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Recent advances in understanding endogenous fibrinolysis: implications for molecular-based treatment of vascular disorders

Peter F. Bodary, Kevin J. Wickenheiser and Daniel T. Eitzman

The fate of a forming thrombus is determined through the delicate balance between the coagulation cascade, favouring clot formation, and the fibrinolytic system, favouring clot lysis. These processes occur simultaneously, and enhancement of fibrinolysis has been shown to reduce occlusive thrombus formation in animal models. This review examines the roles of the major fibrinolytic factors involved in clot lysis. The regulation of plasmin activity by plasminogen activators, α-2-antiplasmin, plasminogen activator inhibitor 1, and thrombin-activatable fibrinolysis inhibitor, and their effects on thrombus formation in vivo are discussed. Since alterations in fibrinolytic capacity appear to affect thrombus formation in animal models, there is considerable interest in the pharmacological manipulation of fibrinolysis.

Vascular thrombosis is the leading cause of morbidity and mortality among industrialised countries and results from the formation of a blood clot (thrombus) that can block the flow of blood, either partially (subocclusive) or completely (occlusive). Thrombosis often occurs in the setting of pre-existing atherosclerotic vascular disease following atherosclerotic plaque disruption, and can result in myocardial infarction or stroke (Ref. 1). Alternatively, thrombosis can

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occur secondary to a primary hypercoaguable state as is commonly present with deep vein thrombosis (DVT). In both cases of vascular thrombosis, the balance between coagulation and fibrinolysis is a critical factor in determining the fate of the forming thrombus. It has been shown that non-occlusive thrombi commonly occur after disruption of the atherosclerotic plaque and lead to plaque growth (Ref. 2). This subocclusive thrombus might be an important step in the progression of atherosclerosis. Therefore, therapeutic interventions designed to enhance endogenous lysis of the forming thrombus might not only reduce the frequency of occlusive thrombotic events but also attenuate the growth of atherosclerotic lesions. This review examines the proteins involved in fibrinolysis, their link to vascular disease, and pharmacological enhancement of the fibrinolytic system.

An overview of coagulation and fibrinolysis

The clinical consequences of intravascular thrombosis are determined in large part by a delicate balance between the coagulation cascade, favouring clot formation, and the fibrinolytic system, favouring clot lysis. Both systems involve a complex cascade of proteolytic events with important regulatory influences at each step (Fig. 1).The final effector molecule of the coagulation cascade is the serine protease thrombin, which cleaves fibrinogen to form the fibrin clot. The final effector molecule of the fibrinolytic system is plasmin, which cleaves fibrin into soluble degradation products. Plasmin is a broad-spectrum serine protease that is derived from the inactive precursor plasminogen through the action of two plasminogen activators (PAs): urokinase-type plasminogen activator (uPA) and tissue-type plasminogen activator (tPA). The PAs are in turn regulated by plasminogen activator inhibitors (PAIs), of which PAI-1 is the most physiologically relevant with regards to intravascular fibrinolysis (Ref. 3) (see Fig. 1). Regulation of plasmin activity also occurs through α-2-antiplasmin (α-2-AP) by formation of a 1:1 inhibitory complex (Ref. 4). Recent work has demonstrated an additional anti-fibrinolytic protein that might connect the coagulation and fibrinolytic cascades, known as the thrombin-activatable fibrinolysis inhibitor (TAFI) (Ref. 5). Each of the major proteins involved in the fibrinolysis cascade, and the consequences of their deficiency, is discussed in more detail below.

Proteins involved in fibrinolysis

Plasminogen

Plasminogen is found at a much higher plasma concentration than the PAs. Therefore, the availability of the two PAs in the plasma generally determines the extent of plasmin formation from plasminogen. Administration of exogenous PAs such as recombinant tPA, resulting in high circulating tPA levels, is effective treatment for the occlusive thrombus leading to acute myocardial infarction and stroke (Ref. 6).

Plasminogen-deficiency states associated with the complete absence of plasminogen, as well as dysplasminogenaemias associated with reduced plasmin activity, have been described in humans. In general these disorders are associated with an increased risk for thrombosis and ligneous conjunctivitis (ocular lesions caused by massive depositions of fibrin in the conjunctiva) (Ref. 7). Mice deficient in plasminogen display retarded growth and die prematurely, with widespread intra- and extravascular fibrin deposition (Ref. 8).

PAs

PAs specifically cleave plasminogen to form the active enzyme plasmin. The primary PA involved in intravascular fibrin degradation is tPA. It is produced and secreted from endothelial cells into the blood and is often inactivated by PAI-1 and cleared by the liver (Ref. 9). A rapid release of tPA follows physical stimuli, such as venous occlusion and physical exercise (Ref. 10), as well as chemical stimuli, such as increased catecholamines, bradykinin and desmopressin (Ref. 11). The enzyme activity of tPA on plasminogen is much greater in the presence of fibrin than when not associated with fibrin (Ref. 12). This provides a means of controlling non-specific plasminogen activation. In addition, circulating tPA activity is attenuated through the formation of an irreversible PAI-1–tPA complex.

In contrast to tPA, uPA plays a lesser role in intravascular fibrin degradation and a greater role in the degradation of extracellular matrix (Ref. 13). The serine protease uPA consists of two disulphide-linked chains and is found in large quantities in the urine and located throughout many tissues (Ref. 14). The location of uPA supports the hypothesis that it does not play the same role as tPA in intravascular fibrinolysis;

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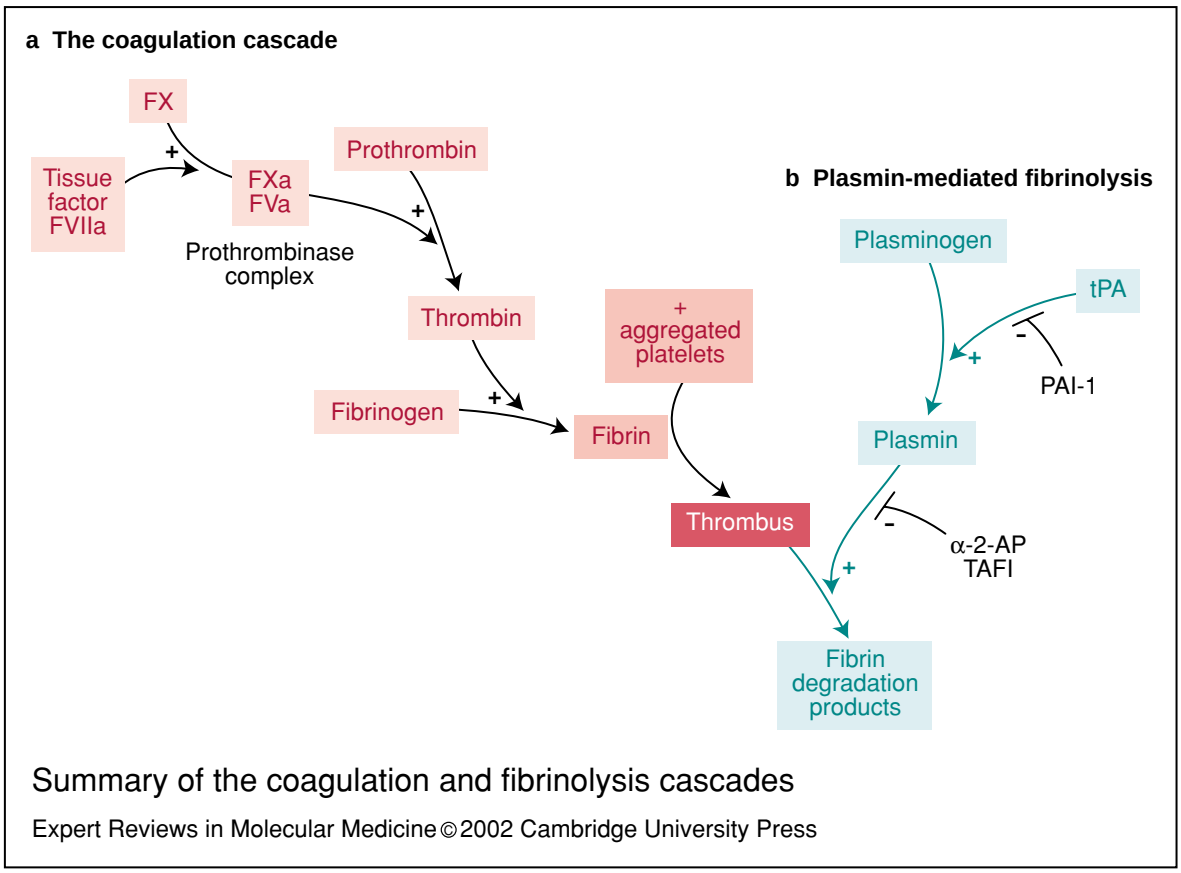

Figure 1. Summary of the coagulation and fibrinolysis cascades. (a) The coagulation cascade, which favours clot formation, is initiated in vivo by tissue factor and factor VIIa (FVIIa) and leads to the conversion of prothrombin to thrombin by the prothrombinase complex (FXa and FVa). Subsequent cleavage of fibrinogen by thrombin, along with the aggregation of platelets, can result in formation of a thrombus. The fibrin clot is further stabilised by FXIII, which is also activated by thrombin, and the clotting process is magnified by other positive-feedback loops (not shown). (b) Plasmin-mediated fibrinolysis, resulting in fibrin degradation products and clot lysis, occurs following the conversion of plasminogen to plasmin by tissue-type plasminogen activator (tPA). Plasminogen activator inhibtor 1 (PAI-1) rapidly inhibits tPA. α-2-Antiplasmin (α-2-AP) inactivates plasmin by forming a 1:1 inhibitory complex with circulating plasmin.Thrombin-activatable fibrinolysis inhibitor (TAFI) cleaves the C-terminal lysine residues of fibrin, preventing the co-activation of plasminogen by fibrin **(fig001dea)**.

however, since the single-chain form of uPA does have specificity for partially degraded fibrin (Ref. 15), it might contribute to fibrinolysis following initiation.

Although complete deficiency states of the PAs in humans have not been described, mice have been developed that are deficient in each PA individually (Ref. 8). Mice deficient in uPA develop fibrin deposits in the liver and intestines. By contrast, mice deficient in tPA do not have spontaneous fibrin deposits. Both tPA- and uPA-deficient mice are, however, more susceptible to the development of DVT after endotoxin injection in the footpad. Similar to the plasminogen-deficient mice, the doubly deficient mice ($uPA^{-/-}$, $tPA^{-/-}$) (Ref. 16) develop spontaneous fibrin deposition in the liver, intestines, gonads and lungs. In addition, these mice display poor survival and a markedly reduced capacity for experimental clot lysis.

α-2-AP

α-2-AP regulates plasmin activity by forming a 1:1 inhibitory complex with circulating plasmin through binding at lysine sites in the plasmin A chain (Ref. 4). Complex formation is initially reversible, but slowly becomes irreversible through covalent bond formation (Ref. 11). α-2-AP has a long half-life (~3 days) and a relatively high plasma concentration (~70 mg/l) (Ref. 17).

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Congenital deficiency of α-2-AP is a rare disease state that is characterised by accelerated fibrinolysis owing to uninhibited plasmin activity, and resulting in abnormal bleeding (Ref. 18). Indeed, the few rare instances of complete deficiency of α-2-AP have been identified as a result of excessive bleeding following trauma. The heterozygous siblings of these individuals appear to have little or no bleeding abnormalities despite having α-2-AP levels that are ~40–60% of normal.

Mice that are deficient in α-2-AP have normal development and fertility, and show enhanced fibrinolytic potential (Ref. 19).

PAI-1

PAI-1 also plays an important regulatory role in fibrinolysis by rapidly inhibiting both PAs, and thereby inhibiting clot lysis. PAI-1 is expressed by many cell types, including endothelial cells (Refs 20, 21), vascular smooth muscle cells, adipocytes (Refs 22, 23) and hepatocytes (Ref. 24). In addition, platelets store and release PAI-1 from their α granules (Ref. 25), which can lead to high local concentrations. PAI-1 secretion from a variety of cell types is stimulated by inflammatory cytokines (Ref. 26), thrombin (Ref. 27), very-low-density lipoprotein (VLDL) (Ref. 20), insulin or proinsulin (Refs 28, 29), and other chemical stimuli (Ref. 30).

Not all of the circulating PAI-1 is active. PAI-1 spontaneously transforms into an inactive or latent conformation that has a half-life of ~90 min in vitro (Ref. 31). Vitronectin, an abundant plasma protein, stabilises PAI-1 in the active form; it prolongs its half-life to 120 min in vitro, and appears to prolong the circulating half-life of PAI-1 in vivo (Ref. 32). Mice that are deficient in vitronectin have a slightly prolonged time to occlusive thrombosis following endothelial injury suggesting that this vitronectin–PAI-1 interaction is physiologically significant (Ref. 33).

Fay et al. have described a large kindred with offspring that have a null mutation in the gene encoding PAI-1 (Ref. 34). These offspring appear normal and have no spontaneous bleeding abnormalities. Nevertheless, several incidents have provided evidence of excessive bleeding following trauma and surgery, demonstrating the importance of PAI-1 in the regulation of fibrinolysis. During these periods of abnormal bleeding, PAI-1-deficient patients appear to respond well to the fibrinolytic inhibitors tranexamic acid and e-aminocaproic acid, indicating that the bleeding complications resulting from PAI-1 deficiency can be managed pharmacologically. There does not appear to be any spontaneous or trauma-induced bleeding abnormalities in individuals heterozygous for the PAI-1 mutation (Ref. 35).

In mice, PAI-1 deficiency leads to an enhanced capacity for clot lysis and a reduced thrombotic tendency (Refs 36, 37). These mice do not show increased spontaneous bleeding, and fertility appears normal.

TAFI

TAFI is a zymogen that can be activated (TAFIa) by plasmin, trypsin or thrombin (Ref. 5). As fibrin is degraded by plasmin, C-terminal lysines are exposed that enhance the rate of plasminogen activation to plasmin. TAFIa lyses the C-terminal lysines from the fibrin and thereby inhibits the cofactor activity of fibrin for plasminogen activation.

Because it has been discovered only recently, there is little known regarding genetic disorders of TAFI in humans. However, when TAFI levels were measured in a case–control study of human DVT, elevated levels (thereby inhibiting fibrinolysis) were found to correlate with a twofold increase in the risk of DVT (Ref. 38). Furthermore, although the results of gene-knockout studies have not been published, administration of a TAFI inhibitor to mice results in a 50% reduction in the mortality associated with thrombin-induced thromboembolism (Ref. 39). The functional importance of this potential link between the coagulative and fibrinolytic cascades will likely be elucidated in the near future.

Fibrinolysis and vascular disease

Several studies have demonstrated a link between alterations in fibrinolysis and the expression of vascular disease, although the direct influence of derangements in fibrinolysis on cardiovascular disease risk is controversial.

Fibrinogen

Elevated levels of plasma fibrinogen, the precursor of the fibrin clot, are associated with risk factors for atherosclerotic vascular disease (Refs 40, 41), such as age, smoking, diabetes mellitus, high levels of low-density lipoprotein (LDL) and obesity. However, fibrinogen also appears to be an independent risk factor for

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cardiovascular events (Refs 42, 43). It has been estimated that the relative risk for a cardiovascular event is 1.8 for individuals with fibrinogen concentrations in the upper third compared with individuals in the lower third of the range (Ref. 44). In addition, plasma fibrinogen affects plasma viscosity, which is also associated with increased risk of cardiovascular disease (Ref. 45). Surprisingly, mice deficient in fibrinogen were not protected from atherosclerosis involving the aortic arch when crossed to the atherosclerotic-prone apolipoprotein E (apoE)-deficient strain (Ref. 46). By contrast, mice deficient in fibrinogen were protected from athersclerosis when crossed to apolipoprotein(a) [apo(a)]-transgenic mice (Ref. 47). Thus, it appears fibrinogen is not essential to the growth of the atherosclerotic plaque but it might play a modifying role.

Plasminogen

Plasminogen deficiency in humans is relatively rare and the impact on atherosclerotic vascular disease is difficult to assess. However, mice deficient in plasminogen are more susceptible to atherosclerosis on the apoE-deficient background (Ref. 48). In support of a role for plasminogen activation affecting atherosclerotic vascular disease in humans, high concentrations of serum lipoprotein(a) [Lp(a)] have been shown to be a risk factor for atherosclerosis, myocardial infarction, stroke and restenosis (Refs 49, 50). Lp(a) consists of LDL with an additional protein component, apo(a), which is a plasminogen homologue and appears to inhibit plasminogen activation. Transgenic mice that express only the apo(a) component of Lp(a) develop vascular lesions when fed a high-fat diet, similar to the fatty streak lesions seen in early human atherosclerosis (Ref. 51). The inhibition of plasminogen activation by apo(a) might contribute to the development of atherosclerosis by inhibiting fibrinolysis or some other activity of plasmin.

PAI-1

An extensively studied fibrinolytic factor in atherosclerosis and thrombosis is PAI-1. Since PAI-1 rapidly inhibits both tPA and uPA, and its expression is highly regulated by a variety of cytokines and growth factors, it appears to be a critical modulator of fibrinolytic activity (Ref. 3). Increased levels of PAI-1 in the circulation are associated with DVT and myocardial infarction (Refs 52, 53). Not all studies have demonstrated a positive correlation between plasma PAI-1 and thrombotic events (Ref. 54), and these conflicting results might reflect the marked variation of PAI-1 levels both between and within individuals, as well as varying methods of sample collection and analysis. In addition, plasma levels of PAI-1 might not reflect a potentially potent local effect of PAI-1 in atherothrombotic processes (Ref. 55).

A common guanine-tract polymorphism (4G/5G) in the PAI-1 promoter has also been studied. As a result of differential binding of transcriptional regulatory proteins, the 4G allele is associated with higher plasma PAI-1 activity than the 5G allele (Refs 56, 57). The prevalence of the 4G allele (and therefore increased PAI-1 levels) is significantly higher in patients with myocardial infarction before the age of 45 than in population-based controls, suggesting an aetiological role for PAI-1 in myocardial infarction (Ref. 58).

In general, patient populations that are at high risk for vascular disease have been shown to have elevated plasma PAI-1 levels. Specifically, elevated PAI-1 is closely associated with insulin resistance and the 'multiple metabolic syndrome' (also known as Syndrome X or dysmetabolic syndrome), which includes hyperinsulinaemia, hypertension, hypertriglyceridaemia, obesity and low plasma levels of high-density lipoprotein (HDL) cholesterol (Ref. 59). These patients are at increased risk for premature atherosclerotic vascular disease. However, it has not yet been established that the elevation of PAI-1 in this syndrome is causally related to the high risk of cardiovascular disease because there are many metabolic perturbations in this syndrome.

The influence of PAI-1 on atherothrombotic disease has been analysed recently in transgenic mouse models. Atherosclerotic-prone apoE$^{-/-}$ mice deficient in PAI-1 (PAI-1$^{-/-}$, apoE$^{-/-}$) were generated and the extent of atherosclerosis was compared with that in apoE$^{-/-}$ mice (Ref. 37). Quantitation of atherosclerotic involvement of the entire macrovasculature from aged mice maintained on normal chow revealed a site-specific protection from atherosclerosis in the PAI-1-deficient mice. It appears that PAI-1 might promote the development of atherosclerosis at arterial bifurcation sites, which might relate to the important changes in flow characteristics that have been noted at these sites. The differential flow characteristics have been demonstrated to

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influence shear stress and shear-stimulated endothelial proteins such as tPA (Ref. 60), which might enhance the fibrinolytic capacity at arterial bifurcation sites. Thus, PAI-1 might play a critical role in the pathogenesis of atherosclerosis through the inhibition of fibrin clearance, and might also be an important regulator of the thrombus that forms following arterial injury (Ref. 37).

Different models of exogenous arterial injury have led to different conclusions regarding the role of PAI-1 in vascular disease. Using a perivascular electrical injury model in mice, Carmeliet et al. (Ref. 16) have demonstrated impaired intimal accumulation of vascular smooth muscle cells or 'neointima' formation in plasminogen- and uPA-deficient mice. Similarly, they have shown enhanced neointima formation in PAI-1-deficient mice, suggesting a critical role for plasmin-mediated cell migration in this model, which involves injury to arteries free of vascular disease. Similarly, in a transplant arteriosclerosis model, plasminogen deficiency was associated with reduced arteriosclerosis (Ref. 61). By contrast, using a copper cuff carotid injury model, Ploplis et al. demonstrated marked protection from lesion development in PAI-1-deficient mice (Ref. 62). Since neointima formation is most clinically relevant in the setting of pre-existing vascular disease, Zhu et al. studied the effects of ferric chloride arterial injury in atherosclerotic-prone apoE$^{-/-}$ mice with and without PAI-1 (Ref. 63). In this model, with high-fat feeding, complex lesions formed with features similar to atherosclerosis. PAI-1-deficient mice were also protected from lesion development in this model. The possibility exists that PAI-1 deficiency was protective in the latter two arterial injury models because fibrin deposition played a greater role in the genesis of the complex lesions that developed.

Pharmacological enhancement of the fibrinolytic system

Since cardiovascular events are a consequence of occlusive thrombosis, and enhancement of fibrinolysis has been demonstrated to reduce occlusive thrombus formation in animal models, there is considerable interest in the therapeutic manipulation of fibrinolysis. The administration of high doses of PAs has proven beneficial in lysing occlusive thrombi in patients presenting with acute myocardial infarction (Ref. 6). Chronic therapies aimed at improving fibrinolysis might also be beneficial and potentially safer than other chronic potent anticoagulants used for the treatment of atherothrombotic disease. PAI-1 might be a suitable target since it regulates the endogenous activity of both PAs. Several studies have demonstrated beneficial effects on in vivo thrombus formation in animal models using an inhibitory anti-PAI-1 antibody (Refs 64, 65, 66). Similarly, small-molecule inhibitors of PAI-1 have been successful in attenuating thrombosis in animal models (Ref. 67). Charlton et al. demonstrated a prolonged time to blood vessel occlusion in an electrically stimulated rat carotid artery thrombosis model (Ref. 68), and Friederich et al. (Ref. 67) demonstrated reduced thrombus growth in rabbits treated with XR5118 (a novel low-molecular-weight inhibitor of PAI-1).

Some of the beneficial effects of drugs used currently to treat humans with cardiovascular disease might be mediated by enhancement of fibrinolysis. For example, angiotensin-converting enzyme (ACE) inhibitors have been shown to provide protection against ischaemic, presumably thrombotic, events (Ref. 69). Although the mechanism of this protection is not completely understood, ACE inhibition significantly reduces plasma PAI-1 levels in patients with cardiovascular disease (Ref. 70). Kruszynska et al. (Ref. 71) have demonstrated that the insulin-sensitising drug troglitazone can significantly reduce PAI-1 in diabetic patients. By normalising the elevated PAI-1 levels in these individuals, troglitiazone might attenuate the risk of a thrombotic event. Oestrogen replacement therapy has also been shown to reduce PAI-1 levels in postmenopausal women (Ref. 72), although the net effect of oestrogen replacement therapy on thrombotic events appears to be deleterious (Ref. 73).

In conclusion, the weight of the current evidence favours an important role of fibrinolysis in the prevention of atherothrombotic vascular disease. Further advances in the field await the development of safe, effective drugs that will enhance fibrinolysis. In particular, inhibition of PAI-1 might be a particularly attractive target given its predicted wide therapeutic index.

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Further reading, resources and contacts

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The Medical Biochemistry Page, created by Michael King at Terre Haute Center for Medical Education, Indiana University School of Medicine, USA, includes a section on blood coagulation that describes the process and molecules involved in detail.

http://web.indstate.edu/thcme/mwking/blood-coagulation.html

Features associated with this article

Figure

Figure 1. Summary of the coagulation and fibrinolysis cascades (fig001dea).

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