

Display Settings: AbstractSend to: 

Biochemistry. 2010 Nov 23;49(46):9997-10005. Epub 2010 Oct 27.

The regulation of factor IXa by supersulfated low molecular weight heparin.

Misenheimer TM, Sheehan JP.

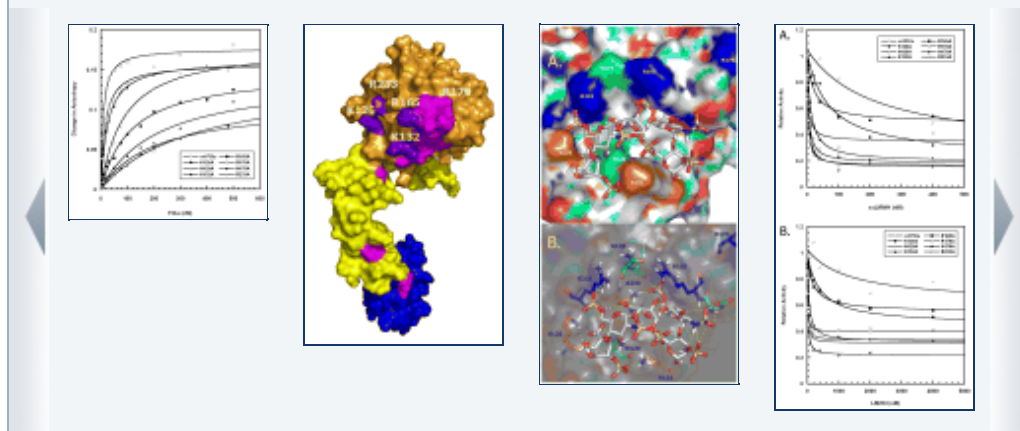
Department of Medicine/Hematology-Oncology, University of Wisconsin-Madison, Madison, Wisconsin 53706, United States.

Abstract

Supersulfated low molecular weight heparin (ssLMWH) inhibits the intrinsic tenase (factor IXa-factor VIIIa) complex in an antithrombin-independent manner. Recombinant factor IXa with alanine substitutions in the protease domain (K126A, N129A, K132A, R165A, R170A, N178A, R233A) was assessed with regard to heparin affinity in solution and ability to regulate protease activity within the factor IXa-phospholipid (PL) and intrinsic tenase complexes. In a soluble binding assay, factor IXa K126A, K132A, and R233A dramatically (10-20-fold) reduced ssLMWH affinity, while factor IXa N129A and R165A moderately (5-fold) reduced affinity relative to wild type. In the factor IXa-PL complex, binding affinity for ssLMWH was increased 4-fold, and factor X activation was inhibited with a potency 7-fold higher than predicted for wild-type protease-ssLMWH affinity in solution. In the intrinsic tenase complex, ssLMWH inhibited factor X activation with a 4-fold decrease in potency relative to wild-type factor IXa-PL. The mutations increased resistance to inhibition by ssLMWH in a similar fashion for both enzyme complexes (R233A > K126A > K132A/R165A > N129A/N178A/wild type) except for factor IXa R170A. This protease had ssLMWH affinity and potency for the factor IXa-PL complex similar to wild-type protease but was moderately resistant (6-fold) to inhibition in the intrinsic tenase complex based on increased cofactor affinity. These results are consistent with conformational regulation of the heparin-binding exosite and macromolecular substrate catalysis by factor IXa. An extensive overlap exists between the heparin and factor VIIIa binding sites on the protease domain, with residues K126 and R233 dominating the heparin interaction and R165 dominating the cofactor interaction.

PMID: 20945941 [PubMed - indexed for MEDLINE] PMCID: PMC2996140

Free PMC Article

Images from this publication. See all images (6) [Free text](#)
 Publication Types, MeSH Terms, Substances, Grant Support

 LinkOut - more resources

Related citations

The factor IXa heparin-binding exosite is a [Biochemistry. 2005]

The heparin-binding exosite is critical to all [Biochemistry. 2007]

Heparin inhibits the intrinsic tenase com [Biochemistry. 2003]

Review Role of heparin and heparinlike mol [Fed Proc. 1985]

Review Region of factor IXa protease [Thromb Haemost. 1999]

See reviews...

See all...

Related information

[Related Citations](#)
[References for this PMC Article](#)
[Substance \(MeSH Keyword\)](#)
[Free in PMC](#)

Search details

Search

See more...

Recent activity

[Turn Off](#) [Clear](#)

The regulation of factor IXa by supersulfated low [PubMed](#)

20945941[uid] (1)

[PubMed](#)

See more...



You are here: [NCBI](#) > [Literature](#) > [PubMed](#)

[Write to the Help Desk](#)

GETTING STARTED

[NCBI Education](#)
[NCBI Help Manual](#)
[NCBI Handbook](#)
[Training & Tutorials](#)

RESOURCES

[Chemicals & Bioassays](#)
[Data & Software](#)
[DNA & RNA](#)
[Domains & Structures](#)
[Genes & Expression](#)
[Genetics & Medicine](#)
[Genomes & Maps](#)
[Homology](#)
[Literature](#)
[Proteins](#)
[Sequence Analysis](#)
[Taxonomy](#)
[Training & Tutorials](#)
[Variation](#)

POPULAR

[PubMed](#)
[Nucleotide](#)
[BLAST](#)
[PubMed Central](#)
[Gene](#)
[Bookshelf](#)
[Protein](#)
[OMIM](#)
[Genome](#)
[SNP](#)
[Structure](#)

FEATURED

[GenBank](#)
[Reference Sequences](#)
[Map Viewer](#)
[Genome Projects](#)
[Human Genome](#)
[Mouse Genome](#)
[Influenza Virus](#)
[Primer-BLAST](#)
[Sequence Read Archive](#)

NCBI INFORMATION

[About NCBI](#)
[Research at NCBI](#)
[NCBI Newsletter](#)
[NCBI FTP Site](#)
[NCBI on Facebook](#)
[NCBI on Twitter](#)
[NCBI on YouTube](#)

[Copyright](#) | [Disclaimer](#) | [Privacy](#) | [Accessibility](#) | [Contact](#)

National Center for Biotechnology Information, U.S. National Library of Medicine
8600 Rockville Pike, Bethesda MD, 20894 USA

