

Physiological Effects of the Plasma Kallikrein-Kinin System: Roles of the Blood Coagulation Factor XII (Hageman Factor)

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Abstract

For many decades the intrinsic coagulation research has focused on factor XII (Hageman factor; FXII) and its significant role as a sole instigating factor driving the stabilization of thrombotic clotting. FXII is a relatively weak risk factor for thrombosis although its amidolytic and proteolytic function renders its presence important. Accumulating evidence suggests that FXII is pivotally involved in pathologic coagulation. In particular, the role of FXII in initiation and propagation of the blood coagulation and fibrinolytic systems has impeccable scientific support to the extent of which the existence of a "FXII-dependent pathway of thrombosis" is now generally accepted. The concept, although not a new one to scientists in the field of coagulation, is a caveat to the pathologic clot forming FXII concept in that it appears to cause a conceptual shift in de-emphasizing the inherent complexity of FXII activation representing a spectrum of responses. For instance, FXII contributes to the activation of inflammation and complement systems and influences catecholamine release from the adrenal system, suggesting that FXII can trigger multiple signaling pathways upon activation. The nature and duration of each of the FXII-dependent pathways may depend not only on the kind of stimulus, but also it may have a distinct response pattern under normal and pathophysiologic conditions.

Because a plethora of pathophysiological pathways are influenced by FXII, additional studies into its role as an important first step behind regulating common daily stresses may promise to provide new insight to better understand the unique and subtle biology behind FXII.

Keywords: Hereditary Angioedema (HAE); Disseminated Intravascular Coagulopathy (DIC); Surgery; Stroke; Infection

Introduction

Blood coagulation is an essential element in maintaining homeostasis, in particular, helping the formation of blood clots. The blood coagulation system is composed of platelets, a large number of proteases and protease inhibitors, and cofactors. Due to the complexity of blood coagulation system, these proteases are mechanistically and functionally subdivided into procoagulant, anticoagulant, fibrinolytic, or antifibrinolytic proteases. While proteases along with their respective cofactors of the blood coagulation system could act as specialized effectors and/or modulators during vascular injury, they work in concert with each other with varying ratios of one protease to other coagulation proteases and in conjunction with the complement and immune systems, as well as vascular endothelium to control blood loss, the growth of clots, vascular repair, and maintenance.

There are two classical pathways that describe the activation of the coagulation cascade which include the intrinsic pathway [also known as the contact activation system and the plasma Kallikrein-Kinin System (KKS)] and the extrinsic pathway. The components of the KKS include Factor XII (FXII), plasma Prekallikrein (PK), and High molecular weight Kininogen (HK). There is some debate over a useful and appropriate name of the "KKS" as well as the components of the KKS.

FXII (Hageman factor), which is produced and secreted by the liver, is a multifunctional serine protease protein that is encoded by the *F12* gene, which has been mapped to 5q33-qter in humans [1]. A deficiency of FXII has been linked to numerous loss-of-function mutations in the *F12* gene [2-6]. Among these mutations, the C46T mutation in human *F12* causes a new start codon leading to a truncated FXII and risk of venous and arterial thrombosis, deciphering one of the physiological functions of FXII [7]. However, mice with a deficiency of FXII are protected against arterial thrombosis and stroke. These

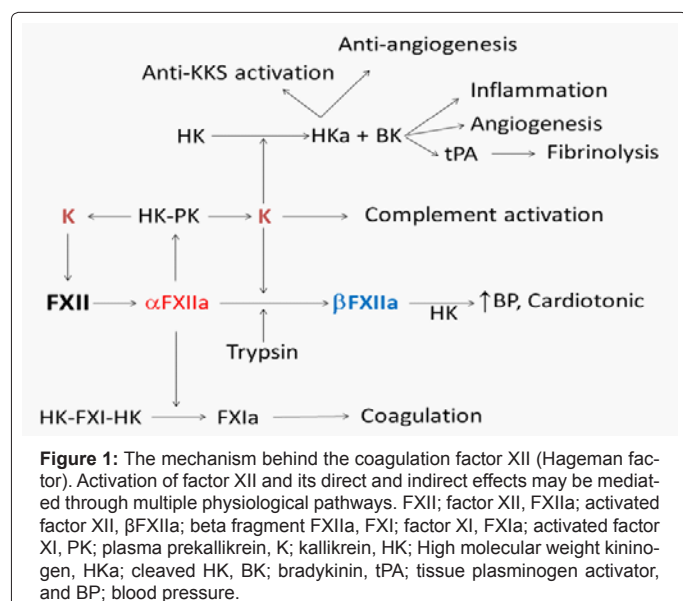
controversial results could stem from the evolution of FXII in each species. A plausible alternative explanation for the observed trait in patients with C46T mutation could be due to inability of kallikrein to activate mutant FXIIa and/or an overall decrease in fibrinolytic activity, tipping the balance toward thrombosis (Figure 1). The findings from these studies indicate that the physiological role of FXII is still an enigma. Further investigations are warranted to provide insights into possible answers concerning the controversial topic of FXII function in coagulation. FXII in the intrinsic pathway is a precursor to alpha activated factor XII (α FXIIa), (Figure 1). FXII circulates in the body as an inactivated zymogen. The activation of FXII is mediated via multiple mechanisms of action including contact with physiological and non-physiological surfaces possessing a negatively charged property [8]. Moreover, a growing body of evidence for multiple mechanisms of FXIIa action has been accumulated as well (Figure 1). It appears that its roles are a matter of intense debate because it is not yet clear which of these physiological responses is/are most important in humans under normal and pathological conditions. The findings of these studies may indeed represent the solitary role of FXII in the pathophysiology of stress-related dysfunctional endothelium. Although its activation is not mediated by immune complexes [9], activation of FXII during the initial event in Disseminated Intravascular Coagulopathy (DIC), Rheumatoid Arthritis (RA), inflammation, complement system, and lupus have

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been described [10-13]. FXIIa might be a biomarker for endothelial cell activation and early development of endothelial dysfunction in the blood vascular system. Further investigations are warranted to determine if there is an association.

FXIIa activates plasma Prekallikrein (PK) to Kallikrein (K), which in turn cleaves FXII to alpha FXIIa (αFXIIa) (Figure 1). αFXIIa activates FXI in the presence of high molecular weight kininogen (HK), which contributes to thrombin generation (Figure 1). Thrombin activates FXI independent of FXII. FXIa generated through this loop further enhances thrombin generation, leading to a faster and more stable thrombus formation. FXIIa deficiency has been shown to be associated with a prolonged activated Partial Thromboplastin Time (aPTT), suggesting that FXII has a useful predictive value of the vascular blood flow [14]. Although FXII was considered to have a major role in the activation of the fibrinolytic pathway, recent reports indicate that its role may be limited [15].

In the presence of HK, FXIIa activates plasma Prekallikrein (PK) to kallikrein (Figure 1). Kallikrein has unique substrates *in-vivo*, serving different physiological requirements and biochemical functions, and allowing the injured tissues to heal. As shown in Figure 1, firstly, in a reciprocal feedback mechanism, kallikrein accelerates not only FXII activation but also PK activation. Secondly, cleavage of HK by kallikrein results in liberation of the angiogenic and inflammatory mediator Bradykinin (BK) and cleaved high molecular weight kininogen (HKa, anti-angiogenic and anti-infection properties), each of which have evolved to occupy a unique physiological niche [16]. Both BK and HKa protect injured/dysfunctional tissues in a cooperative manner but they exert opposite effects [17,18]. Thirdly, kallikrein activates major components of complement system C3 and C5, which could subsequently activate both classical and alternative complement activation pathways [19,20]. Fourthly, kallikrein converts αFXIIa to βFXIIa, leading to activation of the sympathoadrenal system the which in turn raises blood pressure and heart rate in the presence of bradykinin or kininogen [21]. Interestingly, kallikrein appears to turn on and propagate the activity of several key enzymes involved in multiple regulatory pathways or turn them off depending on whether injured tissues are healed. Since the plasma concentrations of PK (0.58 μM) and βFXIIa (no assayable

activity) are almost always constant in healthy individuals and the activation of KKS has been implicated in the pathogenesis of numerous diseases, investigations should be performed to determine whether the βFXIIa -to-PK ratio in the plasma can be used for predicting disease severity to that of KKS activity. For instance, βFXIIa -to-PK ratio might be used to predict likely BK level during hereditary angioedema (HAE), DIC, surgery, stroke, and infection.

In conclusion, activated FXII appears to mediate the activation of multiple physiological pathways during pathophysiological disturbances, promoting the injured tissues to heal. The identification of the cellular substrates regulated by FXII during pathophysiological conditions and signaling pathways that respond to FXIIa will indeed represent a robust advancement in the study of KKS. The plasma KKS will have great promise for both therapeutic applications and clinical assays in diseases linked to hyperactivation of the components of KKS. Although feedback mechanisms of FXII-mediated pathways are unknown, the FXII metabolite levels may provide a unique trigger mechanism for activation of each of the FXII-mediated diverse signaling pathways. It seems reasonable to suggest that FXII has one interesting physiological property; the ability to assist in creating a more supportive microenvironment within the damaged tissues to promote wound healing.

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