

Editorial

Ovarian Cancer and Haemostatic Defect

The haemostatic system is anatomically and functionally inseparable from the vasculature. It is therefore somewhat ironic that in the context of cancer, these respective host elements have, until recently, been studied as virtually independent entities. Close association between malignant disorders and various perturbations in blood coagulation has been recognized for over 130 years. Coagulation dysfunctions of different nature and magnitude, ranging from subtle laboratory abnormalities to overt thromboembolism, thrombophlebitis, and disseminated intravascular coagulation, are routinely found in cancer patients. Cancer related haemostatic complications are usually heterogeneous in nature and their pathogenesis is often poorly understood. This is why they are often collectively referred to as “cancer coagulopathy” or “paraneoplastic syndrome”, as their manifestations are found at both the systemic level (deregulation of blood coagulation) and locally at the tumour site (crosslinked extravascular fibrin and fibrinogen). There are ample data suggesting that these respective changes are not merely an epiphenomenon of the disease, but rather represent an integral part of the pathobiology of tumour growth and dissemination. The most common malignancies associated with thrombosis are derived from breast, colon, and lung, reflecting the prevalence of these tumours in the general population. However, when adjusted for disease prevalence, the cancers most significantly associated with thrombotic disorders are derived from pancreas, ovary, and brain

Epithelial ovarian cancer (EOC) represents the most frequent cause of death in the West from a cancer involving the female genital tract. Contributing to the overall poor outcome in EOC patients, are the metastases to the peritoneum and stroma that are common in this cancer pathogenesis of which is poorly understood. Evidence is mounting that an inflammatory process contributes to tumour growth and metastasis to the peritoneum in EOC. Strong interaction between intrinsic and extrinsic

pathways of coagulation helps the tumour in local angiogenesis and metastasis. Factor XII because of two homologous epidermal growth factor (EGF) domains in the amino terminal may act as EGF biological characteristic and act as a growth factor. The human kallikreins (hK) are a subfamily of the Serine protease enzyme family, which consists of proteolytic enzymes important to various physiologic processes¹. The hK gene family, which includes 15 members (hK1-hK15) clustered in a 300-kb region on chromosome 19q13.4, could be altered in cancer. At least 11 kallikrein genes or proteins have been found to be over expressed in EOC. Although many hKs are over expressed in EOC tissues and in ascites, it is unknown whether this phenomenon reflects increased proteolytic activity because of the heterogeneity of hK forms and the presence of active enzymes found in the extracellular matrix (ECM). This apparent paradox in which the clinical outcome differs with different hKs might be due to different biologic roles of hKs in the tumour progression process, either stimulating or inhibiting the development of the tumour and its microenvironment. HK-mediated pericellular proteolysis in the ECM might help regulate tumour cell growth, angiogenesis, invasion, and metastasis, which could contribute to tumour progression. Another important mediator is ‘Tissue factor’ which is over expressed on the cancer cells and helps in angiogenesis and metastasis. Similarly angiogenesis is promoted by thrombin- PAR system. Factor XIII, fibrinogen, and fibrin contribute to the final step in the coagulation cascade. They are involved in some pathologic states, including solid tumour growth and the formation of ascites. Interplay of various inflammatory mediators also facilitates local invasion. In this issue of IJMPO, Sitalaksmi et al have conducted a prospective study in which PT, APTT, TT, platelet count, factor VIII, factor IX and fibrinogen assay and semiquantitative measurement of D-dimer and FDP levels were performed on 23 patients with ovarian adenocarcinoma at the time of diagnosis². They found that the percentage of cases with increased D-dimer and FDP values were higher

in the advanced disease when compared to early stage.

What is the importance of this translational research to patient?

Factors from the extrinsic and intrinsic coagulation cascades play complex and important roles in cancer progression by promoting blood clotting; in the microenvironment of cancer (e.g., ECs, platelets, fibroblasts, leukocytes, and the ECM), altered gene expression affects key intracellular signaling events. Thus, products of the peritoneal environment, which include chemokines, cytokines, and coagulation factors or their receptors, are evolving as potential targets for biologic therapy or *in vivo* diagnostic tools. The number of humanized monoclonal antibodies applicable to cancer treatment is increasing as more targets are being discovered. Other approaches to treatment might include: inhibitory oligonucleotides packaged to avoid degradation and small molecules that block specific pathways. Retrospective studies have

shown that antithrombotic therapy may be associated with a lower incidence of certain types of cancer. Clinical trials need to be expanded to target the production of certain coagulation factors or receptors in the coagulation cascade of advanced ovarian cancer. Such studies may reveal new approaches for chemoprevention or combination therapy that include chemotherapy to control tumour proliferation, angiogenesis, and metastasis.

REFERENCES:

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- 2) Sitalakshmi.S, Rameshkumar K and Damodar P. *Significance of haemostatic markers in ovarian carcinoma. Ind J Med & Paed Oncol* 2008; 29(2): 6-10.

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