

Advances of Coagulation Factor XIII

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Abstract

Objective: To provide a comprehensive literature review on roles of coagulation factor XIII (FXIII) in coagulation, wound healing, neoplasm, bone metabolism, and pregnancy.

Data Sources: All articles in PubMed with key words “Coagulation factor XIII”, “wound”, “leukemia”, “tumor”, “bone,” and “pregnancy” with published date from 2001 to 2016 were included in the study. Frequently cited publications before 2000 were also included.

Study Selection: We reviewed the role of FXIII in biologic processes as documented in clinical, animal, and *in vitro* studies.

Results: FXIII, a member of the transglutaminase (TG) family, plays key roles in various biological processes. Besides its well-known function in coagulation, the cross-linking of small molecules catalyzed by FXIII has been found in studies to help promote wound healing, improve bone metabolism, and prevent miscarriages. The study has also shown that FXIII concentration level differs in the blood of patients with leukemia and solid tumors and offers promises as a diagnostic indicator.

Conclusions: FXIII has many more biologic functions besides being known as coagulation factor. The TG activity of FXIII contributes to several processes, including wound healing, bone extracellular matrix stabilization, and the interaction between embryo and decidua of uterus. Further research is needed to elucidate the link between FXIII and leukemia and solid tumors.

Key words: Coagulation Factor XIII; Protein Cross-linking; Transglutaminase

INTRODUCTION

The discovery of coagulation factor XIII (FXIII) dates back to 1940s when a “serum factor” was found to make the fibrin clot insoluble in concentrated urea solution. It was then named “fibrin stabilizing factor.” In 1960, a case report demonstrated that the severe bleeding of a patient was due to the deficiency of fibrin stabilizing factor.^[1] Soon after this clinical finding, such fibrin stabilizing factor was formally termed FXIII in 1963.

FXIII is a transglutaminase (TG) that circulates in tetrameric form (FXIII-A₂B₂), consisting of two A subunits (FXIII-A) and two B subunits (FXIII-B). The A subunit, as the pro-TG, is made up of 732 amino acids with a molecular mass of 83,000. FXIII-A comprised five domains: The N-terminal activation peptide (AP-FXIII) (amino acids 1–37), β-sandwich (38–184), catalytic core (185–515), β-barrel 1 (516–628), and β-barrel 2 (629–731). FXIII-B is a glycoprotein consisting of 641 amino acids; its molecular mass is 80,000. It is a typical mosaic protein consisting of 10 short tandem repeats, called sushi domains.^[2] FXIII-B serves as a carrier protein and is essential for the stabilizing of FXIII-A. It accelerates

cross-linking of fibrin by promoting the formation of a ternary complex between proenzyme FXIII, prosubstrate fibrinogen, and activator thrombin.^[3] The catalytic site of FXIII-A₂ is Cys314, which is normally occluded by AP-FXIII. Initiated by thrombin, AP-FXIII is cleaved and plasma FXIII-A₂B₂ is converted to FXIIIa₂B₂. After further disassociation of FXIII-B₂ as a result of conformational change after Ca²⁺ binding, FXIII is finally transformed into activated FXIII (FXIIIa) [Figure 1].^[4] FXIII-A is mainly formed by cells originated from the bone marrow. In plasma, all FXIII-A exists in a complexed form of FXIII-A₂B₂. While the free form, FXIII-A₂ is only found intracellularly, mainly in platelets, megakaryocytes, monocytes, and macrophages.

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It is also present in chondrocytes, osteoblasts, and osteocytes. FXIII-B, synthesized by the hepatocyte, presents both as free form of FXIII-B and a complexed form of FXIII-A₂B₂ in the plasma.^[4]

As a TG, FXIII catalyzes the cross-linking of fibrin and stabilizes the fibrin clot. The substrates of FXIII add up to more than 140, including fibrinogen, fibronectin, and vitronectin. The whole complement system, including C3, C4b, C5a, can be cross-linked and immobilized by FXIII; hence, a pro-inflammatory environment is created, providing a suitable microenvironment for cellular growth.^[5] Interaction between these proteins and signal molecules on the cellular surface may activate signal pathways.

FACTOR XIII IN COAGULATION AND THROMBOSIS

FXIII is essential to form insoluble clot in coagulation to stop bleeding. FXIII is transformed to activated FXIII by thrombin with the help of Ca²⁺ and catalyzes cross-linking of fibrin, converted from fibrinogen by activated thrombin [Figure 1]. Fibrin cross-linking is a highly specific acyl transfer reaction consisting of two steps: (1) glutamine of the substrate forms a binary complex with the active site cysteine of the enzyme through the thioester linkage, accompanied by ammonia release; (2) the acyl group of the binary complex is transferred to the acyl acceptor amine and form an isopeptide, releasing the enzyme at the same time.^[6] Fibrin included two α-chains, two β-chains, and two γ-chains, linked by the disulfide bond. FXIIIa cross-links fibrin chains, during which γ-chain dimers and α-chain polymers are formed. γ-chain dimer formation between lysine of one γ-chain and glutamine of the other γ-chain is fast, followed by the formation of α-polymers.^[7] γ-chain multimers from progressive cross-linking of γ-chain dimers, accompanied by cross-linking between α-chain and γ-chain, further stabilize the fibrin clot.^[8,9]

α₂-antiplasmin (α₂AT) is one of the substrates of FXIII that can be cross-linked to fibrin, further strengthening its antifibrinolytic ability.^[10] Other substrates of FXIII include plasminogen activator inhibitor 2, plasminogen, and thrombin activatable fibrinolysis inhibitor, whose roles in fibrinolysis and thrombosis remain to be studied.^[5]

FXIII deficiency is a rare type of disorder that often causes bleeding manifestations, sometimes life-threatening central nerve system (CNS) bleeding.^[11] FXIII deficiency could be congenital or acquired. The prevalence of congenital FXIII deficiency is about 1:2,000,000 in general population. It is often caused by mutation in either subunit A or B gene.^[12] A research of 190 patients with congenital FXIII deficiency revealed that major clinical manifestations include umbilical bleeding of neonates, deep soft tissue hematoma, prolonged wound bleeding, mucosal bleeding (gum bleeding, epistaxis, prolonged menstrual bleeding), and CNS bleeding. After purified human plasma FXIII treatment, the chance of major bleeding decreased.^[13]

Researches on acquired FXIII deficiency are mostly case reports. Patients may develop antibodies for FXIII-A or FXIII-B from autoimmune or neoplastic disease and usages of certain medications. Soft tissue bleeding is most commonly seen. There are also cases of life-threatening bleeding.^[12] FXIII deficiency has been found in children with malignant disease including acute myeloid leukemia and acute lymphoblastic leukemia (ALL), and solid tumor such as neuroblastoma, non-Hodgkin lymphoma and disseminated alveolar rhabdomyosarcoma, with the presence of bleeding manifestations.^[14]

Link between FXIII level and thrombosis is not yet clear. One research focused on pulmonary embolism (PE) demonstrated that patients with PE (*n* = 71) have lower FXIII levels than patients without (*n* = 49). Similar results were observed in fibrinogen level, indicating that lower level of FXIII in

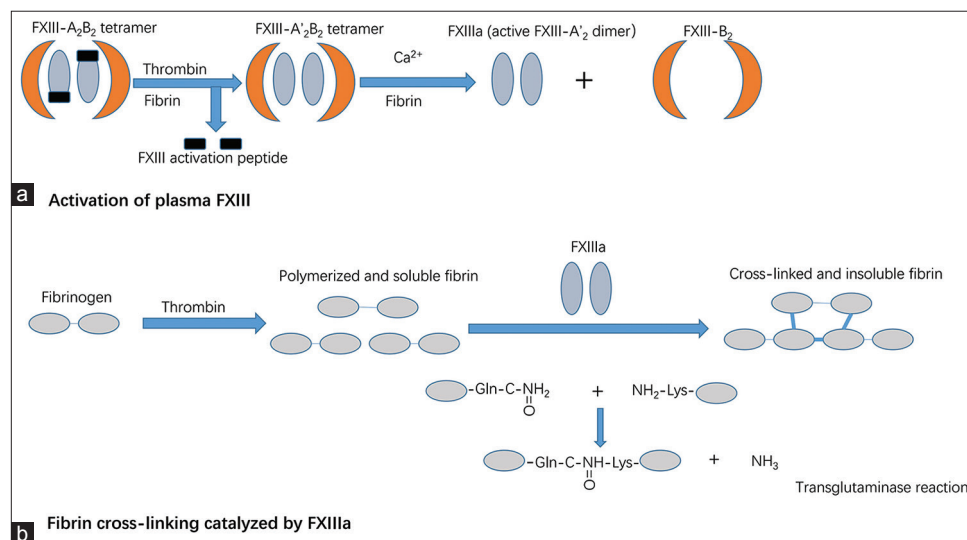


Figure 1: (a) Initiated by thrombin, the AP-FXIII is cleaved. FXIII is converted to FXIIIa after further disassociation of FXIII-B₂. (b) After the initial conversion of fibrinogen into soluble fibrin by thrombin, FXIIIa cross-links Gln and Lys residues of fibrins, which further leads to the formation of insoluble fibrin network. AP-FXIII: Activation peptide factor XIII; FXIII: Factor XIII; FXIIIa: Activated factor XIII; Gln: Glutamine; Lys: Lysine.

patients with PE might be a result of consumption during clot formation.^[15] Studies have also shown that the role of FXIII in thrombosis may be affected by factors such as age and gender. Two studies with 955 and 278 patients, respectively, reported that increased FXIII plasma concentration was associated with increased incidence rate of myocardial infarction and peripheral artery disease in female patients.^[16,17]

FACTOR XIII IN WOUND HEALING

Proliferation of granulation tissues is one of the major processes of wound healing. Coagulation cascade usually starts right after the wound is formed. Inflammatory cells such as macrophages and neutrophils will migrate to the wounded area due to the chemotactic effect induced by cytokines. Angiogenesis then starts under the influence of growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factor, and transforming growth factor- β . The newly synthesized small vessels, together with fibrin, will form the granulation tissue. FXIII also plays an important part in the process. Besides the significant role in the coagulation cascade, immobilized FXIIIa in the tissue of the wound supports platelet adhesion through integrins ($\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$) on the surface of the platelet, a process independent of FXIIIa TG activity,^[18] thus stabilizing the provisional matrix at the very early stage of wound healing. Bacteria are immobilized via cross-linking to fibrin fibers by the action of FXIII.^[19] FXIII is also able to cross-link with many molecules such as fibronectin and vitronectin, which adheres to the integrin of inflammatory cells that would migrate to the wound later. As a result, adhesion of the inflammatory cells is enhanced, and integrin-related signal pathway is activated. It is found that fibronectin plays a potential role in the activation of macrophage,^[20] and cross-linked vitronectin can inhibit apoptosis of neutrophils.^[21]

FXIII also plays an important role in angiogenesis. VEGF receptor-2 (VEGFR-2) and $\alpha_v\beta_3$ on the surface of vascular endothelial cells are both signal molecules in angiogenesis, which can be activated by fibronectin and vitronectin when cross-linked with FXIII.^[22] VEGFR-2/ $\alpha_v\beta_3$ complex formation mediated by FXIII further activates the signal pathway of both molecules.^[23]

The role of FXIII in wound healing is supported by research in both animal studies and clinical cases. Exposure to dextran sulfate sodium (DSS) causes mucosa damage of colon in mice. The colon damage of wild-type mice was found to recover better than FXIII^{-/-} mice after DSS exposure.^[24] A research on skin wound healing of mice showed similar result. For FXIII deficient mice, the tissue defect could be corrected with FXIII.^[25] A research study including 31 patients of Crohn's disease (CD) reported that plasma FXIII level was lower in patients with active CD than patients in remission, indicating FXIII consumption during the healing of damaged colons.^[26] Another study including 249 patients of ulcerative colitis showed that

plasma FXIIIa was lower in more severe patients (measured by clinical activity index, endoscopic and histologic scores). Immunohistochemistry also reported FXIII localization in extracellular matrix of damaged mucosa, a strong evidence of FXIII participating in wound healing process.^[27]

FACTOR XIII IN NEOPLASM

Researchers have found abnormal FXIII expression level or activity in patients with leukemia and solid tumors. The cellular form of FXIII (FXIII-A₂) is present mainly in platelets, megakaryocytes, monocytes, and macrophages.^[4] Synthesis of FXIII-A₂ differs in different subtypes of leukemia. It was found that FXIII-A₂ expression level of tumor cells was significantly elevated in patients with acute myelomonocytic leukemia (AML-M4) and acute monocytic leukemia (AML-M5). The author suggested that FXIII level could be used to differentiate myeloblast and monoblast.^[28,29] Research on acute promyelocytic leukemia reported similar results.^[30] Elevated FXIII-A₂ expression is also found in neoplastic cells of ALL patients.^[29,31]

Abnormal FXIII activity has been found in patients with solid tumors. A research including 28 patients of nonsmall cell lung cancer (NSCLC) found that FXIII activity level of patients in advanced-stage is higher than that of patients in early-stage and healthy controls, indicating that FXIII activity level could be potentially used as a marker of advanced NSCLC.^[32] V34L polymorphism is a common mutation of FXIII gene that affects enzyme activity. The L allele is found to have higher activity level. Vairaktaris *et al.* analyzed 130 patients of oral squamous cell carcinoma and 135 healthy controls and found that L allele was associated with higher oral cancer risk. It was observed that patients with LL homozygotes had a 3-fold higher risk for oral cancer, while in VL, the risk was 2-fold higher.^[33]

Fibrins are found in neoplastic tissues, as well as many tumor-associated macrophages (TAMs) which express FXIII-A₂. FXIII-A₂ released from damaged TAMs was involved in the stabilization of fibrin network which facilitated tumor growth.^[34] FXIII was found to be involved in tumor metastasis in the research of mice by limiting natural killer cell-mediated clearance of micrometastatic tumor cell.^[35] However, the role of FXIII in tumorigenesis is still unclear, and the relationship between FXIII and leukemia and solid tumors needs to be further elucidated.

FACTOR XIII IN BONE METABOLISM

Bone remodeling is a life-long process, involving osteoclasts that resorb bone and osteoblasts that form new bone tissues. Bone extracellular matrix is essential in the process by facilitating cell attachment, cell differentiation, and bone mineralization. FXIII is found to participate in the formation of extracellular matrix.

Researches in mice have reported the activation of FXIII-A gene in osteocytes of long bones (femur) and flat bones (calvaria and mandible). A 37,000 protein expressed in bone

and was confirmed to be the active product of FXIII-A after posttranslational proteolytic processing.^[36] The protein was able to stabilize the interaction of microtubules with the plasma membrane, making it possible for the secretion of exosomes which contain collagen and fibronectin, both of which were predominant composition of bone extracellular matrix.^[37,38] Collagen and fibronectin secreted outside the cell could form stable interaction with osteonectin and osteopontin, catalyzed by TG.^[39] The deposition of Ca²⁺ and collagen would decrease after suppression of TG activation, indicating the important role TG played in the mineralization and collagen deposition of bone extracellular matrix. The main TG family enzymes functioned in these processes were TG2 and FXIII.^[37]

However, other researches have observed mineralization and collagen deposition of extracellular matrix in TG2 and FXIII-A knockout mice. Another protein of 37,000, with similar function to the active product of FXIII-A mentioned above, has been found. It is reasonable to believe that other kinds of protein may also be involved in bone remodeling.^[40] Further research about such protein is needed.

FACTOR XIII IN PREGNANCY

Women with congenital FXIII deficiency often suffer from miscarriage. A systemic review by Sharief and Kadir found 127 (66%) miscarriages in 192 pregnancies of 63 women with congenital FXIII deficiency. For those without prophylactic therapy, as high as 91% of 136 pregnancies resulted in miscarriage.^[41] FXIII-A is present in normal uterus, implantation tissues, and placenta in normal pregnant women, but missing in women of congenital FXIII deficiency.^[42] Extravillous cytotrophoblasts formed the cytotrophoblastic shell which stabilized the interaction between embryo and decidua of uterus. It was reported that FXIII-A was missing in the placenta in woman with FXIII deficiency, leading to insufficient formation of the cytotrophoblastic shell.^[43] The cross-linking between proteins such as fibrin and fibronectin was also important for the attachment of placenta to uterus.^[42]

However, a research including 536 cases reported that the plasma level of FXIII could not predict recurrent miscarriage.^[44] One potential explanation is that FXIII in plasma is not equal to that in placenta tissues while the latter is the key to pregnancy loss.

CONCLUSIONS

FXIII has been treated as merely a coagulation factor for a long time by the medical community. Recent studies have shown that FXIII, with the essence of TG, is involved in many more processes besides coagulation such as wound healing, bone extracellular matrix stabilization, and the interaction between embryo and decidua of uterus, as well as some rare processes [Table 1].^[45-49] The expression and activity level of FXIII also changes in leukemia and solid

Table 1: Rare processes in which FXIII functions

Process	Author	Year	Type of study
Vascular permeability	Hirahara <i>et al.</i> ^[45]	1993	Animal
Insulin resistance in Type 2 diabetes mellitus	Mansfield <i>et al.</i> ^[46]	2000	Clinical
Corneal wound healing	Orosz <i>et al.</i> ^[47]	2011	Clinical
Liver remodeling	Tsujimoto <i>et al.</i> ^[48]	2011	Animal
Optic nerve regeneration	Sugitani <i>et al.</i> ^[49]	2012	Animal

FXIII: Factor XIII.

tumors, but its underline mechanism is still unknown and more research is needed.

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Conflicts of interest

There are no conflicts of interest.

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