



Editorial

# The Role of Fibrinolytic System in Health and Disease

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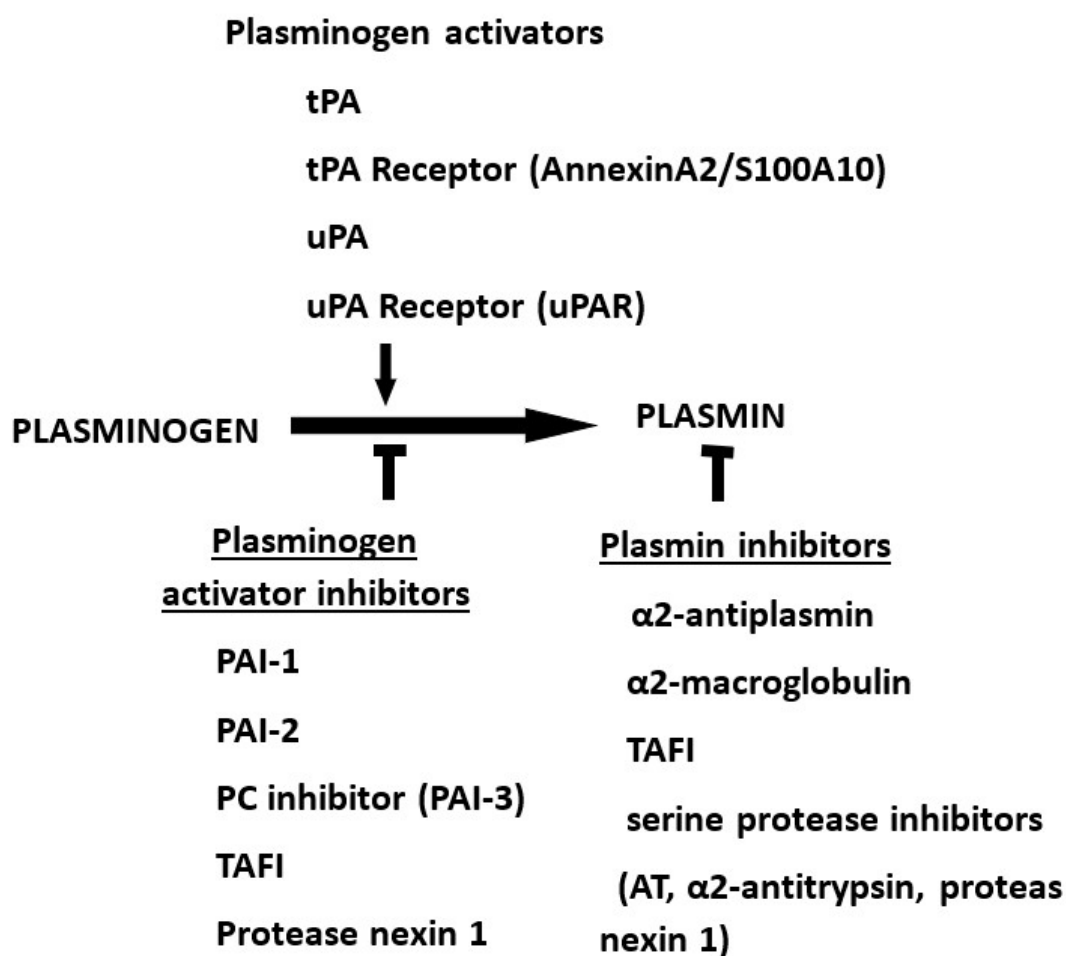


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**Abstract:** The fibrinolytic system is composed of the protease plasmin, its precursor plasminogen and their respective activators, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), counteracted by their inhibitors, plasminogen activator inhibitor type 1 (PAI-1), plasminogen activator inhibitor type 2 (PAI-2), protein C inhibitor (PCI), thrombin activable fibrinolysis inhibitor (TAFI), protease nexin 1 (PN-1) and neuroserpin. The action of plasmin is counteracted by  $\alpha$ 2-antiplasmin,  $\alpha$ 2-macroglobulin, TAFI, and other serine protease inhibitors (antithrombin and  $\alpha$ 2-antitrypsin) and PN-1 (protease nexin 1). These components are essential regulators of many physiologic processes. They are also involved in the pathogenesis of many disorders. Recent advancements in our understanding of these processes enable the opportunity of drug development in treating many of these disorders.

**Keywords:** fibrinolysis; plasmin; plasminogen activator; PAI-1; PAI-2; antiplasmin

The fibrinolytic system, also known as the plasminogen–plasmin system, is composed of a proteolytic enzyme plasmin (Pm) with its precursor plasminogen (Pg) (Figure 1) [1–7]. There are two naturally occurring activators of plasminogen, tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). In addition, the conversion from Pg to Pm can be accomplished by other proteases such as streptokinase, staphylokinase and plasmin. The actions of activators are counteracted by inhibitors, plasminogen activator type 1 (PAI-1), plasminogen activator type 2 (PAI-2), protein C inhibitor (PCI), thrombin activable fibrinolysis inhibitor (TAFI), protease nexin 1 (PN-1) and neuroserpin. Pm, on the other hand, are inhibited by  $\alpha$ 2-antiplasmin,  $\alpha$ 2-macroglobulin, TAFI and serine protease inhibitors, including antithrombin and  $\alpha$ 2-antitrypsin, and by PN-1. In addition, there are receptors for plasminogen [8] and for tPA in the form of annexin II [9–11], which is co-localized on the cell surface S-100A10 [12], as well as a receptor for uPA, uPAR [13].



**Figure 1.** The fibrinolytic (plasminogen–plasmin) system.

When first discovered, the fibrinolytic system was thought to primarily function as a regulator of fibrin formation and breakdown. Soon it was found that it is involved in many physiological and pathological functions (Tables 1 and 2). A complete review is beyond the scope of this article, but a few examples are shown below.

**Table 1.** Physiological functions of the fibrinolytic system.

|                                   |
|-----------------------------------|
| Embryogenesis                     |
| Ovulation, menstruation           |
| Pregnancy                         |
| Neuron growth                     |
| Brain function                    |
| Regulation of blood–brain barrier |
| Immunity                          |
| Wound healing                     |
| Senescence                        |
| Fibrosis                          |

**Table 2.** Role of the fibrinolytic system in multiple disorders.

|                                   |
|-----------------------------------|
| Neurologic disorders              |
| Stroke/Hemorrhagic transformation |

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|                                                         |
|---------------------------------------------------------|
| Degenerative disorders                                  |
| Cancer proliferation, invasion/metastasis, angiogenesis |
| Vascular diseases                                       |
| Atherosclerosis, myocardial infarction                  |
| Metabolic syndrome                                      |
| Trauma                                                  |
| Fibrosis                                                |

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Components of the Pg–Pm system are involved in the regulation of menstruation and pregnancy [14], with interactions between the gonadotrophins and tPA, uPA and uPAR. tPA is involved in neuronal growth and learning [15], the regulation of the blood–brain barrier [16–19], and the regulation of glucose metabolism in the brain [20]. Through multiple pathways, fibrinolytic components can modulate host immunity [21–23]. PAI-1 is involved in cell senescence [24] and physiological aging [25]. uPA/uPAR and PAI-1 regulate cell motility and migration and thus are important in wound healing [26,27].

In many types of cancer, there is evidence that there is a correlation between uPA, uPAR and PAI-1 and the aggressiveness and metastatic potential in both tumor cell cultures and tumor tissues [28–33]. In carcinoma of the breast, elevated levels of uPA and PAI-1 were found to be associated with a worse prognosis [34]. This association was used in the management of the tumor [35,36]. In carcinoma of the pancreas, the postoperative survival of those with high uPA and PAI-1 was found to be 9 months, while those without these markers was 18 months [37]. A poor response to chemotherapy in small-cell carcinoma of the lung was observed in those with high uPAR [38]. In an athymic mouse model, the transfection of PAI-1 to prostate cancer cells (PC-3) was found to inhibit growth and metastasis [39].

Fibrinolysis is a major component of trauma-induced coagulopathy [40]. As hemorrhage is the major cause of death, excessive fibrinolysis has been observed early after injury and showed a negative predictive value of outcome [41–46]. However, the status of fibrinolysis rapidly changes to a hypofibrinolytic phase, often referred to as “fibrinolytic shutdown”. Such a temporal change is part of the body’s response to injury. Persistent low fibrinolytic activity is, however, associated with poor outcomes with multi-organ failure. In one study, patients with low fibrinolytic activity for 7 days had an eightfold higher mortality rate than those whose fibrinolytic activity recovered [47]. In another study, a threefold higher mortality was seen in those with persistent fibrinolytic shutdown at 24 h after injury [48]. Furthermore, the fibrinolytic components play a major role in the pathogenesis of intracranial hemorrhage in trauma patients [40]. Notably, hyperfibrinolysis carries with it a poor prognosis. This is due in part to a breakdown of the blood–brain barrier [16,18,40], as discussed below.

In acute and chronic stress, the hemostatic balance, including endothelial activation, the activation of coagulation and altered fibrinolytic balance, are altered [49]. These changes are pro-thrombotic and hypofibrinolytic with an increase in PAI-1.

Impaired fibrinolysis has been observed in depression with an increase in PAI-1 [50]. Fibrinolysis is an important factor in brain remodeling [51]. Biomarkers for depression are correlated with hypofibrinolysis.

Neurologic functions are another area where tPA and PAI-1 are involved. A wide range of these functions includes ovulation [52], embryogenesis [53], neuronal migration [54], learning [55], the degradation of amyloid [16], stress/fear response [56], and the regulation of the blood–brain barrier [10,12,34]. Notably, tPA increases the permeability of the blood–brain barrier in both a plasmin-dependent and a plasmin-independent pathway. Plasmin activates metalloproteinase directly. Alternatively, tPA can directly activate latent platelet-derived growth factor CC (PDGF-CC), and the tPA–PAI-1 complex activates PDGF receptor alpha (PDGFRα), thus signaling intracellular PI 3K, Ras MAPK, p38

MAPK and PLC- $\gamma$ . These signal an increase in vascular permeability and open the blood–brain barrier [16,18,57,58].

Clinically, these characteristics of tPA are seen as adverse effects. In the treatment of acute ischemic stroke, tPA can increase the risk of hemorrhagic conversion. In nine clinical trials [59,60], hemorrhagic conversion resulted in severe intracranial hemorrhage within 24–36 h in 6.8% of patients, while this figure is 1% in those not receiving tPA, an increase of over fivefold. Fatal intercranial hemorrhage within 7 days occurred in 2.7% of the tPA-treated patients versus 0.4% in those not treated, an over sixfold increase.

In the cardiovascular system, PAI-1 is elevated in cardiovascular diseases [61–63] and in metabolic syndrome [64]. In a clinical trial assessing the dietary intake of saturated fatty acids, PAI-1 concentrations were twofold higher in participants at increased risk for cardiometabolic diseases compared with healthy participants. Patients with acute myocardial infarction and acute ischemic strokes were found to have higher PAI-1 levels [63]. In patients with metabolic syndrome, dietary restriction results in the lowering of the PAI-1 level [61].

During response to injury, plasmin and PAI-1 are involved in the wound healing process. Plasmin activates many latent growth factors and proteases, including metalloproteinases (MMP). The latter are responsible for the breakdown of the intercellular matrix. The failure of this process results in delayed healing and chronic inflammation with fibrosis [65]. PAI-1 enhances fibrosis in chronic inflammation in many organs [66–68]. In experimental animals, for example, transgenic mouse with the PAI-1  $-/-$  genotype, fibrosis does not occur following injury, such as the bleomycin injury model, to the lung.

In COVID-19, both tPA and PAI-1 are involved in the complex pathway in which the spike protein of SARS-Co-2 attaches to a component of the renin–aldosterone–angiotensin system, ACE 2, during the invasion of the host cells [69–71]. First, plasmin and with other proteases, trypsin and transmembrane proteases (TMPRSS 2), facilitate the binding of the spike protein to ACE 2. Following binding, ACE is internalized and unable to process the breakdown of angiotensin II, leading to its excess. The excess of angiotensin II leads to an increase in PAI-1 [72]. This contributes to the hypercoagulable state seen in COVID-19. In addition, the excess of angiotensin II binds to its receptor angiotensin II receptor 1a, causing lung injury and leading to pulmonary edema with the formation of a hyaline membrane with fibrin in the alveoli [73,74]. Here, again, plasmin is involved in clearing fibrin. Furthermore, the diffuse alveolar damage with damaged type II alveolar cells leads to decreased surfactant, which results in the induction of the p53 pathway and increased PAI-1 [75].

In summary, the role of the fibrinolytic system is not limited to the resolution of fibrin and thrombi, but is involved a wide range of physiologic conditions and pathologic disorders. The intensive research carried out in recent years has revealed many new findings. This knowledge offers an opportunity for therapeutic development, particularly in the mitigation of the adverse effects of PAI-1. Greater understanding of these functions is essential for the management of many disorders.

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