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Role of blood coagulation factor XIII in vascular diseases

Hans-Peter Kohler

Laboratory for Thrombosis Research, Department of Clinical Research, University Hospital, Inselspital, Bern, Switzerland

Until recently, blood coagulation factor XIII (FXIII), also called fibrin-stabilizing factor, has not been studied in relation to cardio- and cerebrovascular disease despite its important role in the final stage of the coagulation process. New insights regarding the role of FXIII in vascular diseases indicate a major role of this coagulation factor in vascular thrombotic disorders. It now seems reasonable to view FXIII as one of the factors contributing to the complex gene-environment interactions involved in the pathogenesis of vascular diseases such as myocardial infarction, stroke and deep venous thrombosis.

Structure and function of blood coagulation FXIII

FXIII, also called fibrin-stabilising factor [1] , is a transglutaminase composed of two A subunits and two B subunits circulating in plasma as a tetramer (A_2B_2) (Figure 1). FXIII plays an important role in clot stabilisation by cross-linking fibrin chains [2] after activation by thrombin (Figure 1). In addition, a number of other proteins are substrates for activated FXIII, such as α_2-antiplasmin, von Willebrand factor, factor V, thrombospondin, vitronection and thrombin-activable fibrinolysis inhibitor (TAFI) [3–7]. All A-subunit molecules in plasma are in complex with the B-subunit (carrier protein) at a concentration of approximately 21 µg/ml, whereas the B-subunit is present in both free and complexed form [8]. FXIII was discovered over 70 years ago by Barkan et al., who observed the insolubility of fibrin clots in the presence of calcium [9]. Until recently little was known about the role of FXIII in vascular diseases, since most studies have been carried out in patients with congenital FXIII deficiency, which results in a serious bleeding diathesis and defective wound healing [10]. These patients show a complete absence of the A-subunit in plasma due to different mutations in the A-subunit gene [11].

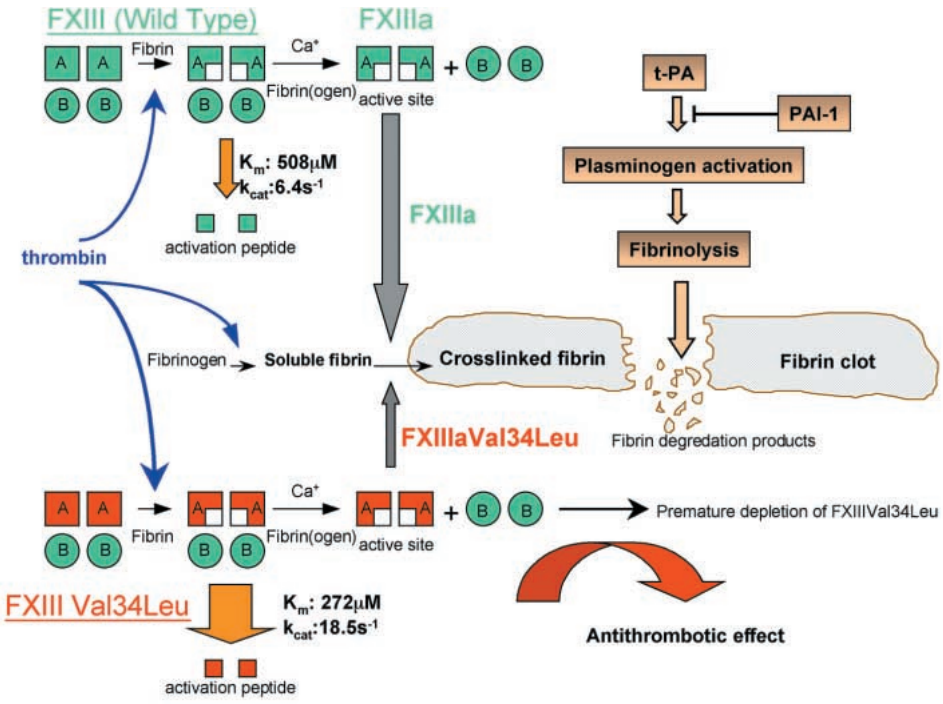

Figure 1

FXIII pathway and possible effects on clot formation by genotype. After activation by thrombin, a small activation peptide is cleaved from the A-subunit (FXIII wild type: shown in green, FXIIIVal34Leu: shown in red). In a further step, the FXIII tetramer dissociates by separating the B subunits (carrier protein) from both A subunits. The active site of FXIII is now ready for the crosslinking reaction. The rate of FXIII activation and therefore cleavage of the activation peptide is influenced by FXIII genotype with an increase in k_{cat} but a decrease in K_m in possession of the Leu allele (orange arrows). These changes lead to premature depletion of FXIII-Val34Leu and a decrease in cross-linking reaction (grey arrows). Fibrinogen is activated by thrombin to form soluble fibrin. In a further step, soluble fibrin is cross-linked by FXIII to form a stable, insoluble fibrin network. Plasminogen activation by tissue plasminogen activator (t-PA) and therefore initiation of fibrinolysis is inhibited by plasminogen activator inhibitor-1 (PAI-1), a strong marker of insulin resistance.

Factor XIIIVal34Leu. Effects on FXIII cross-linking activity *in vitro*

A common G → T point mutation in codon 34, exon 2 of the A-subunit gene which codes for a valine → leucine change (FXIIIVal34Leu) only three amino acids from the thrombin activation site, has been described in subjects without FXIII A-subunit deficiency [10, 12, 13], indicating that this polymorphism is not involved in the pathogenesis of this rare condition. In Caucasians, the allele frequency has been shown to be around 23% [10, 13]. Because of the high allele frequency and the proximity of the amino acid change to the thrombin activation site, this polymorphism was a candidate for a role in the pathogenesis of thrombotic disorders. The polymorphism leads to a more extensive interaction with the surface of thrombin and hence to cross-linking activity *in vitro* [13, 14], possibly leading to wasteful conversion of zymogen to activated enzyme *in vivo* [15]. Premature depletion of the mutant protein from circulation may provide the antithrombotic effects *in vivo* [15]. Further studies are currently being carried out to gain an understanding of the true *in vivo* effects of FXIIIVal34Leu on clot formation and stabilisation.

Prevalence of FXIIIVal34Leu in patients with coronary artery disease

It has recently been shown that possession of FXIIIVal34Leu protects against myocardial infarction, suggesting for the first time a role for FXIII in thrombotic disorders [16]. This first observation was made in a case control study of 398 Caucasian patients with coronary artery disease and 196 healthy controls [16]. The cardioprotective effect of FXIIIVal34Leu has been confirmed in other studies [17–19].

Interestingly, the prevalence of FXIIIVal34Leu (the presence of the protective Leu allele) seems to depend on ethnic background. Pima Indians from the Gila River Indian Community in Arizona, USA, have a low incidence of coronary artery disease despite a high prevalence of non-insulin-dependent diabetes. In South Asians there is also a high incidence of type II diabetes but also a high incidence of coronary artery disease. It has been shown that the prevalence of FXIIIVal34Leu in these different ethnic groups is inversely related to the prevalence of coronary artery disease in these populations. In other words, the protective leucine allele was more common in those subjects at low cardiovascular risk [20]. This finding supports a cardioprotective effect of FXIIIVal34Leu. In addition, this common polymorphism possibly contributes to the contrasting cardiovascular risk in different ethnic groups.

FXIIIVal34Leu in subjects with stroke or venous thrombosis

The first study on the effect of FXIIIVal34Leu in stroke patients showed that the mutant Leu allele was more frequent in patients with haemorrhagic stroke than in controls, providing further evidence in favour of a role for FXIII in vascular diseases [21]. It has been suggested that FXIIIVal34Leu might favour the formation of weaker fibrin structures, thereby affording protection against arterial thrombosis in patients with coronary artery disease [16] or predisposing to haemorrhagic stroke [21]. In the study of Catto et al. [21] there was no difference between cases with brain infarction and controls. However, a large multicentre study from France showed a negative association of FXIIIVal34Leu polymorphism with brain infarction, thus confirming that the Leu allele also has a protective effect in patients with thrombotic cerebral artery occlusion [22]. Interestingly, the effect of smoking was weaker among stroke patients possessing the Leu allele than among non-carriers, suggesting that the effect of the polymorphism outweighed the effect of smoking among Leu carriers.

Fibrin cross-linking by FXIII is also important in the development of venous thrombosis. Patients with deep venous thrombosis (DVT) show increased frequency of the Val/Val genotype and a lower frequency of the Val/Leu genotype, indicating that possession of FXIIIVal34Leu could also protect against venous thrombosis, in a manner similar to that seen in subjects with MI and ischaemic stroke [23–25]. However, an interesting recent observation suggests that carriers of the polymorphism seem to be better protected against pulmonary embolism than against DVT, possibly due to a thrombus structure thought to be more adherent to the vessel wall and thus less prone to embolise [26]. The data in subjects with DVT and pulmonary embolism therefore suggest a role for FXIII in both arterial and venous thrombosis.

Role of plasma levels of FXIII activity and antigen levels in vascular diseases

Little is known about plasma activity and antigen levels (A and B subunits) in subjects with vascular diseases. It has been shown that in healthy individuals age and smoking is related to increased A-subunit antigen levels, whereas the FXIII B subunit and FXIII activity are associated with FXIII A-subunit levels and fibrinogen, suggesting a role for elevated A-subunit levels in the pathogenesis of vascular disease [27]. Studies on FXIII measurements in subjects with cardio- or cerebrovascular diseases are ongoing. However, preliminary results have shown increased FXIII A-subunit levels in patients with coronary artery diseases compared to controls [28]. Further work is needed to understand the role of FXIII plasma antigen levels in vascular diseases.

Interaction between FXIII and features of insulin resistance

Subjects possessing the protective Leu allele in whom there was still a history of MI were further investigated [16, 29]. These subjects had higher concentrations of plasminogen activator inhibitor-1 (PAI-1), insulin, proinsulin, factor XII (Hageman factor, which may itself represent a risk factor for CAD [30, 31]) and an increased body mass index (BMI), changes which were not observed in subjects possessing the Val/Val genotype [32]. These findings indicate that inhibition of fibrinolysis through increased PAI-1 levels negates the protective effect of the Leu allele and suggest interaction with insulin resistance. The original description of the insulin resistance syndrome by Reaven in 1988 proposed clustering of atheromatous risk factors in insulin-resistance states [33]. Elevated concentrations of PAI-1 are also associated with features of insulin resistance to provide a thrombotic component to this metabolic disorder [34]. Levels of FXIII A- and B-subunit antigen are elevated in subjects with type 2 diabetes, and levels of FXIII A-subunit antigen are also elevated in relatives of subjects with type II diabetes [35]. In addition, levels of the FXIII B-subunit antigen (carrier protein) show a consistent pattern of correlation with other vascular risk markers, which supports the possibility of an underlying association with the insulin resistance syndrome [35]. The insulin resistance syndrome, in which risk factors for thrombosis and progression of atheroma co-exist, therefore reflects the underlying pathophysiology of atherothrombotic disease. These new findings on FXIII also shed light on the interaction between the haemostatic system and metabolic features of the insulin resistance syndrome.

Conclusion

All the clinical observations mentioned above indicate a major role for FXIII in vascular thrombotic disorders. It now seems reasonable to view blood coagulation FXIII as one of the factors contributing to the complex gene-environment interactions involved in the pathogenesis of vascular diseases such as MI, stroke and deep venous thrombosis. In addition, the relation between FXIII and classical metabolic risk factors further helps to explain the association between insulin resistance and the risk of thrombosis.

Correspondence
H. P. Kohler, MD
Laboratory for Thrombosis Research
Department of Clinical Research
Kinderklinik G3, Room 835
University Hospital, Inselspital
CH-3010 Bern
e-mail: hanspeter.kohler@insel.ch

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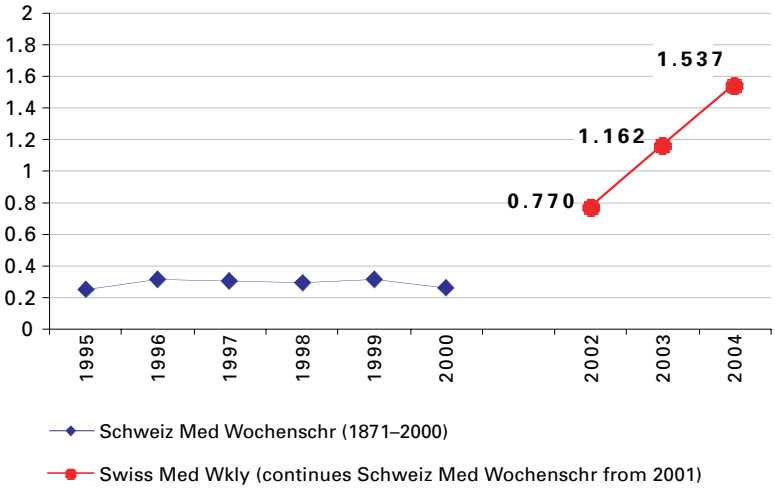

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