TFPI: New insights into an old inhibitor

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Tissue factor pathway inhibitor alpha (TFPIα) is a multivalent kunitz-type protease inhibitor that down-regulates coagulation *via* inhibition of the tissue factor (TF)/factor VIIa (FVIIa) complex and factor Xa (FXa). Structurally, it comprises an acidic N-terminus, three consecutive kunitz domains (K1, K2 and K3) and a basic C-terminus. TFPIα circulates in plasma at a concentration of ~2.5 nM, of which 90% is C-terminally truncated and bound to lipoproteins. Only 10% (~0.25 nM) is in the free full-length form, which is the most active as an anticoagulant. 'Free' plasma TFPIα actually circulates in complex with protein S and/or factor V (FV), which protect TFPIα from truncation and clearance. These complexes also have functional significance, as both protein S and FV stimulate the inhibition of FXa by full-length TFPIα by enhancing TFPIα binding to phospholipids.
Conversely, it is slowly emerging that the interaction between TFPIα and FV also influences FV function. FV is maintained in its inactive state by a high-affinity interaction between a basic region and an acidic region in its B-domain. Limited proteolysis of FV by FXa or thrombin at Arg^{709}, Arg^{1018} and Arg^{1545} eliminates this constraint and converts FV to its active form (FVa), which acts as a potent cofactor of FXa in the prothrombinase complex. The C-terminus of TFPIα is highly homologous to the FV basic region ad competes with it for binding to the acidic region of FV. Recent work from our and other laboratories indicates that binding of TFPIα to the FV acidic region interferes with cleavage of FV at Arg^{1545}, thereby preventing full FV activation as well as incorporation of the partially activated FV(a) intermediates into the prothrombinase complex. This points at a novel anticoagulant function of TFPIα as an inhibitor of both FV activation and prothrombinase activity.
The present lecture will discuss these new developments and their implications for haemostatic disorders, such as the recently described East Texas bleeding disorder.