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1BR8: Implications For Function And Therapy Of A 2.9A Structure Of Binary-Complexed Antithrombin

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The crystal structure of a binary complex of human antithrombin with a peptide of the same sequence as its reactive loop (P14-P3) has been determined at 2.9 A. The peptide binds as the middle strand s4A in the A beta-sheet, homologously to that of the reactive loop in the latent and cleaved forms of antithrombin. Peptide binding results in the complete expulsion of the hinge region of the loop from the A beta-sheet although the conformation differs from that of heparin-activated antithrombin. The 36-fold increase in the rate of reaction of the binary complex with factor Xa indicates that full loop expulsion alone is not sufficient for complete heparin activation of antithrombin but that this is also dependent on the overall conformation of the molecule. Previous studies have demonstrated that reactive loop peptides can block or reverse the polymerisation of serpins associated with cirrhosis and thrombosis. The antithrombin binary complex structure defines the precise localisation of the blocking peptide in a serpin and provides the basis for rational drug design for mimetics that will prevent polymerisation in vivo and so ameliorate the associated disease.
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