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Mini-review

Anticoagulants in cancer treatment: malignancy as a solid phase coagulopathy

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Abstract

The purpose of this review is to demonstrate the potential for development of coagulation-reactive drugs for experimental cancer treatment. Improved cancer outcome has been reported in several tumor types with drugs that interfere with thrombin-generating or urokinase-initiated pathways expressed by tumor cells. These pathways participate in the response to injury and their inappropriate expression by malignant cells supports tumor growth. A proposed classification of tumor types based on the differential occurrence of these pathways may account for variation in drug responsiveness and guide clinical trial design. Among drugs available for testing, aprotinin and low molecular weight heparin have particular appeal. The former blocks a pathway of tumor cell growth, invasion and metastasis while the latter blocks growth factor activity, angiogenesis, and other tumor growth mechanisms as well as coagulation activation. Conceiving of malignancy as a solid phase coagulopathy may facilitate development of effective but non-toxic cancer treatments and encourage inquiry into the putative 'injury' responsible for both coagulation activation and carcinogenesis.

Keywords: Blood coagulation; Cancer; Anticoagulants; Heparin; Warfarin; Extracellular matrix

1. The oncologic view of coagulation: the need for communication

Visualize a treatment shown in four retrospective meta-analyses of randomized trials involving hundreds of patients to reduce mortality at 3–6 months by two-thirds in several advanced malignancies without toxicity. Visualize again a non-toxic treatment studied in a double-blind trial in which mortality at 1 year from metastatic colorectal cancer in the placebo group was 50% while only two drug-treated patients died and both were attributed to post-operative complications. Such remarkable results seem worthy of news headlines but have attracted little attention. The former drug is low molecular weight heparin (LMWH) given for a few days in randomized trials for treatment of deep vein thrombosis (DVT) associated with advanced cancer [1,2]. The latter is aprotinin given as a 6 h infusion to reduce blood loss during resection of solitary hepatic metastasis from colorectal cancer [3]. Why are these reports uninteresting? Perhaps its because anticoagulants and antifibrinolytics don't seem like anti-tumor drugs and the results appear too good to be true! Perhaps its because coagulation activation is thought of as an annoying 'paraneoplastic' concomitant of cancer but not mainstream cancer biology. Wasn't the old idea that the

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coagulation mechanism supports tumor dissemination disproved long ago?

The possibility that coagulationists are not communicating effectively prompted perusal of the Table of Contents of the latest edition of a 3000-plus-page oncology text for the oncologist's view of coagulation and cancer [4]. There were sections on everything from hair loss to sexual dysfunction but not on the coagulation mechanism that is almost universally activated in malignancy. DVT is a common cause of morbidity and mortality with cancer but was mentioned in only a phrase in the differential diagnosis of lymphedema in chapter 57 on rehabilitation. 'Thrombophlebitis', disseminated intravascular coagulation (DIC), and non-bacterial thrombotic endocarditis together got the space of about a column on page 2518. There was no mention that coagulation test abnormalities are strong independent markers of cancer survival [5]. Idiopathic DVT carries about a 10% risk of malignancy that may occur years or decades after the thrombosis. This information was missing from chapter 11 on '…population-based risk assessment'. Doesn't this association suggest clues to mechanisms of tumor initiation/promotion and the need for patient screening? Absent from chapter 8 on invasion and metastasis was reference to scores of articles showing that virtually any intervention aimed at the coagulation mechanism reduces tumor dissemination in appropriate animal models. Chapter 18 on 'biotherapy' discussed antibodies and armed cells as smart extensions of chemotherapy. However, no description existed of properties of tumor cells recognizable from coagulation biology that contribute to proliferation, invasion and metastasis that might also be intercepted 'biologically'. For example, in tumor-bearing animals, subtle modification of heparin-like glycosaminoglycans (HLGAGs) on tumor cell surfaces virtually shuts down tumor growth [6]. A popular review on small cell carcinoma of the lung (SCCL) described limitations of current therapy and speculated on future avenues [7]. However, no mention was made of three prospective randomized trials (PRT) of a vitamin K antagonist (warfarin), one PRT of unfractionated heparin, a large phase II trial of pro-urokinase, and anecdotal reports of streptokinase, all of which showed improved SCCL outcome [1,8–14]. The authors speculated on new treatments but didn't explain why intercepting an intracellular transduction pathway is inherently more appealing than inhibiting growth factor-receptor binding, extracellular matrix formation, or the multiple effects of thrombin that may support SCCL growth [8].

2. A coagulationist's view of cancer

Addressing this communication gap presented a two-fold challenge. The first was to coax readers to glimpse malignancy through 'coagulation-colored glasses' and the second was to review concisely what they might see. While this is no easy task because of the volume of material on the subject, help is at hand. Notice the contrast between the lack of material on coagulation in the oncology text and the abundant material on oncology in a leading coagulation text. In their chapter, Rickles, Levine, and Dvorak masterfully condensed this field into 21 text pages and 354 references [15]. Our task here is to portray even more concisely what cancer looks like to a coagulationist. This subject has occupied numerous books, journal volumes, and symposia, and is the focus of an international working subcommittee established in 1984. Reference here will be primarily to reviews. The goal is to whet the appetite for more.

The coagulation mechanism is an exquisitely sensitive response to injury. It serves the organism by preventing blood loss, and initiating wound healing and tissue remodeling by orchestrating cell proliferation, migration, synthesis and secretion, etc. [5,8,15]. This is accomplished by a tension of opposing biochemical algorithms that restore anatomic integrity. Normal cells respond to various chemical and physical injuries in two ways. One is by expressing procoagulants, primarily tissue factor (TF), that initiate thrombin generation and clot formation. The second is by expressing urokinase-type plasminogen activator (uPA) that initiates plasminogen activation to coordinate cell proliferation and tissue remodeling notably in secretory organs that depend on a tubular architecture such as the breast and kidney.

DVT and DIC show the strong tilt toward excessive and persistent coagulation activation with malignancy. Coagulation can be activated in cancer by several mechanisms summarized in Table 1 [8]. Exaggerated activation can easily spill over systemically to obscure subtle local reactions important for tumor cell

Table 1
Mechanisms of systemic coagulation activation in cancer (adapted from Ref. [8])

I. Tumor cell-specific causes
1. 'Direct' generation of thrombin by tumor cell procoagulants
2. 'Indirect' generation of thrombin through production of cytokines by tumor cells that activate host cells (e.g. macrophages, endothelial cells)
II. Non-specific causes
3. Damage to normal tissues from tumor masses
4. Infection, host inflammatory response
5. Tissue necrosis
6. Introduction of mucin into the circulation
7. Surgical trauma
8. Chemotherapy toxicity
9. Effects of venous access devices

growth. Numerous individual reactants from coagulation biology are capable of influencing neoplastic behavior. A partial list of these is presented in Table 2. Of these, thrombin and uPA command special interest. Table 3 summarizes the basis for postulating that a thrombin-generating pathway may support growth of certain tumor types [5,8–15]. A large literature summarized in Table 4 also implicates uPA in the pathogenesis of cancer [8,9,16].

Determining whether these pathways existed in human malignancy in situ became of first importance. It is not possible to quantitate enzymatic reactions in solid tissue as it is in plasma ordinarily used for studies of coagulation reactivity. Rather, activated coagulation intermediates can be mapped microanatomically using immunohistochemical probes that react specifically with the active serine site on factor Xa and thrombin, and monoclonal antibodies that react with thrombin–anti-thrombin complex neoantigen, and when thrombin-specific cleavage sites on fibrinogen are either intact or broken (i.e. fibrinogen and fibrin, respectively). Similar techniques detected components of the uPA pathway. Such studies permitted classification of several tumor types based on whether the tumor cells expressed primarily a thrombin-generating pathway or uPA [8]. Examples of tumor types having a tumor cell thrombin-generating pathway in situ included SCCL, renal cell carcinoma (RCC), and malignant melanoma. The occurrence of fibrin (thrombin-cleaved fibrinogen) plastered against viable RCC cells is illustrated in Fig. 1. RCC tumor cells also stained for the active serine site of factor Xa and thrombin indicating their role in stromal fibrin formation [17]. By contrast, the tumor cells in breast, prostate, colon, and non-small cell lung cancer expressed uPA and its receptor but not a thrombin-generating pathway. Numerous studies have shown that tissue levels of uPA and its receptor are strong predictors of clinical outcome suggesting that this 'marker' also promotes disease progression (Table 4) [18].

Table 2
Partial list of substances from coagulation biology that influence tumor growth [5,8,9,15,16]

Substance	Effect
1. Tissue factor (TF)	Initiator of coagulation activation
	Participant in angiogenic pathway
2. Fibrinogen/fibrin	Constituent of extracellular matrix
	Support of angiogenesis
3. Tissue factor pathway inhibitor	Inhibitor of TF/VIIa/Xa
	Inhibitor of angiogenesis
4. Activated factors VII, X, XII	Cellular mitogens
5. Platelets	Support of metastatic nidation
	Delivery of growth factors
6. Thrombin and urokinase	See Tables 3 and 4

This classification helps explain the heterogeneous results from drug intervention studies and guides drug selection for future clinical trials. For example, SCCL appears to respond to inhibitors of coagulation (warfarin, heparin) and disruption of the extracellular matrix [8–15]. By contrast, colon cancer appears to respond to inhibition of uPA-induced plasminogen activation (aprotinin) [3] but not warfarin [19]. In fact, no tumor type that expresses primarily tumor cell uPA but not a coagulation pathway has responded to warfarin in PRTs [19]. Of course, tumors in either group may share other features such as interaction with platelets, growth factor dependence, and pathways of new vessel formation [1,8]. Thus, tumors in either group may respond to heparin that interferes with growth factor activity, angiogenesis, or other growth-promoting mechanisms as well as coagulation activation.

Evidence that tumor cells appear to be responding to injury by expressing a procoagulant pathway or

Table 3
Basis for hypothesis that a thrombin-generating pathway may contribute to growth of certain tumors [8,15,17]

1. Hirudin, antistasin, warfarin, NAP C-2, etc. inhibit tumor progression in appropriate experimental animal models
2. Thrombin supports neoplastic behavior of cells
   mitosis, angiogenesis, motility, adhesion, chemotaxis, platelet activation, oncogene expression, nuclear transcription factor activation, growth factor production (PDGF, bFGF), inhibition of differentiation, regulation of extracellular matrix deposition, enhancement of metastatic potential
3. The thrombin–thrombin receptor mechanism is abnormal in cancer cells
   thrombin receptor antisense cDNA blocks metastatic phenotype
4. Clinical trials suggest effects in selected tumor types

uPA invites speculation on what the invisible, time-dependent 'injury' might be. Perhaps the tumor doesn't go away because the unidentified injury remains. A relatively narrow field of candidates exists for such a carcinogenic and coagulation-activating 'injury'. Alternatively, perhaps neoplasia persists because expression of these reaction pathways is part of the assemblage of properties that enable malignant cells to succeed. This isn't a far-fetched idea. Clinical trials have shown that a relatively short (hours to days) course of treatment, for example with LMWH or aprotinin, improves cancer outcome months to years later perhaps by re-programming the tumor cell [1–3].

To sum up, the phrase 'coagulation biology of cancer' refers to the aggregate data on hemostatic and thrombotic mechanisms, and coagulation-reactive drug effects from studies in malignancy. Activation and de-activation of cells and enzymatic algorithms, and cell movement, attachment/detachment and proliferation are all included.

Table 4
Basis for hypothesis that a uPA-initiated pathway of proteolysis may support growth of certain tumor types (adapted from Ref. [16])

1. uPA gene transfection confers invasive and metastatic phenotype

2. Cellular uPA amplification enhances tumorigenesis
   A. Tumor promoters
   B. Transforming tumor viruses
   C. Incubation of cells at permissive temperatures (in temperature-sensitive transformants)
   D. Transfection with specific oncogenes

3. Augmentation of cellular uPA expression confers malignant phenotype
   A. Enhanced proliferation
   B. Degradation of extracellular matrix
   C. Increased tumor cell invasiveness and metastasis
   D. Loss of anchorage-dependent growth
   E. Loss of contact inhibition of cell growth
   F. Rounded morphology
   G. Increased lectin agglutinability
   H. Loss of intracellular actin cables
   I. Increased cell motility
   J. Enhanced angiogenesis

4. Inhibition of uPA expression or activity blocks expression of the malignant phenotype and angiogenesis
   A. Antibodies to uPA
   B. Inhibitors of uPA/uPA receptor binding
   C. Chemical/pharmacologic inhibitors of uPA/plasmin activity
   D. Antisense uPA oligonucleotides

3. Coagulation and the natural history of cancer

Coagulation and cancer are intertwined from inception to patient demise. Idiopathic DVT in an apparently healthy individual has been a recognized harbinger of subsequent malignancy since the description by Trousseau over 100 years ago of the syndrome bearing his name [15,20]. Cancer risk within the first 2 years after idiopathic DVT is about 10% and includes many, but not all, tumor types. High on this list are pancreatic, ovarian, hepatic, and brain tumors. This risk persists for a quarter of a century or more after the DVT. Prandoni et al. surveyed the clinical course of 355 cases of all-cause DVT followed for an average of 8 years. Fully 9% of patients were later diagnosed with malignancy and 25% of deaths were attributed to cancer [21]. Could incipient malignancy and clotting activation share common causes? What might the coagulation activator/tumor promoter be that is at work years before clinical cancer?

This riddle remains unsolved but clues have come

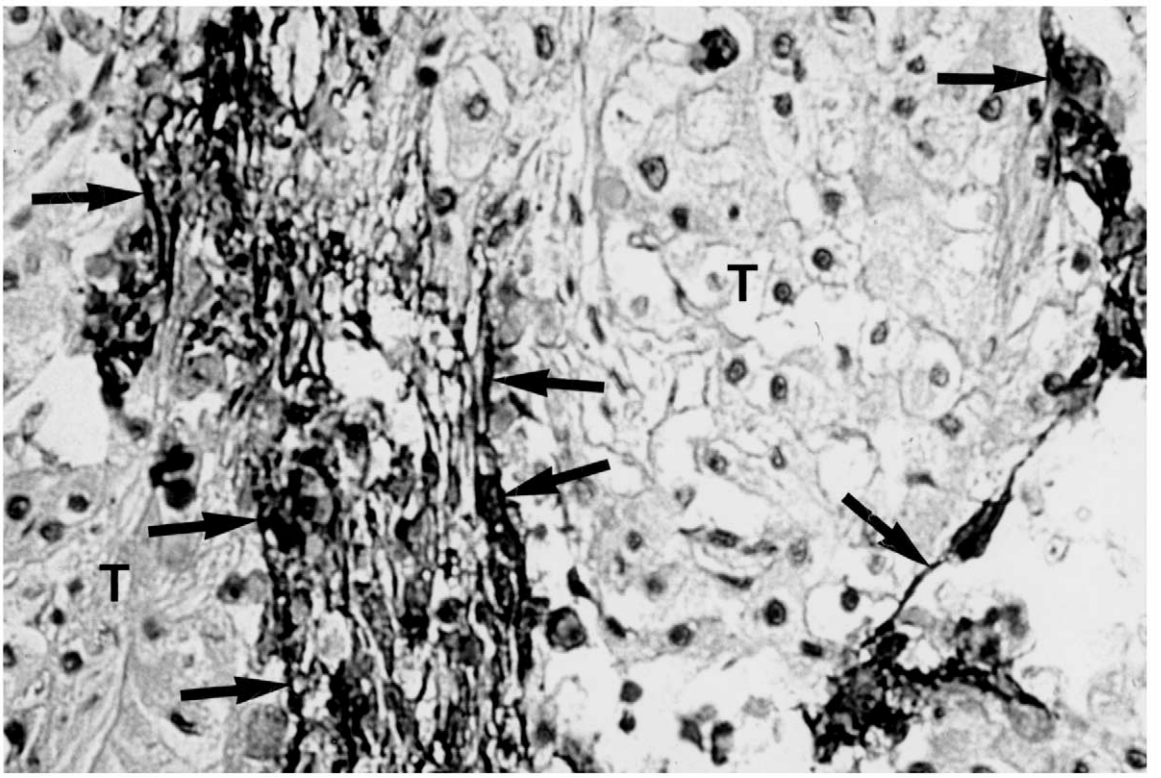

Fig. 1. Renal cell carcinoma. Specific staining (arrows) for chemically-defined fibrin using the peroxidase reaction with monoclonal antibody to the thrombin cleavage site on fibrinogen immediately adjacent to viable tumor cells (T). In other studies, the tumor cells were found to stain specifically using probes for the activated factor X and thrombin [8,17].

from both basic and clinical sources. For example, phorbol ester tumor promoters and the carcinogen, methylcholanthrene, are also initiators of cellular procoagulant activity [22,23]. A drug surveillance sub-study conducted with VA Cooperative Study #188 between 1981 and 1986 identified takers of non-steroidal anti-inflammatory drugs as having unusually long survival with colorectal cancer [24]. Information available showed that the arachidonic acid pathway familiar to students of platelet function was important for experimental colonic carcinogenesis [25]. Subsequent years have brought increasing evidence that inhibitors of the arachidonic acid cascade (non-steroidal anti-inflammatory drugs that are also anti-thrombotic) reverse pre-malignant lesions and improve cancer outcome [26–28]. Schulman and Lindmaker found that prolonged warfarin treatment for idiopathic DVT led, years later, to significantly reduced risk of urogenital (especially prostate) cancer [29]. This was not due to an anti-tumor effect because warfarin does not improve outcomes in established prostate cancer [30]. This early protective effect seemed best explained by known anti-carcinogenic properties of this class of familiar anticoagulant drug [30]. Extensive links between induction of uPA expression and basic mechanisms of malignancy are summarized in Table 4. Oxidative stress is also capable of inducing both malignancy and coagulation activation.

4. Hypercoagulability complicating the course of cancer

Once cancer is diagnosed, all the rules change. Clotting activation escapes the local mass lesion and hypercoagulability becomes systemic (Table 1). Coagulopathies associated with malignancy include

arterial thrombosis, development of antibodies to coagulation factors, the so-called 'lupus anticoagulant', etc. [15,20]. Best known is DVT occurring in about 25% of patients during life and in about 50% at autopsy [15,20]. DVT with malignancy may occur anywhere in the circulation, is prone to recurrence, often resists treatment with common anticoagulants and signals poor cancer outcome.

DIC, indicating systemic thrombin generation with malignancy, is more common than DVT. Decompensated (clinically symptomatic or having overt laboratory manifestations) DIC is relatively uncommon, but compensated DIC is almost universal. Sub-clinical DIC factors into the differential diagnosis of thrombocytopenia and routine coagulation test abnormalities, the etiology of cancer-associated multi-organ dysfunction, and the interpretation of 'acute phase' alterations in levels of plasma proteins, increased or decreased coagulation factor levels, and decreased levels of coagulation inhibitors. DIC with malignancy may be aggravated by impaired liver function, poor diet, effects of medications, etc. Sub-clinical DIC is generally thought not to require treatment. However, the extent to which improved cancer outcome with anticoagulants may be attributable to amelioration of coagulopathy is unknown and it remains to be seen whether normalization of coagulation test abnormalities by treatment might be useful for predicting patient outcome [5].

5. Effect of coagulation activation/inhibition on the course of malignancy

Pathologists who observed clots associated with embolic tumor masses provided the first clues to a role for blood coagulation in tumor dissemination [8]. Numerous studies showed that virtually any intervention affecting the coagulation mechanism altered tumor growth. Among the many beneficial effects of coagulation-reactive drugs were inhibition of metastasis, slowed tumor growth, increased tumor regression, and prolonged survival [1,8,15]. A hallmark of these early studies was heterogeneity in responsiveness owing undoubtedly to mechanisms that varied between tumor types and that remained unexplained because of technological limitations. The coagulation mechanism of animals differs from that of humans and results in the tumor model were not readily translatable to the human setting. Oncologists generally did not do this work, and the chemotherapy treatment paradigm was on the horizon. These considerations may account for the paucity of reference to the coagulation mechanism in the oncology literature.

6. Anticoagulant effects on human cancer

Effects of anticoagulant drugs on human malignancy have been described in case reports, cohort studies, retrospective meta-analyses, uncontrolled clinical trials, and controlled PRTs. These have been summarized previously [8,31]. Table 5 illustrates the results of several anticoagulant trials in which patients were randomized according to tumor type, stage, and therapy common to both groups. The experimental variable was the coagulation-reactive drug. These 'tests of concept' provide a starting point for future trials because drug effects can be linked to disease mechanisms that can be further clarified. Thus, effects of treatment on relevant tests may provide an intermediate measure of efficacy [5]. Non-invasive scanning procedures in development may reveal effects on angiogenesis. Incomplete efficacy can be improved by adding drugs having complementary mechanisms. While further clinical trials of warfarin would be difficult to support [10–12,19], new drugs are now available having novel mechanisms that may be more effective. These include inhibitors of TF, Xa, thrombin, uPA and platelets, recombinant tissue factor pathway inhibitor (TFPI), etc. Clinical trials of LMWH are particularly appealing because of the strong showing that HLGAGs have had so far and because LMWH alters tumor growth by several mechanisms [1]. LMWH is preferred to unfractionated heparin for randomized trials because of its superior pharmacodynamic properties, lower toxicity, and greater inhibitory activity against growth factors, heparinase, angiogenesis, and coagulation activation (Table 6) [1].

7. Future directions

Neoplasia is much more than a disorder of cell proliferation. Malignant behavior is linked to physiologic processes that regulate cellular organization

Table 5
Effects of coagulation-reactive drugs observed in clinical trials controlled for tumor type, disease stage, and standard treatment (see Refs. [1,8,9,31] for the results of other clinical trials)

Tumor type	Findings
Small cell carcinoma of the lung	
VA Cooperative Study #75 [10]	Significantly improved survival with warfarin
CALGB 8084 [11]	Significantly improved response rates, improved failure-free and overall survival with warfarin for extensive disease
CALGB 8534 [12]	Borderline improved adjusted overall and progression-free survival ($P = 0.07$); improved long-term survival on landmark analysis ($P = 0.05$)
Petit Cellules Group [13]	Significantly improved response rates and survival with adjusted dose, subcutaneous unfractionated heparin
Colorectal cancer	
Kohanna et al. [32]	Significantly improved long-term survival with heparin DVT prophylaxis in resected Dukes B2 and C disease
Lentschener et al. [3]	Significant improvement in 1 year survival with aprotinin given during resection of solitary hepatic metastasis from colorectal cancer (double-blind trial)
Non-small cell lung cancer	
VA Cooperative Study #188 [33]	Significantly improved survival in stage III disease with RA-233 (double-blind trial)
Blaha et al. [34]	Significantly improved survival in stage III disease with RA-233 (double-blind trial)
Pelvic cancer	
Von Tempelhoff et al. [35]	Significantly improved long-term survival with endometrial and ovarian cancer with LMWH compared to unfractionated heparin given peri-operatively for DVT prevention (double-blind trial)

within tissues that can be understood in terms of coagulation biology. Physiologic coagulation activation is generally conceived of as occurring primarily in fluid phase within the blood. However, all coagulation activation occurs in response to altered properties of injured cells and is attenuated upon recovery of the injured cell. Malignancy can be viewed as a 'solid phase coagulopathy' because tumor cells engage coagulation- and plasminogen activator-initiated pathways and platelets as if responding to injury. The difference is that the 'response' takes place within the economy of a mass lesion and is not self-attenuating. These properties contribute to neoplastic growth because their manipulation changes the course of the disease. This old idea has gained credibility with time. Recent evidence strongly supports the need for properly designed clinical trials that take into consideration heterogeneous tumor and drug mechanisms. Amazing improvement in long-term patient outcome with seemingly minimal treatment suggests that subversion of the coagulation mechanism by the tumor cell may help explain why the transformed cell is so successful. This basis for clinical trial design is mechanistically plausible and interventions should be relatively non-toxic. Rational experimental design should lead to more effective cancer treatments and

Table 6
Properties of heparin that may influence tumor growth [1]

Major effects
Inhibition of:
Coagulation factors
Angiogenesis
Growth factors
Non-coagulation proteases
Minor effects
Inhibition of:
Cell motility
Multi-drug resistance phenotype
Oncogene expression
Oxygen free radical effects
Stimulation of:
Immune competence
Cell differentiation and apoptosis

Table 7
Candidate agents for future clinical trials based on data from experimental tumor systems

Tissue factor inhibitors (chemical inhibitors, monoclonal antibodies)
Inhibitors of tissue factor/VIIa/Xa complex (NAP C-2)
Tissue factor pathway inhibitor (rTFPI) or releasers of TFPI (heparins)
Inhibitors of platelet accumulation at tumor sites (anti-IIbIIIa)
Inhibitors of activated factor X (antistasin, pentasaccharide, chemical inhibitors)
Direct thrombin inhibitors (hirudin and derivatives, ximelagatran)
Heparinases
Selective growth factor antagonists (heparin fractions)

also provide insight into basic disease mechanisms (see Table 7).

It is intriguing that during neoplastic transformation cells become programmed to interact in an unregulated way with coagulation and fibrinolytic pathways. From this point of view, the tumor cell seems to be responding to an as yet unidentified injury. It should be possible to work backwards to identify the injury knowing it is the response that is the giveaway.

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