Factor Xa

Factor Xa is the activated form of the coagulation factor thrombokinase, known eponymously as Stuart-Prower factor.

Factor X is an enzyme, a serine endopeptidase, which plays a key role at several stages of the coagulation system. Factor X is synthesized in the liver. The most commonly used anticoagulants in clinical practice, warfarin and the heparin series of anticoagulants and fondaparinux, act to inhibit the action of Factor Xa in various degrees.

Traditional models of coagulation developed in the 1960s envisaged two separate cascades, the extrinsic tissue factor (TF) pathway and the intrinsic pathway. These pathways converge to a common point, the formation of the Factor Xa/Va complex which together with calcium and bound on a phospholipids surface generate thrombin (Factor IIa) from prothrombin (Factor II).

A new model, the cell-based model of anticoagulation appears to explain more fully the steps in coagulation. This model has three stages: 1) initiation of coagulation on TF-bearing cells, 2) amplification of the procoagulant signal by thrombin generated on the TF-bearing cell and 3) propagation of thrombin generation on the platelet surface. Factor Xa plays a key role in all three of these stages.

In stage 1, Factor VII binds to the transmembrane protein TF on the surface of cells and is converted to Factor VIIa. The result is a Factor VIIa/TF complex which catalyzes the activation of Factor X and Factor IX. Factor Xa formed on the surface of the TF-bearing cell interacts with Factor Va to form the prothrombinase complex which generates small amounts of thrombin on the surface of TF-bearing cells.

In stage 2, the amplification stage, if enough thrombin has been generated, then activation of platelets and platelet associated cofactors occurs.

In stage 3, thrombin generation, Factor XIa activates free Factor IX on the surface of activated platelets. The activated Factor IXa with Factor VIIIa forms the “tenase” complex. This “tenase” complex activates more Factor X, which in turn forms new prothrombinase complexes with Factor Va. Factor Xa is the prime component of the prothrombinase complex which converts large amounts of prothrombin—the “thrombin burst”. Each molecule of Factor Xa can generate 1000 molecules of thrombin. This large burst of thrombin is responsible for fibrin polymerization to form a thrombus.

Inhibition of the synthesis or activity of Factor X is the mechanism of action for many anticoagulants in use today. Warfarin, a synthetic derivative of coumarin, is the most widely used oral anticoagulant in the US. In some European countries, other coumarin derivatives (phenprocoumon and acenocoumarol) are used. These agents are vitamin K antagonists (VKA). Vitamin K is essential for the hepatic synthesis of Factors II (prothrombin), VII, IX and X.

Heparin (unfractionated heparin) and its derivatives low molecular weight heparin (LMWH) bind to a plasma cofactor, antithrombin (AT) to inactivate several coagulation factors IIa, Xa, XIa and XIIa. The affinity of unfractionated heparin and the various LMWHs for Factor Xa varies considerably. The efficacy of heparin-based anticoagulants increases as selectivity for Factor Xa increases. LMWH shows increased inactivation of Factor Xa compared to unfractionated heparin, and fondaparinux, an agent based on the critical pentasacharide sequence of heparin, shows more selectivity than LMWH. This inactivation of Factor Xa by heparins is termed “indirect” since it relies on the presence of AT and not a direct interaction with Factor Xa.

Recently a new series of specific, direct acting inhibitors of Factor Xa has been developed. These include the drugs rivaroxaban, apixaban, betrixaban, LY517717, darexaban (YM150), edoxaban and 813893. These agents have several theoretical advantages over current therapy. They may be given orally. They have rapid onset of action. And they may be more effective against Factor Xa in that they inhibit both free Factor Xa and Factor Xa in the prothrombinase complex.

Inhibitors

see Factor Xa inhibitors