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Factor XIII and inflammatory cells

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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

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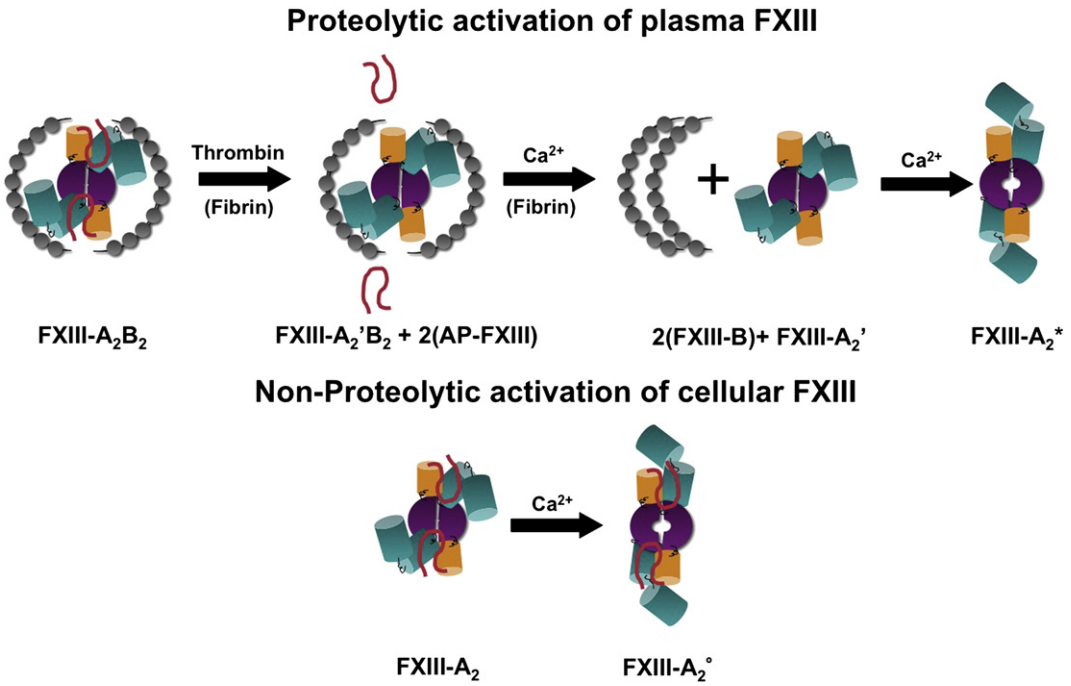

Fig. 1. The main physiological activation mechanisms of plasma and cellular FXIII. During the proteolytic activation of plasma FXIII (FXIII-A_2B_2) thrombin cleaves off the activation peptide from the A-subunits (FXIII-A), then, in the presence of Ca^{2+} the B subunits (FXIII-B) dissociate from the 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

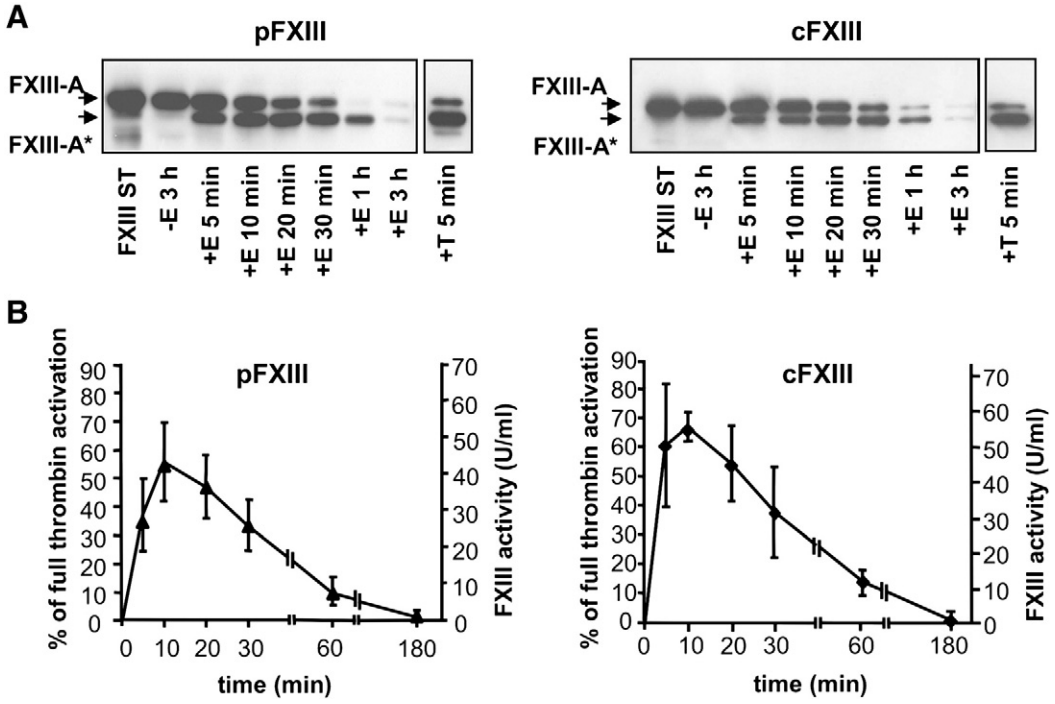

Fig. 2. Transient proteolytic activation followed by complete inactivation of plasma FXIII (pFXIII) and cellular FXIII (cFXIII) by human neutrophil elastase (HNE). The time course of FXIII activation by HNE was followed by Western blotting (A) and by spectrophotometric transglumatinase activity measurements (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).

was highly increased [14]; pFXIII also appeared in BALF. In the same patients the level of D-dimer, the fibrinolytic degradation product of fibrin(ogen) cross-linked by FXIIIa, was also elevated in BALF and showed a high level of correlation with PMN count. It seems plausible that during inflammation HNE released from activated PMN leukocytes activates FXIII present in the bronchoalveolar lining fluid and FXIIIa stabilizes fibrin(ogen) deposits, the persistence of which is a hallmark of many acute and chronic inflammatory lung diseases. Such mechanism might also operate in other body fluids.

Down-regulation of active FXIII by granulocyte proteases within the clot

PMN leukocytes incorporated in the fibrin clot became activated without any external stimulus and released proteolytic enzymes, such as HNE, cathepsin G and matrix metalloproteinase-9, which then degraded FXIIIa and resulted in the parallel loss of transglutaminase activity [15]. The proteolytic degradation of FXIIIa by PMN leukocytes was also significant in clots made from whole plasma or from fibrinogen supplemented with α_1-antitrypsin (α_1AT), the main inhibitor of PMN proteases. In the presence of α_1AT the degradation of FXIIIa by PMN proteases occurred significantly faster than that of cross-linked fibrin, which suggested that proteases released from PMN leukocytes could effectively be involved in the inactivation of FXIIIa within the fibrin clot and down-regulate the cross-linking process. This mechanism could prevent the formation of an over-cross-linked fibrin clot difficult to eliminate when it is no longer needed.

The effect of active FXIII on leukocytes

Another aspect of the interaction between leukocytes and FXIII is the effect of FXIII on these cells. FXIIIa enhanced the proliferation of peripheral blood monocytes, accelerated their migration and significantly inhibited monocyte apoptosis [16]. These changes were related to the down-regulation of thrombospondin-1 and to the up-regulation of c-Jun and Egr-1. Another interesting indirect interaction between FXIII and macrophages concerns the FXIII-dependent generation of monocyte chemotactic factor during coagulation [17]. It was suggested that the cross-linking of active complement fragment C5a or C5a des-Arg to another plasma protein was involved in the formation of the major monocyte chemotactic factor present in the serum. However no clear-cut proof has been provided. Most recently it was shown that a plasma protein with the features of ribosomal protein S19 (RP S19) is dimerized by FXIIIa on the surface of activated platelets during the clotting process, and converted into a monocyte-selective chemoattractive factor [18]. Interestingly, RP S19 showed immunological cross-reactivity with C5a. Such monocyte specific chemotactic factor(s) formed during clotting could be involved in recruiting monocytes/inflammatory macrophages to the site of injury. FXIII might also affect PMN leukocytes, since neutrophils from FXIII-treated rats had lower respiratory burst activity [19].

Cellular factor XIII in monocytes and macrophages

Expression of FXIII in monocytes/macrophages and its changes during cell activation

It has been known for a long time that cFXIII is present in platelets in huge quantity. 27 years ago when we first reported the presence of FXIII-A in monocytes [20] and peritoneal macrophages [21], the finding was received with some skepticism. However, soon similar results were reported independently [22] and since then over two hundred articles have been published on this topic. FXIII-A was detected in a number of monocyte-derived macrophages including macrophages of serous cavities, alveolar macrophages, tumor associated macrophages, histiocytic and dendritic reticulum cells, connective tissue histiocytes, perivascular dendritic macrophages, dermal dendrocytes etc. [23,24]. The demonstration of the specific mRNA in the above cell types strongly suggests that they synthesize FXIII-A [25–28]. The expression of FXIII-A in monocytes is up-regulated after malignant transformation as observed in acute and chronic myelomonocytic and monocytic leukemias [29].

The possible co-existence of cFXIII with another transglutaminase, transglutaminase-2 (TG-2; tissue TG), in monocytes/macrophages was a debated issue. Now it is clear that in resting non-activated monocytes cFXIII is the major TG. However, during differentiation or following activation considerable changes occur. A significant elevation of FXIII-A mRNA and protein level was observed during monocyte/macrophage differentiation in cell culture [30,31] and TG-2 also became up-regulated [32–34]. Induction of in vitro differentiation of monocytes into antigen presenting dendritic cells resulted in highly elevated FXIII-A expression [35–37].

Induction of the classical activation pathway by interferon γ or *Mycobacterium bovis* vaccine down-regulated FXIII-A mRNA and protein expression in cultured macrophages. In contrast, activation by IL-4 through the alternative pathway resulted in highly elevated FXIII-A mRNA and FXIII-A antigen level [35]. In line with the in vitro investigations FXIII-A was detected in tumor-associated macrophages that are considered as alternatively activated, but not in macrophages of tuberculotic granulomas that go through the classical activation pathway [35]. Using microarray technique, comparison of normal and FXIII-A-deficient cultured macrophages demonstrated that in alternatively activated human macrophages cFXIII was involved in the regulation of gene expression [38]. The most prominent differences concerned proteins involved in immune functions and wound healing.

Intracellular localization of FXIII in monocytes/macrophages

cFXIII in monocytes/macrophages is of cytoplasmic localization. However, a few studies indicated that in cultured cells it could be translocated to the surface [26,30,39]. The appearance of FXIII-A in the culture medium suggested its secretion by dendritic cells [37]. However, dying or dead cells may be the source of cell surface associated or soluble phase FXIII. Although there is evidence for cFXIII entering the alternative secretory pathway [40], its actual secretion has not been demonstrated. The involvement of cFXIII secreted or surface exposed by resident macrophages in the organization and remodeling of extracellular matrix by cross-linking matrix proteins is plausible, however, no experimental proof has been provided to support this hypothesis. Transient translocation of cFXIII to the nuclei and the incorporation of FXIIIa substrate into nuclear proteins have also been demonstrated [41]; the function of FXIIIa in the nuclear environment is not known.

Functions of cellular FXIII in monocytes and macrophages

A few studies have concerned the intracellular function of cFXIII in monocytes/macrophages. Several lines of experiments suggest that cFXIII is involved in the mechanism of phagocytosis by monocytes and macrophages. Monocytes prepared from FXIII deficient patients showed an impaired capacity of receptor-mediated phagocytosis [31]. In cultured monocytes the competitive FXIIIa substrate, MDC, significantly inhibited phagocytosis [31]. A human myelomonocytic cell line (DD cell line), incapable of phagocytosis and expressing FXIII-A, demonstrated phagocytosis and FXIII-A expression after partial differentiation following phorbol ester treatment [42]. Another report suggested the involvement of cFXIII in cell locomotion of dendritic cells [36]. As both phagocytosis and cell locomotion involve intracellular contractile elements, the interaction of cytoplasmic FXIIIa with cytoskeletal components seems feasible. Indeed, FXIIIa-induced cross-linking of cytoskeletal proteins has been demonstrated in activated platelets [1].

An interesting intracellular function of cFXIII in monocytes is the covalent dimerization of angiotensin receptor 1 (AT_1) by non-proteolytically activated cFXIII in monocytes [5]. This phenomenon can be elicited by angiotensin II-induced activation of AT_1 plus by ionomycin-induced elevation of intracellular Ca^{2+} concentration. Cross-linked AT_1 dimers displayed enhanced $G\alpha_{q/11}$-stimulated signaling, increased internalization, desensitization and enhanced adhesion of monocytes to endothelial cells. Such mechanism seems to operate in hypertensive patients and in apoE deficient mice. Follow-up studies confirming these findings are awaited.

Conclusions

PMN leukocytes release proteolytic enzymes upon activation among which HNE is able to activate FXIII. Activation of FXIII by HNE in the extravascular compartment might play a role in the cross-linking of fibrin(ogen) at the site of inflammation and this way might be involved in the pathomechanism of inflammatory diseases. Within fibrin clot PMN leukocytes become activated and proteases released by these cells inactivate FXIIIa. This is the only known mechanism for the down-regulation of FXIIIa within the clot. This down-regulation is important in preventing the formation of over-cross-linked fibrin. Treatment of peripheral blood monocytes by FXIIIa enhances their proliferation, accelerates their migration and inhibits their apoptosis. FXIII might also be involved in the production of monocyte specific chemotactic factor(s).

cFXIII, the dimer of FXIII-A, is expressed in monocytes/macrophages and in a number of related cell types. It is of cytoplasmic localization, but in certain conditions it can be translocated to the cell surface or to the nucleus. The mechanism and physiological implications of these translocations have not been revealed. The expression of cFXIII is significantly increased during monocyte/macrophage differentiation in cell culture and following malignant transformation. The effect of monocyte activation on cFXIII expression depends on the activation pathway. Activation by the classical pathway down-regulates cFXIII expression, while activation through the alternative pathway up-regulates it. The intracellular function of cFXIII in monocytes and macrophages is still to be explored. A few data indicate its involvement in the mechanism of receptor-mediated phagocytosis and in the locomotion of dendritic cells, perhaps through interaction with cytoskeletal elements. A single report implicates cFXIII in the covalent dimerization of AT1 receptor in activated monocytes that enhances monocyte-endothelial cell interaction and might play a role in the process of atherogenesis.

The data summarized above are interesting pieces of a puzzle with the potential of initiating new investigations. However, more research is needed to discover still missing important parts and to assemble the pieces into a clear picture that could reveal the full scope of interactions between FXIII and inflammatory cells.

Conflict of interest disclosure

The authors stated that there is no conflicts of interest regarding the publication of this article.

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