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Current status and potential future of PAI-1 inhibitors

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ABSTRACT

PAI-1 is an important factor in the fibrinolytic system. It is also involved in the etiopathogenesis of atherosclerotic processes, metabolic syndrome, obesity, and a significant number of solid and some of the hematological malignancies and even has valuable prognostic value. In this article, we review involvement of PAI-1 in areas other than the fibyrinolytic system, its roles, and its potential contribution to regulatory mechanisms and inhibition pathways. Many important studies proved that PAI-1 is significantly increased in obesity, metabolic syndrome, a significant proportion of malignancies. Although cell culture studies, in vivo studies and animal experiments have provided data on PAI-1 inhibition and models that block the pathways through which PAI-1 is metabolized and acts, suggesting that this blockade can reverse tumor progression, improve metabolic syndrome parameters and improve atherosclerotic processes, the results of these inhibitory agents in humans are still unknown and worth investigating. The upcoming phase 1-2 studies will answer these questions.

Keywords: PAI-1, PAI-1 inhibitors, malignancies, potential, metabolic syndrome

INTRODUCTION

Fibrinolysis is vital for mammalian physiology. The main component of fibrinolysis is plasmin, which breaks down fibrin. Existing other components form the main stem of the system.

Plasminogen is the pro-enzyme for plasmin and can be converted to plasmin by tissue-type plasminogen activator (tPA) or urokinase-type plasminogen activator (uPA). tPA is synthesized mainly by endothelial cells through multiple special stimuli and receptors. Plasminogen activator inhibitor type 1 (PAI-1), an antagonizing structure to this mechanism, acts as an inhibitor of tPA and Upa.[1,2]

PAI-1 is a prominent member of the serine protease inhibitor family (SERPIN). PAI-1 is a single-chain glycoprotein produced primarily by endothelial cells and platelets, but can also be produced by peritoneum, endometrium, megakaryocytes, mesenchymal stem cells, monocytes/macrophages, cardiomyocytes, hepatocytes, smooth muscle cells, fibroblasts and adipocytes.[3-5]

Similarly, although previous research has mainly focused on the function of PAI-1 in the coagulation and fibrinolytic system, a growing number of studies have shown that abnormal expression of PAI-1 is also associated with various pathological conditions such as blood diseases, obesity, metabolic syndrome and tumors.[6]

Since PAI-1 is recognized as a risk factor in the development of various pathological conditions, there has been an intense effort to develop inhibitors of PAI-1.

PAI-1 inhibitors have a potential therapeutic role in both for etiopathogenesis and treatment of chronic complex inhibitors.

STRUCTURE OF PAI-1

Features of the three-dimensional structure of PAI-1 have provided insight to the function and activity status of the molecule. PAI-1 is unstable in the absence of a carrier protein vitronectin.[7]

PAI-1 has a flexible reactive center loop (RCL) at its surface, which contains the substrate-mimicking peptide sequence. The structure of the PAI-1 has been the target for developing its inhibitors. Understanding the structure and function of the PAI-1 protein is crucial to develop its inhibitors.

PAI-1 blocks the actions of t-PA and u-PA. Additionally, PAI-1 interacts with cofactors of vitronectin or the glycosaminoglycan heparin to inhibit thrombin.

There have been intensive studies on the interaction of PAI-1 with these cofactors at the tissue level. Experimental and clinical studies have elucidated the significance of the binding

of PAI-1 to intact fibrin for the mechanism of t-PA-mediated fibrinolysis.[8]

DEVELOPMENT OF PAI-1 INHIBITORS

PAI-1 inhibitors consist of 5 main groups: small molecules, synthetic peptides, RNA aptamers, monoclonal antibodies (mAbs), and antibody derivatives. The working principle of these groups can be summarized as follows:

- Directly blocking the initial formation of specific complexes between PAI-1 and Plasminogen activators (PA),
- Preventing the formation of the final complex, or
- Causing/accelerating the transition of the active PAI-1 molecule into a latent or inactive form.

Although numerous well-equipped and extensive in vitro and in vivo studies, clinical phase studies for various indications have been performed, no PAI-1 inhibitor is currently approved for therapeutic use in humans. Tremendous potential exists for the future.

We need to resolve the affinity and specificity issues, which are common, especially when using small molecules.

In addition, the structural plasticity of PAI-1 and its counteraction to other potential binding partners pose a real challenge for developing PAI-1 inhibitors. Therefore, a better drug design and deeper understanding of PAI-1 inhibition at the molecular level are essential to be able to use these drugs in humans to produce real and effective inhibition.[9,10]

From the hematologic point of view, PAI-1 is a negative regulator of the fibrinolytic system in the bone marrow and is also thought to act as an inhibitor of hematopoietic regeneration. After myeloablative irradiation, PAI-1 concentration is significantly increased in hypocellular bone marrow (BM) containing abundant bone marrow adipocytes (BMA). The BM-rich microenvironment harboring obese individuals is thought to be associated with the higher PAI-1 concentrations observed in this population.

Therefore, Harata et al.[11] hypothesized that PAI-1 produced by BMAs would be associated with impaired hematopoietic regeneration observed in BMA-rich microenvironments and examined whether blocking PAI-1 activity using TM5614, a PAI inhibitor, facilitates hematopoietic regeneration after HSCT in BMA-rich recipients. At the end of this investigation, they showed that higher PAI-1 concentration inhibited hematopoietic regeneration and that blocking PAI-1 activity facilitated hematopoietic regeneration in BMA-rich microenvironments after HSCT.[11-13]

In addition to this, chronic myeloid leukemia (CML) also attracts attention as an area where PAI-1 inhibitors are intensively studied. Yahata et al.[14] showed that; inhibiting PAI-1 activity can increase hematopoietic stem cell (HSC) motility, and this process may result in HSC dissociation from their niche.

These cardinal observations brought insight information that stimulated the research community to look for answers for the following questions:

- Can we improve the PAI-1 inhibition safely?
- Which of the above is the most effective method to inhibit PAI-1?
- What is the fine border between the efficacy versus safety for PAI-1 inhibitors?
- Can PAI-1 inhibition have a potential antitumor effect?
- Will PAI-1 inhibition result in CML-defective cells leaving their niches and being exposed to tyrosine kinase inhibitors more intensely and incrementally?
- Will PAI-1 inhibition result in systemic side effects?

To answer all these questions, Tohoku University group and Sasaki et al.[15] performed an in vitro experiment in which they aimed to evaluate the effect of TM5614, a PAI-1 inhibitor, on CML cells. PAI-1 inhibition has a direct and profound anti-tumor activity on CML cells. These seminal observations led to the landmark phase and phase 2 trials.

Another area of intensive research has been the use of PAI-1 inhibitors in solid tumors. Studies on experimental models report that PAI-1 plays an essential role in tumor growth, invasion, metastasis, and angiogenesis.[16,17]

PAI-1 generally plays a tumor-promoting role in cancer development and tumorigenesis. PAI-1 is a biomarker of poor prognosis. Medical community is expecting to see a future role for PAI-1 inhibitors in solid tumors based on these significant associations. Potential types of cancer for therapeutic role of PAI-1 inhibitors, include breast cancers, gastric, head and neck cancers and ovarian cancers.[18-21]

PAI-1 level serves as a biomarker target or follow-up parameter in cancer treatment. The PAI-1 inhibitors that have been evaluated previously in preclinical trials are PAI-039, SK-216, SK-116, TM5441, TM5275 and TM5614. These studies have yielded promising results and are still a matter of curiosity.[22-26]

Other types of PAI-1 inhibitors have been intensely studied. Fortenberry et al.[27] aimed to inhibit intracellular PAI-1 using RNA aptamers in their study by transfecting human breast cells. Aptamer-expressing cells exhibited decreased cell migration and invasion. Furthermore, intracellular PAI-1 and urokinase plasminogen activator (uPA) protein levels decreased, while PAI-1/uPA complex increased.

Another PAI-1 inhibitor that attracts attention with its antiangiogenic properties is SK-216. Its significant feature is that it contains an antitumor effect regardless of PAI-1 levels. In the study conducted by Masuda et al.[28] with melanoma and lung carcinoma cells; they showed that SK-216 reduced the size of subcutaneous tumors and the extent of metastases regardless of PAI-1 secretion levels from the tumor cells.

In the study conducted by Tzekaki et al.[29] on breast cancer cells using oleuropein, a natural PAI-1 inhibitor, they obtained a promising response in Er-/PR- tumors.

PAI-1 IN METABOLIC AND CARDIOVASCULAR DISEASES

PAI-1 has long been a therapeutic target in metabolic and cardiovascular diseases. High plasma concentrations of PAI-1 are well known to be associated with the development

of coronary artery disease and other vascular thrombotic diseases.[30-33] The potential effects of agents with demonstrated cardiovascular benefits on PAI-1 concentrations, particularly in type 2 diabetic patients with cardiovascular disease or increased cardiovascular risk factors, are of interest.

Sakurai et al.[34] investigated the treatment-related change in plasma PAI-1 from baseline to week 12 in type-2 DM patients treated with empagliflozin and they showed that empagliflozin decreased PAI-1 concentration.

Studies on obesity and fibrinolytic processes have helped us to understand PAI-1 better. McGill et al.[35] showed that obese diabetic subjects had a threefold increase in PAI-1 concentrations, but no significant difference in (t-PA) plasma concentrations compared to healthy lean subjects and attributed this significant increase in PAI-1 to an increase in immunoreactive insulin and C-peptide concentrations, indicating a stimulatory effect of insulin. This and similar studies in this field suggest that enlarged adipose tissue is closely associated with impaired fibrinolytic processes.[35,36]

Pharmacological agents such as thiazolidinediones, metformin and AT1-receptor antagonists have been shown to reduce adipose expression of PAI-1.[37-40] PAI-1 can explain the cardiovascular benefit of these therapeutic agents.

In addition, weight loss through dietary restriction or lifestyle modification has been shown to be effective in reducing PAI-1 plasma levels.[41] These studies suggest that increased PAI-1 expression in adipose tissue may be a cause of impaired fibrinolysis in obesity.

CONCLUSION

As a result despite the fact that PAI-1 is an important factor in the fibrinolytic system, it is also involved in the etiopathogenesis of atherosclerotic processes, metabolic syndrome, obesity, and a significant number of solid cancers, and even has valuable prognostic value. PAI-1 is likely in the crossroad of metabolic diseases and cancer. In this article, we review PAI-1 inhibitors. We summarize the role of PAI-1 in areas other than the fibrinolytic system, and its potential contribution to regulatory mechanisms and inhibition pathways. Most studies confirm that PAI-1 is significantly increased in obesity, metabolic syndrome, a significant proportion of solid cancers and some hematologic malignancies. Cell culture studies, in vivo studies and animal experiments have provided data on PAI-1 inhibition with novel agents. Studies are performed on several models that block the pathways through which PAI-1 operates. PAI-1 blockade can halt/reverse tumor progression, improve metabolic syndrome parameters and improve atherosclerotic processes.

Currently, thrombolytic agents represent the only direct way of augmenting fibrinolytic activity in humans. The results of clinical trials with novel PAI-1 inhibitors in the upcoming phase 1-2-3 studies will answer these questions.

Cancer and metabolic diseases are age related conditions. Age-related diseases are associated with inhibition of the fibrinolytic system. In the aging populations, there is tremendous potential for PAI-1 inhibitors in cardiovascular disease, arterial and venous thrombosis, aging, amyloidosis, obesity, and type 2 diabetes mellitus.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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