Platelets, Coagulation and Cancer: Multifaceted Interactions

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Abstract: Approach: Literature review of the multifaceted interactions between platelets, coagulation and cancer. Results: Over the years, the links existing between cancer development, progression and occurrence of metastasis on one side and coagulation on the other have become obvious. Tumors seem to activate platelets whereas, platelets, on the other hand, through their capacity to activate and release soluble factors and microparticles, interact with tumor cells and influence immune regulation. They appear to be key regulators of many cancer events. Furthermore, coagulation with its different facets also interplays and significantly crosstalks with malignancy. The objectives of this article are to review the mechanisms through which cancer interacts with platelets and the coagulation, triggering thrombosis and the role played by platelets and coagulation factors in the regulation of cancer and to underline the perspectives that are now open in the development of novel diagnostic tools and new cancer treatment strategies. Conclusion/Recommendations: Challenging issues and unresolved questions still need to be addressed to understand the complexity existing between coagulation factors and platelet components and the different stages of cancer progression. Recent discoveries are leading clinicians to consider new therapeutic applications of anticoagulant therapies or new drugs targeting specific platelet functions in cancer patients’ management. Furthermore, markers of coagulation and platelet activity may prove to serve as biomarkers for dormant tumors.

Key words: Cancer, thromboses, coagulation, platelets and metastasis

INTRODUCTION

The objectives of this article are to review the mechanisms through which cancer interacts with platelets and the coagulation, triggering thrombosis and the role played by platelet and coagulation factors in the regulation of cancer and to underline the new perspectives that are now open in the development of novel diagnostic tools and new cancer treatment strategies.

I-Clinical facts: venous thromboembolism manifestations in cancer: The most clearly established relationship existing between coagulation and cancer is evidenced by the frequent complication of Venous Thromboembolism (VTE) in cancer patients. Indeed, VTE may represent its first clinical manifestation, often antedating any clinically objective sign of the malignancy itself (Baron et al., 1998; Sorensen et al., 1998). Migratory superficial thrombophlebitis was first described by Trousseau (1865) as forewarning of an occult visceral malignancy and his sign, known as “Trousseau’s syndrome”, is almost synonymous to occult malignancy (Varki, 2007). Ironically, he reported a similar finding in himself, when he developed a gastric cancer two years later. Greenwell (1991) and Sack et al. (1977) extended the term Troussseau’s syndrome to include chronic disseminated intravascular coagulopathy associated with microangiopathy, verrucose endocarditis and arterial emboli in patients with cancer, often occurring in the context of making-positive carcinomas. In recent times, the term has been ascribed to any kind of coagulopathy occurring in the setting of any type of malignancy (Varki, 2007).

There is a statistically significant and clinically important association between idiopathic venous thrombosis and the subsequent development of clinically overt cancer, especially among patients in whom VTE recurs during follow-up. About 10% of patients presenting with unprovoked - idiopathic thrombosis are diagnosed with cancer within a few years (Prandoni et al., 1992). Even more, during the first year, the incidence of cancer in these patients is as high as 2.1-4.6%, (Baron et al., 1998; Sorensen et al., 1998; Prandoni et al., 1992) with an incidence at its peak within the first 6 months (Nordstrom et al., 1994). Approximately 40% of those cases are already presenting metastasis at the time of diagnosis (Baron et al., 1998; Sorensen et al., 1998; Nordstrom et al., 1994). Cancer diagnosed at the same time as or within
one year after an episode of VTE is associated with an advanced stage and a poor prognosis (Sorensen et al., 2000). Epidemiological estimates show that the annual incidence of VTE in cancer patients may be as much as 1:200/year compared to ≈70-113 cases/100,000/year in the general population (Silverstein et al., 1998). A large Dutch population-based case control study of 3220 patients found that the Overall Risk (OR) of VTE was significantly increased in patients with malignancy (adjusted OR 6.7) and even more so in patients with metastasis (adjusted OR 19.8) (Blom et al., 2005). The highest risk was observed in patients with lung cancer (Odds Ratio (OR): 22.2), hematological malignancies (OR: 28.0) and gastrointestinal cancer (OR: 20.3) (Blom et al., 2005). There was a moderately increased risk in patient’s ovarian cancer (OR: 3.1; 95%CI: 0.6-15.3) and prostate cancer (OR: 2.2; 95%CI: 0.9-5.4). The risk is enhanced by anticancer therapy, such as surgery and chemotherapy.

Thrombocytosis could reflect inflammation but is considered by some as a paraneoplastic phenomenon (Estrov et al., 1995). Its presence warrants thorough investigation for the presence of severe underlying disease, most complicated pyogenic infections, inflammatory rheumatic diseases and malignancy. Moreover, thrombocytosis is a marker for major complications and is an independent predictor of mortality in hospitalized patients for non-malignant as well as malignant conditions (Tchebener et al., 2011).

The evidence of a relationship between cancer and VTE was, understandably, used to attempt to develop diagnostics tools. Many screening strategies to identify occult or overt malignancies including testing for tumor markers and advanced imaging have been applied to patients with unprovoked VTE (Monreal et al., 2004). However, for the time being, these offer questionable predictive value (Nordstrom et al., 1994) and may not be cost-effective.

In spite of such failures, there is an urgent need to identify reliable markers of cancers, presumably based on the identification of early hemostatic markers of activation of the coagulation cascade conferring a specific pattern for malignancy. The findings in this field may pave the way for the development of commercially available diagnostic kits capable to identify cancers at an early phase.

Interactions between hemostasis factors and cancer cells: The interactions between components of the hemostatic system and cancer cells are multifaceted and complex. The physiological mechanisms of thrombus promotion in malignancy include some general responses of the host to the tumor (acute phase, inflammation, angiogenesis) and specific interactions of tumor cells expressing Tissue Factor (TF), with the clotting/fibrinolysis systems and with blood (leukocytes, platelets) or vascular cells. It is still difficult to rank the relative weight of these multiple interactions only on the basis of the well-recognized clinical evidence of enhanced thrombotic episodes in tumor patients (Donati and Falanga, 2001).

There is currently renewed increasing scientific evidence that the coagulation system and the activation of platelets play an instrumental role in the progression and regulation of malignant growth and facilitation of metastasis. Important molecular crosstalk occurs between platelets, leukocytes, endothelial cells and tumor cells controls. Understanding such interactions clearly opens the potential for the development of novel cancer treatments based on the inhibition of cancer promoters (Labelle et al., 2001). As such, the underlying mechanism by which coagulation factors promote tumor cell growth, invasion, metastasis and angiogenesis has recently become a hot topic in the field of cancer research (Ma et al., 2011).

The confirmation that small daily doses of aspirin reduce metastasis and help treatment of some cancers is a most recent indicator of the role that platelets and coagulation factors can play in cancer (Rothwell et al., 2012). It is increasingly believed that blocking the chain of events of the coagulation cascade upstream of its activation process have a strong potential for limiting the progression of tumors (Zacharski, 2011) and may translate into improved therapy and patient survival. Although, the beneficial effects of low molecular weight heparins (LMWH) in cancer-related VTE prevention and treatment is well established, their effect on survival in cancer patients, remains controversial (Meyer et al., 2011; Doormaal et al., 2011), suggesting that every anticoagulation approach to restrain activation of coagulation and platelets should be looked for.

III-Platelet role in cancer:

III-a Platelet count: By their capacity, upon activation, to adhere to exposed sub-endothelium in a flow-dependent manner, to aggregate and to facilitate thrombin generation, platelets have long been recognized as the primary hemostatic tool, with deficiencies resulting in bleeding and up-regulation favoring thrombosis. Yet, increasing evidence indicates that platelets fulfill a much wider role in balancing health and disease. Platelets are a source of active metabolites and proteins, promote heterotypic cell interactions and provide a biologically active surface, together with a capacity to release cell-derived micro particles that promote coagulation and protease activation. Platelets also exert an active role in sepsis, inflammation, tissue regeneration and control of
infection (including promoting the innate immune response) (Nurden, 2011).

Furthermore, observations have suggested that platelets not only augment the growth of primary tumors via angiogenesis but endow tumor cells physical and mechanical support to evade the immune system and, through induction of Epithelial-Mesenchymal-Like Transition (EMT) of tumor cells, facilitating extravasation to secondary organs, the basis of metastatic disease. Many laboratory and animal studies have identified specific targets for antiplatelet therapy that may be advantageous as adjuncts to existing cancer treatments (Jain et al., 2010).

The involvement of platelets and coagulation factors in hematogenous tumor metastasis has long been recognized. As a more direct evidence of platelet involvement in the development of malignant tumors, a relationship between elevated platelet count and malignant tumors was reported as early as 1872 by (Tranum and Haut, 1974). Ayhan et al. (2006), demonstrated that higher preoperative platelet counts, even if lying within the normal range (150,000-400,000 microl⁻¹), may reflect poor prognostic factors such as cervical involvement and high grade among patients with endometrial carcinoma. These authors went even further, questioning the necessity of radical hysterectomy in patients with higher counts (Ayhan et al., 2006). Similar observations were made in other gynecological malignancies (Hernandez et al., 1992; Zeimet et al., 1994) and in gastrointestinal tumors (Ikeda et al., 2002; Shimada et al., 2004).

III-b Platelet activation markers: Platelets can be activated by human and experimental tumor cells, a process described in 1968 as “Tumor Cell-Induced Platelet Aggregation» (TCIPA). It became apparent that this aggregation correlates with the metastatic potential of cancer cells in vivo (Karpatkin et al., 1988; Joseph, 1995; Al-Mondhry, 1983). Compared with those in complete remission, patients with active malignant disease have elevated levels of beta-thromboglobulin and platelet factor 4 (Al-Mondhry, 1983) Circulating activated platelets have also been evidenced in cancer patients by detection of the platelet membrane antigens CD62 (p-selecting) and CD63 (Wehmeier et al., 1991). Tumor cells or membrane vesicles that have been shed spontaneously from tumor cells can directly aggregate platelets in vitro (Jamieson and Scipio, 1982) and can induce platelet aggregation through the release of proaggregatory mediators including adenosine diphosphate, thrombin and a cathepsin-like cysteine proteinase (Grignani and Jamieson, 1988).

Metastasis comprises multiple, consecutive steps. Several cell adhesion molecules are involved in the various stages of cancer metastasis (Huang et al., 1997). CD 62P-derived from platelets can bind to a variety of human cancers and human cancer-derived cell lines, such as colon cancer, lung cancer including small-cell lung cancer, breast cancer, malignant melanoma, gastric cancer, neuroblastoma and adenoid cystic carcinoma of the salivary gland. An increasing body of in vivo experimental evidence indicates that P-selection plays important roles in the growth and metastasis of cancers (Chen and Geng, 2006). The ligand molecules on cancer cells for P-selection, however, remain unidentified. Several lines of evidence suggest that the binding of human cancer cells, derived from various organs and/or tissues, to P-selection may be mediated by very different glycoprotein ligands (Palumbo et al., 2005). Platelet depletion, or even an inhibition of TCIPA, reliably diminishes metastasis, seemingly without affecting the growth of established tumors, in different in vivo models of experimental pulmonary metastasis as well as in a murine model of spontaneous metastasis (Palumbo et al., 2005). Platelet/tumor cell/endothelial interactions have also been reported helping in establishing metastatic lesions (Rickles and Falanga, 2001).

III-c Platelet growth factors on immune cell function, tumor progression and tethering: Platelets and their byproducts, released upon platelet activation through degranulation, appear to limit the ability of Natural Killer (NK) cells to lyse tumor cells in vitro and in vivo (Palumbo et al., 2005). Furthermore, platelet-derived transforming growth factor-β (TGF-β) down-regulates the activating immunoreceptor NKG2D on NK cells (Kopp et al., 2009) and has been shown to favor EMT in various cancer cell lines, thereby potentially facilitating metastasis.

A number of growth factors supporting tumor growth and possibly angiogenesis, such as Platelet-Derived Growth Factor (PDGF), Vascular Endothelial Growth Factor (VEGF) and angiopoietin-1, are released by platelets, further interplaying and enhancing tumor progression (Kepner and Lipton, 1981; Mohle et al., 1997; Nierodzik and Karpatkin, 2006) and regulating tumor vascular biology, preventing intralesional hemorrhages (Noe et al., 2008; 2009). Furthermore, some platelet byproducts/tumor cell receptor interactions are associated with more tumor biological aggressiveness. PDGFR-alpha, a receptor for PDGF, expressed in invasive breast carcinomas is a good example of this phenomenon (Oft et al., 1998).

Dendritic Cells (DCs) are key players in the initiation of adaptive immune responses and are currently exploited in immunotherapy for treatment of cancer (Cruz et al., 2012). Platelets seem to secrete a soluble DC-activating factor and are active elements of the immune system that might play a role in balancing
the ability of DCs to polarize T cell responses (Cognasse et al., 2008).

Glycoprotein Ib-IX-V-complex (GPIb-IX-V) along with GPVI on the surface of platelets are primarily responsible for initial platelet adhesion and activation by binding to their major ligand, von Willebrand Factor (VWF) and collagen, respectively (Smyth et al., 2009). Glycoprotein GPIba and the A1 domain of VWF immobilized on collagen or on the surface of activated platelets are crucial for the initial tethering and rolling of platelets at the site of vascular injury. Engagement of GPIbα is required for downstream activation of the integrin receptor and is thus an important initial step in the cascade that can finally lead to firm thrombus formation (Erpenbeck and Schon, 2010). Exceptionally, some tumor cell lines, such as MCF7 cells, derived from a human breast cancer, may express GPIbα themselves (Oleksowicz et al., 1995). Inhibition of GPIbα could enhance metastasis, an observation in apparent contrast to most publications dealing with platelets and metastasis. It is conceivable that blockade of platelet GPIbα could result in an increased availability of P-selectin for tumor cell-endothelial interactions, thus supporting the attachment of tumor cells to the vascular (Erpenbeck and Schon, 2010).

III-d Platelet integrins: Heterodimeric receptors of the β1 and β3 integrin families mediate platelet adhesion and aggregation in hemostasis and thrombosis. In resting platelets, integrins are expressed in a low-affinity state but they shift to a high-affinity state in response to cell-matrix interactions, thus supporting the attachment of tumor cell-endothelial interactions, thus supporting the attachment of tumor cells to the endothelium (Erpenbeck and Schon, 2010).

III-e Adenosine diphosphate: Adenosine Diphosphate (ADP) is a platelet agonist that causes platelet shape change and aggregation as well as generation of thromboxane A2, another platelet agonist, through its effects on a family of purinergic receptors: P2Y1, P2Y12 and P2X1 (Jianguo et al., 2002). Several tumor cell lines possess the ability to generate ADP themselves inducing a TCIPA (Boukerche et al., 1994).

IV Activation of Coagulation and cancer: The prothrombotic state of cancer is driven by specific oncogenic events. Activation of the coagulation cascade appears integrally linked to the processes of tumor growth, metastasis and angiogenesis (Tarek and Khorana, 2009).

IV-a Tissue factor: Tissue Factor (TF) is best known as the primary cellular initiator of blood coagulation. After vessel injury, the TF: FVIIa complex activates the coagulation protease cascade, which leads to fibrin deposition and activation of platelets (Mackman, 2004).

In cancer-related thrombosis, the role of TF has gathered the most attention (Tarek and Khorana, 2009). This trans-membrane glycoprotein is expressed in a variety of human cancers, induced by activation of oncogenes or inactivation of tumor suppressor genes (Yu et al., 2005). Over-expression of TF in tumor cells or elevated TF levels in association with micro-particles in the systemic circulation may contribute to systemic hypercoagulability (Dvorak et al., 1981; Khorana et al., 2007; 2008; Tesselaar et al., 2007; Uno et al., 2007). In experimental models, cell lines often release TF-positive Microparticles (MP) triggering thrombosis (Wang et al., 2012). Translational research in humans, conducted by Doormaal et al. (2012) on 43 cancer patients without VTE at study entry and 22 healthy volunteers, followed the markers of in vivo and MP-dependent coagulation prospectively for six months and for the development of VTE. They concluded that although, median TF-mediated Xa-generation and median VIIa-dependent fibrin generation test were higher in the VTE group compared with the non-VTE group. In this exploratory study the overall hypercoagulable state in cancer patients was not associated directly with the MP phospholipid-dependent procoagulant activity. However, in the patients who developed VTE within six months when compared to those who did not, an increased MP procoagulant activity was present already at baseline, suggesting it could be used to predict VTE (Doormaal et al., 2012).

Furthermore, TF may exert non-hemostatic roles in the generation of coagulation proteases and subsequent
activation of Protease Activated Receptors (PARs) on vascular cells. This TF-dependent signaling contributes to a variety of biological processes, including inflammation, angiogenesis, metastasis and cell migration (Tarek and Khorana, 2009). Interestingly, inhibition of PAR1 or the presence of specific polymorphism such as 506I/D are associated with a better outcome in patients with breast cancer (Eroglu et al., 2012).

Finally, TF pathway regulates mechanisms which involve plasmin and matrix metalloproteinas, both of which seem to be critical in oral carcinogenesis (Yapijakis et al., 2012).

IV-b Factor Xa and TF-FVIIa-FXa complex: Coagulation factor zymogens activated upstream of thrombin, including Factor Xa (FXa), may also exert signalling via PARs and thus induce cellular effects independent of thrombin generation (Krupiczkojc et al., 2008). The combination of FVIIa and FXa, but not FVIIa alone, strongly induced migration of tumor cells by a pathway that probably involves PAR2, but not PAR1, activation. TF-FVIIa-mediated signaling in human breast cancer cells occurs most efficiently by formation of the TF-FVIIa-FXa complex (Jiang et al., 2004). One of the physiological consequences of this signaling pathway is enhanced cancer cell migration mediated by mTOR pathway activation (Jiang et al., 2008). Furthermore, the TF-FVIIa-FXa complex prevents apoptosis in breast cancer cells by a thrombin-independent pathway (Jiang et al., 2006). Quite unexpectedly, FXa alone markedly diminished the migration of different cancer cell lines of various origins (breast, lung and colon cancer cells) and FXa mediated inhibition of cancer cell migration was specific, as it was inhibited by TAP (a specific FXa inhibitor) but not by Hirudin (a specific thrombin inhibitor) (Borensztajn et al., 2009). The role of specific Xa inhibitors in the prevention of cancer related thrombosis, remains however controversial although initial results support further study of apixaban, a specific oral FXa inhibitor, in phase III trials to prevent VTE in cancer patients receiving chemotherapy (Levine et al., 2012).

IV-c Thrombin: Thrombin, the key terminal enzyme of coagulation, also promotes angiogenesis and stimulates tumor-platelet adhesion, adhesion to endothelium, tumor implantation, tumor cell growth and metastasis. The thrombin receptor is expressed on many tumor cell lines and on breast tumor biopsy specimens (Ruf et al., 2010). In addition to the mitogenic effects on fibroblast, smooth muscle cells and endothelial cells, thrombin also exerts direct effects on cancer cells (Green and Karpatkin, 2010). It is also worth noting that thrombin is the key legend of PAR firing inflammation and cell migration (Eroglu et al., 2012). Furthermore, thrombin-induced Cathepsin D, in term, contributes to the malignant phenotype by inducing tumor cell migration, nodule growth, metastasis and angiogenesis (Hu et al., 2008). The activation of fibrinogen by thrombin and its cleavage to fibrin monomers result in the rapid formation of fibrin matrix. Furthermore, it is well documented that fibrinogen and cross-linked fibrin reside inside the tumor stroma (Yapijakis et al., 2012). Paradoxically, thrombin-mediated thrombomodulin may act through attenuation of the tumor-promoting properties of thrombin, but it also may function as a cell-to-cell adhesion molecule, independently of its anticoagulant action (Yapijakis et al., 2012). Not surprisingly, in xenograft tumor models, direct thrombin inhibitors-like hirudin-have shown a significant carcinostatic effect (Nowak et al., 2007). By virtue of their anti-thrombin properties and beyond, heparin or LMWH remain the cornerstone agents for the treatment and prevention of cancer-related thrombosis (Kahn et al., 2012).

Many studies alluded to the beneficial effects of LMWH on survival in cancer patients and a systematic review concluded that LMWH improves overall survival in cancer patients, even in those with advanced disease (Lazo-Langner et al., 2007). A recent study, however, did not show a survival benefit of nadroparin in patients with advanced prostate, lung, or pancreatic cancer (Doormaal et al., 2011).

IV-d Fibrinogen and Fibrin: Fibrinogen is the final and most important component of the coagulation cascade, as well as a major determinant of blood viscosity and blood flow and an important acute phase reactant. Epidemiological studies increasingly suggests that elevated plasma fibrinogen levels are associated with an increased risk of cardiovascular disorders, including Ischaemic Heart Disease (IHD), stroke and other thromboembolisms (Meade et al., 1986; Wilhelmsen et al., 1984). Hyperfibrinogenemia may be a predictor for poor chemo-response and has a potential role as independent prognostic factors in ovarian, rectal and renal cell carcinoma patients. Moreover, it can be used as a biomarker to predict therapeutic response (Qiu et al., 2012; Xiao et al., 2011; Lu et al., 2011) or a risk predictor for smoking-related cancers (Silva et al., 2010).

There is also evidence that fibrin deposition induced by tumour cell-associated tissue factor and probably platelets, protect tumor cells from a recognition by NK cells contributing to enhancing metastasis.

IV-e Natural anticoagulants: Activated Protein C (APC) and Protein C Inhibitor (PCI) are the major components of the anticoagulant protein C pathway and are the two proteins raising most interest for their
potential role in regulating cancer. APC and PCI play many roles not only in the regulation of hemostasis but also in cell inflammation, proliferation, apoptosis, tumor cell migration, invasion and metastasis. APC promotes tumor cell invasion by EPCR-mediated and PAR-1-mediated protease activity whereas PCI inhibits tumor cell invasion in vitro by its protease inhibitory activity and suppresses tumor cell growth, metastasis and angiogenesis independent of its protease inhibitor activity (Suzuki and Hayashi, 2007).

Abnormalities in Protein S seem to be rather functional with reported dysregulation of S-nitrosylation, a process that related to cancer progression and dissemination (Wang, 2012). Quantitation of protein S, seems however, non-specific and redundant (Battistelli et al., 2005).

The role of Antithrombin (AT) is controversial as early studies have reported an elevated level of AT in patients with bladder and renal malignancy (Zietek et al., 1997a; 1997b). Others have reported that their cancer patients with localized prostate cancer had significantly lower levels of AT III activity and higher plasma D-dimer levels (Fidan et al., 2012). Furthermore, others have advocated the use of low AT and raised D-Dimer as prognostic markers for gynecological malignancy (Koh et al., 2001; 2006). As one would have expected, elevated Thrombin Antithrombin Complex (TAT) observed in malignancy with its severity and was often associated with abnormalities in the Thrombin Activatable Fibrinolysis Inhibitor (TAFI) (Hong et al., 2010; Kaftan et al., 2011). Further studies are deemed necessary to clarify the possible relation between AT level and cancer.

Tissue factor pathway inhibitor, the physiological inhibitor of TF, may also play a role in cancer. A pro-apoptotic effect of TFPI has been found in breast cancer cells in vitro, while corresponding downregulation of endogenous TFPI resulted in reduced apoptotic activity. Newer data suggest an anti-metastatic effect of TFPI and suggest it can be a novel therapeutic approach in cancer.

IV-f Fibrinolysis: Early studies have demonstrated without doubt, the role of activated coagulation and impaired fibrinolysis in patients with cancer (Laug et al., 1975; Rocha et al., 1989; Zacharski et al., 1992). There is now, however, good evidence that parts of the fibrinolytic system, such as urokinase-type plasminogen activator and its receptor ("uPAR"), can be used as strong predictors of outcome and targets in several types of cancer, specifically breast cancer (Korte, 2000; Al-Hassan et al., 2012). Disseminated intravascular coagulation with excessive fibrinolysis has been described in the context of advanced prostatic carcinomas (Hyman et al., 2011). Adjuvant chemotherapy in cases of breast or prostatic carcinomas further interferes with the fibrinolytic system favoring thrombosis (Oberhoff et al., 2000; Varenhorst and Risberg, 1981).

CONCLUSION

Applications for translational therapy of cancer: Challenging issues and unresolved questions still need to be addressed to understand the complexity existing between coagulation factors and platelet components and the different stages of cancer progression. However, important findings have been obtained in the last few years in the understanding of cancer-associated thrombosis that can serve to understand the link between coagulation and cancer. Such knowledge is opening perspectives not only to better identify and treat patients at risk of VTE, but also possible to design new, possibly individualized therapy, to stop cancer progression and metastasis. Much bench work and clinical developments are still needed in the comprehension of the intimate relationships existing between activation of the coagulation system and platelets and cancer progression and metastasis. The role that coagulation and platelets play at the distinct stages involved in cancer progression, in particular in tumour cell protection and hematogenous metastasis, needs major clarifications. Recent discoveries are leading clinicians to consider new therapeutic applications of anticoagulant therapies or new drugs targeting specific platelet functions in cancer patients’ management. Possibility to use anticoagulants, either already available or to be developed (LMWH, aspirin, warfarin, cyclooxygenase inhibitors, P-selectin inhibitor, integrin αIIbβ3 antagonists and others) in the treatment of tumour progression and inhibition of metastasis represent a promising avenue of clinical research development, already found effective in animal models (Gay and Felding-Habermann, 2011).

Coagulation (TF, FXa, FVIIa, AT, fibrinogen, thrombin, PC, PCa, TFPI) and platelet (P-selectin, PDGF, TGF-β, VEGF, PF4) markers are clearly associated, as causative agents or as markers, to cancer development and evolution. Following their evolving levels in patients can therefore also be considered as a means to optimize treatment options and possibly they can also serve as early biomarkers for dormant tumors.

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