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Depolymerized holothurian glycosaminoglycan and heparin inhibit the intrinsic tenase complex by a common antithrombin-independent mechanism.

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Abstract

Depolymerized holothurian glycosaminoglycan (DHG) is a fucosylated chrondroitin sulfate that possesses antithrombin-independent antithrombotic properties and inhibits factor X activation by the intrinsic tenase complex (factor IXa-factor VIIIa). The mechanism and molecular target for intrinsic tenase inhibition were determined and compared with inhibition by low-molecular-weight heparin (LMWH). DHG inhibited factor X activation in a noncompetitive manner (reduced V(max(app))), with 50-fold higher apparent affinity than LMWH. DHG did not affect factor VIIIa half-life or chromogenic substrate cleavage by factor IXa-phospholipid but reduced the affinity of factor IXa for factor VIIIa. DHG competed factor IXa binding to immobilized LMWH with an EC(50) 35-fold lower than soluble LWMH. Analysis of intrinsic tenase inhibition, employing factor IXa with mutations in the heparin-binding exosite, demonstrated that relative affinity (K(i)) for DHG was as follows: wild type > K241A > H92A > R170A > > R233A, with partial rather than complete inhibition of the mutants. This rank order for DHG potency correlated with the effect of these mutations on factor IXa-LMWH affinity and the potency of LMWH for intrinsic tenase. DHG also accelerated decay of the intact intrinsic tenase complex. Thus, DHG binds to an exosite on factor IXa that overlaps with the binding sites for LMWH and factor VIIIa, disrupting critical factor IXa-factor VIIIa interactions.

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