Platelet Polyphosphate Accelerates the Inhibition of Tissue Factor Pathway Inhibitor by Factor XIa.

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Introduction: Our group has recently identified that alpha tissue factor pathway inhibitor (TFPIa) can be neutralized by activated factor XI (FXIa), accelerating plasma clotting time and fibrin generation, although this reaction was slow and required relatively high concentrations of FXIa. Activated platelets secrete the anionic polymer polyphosphate (polyP), which potently accelerate the activation of FXI by thrombin and the activation of FV by FXIa. PolyP is also able to inhibit the anticoagulant effect of TFPIa in plasma but the mechanism for this reaction is still uncertain. We assessed the hypothesis that polyP of the size secreted by activated human platelets is cofactor for the inhibition of TFPIa by FXIa.

Methods: To measure the binding of polyP to TFPI, biotinylated-polyP was added to TFPIa-coated wells. Binding was detected with HRP-streptavidin. Activated FX (FXa) inhibition by TFPIa was measured in the FXa-initiated clotting time of FX-depleted plasma. TFPIa inhibition of FXa generation by the tissue factor (TF)-FVIIa complex was measuring using a FXa chromogenic substrate. TFPIa was pretreated with FXIa in the absence or presence of polyP.

Results: We found that polyP was able to bind to TFPIa in a concentration-dependent manner. In the absence of polyP, the pretreatment of TFPIa (5 nM) with 1 nM FXIa for 1 hour abrogated the anticoagulant effect of TFPIa in the FXa-initiated clotting time of FX-depleted plasma. In the presence of polyP (10 μM), the pretreatment of TFPIa (5 nM) with 0.25 nM FXIa for 30 min was enough to completely abrogate the anticoagulant effect of TFPIa in plasma. Also, the presence of polyP potently accelerated the effect of FXIa to inhibit the capacity of TFPIa to block the generation of FX by the TF-FVIIa complex.

Conclusion: Our study provides a novel molecular link between hemostatic activation of platelets and FXI. The results suggest that the hemostatic role of FXIa may be attributed not only to activation of FIX but also to promoting the extrinsic pathway of thrombin generation through inactivation of TFPIa by FXIa, which is significantly enhanced by the release and presence of activated platelet-derived polyphosphates.