Review article

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PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1) AS A POTENTIAL DIAGNOSTIC AND THERAPEUTIC TARGET

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The plasminogen activator inhibitor type 1 (PAI-1) is the main inhibitor of tissue plasminogen activator and urokinase type plasminogen activator in the blood. Besides the key regulatory role in fibrinolysis, plasmin and its activators and inhibitors are responsible for the processes of extracellular matrix turnover and remodeling, cellular adhesion and migration, thus they participate in many pathophysiological processes such as thrombosis, fibrosis, atherosclerosis, cancer spread, and other. The measurement of PAI-1 expression and its levels is suggested for a risk factor assessment in certain diseases. Also, PAI-1 is being considered a potential therapeutic target that could modify disease development and progression. The aim of this work is to outline significant findings regarding PAI-1 application in diagnostics, risk factor assessment, and pathogenetic treatment of different diseases.

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Introduction

The plasminogen activator inhibitor type 1 (PAI-1) is a serine protease inhibitor, specifically – tissue plasminogen activator (t-PA) and urokinase plasminogen activator (u-PA). Plasminogen activators convert plasminogen into plasmin, a key regulator of fibrinolysis, which is responsible for fibrin degradation and, in conjunction with matrix metalloproteinases, for tissue stroma turnover and remodeling (1-3). Besides important role in fibrinolysis, PAI-1 is involved in the processes of extracellular matrix (ECM) remodeling that include cellular adhesion and migration, fibrogenesis, angiogenesis, etc. (4-6).

Many cells can produce and secrete PAI-1, such as endothelial cells (ECs), macrophages, adipocytes, smooth muscle cells (SMC), hepatocytes, and fibroblasts. It is partly stored in platelets and when in bloodstream it may be active or complexed with t-PA or vitronectin (VN), that stabilizes it and prolongs its half-life (2, 6).

Increased or decreased PAI-1 levels and expression were determined in different diseases and are suggested to have modifying role in these diseases pathogenesis (atherosclerosis, fibrosis, cancer spreading, obstetric complications, etc.). It is well known that elevated PAI-1 levels are associated with venous and arterial thrombus formation, and subsequently thromboembolism. Nevertheless, PAI-1 was shown to participate in complex processes of vascular and stromal remodeling. It influences cellular responsiveness, particularly migration (6-8). Taken together, measuring of PAI-1 levels is supported as a risk factor assessment for certain disease states and potential therapeutic target, that could modify disease development and progression.

Considering previously mentioned PAI-1 functions, the aim of the study was to outline findings regarding PAI-1 application in diagnostics, risk factor assessment, and pathogenetic treatment of different diseases.

PAI-1 and vascular wall injury and thrombosis

Plasminogen activator inhibitor 1 has an important role in the modulation of injury reparation process through the control of plasmin mediated ECM remodeling, cell migration and apoptosis. Primary response to vascular endothelial injury requires ECs and SMCs migration and proliferation. Various local factors may influence PAI-1 function, particularly adhesion/deadhesion responses of SMCs in migra-

tion process (7-11). Additionally, vascular injury is associated with inflammation, thus increased endothelial permeability and *in situ* activation of coagulation system components, as well as macrophage specific u-PA overexpression (6).

Plasminogen activator inhibitor 1 levels were shown to correlate with neointima formation upon fibrin deposition and thrombus formation at the injury site (murine animal model). At the same time, PAI-1 promoted VN dependent SMC-fibrin interacttions necessary for cellular motility in the healing process. On the contrary, PAI-1 deficient mice had significantly attenuated neointima formation compared to controls (12). Interestingly, PAI-VN complex hindered thrombin mediated SMC proliferation, implying a complex dynamic interaction of plasminogen and coagulation system components (13).

Specific PAI-1 inhibitors are an emerging drug class which could affect ECs and SMCs migration. The specific PAI-1 inhibitor (PAI-039, tiplaxtinin) hindered SMC migration, intimal hyperplasia and inflammation in murine model of adverse vascular remodeling. PAI-039 showed no effect on PAI-1-deficient SMCs nor ECs and re-endothelization after endothelium denuding vascular injury. Proposed explanation is a significantly lower expression of low-density lipoprotein receptor-related protein 1 (LRP-1), a motogenic PAI-1 receptor, on ECs than SMCs. The results suggest that PAI-1 could be an important therapeutic target that modulates neointimal hyperplasia and vascular stenosis (8). However, therapies using PAI-1 antagonists should be used with caution, because of the PAI-1 mediated direct effect on vascular integrity and permeability. By controlling VE-cadherin cellular trafficking, PAI-1 maintains ECs junctions. *In vivo* PAI inhibition showed vascular leakage in the zebrafish hindbrain embryos as well as decreased transendothelial resistance and disrupted ECs junctions in human umbilical vein endothelium (14).

Increased PAI-1 serum levels were found to be associated with atherosclerosis, coronary artery disease, myocardial infarction (MI), and cerebrovascular events (CVE) (4,15-17). The importance of fibrinolytic potential in cerebrovascular disease was investigated in the Framingham Heart Study offspring cohort, among individuals without prior CVE. PAI-1 and t-PA levels had a strong unadjusted linear correlation with incident CVE and were found predictive of CVE after accounting for established risk factors (15). The prospective EPICOR study determined significantly increased risk of acute coronary syndrome and ischemic stroke in individuals with highest PAI-1 levels compared to the lowest, after adjustment for sex, age, insulin and other metabolic variables (18).

Various cytokines, growth factors and hormones can induce PAI-1 gene transcription, such as interleukin-1, tumor necrosis factor-α (TNF-α), transforming growth factor β (TGFβ), thrombin, angiotensin II, etc. (1, 19, 20). Important inherited predisposition for increased PAI-1 expression is 4G/5G polymorphism in promoter of the PAI-1 gene (SERPINE1). The prevalence of 4G allele was found higher in coronary artery disease, preeclampsia, and pulmonary thromboembolism patients. This is reported as a risk factor for MI in Caucasian and Asian populations. The polymorphism was associated with early-onset cardiovascular risk and male sex (21, 22). The 4G/4G PAI-1 genotype correlated with a higher risk of thrombosis, particularly in vessels of internal organs such as the portal veins (22). However, several studies found no association of 4G/4G polymorphism with thrombotic disorders (23, 24), pointing to a necessary additional prothrombotic risk factors for disease to be manifested.

A fine control is necessary to prevent excess fibrin deposition in placental vessels and intervillous spaces, for successful endometrial vascular remodeling and angiogenesis, during implantation. Pregnancy is hypercoagulable state, thus the thrombophilic predisposition may become evident. Pathologic tendency towards hemorrhage or thrombosis is a risk factor for miscarriages. Females with obstetric complications (severe preeclampsia, placental abruption, fetal growth restriction, and stillbirth) had increased incidence of 4G/4G polymorphism than females with normal pregnancies (25). On the other hand, Said et al. (26) found no association between 4G/5G polymorphism and increased risk of serious adverse pregnancy outcome in asymptomatic nulliparous women. PAI-1 effects on adverse pregnancy outcome are at least additive to other inherited and/or acquired thrombophilic factors (mutations in coagulation factor V (FV), prothrombin (FII), methylenetetrahydrofolate reductase, fibrin-stabilizing factor (FXIII), autoantibodies, etc.) (27).

Although major guidelines do not recognize 4G/5G PAI-1 polymorphism as a significant factor for anticoagulants use, many medical centers consider it for assessment of combined heterozygosity risk. In cases of a single venous thromboembolism and known combined heterozygosity (FV, FII) the guidelines of relevant medical associations recommend prophylactic or therapeutic doses of low molecular weight heparin (LMWH) or unfractionated heparin, both antepartum and postpartum (28). The recommendations are subjected to individual variations between patients. Certainly, the best strategy for prevention of venous thromboembolism and related pregnancy complications is by following the guidelines.

PAI-1 and tissue fibrosis

Elevated PAI-1 levels have been associated with tissue fibrosis, while PAI-1 deficiency showed protection from stress-induced tissue fibrosis of different organs. Increased PAI-1 expression is observed in the early phases of tissue injury and responds to the intensive cellular migration. In induced proliferative glomerulonephritis (animal model), PAI-1 was expressed by mesangial cells at the margins of glomerular lesions between 8-24h post injury (6, 29).

Fibrotic renal disease is characterized by increase in TGF-β, angiotensin II, and PAI-1 transcri-

ption and protein levels. These three factors are in complex relationship where angiotensin II upregulates PAI-1 gene via angiotensin receptor antagonist (AT) 1 receptor, promotes TGF-β and collagens I and III expression (30). TGF-β is a multifunctional protein with strong pro-fibrotic action. It stimulates PAI-1 and collagen expression, while PAI-1 was described to increase TGF-β expression, via ERK/MAPK signaling, or may suppress TGF-β levels, through the lack of plasmin dependent TGF-β conversion into active form (6,31-33).

Therapies that apply angiotensin II converting enzyme (ACE) or AT inhibitor are applied in fibrogenic conditions. AT1 and aldosterone receptor antagonism were shown to reduce PAI-1 levels (34). The reduction lasts longer with ACE inhibitors when used in short term compared to AT1 receptor antagonist (35). Interestingly, the use of high tissue penetrating ACE inhibitors after MI had greater reduction of PAI-1 levels than low tissue penetrating medications. However, the potential beneficial effects of this change need to be elucidated (36). Also, the use of ACE inhibitor reduces morning PAI-1 levels. Namely, PAI-1 plasma levels exhibit a circadian variation, with its highest concentration in the morning and lowest in the afternoon (1, 37) which accordingly influences diurnal variation of fibrinolytic activity (38). Homozygosity for the D allele in the ACE gene was shown to increase PAI-1 gene expression, and in synergy with 4G polymorphism further increases PAI-1 plasma levels. These genotypes were associated with more frequent recurrent miscarriages and thus the application of LMWH is suggested to prevent uteroplacental insufficiency (27).

Future fibrosis treatment might involve antibodies that target TGF-β (39). Interruption of integrin αvβ6 protects against tubulointerstitial fibrosis after unilateral ureteral obstruction in mice. This integrin binds and activates latent TGF-β1. Mice lacking αvβ6 had less kidney injury than wild type, seen through the lower collagen content, and PAI-1 and TGF-β1 mRNK levels. Tubulointerstitial fibrosis was restored after 2 weeks' treatment with aldosterone or angiotensin II in αvβ6 (-/-) mice suggesting TGF-β1 independent pathway of fibrosis induction. The fibrosis correlated with increased PAI-1 expression. Robust macrophage infiltration in αvβ6 (-/-) mice with hindered fibrosis, including the infiltration reduction in angiotensin-restored fibrosis, point to the partial role of these cells in fibrogenesis and dependence on additional factors, such as PAI-1 expression (40).

Free radicals are involved in renal fibrogenesis by activation of profibrogenic mediators, among other TGF-β. Oxidative injury increases PAI-1 expression while increased intracellular antioxidants showed its inhibition. These results point that oxidative stress lowering therapies would have beneficial effect in slowing down the process of fibrosis (6, 41).

Likewise, significant PAI-1 influence is determined in the pathogenesis of lung fibrosis. Several mechanisms are described to enhance fibrosis after alveolar epithelium injury involving plasminogen system. Those are PAI-1 to VN binding and decreased cell motility, prolonged PAI-1 and VN accumulation, inhibition of fibrin and matrix degradation. Therefore, pharmacological inhibitors of PAI-1 or siRNA therapy should be considered in its treatment (6).

Several reports described a direct correlation of PAI-1 levels and steatosis, obesity, and other metabolic disturbances (42, 43). Activation of PAI-1 by TGF-β leads to the progression of steatohepatitis. Significant reversal of progressive fibrosing steatoheaptitis was achieved in mice model by using fenofibrate (a peroxisome proliferator-activated receptor alpha (PPARalpha) agonist). The reversal was mediated by the adenosine monophosphate-activated protein kinase (AMPK) induced small heterodimer partner (SHP) gene expression, in a PPARalpha-independent manner, and was followed by marked decrease in PAI-1 transcription. The pathway is specific for SHP and AMPK signaling. The results suggest a potential therapeutic option for AMPK activators in ameliorating hepatic syndromes (44).

The use of an antifibrotic drug (IFN-α 2a) led to reduced collagen and PAI-1 production in a rat model of liver fibrosis. Also, the administration of Pirfendione (used for treating idiopathic pulmonary fibrosis) was shown to significantly reduce liver fibrosis and demonstrated higher active cell regeneration. The gene expression of collagens, TGF, Smad-7, and PAI-1 were considerably decreased in this model (45).

PAI-1 and cancer

Malignant cells may exploit plasminogen system, aiming to modify microenvironment for its progression. This is partly explained through the enhanced plasmin *de novo* generation by malignant cells, which further induces pericellular proteolysis and ECM degradation, outside-in signaling, activation of TGF-β, etc. (33, 46). High PAI-1 concentrations in cancer microenvironment markedly accelerate migration of invasive cell lines (47, 48).

The American Society of Clinical Oncology has recommended u-PA and PAI-1 as cancer biomarkers for assessment of adjuvant chemotherapy application in node-negative breast cancer patients (49). High local PAI-1 levels were determined in the primary tumor tissue of solid cancers and correlated with disease recurrence. Individuals with the highest PAI-1 values had significantly increased risk of colorectal and breast cancer compared to those with the lowest values, and importantly, the associations remainned after adjustment for sex, age, insulin or other metabolic variables (18).

Because of their role in cancer migration, invasion and metastasis, plasminogen system components are considered an important target for anticancer treatment. Many different approaches for anticancer treatment have been analyzed so far, or are under investigation, such as development of u-PA inhibitors, soluble u-PA receptor, monoclonal antibodies, antisense oligodeoxynucleotides, and others. The approaches are mainly directed toward u-PA cancer activity. The first u-PA inhibitors are tested in oncology in combination with chemotherapy (46, 50, 51). Furthermore, combined evaluation of u-PA and

PAI-1 in breast cancer was shown to improve the clinical risk assessment. Patients with high u-PA/PAI-1 ratio had significantly increased early relapse risk, and a benefit from adjuvant therapy is recommended in these high-risk patients (48).

Interesting usage of a novel tumor targeting drug carrier was investigated by Li et al. (52) with the concept that takes advantage of specific u-PA receptor overexpression in malignant cells. They generated recombinant protein, human serum albumin fused with the amino-terminal urokinase fragment, that enables binding to u-PA receptor. Human albumin has been used as a drug carrier, and the tumor-killing potential of this fused protein complexed with cytotoxic agent was demonstrated in a mouse model. Besides the accumulation of the cytotoxic agent, the complex can be also useful for tumor specific imaging probe.

Even though PAI-1 is a natural inhibitor of u-PA, and thus should have cancer-inhibiting effect, it can enhance tumor growth by acting via several mechanisms such as inhibition of apoptosis, cell proliferation and promotion of angiogenesis (53, 54).

One of the investigated therapeutic approaches is application of aptamers, oligonucleotides or peptides that bind to a specific target molecule. RNA aptamers that target PAI-1 were demonstrated to inhibit extracellular and intracellular PAI-1. Intracellular PAI-1 levels are increased in cancer cells and are thought to contribute cancer progression. Aptamer transfected human breast cancer cells line showed decreased PAI-1 and u-PA protein levels, as well as cancer cell migration and invasion. However, these cells' line medium expressed slight pro-angiogenic effect, while when in human umbilical vein ECs, the aptamer decreased endothelial tube formation, and subsequently angiogenesis (54).

Micro RNA-143 was reported to significantly suppress lung metastasis of osteosarcoma in a mouse model. PAI-1 and matrix metalloproteinase-13 (MMP-13) genes are direct targets of miR-143. *In vitro* osteosarcoma cells that were transfected with this silencing RNA showed downregulation of PAI and suppressed cell invasion, but not proliferation. Also, miR-143 injection into the primary osteosarcoma lesion inhibited lung metastasis. Higher expressing miR-143 cells had poorer PAI-1 expression and belonged to the metastasis negative group. PAI-1 knockdown resulted in downregulation of MMP-13 expression, a MMP that participate in tumor osteolysis. Taken together, the results indicate PAI-1 and MMP-13 genes as potential therapeutic targets for the prevention of lung metastasis (55).

In conclusion, development of new diagnostic and therapeutic strategies is necessary particularly for those patients that do not or poorly respond to the current treatments. Targeted therapy is an evolving field that seems to be increasingly used in the future. Plasminogen system represents a significant target for therapeutic intervention of vascular pathology, fibrosis, and tumor growth and metastasis. Regarding the interaction complexity of plasminogen system components and additional factors of specific disease conditions, therapeutics design requires detailed and thorough understanding of pathogenetic mechanisms.

Acknowledgments

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PLAZMINOGEN AKTIVATOR INHIBITOR 1 (PAI-1) KAO MOGUĆI CILJ DIJAGNOSTIČKIH I TERAPIJSKIH POSTUPAKA

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Plazminogen aktivator inhibitor tip 1 (PAI-1) je glavni inhibitor tkivnog aktivatora plazminogena i urokinaznog tipa aktivatora plazminogena u krvi. Pored ključne regulatorne uloge u fibrinolizi, plazmin i njegovi aktivatori i inhibitori su odgovorni za procese prometa i remodelovanja ekstraćelijskog matriksa, ćelijsku atheziju i migraciju, tako da učestvuju u puno patofizioloških procesa, kao što su tromboza, fibroza, ateroskleroza, širenje kancera i drugih. Merenje ekspresije i nivoa PAI-1 se sugeriše u proceni faktora rizika pojedinih bolesti. Takođe, PAI-1 se smatra mogućim terapijskim ciljem koji bi modifikovao razvoj i progresiju bolesti. Cilj ovog rada bio je da istakne značajna otkrića vezana za upotrebu PAI-1 u dijagnostici, proceni faktora rizika i patogenetskom tretmanu različitih bolesti.

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Ključne reči: *sistem plasminogena, ekstraćelijski matriks, fibrogeneza, metastaza kancera*