



The hemostatic role of factor XI

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ABSTRACT

Coagulation factor (F)XI has been described as a component of the early phase of the contact pathway of blood coagulation, acting downstream of factor XII. However, patients deficient in upstream members of the contact pathway, including FXII and prekallikrein, do not exhibit bleeding complications, while FXI-deficient patients sometimes experience mild bleeding, suggesting FXI plays a role in hemostasis independent of the contact pathway. Further complicating the picture, bleeding risk in FXI-deficient patients is difficult to predict because bleeding symptoms have not been found to correlate with FXI antigen levels or activity. However, recent studies have emerged to expand our understanding of FXI, demonstrating that activated FXI is able to activate coagulation factors FX, FV, and FVIII, and inhibit the anti-coagulant tissue factor pathway inhibitor (TFPI). Understanding these activities of FXI may help to better diagnose which FXI-deficient patients are at risk for bleeding. In contrast to its mild hemostatic activities, FXI is known to play a significant role in thrombosis, as it is a demonstrated independent risk factor for deep vein thrombosis, ischemic stroke, and myocardial infarction. Recent translational approaches have begun testing FXI as an antithrombotic, with one promising clinical study showing that an anti-sense oligonucleotide against FXI prevented venous thrombosis in elective knee surgery. A better understanding of the varied and complex role of FXI in both thrombosis and hemostasis will help to allow better prediction of bleeding risk in FXI-deficient patients and also informing the development of targeted agents to inhibit the thrombotic activities of FXI while preserving hemostasis.

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Introduction

Hemostasis is a process in which a damaged blood vessel wall is closed off by a fibrin-rich platelet plug to stop the loss of blood into the extracellular space and initiate the repair of the damaged endothelium. This process begins with the activation of coagulation factors in the blood and is classically divided into two pathways known as the intrinsic and the extrinsic pathways of coagulation, which converge on the generation of thrombin and fibrin to form a hemostatic plug or clot. The intrinsic pathway, also called the contact pathway, can be activated *in vitro* when blood is exposed to negatively charged substances or artificial surfaces, which causes the conversion of factor XII (FXII) into activated FXII (FXIIa) [1]. FXIIa cleaves the coagulation factor prekallikrein (PK) to generate active kallikrein, which in turn feeds back to activate additional FXII. Activated FXII initiates the activation of factor XI (FXI) to FXIa, which in turn activates factor IX (FIX) to FIXa. Activated FIX activates factor X (FX) to FXa, after

which the contact pathway leads into the common or final pathway, resulting in the generation of thrombin and fibrin formation. Meanwhile, the extrinsic pathway of coagulation is initiated by the exposure of blood to tissue factor (TF) in complex with activated FVII (FVIIa), which induces the activation of FX and FIX and initiation of the common pathway leading to thrombin and fibrin formation [2]. Blood platelets also become activated and play an important role in hemostasis, releasing additional activating compounds, providing a surface to accelerate reactions, and aggregating to form the bulk of the clot.

Deficiency in some coagulation factors is associated with bleeding disorders. FIX deficiency is associated with the severe bleeding disorder hemophilia B, and FVIII deficiency causes hemophilia A. However, despite the ability of the contact activation pathway to initiate coagulation *in vitro*, FXI appears to be the only contact factor required for hemostasis. Deficiencies in FXII, PK or HK are not associated with bleeding tendencies, while FXI-deficient patients sometimes present with mild bleeding, suggesting that the role of FXI in hemostasis is independent of contact activation [1]. While FXI appears to play a modest role in hemostasis, clinical trials and epidemiologic data indicate that FXI is a key contributor to thromboembolic diseases. Studies with animal models also suggest that the activation of FXI by FXIIa promotes pathological thrombus formation [3].

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In this review, we will discuss our emerging understanding of the role of FXI in both hemostasis and thrombosis and the important clinical implications of this research.

Role of FXI in the intrinsic and extrinsic pathway

The role of FXI in activating the extrinsic pathway involves multiple mechanisms, due to the promiscuous interaction of FXI with a number of enzymatic substrates. The previous understanding that FXI only participated in the contact pathway was first questioned upon the discovery that FXI can be activated by thrombin downstream of the extrinsic pathway (Figure 1)[4,5]. Although FXIa's primary substrate is the contact pathway factor FIX, more recently FXI has also been shown to activate FX *in vitro* and to promote thrombin generation by activating the cofactors FVIII and FV [6,7]. FXIa is also known to shorten the clotting time of recalcified FIX-depleted plasma, again revealing its pro-coagulant activity independent of FIX [8]. We have also recently discovered that FXIa promotes activation of the extrinsic pathway through proteolysis of tissue factor pathway inhibitor (TFPI) [9], a Kunitz-type protease that is the primary inhibitor of the TF/FVIIa/FXa complex (Figure 1)[10]. This inhibitory activity of FXI against TFPI may represent an important new mechanism by which FXI promotes coagulation independent of the contact pathway.

Additionally, it appears that the presence of platelets is required for FXIa to support hemostasis through the extrinsic pathway. Activated platelets release short-chain polyphosphates (polyP; 70-100-mer), which are linear polymers of orthophosphate linked by phosphoanhydride bonds. Platelet polyP can enhance the feedback activation of FXI by thrombin by approximately three thousand-fold [11,12] and has also been shown to enhance the activation of FV, a cofactor that promotes thrombin generation [13]. Interestingly, platelet-derived polyP has been shown to enhance the activation of FXI in a flow chamber model

independently of FXIIa and the contact pathway, and this activation requires the participation of the extrinsic pathway [14]. In addition, we recently observed that short-chain polyP increases the capacity of FXIa to inactivate TFPI (unpublished observation), further supporting the combined role of platelet polyP and FXIa in promoting hemostasis.

FXI and Hemostasis

Hemophilia C, the congenital deficiency of coagulation FXI, is associated with postoperative or posttraumatic bleeding, especially in tissues with robust fibrinolytic activity such as the nose, oral cavity, and urinary tract [15]. However, current diagnostic tests are unable to accurately predict bleeding tendencies in FXI-deficient patients, as the symptoms are highly variable between patients and poorly correlated with plasma FXI levels. As a result, some FXI-deficient individuals may receive unnecessary FXI replacement therapy, which has been shown to enhance the risk of thrombosis or transfusion-related complications. Conversely, FXI-deficient patients left untreated can be at increased risk of life-threatening hemorrhage during surgery, presenting a serious dilemma for clinicians and patients.

One common diagnostic test, the activated partial thromboplastin time (aPTT) assay, which measures thrombin generation in platelet-poor plasma (PPP) following contact pathway activation, has not been found to accurately predict the bleeding phenotype of FXI-deficient patients. In contrast, a recent study demonstrated that a thrombin generation assay in platelet-rich plasma (PRP) in which the contact pathway was inhibited while the extrinsic pathway was activated via TF was able to successfully identify which FXI-deficient patients demonstrated a bleeding phenotype [16]. These differing results suggest that FXI does not play a role hemostasis via the contact pathway but that FXI can initiate coagulation via the extrinsic pathway in the presence of TF and platelets. This claim is supported by studies showing that patients deficient in the contact activation

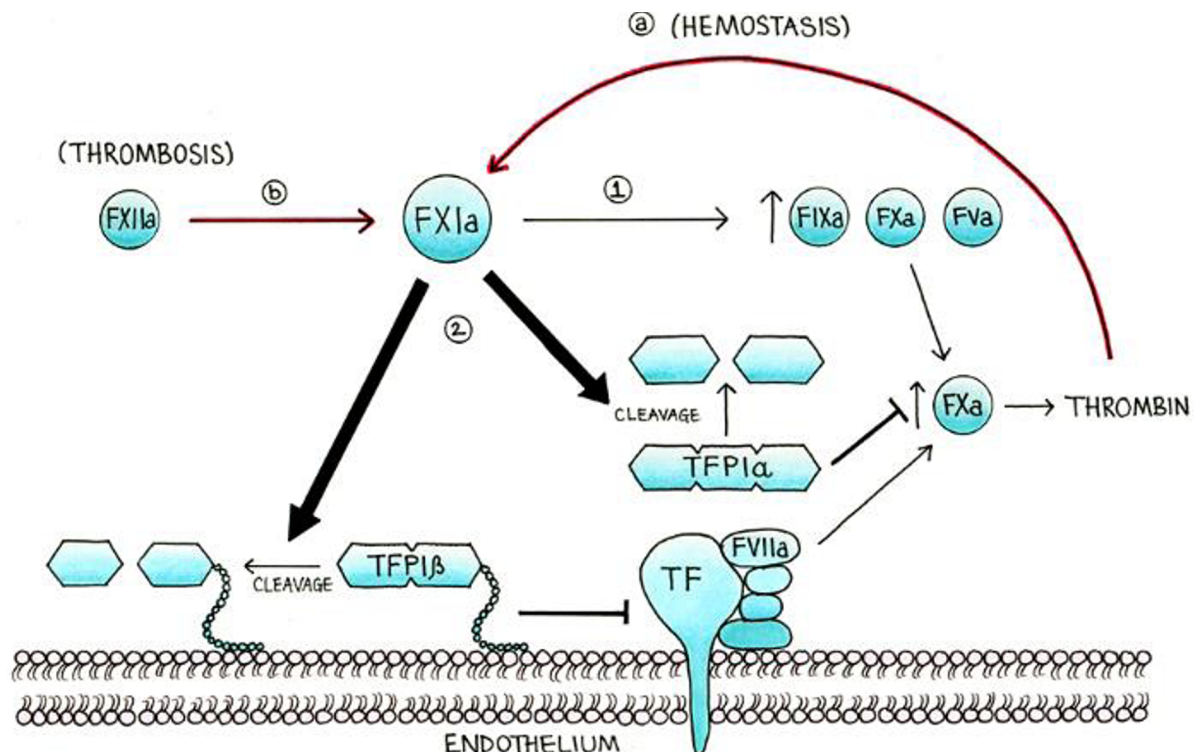


Figure 1. The role of FXI in thrombosis and hemostasis. In addition to the activation of FIX, X and V (step 1), we hypothesize that FXIa promotes thrombin generation by enhancing the TF-FVIIa pathway (step 2), including via the inactivation of TFPI α from platelets and TFPI β from endothelial cells. Moreover, we hypothesized that in hemostasis, the main activator of FXI is thrombin (a), while in thrombosis the main activator of FXI is FXIIa (b).

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