Neukam, F. W. (2006). Plasminogen activator inhibitor-1 polymorphism is associated with increased risk for oral cancer. *Oral Oncology, 42*(9), 888–892. https://doi.org/10.1016/j.oraloncology.2005.12.005.
36. Forsti, A., Lei, H., Tavelin, B., Enquist, K., Palmqvist, R., Altieri, A., Hallmans, G., Hemminki, K., & Lenner, P. (2007). Polymorphisms in the genes of the urokinase plasminogen

activation system in relation to colorectal cancer. *Annals of Oncology, 18*(12), 1990–1994. https://doi.org/10.1093/annonc/mdm361.

37. Sternlicht, M. D., Dunning, A. M., Moore, D. H., Pharoah, P. D., Ginzinger, D. G., Chin, K., et al. (2006). Prognostic value of PAI1 in invasive breast cancer: evidence that tumor-specific factors are more important than genetic variation in regulating PAI1 expression. *Cancer Epidemiology, Biomarkers & Prevention, 15*(11), 2107–2114. https://doi.org/10.1158/1055-9965.epi-06-0351.
38. Li, H., Shinohara, E. T., Cai, Q., Chen, H., Courtney, R., Cao, C., Wang, Z., Teng, M., Zheng, W., & Lu, B. (2006). Plasminogen activator inhibitor-1 promoter polymorphism is not associated with the aggressiveness of disease in prostate cancer. *Clinical Oncology (Royal College of Radiologists), 18*(4), 333–337.
39. Loktionov, A., Watson, M. A., Stebbings, W. S., Speakman, C. T., & Bingham, S. A. (2003). Plasminogen activator inhibitor-1 gene polymorphism and colorectal cancer risk and prognosis. *Cancer Letters, 189*(2), 189–196.
40. Blasiak, J., & Smolarz, B. (2000). Plasminogen activator inhibitor-1 (PAI-1) gene 4G/5G promoter polymorphism is not associated with breast cancer. *Acta Biochimica Polonica, 47*(1), 191–199.
41. Lee, J. H., Kim, Y., Choi, J. W., & Kim, Y. S. (2013). Clinicopathological significance of plasminogen activator inhibitor-1 promoter 4G/5G polymorphism in breast cancer: a meta-analysis. *Archives of Medical Research, 44*(1), 39–45. https://doi.org/10.1016/j.arcmed.2012.12.002.
42. Baker, S., Ali, I., Silins, I., Pyysalo, S., Guo, Y., Hogberg, J., et al. (2017). Cancer hallmarks analytics tool (CHAT): a text mining approach to organize and evaluate scientific literature on cancer. *Bioinformatics, 33*(24), 3973–3981. https://doi.org/10.1093/bioinformatics/btx454.
43. Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: the next generation. *Cell, 144*(5), 646–674.
44. Giacoia, E. G., Miyake, M., Lawton, A., Goodison, S., & Rosser, C. J. (2014). PAI-1 leads to G1-phase cell-cycle progression through cyclin D3/cdk4/6 upregulation. *Molecular Cancer Research, 12*(3), 322–334. https://doi.org/10.1158/1541-7786.mcr-13-0543.
45. Vial, D., Monaghan-Benson, E., & McKeown-Longo, P. J. (2006). Coordinate regulation of fibronectin matrix assembly by the plasminogen activator system and vitronectin in human osteosarcoma cells. *Cancer Cell International, 6*, 8. https://doi.org/10.1186/1475-2867-6-8.
46. Kortlever, R. M., & Bernards, R. (2006). Senescence, wound healing and cancer: the PAI-1 connection. *Cell Cycle, 5*(23), 2697–2703.
47. Aguirre-Ghiso, J. A., Estrada, Y., Liu, D., & Ossowski, L. (2003). ERK(MAPK) activity as a determinant of tumor growth and dormancy; regulation by p38(SAPK). *Cancer Research, 63*(7), 1684–1695.
48. McEachron, T. A., Church, F. C., & Mackman, N. (2011). Regulation of thrombin-induced plasminogen activator inhibitor-1 in 4T1 murine breast cancer cells. *Blood Coagulation & Fibrinolysis, 22*(7), 576–582. https://doi.org/10.1097/MBC.0b013e3283497647.
49. McEachron, T. A., Pawlinski, R., Richards, K. L., Church, F. C., & Mackman, N. (2010). Protease-activated receptors mediate crosstalk between coagulation and fibrinolysis. *Blood, 116*(23), 5037–5044. https://doi.org/10.1182/blood-2010-06-293126.
50. Mazzieri, R., & Blasi, F. (2005). The urokinase receptor and the regulation of cell proliferation. *Thrombosis and Haemostasis, 93*(4), 641–646. https://doi.org/10.1160/th05-01-0021.
51. Lademann, U. A., & Romer, M. U. (2008). Regulation of programmed cell death by plasminogen activator inhibitor type 1 (PAI-1). *Thrombosis and Haemostasis, 100*(6), 1041–1046.
52. Balsara, R. D., & Ploplis, V. A. (2008). Plasminogen activator inhibitor-1: the double-edged sword in apoptosis. *Thrombosis and Haemostasis, 100*(6), 1029–1036.
53. Fang, H., Placencio, V. R., & DeClerck, Y. A. (2012). Protumorigenic activity of plasminogen activator inhibitor-1 through an antiapoptotic function. *J Natl Cancer Inst, 104*(19), 1470–1484. https://doi.org/10.1093/jnci/djs377.
54. Valiente, M., Obenauf, A. C., Jin, X., Chen, Q., Zhang, X. H., Lee, D. J., et al. (2014). Serpins promote cancer cell survival and vascular co-option in brain metastasis. *Cell, 156*(5), 1002–1016. https://doi.org/10.1016/j.cell.2014.01.040.
55. Bajou, K., Peng, H., Laug, W. E., Maillard, C., Noel, A., Foidart, J. M., et al. (2008). Plasminogen activator inhibitor-1 protects endothelial cells from FasL-mediated apoptosis. *Cancer Cell, 14*(4), 324–334.
56. Isogai, C., Laug, W. E., Shimada, H., Declerck, P. J., Stins, M. F., Durden, D. L., Erdreich-Epstein, A., & DeClerck, Y. (2001). Plasminogen activator inhibitor-1 promotes angiogenesis by stimulating endothelial cell migration toward fibronectin. *Cancer Research, 61*(14), 5587–5594.
57. Olander, J. V., Bremer, M. E., Marasa, J. C., & Feder, J. (1985). Fibrin-enhanced endothelial cell organization. *Journal of Cellular Physiology, 125*(1), 1–9. https://doi.org/10.1002/jcp.1041250102.
58. Qi, J., Goralnick, S., & Kreutzer, D. L. (1997). Fibrin regulation of interleukin-8 gene expression in human vascular endothelial cells. *Blood, 90*(9), 3595–3602.
59. Liu, G., Shuman, M. A., & Cohen, R. L. (1995). Co-expression of urokinase, urokinase receptor and PAI-1 is necessary for optimum invasiveness of cultured lung cancer cells. *International Journal of Cancer, 60*(4), 501–506.
60. Maillard, C. M., Bouquet, C., Petitjean, M. M., Mestdagt, M., Frau, E., Jost, M., Masset, A. M., Opolon, P. H., Beermann, F., Abitbol, M. M., Foidart, J. M., Perricaudet, M. J., & Noel, A. C. (2008). Reduction of brain metastases in plasminogen activator inhibitor-1-deficient mice with transgenic ocular tumors. *Carcinogenesis, 29*(11), 2236–2242. https://doi.org/10.1093/carcin/bgn204.
61. Zhang, W., Xu, J., Fang, H., Tang, L., Chen, W., Sun, Q., Zhang, Q., Yang, F., Sun, Z., Cao, L., Wang, Y., & Guan, X. (2018). Endothelial cells promote triple-negative breast cancer cell metastasis via PAI-1 and CCL5 signaling. *The FASEB Journal, 32*(1), 276–288. https://doi.org/10.1096/fj.201700237RR.
62. Tsuchiya, H., Katsuo, S., Matsuda, E., Sunayama, C., Tomita, K., Ueda, Y., et al. (1995). The antibody to plasminogen activator inhibitor-1 suppresses pulmonary metastases of human fibrosarcoma in athymic mice. *General & Diagnostic Pathology, 141*(1), 41–48.
63. Tsuchiya, H., Sunayama, C., Okada, G., Matsuda, E., Tomita, K., & Binder, B. R. (1997). Plasminogen activator inhibitor-1 accelerates lung metastasis formation of human fibrosarcoma cells. *Anticancer Research, 17*(1A), 313–316.
64. Chen, H., Peng, H., Liu, W., Sun, Y., Su, N., Tang, W., Zhang, X., Wang, J., Cui, L., Hu, P., & Liu, S. (2015). Silencing of plasminogen activator inhibitor-1 suppresses colorectal cancer progression and liver metastasis. *Surgery, 158*(6), 1704–1713. https://doi.org/10.1016/j.surg.2015.04.053.
65. Nishioka, N., Matsuoka, T., Yashiro, M., Hirakawa, K., Olden, K., & Roberts, J. D. (2012). Plasminogen activator inhibitor 1 RNAi suppresses gastric cancer metastasis in vivo. *Cancer Science, 103*(2), 228–232. https://doi.org/10.1111/j.1349-7006.2011.02155.x.
66. Alizadeh, H., Ma, D., Berman, M., Bellingham, D., Comerford, S. A., Gething, M. J., et al. (1995). Tissue-type plasminogen activator-induced invasion and metastasis of murine melanomas. *Current Eye Research, 14*(6), 449–458.

67. Masuda, T., Hattori, N., Senoo, T., Akita, S., Ishikawa, N., Fujitaka, K., Haruta, Y., Murai, H., & Kohno, N. (2013). SK-216, an inhibitor of plasminogen activator inhibitor-1, limits tumor progression and angiogenesis. *Molecular Cancer Therapeutics, 12*(11), 2378–2388. https://doi.org/10.1158/1535-7163.mct-13-0041.
68. Soff, G. A., Sanderowitz, J., Gately, S., Verrusio, E., Weiss, I., Brem, S., & Kwaan, H. C. (1995). Expression of plasminogen activator inhibitor type 1 by human prostate carcinoma cells inhibits primary tumor growth, tumor- associated angiogenesis, and metastasis to lung and liver in an athymic mouse model. *J.Clin.Invest., 96*(6), 2593–2600.
69. Inoue, M., Sawada, T., Uchima, Y., Kimura, K., Nishihara, T., Tanaka, H., Yashiro, M., Yamada, N., Ohira, M., & Hirakawa, K. (2005). Plasminogen activator inhibitor-1 (PAI-1) gene transfection inhibits the liver metastasis of pancreatic cancer by preventing angiogenesis. *Oncology Reports, 14*(6), 1445–1451.
70. Ma, D., Gerard, R. D., Li, X. Y., Alizadeh, H., & Niederkorn, J. Y. (1997). Inhibition of metastasis of intraocular melanomas by adenovirus- mediated gene transfer of plasminogen activator inhibitor type I (PAI-1) in an athymic mouse model. *Blood, 90*(7), 2738–2746.
71. Park, J., Wysocki, R. W., Amoozgar, Z., Maiorino, L., Fein, M. R., Jorns, J., et al. (2016). Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps. *Sci Transl Med, 8*(361), 361ra138. https://doi.org/10.1126/scitranslmed.aag1711.
72. Noubouossie, D. F., Reeves, B. N., Strahl, B. D., & Key, N. S. (2019). Neutrophils: back in the thrombosis spotlight. *Blood, 133*(20), 2186–2197. https://doi.org/10.1182/blood-2018-10-862243.
73. Oda, T., Jung, Y. O., Kim, H. S., Cai, X., Lopez-Guisa, J. M., Ikeda, Y., et al. (2001). PAI-1 deficiency attenuates the fibrogenic response to ureteral obstruction. *Kidney International, 60*(2), 587–596. https://doi.org/10.1046/j.1523-1755.2001.030002587.x.
74. Gupta, K. K., Xu, Z., Castellino, F. J., & Ploplis, V. A. (2016). Plasminogen activator inhibitor-1 stimulates macrophage activation through Toll-like Receptor-4. *Biochemical and Biophysical Research Communications, 477*(3), 503–508. https://doi.org/10.1016/j.bbrc.2016.06.065.
75. Ichimura, A., Matsumoto, S., Suzuki, S., Dan, T., Yamaki, S., Sato, Y., Kiyomoto, H., Ishii, N., Okada, K., Matsuo, O., Hou, F. F., Vaughan, D. E., van Ypersele de Strihou, C., & Miyata, T. (2013). A small molecule inhibitor to plasminogen activator inhibitor 1 inhibits macrophage migration. *Arteriosclerosis, Thrombosis, and Vascular Biology, 33*(5), 935–942. https://doi.org/10.1161/atvbaha.113.301224.
76. Kubala, M. H., Punj, V., Placencio-Hickok, V. R., Fang, H., Fernandez, G. E., Sposto, R., et al. (2018). Plasminogen activator inhibitor-1 promotes the recruitment and polarization of macrophages in cancer. *Cell Rep, 25*(8), 2177–2191.e2177. https://doi.org/10.1016/j.celrep.2018.10.082.
77. Beaulieu, L. M., Whitley, B. R., Wiesner, I. T. F., Rehault, S. M., Palmieri, D., Elkahloun, A. G., et al. (2007). Breast cancer and metabolic syndrome linked through the plasminogen activator inhibitor-1 cycle. *Bioessays, 29*(10), 1029–1038.
78. Schneider, D. J., Chen, Y., & Sobel, B. E. (2008). The effect of plasminogen activator inhibitor type 1 on apoptosis. *Thrombosis and Haemostasis, 100*(6), 1037–1040.
79. Bajou, K., Masson, V., Gerard, R. D., Schmitt, P. M., Albert, V., Praus, M., Lund, L. R., Frandsen, T. L., Brunner, N., Dano, K., Fusenig, N. E., Weidle, U., Carmeliet, G., Loskutoff, D., Collen, D., Carmeliet, P., Foidart, J. M., & Noël, A. (2001). The plasminogen activator inhibitor PAI-1 controls in vivo tumor vascularization by interaction with proteases, not vitronectin. Implications for antiangiogenic strategies. *The Journal of Cell Biology, 152*(4), 777–784.
80. Brooks, T. D., Slomp, J., Quax, P. H., De Bart, A. C., Spencer, M. T., Verheijen, J. H., et al. (2000). Antibodies to PAI-1 alter the invasive and migratory properties of human tumour cells in vitro. *Clinical & Experimental Metastasis, 18*(6), 445–453.
81. Eitzman, D. T., Krauss, J. C., Shen, T., Cui, J., & Ginsburg. (1996). Lack of plasminogen activator inhibitor-1 effect in a transgenic mouse model of metastatic melanoma. *Blood., 87*(11), 4718–4722.
82. Almholt, K., Nielsen, B. S., Frandsen, T. L., Brunner, N., Dano, K., & Johnsen, M. (2003). Metastasis of transgenic breast cancer in plasminogen activator inhibitor-1 gene-deficient mice. *Oncogene, 22*(28), 4389–4397.
83. Bajou, K., Maillard, C., Jost, M., Lijnen, R. H., Gils, A., Declerck, P., Carmeliet, P., Foidart, J. M., & Noel, A. (2004). Host-derived plasminogen activator inhibitor-1 (PAI-1) concentration is critical for in vivo tumoral angiogenesis and growth. *Oncogene, 23*(41), 6986–6990.
84. Declerck, P. J., Gils, A., & De Taeye, B. (2011). Use of mouse models to study plasminogen activator inhibitor-1. *Methods in Enzymology, 499*, 77–104.
85. Levi, M., & van der Poll, T. (2017). Coagulation and sepsis. *Thrombosis Research, 149*, 38–44. https://doi.org/10.1016/j.thromres.2016.11.007.
86. Srikanthan, K., Feyh, A., Visweshwar, H., Shapiro, J. I., & Sodhi, K. (2016). Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the west Virginian population. *International Journal of Medical Sciences, 13*(1), 25–38. https://doi.org/10.7150/ijms.13800.
87. Russolillo, A., Iervolino, S., Peluso, R., Lupoli, R., Di Minno, A., Pappone, N., et al. (2013). Obesity and psoriatic arthritis: from pathogenesis to clinical outcome and management. *Rheumatology (Oxford), 52*(1), 62–67. https://doi.org/10.1093/rheumatology/kes242.
88. Mertens, I., Verrijken, A., Michiels, J. J., Van der Planken, M., Ruige, J. B., & Van Gaal, L. F. (2006). Among inflammation and coagulation markers, PAI-1 is a true component of the metabolic syndrome. *International Journal of Obesity, 30*(8), 1308–1314. https://doi.org/10.1038/sj.ijo.0803189.
89. Franceschi, C., Bonafe, M., Valensin, S., Olivieri, F., De Luca, M., Ottaviani, E., et al. (2000). Inflamm-aging. An evolutionary perspective on immunosenescence. *Annals of the New York Academy of Sciences, 908*, 244–254. https://doi.org/10.1111/j.1749-6632.2000.tb06651.x.
90. Kruithof, E. K., Mestries, J. C., Gascon, M. P., & Ythier, A. (1997). The coagulation and fibrinolytic responses of baboons after in vivo thrombin generation–effect of interleukin 6. *Thrombosis and Haemostasis, 77*(5), 905–910.
91. Sawdey, M. S., & Loskutoff, D. J. (1991). Regulation of murine type 1 plasminogen activator inhibitor gene expression in vivo. Tissue specificity and induction by lipopolysaccharide, tumor necrosis factor-alpha, and transforming growth factor-beta. *The Journal of Clinical Investigation, 88*(4), 1346–1353. https://doi.org/10.1172/jci115440.
92. Varki, A. (2007). Trousseau's syndrome: multiple definitions and multiple mechanisms. *Blood, 110*(6), 1723–1729. https://doi.org/10.1182/blood-2006-10-053736.
93. Xu, X., Wang, H., Wang, Z., & Xiao, W. (2009). Plasminogen activator inhibitor-1 promotes inflammatory process induced by cigarette smoke extraction or lipopolysaccharides in alveolar epithelial cells. *Experimental Lung Research, 35*(9), 795–805. https://doi.org/10.3109/01902140902912519.
94. Ashton-Rickardt, P. G. (2013). An emerging role for serine protease inhibitors in T lymphocyte immunity and beyond. *Immunology Letters, 152*(1), 65–76. https://doi.org/10.1016/j.imlet.2013.04.004.

95. Rouch, A., Vanucci-Bacque, C., Bedos-Belval, F., & Baltas, M. (2015). Small molecules inhibitors of plasminogen activator inhibitor-1 - an overview. *European Journal of Medicinal Chemistry, 92*, 619–636. https://doi.org/10.1016/j.ejmech.2015.01.010.
96. Mutoh, M., Niho, N., Komiya, M., Takahashi, M., Ohtsubo, R., Nakatogawa, K., Ueda, K., Sugimura, T., & Wakabayashi, K. (2008). Plasminogen activator inhibitor-1 (Pai-1) blockers suppress intestinal polyp formation in min mice. *Carcinogenesis, 29*(4), 824–829. https://doi.org/10.1093/carcin/bgn028.
97. Takayama, Y., Hattori, N., Hamada, H., Masuda, T., Omori, K., Akita, S., Iwamoto, H., Fujitaka, K., & Kohno, N. (2016). Inhibition of PAI-1 limits tumor angiogenesis regardless of angiogenic stimuli in malignant pleural mesothelioma. *Cancer Research, 76*(11), 3285–3294. https://doi.org/10.1158/0008-5472.can-15-1796.
98. Gomes-Giacoia, E., Miyake, M., Goodison, S., & Rosser, C. J. (2013). Targeting plasminogen activator inhibitor-1 inhibits angiogenesis and tumor growth in a human cancer xenograft model. *Molecular Cancer Therapeutics, 12*(12), 2697–2708. https://doi.org/10.1158/1535-7163.mct-13-0500.
99. Placencio, V. R., Ichimura, A., Miyata, T., & DeClerck, Y. A. (2015). Small molecule inhibitors of plasminogen activator inhibitor-1 elicit anti-tumorigenic and anti-angiogenic activity. *PLoS One, 10*(7), e0133786. https://doi.org/10.1371/journal.pone.0133786.
100. Mashiko, S., Kitatani, K., Toyoshima, M., Ichimura, A., Dan, T., Usui, T., Ishibashi, M., Shigeta, S., Nagase, S., Miyata, T., & Yaegashi, N. (2015). Inhibition of plasminogen activator inhibitor-1 is a potential therapeutic strategy in ovarian cancer. *Cancer Biology & Therapy, 16*(2), 253–260. https://doi.org/10.1080/15384047.2014.1001271.
101. Gorlatova, N. V., Cale, J. M., Elokdah, H., Li, D., Fan, K., Warnock, M., Crandall, D. L., & Lawrence, D. A. (2007). Mechanism of inactivation of plasminogen activator inhibitor-1 by a small molecule inhibitor. *The Journal of Biological Chemistry, 282*(12), 9288–9296. https://doi.org/10.1074/jbc.M611642200.
102. Wun, T. C., & Kretzmer, K. K. (1987). cDNA cloning and expression in E. coli of a plasminogen activator inhibitor (PAI) related to a PAI produced by Hep G2 hepatoma cell. *FEBS Letters, 210*(1), 11–16. https://doi.org/10.1016/0014-5793(87)81288-7.
103. Busso, N., Belin, D., Failly-Crepin, C., & Vassalli, J. D. (1987). Glucocorticoid modulation of plasminogen activators and of one of their inhibitors in the human mammary carcinoma cell line MDA-MB-231. *Cancer Research, 47*(2), 364–370.