The clinical significance of circulating tissue factor in prostate cancer

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More than 142 years ago, Armand Trousseau observed that cancer is associated with venous thrombosis; however, it is only in the last 30 years that we have had the experimental tools permitting careful analysis of the humoral factors involved in producing the clinical syndrome bearing his name. The two most commonly cited circulating factors responsible for Trousseau’s syndrome are cancer procoagulant and tissue factor, the latter of which is the focus of the report by Langer et al. (1) in this issue of Thrombosis and Haemostasis (see article beginning page 464).

Cancer procoagulant is a cysteine protease with a molecular weight of 68,000 which was first purified in 1985 (2). Unfortunately, since its original description, there have been no reports of its sequence or structure, and in the last decade there have been relatively few publications characterizing this molecule. Additional progress in the molecular characterization of cancer procoagulant is awaited. Definitive clinical association between cancer procoagulant and the pro-thrombotic phenotype in cancer patients is lacking.

There has been appropriately greater interest in tissue factor, in its variety of forms, as the principal soluble mediator of Trousseau’s syndrome. Tissue factor is expressed both directly on tumor cells and on circulating microparticles that are derived from platelets, endothelial cells, or leukocytes (3). It was purified in 1985 (4) and sequenced in 1987 (5). The structure of the extracellular domain was determined in 1994 (6). Tissue factor, a 47-kD transmembrane protein, is not only the primary physiologic initiator of coagulation, it is also implicated in angiogenesis, tumor cell invasion, migration and growth (7). Antibody to human tissue factor inhibits both tumor growth and metastasis formation in xenograft models (8), and there is therefore significant interest in tissue factor, as a drug target in cancer. There have, however, been relatively few publications investigating the prognostic significance of tissue factor in cancer patients. In two small studies, one in colorectal cancer and the other in ovarian cancer, tissue factor expression on the primary tumor was not observed to be associated with survival (9, 10), although in the ovarian cancer study there was a correlation between tissue factor expression on cancer cells and clinically apparent venous thrombosis.

The relationship between tissue factor expression on the primary tumor and circulating tissue factor has not been characterized. Non-tumor cell products, such as platelet and monocye microparticles, are significant contributors to the total circulating tissue factor activity. Circulating tissue factor is not present in healthy persons (11) but may be detectable in persons with disease. A prior clinical study in ovarian cancer demonstrated that those patients with the highest circulating tissue factor concentration had worse survival. This finding was not explained by a higher rate of death from venous thromboembolism (12). Ideally, investigators with an interest in the role of tissue factor in cancer should study both tumor expression as well as circulating levels; however, the absence of robust quantitative assays for tissue factor expression on primary tumor specimens presents a significant challenge.

The report by Langer et al. (1) describes a cohort of 140 males with localized prostate cancer who underwent surgery as the primary treatment modality for their disease. They found that circulating tissue factor, as measured using a commercially available ELISA kit, was increased relative to a population of healthy controls. Although there was a trend toward higher levels of tissue factor in patients who ultimately relapsed, these differences were not statistically significant. Given that there were only 17 biochemical relapses in the entire patient cohort, the study was unfortunately underpowered to detect meaningful differences in clinical outcome in what proved to be a relatively low risk patient population. Future studies examining the prognostic importance of circulating tissue factor in cancer should either focus on those diseases and clinical subgroups where a larger percentage of the population reaches the end point of interest or, alternatively, increase the number of patients enrolled. The fundamental hypothesis that soluble tissue factor conveys prognostic information in cancer is worthy of ongoing clinical investigation in an appropriate clinical setting.

Many fundamental clinical questions remain unanswered. It is still not known as to whether patients with high levels of circu-
lating tissue factor activity are at increased risk for thromboembolic complications. The appropriate clinical populations in which tissue factor expression could provide useful prognostic information has not yet been identified. Additionally, the relative contribution of tissue factor to tumor growth and metastasis in humans has not been elucidated. The report by Langer et al. will provide useful guidance and data to clinical investigators who will need to direct future studies attempting to answer these questions.

References