Thrombin-activatable fibrinolysis inhibitor (TAFI) is a 60kDa metallocarboxypeptidase produced by the liver and present in plasma. Independently discovered by several groups, the enzyme is also known as plasma procarboxypeptidase B, procarboxypeptidase R, or procarboxypeptidase U (1-5). TAFI as nomenclature was introduced by Bajar et al. (5). TAFI is expressed as a latent precursor requiring maturation via proteolytic cleavage of a 92 amino acid-long activation peptide to achieve biological activity. The activation of TAFI is known to be catalysed by plasmin, trypsin, or thrombin. Indeed, it is the thrombin-dependent activation of TAFI that represents an interesting link between coagulation and fibrinolysis, which is further supported by the marked enhancement of TAFI-activation via the endothelial receptor thrombomodulin (6). In this context, upon activation, TAFI cleaves carboxy-terminal lysine residues from partially degraded fibrin. These lysine residues can function as high affinity binding sites for tissue-type-plasminogen activator (t-PA) and plasminogen. By removing these lysine residues TAFI dampens the cofactor activity of fibrin in the activation of plasminogen resulting in a decrease of fibrinolysis (7).

The burst of thrombin during the propagation phase of coagulation has been suggested to be sufficient to activate TAFI, thereby suppressing fibrinolysis and prolonging clot lysis time (8, 9). In this issue of Thrombosis and Haemostasis, Guimaraes and Rijken (10) investigate the role TAFI might have on plasma clot lysis. Employing a choice of t-PA- (t-PA, tenecteplase, DSPA), bacterial- (staphylokinase, APSAC), and urokinase-related plasminogen activators (tcu-PA, amediplase) they demonstrate that (i) TAFI delays plasma clot lysis mediated by the plasminogen activators tested, (ii) the delay of clot lysis is dependent on the concentration of the plasminogen activators, and (iii) that α2-plasmin inhibitor does not significantly interfere with the inhibition of clot lysis by TAFI. Thus, the paper highlights the potential pivotal role of TAFI inhibition in clinical thrombolysis, since most of the plasminogen activators tested are in clinical use or evaluation for thrombolytic therapy and existing knowledge is mostly based on experiments employing t-PA.

Several investigators have shown this antifibrinolytic effect of TAFI in vitro and in vivo by using clot models generated from plasma or whole blood (mimicking endogenous fibrinolysis) or thrombolytic therapy (mimicking exogenous clot lysis), respectively (5-7, 11, 12). Applying Carboxypeptidase inhibitor from potato (CPI) has been demonstrated to be a specific inhibitor of TAFI (13). Incorporation of CPI into plasma clots or the clot surrounding plasma shortened t-PA-mediated clot lysis time by several fold on average, again suggesting that TAFI can markedly prolong clot lysis time (11). Guimaraes and Rijken also employed CPI in the present study (10): They created plasma-derived thrombi by adding thrombin to pooled blood bank plasma. Before clotting, plasminogen activators such as t-PA were added with or without CPI. Subsequently, internal clot lysis was monitored and a retardation factor was determined. For all plasminogen activators employed a relevant retardation factor could be observed demonstrating that retardation of clot lysis is not limited to t-PA mediated clot lysis. Furthermore, no correlation between the magnitude of the retardation factors and the fibrin specificity of the plasminogen activators was apparent. These data are in agreement with the recent report by Mutch et al. (14) on TAFI regulated thrombus lysis by urokinase plasminogen activator (uPA), single chain plasminogen activator (scuPA), and tPA. In a similar model employing whole blood thrombi, Mutch et al. showed that uPA mediated thrombus lysis is susceptible to

TAFI: a promising drug target?

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TAFI modulation and that increasing plasminogen concentrations partly overcome prolongation of clot lysis time by TAFI. Thus, it seems likely that TAFI acts through modulation of plasminogen binding to fibrin rather than through modulation of the binding of plasminogen activators to fibrin.

Does, and if so how does this study affect clinical applications? It favours the thrilling concept of TAFI inhibition as adjuvants in thrombolytic therapy. The principle of thrombolytic therapy is to activate the fibrinolytic system of the patient by infusing natural or chemically modified plasminogen activators. First generation thrombolytics such as streptokinase and urokinase have considerably changed the therapy of myocardial infarction, pulmonary embolism and other thrombotic diseases decades ago. Because of their considerable side effects, second and third generation thrombolytics have been developed such as rt-PA, reteplase, tenecteplase, lanoteplase, DASP, and staphylokinase, mostly differing as to their fibrin selectivity and serum half life (15, 16). Despite hypothetical advantages over established thrombolytic regimens, members of the new generation do not appear to provide benefit with respect to mortality in large clinical trials, the overall results proved rather disappointing (17-19). As far as major bleeding complications are concerned, recent trials even suggest an increased incidence of severe bleeding with some of these agents (19, 20). Adjunctive therapy with a TAFI inhibitor may therefore present a powerful tool to potentiate the thrombolytic effect and could simultaneously reduce the dose of plasminogen activators required, potentially reducing unfavourable side effects. Furthermore, current thrombolytic research focused on the development of drugs with high fibrin selectivity in order to selectively target thrombi and emboli - a goal that has hardly been achieved, yet. By its mode of action - on and within the thrombus only - a TAFI inhibitor administered along with a plasminogen activator could be a major improvement in target specific thrombolysis.

The concept of adjunctive therapy for clinical thrombolysis to improve the thrombolytic effect and/or reduce complications is not a new one. Currently, several trials are under way evaluating adjunctive therapy with GPIIb-IIIa integrin- and thrombin-inhibitors during thrombolytic therapy of acute myocardial infarction. Initial data suggest improved patency but - again - there seems to be no improvement of overall mortality and some trials suggest increased bleeding complications (21, 22). Furthermore, so-called fusion proteins combining fibrinolytic with platelet inhibitory or thrombin inhibitory properties are under investigation in preclinical studies (23, 24). Whether these approaches will generate better results remains to be proven. The same applies to TAFI inhibition. Yet, existing in vivo data are intriguing and call for further investigation: TAFI has been implicated in endogenous and exogenous clot lysis in animal models (13, 25 to 28). Klement et al. administered CPI along with t-PA in a rabbit model of arterial thrombosis and reported improved reperfusion time and patency rate (26). In a similar study Nagashima et al. assessed the impact of TAFI inhibition by CPI on t-PA mediated clot lysis, again in a rabbit model (27). Here, t-PA was administered with saline or CPI and thrombi were weighed 90 min after drug application. Coadministration of CPI markedly decreased clot weight compared to the corresponding control with t-PA alone (28). To achieve the same reduction with t-PA alone, a three-times higher dose had to be administered, demonstrating the potential of TAFI inhibition. Furthermore, Mattson et al. showed in a dog model that TAFI activation during coronary thrombosis could be inhibited by melagatran, a direct thrombin inhibitor (29). Of potential help in future investigations might be the recently generated TAFI gene deficient mouse, for which no phenotype has been reported (30). By crossing TAFI knock out mice to a heterozygous plasminogen background, Swaisgood et al. showed that inhibition with CPI resulted in a marked increase of fibrinolysis, lending additional evidence for a functional role of TAFI in this process in vivo (31). The hypothesis of a regulatory role for TAFI in fibrinolysis is also supported in humans, since TAFI levels correlated with clot lysis time in healthy individuals (32).

Finally, the function of TAFI is probably not limited to its role in thrombolysis. Several reports suggested a function as marker and possibly also mediator of deep vein thrombosis (33), type-II diabetes (34), the metabolic syndrome (35), and ischemic stroke (36). However, some of these associations have been rather weak. Also, there is conflicting data as to an association of TAFI levels and the incidence of unstable angina and acute myocardial infarction (37-40). More recently, TAFI has been implicated in wound healing (41) as well as inflammation and cell migration (31, 42). These phenomena might be directly linked to thrombosis and atherosclerosis (43). Thus, TAFI inhibition might have other favourable effects beyond or additive to its potential role as adjuvants for thrombolytic therapy, rendering the need for more in vivo data to draw definitive conclusions pertinent to this hypothesis an urgent one.

References


