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REVIEW

Blood coagulation factor XIII and factor XIII deficiency

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ABSTRACT

Factor XIII (FXIII) is a multifunctional pro-γ-transglutaminase that, in addition to its well-known role in hemostasis, has a crucial role in angiogenesis, maintenance of pregnancy, wound healing, bone metabolism, and even cardio protection. FXIII deficiency (FXIIID) is a rare bleeding disorder (RBD) with an estimated incidence of one per two million that is accompanied by life-threatening bleeding such as umbilical cord bleeding, recurrent spontaneous miscarriage, and intracranial hemorrhage (ICH). Today, the disease is successfully managed by FXIII concentrate and recombinant FXIII for prophylaxis, management of minor and major bleeding, treatment of ICH, and successful delivery in women with recurrent pregnancy loss. Molecular analysis of patients with FXIIID revealed a wide spectrum of mutations, most frequently missense mutations in the FXIII-A subunit, with a few recurrent mutations observed worldwide. In vitro expression studies revealed that most of the missense mutations cause intracellular instability of the FXIII protein and, subsequently, FXIIID.

1. Introduction

Coagulation factor XIII (FXIII) is a pro-γ-transglutaminase that circulates in the plasma as heterotetramers (FXIII-A_2B_2) composed of two carrier subunits (FXIII-B_2) and two catalytic subunits (FXIII-A_2) [1]. This pro-enzyme is an important multifunctional protein that presents in a wide range of cells including platelets, megakaryocytes, monocytes, and monocyte-derived cells [1–2]. In addition to its role in the coagulation cascade, FXIII is crucial in several vital biological processes including angiogenesis, wound healing, maintenance of pregnancy, bone metabolism, and cardio protection [3–5]. Thus, patients with severe FXIII deficiency (FXIIID) present with delayed wound healing, recurrent spontaneous miscarriage, and umbilical cord bleeding as well as intracranial hemorrhage (ICH) [6]. While FXIIID can be acquired, congenital FXIIID is extremely rare. Severely affected patients require regular replacement therapy that traditionally used fresh frozen plasma (FFP) and cryoprecipitate; they now receive FXIII concentrate and recombinant FXIII (rFXIII) that is FXIII-A dimer [6–8]. Based on residual plasma FXIII activity, patients with severe FXIIID have no detectable FXIII activity while in heterozygous FXIIID, factor activity is usually 50%–70% [9]. Diagnosis of this bleeding disorder was reached by the clot solubility test that is not now recommended even for FXIIID screening; a functional FXIII activity assay should be used for this purpose, with molecular diagnosis for confirmation of disease [9,10].

2. Structure and activation of factor XIII

FXIII is a zymogen of the transglutaminase family (EC2.3.2.13) that, after activation, can covalently cross-link two fibrin molecules [11,12]. Mature FXIII-A is a 731-amino acid protein without hydrophobic leader sequence [12]. It consists of an activation peptide (AP-FXIII) that comprises the first 37 amino acids of the N-terminus (R 1–37) which buries the active site cysteine to prevent access to substrate and holds the FXIII in inactive state. So, clearly, its cleavage is necessary for FXIII-A activation. This cleavage site is between Arg37 of AP-FXIII and Gly38 of the β-sandwich domain and is typically cleaved by thrombin [13–15] (Fig. 1).

Despite the negative net charge of FXIII-A, there is a strongly positive charge around Arg37, that is in accord with the negative charge of thrombin. During activation of FXIII, AP-FXIII is cleaved by thrombin and released in the plasma [15,16]. Interestingly, full FXIII-A activity can be provided by removal of the AP-FXIII from one subunit of FXIII-A dimer [17]. Another recent study showed that the activated peptide of FXIII has a crucial role in the stability of FXIII-A_2 dimer [18] (Fig. 2).

In addition to activation of FXIII by thrombin action, this factor can be activated by high concentrations of calcium or even, at physiological ionic strength, low concentrations of calcium ions [19,20] (Fig. 3).

A trace amount of FXIII-A antigen can be detected in plasma after activation, most of which is tightly bound to fibrin trapped within the formed clot and removed from serum; meanwhile, AP-FXIII circulates in the serum [4,21]. Moreover, after FXIII-A activation, the molecular weight of this subunit decreases 4000 Da, indicating the release of AP-FXIII [22]. Next domains in the FXIII-A subunit are the β-sandwich domain (R38–184) and the catalytic core domain (R185–515). Arg260 in the catalytic core domain of one FXIII-A monomer forms a salt bridge

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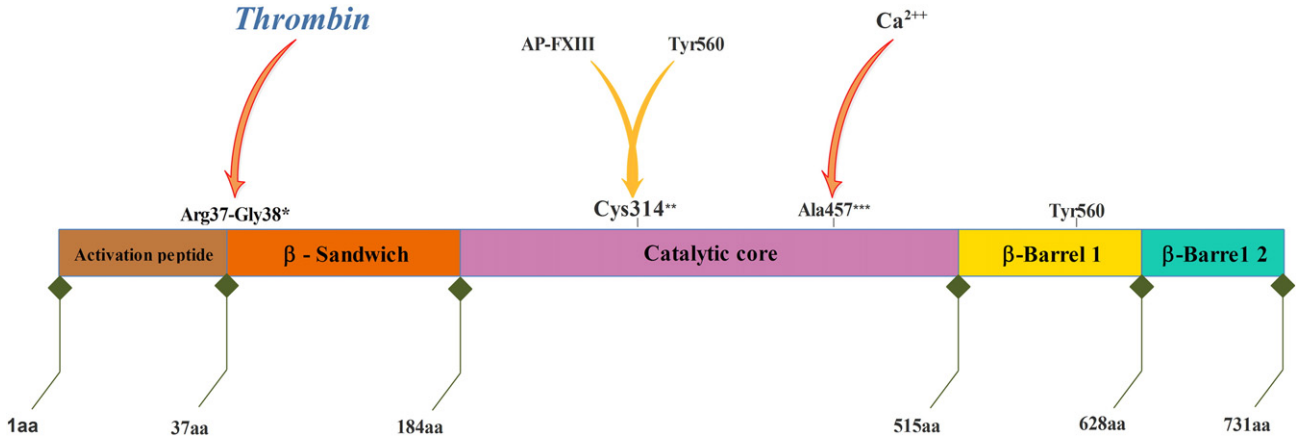

Fig. 1. Schematic structure of factor XIII-A subunit, borderline of each domain shown by arrows. *Cleavage site of thrombin is between Arg37 and Gly38 **Factor XIII-A activation peptide buries the Cys 314 in the active site of factor XIII-A subunit. ***Ala457 of the core domain is the main amino acid residue that directly binds to Ca2 +.

with Asp404 amino acid in another catalytic core domain to form a homodimer [2] (Fig. 4).

There are nine cysteines in FXIII-A; among them, Cys314 forms the active site of FXIII-A enzyme [23]. Cys314 is buried by AP-FXIII and Tyr560 side chain in β-barrel 1 (R516–628) that keeps FXIII enzyme in zymogen form. Therefore, removal of AP-FXIII and dislocation of Tyr560 is crucial for activation of the FXIII-A zymogen [24,25]. The Ca2 + cation has a crucial role in disassociation of FXIII-A and FXIII-B subunits and final activation of FXIII-A [16] (Fig. 5).

The final domain of FXIII-A, located at the C-terminal of the protein, is β-barrel 2 (R629–731) [2].

Mature FXIII-B has 641 amino acids that are synthetized by hepatocytes. The FXIII-B subunit is assembled from 10 repeated domains, also named sushi domains, each of which consists of about 60 amino acids [26,27]. The amount of FXIII-B in plasma is greater than that of FXIII-A; about 50% of FXIII-B in plasma is free [28]. During activation of FXIII, after cleavage of AP-FXIII in the presence of Ca2 +, disassociation of FXIII-B subunit occurs and finally FXIII-A is fully active [2] (Fig. 3). The precise mechanism of interaction between FXIII-A and FXIII-B is not clear and there is little information in this regard. It seems that sushi numbers 4 and 9 have a crucial role in FXIII-B dimerization while sushi number 1 has a role in the formation of FXIII-A_2B_2 heterotetramers [26,29].

3. Other roles of factor XIII

FXIII is a multifunction protein; in addition to its well-known role in the coagulation cascade, it has a critical role in the maintenance of pregnancy, angiogenesis, and wound healing as well as cardio protection and maintenance of vascular permeability. Many of these functions, such as bone deposition, vascular remodeling ,and angiogenesis, are attributed to transglutaminase activity of FXIII [30,31].

4. Factor XIII and maintenance of pregnancy

Among all the coagulation factor deficiencies, only FXIIID and fibrinogen deficiency are associated with pregnancy loss [32,33]. The exact process of pregnancy loss in FXIIID is not clear but it seems that maternal FXIII-A subunits accumulate in the placenta, at the joining site of maternal and fetal tissues, there contributing to the formation of the cytotrophoblastic shell and stabilization of the fibrinoid layer. Severe deficiency in the FXIII-A subunit gives rise to failure in the formation of the shell and layers, leading to detachment of the placenta and subsequent spontaneous miscarriage. Fibrinogen-deficient mice also suffer a loss of pregnancy, suggesting that FXIII-mediated fibrin cross-linking may be a critical mechanism underlying the loss of pregnancy in humans and mice with FXIII deficiency [34–36].

5. Factor XIII and wound healing

There are several facts that show FXIII's important role in wound healing, including the following [4,5,37–44]:

1) the successful use of fibrin sealants in surgical procedures [38],
2) delayed wound healing in patients with FXIIID as well as in FXIII-deficient mice [37],

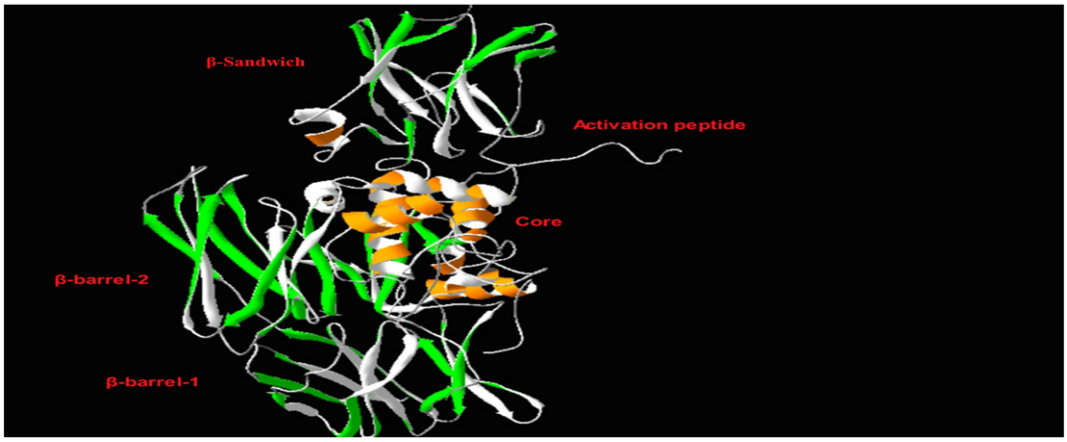

Fig. 2. X-ray structure of factor XIII-A subunit. PDB of factor XIII-A crystal structure (1f13) downloaded from Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (www.pdb.org).