Regulation of Fibrinolysis by Thrombin Activatable Fibrinolysis Inhibitor, an Unstable Carboxypeptidase B That Unites the Pathways of Coagulation and Fibrinolysis

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Abstract—The coagulation and fibrinolytic systems safeguard the patency of the vasculature and surrounding tissue. Cross regulation of coagulation and fibrinolysis plays an important role in preserving a balanced hemostatic process. Identification of Thrombin Activatable Fibrinolysis Inhibitor (TAFI) as an inhibitor of fibrinolysis and one of the main intermediates between coagulation and fibrinolysis, greatly improved our understanding of cross regulation of coagulation and fibrinolysis. As TAFI is an enzyme that is activated by thrombin generated by the coagulation system, its activation is sensitive to the dynamics of the coagulation system. Defects in coagulation, such as in thrombosis or hemophilia, resonate in TAFI-mediated regulation of fibrinolysis and imply that clinical symptoms of coagulation defects are amplified by unbalanced fibrinolysis. Thrombomodulin promotes the generation of both antithrombotic activated protein C (APC) and prothrombotic (antifibrinolytic) activated TAFI, illustrating the paradoxical effects of thrombomodulin on the regulation of coagulation and fibrinolysis. This review will discuss the role of TAFI in the regulation of fibrinolysis and detail its regulation of activation and its potential therapeutic applications in thrombotic disease and bleeding disorders. (Arterioscler Thromb Vasc Biol. 2006;26:2445-2453.)

Key Words: coagulation ■ fibrinolysis ■ carboxypeptidase B ■ TAFI ■ thrombomodulin ■ APC ■ hemophilia

Thrombin Activatable Fibrinolysis Inhibitor (TAFI) is an enzyme that is activated by thrombin generated by the coagulation system and which downregulates fibrinolysis. It is, therefore, considered to play an important role in the regulation of fibrinolysis by the coagulation system. Independent identification of TAFI by different groups resulted in different nomenclature for the same protein. Consequently, activated TAFI (TAFIa), plasma carboxypeptidase B (pCPB), carboxypeptidase U (CPU), or carboxypeptidase R (CPR) are all used in literature to denote the active enzyme TAFIa, whereas TAFI, procarboxypeptidase U (pro-CPU), plasma procarboxypeptidase B (pro-pCPB), or procarboxypeptidase R (pro-CPR) are used to denote thezymogen, TAFI.1–4 In this review TAFI will be used to indicate the zymogen and TAFIa to indicate the enzyme.

Activation of TAFI by thrombin is greatly enhanced in the presence of thrombomodulin and this presents two distinct pathways for TAFI activation: (1) by relative low concentrations of thrombin in the presence of thrombomodulin, and (2) by relative high concentrations of thrombin generated via the intrinsic pathway of coagulation in the absence of thrombomodulin. Activation of TAFI is therefore sensitive to the dynamics of coagulation and so is its inhibition of fibrinolysis. The fact that TAFIa inhibits fibrinolysis by modulating the fibrin cofactor function for plasmin generation, rather than by direct irreversible inhibition, and the fact that the activity of TAFIa is short-lived contribute to the dynamics of this system.

The discovery of TAFI greatly facilitated our understanding of cross regulation between coagulation and fibrinolysis. The redundancy in the fibrinolytic pathway hampered much of the earlier work addressing the physiological role of TAFI.5–7 Initially, only a role for TAFI in exogenous (tPA-induced) fibrinolysis could be demonstrated.8–11 Nevertheless, its (anticipated) important role in the regulation of endogenous fibrinolysis is now slowly crystallizing.12–15 Increased risks of thrombotic complications associated with an overacting coagulation pathway or the chance of bleeding accompanying coagulation defects are generally accepted. Much less appreciated is the fact that changes in thrombin formation resonate in the degree of clot protection via the activation of TAFI. For instance, to what degree is the bleeding diathesis in hemophilia patients attributable to defects in clot protection versus defects in clot formation? How much does increased activation of TAFI contribute to the elevated risk of venous thrombosis associated with high levels coagulation factors II, VIII, IX, and XI? These questions highlight the importance and complexity of cross-
Inhibition of Fibrinolysis by Activated TAFI
TAFIa inhibits fibrinolysis by abrogating plasmin-mediated auto-feedback loops designed to generate a burst of plasmin formation. Plasmin promotes its own formation in at least two ways (Figure 1). On one hand, continuous cleavage of fibrin by plasmin generates new C-terminal lysine residues that act as binding sites for plasminogen and tPA and greatly enhance the efficiency of tPA-mediated plasminogen activation. Proteolysis of these C-terminal Lysine residues from partially degraded fibrin by TAFIa abrogates the fibrin cofactor function for tPA-mediated plasminogen activation and effectively shuts down plasmin formation. On the other hand, plasmin promotes its own formation by proteolytically truncating native Glu-plasminogen to generate Lys-plasminogen. Lys-plasminogen is a better substrate for tPA and it does not have the stringent requirement for partially degraded fibrin (C-terminal Lys) as a cofactor in the activation by tPA. The diminished cofactor role of partially degraded fibrin in the activation of Lys-plasminogen is most likely the reason why the activation of Lys-plasminogen is not (less) susceptible to downregulation by TAFIa. Therefore, on the generation of Lys-plasminogen fibrinolysis is no longer opposed by TAFIa and proceeds into the propagation phase (Figure 1). Nevertheless, TAFIa prevents the progression of fibrinolysis into the propagation phase by directly inhibiting the conversion of Glu to Lys-plasminogen by abrogating the fibrin cofactor function and indirectly by inhibition of plasmin formation from Glu-plasminogen.

Recent data from two groups indicate that TAFI affects the clot dissolution through a threshold-dependent mechanism: as long as the TAFIa concentration remains above the threshold, TAFIa prevents the progression of lysis into the propagation phase. Removal of the available plasminogen binding sites on fibrin combined with the inhibition of Lys-plasminogen formation are the basis for this phenomenon. From the moment the TAFIa concentration drops below its threshold value, plasminogen binding sites become available, plasmin is generated and via plasmin-mediated feedback the number of C-terminal lysine residues increases exponentially. Plasmin can now truncate native Glu-plasminogen into Lys-plasminogen, which is not only a better substrate for tPA but its activation is no longer under control by TAFIa. Thus, a TAFIa concentration below the threshold results in an accelerated rate of lysis and abrogation of TAFIa-mediated inhibition of lysis. This threshold value for TAFIa-mediated inhibition of fibrinolysis is dependent on the rate of TAFIa formation, the intrinsic instability of TAFIa, the presence of plasmin inhibitors, and the tPA concentration.

Although the discussion in this review is limited to tPA-mediated fibrinolysis, TAFIa also inhibits fibrinolysis...
initiated by other plasminogen activators (such as urokinase). In addition, TAFIa inhibits plasminogen binding and activation on cells suggesting a possible role for TAFI in cellular fibrinolysis and possibly inflammation as well.

**Activation of TAFI by the Extrinsic and Intrinsic Coagulation Pathway**

Activation of TAFI by thrombin is an inefficient process and requires relatively high concentrations of thrombin. At high tissue factor concentration, the initial generation of factor Xα exceeds inhibition by its inhibitors tissue factor pathway inhibitor (TFPI) and ATIII and thrombin formation continues inside the fibrin clot (Figure 2). In contrast, at low tissue factor concentrations, when generation of factor Xα is limited, thrombin-catalyzed activation of factor XI continues the generation of thrombin via the intrinsic pathway after clot formation. Although only small amounts of factor Xα are initially formed, the intrinsic pathway, because of the continued activation of factor XI by thrombin and the amplification power of both the tenase and the prothrombinase complex, provides for a secondary burst of thrombin formation. These relatively high concentrations of thrombin are required for the activation of TAFI and contrast the small initial amounts of thrombin that are sufficient for fibrin formation. Thus dependent on the concentration of tissue factor during initiation of coagulation the secondary burst of thrombin formation required for activation of TAFI is generated by the extrinsic pathway (high tissue factor concentrations) or the intrinsic pathway (low tissue factor concentrations) (Figure 2). Although TAFIa-mediated prolongation of the clot lysis is indifferent as to how the thrombin is generated and the degree of downregulation of fibrinolysis remains the same over a broad range of tissue factor concentrations (Figure 3), the pathways responsible for TAFI activation shift from extrinsic pathway–mediated TAFI activation to intrinsic pathway–mediated TAFI activation with decreasing concentrations of tissue factor. The thrombin requirements for TAFI activation are different in the presence of thrombomodulin as discussed below.

**Activation of TAFI by Thrombin–Thrombomodulin**

The endothelial cell receptor thrombomodulin stimulates the activation of TAFI by thrombin ~1250-fold and eliminates the need for high thrombin concentrations. In the presence of thrombomodulin, the activation of TAFI is therefore independent of thrombin generation via the intrinsic pathway. Accordingly, thrombomodulin corrects the premature lysis of clots from factor X-, IX-, VIII-, and XI-deficient plasmas in vitro and potentially provides an additional way to correct the hyper fibrinolysis in patients with hemophilia (see below). The cofactor role of thrombomodulin in the activation of TAFI and regulation of fibrinolysis by TAFI adds an additional layer of complexity as thrombomodulin is also an essential cofactor for thrombin-mediated activation of anticoagulant protein C. APC, together with its cofactor protein S, inactivates the coagulation cofactors Va and VIIIa that are required for efficient thrombin generation. It is via inhibition of thrombin formation and subsequent decreased TAFI activation that APC exerts its profibrinolytic effect (Figure 3).
The relative concentration of thrombomodulin is an important factor in the regulation of profibrinolytic (stimulation of protein C activation) and antifibrinolytic (stimulation of TAFI activation) effects by thrombomodulin. We found that at relative low thrombomodulin concentrations, fibrinolysis is downregulated by stimulation of TAFI activation, whereas the profibrinolytic effects of protein C activation becomes more pronounced at relative high concentrations of thrombomodulin. Inhibition of thrombin formation by APC then limits TAFI activation. Therefore, stimulation of protein C activation at relatively high concentrations of thrombomodulin results in an upregulation of fibrinolysis. The basis for the different thrombomodulin requirements is most likely in the fact that thrombomodulin directly stimulates TAFI activation, whereas inhibition of TAFI activation via stimulation of protein C activation by thrombomodulin is indirect. Thus, indirect inhibition of TAFI activation via protein C activation requires a more robust activation by thrombin–thrombomodulin than the direct activation of TAFI by thrombin–thrombomodulin. Competition between protein C and TAFI at physiological concentrations is not anticipated to make a significant difference given the similar activation kinetics of TAFI (K_M = 0.6 to 1 μmol/L; k_cat = 0.5 to 1.2 sec^-1; plasma concentration = 70 to 275 nM) and protein C (K_M = 1 to 8 μmol/L; k_cat = 250 sec^-1; plasma concentration = 65 nM) by the thrombin–thrombomodulin complex and their plasma concentrations of 5 to 50-fold below K_M values.

Endothelial cells derived from different tissues/organ display considerable heterogeneity in their expression of thrombomodulin. Expression of thrombomodulin is dependent on the extracellular environment, the components of the extracellular matrix, and the surface to blood ratio of the vessel. Hence, the effective thrombomodulin concentration on endothelial cells can rise from less than 1 nM in the large arteries to more than 100 nM in the capillary beds. The paradoxical effects of thrombomodulin imply that TAFI is more readily activated in the larger blood vessels with relatively low thrombomodulin expression, whereas TAFI activation in the smaller capillaries with relatively high thrombomodulin expression is inhibited by APC generation (Figure 5). However, this does not take into account the presence of additional cofactors for protein C generation and function and other modulators of thrombomodulin availability.

The endothelial protein C receptor (EPCR) is such an important cofactor for protein C activation as it enhances protein C activation by thrombin–thrombomodulin up to 20-fold. Physiological activation of protein C by thrombin occurs on the endothelial cell surface, and localization of protein C on the endothelial surface by binding to EPCR greatly facilitates activation of protein C by the thrombin–thrombomodulin complex. As the expression pattern of EPCR is opposite to that of thrombomodulin, in that EPCR is relatively abundant on larger vessels with low thrombomodulin expression but its expression on small capillaries is much lower, it is suggested that EPCR allows for efficient protein C activation on larger vessels where the thrombomodulin concentration is relatively low. Thus, in the presence of EPCR profibrinolytic effects of APC will be more pronounced at lower thrombomodulin concentration because of more efficient generation of APC in the presence of EPCR (Figure 5).
Platelet factor 4 (PF4) is released from the alpha granules on platelet activation and is a soluble cofactor for protein C activation. PF4 enhances protein C activation both in vitro and in vivo, presumably via the formation of an electrostatic bridge between protein C and thrombomodulin. In contrast to stimulation of protein C activation, PF4 inhibited the activation of TAFI by the thrombin–thrombomodulin complex, indicating that PF4 enhances profibrinolytic effects of thrombomodulin. Cofactors that stimulate protein C activation, stimulate APC anticoagulant activity, inhibit TAFI activation, or modulate the availability of thrombin–thrombomodulin shift the balance between anti- and profibrinolytic effects of thrombomodulin as indicated.

Protein C inhibitor (PCI) functions in plasma as an effective inhibitor of thrombin in complex with thrombomodulin. Inhibition of thrombin by PCI is enhanced by two orders of magnitude in the presence of thrombomodulin. PCI-mediated inhibition of thrombin bound to thrombomodulin decreases the availability of thrombin–thrombomodulin complexes and thereby the activation of protein C and TAFI. Because the effects of thrombomodulin-dependent protein C and TAFI activation on fibrinolysis are dependent on the thrombomodulin concentration, the effects of PCI on fibrinolysis are similarly dependent on the thrombomodulin concentration. At low thrombomodulin concentrations, when antifibrinolytic effects of thrombomodulin dominate, PCI has a profibrinolytic effect via inhibition of TAFI activation by thrombin–thrombomodulin. In contrast, at high concentrations of thrombomodulin, PCI has an antifibrinolytic effect. This antifibrinolytic effect of PCI is attributable to inhibition of protein C activation, which results in increased thrombin formation, and increased TAFI activation. Hence, the antifibrinolytic effect of PCI (Figure 5).

Protein S is a physiological important cofactor for APC anticoagulant activity in the inactivation of factors Va and VIIIa. In addition to its cofactor role for APC anticoagulant activity, protein S has also an APC-independent direct anticoagulant effect that was recently suggested to involve stimulation of TFPI-mediated inhibition of tissue factor induced thrombin formation. Accordingly, protein S has two effects on TAFI activation and TAFIa-mediated down-regulation of fibrinolysis. The direct anticoagulant activity of protein S prolongs the lag-time of TAFI activation, whereas the APC cofactor function of protein S decreases the amplitude of TAFI activation. Collectively, these two effects of protein S on TAFI activation stimulate fibrinolysis markedly (Figure 5).

These examples highlight the complexity of TAFI activation and the regulation of fibrinolysis by TAFI. Notwithstanding, our current understanding of this system has led to the appreciation of coagulation and fibrinolysis crossregulation, and this will improve our ability to anticipate the effects of crossregulation in various diseases. One such area where our evolving understanding of TAFI-mediated cross regulation of coagulation and fibrinolysis could benefit is hemophilia.

**Antifibrinolytic Treatment for Hemophilia**

Bleeding in hemophiliacs occurs predominantly hours or days after injury despite normal plasma levels of factors VII and X. These phenomena have been attributed to defective fibrin formation, but these observations also point to a potential role for impaired downregulation of fibrinolysis by TAFIa in the bleeding manifestation of hemophiliacs. Indeed, in a controlled trial of antifibrinolytic therapy in hemophilia, patients undergoing dental extractions characteristically bled from tooth sockets after 3 to 5 days, whereas bleeding was completely prevented in patients receiving the antifibrinolytic agent e-aminocaproic acid (eACA). This lysine analogue acts very similar to TAFIa in that it inhibits plasmin formation by preventing the binding of plasminogen to C-terminal Lysine residues on partially degraded fibrin that are required for efficient plasmin formation. These observations support the idea that the severe bleeding disorder in hemophilia patients may be attributable to triple defect: (1) reduced thrombin generation via the extrinsic pathway at low tissue factor concentrations; (2) a reduced secondary burst of thrombin generation via the intrinsic pathway, and (3) a defective downregulation of the fibrinolytic system by the intrinsic pathway. This triple defect results not only in an inadequate hemostatic response for initial clot formation but also in a lysis susceptible clot when a fibrin clot is eventually formed.

Thrombomodulin corrected the premature lysis of clots from plasmas deficient in factors of the intrinsic pathway via stimulation of TAFI activation and provided, at least in vitro, support for the idea that stimulation of TAFI activation might help prevent bleeding in hemophilia. Application of thrombomodulin in hemophilia seems counter intuitive because of its anticoagulant effect. The use of variants of
thrombomodulin that lack the ability to generate APC could, at least theoretically, overcome most of the undesired anticoagulant effects of thrombomodulin.73

Recombinant factor VIIa is a generally accepted treatment for hemophilia A and B patients with inhibitory antibodies. Factor VIIa not only improves clot formation but also improves TAFIa-dependent clot protection.74 Concentrations of factor VIIa required to normalize TAFIa-dependent clot protection varied greatly in individual plasmas of hemophilia A patients, a phenomenon that could be attributed to variations in TFPI levels. Molecular engineering of factor VIIa variants with increased catalytic activity greatly improved efficiency of factor VIIa-mediated stimulation of TAFI activation as the concentration of factor VIIa required for normalization of TAFIa-dependent clot protection decreased by two orders of magnitude.75 Therefore, enhanced inhibition of fibrinolysis by TAFI in hemophilia patients receiving recombinant factor VIIa is likely to contribute to the prevention of bleeding complications in these patients.

TAFI levels in plasma correlate with TAFIa-mediated inhibition of fibrinolysis in normal individuals, indicating that activation of TAFI by thrombin is dependent on its concentration.71 Extrapolation of this phenomenon to hemophilia A suggests that increasing the TAFI concentration should improve TAFIa-mediated inhibition of fibrinolysis in these patient plasmas. Indeed, a two-fold increase of the TAFI plasma concentration resulted in a normalization of TAFIa-dependent clot protection.83 This suggests that hemophilia patients could potentially benefit from therapeutic application of TAFI to enhance clot stability. Recent advances in molecular engineering of TAFI variants with increased enzymatic stability have reignited an interest for antifibrinolytic therapeutic applications for TAFI.

**Advances in Molecular Engineering of TAFIa Variants**

The enzymatic activity of TAFIa is unstable and highly sensitive to temperature (the half-life of TAFIa at 37°C is \(\sim\)10 minutes, 1 to 2 hours at 22°C, and several hours at 4°C).52 Inactivation of TAFIa is caused by a spontaneous conformational change. Proteolytic inactivation of TAFIa is not involved in decay of TAFIa enzymatic activity as mutagenesis of the sites responsible for proteolytic degradation of TAFIa (Arg302 for thrombin and Lys327 and/or Arg330 for plasmin) does not prevent the decay of TAFIa activity, although it prevents proteolytic degradation.76–78 In fact, mutation at these residues further decreased the stability of enzymatic activity of TAFIa. A naturally occurring TAFI polymorphism encodes a TAFI isoform (Thr325Ile) that after activation has a 2-fold prolonged half-life compared with its counterpart (Thr325). Accordingly, Ile325-TAFIa inhibited fibrinolysis 50% more effectively than Thr325-TAFIa, both in the presence and absence of thrombomodulin. This confirms that TAFI variants with a prolonged half-life inhibit fibrinolysis more effectively. It also indicates that a relatively small structural change in TAFI, such as a single amino acid change, can have marked effects on the enzymatic stability and suggests that molecular engineering approaches to construct stable TAFIa variants are ultimately feasible.

Attempts to stabilize TAFIa were first directed toward exploration of the homology with the enzymatic stable carboxypeptidase B from pancreas (CPB). Pancreatic CPB is \(\sim\)40% identical to TAFIa (note: plasma CPB [pCPB] is 100% identical to TAFIa) but in contrast to TAFIa its enzymatic activity is stable over time. Construction of a TAFI-CPB chimera (TAFI containing residues 293 to 401 of pancreatic CPB) increased the half-life of TAFIa enzymatic activity by 10-fold.79 Unfortunately, the antifibrinolytic activity of the chimeric molecule was severely compromised.

Recent molecular engineering approaches identified several residues that either alone or in combination greatly increase the TAFIa enzymatic activity without compromising antifibrinolytic activity.80,81 TAFIa variants Ser305Cys-Thr325Ile-Thr329Ile and Ser305Cys-His333Tyr-His335Gln have a prolonged half-life of 10- and 25-fold, respectively. These residues are generally located in a region (residues 300 to 340) that was previously suspected to mediate the enzymatic stability of TAFIa. Although the molecular mechanism behind TAFIa’s instability remains elusive, it is likely that the flexibility of the \(\alpha\)-helix and connecting segments (blue residues, 300 to 340; Figure 6) affects the orientation of the substrate binding residues Tyr341 and Asp349 and thus TAFIa enzymatic activity. The most stable TAFIa variant (Ser305Cys-His333Tyr-His335Gln, T1/2=5.5 hour) to date is still less stable than carboxypeptidase B from pancreas, but continuing effort will no doubt result in even more stable...
TAFIa variants. As for correcting the premature lysis of clots in hemophilia, further studies will be needed to determine the optimal stability of TAFIa for prevention of bleeding as ultimately stable TAFI also conveys a possible risk for thrombotic complications.

**Clinical Implications in Relation to Possible Therapeutic Applications for TAFI**

**Treatment of Bleeding Disorders**

A potential complication of the therapeutic application of TAFI in the treatment of bleeding disorders would be the inappropriate inhibition of fibrinolysis by increase in TAFI levels or by the use of stable TAFIa variants that may lead to thrombotic complications. High TAFI levels (above the 90th percentile) were associated with a mild increased risk for venous thrombosis.83–86 In contrast, elevated TAFI levels seemed to convey a decreased risk for arterial thrombosis.87,88 This remarkable observation prompted the hypothesis that the antifibrinolytic activities of TAFI via inactivation of complement mediators C3a and C5a and protection against bradykinin-induced hypotension might contribute to a decreased risk for arterial thrombosis (for review see refs 21,89). This hypothesis is further supported by the observation that patients with factor XI deficiency are not protected against arterial thrombosis.90 Because of the impaired activation of TAFI via the extrinsic pathway, these patients may lack the potential beneficial effects of TAFIa on the inhibition of inflammation, which plays a role in the early development of atherosclerosis. These observations illustrate our limited understanding of the interactions between TAFI and thrombosis, but also suggest that major thrombotic complications associated with therapeutic application of TAFI or stable TAFIa variants is not anticipated.

**Thrombolytic Therapy**

Inhibition of TAFIa by inhibitors (such as CPI from potato tubers) increased the efficiency of tPA-mediated thrombolysis in several in vivo animal models and accelerated the development of novel inhibitors for TAFIa.8–11 An alternative or adjunct approach is to target the activation of TAFI by using inhibitors of factor Xa. The advantage of factor Xa inhibitors over, eg, thrombin inhibitors, is that inhibition of factor Xa inhibits the generation of thrombin via the intrinsic pathway responsible for clot protection while leaving the extrinsic pathway responsible for clot formation intact. Presumably, the risk of bleeding associated with inhibition of factor Xa is less compared with the bleeding risk conveyed by the use of thrombin inhibitors. However, one should keep in mind that inhibition of TAFI activity and/or activation during thrombolysis might also result in inhibition of the beneficial effects of TAFI on inflammation (C3a, C5a, and bradykinin) and other yet unknown substrates. It may be worthwhile to pay attention to the specificity of these novel inhibitors for the different TAFIa substrates. Ideally, such thrombolytic TAFIa inhibitor will inhibit down-regulation of fibrinolysis by TAFIa without affecting its reactivity toward small peptides in order to preserve antiinflammatory effects of TAFI.

**Future Directions and Conclusions**

The discovery of TAFI greatly facilitated our understanding of crossregulation between coagulation and fibrinolysis. Our understanding of the regulation of TAFI activation and activity is evolving and aids in the unraveling of the role for TAFI in health and disease. The possibilities of therapeutic applications of TAFIa inhibitors for the improvement of thrombolysis are promising. Recent advancements in the engineering of TAFI variants with increased enzymatic stability have given new hope for possible applications where inhibition of fibrinolysis would be beneficial such as for hemophilia.

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**Disclosures**

None.

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