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Review Article

Plasminogen activator inhibitor-1 is an aggregate response factor with pleiotropic effects on cell signaling in vascular disease and the tumor microenvironment

Mark W. Gramling [a], Frank C. Church [a,b,c,d,*]

[a] Department of Pathology and Laboratory Medicine, The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599-7035, USA
[b] Department of Pharmacology, The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599-7035, USA
[c] Department of Medicine, The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599-7035, USA
[d] UNC McAllister Heart Institute, The University of North Carolina at Chapel Hill, School of Medicine, Chapel Hill, NC 27599-7035, USA

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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.

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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

Abbreviations: 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.

* Corresponding author. University of North Carolina-Chapel Hill, 932 Mary Ellen Jones Building, CB# 7035, Chapel Hill, NC, 27599-7035. Tel.: +1 919 966 3313; fax: +1 919 966 7639.
E-mail address: fchurch@email.unc.edu (F.C. Church).

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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 plasma 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 plasma would lead to thrombosis. With regard for thrombosis in the coronary arteries, elevated PAI-1 levels have been documented in the plasma 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 [25,33,34]. Furthermore, PAI-1