

# Tissue factor inhibition: Another approach reducing thrombosis after vascular injury

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Vascular injury induces haemostasis with subsequent thrombus formation. Accumulating evidence indicates that activation of the tissue factor (TF) pathway may play an important role in the pathophysiology of intravascular thrombus formation following arterial injury. A variety of cell types like monocytes, smooth muscle cells, foam cells and endothelial cells express TF in atherosclerotic lesions (1). In the plaque, TF is also present on microparticles within the necrotic core that are derived from apoptotic foam cells or macrophages, respectively. Moreover, the number of circulating TF-positive microparticles is increased in patients with acute coronary syndromes, endotoxaemia and cancer and may contribute to thrombotic events (2).

Activation of the coagulation cascade consists of three overlapping phases: initiation, amplification and propagation. The initiation phase is localized to TF expressing surfaces that are exposed from the sub-endothelial tissue to flowing blood after vascular injury or plaque rupture. The proteolytic TF/factor (F)VIIa complex activates small amounts of FIX and FX. On TF-exposing cells FXa then associates with FVa to form the prothrombinase complex. In the amplification phase low concentrations of thrombin activate platelets to release FV. A positive feedback loop is generated whereby thrombin activates FV and FVIII. During the propagation phase the phospholipids surface of activated platelets acts

as a cofactor for the generation of the FVIIIa-FIXa and of FVa-FXa which accelerate the generation of and FXa thrombin (3).

Targeting the initiation phase may prevent thrombus formation more efficiently than at later stages, since the coagulation cascade is specifically blocked right from the beginning. The activity of the TF/FVIIa complex can be inhibited by TF antibodies, recombinant tissue factor pathway inhibitor (tifagasin), recombinant nematode anticoagulant (NAPc2) or active-site blocked FVIIa (ASIS). Experimental studies with these compounds in various vascular injury models suggest an effective reduction in thrombosis with a lower bleeding risk as compared to other types of coagulation inhibitors such as heparin or direct thrombin inhibitors (4).

Recently, a chimeric mouse/human monoclonal antibody to TF (ALT836) has been developed. This antibody binds specifically to human TF at the FX binding site, thereby preventing formation of the TF:FVIIa-FX or TF=FVIIa-FIX complex. First clinical studies in subjects with stable coronary artery disease showed a dose-dependent anticoagulant effect with only minor bleeding (5). In the study by Jiao et al. (6) in this issue of *Thrombosis and Haemostasis* the authors describe that application of ALT836 after endarterectomy in chimpanzees results in a significant reduction in local thrombus formation, as assessed by platelet deposition and an improved 30 days vessel patency. This anti-thrombotic effect was not associated with an increase in bleeding time or surgical blood loss. These results indicate that early inhibition of the coagulation cascade using TF-inhibitory antibodies is effective in reducing thrombus formation after arterial injury. Since in the experiments by Jiao et al. the antibody was administered immediately before the restoration of blood flow, the prediction of efficacy in the clinical situation will need to be proven. Thus, ALT836 may

be a novel tool to reduce thrombotic complications after intravascular interventions with an increased thrombotic risk e.g. in acute coronary syndromes. Despite improved interventional techniques and pharmacologic platelet inhibition thrombotic complications in these patients remain a major problem.

The fact that TF inhibition by ALT836 was not associated with an increase in bleeding time (6) is encouraging, yet it has to be shown that in the presence of dual platelet inhibition, additional TF antibody-therapy does not increase bleeding complications. Moreover, the role of additional heparin that may be necessary for interventional procedures remains to be investigated as well.

There is now increasing evidence that, in addition to initiating haemostasis, FVIIa in a complex with TF can directly cleave and activate protease-activated receptor-2 (PAR-2), resulting in phosphorylation of the TF cytoplasmic domain. Subsequently, the negative regulatory control of PAR-2 mediated signalling is lost, leading to promotion of angiogenesis (7). Binding of FVIIa to TF also mediates migration and proliferation of vascular smooth muscle cells. Together, these processes may contribute to vessel wall remodelling. Whether TF inhibition by targeting the FX binding site of TF with ALT836 may alter other cellular responses to the TF:FVIIa complex and if this effect is clinically relevant remains to be determined. Other studies have shown that TF-FVIIa signalling also supports tumour metastasis and improves tumour cell survival. Since preclinical studies with TF-targeted cancer therapeutics have demonstrated efficacy, further studies have to prove if these results may translate into inhibition of tumor growth and metastasis in a clinical setting. Application of ALT836 in experimental models may aid to decipher the anti-cancer potential of TF inhibition.

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Received: October 20, 2009  
Accepted: October 20, 2009  
Prepublished online: October 26, 2009

doi:10.1160/TH09-10-0712  
*Thromb Haemost* 2010; 103: 7-8

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