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# **Fucosylated chondroitin sulfate inhibits plasma thrombin generation via targeting of the factor IXa heparin-binding exosite.**

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## **Abstract**

Depolymerized holothurian glycosaminoglycan (DHG) is a fucosylated chondroitin sulfate with antithrombin-independent antithrombotic properties. Heparin cofactor II (HCII)-dependent and -independent mechanisms for DHG inhibition of plasma thrombin generation were evaluated. When thrombin generation was initiated with 0.2 pM tissue factor (TF), the half maximal effective concentration (EC(50)) for DHG inhibition was identical in mock- or HCII-depleted plasma, suggesting a serpin-independent mechanism. In the presence of excess TF, the EC(50) for DHG was increased 13- to 27-fold, suggesting inhibition was dependent on intrinsic tenase (factor IXa-factor VIIIa) components. In factor VIII-deficient plasma supplemented with 700 pM factor VIII or VIIIa, and factor IX-deficient plasma supplemented with plasma-derived factor IX or 100 pM factor IXa, the EC(50) for DHG was similar. Thus, cofactor and zymogen activation did not contribute to DHG inhibition of thrombin generation. Factor IX-deficient plasma supplemented with mutant factor IX(a) proteins demonstrated resistance to DHG inhibition of thrombin generation [factor IX(a) R233A > R170A > WT] that inversely correlated with protease-heparin affinity. These results replicate the effect of these mutations with purified intrinsic tenase components, and establish the factor IXa heparin-binding exosite as the relevant molecular target for inhibition by DHG. Glycosaminoglycan-mediated intrinsic tenase inhibition is a novel antithrombotic mechanism with physiologic and therapeutic applications.

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