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## Activation of factor XI by products of prothrombin activation.

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### Abstract

The prothrombinase complex converts prothrombin to  $\alpha$ -thrombin through the intermediate meizothrombin (Mz-IIa). Both  $\alpha$ -thrombin and Mz-IIa catalyze factor (F) XI activation to FXIa, which sustains  $\alpha$ -thrombin production through activation of FIX. The interaction with FXI is thought to involve thrombin anion binding exosite (ABE) I.  $\alpha$ -Thrombin can undergo additional proteolysis to  $\beta$ -thrombin and  $\gamma$ -thrombin, neither of which have an intact ABE I. In a purified protein system, FXI is activated by  $\beta$ -thrombin or  $\gamma$ -thrombin, and by  $\alpha$ -thrombin in the presence of the ABE I-blocking peptide hirugen, indicating that a fully formed ABE I is not absolutely required for FXI activation. In a FXI-dependent plasma thrombin generation assay,  $\beta$ -thrombin,  $\gamma$ -thrombin, and  $\alpha$ -thrombins with mutations in ABE I are approximately 2-fold more potent initiators of thrombin generation than  $\alpha$ -thrombin or Mz-IIa, possibly because fibrinogen, which binds to ABE I, competes poorly with FXI for forms of thrombin lacking ABE I. In addition, FXIa can activate factor FXII, which could contribute to thrombin generation through FXIIa-mediated FXI activation. The data indicate that forms of thrombin other than  $\alpha$ -thrombin contribute directly to feedback activation of FXI in plasma and suggest that FXIa may provide a link between tissue factor-initiated coagulation and the proteases of the contact system.

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