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Serine protease homolog from snake venom, a promising new anticoagulant lead molecule

Igor Križaj[1], Latinović Z[1, 2], Leonardi A[1], Pungerčar J[1], Koh C Y[3] and **Kini R M[3]**
[1]Jožef Stefan Institute, Slovenia
[2]Jožef Stefan International Postgraduate School, Slovenia
[3]National University of Singapore, Singapore

Most frequently used anticoagulant therapies may induce severe complications. To overcome these limitations, new anticoagulants have been intensively searched for. We report here the purification and characterization of a glycoprotein from the venom of the nose-horned viper (*Vipera ammodytes*), which significantly prolonged activated partial thromboplastin time in human plasma. Amino acid sequence of this protein (VaaSPH) revealed it as a serine protease possessing two mutations in its catalytic triad that renders it enzymatically inactive. Detailed analysis of the mechanism of blood coagulation inhibition by VaaSPH unveiled that the molecule inhibits the activity of tenase and prothrombinase complexes, with IC_{50} values of 142 nM and 134 nM, respectively. It was demonstrated that inhibition of the complexes formation was due to the binding of VaaSPH to blood coagulation factors VII, IX and X, to their activated forms and to FVa and FII. In addition, VaaSPH was also found to bind specifically to phosphatidylserine, a negatively charged phospholipid, which directed the assembly of the enzyme–cofactor complexes on membrane surface of platelets. Three-dimensional structure comparison of FVII, FIX, FX, FII and their respective activated forms suggested two areas on their surfaces, in proximity of their active sites, where VaaSPH binds. Such a proposal was also experimentally supported. As a potent non-enzymatic and coagulation factor active-site independent inhibitor of blood coagulation process, VaaSPH is unique and therefore, very interesting for a further characterization to design, based on its structure, a novel family of selective coagulation factor inhibitors of therapeutic relevance for anticoagulant therapy.

Biography

Igor Križaj completed his Doctoral studies at Jožef Stefan Institute in Ljubljana (JSIL) and at Imperial College in London. He completed his Post-doctorate studies at Institute Pasteur in Paris. He is the Head of Department of Molecular and Biomedical Sciences at JSIL and full Professor of Biochemistry at University of Ljubljana. He has published more than 130 research papers in the SCI-journals. He has been serving as an Editorial Board Member at several scientific journals and as Secretary of the European Section of the International Society on Toxinology.

igor.krizaj@ijs.si

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