CORRESPONDENCE

When and Where Is Factor XI Activated by Thrombin?

To the Editor:

In a recent report, von dem Borne et al. elegantly addressed the controversy regarding the role of thrombin in the activation of factor XI. In purified systems, Naito and Fujikawa and Gailani and Broze showed that thrombin can convert factor XI to factor XIa in the presence of the nonphysiologic, negatively charged surface, dextran sulfate. The latter investigator even proposed a "revised model of blood coagulation," implying that this finding accounts for the paradox that half of the patients with factor XI deficiency have a hemostatic defect, but patients with factor XII deficiency do not. However, because thrombin is the final enzyme in the blood coagulation cascade, it clearly cannot be involved in its initiation. The occurrence of this reaction in plasma was challenged by our laboratory. We showed that fibrinogen, the preferred substrate for thrombin in plasma, completely prevented the thrombin-mediated activation of factor XI, the occurrence of which we confirmed in purified systems. Moreover, we also showed that high molecular weight kininogen dramatically curtailed the activation of factor XI activation by thrombin. We suggested that this reaction did not proceed in the plasma, but might occur on blood cell membranes or other physiologic surfaces. Our observations were confirmed by Brunnee et al. who found that activation in plasma of factor XI depends on factor XII and does not occur with thrombin at physiologic concentrations. A subsequent study by Gailani and Broze claimed that the reaction occurred in plasma, but the investigators used diluted plasma (with decreased fibrinogen and high molecular weight kininogen), an extremely high concentration of thrombin, and a surface-sulfatide not present in the human vascular system. The paradox has been solved by von dem Borne et al., who studied tissue factor-induced coagulation. They showed, at high tissue factor concentrations, that factor XI played no acceleratory role in fibrin formation. However, at a low tissue factor concentration, factor XI could accelerate the formation of fibrin modestly (about 35%). More importantly, factor XI inhibited fibrinolysis by providing additional thrombin after clot formation had taken place. Thus, the major feedback of thrombin on factor XI takes place within the fibrin clot in an environment free of fibrinogen and high molecular weight kininogen. Thrombin bound to the clot is protected and is no longer subject to inhibition by the competitive substrate, fibrinogen, and is able to catalyze the feedback to activate factor XI and enhance the intrinsic cascade. The pathway by which factor XI is initially activated is still unclear, because the autolysis of factor XI is completely inhibited by fibrinogen and high molecular weight kininogen. Perhaps platelet-derived factor XI plays an initiating role when expressed on the external membrane of the platelet, where thrombin also binds.

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1. Von dem Borne PA, Meijers JC, Bouma BN: Feedback activation of factor XI by thrombin in plasma results in additional formation of thrombin that protects fibrin clots from fibrinolysis. Blood 86:3035, 1995

Response

In our article, we observed that feedback activation of factor XI by thrombin in plasma results in additional generation of thrombin that protects the fibrin clot from lysis. Thrombin generation predominantly takes place after clot formation. Colman and Scott state in their letter that this generation of thrombin can occur because of the fibrinogen- and HK-free environment in the clot. They reach this conclusion on the basis of their finding that fibrinogen and HK completely prevent thrombin-mediated factor XI activation in a system using purified proteins. However, we question this regulatory role of fibrinogen and HK. Firstly, we showed that the inhibitory effect of HK is only minor in the absence of a dextran sulfate-like surface. Even in the presence of HK and dextran sulfate, trace amounts of factor XIa are still formed that can play a role in blood coagulation because of the amplification potential of the coagulation cascade. Secondly, in the report by Scott and Colman, thrombin-mediated activation of factor XI was studied with dextran sulfate as a surface in the presence of fibrin monomers instead of fibrinogen. To keep the fibrin monomers in a nonpolymerized state, Gly-Pro-Arg-Pro peptide had to be added. In our hands, the fibrin monomers remained soluble at a low concentration in the absence of the peptide. In the presence of the Gly-Pro-Arg-Pro peptide a direct inhibitory effect on the activation of factor XI by thrombin was observed and we concluded that the use of this peptide is not appropriate in factor XI activation studies. Therefore, we are currently investigating the activation of factor XI in the presence of fibrin monomers immobilized on Sepharose. Preliminary results indicate that activation of factor XI by thrombin is not affected by the binding of thrombin to fibrin.

We agree that it is important to know when and where factor XI is activated by thrombin to get a better understanding of this pathway. We think that fibrin may play an important role in localizing


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thrombin-mediated factor XI activation and that it may even be the site of initial factor XI activation. In our opinion, it is not necessary to have an environment free of fibrinogen and HK.

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