STRATEGIES FOR THE CONTROL OF BLOOD COAGULATION: POSSIBLE NEW PLATFORMS FOR DRUG DESIGN

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Haemostatic diseases such as thrombosis and its variations lead to acute health problems and billions of dollars are invested in research and treatment. Current clinical strategies for the control of blood coagulation are primarily based on molecules derived from coumarins that inhibit the post-translational γ-carboxylation of glutamate residues on vitamin K-dependent coagulations factors and heparin analogues that enhance inhibition of thrombin and fXa by antithrombin III. These anticoagulant drugs are non-selective and display therapeutic limitations in their ability to maintain the balance of the haemostatic system. Worm, snake, leech, tick and lizard gland secretions contain a wide variety of haemostatically-active proteins, which interfere at different levels in the coagulation cascade and fibrinolytic system and serve as promising drugs for the treatment of haemostatic disorders. Nematode anticoagulant proteins from the hematophagous nematode *Ancylostoma caninum* have been targeted for the control and regulation of thrombosis and are significantly more potent than low molecular weight heparins. One of these, NAPc2 only partially inhibits the amidolytic activity of fXa, but prevents the formation of thrombin by fXa at a site distinct and remote from the active site with the resultant binary complex inactivating the TF-FVIIa complex (K_i = 8.4 pM). On the other hand, the highly homologous NAP5, the most potent natural fXa inhibitor, uses a different strategy for the binding to the active site of fXa (Ki = 43 pM) modifying the hydrogen bond network at the active site. The crystal structures of both inhibitors have been solved complexed with Gla-domainless fXa and reveals a novel inhibitory exosite of fXa formed by residues 87-93 and C-terminus. This novel exosite is physiologically highly relevant for the recognition and inhibition of factor X/Xa by macromolecular substrates and provides a structural motif for the development of a new class of inhibitors for the treatment of deep vein thrombosis and angioplasty.

Acknowledgements: We are grateful to FAPESP, CAT/CEPID, SMOLBNet, CNPq and DAAD for financial support.