Development of New Anticoagulant Drugs

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Blood coagulation is initiated by interaction of coagulation factor VIIa with tissue factor (TF) expressed on the cells at the site of injured tissues and also on the activated leucocytes adhered at the injured sites, which is followed by activation of factors IX and X by factor VIIa-TF complex. Activated factor IXa forms a complex with factor VIIIa and activates factor X on the platelets aggregated at the site of tissue injury. Similarly factor Xa-factor Va complex on the platelets activates prothrombin leading to abundant thrombin generation to prevent bleeding from the tissues. This blood coagulation process is normally regulated by several natural anticoagulants, such as TF pathway inhibitor, antithrombin, heparin cofactor II, and components in the anticoagulant protein C pathway. However, excessive thrombin generation inducing severe thrombotic diseases such as venous thromboembolism (VTE) is frequently occurred in patients with inherited thrombophilia and acquired thrombophilia such as after major surgery. Heparin and warfarin have been used for long times to prevent VTE and other thrombotic diseases, but limitations of these drugs have prompted the development of new anticoagulant drugs. Novel parenteral agents include synthetic analogs of the pentasaccharide sequence of heparin that mediates its interaction with antithrombin. Synthetic pentasaccharide is used for prevention of VTE after major orthopedic surgery and for initial treatment of patients with VTE. Natural anticoagulant antithrombin and activated protein C are also used for severe sepsis. New oral anticoagulants including direct inhibitors of thrombin, factor Xa and factor IXa have been developed. In this symposium, I will review briefly coagulation pathways and new anticoagulants in advanced stages of clinical testing.