TFPI - Tissue Factor Pathway Inhibitor

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The role of tissue factor pathway inhibitor in atherosclerosis and arterial thrombosis.


Summary:
In a recent review article Winckers and colleagues summarize the role tissue factor pathway inhibitor in atherosclerosis and arterial thrombosis. The article provides a good overview on clinical studies in which TFPI was studied in the context of atherosclerosis, coronary artery disease and ischemic stroke. The authors discuss potential atheroprotective actions of TFPI.

Expression of tissue factor and tissue factor pathway inhibitor in microparticles and subcellular fractions of normal and malignant prostate cell lines.


Summary:
Lwaleed and colleagues studied expression of tissue factor (TF) and tissue factor pathway inhibitor (TFPI) in microparticles and subcellular fractions (cytosol, membrane and nuclei) of normal and malignant prostate cell lines by using ELISA. They found that TF expression was higher in subcellular fractions and microparticles of normal prostate cells than cancer cells. In contrast, levels of TFPI which structurally resembled a secreted, rather than transmembrane protein in microparticles of normal prostate cells were much lower than tumour cells. They concluded, that the “activity of prostate cancer cells themselves is unlikely to be the source of hypercoagulability in patients, but might precipitate chains of events that would produce such an effect”.

TFPIα and TFPIβ are expressed at the surface of breast cancer cells and inhibit TF-FVIIa activity.


Summary:
TFPI exists in two forms: TFPI-alpha circulates in plasma whereas TFPI-beta is cell surface bound via a glycosylphosphatidylinositol (GPI) anchor. Stavik and colleagues analysed breast cancer cell lines for the presence of both isoforms. The found GPI-anchored TFPI at the surface breast cancer cells which is functionally active, i.e. it has TF-FVIIa inhibitory activity. They conclude that “GPI-attached TFPI located at the surface of breast cancer cells inhibited TF activity and could possibly reduce TF signalling and breast cancer growth locally, indicating a therapeutic potential of the TFPIβ isoform.”

TFPI resistance related to inherited or acquired protein S deficiency.


Summary:
Tardy-Poncet et al. studied the role of Protein S as a cofactor for TFPI activity. In a two-step diluted prothrombin time (dPT) assay they studied the response to added TFPI. The response of the different plasmas to the anticoagulant activity of TFPI was expressed as “TFPI Normalised Ratio”. Taken together, they found that a deficiency in Protein S results in a poor anticoagulant response to TFPI, which demonstrates the cofactor role of Protein S in TFPI activity.
Low amounts of platelet TFPI and protein S are highly effective in regulating local thrombin generation which is not affected by proteolysis of protein S.

Winckers K, Thomassen MC, ten Cate H, Rosing H., Hackeng T.
Abstract no. OC 73.3, ISTH 2013

Summary:
Along these lines Winckers and colleagues studied the role of platelet TFPI and protein S in regulating local thrombin generation. Basically they could show by testing in the absence or presence of anti-protein S antibodies that platelet protein S enhanced the anticoagulant of platelet TFPI 3-fold. In further detailed experiments they provide evidence that half of inhibitory capacity of TFPI for thrombin generation was contributed to the cofactor activity of protein S for TFPI. Moreover, cleavage of protein S by platelet proteases did not inhibit its TFPI cofactor activity. The authors conclude “Although platelets contain less than 2% of plasma protein S, platelet protein S plays a crucial role in TFPI-mediated FXa inhibition. As platelets localize at sites of vascular injury, the platelet-dependent TFPI/protein S system is likely to play an important role in modulating procoagulant activity at the growing thrombus.”

TF, TFPI and TAT complexes in myeloproliferative neoplasms.

Gadomska G, Stankowska K, Boinska J, Swistek W, Drela E, Zekanowska E, Rosc D.
Abstract no. PB 3.60-5, ISTH 2013

Summary:
Gadomska and colleagues studied Tissue Factor, TFPI and TAT complexes in myeloproliferative diseases. In the different disease entities Essential Thrombocythemia, Polycythemia vera, Chronic Myelogenous Leukemia and Primary Myelofibrosis they found increased levels of Tissue Factor. In Essential Thrombocythemia and Polycythemia vera they also found lower levels of TFPI. In patients with Chronic Myelogenous Leukemia they found significantly higher levels of TAT. The authors conclude that in some of the disease entities (ET and PV) lower concentrations of TFPI contribute to the increased tendency to hypercoagulability.

Changes in haemostatic parameters during the menstrual cycle and drospirenone-containing oral contraceptive use.

Tchaikovski S, Thomassen M, Costa S, Bremme K, Rosing J.
Abstract no. PB 2.66-5, ISTH 2013

Summary:
Tchaikovski and colleagues analysed the prothrombotic activity of contraceptives containing a new progesterone-drospirenone (DRSP-OC) compound. The analysed various components of the coagulation system. With respect to TFPI they concluded that “DRSP-OC may influence TFPI activity at various regulatory levels, such as synthesis, cleavage, binding to lipoproteins or cleavage”. Also they summarize that “the changes in anticoagulant pathways such as protein C- TFPI-systems are more pronounced than then changes in the coagulation pathways”.

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<table>
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<th>Title</th>
<th>Summary</th>
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<td>Increased tissue factor pathway inhibitor activity is associated with myocardial infarction in young women: results from the RATIO study.</td>
<td>Winckers K, Siegerink B, Duckers C, Maurissen LF, Tans G, Castoldi E, Spronk HM, ten Cate H, Algra A, Hackeng TM, Rosendaal FR. J Thromb Haemost. 2011 Nov;9(11):2243-2250. Winckers and colleagues studied the influence of the TFPI/Protein S anticoagulant system on the risk of myocardial infarction (MI) in young women. They found that women with MI had higher TFPI levels as compared to controls. It remains open whether the increase in TFPI acts as compensating mechanism for an increased pro-coagulant state or is a marker of endothelial damage.</td>
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<td>Tissue Factor, Tissue Factor Pathway Inhibitor and Factor VII Activity in Cardiovascular Complicated Type 2 Diabetes Mellitus.</td>
<td>El-Hagracy RS, Kamal GM, Sabry IM, Saad AA, Abou El Ezz NF, Nasr HA. Oman Med J. 2010 Jul;25(3):173-178. El-Hagracy and colleagues studied Tissue Factor (TF), Tissue Factor Pathway Inhibitor (TFPI) and Factor VII (FVII) activity in patients with Type 2 Diabetes (T2DM) and cardiovascular complications. TF and TFPI were measured by ELISA and Factor VIIa activity was tested by using the prothrombin time assay and factor VII depleted plasma. In conclusion, the authors found that “there was a correlation between high TF, TFPI plasma levels, Factor VIIa activity and cardiothrombotic complications in T2DM especially in the presence of high risk factors such as poor glycemic control, dyslipidemia and obesity.” They suggest that “Future target therapy against TF may be beneficial for T2DM patients.”</td>
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<td>Hereditary and acquired protein S deficiencies are associated with low TFPI levels in plasma.</td>
<td>Castoldi E, Simioni P, Tormene D, Rosing J, Hackeng TM. Thromb Haemost. 2010 Feb;8(2):294-300. Protein S and TFPI act together in down-regulating coagulation. Castoldi and colleagues studied full length TFPI levels in Protein S deficient individuals as compared to controls. Protein S deficient individuals did not only have lower protein S levels but also lower TFPI levels. When triggered with tissue factor, plasma from Protein S deficient individuals generated 3-5-fold more thrombin than control plasmas. The difference was only fully corrected when not only Protein S levels were normalized but also the TFPI levels. The authors conclude that “Full-length TFPI binds to protein S in plasma and is reduced in genetic and acquired protein S efficiency. The concomitant TFPI deficiency substantially contributes to the hypercoagulable state associated with protein S deficiency.”</td>
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