DIAGNOSIS AND MANAGEMENT OF THROMBOSIS

The importance of the protein C system in the pathogenesis of venous thrombosis

BJÖRN DAHLBÄCK

Department of Laboratory Medicine, Clinical Chemistry, Lund University, The Wallenberg laboratory, University Hospital, Malmö, SE-205 02 Malmö, Sweden

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Primary haemostasis and blood coagulation have evolved as important defence mechanisms against bleeding. The formation of the platelet plug is timely co-ordinated with the activation of the coagulation system, which occurs in response to the exposure of blood to extravascular tissues. The reactions of blood coagulation are carefully controlled by several anticoagulant mechanisms and under normal conditions they prevail over the procoagulant forces. The protein C system provides important control of blood coagulation by regulating the activities of factor VIIIa (FVIIIa) and factor Va (FVa), cofactors in the activation of factor X and prothrombin, respectively. The system comprises membrane-bound and circulating proteins that assemble into multi-molecular complexes on cell surfaces.

Vitamin K-dependent protein C, the key component of the system, circulates in blood as zymogen to an anticoagulant serine protease. It is efficiently activated on the surface of endothelial cells by thrombin bound to the membrane protein thrombomodulin. The endothelial protein C receptor (EPCR) further stimulates the protein C activation. Activated protein C (APC) together with its cofactor protein S inhibits coagulation by degrading FVIIIa and FVa on the surface of negatively charged phospholipid membranes. Efficient FVIIIa degradation by APC requires not only protein S but also FV, which like thrombin is a Janus-faced protein with both pro- and anticoagulant potential.

Protein S in human plasma is not only an important component of the protein C pathway but also takes part in the regulation of the complement system as it forms a high affinity complex with C4b-binding protein (C4BP), a regulator of the classical complement pathway. In human plasma, 30–40% of the protein S circulates as free protein, the remaining being bound to C4BP. Only free protein S has the ability to function as a cofactor to APC. Recently, it was found that protein S binds to the negatively charged phospholipid surface that is exposed on apoptotic cells and can mediate phagocytosis of the apoptotic cell. This observation might account for the observed lack of coagulation activation in the vicinity of apoptotic cells.

The protein C system is vitally important to keep the blood fluid. This is most clearly illustrated by the severe microvascular thrombotic disease that already in the neonatal period affects individuals with complete inherited protein C deficiency. Heterozygous deficiency is associated with approximately a 5-fold increased risk of venous thrombosis. Heterozygous protein S deficiency is affected by similar thrombosis risk as protein C deficiency. The Factor V Leiden mutation (APC resistance) is the most common gene defect associated with venous thrombosis found in 20–40% of patients with thrombosis in western countries. The Factor V Leiden mutation (G1691A) replaces Arg506 with a Gln. Mutant Factor V has full procoagulant capacity, but the protein C anticoagulant system is affected in two ways by the mutation. The first is impaired degradation of mutant Factor Va by APC because the mutation eliminates one of three APC cleavage sites in Factor Va. The second is impaired degradation of Factor VIIIa because mutant Factor V cannot be cleaved at Arg506 and is therefore a poor cofactor to APC in the degradation of Factor VIIIa. Factor V Leiden is the result of a founder effect. Heterozygous individuals have approximately a 5-fold increased risk of venous thrombosis, whereas homo-
zygotes have around a 50-fold increased risk. The mutation is not a risk factor for arterial thrombosis.

In recent years, protein C has been shown not only to be anticoagulant but also to have anti-inflammatory and anti-apoptotic properties, which are exerted when APC binds to EPCR and proteolytic cleaves protease activated receptor 1 (PAR-1). The unique combination of anticoagulant, anti-inflammatory and anti-apoptotic properties of activated protein C (APC) has made it an attractive candidate as a therapeutic agent and administration of APC has proven beneficial in the handling of patients with severe sepsis.

Significant insights have been gained in to the structure–function relationships of large macromolecular complexes important for the activation of protein C, the regulation of tenase and prothrombinase complexes, and the cell-surface interactions with EPCR/PAR-1 resulting in anti-inflammatory and anti-apoptotic effects. However, many unanswered questions remain and some may be particularly challenging, e.g. the molecular interactions of the synergistic APC cofactor activity of Factor V and protein S in the regulation of Factor VIIIa in the tenase complex and the elucidation of the cellsurface and intracellular events associated with the anti-inflammatory and anti-apoptotic functions of the protein C system. The coming years will no doubt bring further exciting novel insights into these mechanisms.