Thrombosis Research 129 (2012) S77–S81

Contents lists available at SciVerse ScienceDirect

Thrombosis Research

journal homepage: www.elsevier.com/locate/thromres

Regular Article

Factor XIII and inflammatory cells

Zsuzsa Bagoly [a], Éva Katona [a], László Muszbek [a,b,*]

[a] Clinical Research Center University of Debrecen, Medical and Health Science Center, Debrecen, Hungary
[b] Thrombosis, Hemostasis and Vascular Biology Research Group of the Hungarian Academy of Sciences, University of Debrecen, Debrecen, Hungary

ARTICLE INFO

Available online 15 March 2012

ABSTRACT

Factor XIII is a coagulation factor with multiple plasmatic and cellular functions part of which is outside of the field of traditional hemostasis. The aim of the review is to provide a brief summary on the relationship between coagulation factor XIII (FXIII) and the cells of the immune system. In the first part the structure and biochemical functions of plasma and cellular FXIII are briefly summarized. Then, the interaction between leukocytes and factor XIII is discussed. This part includes the activation of FXIII by human neutrophil elastase, the down-regulation of activated FXIII (FXIIIa) by granulocyte proteases within the clot, and the effect of FXIIIa on leukocytes. In the following part data on the expression and subcellular distribution of FXIII in monocytes/macrophages are summarized. Another part of the review is devoted to changes of FXIII expression during monocyte differentiation and monocyte activation by the classical or the alternative pathway. In the final part reports on the possible functions of cellular FXIII in monocytes and macrophages are evaluated.

Introduction

Plasma factor XIII (pFXIII) is a zymogen consisting of two potentially active catalytic A subunits (FXIII-A) and two protective/carrier B subunits (FXIII-B). FXIII-A is synthesized in cells of bone marrow origin, but it is not clear how FXIII-A is released from the cellular compartment. It does not have a signal peptide and there is no proof for its secretion by non-classical alternative pathways. FXIII-B is synthesized and secreted by hepatocytes in excess to FXIII-A. The two subunits form a tight tetrameric complex (FXIII-A_2B_2) in the plasma; practically all FXIII-A is in complex, while about 50% of FXIII-B circulates in free form. A cellular dimeric form of FXIII-A (cFXIII) is also present in the cytoplasm of platelets and monocytes/macrophages [1,2].

The concerted action of thrombin and Ca^{2+} is required for the activation of pFXIII (Fig. 1). By cleaving the Arg37- Gly38 peptide bond thrombin removes the activation peptide from the N-terminus of FXIII-A. Then, in the presence of Ca^{2+}, FXIII-B dissociates and the remaining FXIII-A dimer assumes an enzymatically active configuration (FXIIIa). The activation of pFXIII occurs rapidly on the surface of fibrin, which accelerates the activation process 80-100-folds [1,2]. The activation of cFXIII in the cytoplasm occurs through a non-proteolytic mechanism and the rise of intracellular Ca^{2+} concentration seems sufficient to bring about the active configuration [3–5].

FXIIIa, a transglutaminase (TG), catalyzes an acyl transfer reaction, resulting in ε(γ-glutamyl)lysyl cross-links between peptide chains [1,2]. The main hemostatic function of FXIIIa is to cross-link fibrin chains and covalently attach the main inhibitor of plasmin, α_2-plasmin inhibitor (α_2PI), to fibrin. The cross-linking of fibrin considerably enhances its stiffness and rigidity and makes it more resistant against shear stress. α_2PI to fibrin cross-linking has the predominant role of protecting newly formed fibrin from elimination by the fibrinolytic enzyme, plasmin [1,6,7]. The importance of these mechanisms is underlined by the severe bleeding diathesis of non-substituted FXIII-A deficient patients [8,9].

Factor XIII-leukocyte interaction

Activation of FXIII by human neutrophil elastase

Polymorphonuclear (PMN) leukocytes represent a rich source of proteolytic enzymes; they contain human neutrophil elastase (HNE), cathepsin G and metalloproteinases, which are released upon activation. In a few early studies it has been demonstrated that HNE and cathepsin G proteolytically degrade FXIII [10–12]. More recently, it was shown that HNE induced a limited cleavage of pFXIII or cFXIII that resulted in their activation, followed by much slower proteolytic inactivation (Fig. 2) [13]. Val39-Gln40 was identified as the peptide bond that was cleaved by HNE to activate FXIII. HNE-activated FXIII was capable of cross-linking fibrin γ-, and α-chains.

Since a sufficient amount of thrombin is formed during blood coagulation to activate pFXIII, HNE-induced FXIII activation is not likely to contribute significantly to the formation of FXIIIa. However, in the extravascular compartment the situation could be different. cFXIII

* Corresponding author at: University of Debrecen, Medical and Health Science Center, Clinical Research Center, 98 Nagyerdei Krt. 4032 Debrecen, Hungary. Tel.: +36 52431956; fax: +36 52340011.
E-mail address: muszbek@med.unideb.hu (L. Muszbek).

0049-3848/$ – see front matter © 2012 Published by Elsevier Ltd.
doi:10.1016/j.thromres.2012.02.040

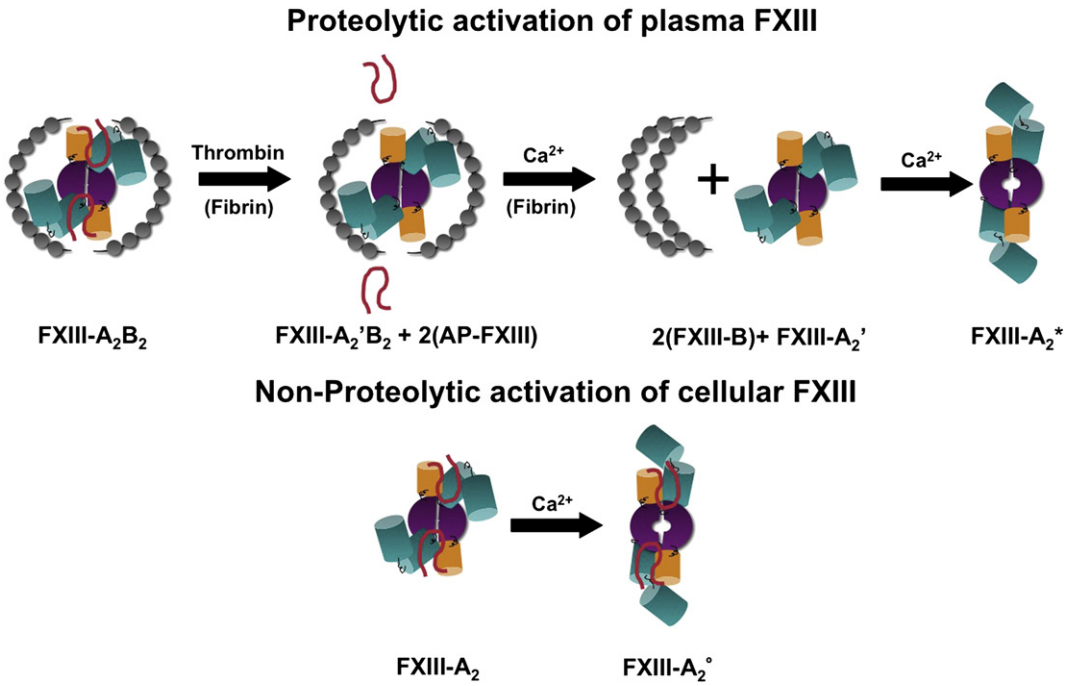

Fig. 1. The main physiological activation mechanisms of plasma and cellular FXIII. During the proteolytic activation of plasma FXIII (FXIII-A_2B_2) thrombin cleaves off the activation peptide from the A-subunits (FXIII-A), then, in the presence of Ca^{2+} the B subunits (FXIII-B) dissociate from the complex and the cleaved dimer (FXIII-A_2') assumes an enzymatically active configuration (FXIII-A_2*). The non-proteolytic activation of cellular FXIII (FXIII-A_2) occurs in the presence of Ca^{2+} and involves a slow transformation of the non-cleaved, inactive FXIII-A dimer into an active conformation (FXIII-A_2°). Green and orange cylinders represent β-barrel and β-sandwich domains of FXIII-A, respectively. The central core domains in FXIII-A are depicted as horseshoes in magenta. The activation peptide is shown as red loop. The elongated bended structure consisting of 10 pearls surrounding FXIII-A_2 corresponds to FXIII-B; the pearls represent individual sushi domains. The figure was originally published as a part of a complex figure in reference [1].

produced by macrophages and pFXIII leaked out from the plasma through capillaries could be present in extravascular body fluids and serve as a substrate for HNE released by activated inflammatory PMN leukocytes. cFXIII derived from alveolar macrophages was detected in bronchoalveolar lavage fluid (BALF). In children with chronic bronchoalveolar inflammatory diseases, the amount of cFXIII

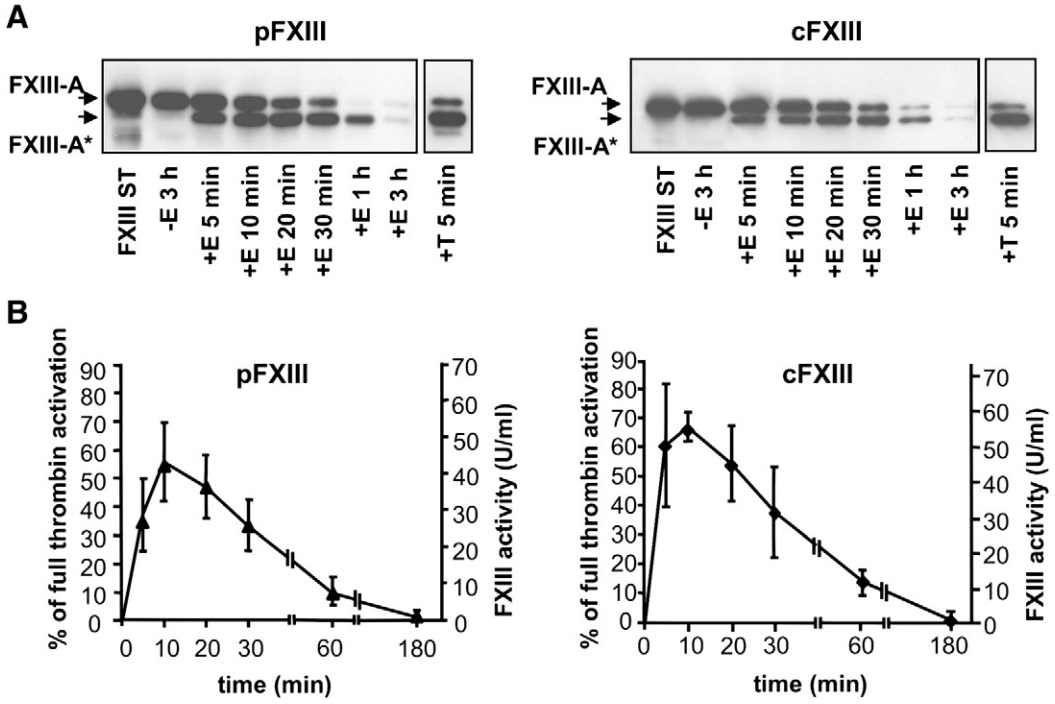

Fig. 2. Transient proteolytic activation followed by complete inactivation of plasma FXIII (pFXIII) and cellular FXIII (cFXIII) by human neutrophil elastase (HNE). The time course of FXIII activation by HNE was followed by Western blotting (A) and by spectrophotometric transglumatinase activity measurements (B). In the absence of HNE (−E) only non-activated FXIII is present. After 5 min of incubation with HNE (+E) a considerable amount of truncated FXIII-A appears and at the same time, significant transglutaminase activity is measured. The amount of activated FXIII is maximal between 10–20 minutes, then it gradually decreases due to further proteolysis. For comparison FXIII activated by thrombin is also shown on the right lanes of the gels. FXIII-A: intact A subunit of FXIII, FXIII-A*: truncated active form of FXIII-A, E: purified human neutrophil elastase, T: thrombin. The figure was originally published in reference [13] and was reproduced by the permission of the publisher (Schattauer GmbH, Stuttgart, Germany).