Chapter 1

Hemostatic System in Malignancy: Providing the "Soil" in Metastatic Niche Formation

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Abstract

Malignancy arises and progresses in tight association with changes in the tumor microenvironment and deregulation of hemostatic system. Cancer induces hemostatic imbalance through production and secretion of procoagulant substances, suppression of anticoagulant mechanisms, endothelial activation, and angiogenic switch. Cancer cells are equipped with certain coagulation signaling receptors such as tissue factor (TF) and urokinase plasminogen activator receptor (uPAR). Tissue factor: as major initiator of coagulation, TF is considered the main cause for hypercoagulability in cancer. Constitutive TF expression by cancer cells is a hallmark of malignancy rendering tumors proangiogenic and prometastatic. TF fosters metastasis through coagulation-dependent pathways leading to fibrin deposition in the evolving premetastatic niche. TF has been identified as an independent predictor for metastatic development and adverse prognosis. uPAR: Tissue overexpression of uPAR is demonstrated in almost all human cancers and is associated with advanced disease. Increased uPAR expression is driven by molecular events involving K-ras and SRC oncogenes. Transactivation of these receptors, mediated by binding to hemostatic proteins, activates intracellular signaling pathways, modulates gene expression and facilitates processes of tumor initiation, epithelial-to-mesenchymal transition, anoikis, and metastasis. By manipulating hemostatic processes, tumor induces tolerant host environment necessary for evasion of defense attacks, survival, and progression.

Keywords: hemostasis, cancer, metastasis, tissue factor, urokinase plasminogen activator

1. Introduction

Malignancy is associated with derangement of the dynamic homeostasis of hemostatic system. Associated perturbations are characterized by various clinical manifestations with some of them infrequently being indicative of an occult cancer. The interaction between the presence of hemostatic imbalance and cancer has long been recognized. Starting first with the clinical observations by the French surgeon Armand Trousseau of increased thrombotic tendency in patients with advanced gastric cancer knowledge of the interrelationship between malignancy and hemostasis has since evolved conceptually into understanding its intrinsic biology. Relationship between hemostasis and cancer is bidirectional. On the one side, it is viewed as a process where the innate defense system of hemostasis modulates cancerous development. On the other side, tumor itself manipulates hemostatic system via paracrine regulatory mechanisms and utilizes hemostatic functions to induce host tolerance for its development and evasion of immune surveillance. Knowledge of the molecular and cellular processes involved in thrombosis in cancer and their differentiation from the physiological hemostasis is essential for understanding the factors driving the increased tumor-associated prothrombotic tendency. It also allows for identifying the certain hemostatic components as determinants of the neoplastic process and their incorporation into development of antitumor strategies.

2. Tumor prothrombotic mechanisms

Factors that enhance thrombogenicity of neoplasms are complex and reflect the interaction of a variety of mechanisms that can be summarized on the basis of the classical triad suggested by Virchow: hypercoagulability, vascular endothelial injury, and stasis.

2.1. Changes in hemostasis factors

Tumor cells have the properties to qualitatively and quantitatively modify plasma and cellular components of hemostasis either directly by synthesis and secretion of procoagulant substances or indirectly by intracellular cytokine-mediated mechanisms (**Table 1**).

2.1.1. Synthesis and secretion of procoagulant substances

Production of procoagulant components by the tumor cells enhances fibrin deposition at the sites of extravasation and extracellularly within the tumor microenvironment.

Tissue factor (TF)—cellular procoagulant and the main initiator of coagulation. Under physiological conditions, procoagulant active form of TF cannot be detected in circulation and on the surface of intact endothelium [1]. TF overexpression is considered a hallmark of the malignant phenotype, identified for the first time in the description of thromboplastin properties of leukemic cells [2]. Subsequently, high activity of TF was observed in the supernatant samples from patients with promyelocytic leukemia [3]. Constitutive expression of TF

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on neoplastically transformed cells has been confirmed by other authors. TF was found overexpressed on tumor cell surface of a number of cancers. TF overexpression is found on the surface of microparticles or is secreted into the tumor microenvironment [3, 4]. Increased TF-dependent procoagulant activity is observed in circulating tumor cells with stem cell phenotype [5]. By inducing proinflammatory response through synthesis and secretion of tumor cytokines: IL-1β, TNF-α, vascular endothelial growth factor (VEGF), malignant cells upregulate TF expression on the surface of monocytes/macrophages, endothelium [6–9], and the degree of tissue expression of TF in the primary tumor correlates with levels of the circulating antigen [10]. Overexpression of TF has a specific biological role in mediating tumor growth and metastasis [11].

Cysteine proteinase (CP)—endopeptidase with a molecular weight of 68 KDa, whose only known substrate is f.X. CP can directly activate f.X to f.Xa without involving f.VII, and unlike other activators of f.X, CP proteolytically cleaves its molecule at several sites [12]. It has been identified in extracts from embryonic tissues (amnion and chorion), solid tumors, and leukemic blasts [13–15]. CP has not been detected in extracts from normal tissues as well as in patients in complete remission. Its expression in acute promyelocytic leukemia is inhibited by treatment with all-trans-retinoic acid, which confirms the hypothesis that undifferentiated cells express CP and upon recovery of differentiation its expression is suppressed [16].

F.VII—a cofactor of tissue factor required for its procoagulant activity. Endogenously synthesized f.VII from non-hepatic tumor cells capable of activating the coagulation via f.Xa mediates proinvasive signaling pathways [17]. Proteolytically active f.VII in combination with TF induces anti-apoptotic effects and inhibits anoikis [18].

Prothrombin/thrombin—a key proteolytic enzyme of coagulation. It is produced by different tumor types and exerts pleiotropic biological effects in the processes of angiogenesis and tumor proliferation [19]. In patients with low-grade carcinoma, f.II induces intravascular coagulation, increases tumor platelet adhesion in vitro, and the formation of metastases in vivo [20].

F.VIII: vWF—various cancers are associated with elevated levels of von Willebrand factor (vWF) and f.VIII as a consequence of tumor-induced proinflammatory cytokine response (TNF-α, IL-6) [21–25].

F.V—cofactor of f.X. By expressing f.V receptor, activity tumor cells are functionally involved in catalyzing the prothrombinase complex [26]. Increased coagulation activity in patients with breast cancer is correlated with the presence of single nucleotide polymorphisms in the gene of f.V and increased thrombotic risk [27].

F.XIII—fibrin stabilizing factor. Tumor cells from breast cancer have f.XIII-like activity. By catalyzing fibrin cross-linking and deposition, they potentiate tumor growth and metastasis [28].

Fibrinogen/fibrin—electron microscopy analysis demonstrated that fibrin is an integral component of the examined tumors [29]. Fibrin deposition potentiates formation of metastatic emboli that trap circulating tumor cells in the vascular bed and promote adhesion to the endothelium [30]. Plasma fibrinogen levels are significantly elevated in patients with multiple

myeloma and breast cancer at the time of diagnosis and during follow-up compared to healthy controls [31, 32].

Procoagulant microparticles (MP)—submicron extracellular vesicles. Their procoagulant capacity is determined by the expression of negatively charged phosphatidylserine and functionally active TF [33]. Increased MP-associated procoagulant activity was detected in patients with myeloproliferative neoplasms [34]. By intracellular exchange of MP, tumor cells transfer oncogenic signal and amplify the angiogenic phenotype [35].

Heparanase—endoglucuronidase that degrades heparan sulfate. Overexpressed in almost all known malignancies but has not been detected in normal tissue adjacent to the tumor. Tumor cells secrete heparanase, which induces the expression of TF, activates directly f.X, and inactivates tissue factor pathway inhibitor [36].

2.1.2. Suppression of natural anticoagulant mechanisms

Protein C (PrC)—inactivates Va and VIIIa in the presence of thrombin, and its functions are mediated by specific endothelial receptor. PrC performs cytoprotective and antimetastatic effects independently of coagulation [37]. Association between increased incidence of thrombotic events and acquired resistance to PrC (APC), unrelated to factor V Leiden, has been observed in multiple myeloma and colorectal cancer [38, 39]. There could be mechanisms of cell resistance due to the modification of the endothelial receptor and induction of APC under the influence of tumor proinflammatory cytokines [39, 40].

Protein S—cofactor PrC whose activity can be inhibited by circulating paraproteins [24].

Antithrombin III (ATIII)—a major serpin that inactivates factors IIa, IXa, Xa, XIa, XIIa, kallikrein, plasmin. Decreased levels of ATIII are found in patients with malignant diseases and decreased survival [41, 42].

Tissue factor pathway inhibitor (TFPI)—main inhibitor of the complex TF:VIIa. Overexpression of heparanase induces increase of functionally inactive TFPI in plasma (36), a putative role of a tumor suppressor gene [43, 44].

2.1.3. Defective fibrinolysis—hypofibrinolysis

Tumor cells expressed on their cellular surface all proteins necessary for regulation of the fibrinolytic pathways. Deregulation in generating normal fibrinolytic activity was observed in patients with solid tumors and is a mechanism for the development of thrombotic tendency [45].

Plasminogen activator inhibitor-1 (PAI-1)—important regulator of plasminogen activity. PAI-1 is overexpressed in different types of tumors [21]. Genomic sequencing of hepatocytes expressing the MET oncogene demonstrated significantly increased expression of the gene for PAI-1 and COX-2 that corresponded with triple increase in levels of circulating plasma proteins [46].

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Thrombin-activated fibrinolysis inhibitor (TAFI)—blocks the binding of plasminogen to fibrin. Reported elevated levels of TAFI in patients with cancer and thromboembolic events were compared to patients with acute venous thrombosis and normal controls [47, 48].

Proteinase inhibitor of fibrinolysis (α2-antiplasmin, α2-macroglobulin)—secreted in the tumor microenvironment/in high doses/in cancers with increased risk of venous thromboembolism [49]. Immunohistochemical studies demonstrate the expression of fibrinolytic inhibitors only in tumor cells, which could explain the absence of fibrinolytic activity in some tumors [50].

2.2. Endothelial activation

Blood vessels and endothelial cells play a major role in the control of the processes of hemostasis, thrombosis, and inflammation. Endothelial tromboregulation is accomplished by selective expression of mediators (autacoids and cell adhesion molecules) in response to specific agonists. The synthesized mediators are involved in all phases of the hemostasic process and regulate/maintain vascular reactivity. Intact endothelium is anticoagulant and profibrinolytic under physiologic conditions. From the perspective of the Virchow's triad, endothelium loses its tromboresistive properties upon damage—for example, stretching of the vessel wall, mechanical and chemical injury, turbulent flow, inflammation. Malignant process causes deregulation of endothelial homeostasis, which can be defined more precisely as activation rather than damage as endothelial cells alter their functional capacity and acquire new properties in the absence of violation of tissue integrity [51]. Factors of endothelial activation in the presence of malignant process include the following: (a) dysfunctional endothelium—overexpression of adhesion molecules; (b) loss of anticoagulant and acquisition of procoagulant properties; and (c) switch to proangiogenic phenotype [52].

2.2.1. Overexpression of adhesion molecules

Endothelial expression of selectins and ligands from the immunoglobulin superfamily is increased under the effect of tumor-induced cytokine and cellular interactions. Tumor-associated macrophages secrete TNF-α, IL-1, IL-6, IFN-γ, which increase the expression of adhesion molecules through activation of de novo synthesis of mRNA [22]. Increased expression of adhesion molecules ICAM-1, VCAM-1, and E-selectin mediated by NF-κB transcriptional activation was found when co-culturing endothelial and tumor cells [53]. Gene profiling of bone marrow cells from patients with multiple myeloma shows increased expression of genes BNIP3, IER3, and SEPW1. Through their silencing by small interfering RNA processes such as endothelial proliferation, adhesion and capillary formation are influenced [54].

2.2.2. Procoagulant conversion and loss of anticoagulant properties

Thrombomodulin (TM)—important endothelial cell-associated receptor that acts as direct anticoagulant. Binding of thrombin activates PrC system and inactivates the proteolytic degradation of procoagulant substrates [55]. Circulating tumor cytokines decreases TM levels causing degradation of its molecule and increased endothelial expression of TF [56]. There is inverse proportional relationship between TM expression and cellular proliferation in vivo.

Downregulated to absent TM expression is found in metastatic foci, while forced expression of TM in transgenic mouse models of squamous cell carcinoma lacking TM expression leads to a differentiated epithelial-like phenotype—effect regulated by Snai1 transcription factor [57]. Interference of the TM-PrC system that occurs as a result of lower TM and development of acquired resistance to PrC of cellular type is one of the factors for procoagulant conversion of endothelium.

In response to stimuli from the tumor microenvironment, antagonistic deregulation is observed in endothelial expression of the pairs of vWF/ADAMTS13, TF TFPI, PAI-1/plasminogen activators. Cytokine-activated endothelium releases high-molecular complexes of vWF, which are hyper-reactive to platelet aggregation, thrombus formation, and adhesion, whereas expression of ADAMTS13 depolymerase is suppressed [58]. Local procoagulant activity of endothelium is potentiated further by the effects of heparanase, which induces expression of TF and simultaneously dissociates its inhibitor TFPI from the endothelial cell surface [59]. And last but not least, the endothelial cells as a primary source of fibrinolytic activators participate in the induction of hypofibrilinolitic state by defective secretion of plasminogen activators in enhancing the expression of a fibrinolytic inhibitor PAI-1 [60]. Different mechanisms of microvascular dysfunction in combination with activated coagulation are the main pathogenetic factors in the development of thrombotic microangiopathy in malignancies.

2.2.3. Switch to proangiogenic phenotype

Increased angiogenic activity is due to complex processes in which fully differentiated, non-proliferating endothelial cells acquire invasive, migratory, and proliferative properties. The processes of the angiogenic switch are determined by the increased production of positive regulators of angiogenesis (VEGF, FGF2, IL-8, PIGF, FGF-β, PDGF), which originate from tumor cells—they can be mobilized from the extracellular matrix or are released by stromal cells, recruited in the tumor [61]. At the same time, many of these processes are coupled with regulatory coagulation processes. For example, endothelial growth factor VEGF, secreted by the tumor cells, increases endothelial expression of TF, which causes inverse decrease in the expression of the negative angiogenic regulator—thrombospondin [62]. Synthesis and secretion of another potent proangiogenic cytokine—interleukin-8 (IL-8) from endothelial cells —are increased, and the effect is dose dependent on the levels of fibrin deposits [63]. A similar mechanism is responsible for fibrin-induced expression of the gene for TF from umbilical vascular endothelial cells [64]. Additionally, thrombin and coagulation degradation products mediate haptotaxis of endothelial cells by selective exposure of a set of integrins. Thereby, they orientate the formation of capillaries and vasculogenesis in the direction of the angiogenic stimulus [65, 66].

Angiopoietin-1,2/Tie2 system is a key regulator of physiologic endothelial angiogenic activity, which controls the proliferation and differentiation of endothelial cells during embryonic development. Tie2 is an endothelial-specific receptor tyrosine kinase whose ligands are angiopoietin-1 (Ang-1) and angiopoietin-2 (Ang-2). Angiopoietin-1 is secreted by perivascular cells and in complex with Tie2 stabilizes the endothelium in quiescent state and potentiates the maturation of blood vessels. Angiopoietin-2 acts as an antagonist of Ang-1/Tie2. It is

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overexpressed during tumor angiogenesis and is responsible for pro-angiogenic endothelial conversion [67]. Tumor blood vessels express structural and functional abnormalities such as abnormal vascular permeability and increased potential for rapid growth and remodeling due to overexpression of Ang-2 [68]. Experimental data support the interdependence of the processes of procoagulant and pro-angiogenic endothelial conversion. Ang-1 inhibits overexpression of TF in HUVECs in a putative mechanism of PI3/Akt signal activation [69]. Thrombin-induced angiogenesis in an in vivo model of chorion allantoic membrane is accompanied by a double increase in expression of mRNA, encoding VEGF and Ang2 [70].

Endothelium performs a crucial role as a regulatory nexus in the processes of hemostasis and angiogenesis. The complexity of interactions allows on the one hand multiple targeting of several pathological mechanisms involved in angiogenesis and tumor progression and on the other hand mediates expression of side effects associated with the system of hemostasis.

2.3. Impaired blood flow

In the context of Virchow triad, disturbed blood flow is a predisposing factor for thrombosis. Venous stasis is most often secondary—due to external compression of local or metastatic tumor masses, adenopathy—inflammation caused by the tumor. The main mechanism involves inadequate clearance of coagulation factors and local endothelial hypoxia that induces endothelial expression of TF and platelet activating factor, increased leukocyte adhesion and platelet activation. Additional predisposing factor is the prolonged immobilization of cancer patients both in hospital and at home. Additive effect of disturbances clearance of activated coagulation factors and hypoxic endothelial damage in conditions of prolonged immobilization contribute to the development of a thrombotic process.

3. Tissue factor

Besides its major role in hemostasis, TF has been identified as an important signaling receptor in cancer biology. Ample preclinical evidence has accumulated over the past decade, implicating TF as an important effector in the processes of tumor initiation, growth, angiogenesis, and metastasis. Moreover, this has led to the development of approaches exploring TF as a potential target for anticancer therapy [71]. TF is overexpressed in many types of human tumors, including breast cancer, pancreatic cancer, gastric cancer, prostate cancer, colorectal cancer, non-small-cell lung cancer, melanoma, leukemia, lymphoma, esophageal cancer, hepatocellular carcinoma, brain glioblastoma, but not in their normal tissue counterparts [1]. TF overexpression in cancer cells has been correlated with tumor progression and unfavorable prognostic indicators such as increased angiogenesis, advanced disease stage, and resistant phenotype [72–74]. Therefore, TF overexpression in situ could be considered a biomarker for solid tumors.

Enhanced TF expression in cancer has been reported to be an oncogenic-driven event. In colorectal cancer, activation of the K-ras oncogene and loss-of-function mutation of p53 result in constitutive activation of mitogen-activated protein kinase (MAPK) and PI3K pathways

leading to increased TF expression [75]. In turn, inhibition of the PI3K and MAPK by restoration of the PTEN tumor suppressor gene in glioma cells downregulates TF expression dependent on EGFR amplification [76]. In medulloblastoma cell lines, TF expression has been shown to result from mutation in the c-Met oncogene and subsequent activation of Src kinases [77]. It has been observed that a certain subset of tumor cells, known as cancer stem cells, which constitutively express activated oncogenes and are capable of undergoing multilineage differentiation, are characterized by TF abundant phenotype [5]. Moreover, enhanced TF expression is observed during the processes of epithelial-to-mesenchymal-transition, whereby epithelial cells acquire a mesenchymal, more aggressive and motile phenotype [78]. This indicates that TF is possibly involved in maintaining cancer cell self-perpetuance.

There is a structure function dependency in TF mode of action. TF plays a role in cancer progression both by initiating tumor growth and by promoting efficient tumor cell dissemination. Tumor-promoting activities of TF occur via non-hemostatic mechanism and can be attributed to the cytoplasmic domain signaling dependent mostly on the activation of the protease activated receptor 2 (PAR2). Prometastatic properties of TF can rather be coupled with its extracellular domain and the subsequent generation of thrombin, which, as a potent growth factor, exhibits further pleiotropic cellular effects.

TF-mediated signaling is critical for both physiological and pathological angiogenesis. TF deficiency in murine knockout experiments caused early embryonic lethality due to impaired vasculature development [79]. Zhang et al. demonstrated that tumors overexpressing TF become highly vascularized once implanted into mice and the observed growth induction could not be inhibited despite maximal anticoagulation [80]. It has been revealed that involvement of TF cytoplasmic domain in several transduction cascades accounts for the production by tumor cells of angiogenic cytokines and contributes to increased angiogenesis in a paracrine fashion [81]. Formation of the complex TF/VIIa leads to increase of intracellular Ca^{2+} and phosphorylation of serine residues on TF cytoplasmic tail. This triggers signaling via the G-protein coupled membrane receptor PAR2 that activates MAPK and PI3K transduction cascades, resulting in increased gene expression of the angiogenic cytokines VEGF, VEGF-C, CXCL1, Il-8, and Cyr61 [82–84]. In addition to PAR2 signaling, the cytoplasmic domain of TF can be phosphorylated independently of f.VII ligand binding by protein kinase C (PKC) resulting in the transcriptional activation of VEGF, VEGFR, TGF, and suppressed expression of anti-angiogenic molecules such as thrombospondin [85, 86]. The relationship between TF and VEGF has been extensively studied and is manifested by reciprocal co-stimulation of their expression profiles. VEGF induces TF expression by orchestrating the binding of nuclear factors NFAT and AP-1 to the promoter region of TF gene [87]. Regulation of VEGF is in turn dependent on the TF cytoplasmic domain signaling, which is demonstrated by the finding that tumor cells transfected with truncated TF cDNA lacking the cytoplasmic domain fail to produce VEGF, but preserve the TF procoagulant function [86]. Experimental ex vivo and in vivo studies have further supported the TF-VEGF interrelationship by finding increased co-expression on tumor sections and their association with increased angiogenesis and malignant potential in human tumors [73–75, 88, 89].

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TF enhances tumor growth via TF/VIIa/PAR2 signaling. This is evidenced by studies on cancer cell lines, where overexpression of TF by cancer cells conferred growth advantage compared to cell lines expressing low levels of TF [71, 86]. Delay in primary and metastatic tumor growth was observed after specific TF/VIIa inhibition with the anticoagulant rNAPc2 but not after inhibition of f.Xa [90]. Studies on selective targeting of different domains of the complex TF:VIIa revealed that PAR2 signaling and integrin ligation is sufficient for TF tumor-promoting properties [91].

Prometastatic properties of TF can be attributed to its extracellular domain, which is required for its major role in triggering coagulation. The extracellular mutant domain (TFmut) has markedly diminished function for activation of f.X, while full-length or cytoplasmic tail-deleted TF retains its procoagulant activity [85, 92]. The expression of TF in tumors can induce downstream coagulation activation via the TF/VIIa/Xa pathway leading to fibrin and tumor stroma formation. Tumor cells become encapsulated in fibrin and platelet-rich thrombi, being protected from the host immune defense and arrest in the microcirculation. Local thrombin formation facilitates arrest of tumor cells to the vessel wall by upregulation of adhesion molecules and strengthening cell-to-cell junctions [93]. Fibrin matrix in the tumor stroma builds itself a multifunctional scaffold rich on growth factors such as platelet derived growth factor (PDGF), transforming growth factor (TGF), fibroblast growth factor (FGF), that is not only protective, but also promotes matrix-cell interactions necessary for neovascularization [94]. Thrombin, constitutively generated by the activated coagulation cascade in the tumor surrounding, mobilizes the adhesion molecules αIIbβ3-integrin, P-selectin, CD40 ligand, and enhances tumor cell interactions to platelets, endothelial cells and matrix [95–97]. Thrombin has also an important function in angiogenesis by inducing the activation of endothelial-secreted collagenase type IV, which degrades basement matrix proteins and collagen during neoangiogenesis [98]. In vivo experimental models of metastasis demonstrated dramatic increase of lung metastasis with thrombin-treated tumor cells compared with untreated cells [99].

In summary, TF-mediated effects either in a coagulation-independent mechanism via direct cytoplasmic domain signaling and TF/VIIa/PAR2 or dependent on the coagulation products induce diverse sets of cellular responses inherent to tumor cells including tumor growth, neoangiogenesis, cell migration, and metastasis. Taking into account the specific biologic role of TF in the malignant tissue, detecting circulating TF in cancer patients might be informative of active disease and ongoing processes of matrix reorganization, cell destruction, and neovascularization.

4. uPA/uPAR system

The physiologic role of fibrinolysis is dissolution of the fibrin clot and collagen degradation exerted by the action of plasmin. Generation of plasmin, the main enzyme in fibrinolysis, occurs upon activation of plasminogen by the tissue plasminogen activator (tPA) and the urokinase plasminogen activator (uPA).Therefore, function of the urokinase plasminogen

activator (uPA) and its high-affinity cellular receptor (uPAR) is critical for fibrinolytic activities including targeted degradation of the basement matrix. Moreover, uPAR is motile within the cellular membrane, which allows its allocation at the cellular front of desired direction for proteolysis [100]. Under normal conditions, the process of active proteolysis is tightly controlled by the proteolytic systems.

In cancer, biology activation of uPA/uPAR system is a prerequisite for efficient focal proteolysis, adhesion, migration and enables penetrating tumor cells to invade and metastasize [101]. Extracellular matrix proteolysis acts at all stages of the metastatic cascade: detachment of tumor cells from primary site, intravasation, hematogeneous dissemination, extravasation, and metastases formation. These processes are executed by proteolytic enzymatic systems, including uPA/uPAR, matrix metalloproteinases, and cysteine proteinases, which interact synergistically and are responsible for the complex proteolytic activity of tumors [102].

The cellular receptor for the urokinase plasminogen activator (uPAR) is a key molecule for efficient pericellular proteolysis. Apart from potentiating proteolytic activity, the complex uPA/uPAR ignites series of intracellular signaling events associated with the processes of proliferation, adhesion, chemotaxis, migration, and angiogenesis. Tissue overexpression of uPA/uPAR is found in various human tumors—breast, prostate, GIT, and lung. It is associated with advanced disease and is independent adverse prognostic factor for survival [103]. Direct involvement of uPAR in processes of tumor biology characterizes it as a hallmark of the malignant invasive phenotype. Overexpression of uPAR cDNA in osteosarcoma cells increases its ability to penetrate the basal membrane [104]. Invasive potential of tumor cells in chorion-allantois membrane of chicken embryos correlates with uPAR-associated proteolytic activity [105]. Expression of uPAR gene by tumor cells is required for vascular intravasation, whereas uPAR gene expression decreases invasive potential of transformed fibroblasts in vitro [106]. Experiments with anti-uPAR inhibitory antibodies demonstrate reduction of the matric proteolytic activity [107, 108]. Levels and activity of uPAR are regulated at the transcriptional level by oncogene-controlled promoter activation. uPAR promoter region contains binding motifs for several transcriptional factors that regulate cellular differentiation, migration, and apoptosis: specific protein 1 (SP1), activator protein 1 (AP1) and activator protein 2 (AP2) [109]. uPAR basal expression is regulated proximally from SP1 transcriptional starting point. In tumor models of colorectal cancer, constitutive, and induced uPAR expression is regulated by AP1 binding motif via MAPK and c-JUN NH_2-terminal kinase (JNK) signaling [110]. AP2 binding motif is required for constitutive overexpression of uPAR promoter activity in invasive tumor cells after stimulation by the tumor promoter phorbol acetate.

The role of K-ras and SRC oncogenes in uPAR regulation has been identified. K-ras regulates uPAR mediated proteolysis by transcriptional binding of AP1 to the promoter motif. Down-regulation of promoter activity as in deletion of the AP1 binding activity has been observed in tumor clones with K-ras allelic deletion. The knockout effect is accompanied by significant reduction of uPAR expression and tumor-associated proteolysis [111]. Increased uPAR protein expression and laminin degradation parallel to c-SRC activation are observed in SW 480 cells transfected to constitutively overexpress s-SRC. Elevated uPAR expression is due to transcriptional activation secondary to increased binding of SP1 to the complementary promoter

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motif. This defines SP1 as distal factor of c-SRC-mediated regulation of uPAR [109]. Tissue overexpression of uPA/uPAR has been detected in many human tumors like breast, prostate, gastrointestinal, and lung cancers. Oncogenes responsible for enhancement of uPA/uPAR expression in malignant tissue include ras, jun, myc, fos, rel, and ets. uPAR expression can also be stimulated by the expression of TF and the epidermal growth factor receptor (EGFR) [112].

Factor	Coagulation function	Role in tumor biology
f.I (fibrinogen)	Formation of the hemostatic clot	Potentiates formation of metastatic emboli and enhances survival of tumor cells
f.II (prothrombin/thrombin)	Converts fibrinogen to fibrin	Growth factor, role in angiogenesis, tumor proliferation, and metastasis formation
f.III (tissue factor)	Major initiator of coagulation	Exerts proangiogenic and prometastatic effects, role in tumor growth initiation
f.VII	Cofactor for TF	Inhibition of anoikis, supports tumor invasion
f. XIII	Stabilizes fibrin	Potentiates tumor growth and metastasis
Cysteine proteinase	Direct activator of f.X has not been identified in healthy individuals	Suppressed expression by blasts upon differentiation
Heparanase	Degradation of heparan sulfate	Local invasion and metastasis
Protein C	Anticoagulant function via Va and VIIIa inactivation	Activated PrC resistance related to loss of cytoprotective and antimetastatic effects
Tissue factor pathway inhibitor	Main inhibitor of the complex TF:VIIa	Putative role of a tumor suppressor gene
Plasminogen activator inhibitor-1 (PAI-1)	Regulator of plasminogen activity	Overexpression found in various tumor types, related to MET oncogene
uPA/uPAR system	Generation of plasmin	Focal proteolysis, tumor cell invasion and migration
Thrombomodulin	Direct anticoagulant via thrombin binding and PrC activation	Forced TM expression in cancer cells lacking TM leads to differentiated phenotype via Snai1

Table 1. Coagulation function vs. role in tumor biology of hemostatic factors.

Fibrinolytic system components can be identified as determinants of invasion in tumor biology and reflect the metastatic potential of tumors.

5. Conclusion

Identification of hemostatic system as a component of the tumor microenvironment would provide a research scaffold for novel determinants of tumor progression. The role of hemostatic components in the processes of tumor growth, angiogenesis, invasion, and metastasis makes them an accessible potential target for targeted therapy. Analysis of their predictive and prognostic value as surrogate biomarkers for tumor-induced events would yield development of novel tools for monitoring and antitumor strategies.

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