

## Editorial Focus

# New risk factor for venous thromboembolism?

David H. Farrell

Department of Pathology, L113, Oregon Health & Science University, Portland, Oregon, USA

Venous thromboembolism (VTE), particularly recurrent VTE, presents an ongoing challenge to clinical management. Despite Virchow's original insight into the triad of blood stasis, vessel wall changes and hypercoagulability as the underlying causes of VTE (1), the identification of new risk factors for VTE has been problematic. Several well-validated genetic risk factors have been established for VTE, most notably factor V Leiden, antithrombin deficiency, protein C deficiency, protein S deficiency, and the prothrombin G20120A gene mutation, as well as non-genetic risk factors, including oral contraceptives, pregnancy, surgery, cancer, and stasis (2). But new risk factors for VTE have been elusive, prompting the National Heart, Lung and Blood Institute of the National Institutes of Health to issue a recent Request for Proposals to improve diagnosis, therapy, and prevention of venous thrombotic diseases (Deep Vein Thrombosis and Venous Disease, RFA-HL-08-002; <http://grants.nih.gov/grants/guide/rfa-files/RFA-HL-08-002.html>). In this issue of *Thrombosis and Haemostasis*, Pecheniuk et al. identify a potential new risk factor for venous thromboembolism, fibronectin (3).

Until recently, this extracellular matrix molecule has been in the provenance of tumor biologists, who have been studying it for over three decades. Fibronectin, which is often confused by students and trainees with its similarly-named counterpart, fibrinogen, was originally known as "cold insoluble globulin" and is found as a constituent of plasma cryoprecipitate. In the mid-1970s, several laboratories, including those of Richard Hynes (4), Deane Mosher (5), Erkki Ruoslahti (6), Antti Vaheri (5), and Kenneth Yamada (7), identified fibronectin as a cell-surface glycoprotein. At the time, fibronectin was "re-discovered" as CIG (cold-insoluble globulin), FSA (Fibroblast Surface Antigen), and the LETS (Large External Transformation Sensitive) protein, which are absent from the surface of many tumor cells. This 460 kDa glycoprotein is a dimer of two 230 kDa polypeptide chains that are held together by disulfide bonds (8). Several splice variants of fibronectin have been identified, and the biological roles of these isoforms have been investigated (9). Some of the splice isoforms function as cell surface glycoproteins, while others exist as

soluble molecules, including plasma fibronectin. Plasma fibronectin circulates at levels of approximately 300–400 µg/ml, and is also present in platelet  $\alpha$ -granules (8).

The link between fibronectin and coagulation developed as an outgrowth of early studies that investigated the binding of fibronectin to cell surface receptors, including those that would later become known as the integrin superfamily. Fibronectin was shown to compete for binding to the fibrinogen receptor on platelets, glycoprotein IIb-IIIa, later named integrin  $\alpha_{IIb}\beta_3$ . The identification of the canonical arginine-glycine-aspartic acid (RGD) motif in fibronectin was the first demonstration of an integrin recognition sequence, which would later be found in several other integrin ligands, including vitronectin, osteopontin, and fibrinogen (10). In addition, fibronectin was shown to bind to fibrinogen itself and become crosslinked by factor XIIIa (11). These studies established a firm relationship between fibronectin and coagulation.

The results presented in this issue by Pecheniuk et al. (3) demonstrate a significant association between VTE and fibronectin. Intriguingly, fibronectin levels were not only elevated in VTE cases, but were increased to a slightly greater degree in cases of idiopathic VTE. The association between VTE and fibronectin levels above the 90th percentile was quite robust, with an odds ratio of 9.37 (95% confidence interval 2.73–32.2;  $p < 0.001$ ). These findings raise the exciting possibility that fibronectin may become a useful biomarker for the prediction of VTE and/or its recurrence.

The mechanism(s) underlying this association between fibronectin and VTE remains in the realm of speculation. As with any association study, it is possible that the association is an epiphenomenon that is unrelated to the biological properties of fibronectin. However, the physiologic relationship between fibronectin and coagulation suggest that the biochemical properties of fibronectin itself may provide a causal role for fibronectin in VTE. For example, the two RGD sequences in dimeric plasma fibronectin may play a role in bivalent binding to platelet  $\alpha_{IIb}\beta_3$ -integrin. Plasma fibronectin has been shown to promote thrombus growth (12, 13) and another study showed that decreased plasma

Correspondence to:  
Prof. David H. Farrell, PhD  
Department of Pathology, L113, Oregon Health & Science University  
3181 S.W. Sam Jackson Park Road  
Portland, Oregon, 97239-3098, USA  
Tel.: +1 503 4948602, Fax: +1 503 4942025  
E-mail: farrelld@ohsu.edu

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fibronectin leads to delayed thrombus formation (14). The recently described association between elevated fibronectin levels and arterial thrombosis (9) lends further support for the concept

that fibronectin may be causally linked to thrombosis. Future studies will be necessary to determine if such a mechanistic role exists in VTE.

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