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Invited critical review

Thrombin activatable fibrinolysis inhibitor (TAFI): A role in pre-eclampsia?

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Abstract

Pre-eclampsia (P-Ec) is a complex multisystem disorder of unknown aetiology reported to occur in about 6% to 8% of all pregnancies throughout the world. This disease is associated with fibrin deposition and occlusive lesions in placental vessels. Pro-thrombin activatable fibrinolysis inhibitor (pro-TAFI) is a relatively recently described glycoprotein that can be converted into its active form (TAFIa) by thrombin, thrombin–thrombomodulin and plasmin. TAFIa potentially inhibits fibrinolysis by removing C-terminal lysine and arginine residues from fibrin. These residues are required for adsorption of tissue-type plasminogen activator (t-PA) and plasminogen to fibrin. Therefore, TAFIa decreases plasmin formation and protects the fibrin clot against lysis. An increased of pro-TAFI/TAFIa levels has been reported in some clinical conditions associated with thrombotic tendency, as type II diabetes mellitus, deep vein thrombosis and symptomatic artery disease. Few studies have investigated pro-TAFI/TAFIa in normal or complicated pregnancy but contrasting results were reported. Understanding the role of pro-TAFI/TAFIa in the pathogenesis of P-Ec can hold great promise for improving P-Ec management. In this context, a large-scale study evaluating plasma TAFI antigen and activity, its synthesis and metabolism in pre-eclamptic women is required. Recently new selective TAFIa inhibitors have been developed. The design of a new therapy to treat and/or prevent P-Ec, based on successful use of TAFIa inhibitors, may have significant clinical ramifications.

Keywords: Pro-TAFI; TAFIa; Pre-eclampsia

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1. Pre-eclampsia

Pre-eclampsia (P-Ec) is a complex multisystem disorder of unknown etiology reported to occur in about 6% to 8% of all pregnancies throughout the world [1]. P-Ec is defined by blood pressure > 140 mmHg/90 mmHg at bed rest on at least two occasions 6 hours apart, proteinuria >0.3 g/L and edema occurring after the 20th week of pregnancy [2]. Normal pregnancy is associated with increases in the levels of coagulation factors and decreases in the natural anticoagulants that contribute to a hypercoagulable state [3–5]. This hypercoagulable state is thought to be part of a complex physiological adaptation, which ensures rapid and effective control of bleeding from the placental site at the time of placental separation while allowing the expansion of the maternal and fetal circulation at the uteroplacental interface during pregnancy [5,6]. P-Ec is associated with increased hypercoagulable state [7–9]. Activation of coagulation in patients with P-Ec occurs at an early stage of the disease and is often antedates with clinical symptoms and changes in some laboratory parameters. For example, there was an increase in factor VIII [10], von Willebrand factor [11], thrombin–anti-thrombin complex [12], D-Dimers [13] and soluble fibrin [14]. There was also an increased resistance to the anticoagulant property of activated protein C [12]. However, anti-thrombin levels were reduced [15], platelets have a reduced half-life [16] and its count decreased [17]. Interestingly, both anti-thrombin and platelet counts correlated with the severity of the disease [15,17].

The fibrinolytic system is also affected. In severe P-Ec for instance there was a significant reduction in plasma plasminogen activator inhibitor-1 in both peripheral and uterine blood vein [14,18]. The measurements of the end products of both peripheral and uteroplacental circulation in normotensive and P-Ec pregnancies, including soluble fibrin, thrombin anti-thrombin complex, plasmin-α_2-antiplasmin complex and D-Dimer plasma levels, revealed that an abnormal haemostatic pattern occurs in subjects with P-Ec [14]. Fibrin deposition is usually found in the subendothelium of the glomerulus, decidual segments of spiral arteries and occlusive lesions in placental vessels. Clinical manifestations of P-Ec are considered secondary to hypoperfusion, which results from microthrombi formation and excess fibrin deposition that contribute to dysfunction of the placenta and some maternal organs [9].

2. Thrombin activatable fibrinolysis inhibitor (TAFI)

Thrombin activatable fibrinolysis inhibitor (TAFI) was first reported by Hendriks et al. [19]. They described an unstable basic carboxypeptidase activity during blood coagulation and demonstrated that it originated from a previously unidentified enzyme called carboxypeptidase U-CPU (U from unstable). CPU was assumed to participate in the processing of bioactive peptides such as bradykinin and anaphylatoxins by analogy with carboxypeptidase N, another basic carboxypeptidase present in plasma. Further, a possible role of this enzyme in coagulation or fibrinolysis was suggested [20–22]. The initial clue to the important role of CPU in fibrinolysis was identified by Eaton et al. [23]. They purified a new plasminogen-binding protein, isolated the cDNA and deduced the amino acid sequence. Its sequence is similar to other known basic carboxypeptidases, especially with pancreatic carboxypeptidase B. Therefore, it was called plasma carboxypeptidase B (CPB). This enzyme was also referred as carboxypeptidase R (CPR) [24]. Finally, in 1995, Bajzar et al. [25] showed the final link between CPU, coagulation and fibrinolysis. They found that the antifibrinolytic effect of thrombin during fibrinolysis was due to the activation of a proenzyme, which they called thrombin activatable fibrinolysis inhibitor or TAFI. Amino-terminal sequencing demonstrated that TAFI, CPU, CPB and CPR are identical [25]. The preferred nomenclature has been pro-TAFI for the proenzyme and TAFIa for the active form.

3. Pro-TAFI synthesis

Pro-TAFI is a single chain plasma protein of 401 aminoacids and approximately 46,000 D molecular ratio [23]. It is synthesized in liver [25] and megakaryocyte [26] and circulates in blood as a zymogene. Pro-TAFI circulates in plasma at a concentration of approximately 73–250 nmol/L (4.4–15.0 μg/mL) [27,28].

4. Pro-TAFI activation

Physiologically pro-TAFI is cleaved at Arg 92, by thrombin, thrombin–thrombomodulin complex, and plasmin to yield a 92-amino acid fragment from the amino terminus and the TAFIa, from the carboxyl terminus [25,29,30]. Thrombin is a relatively weak activator of pro-TAFI, but in the presence of thrombomodulin the specificity constant of the reaction increases by a factor of 1250. This reaction is calcium dependent [29,30]. The catalytic efficiency of plasmin is about eight-fold higher than the activation by thrombin alone and is calcium independent [31].

Given that the pro-TAFI concentration in plasma is far below its K_m for its activation by the thrombin–thrombomodulin complex, the formation of TAFIa will be dependent on both thrombin–thrombomodulin complex and pro-TAFI concentrations [27,28,32]. A low or high pro-TAFI plasma concentration might therefore tip the balance between profibrinolytic and antifibrinolytic pathways and thereby cause a predisposition to bleeding or thrombosis [33].

5. TFPIa action

Initiation of coagulation via the extrinsic pathway generates small amounts of thrombin from prothrombin in the initiation phase. This is sufficient to form a clot by converting fibrinogen to fibrin. It is also sufficient to initiate the intrinsic pathway through thrombin-catalyzed activation of factor XI. This leads to a large burst of thrombin formation within the clot [34,35]. The thrombin level is sufficiently high in this phase to activate enough pro-TAFI yielding TAFIa. TAFIa cleaves the C-terminal lysine and arginine residues from partially degraded fibrin,