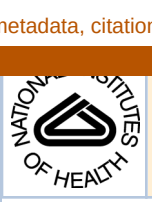

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Plasminogen Activator Inhibitor-1 is an Aggregate Response Factor with Pleiotropic Effects on Cell Signaling in Vascular Disease and the Tumor Microenvironment

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Abstract

In hemostasis, the serine protease inhibitor (serpin) plasminogen activator inhibitor-1 (PAI-1) functions to stabilize clots via inhibition of tissue plasminogen activator (tPA) with subsequent inhibition of fibrinolysis. In tissues, PAI-1 functions to inhibit extracellular matrix degradation via inhibition of urokinase plasminogen activator (uPA). Elevated levels of PAI-1 in the vasculature and in tissues have long been known to be associated with thrombosis and fibrosis, respectively. However, there is emerging evidence that PAI-1 may participate in the pathophysiology of a number of diseases such as atherosclerosis, restenosis, and cancer. In many of these disease states, the canonical view of PAI-1 as an inhibitor of tPA and uPA cannot fully account for a mechanism whereby PAI-1 contributes to the disease. In these cases, one must consider recent data, which indicates PAI-1 can directly promote pro-proliferative and anti-apoptotic signaling in a variety of cell types. Given the wide variety of inflammatory, hormonal, and metabolic signals that increase PAI-1 expression, it is important to consider mechanisms by which PAI-1 can directly participate in disease etiology.

Keywords

Plasminogen activator inhibitor-1; urokinase; tissue plasminogen activator; inflammation; proliferation; and apoptosis

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Introduction

Traditional paradigms for PAI-1 in fibrinolysis and tissue remodeling

Within the intravascular space, the primary role for the serpin (serine protease inhibitor) PAI-1 is to regulate fibrinolysis to stabilize hemostatic plug formation. When bound to fibrin in a clot, the serine protease tissue plasminogen activator (tPA) activates plasminogen to its active form of plasmin, which subsequently degrades fibrin [1]. During thrombus formation, tPA is inhibited by PAI-1 released from platelets [2], thereby limiting further plasminogen activation and fibrinolysis.

The primary role of PAI-1 in the extravascular space is to regulate matrix remodeling via inhibition of the urokinase plasminogen activator (uPA) [3]. uPA bound to cells expressing its cognate receptor uPAR, can catalyze the pericellular conversion of plasminogen to plasmin, which can subsequently cleave and/or activate numerous proteins such as gelatinase, fibronectin, laminin, and latent forms of collagenases including MMP-1 to lead to matrix degradation. As with tPA, PAI-1 forms a 1:1 complex with uPA and renders the protease inactive, thereby inhibiting pericellular proteolysis.

PAI-1 has also been implicated in inhibiting adhesion of cells to extracellular matrix proteins, although the precise mechanism remains debated. uPAR has been shown to associate with multiple different integrin subunits and it has been suggested that uPAR can act as an integrin ligand to promote both cell adhesion to various matrix proteins [4], as well as cell to cell adhesion [5]. Given these findings, it has been suggested that PAI-1 may promote de-adhesion from various substrata via destruction of integrins [6]. Alternatively, is has been suggested that PAI-1 can promote de-adhesion specifically for the extracellular matrix protein vitronectin (VN). PAI-1 and uPAR/uPA complexes compete for binding to VN [7], and binding of PAI-1 to uPA dissociates uPAR from vitronectin. Endocytosis of the uPAR/uPA/PAI-1 ternary complex by the low-density lipoprotein-like receptor 1 (LRP-1) then promotes de-adhesion of cells from VN [8].

Regulation of PAI-1 expression in the intravascular and extravascular space

During the initiation of thrombus formation, release of PAI-1 by platelets represents the most likely primary source of PAI-1 [2]. However, multiple cell types are capable of producing PAI-1 in response to various inflammatory cytokines. The multiplicity of potential sources of PAI-1 as a response factor has implications for PAI-1 function in both physiological and pathophysiological conditions.

As a recognized acute phase reactant, PAI-1 levels in plasma increase quickly in response to vessel injury and a heightened inflammatory state [9]. Like C-reactive protein (CRP) and fibrinogen, PAI-1 levels in plasma have been shown to increase in response both to acute trauma such as local tissue injury [10] and to chronic inflammatory states such as cardiovascular disease [11] and insulin resistance [12]. In mouse models, this increase has been attributed to increased synthesis of PAI-1 by the liver in response to inflammatory cytokines IL-1β [10], IL-6 [13], and tumor necrosis factor-α (TNFα) [14]. Under physiological conditions, acute increases in the plasma concentration of PAI-1 in response to inflammatory cytokines could be viewed as a mechanism to stabilize thrombus formation by inhibiting tPA-mediated plasminogen activation. However, under pathological conditions such as atherosclerosis, sustained elevated levels of PAI-1 could promote thrombosis.

In contrast to fast up-regulation of PAI-1 in plasma as an acute phase reactant, there are also mechanisms by which PAI-1 levels in the intravascular space may be up-regulated in a more sustained fashion via endothelial cell production. Similar to hepatocytes, cultured endothelial cells have been shown to increase PAI-1 production in response to the

inflammatory cytokines IL-1 [15] and TNF-α [16]. PAI-1 synthesis by endothelial cells has also been shown to increase as a consequence of hypoxia [17], the generation of reactive oxygen species [18], and shear stress [19]. Alternatively, increased PAI-1 production by endothelial cells has also been associated with senescence, a process that increases with age [20].

Extravascularly, regulation of PAI-1 expression involves multiple cell types. In fibroblasts, PAI-1 synthesis is increased in response to TGF-β [21] and IL-6 [22]. Perhaps the most important source of PAI-1 in tissues is adipocytes. Mature adipocytes express relatively high basal levels of PAI-I in culture [23]. Despite high basal expression, adipocytes can increase PAI-1 synthesis in response to many cytokines and hormones such as TNF-α, TGF-β, and insulin [24]. Finally, macrophages represent another source of PAI-1 in the extravascular space. Activation of monocytes with endotoxin increases PAI-1 expression and histological studies indicate that tissue macrophages in artheromatous plaques express PAI-1 [25].

Given the diversity of cellular sources and multitude of inflammatory signals which promote PAI-1 expression, it is not surprising that elevated PAI-1 levels in serum and tissue have been observed in a variety of pathological conditions. One might suggest elevated PAI-1 levels could be merely a marker of inflammation. However, multiple studies have shown that PAI-1 participates directly in the pathophysiology of a number of diseases. In some cases, the traditional paradigms for the function of PAI-1 can fully explain its role in pathology. Alternatively, in other disease states, the traditional paradigms for the function of PAI-1 are not sufficient to understand its participatory role. Thus, new data are emerging that strongly suggests PAI-1 has novel functions far beyond its ability to inhibit tPA and uPA.

Pathologic consequences of PAI-1 expression explained by traditional paradigms

PAI-1 in thrombosis

As an inhibitor of plasminogen activation and fibrin degradation, it is logical that elevated PAI-1 levels in serum would lead to thrombosis. With regard for thrombosis in the coronary arteries, elevated PAI-1 levels have been documented in the serum of survivors of a myocardial infarction and patients that have recurrent myocardial infarctions [26]. In an experimental model, transgenic mice that express a stable form of human PAI-1 develop spontaneous coronary thrombi [27]. Elevated levels of PAI-1, especially in the elderly, are thought to be associated with both venous and arterial thrombosis [28].

PAI-1 in fibrosis

In tissues, increased expression of PAI-1 has been associated with multiple forms of fibrosis including glomerulosclerosis [29], liver fibrosis [30], and pulmonary fibrosis [31]. While there are competing schools of thought on the role of PAI-1 in promoting fibrosis, all utilize the traditional paradigm for PAI-1 function. First, it is thought that elevated PAI-1 expression decreases tPA/uPA activity leading to increased fibrin deposition at the site of a vessel injury. Due to the increased fibrin deposition, more cells infiltrate the wound, leading to increased collagen deposition. In an alternative model, it has been suggested elevated PAI-1 promotes de-adhesion, allowing for more cells to infiltrate. Finally, it has also been suggested that the primary consequence of elevated PAI-1 is actually decreased collagenase activity downstream of reduced uPA and MMP activation. In this model PAI-1 directly promotes fibrosis by inhibiting collagen degradation [32].

In contrast to observations linking PAI-1 to thrombosis and fibrotic disease, the role of PAI-1 in other pathological conditions are not explained by traditional paradigms, which focus solely on the protease inhibitor activity of PAI-1. More recent studies elucidating the ability of PAI-1 to alter cell signaling is providing insight to explain how PAI-1 can contribute to other disease states.

Pathologic consequences of PAI-1 expression not explained by traditional paradigms

PAI-1 in vascular disease

PAI-1 has a well-documented association with the development of vascular disease. Multiple studies have demonstrated the presence of excess PAI-1 in atherosclerotic plaques [33] [34] [25]. Furthermore, PAI-1 deposition in the vascular wall [35], and atherosclerotic plaques [36], is elevated in patients with type II diabetes. This is not surprising given that elevated PAI-1 expression has been directly linked to hyperinsulinemia as well as glucose/lipid imbalance [37].

It has been suggested that the presence of PAI-1 in atherosclerotic plaques may directly contribute to atherogenesis primarily via inhibition of MMP activation with subsequent decreased activation of TGFβ [38], which promotes smooth muscle cell proliferation, and decreased processing of cholesterol aggregates [26]. However, there are other mechanisms by which PAI-1 may promote the development of atherosclerosis that reach beyond the traditional paradigms of tPA/uPA inhibition. Of note, PAI-1 has shown to directly promote migration, inhibit apoptosis [39], and promote proliferation [40] of smooth muscle cells. These studies elucidate that PAI-1 has unique capabilities to promote cell signaling. With regard to apoptosis and proliferation, these studies show purified PAI-1 inhibits caspase-3 activity *in vitro* [39], and promotes cell proliferation via activation of the NFκB and ERK signaling [40]. Given the importance of smooth muscle cell proliferation in the development of atherosclerotic lesions, it is important to consider the potential role of PAI-1 directly mediating intracellular signaling events in vascular disease.

Another interesting potential mechanism of PAI-1 mediated signaling in vascular disease involves macrophages recruitment. In *in vitro* studies, PAI-1 in combination with tPA and LRP-1 (the co-receptor for clearance of tPA-PAI-1 and uPA-PAI-1 complexes), has been shown coordinate Mac-1 dependent macrophage migration [41]. While the authors of these studies suggest PAI-1 mediated migration of macrophages is a function of the de-adhesive functions of PAI-1, it is likely to involve more complicated signaling events in light of data which shows the LRP-1 co-receptor acts as a motogenic receptor for PAI-1, and can activate Jak/Stat signaling when it binds PAI-1 [42].

PAI-1 in the tumor microenvironment

The tumor microenvironment represents a heterogeneous mixture of cell types, many of which can produce and respond to PAI-1, including the tumor cells themselves. Considering the well documented role of the immune system and inflammation in cancer and the tight linkage between inflammation and elevated PAI-1, one might hypothesize that PAI-1 could play a direct role in the pathophysiology of cancer. This hypothesis should garner close investigation given that elevated PAI-1 levels in the tumor microenvironment correlates to poor prognosis in multiple cancers including breast [43], ovarian [44], pulmonary adenocarcinoma [45], and neuroblastoma [46]. The commonly observed elevation of PAI-1 in cancer presents a difficult paradox. Given the well-documented association of matrix degradation with tumor viability and metastasis, one would expect that PAI-1, as an inhibitor of uPA, would represent a positive prognostic indicator. However, insights into the

novel functions of PAI-1 as a cell signaling mediator may help explain why PAI-1 is often a poor prognostic indicator.

Most directly, PAI-1 produced by adipocytes, fibroblasts, or macrophages in response to various cytokines in the tumor microenvironment can promote angiogenesis, which is crucial to tumor viability and dissemination. While not without controversy, PAI-1 is generally accepted to promote angiogenesis in the tumor microenvironment. Utilizing PAI-$1^{-/-}$ mice, it has been shown PAI-1 promotes angiogenesis in the tumor microenvironment at low concentrations but inhibits angiogenesis at extremely high concentrations [47]. The precise mechanism by which PAI-1 promotes angiogenesis has remained largely elusive, although it has been suggested that the ability of PAI-1 to promote angiogenesis is dependent on it protease inhibitor activity, not vitronectin binding [48]. This finding would suggest PAI-1 does not promote angiogenesis by promoting de-adhesion of endothelial cells from matrix proteins. The most complete study analyzing angiogenesis suggests that PAI-1 inhibits pro-apoptotic cell signaling by inhibiting plasmin mediated cleavage of Fas-ligand on the surface of endothelial cells [49]. This represents a novel mechanism for how PAI-1 prevents apoptosis of endothelial cells and therefore promotes angiogenesis.

Another mechanism whereby PAI-1 could function to promote cancer dissemination comes from a novel finding with senescence in fibroblasts. PAI-1 has long been known as a marker of senescence in multiple cell types [50] [51]. However, it has been shown that PAI-1 is not only a marker of senescence in fibroblasts, but that it is a critical downstream target of p53 in the induction of senescence, through a PI3K-dependent pathway [52]. If PAI-1 can participate directly in the induction of replicative senescence, it is possible that an excess of PAI-1 in the tumor microenvironment could induce the senescence of fibroblasts, leading to decreased deposition of matrix.

Outside of its influence on endothelial cells and fibroblasts in the tumor microenvironment, emerging data suggests PAI-1 has direct influence over pro-proliferative and anti-apoptotic signaling in tumor cells themselves. While mouse models designed to examine the effect of PAI-1 on tumor development have yielded often-conflicting data [53], *in vitro* examination of various cancer cell lines indicates that PAI-1 has a positive influence on cancer cell growth and survival. While limited, this data may provide the most direct link to explain why elevated PAI-1 levels are associated with poor prognosis in cancer.

One such study demonstrated that both the PC-3 prostate cancer cell line and the HL-60 promyelocytic cell line demonstrated decreased apoptosis in the presence of PAI-1 when treated with apoptosis inducing agents camptothecin or etoposide [54]. Similarly, our laboratory has found that stable expression of wild type PAI-1, but not an inactive mutant of PAI-1, enhances the recovery of MDA-MB-435 cancer cells after exposure to apoptosis inducing agent paclitaxel [55], and enhances motility and adhesion via alteration of the integrin profile at the cell surface [56]. Fibrosarcoma cell lines derived from PAI-$1^{-/-}$ mice were significantly more sensitive to apoptotic stimulus etoposide than counterpart fibrosarcoma cell lines from wild type mice [57].

More recent data reveals how PAI-1 may influence cancer cell viability via direct alteration of cell signaling. An expanded analysis of the murine fibrosarcoma cells discussed above revealed that PAI-1 deficient fibrosarcomas have reduced Akt signaling and reintroduction of PAI-1 expression in deficient cells results in an increase in Akt signaling [58]. Our laboratory has found that stable knockdown of PAI-1 expression in MDA-MB-231 breast cancer cells results in decreased Akt activation (Gramling, M.W. and F.C. Church, unpublished data). Besides regulation of anti-apoptotic Akt signaling, PAI-1 has also been

shown to activate pro-proliferative MAPK signaling. In MCF-7 breast cancer cells, PAI-1 promotes sustained phosphorylation of ERK1/2 via a mechanism which is dependent on its interaction with uPA as well as the activity of uPAR and the LRP-1 co-receptor [59]. This study further showed that the presence of PAI-1 allowed uPA to act as a mitogen for the breast cancer cells [59].

Conclusion

Given that PAI-1 expression is elevated both the intra- and extra-vascular space by such a wide variety of inflammatory, hormonal, and metabolic signals, it has potential to influence many physiological and pathophysiological conditions. The pleiotropic effects of PAI-1 are diagrammed in Figure 1. From thrombosis and fibrosis to atherosclerosis and cancer, PAI-1 directly contributes to the etiology of disease via mechanisms explained by traditional paradigms of its function and by new mechanisms explained by its emerging role in altering cell signaling.

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Abbreviations used

PAI-1	plasminogen activator inhibitor-1
uPA	urokinase plasminogen activator
tPA	tissue plasminogen activator
MMP	matrix metalloprotease
uPAR	urokinase plasminogen activator receptor
VN	vitronectin
LRP-1	low density lipoprotein-like receptor-1
CRP	C-reactive protein
IL	interleukin
TNFα	tumor necrosis factor alpha
TGFβ	transforming growth factor beta
NFκB	nuclear factor kappa-light-chain-enhancer of activated B cells
ERK	extracellular signal-regulated kinase
MAPK	mitogen activated protein kinase

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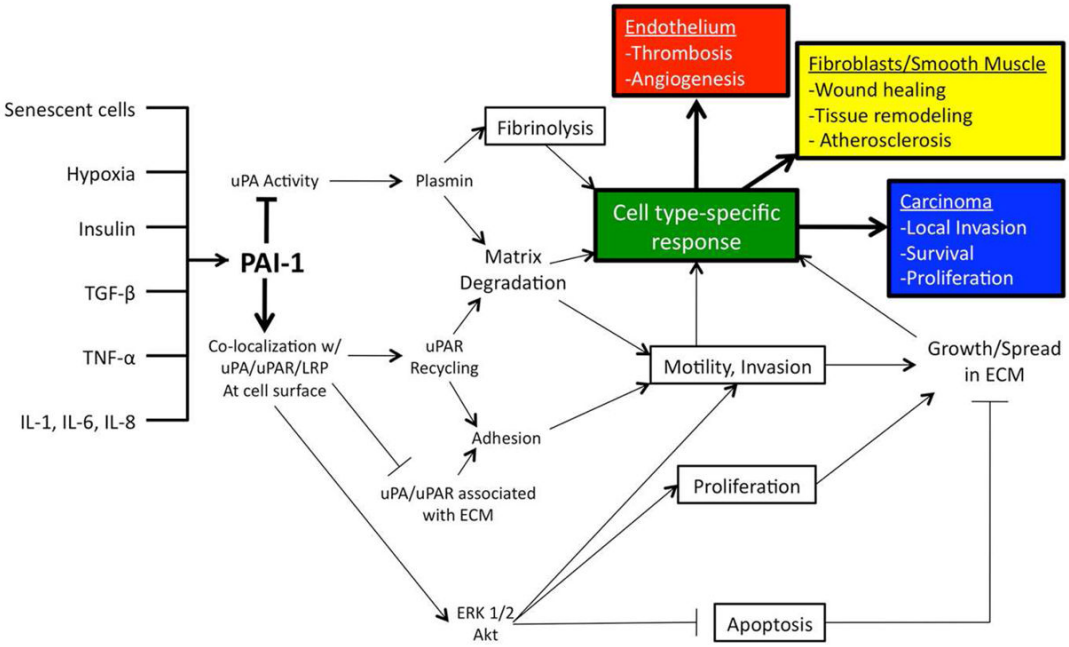

Figure 1.

PAI-1 has been implicated in modulating a variety of physiological and pathophysiological processes. PAI-1 expression in the intra- and extra-vascular space is increased in response to many inflammatory, hormonal, and metabolic signals. By modulating protease activity, adhesion, and altering signaling in multiple cell types, PAI-1 can contribute to many normal and disease processes.