Coagulation Factor IX and Risk of Thrombosis Development

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♦ Abstract

An increased circulating level of coagulation factor is a must for the treatment of both venous and arterial thrombosis. Some of the new oral anticoagulants, when administered optimally, are associated with significant therapeutic effects when compared to the existing anticoagulants. Since factor IX (FIX) plays a key role in tissue factor-mediated thrombin production, it may represent a promising target for drug development. Therefore, this review aims to summarize the current data on FIX and its role in the development of thrombosis.

♦ Coagulation Cascade

Coagulation is a complex process in which circulating cells and coagulation factors interface with tissue-based proteins to form an insoluble clot at the sites of vascular injury. It's mechanism was earlier represented as a classical cascade of three consecutive phases: initial, amplification, and propagation phases.

However, coagulation in vivo is best characterized as a harmonized series of cell-based events. The cell-based model of coagulation represents the interaction between cellular activity and coagulation proteins that leads to thrombus formation and hemostasis. This model proposes that coagulation takes place on different cell surfaces in four distinct steps: initiation, amplification, propagation, and termination (Figure 1).

♦ Factor IX

It is a vitamin K-dependent protein synthesized by hepatocytes as a precursor of a serine protease, FIXa.

The gene for FIX consists of eight exons and seven introns, which is approximately 34 kb long, and is located on the long arm of the X chromosome at Xq27.1.

It is synthesized as a precursor protein of 461 amino acids containing a 28-residue signal prepeptide and an 18-residue leader propeptide.

It plays a key role in blood coagulation because its absence can result in an X-linked bleeding diathesis, hemophilia B.

The activation of FIX by tissue factor (TF)/VIIa and FX by FIXa is significant [1]. Therefore, the FXa produced by the FIXa/FVIIIa complex represents a crucial step in coagulation, and disruption of this step may lead to the development of new antithrombotics.

The presence of FVIIIa and FXa increases the affinity of receptors for FIXa that in turn participates in FX activation.

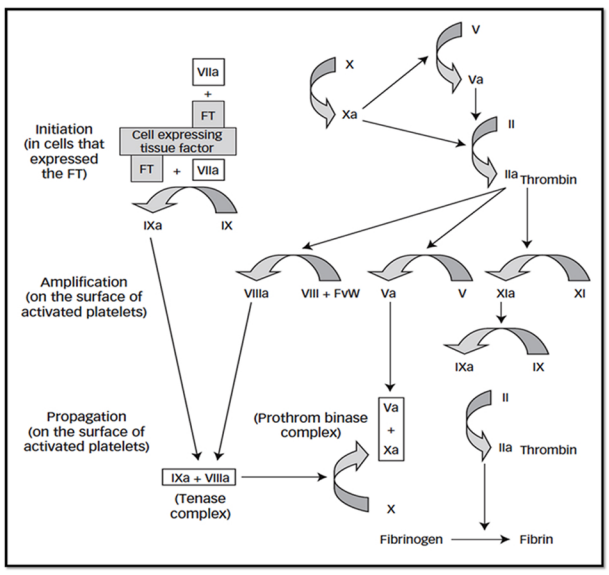


Figure 1: Coagulation cascade

♦ Factor IX-platelet interface

The contribution of platelets to hemostasis and thrombosis is well explained; yet, rising evidence supports the presence of numerous distinct platelet populations within a developing thrombus—each with very specific functional roles [2]. FIXa, viewed originally as a protein responsible exclusively for clot formation, also plays a primary role in platelet-mediated hemostasis as well (Figure 2).

♦ FIX and thrombosis (venous and arterial)

After its activation by tissue factor (TF)/FVIIa complex, FIX plays a key role in thrombin generation in the vicinity of platelets [3]. FIX levels are associated with several thrombotic risk factors, including age, obesity, oral estrogen use, smoking, blood pressure, and low social class. FIXa is also increased in patients with acute coronary artery thrombosis. Van Hylckam a Vlieg et al. [4] showed that subjects with plasma IX antigen above the 90th percentile (≥129 IU/dI) had a 2.5 increased risk of deep vein thrombosis (DVT). Thus, these studies suggest that high FIX (activity or antigen) may be a mechanism for venous thrombogenesis. High levels of FIX might be genetic or reflect environmental effects of risk factors such as estrogen, age, blood lipids, or obesity.

The plasma levels of FIX activity (FIXc) are associated not only with FVIII activity (FVIIIc) but also with several CHD risk factors in the general population [5]. However, there are no reported prospective cohort studies of FIX and risk of stroke or CHD.

In acute myocardial infarction or acute unstable angina pectoris (acute coronary syndromes), plaque rupture exposes circulating blood to tissue factor FVIIa complexes, which can activate factors IX and XI on the local platelet/lipid surface. Minnema et al. [6] reported increased plasma levels of FIX activation peptides in patients with acute coronary syndromes, compared with patients with stable angina. Such activation may play a key role in coronary thrombogenesis through the continuous generation of thrombin and fibrin formation.

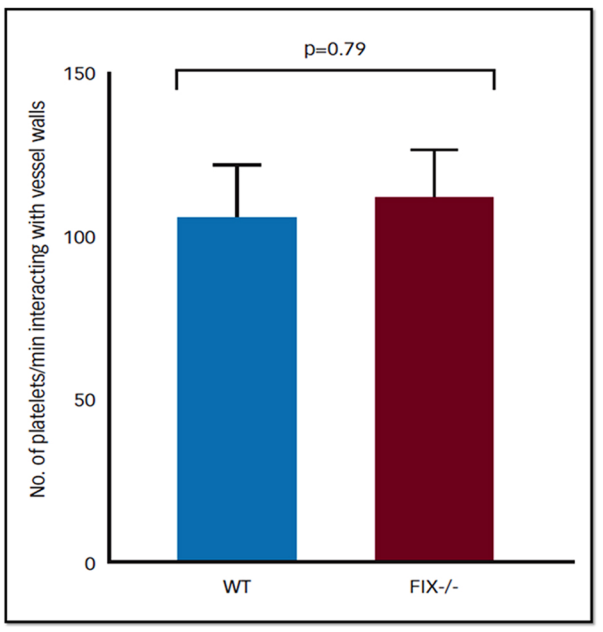


Figure 2: Platelet interaction with injured vessel

♦ Antithrombotic therapy and factor IX

Oral anticoagulants decrease the activity of vitamin K-dependent coagulation factors including prothrombin, FVII, FIX, and FX. Patients having increased sensitivity to oral anticoagulant-induced decrease in FIXc may have anti-phospholipid antibodies or mutations in the propeptide of FIX, causing a reduced affinity of the carboxylase for FIX precursor [7]. Legnani et al. [8] observed that FIX levels varied greatly regardless of the similar achieved anticoagulation intensity, making it difficult to identify those with very low FIXc levels from the APTT. Due to the potential importance of FIXa in thrombogenesis, selective FIX inhibitors should be studied as antithrombotic therapy [9]. FIXa inhibitors may have a higher ratio of anti-thrombotic activity to bleeding risk that heparins have in animal models [10]. Two studies have proposed that the main effect of heparin on the prolongation of the APTT is through blocking of the FIXa activation of FX [11].

An antibody directed against the amino-terminal region of FIX acts as a powerful antithrombotic agent in rat and guinea pig models of arterial thrombosis [12]. Pegnivacogin is also an anti-FIX aptamer that inhibits coagulation FIX activation, preventing FV-mediated generation of thrombin. It has been shown to rapidly induce anticoagulation, thus providing safe and stable anticoagulation in the preclinical and clinical settings. New oral anticoagulants that inhibit either FIXa (rivaro xaban, apixaban) or thrombin (dabigatran etexilate) have gained approval in many countries owing to some clinical indications. Future clinical experiments of FIXa inhibitors in prophylaxis and treatment of thrombosis might test the theory that high levels of FIXa play a key role in venous and arterial thrombogenesis.

♦ Conclusion

In conclusion, it is important to shed light on the importance of FIXa, as it is a key intermediary in the intrinsic pathway, and targeted inhibition of FIXa-dependent coagulation might inhibit microvascular thrombosis development. Further studies on the theoretical benefits of targeting FIXa compared with former anticoagulant targets will translate into better outcomes.

♦ References

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