1AZX: Antithrombin/Pentasaccharide Complex

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Antithrombin, a plasma serpin, is relatively inactive as an inhibitor of the coagulation proteases until it binds to the heparan side chains that line the microvasculature. The binding specifically occurs to a core pentasaccharide present both in the heparans and in their therapeutic derivative heparin. The accompanying conformational change of antithrombin is revealed in a 2.9-A structure of a dimer of latent and active antithrombins, each in complex with the high-affinity pentasaccharide. Inhibitory activation results from a shift in the main sheet of the molecule from a partially six-stranded to a five-stranded form, with extrusion of the reactive center loop to give a more exposed orientation. There is a tilting and elongation of helix D with the formation of a 2-turn helix P between the C and D helices. Concomitant conformational changes at the heparin binding site explain both the initial tight binding of antithrombin to the heparans and the subsequent release of the antithrombin-protease complex into the circulation. The pentasaccharide binds by hydrogen bonding of its sulfates and carboxylates to Arg-129 and Lys-125 in the D-helix, to Arg-46 and Arg-47 in the A-helix, to Lys-114 and Glu-113 in the P-helix, and to Lys-11 and Arg-13 in a cleft formed by the amino terminus. This clear definition of the binding site will provide a structural basis for developing heparin analogues that are more specific toward their intended target antithrombin and therefore less likely to exhibit side effects.

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