Visions & Reflections

Cancer and blood coagulation

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Abstract. In human patients, blood coagulation disorders often associate with cancer, even in its early stages. Recently, in vitro and in vivo experimental models have shown that oncogene expression, or inactivation of tumour suppressor genes, upregulate genes that control blood coagulation. These studies suggest that activation of blood clotting, leading to peritumoral fibrin deposition, is instrumental in cancer development. Fibrin can indeed build up a provisional matrix, supporting the invasive growth of neoplastic tissues and blood vessels. Interference with blood coagulation can thus be considered as part of a multifaceted therapeutic approach to cancer.

Keywords. MET, oncogene, cancer, invasive growth, blood coagulation, haemostasis, PAI-1, COX-2, fibrin.

In human patients, a blood disorder involving hyperactivation of the coagulation system and formation of intravenous fibrin clots (thrombosis) can be the first manifestation of a tumour [1]. The association of venous thrombosis with cancer was named Trousseau’s syndrome after Armand Trousseau, the French clinician who first described it in 1865 [2]. Since then, a long list of medical publications testifies to the occurrence of blood coagulation disorders at every stage of tumour progression. It is almost intuitive that the carefully balanced haemostatic system could collapse in advanced cancer, as a result of systemic spread of neoplastic cells, extensive tissue damage and severe overall decay of the organism. In contrast, it is harder to connect an otherwise unexplained thrombosis with cancer onset. Clinicians can miss this connection, as the early stages of cancer can escape the sensitivity of sophisticated diagnostic tools. Biologists can miss this connection as well because it is difficult to envision a transformed cell affecting the haemostasis system while remaining confined within its tissue of origin, usually an epithelium. However, authoritative clinical studies of patients with Trousseau’s syndrome led to the striking conclusion that ‘either premalignant changes promote thrombosis, or cancer and thrombosis share common risk factors’ [3]. Thus, two questions merit the attention of tumour biologists: First, what is the mechanistic link between cancer and haemostasis activation? Second, is the procoagulant activity of tumours a mere coincidence, or is it instrumental to tumour growth? An answer to the latter question was already proposed in the late 1800s by the pathologist Theodor Billroth, who found cancer cells embedded in circulating microthrombi, and thus suggested that these clots could safely ship cancer cells through the bloodstream, favouring metastasis [4]. If tumours exploit blood coagulation to their advantage, the search for cancer-associated molecules responsible for thrombosis could unveil targets to fight both the side effect (thrombosis, which can be lethal in itself) as well as the primary disease (cancer).

But how do cancer cells trigger blood coagulation? Explanations provided so far include inappropriate expression of factors directly involved in blood coagulation, or molecules inducing platelet aggregation, or cytokines, which modulate endothelial and inflammatory processes.
(for review see [5, 6]). Among the best-documented events is expression of tissue factor (TF) on the surface of transformed epithelial cells ([6] and references therein). TF is usually expressed by endothelial cells in response to severe injury (e.g. endotoxin exposure etc.), and initiates blood clotting by triggering activation of the blood coagulation factor cascade, leading to thrombin formation. Thrombin catalyses conversion of circulating fibrinogen into insoluble fibrin. Fibrin is further modified by other enzymes to form a gel-like provisional matrix that seals vessel and tissue ruptures, providing the first support for tissue regeneration (reviewed in [7]).

TF is membrane-bound, and thus its increased expression by cancer cells may explain the peritumoral activation of blood coagulation favoured by newly formed vessels, which are often leaky and permeable to coagulation factors and fibrinogen [8]. However, in cancer patients with Trousseau’s syndrome, thrombosis usually occurs in regions (such as deep veins of the legs) that are distant from the epithelial organs that usually host the primary tumour. This suggests that the tumour also exerts a systemic procoagulant effect. Interestingly, TF can be released into the blood circulation, mainly in association with membrane microparticles shed from the surface of neoplastic cells, or cells of the tumour microenvironment [9]. Recently it was shown in cell lines that TF expression is increased by genetic lesions responsible for human cancers. This is the case with Ras activation or p53 inactivation, in colorectal cancer [10], and with Pten loss in glioblastomas [11].

Besides TF, oncogenes regulate the expression of other molecules that can be responsible for Trousseau’s syndrome, as shown by a new mouse model which incorporates stepwise cancer progression in association with a progressive haemostatic disturbance [12]. This mouse model was generated through somatic transduction of the MET oncogene, which encodes the tyrosine kinase receptor for hepatocyte growth factor. MET is an unconventional oncogene, able not only to transform cells, but also to induce ‘invasive growth’, a process supporting cell motility and survival through foreign tissues, and metastasis to distant sites [13]. MET was transduced in the liver of adult mice by lentiviral vectors, which can integrate into non-dividing cells and drive expression through a tissue-specific promoter (in this case, albumin). With respect to conventional germ-line transgenesis, lentiviral transduction induced transformation of a small fraction of hepatocytes which remained interspersed among normal cells. MET-transduced mice developed a stepwise tumorigenic process, arising from single transduced hepatocytes. This process was associated with haemostatic disturbances, which started with venous thrombosis, noticeably, before the appearance of the first preneoplastic lesions. This observation suggested that the genetic program activated by the MET oncogene in hepatocytes was responsible for both cell transformation and the concomitant procoagulant activity. The transcriptome of cells expressing the activated MET was then examined, and it was discovered that, among the 12,000 genes analysed by Affymetrix microarray, the two most upregulated genes were plasminogen activator inhibitor-type 1 (PAI-1) and cyclooxygenase 2 (COX-2). Nearly the entire subset of genes involved in haemostasis regulation was analysed in the array (71 genes), and found to be significantly modulated as a whole. However, each single gene (including tissue factor) was only weakly affected.

PAI-1 and COX-2, which are expressed in vivo by MET-transduced mice, are both suitable candidates to support the systemic haemostasis disturbance associated with cancer. PAI-1 is secreted into the blood where it prevents generation of plasmin, the enzyme that dissolves fibrin clots [14]. Therefore, the net effect of an increase in PAI-1 is to promote the persistence and expansion of thrombi. This is confirmed by studies that correlate high levels of plasminogen activator-type 1 (PAI-1) with an increased risk of venous and artery thrombosis (reviewed in [15]). COX-2 encodes an inducible form of prostaglandin synthase that catalyses an intermediate step in the synthesis of prostacyclins and thromboxane. These molecules are also systemically released and modulate functions of platelets (for a review see [16]). Interestingly, the prothrombotic state of cancer patients also depends on increased platelet activation, which is a consequence of several factors. These include circulating molecules such as glycosylated proteins and lipids, and cytokines, released by cancer cells or by their microenvironment [5]. The prominence of PAI-1 and COX-2 in the MET transcriptome led to speculation that the same proteins could be effectors not only for haemostasis disturbances but also for tumour progression itself. In fact, many clues implicate COX-2 and PAI-1 in cancer onset and progression. The case of COX-2 is typical, as its inhibition by specific drugs (e.g. Rofecoxib) can prevent colorectal cancer, both in mouse models and in human patients (for a review see [17]). Circumstantial evidence also implicates PAI-1 in tumorigenesis, as documented by the association of high levels of PAI-1 with cancer metastasis and poor prognosis [18]. In MET-transduced mice, it was shown that inhibition of COX-2 or PAI-1 with specific drugs reduced the haemostatic disturbance, and, in the case of COX-2 inhibition, also the cancer phenotype. The effect of PAI-1 inhibition on cancer growth is still inconclusive, due to the limited availability of inhibitors suitable for long-term treatment.

Taken together, the above studies support the conclusion that, on the one hand, the genetic lesions responsible for cancer onset and progression control genes involved in blood coagulation; on the other hand, blood coagulation promotes cancer onset and progression. But what are the mechanisms involved? It is likely that the fibrin matrix that is quickly deposited around the growing cells provides two advantages (Fig. 1). First, it offers an adhesive