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The heparin-binding exosite of factor IXa is a critical regulator of plasma thrombin generation and venous thrombosis.

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Abstract

The role of the factor IXa heparin-binding exosite in coagulation was assessed with mutations that enhance (R170A) or reduce (R233A) stability of the protease-factor VIIIa A2 domain interaction. After tissue factor (TF) addition to reconstituted factor IX-deficient plasma, factor IX R170A supported a 2-fold increase in velocity index (slope) and peak thrombin concentration, whereas factor IX R233A had a 4- to 10-fold reduction relative to factor IX wild-type. In the absence of TF, 5 to 100 pM of factor IXa increased thrombin generation to approach TF-stimulated thrombin generation at 100% factor IX. Factor IXa R170A demonstrated a 2- to 3-fold increase in peak thrombin concentration and 5-fold increase in velocity index, whereas the response for factor IXa R233A was blunted and delayed relative to wild-type protease. In hemophilia B mice, factor IX replacement reduced the average time to hemostasis after saphenous vein incision, and the time to occlusion after FeCl(3)-induced saphenous vein injury. At 5% factor IX, the times to occlusion for factor IX wild-type, R170A, and R233A were 15.7 minutes, 9.1 minutes (P </= .003), and more than 45 minutes. These data support the role of the factor IXa heparin-binding exosite as a critical regulator of coagulation and novel antithrombotic target.

PMCID: PMC2569175 **Free PMC Article**