



The pathogenesis of cancer-associated thrombosis

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Abstract

Patients with cancer have a higher risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), compared to the general population. Cancer-associated thrombosis (CAT) is a thrombotic event that occurs as a complication of cancer or cancer therapy. Major factors determining VTE risk in cancer patients include not only treatment history and patient characteristics, but also cancer type and site. Cancer types can be broadly divided into three groups based on VTE risk: high risk (pancreatic, ovarian, brain, stomach, gynecologic, and hematologic), intermediate risk (colon and lung), and low risk (breast and prostate). This implies that the mechanism of VTE differs between cancer types and that specific VTE pathways may exist for different cancer types. This review summarizes the specific pathways that contribute to VTE in cancer patients, with a particular focus on leukocytosis, neutrophil extracellular traps (NETs), tissue factor (TF), thrombocytosis, podoplanin (PDPN), plasminogen activator inhibitor-1 (PAI-1), the intrinsic coagulation pathway, and von Willebrand factor (VWF).

Keywords Cancer · Thrombosis · Cancer-associated thrombosis (CAT) · Mechanism

Introduction

Patients with cancer have a fourfold to ninefold increased risk of venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE), compared to the general population [1–6]. Cancer therapy is also associated with VTE and molecularly targeted cancer drugs which increase the risk of atrial thromboembolism (ATE) [7]. These thrombotic events, which occur as complications of cancer, are known as cancer-associated thrombosis (CAT). Of the first VTE events, 2–30% are cancer-associated, and VTE is the second leading cause of death in patients with cancer [2, 8]. Mortality in cancer patients with VTE is twofold higher than that in patients without VTE [4, 9].

Anticoagulation with low-molecular-weight heparin (LMWH), vitamin K antagonists, and direct oral anticoagulants (DOACs) targeting factor X may effectively prevent

VTE in cancer patients with a high VTE risk. However, the risk of anticoagulant-related bleeding is not negligible [6, 10, 11]. Recently, the utility of DOACs (edoxaban, rivaroxaban, and apixaban) for VTE prophylaxis in cancer patients was investigated in large-scale clinical trials (trial names: Hokusai VTE Cancer, Select-D, and CARAVAGGIO) [12–14]. The performance of each drug was assessed and compared to that of LWMH. The VTE rate was lower in the rivaroxaban group than in the LWMH group. Edoxaban and apixaban also demonstrated prophylactic efficacy similar to that of LWMH. However, bleeding events were observed at the same rate (apixaban) or at a higher rate (edoxaban and rivaroxaban) compared to the LWMH group. Developing safer anticoagulant drugs, such as factor XI inhibitors [15], which exert effective anticoagulant activity without exacerbating the bleeding risk, is highly anticipated.

Several risk assessment scores have been developed to predict VTE in patients with cancer. The Khorana Score was developed in 2008 [16], and it was calculated based on cancer type, platelet count, hemoglobin levels, leukocyte count, and body mass index to stratify cancer patients receiving chemotherapy according to their VTE risk. According to their score, patients were classified into low (0.3–0.8%; score 0), intermediate (1.8–2.0%; score 1–2),

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and high (6.7–7.1%; score > 3) VTE risk groups. Based on the Khorana Score, several modified scoring systems, such as the Vienna [17], PROTECHT [18], CONKO [19], and ONKOTEC scores [20], have been developed. Most studies assessing the utility of these scores have clarified that each score can be applied to certain types of cancer but not universally. The establishment of cancer-type-specific scoring systems based on specific biomarkers or characteristics may be needed for a more precise prediction of VTE.

In addition to treatment approaches and patient characteristics, cancer type and site have been regarded as major factors determining the risk of VTE in cancer patients. Cancer types can be broadly divided into three groups based on the VTE risk: high (pancreatic, ovarian, brain, stomach, gynecologic, and hematologic such as lymphoma and myeloma), intermediate (colon and lung), and low (breast and prostate) [21–26]. In the Khorana Score, stomach and pancreatic cancer were classified as high-risk malignancies. This implies that the mechanism of VTE differs between cancer types and that there may be cancer-type-specific VTE pathways. To characterize these pathways, several clinical studies have been performed in which various putative circulating biomarkers used to identify patients at a high risk of VTE were comprehensively measured.

In this review, the pathways proposed to contribute to VTE in cancer patients, that is, “the pathogenesis

of CAT,” are summarized, focusing on leukocytosis, neutrophil extracellular traps (NETs), tissue factor (TF), thrombocytosis, podoplanin (PDPN), plasminogen activator inhibitor-1 (PAI-1), the intrinsic coagulation pathway, and von Willebrand factor (VWF).

Leukocytosis

Leukocytosis is observed in 14–30% of patients with cancer [27–29], while a high white blood cell count before chemotherapy ($> 11 \times 10^9/\text{L}$) is a risk factor for VTE in the Khorana Score [16]. Among different types of cancer, leukocytosis is frequently observed in lung and colorectal cancer [27–29]. Leukocytosis has been associated with an increased risk of VTE in patients with cancer in several studies [16, 30, 31], which indicates the presence of a leukocyte-mediated pathway of thrombosis in this population (Fig. 1). Neutrophils and monocytes are considered responsible for leukocytosis-mediated VTE. Specifically, it has been postulated that neutrophils enhance thrombosis formation by generating neutrophil extracellular traps (NETs) [32], whereas monocytes express the procoagulant protein tissue factor (TF), resulting in the initiation of coagulation [33]. It was recently clarified that eosinophils also contribute to thrombosis through eosinophil extracellular traps (EETs)

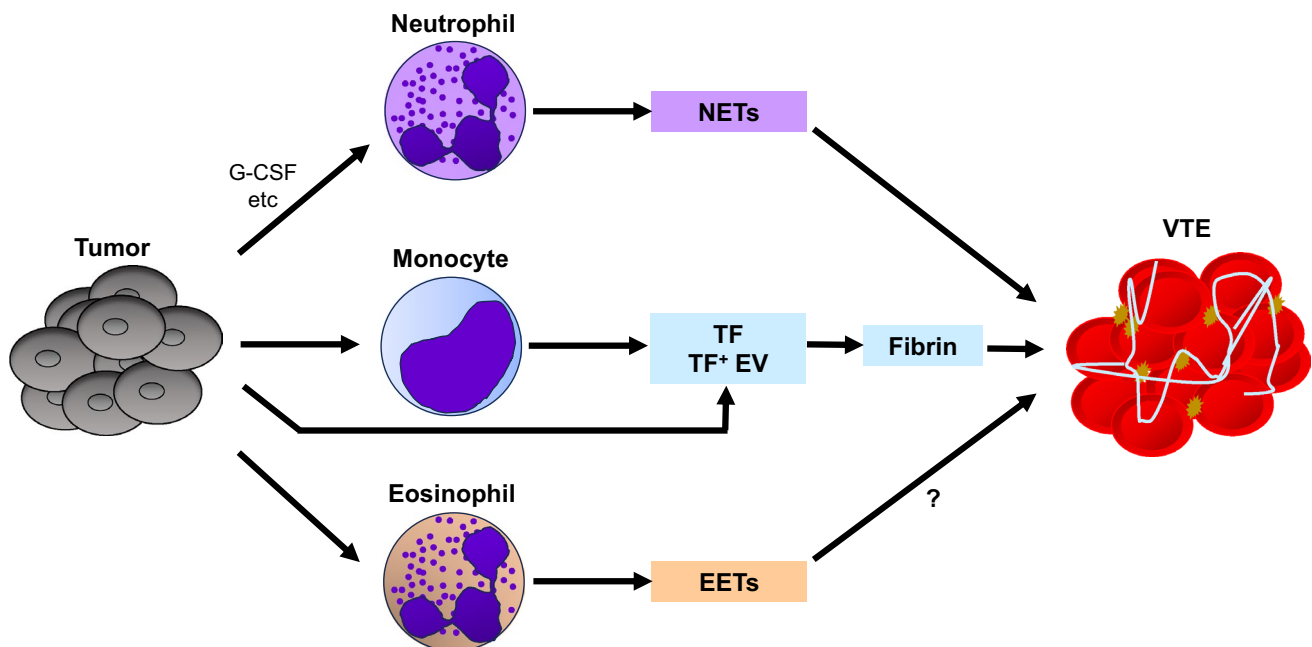


Fig. 1 Suggested pathways of leukocytes-mediated cancer-associated VTE. Tumors stimulate neutrophils and generated neutrophil extracellular traps (NETs) enhance thrombosis formation. Tumors induce tissue factor (TF) expression on monocytes, and TF expressed on monocytes or released as extracellular vesicles (EVs) initiate blood

coagulation leading to thrombosis formation. Certain types of cancer such as pancreatic cancer strongly express TF on the tumor cells and directly trigger blood coagulation. Eosinophils may also contribute to thrombosis formation through eosinophil extracellular traps (EETs) in certain types of cancer

[34] and that eosinophils may be involved in VTE in certain types of cancer.

Neutrophil extracellular traps (NETs)

NETs are released from activated neutrophils and are composed of extracellular chromatin fibers and antimicrobial proteins [32]. Although NETs help neutrophils kill bacteria and play an important role in the innate immune response, it was recently elucidated that they also trigger thrombosis by capturing circulating platelets and extracellular vesicles (EVs) [35–37]. NET formation and release are enhanced by various substances such as G-CSF [38]. Among the various biomarkers of NETs formation, citrullinated histone H3 (H3Cit) and H3Cit-DNA complexes are considered superior in terms of accuracy [39]. These biomarkers are increased in cancer patients compared with healthy controls [40–45]. Furthermore, a correlation between NETs formation biomarkers and thrombotic events has been shown in patients with cancer, especially pancreatic and lung cancer [46–48]. Additionally, NETs have been detected in thrombi of patients [41]. These findings suggest that NETs facilitate thrombosis in cancer patients and that their inhibition may be a treatment option for VTE prophylaxis in cancer patients with leukocytosis.

Tissue factor (TF)

TF is a glycoprotein receptor for factor VII (FVII) and activates FVII (FVIIa). The TF/FVIIa complex initiates the extrinsic coagulation pathway [49]. High TF expression has been observed in various types of cancer, such as pancreatic cancer, head and neck cancer, lung cancer, cervical cancer, prostate cancer, glioma, and leukemia [50–52]. Among these malignancies, association with VTE has been well studied in pancreatic cancer. Pancreatic cancer cells generally express high levels of TF, and their expression level correlates with histological grade [53]. TF expression level in pancreatic tumors correlates with VTE incidence [53]. Additionally, TF expressed in cancer cells can be released as extracellular vesicles (TF + EVs) [54–56], and plasma TF + EVs levels have been associated with VTE in pancreatic cancer in many studies [57–61]. These findings suggest that TF + EVs released from tumor cells into the circulation enhance thrombosis. Furthermore, TF + EV levels correlate with mortality in pancreatic cancer, thus addressing a potential biomarker for VTE onset and pancreatic cancer severity [59, 60]. Plasma TF + EVs levels are also increased in other types of cancer, including brain, lung, gastric, and breast cancer [59, 62, 63]. However, pancreatic cancer exhibits the highest levels of TF + EVs among various types of cancer

[59]. Plasma TF + EVs can be measured using antigen-based assays, such as ELISA and flow cytometry, or activity-based assays. The procoagulant activity of TF + EVs can be more precisely evaluated using activity-based assays in which the extent of TF-dependent factor Xa generation is calculated using an anti-TF antibody [58, 62, 64, 65].

Thrombocytosis

Thrombocytosis, an increase in platelets in peripheral blood, is observed in cancer patients, especially in ovarian, breast, gastrointestinal, and lung cancer [66]. Although platelets play a role in arterial thrombosis, they also contribute to venous thrombus formation in cancer patients (Fig. 2) [67, 68]. Increased platelet count is associated with an increased incidence of VTE in cancer patients [68–71]. Thrombocytosis before chemotherapy ($> 350 \times 10^9/L$) is a risk factor for VTE, according to the Khorana Score [16]. The mechanism of thrombocytosis in patients with cancer remains to be fully elucidated. Nevertheless, one study using mouse models of ovarian cancer suggested that tumor-derived IL-6 stimulates hepatic thrombopoietin synthesis, leading to platelet production [72]. Additionally, IL-6 levels and thrombocytosis were independent predictors of VTE in patients with ovarian clear cell carcinoma [73]. Several biomarkers of platelet activation, including soluble P-selectin, soluble CD40 ligand, thrombospondin 1, and platelet factor 4 (PF4), have been shown to increase in cancer patients [68]. However, few reports have demonstrated an association between these biomarkers and VTE incidence [74, 75]. One study found that increased serum PF4 levels are associated with a higher risk of VTE in pancreatic cancer [76]. Another study found that cancer patients with increased levels of soluble P-selectin exhibited a high rate of VTE [77]. Since it is expressed by endothelial cells and platelets, P-selectin expressed by both types of cells could enhance VTE by recruiting leukocytes. These findings suggest that antiplatelet drugs such as aspirin and clopidogrel may be useful for VTE prophylaxis in patients with certain types of cancer [50, 68, 78].

Podoplanin (PDPN)

PDPN is a transmembrane glycoprotein that binds the C-type lectin-like receptor 2 (CLEC-2) on platelets, leading to platelet aggregation [79]. PDPN is expressed by various types of cells, such as tumor cells, inflammatory macrophages, and cancer-associated fibroblasts, thereby contributing to cancer progression and metastasis [80, 81]. The association between PDPN expression in cancer cells and VTE has been extensively investigated in gliomas. A human glioblastoma cell line expressing PDPN induces

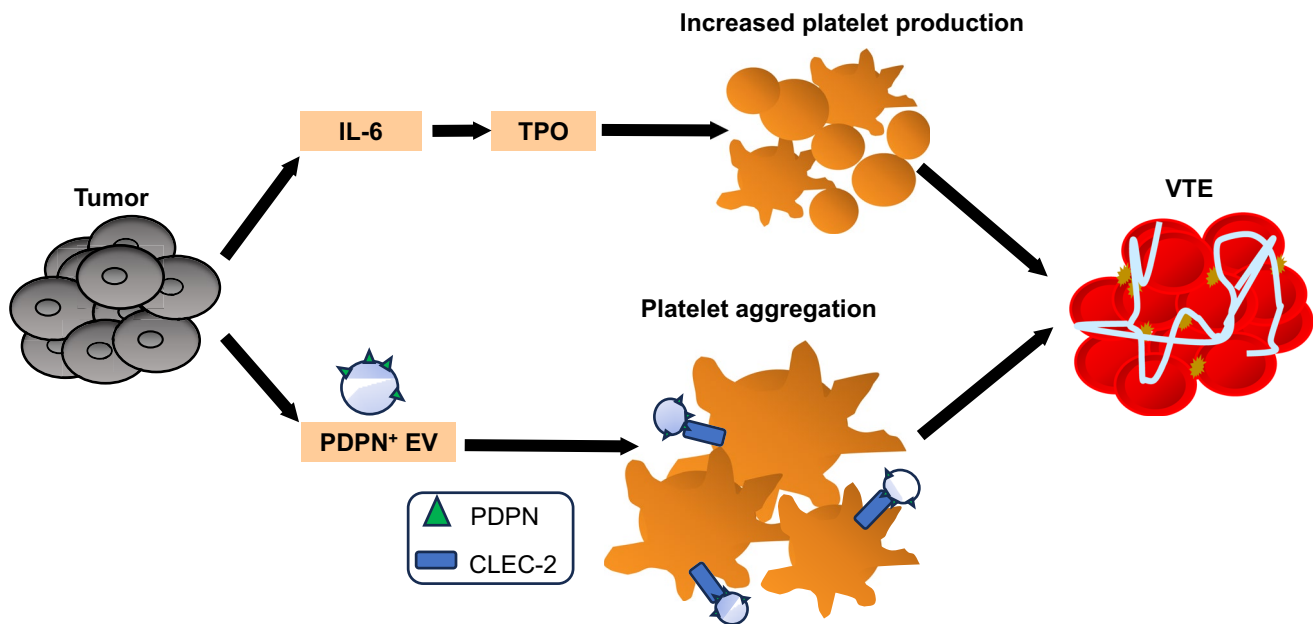


Fig. 2 Suggested pathways of platelet-mediated cancer-associated VTE. Tumor-derived interleukin-6 (IL-6) stimulated hepatic thrombopoietin (TPO) synthesis leading to platelet production and thrombosis formation. Certain types of tumors such as glioma express

podoplanin (PDPN) and the released PDPN-positive extracellular vesicles (EVs) bind to C-type lectin-like receptor 2 (CLEC-2) on platelets, leading to platelet aggregation and thrombosis formation

platelet aggregation in a CLEC-2-dependent manner [82]. PDPN expression is inversely correlated with survival rate of glioma patients [83]. Notably, PDPN protein expression level in tumor cells is associated with low platelet count and risk of VTE in glioma patients [84, 85]. These findings imply that PDPN induces platelet aggregation and consumption, resulting in a low platelet count concomitantly with VTE in patients with glioma. Since PDPN is released from cells in the form of EVs [86], it may induce platelet aggregation not only in cancer cells but also in the circulation.

Plasminogen activator inhibitor-1 (PAI-1)

PAI-1 is a serine protease inhibitor that inhibits plasminogen activators, including tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA), thereby reducing the generation of plasmin, resulting in hypofibrinolysis [87]. PAI-1 is primarily produced by endothelial cells. Plasma levels of PAI-1 are increased by endothelial injury, such as acute/chronic inflammatory diseases, and elevated levels of PAI-1 are associated with thrombosis [87, 88]. Patients with VTE demonstrate higher levels of active PAI-1 than controls [89]. Plasma PAI-1 levels are increased in different malignancies, such as melanoma, colorectal cancer, breast cancer, and pancreatic cancer [90–93]. Hisada et al. recently reported that high plasma PAI-1 activity is associated with VTE in patients with pancreatic cancer [94].

These results suggest that elevated levels of PAI-1 may contribute to VTE in patients with cancer and that drugs that inhibit PAI-1 function may be effective for VTE prophylaxis (Fig. 3). It is also important to clarify the origin of increased PAI-1 (tumor or host endothelium) and investigate the effect of PAI-1 inhibition on the tumor microenvironment [95].

Intrinsic coagulation pathway

In the intrinsic coagulation pathway, factor XII (FXII), activated by collagen, high-molecular-weight kininogen, and kallikrein, activates factor XI (FXI). Activated FXI further activates factor IX (FIX) and converts factor X (FX) to its active form in the presence of activated factor VIII (FVIIIa). Plasma levels of substances that can activate FXII, such as cell-free DNA, are increased in cancer patients. Cell-free DNA increases in cancer patients and tumor-bearing mice [38, 96–98]. Nickel et al. have reported that prostate cancer cells and secreted prostasomes expose long-chain polyphosphates on their surface and initiate coagulation in an FXII-dependent manner (Fig. 4) [99]. In this report, the deficiency of FXI, FXII, or high-molecular-weight kininogen but not plasma kallikrein protected mice from prostatic prostatic-induced thrombosis. Furthermore, targeting polyphosphate or factor XII ameliorates prostate cancer-driven thrombosis without increasing bleeding. Suppression of the intrinsic

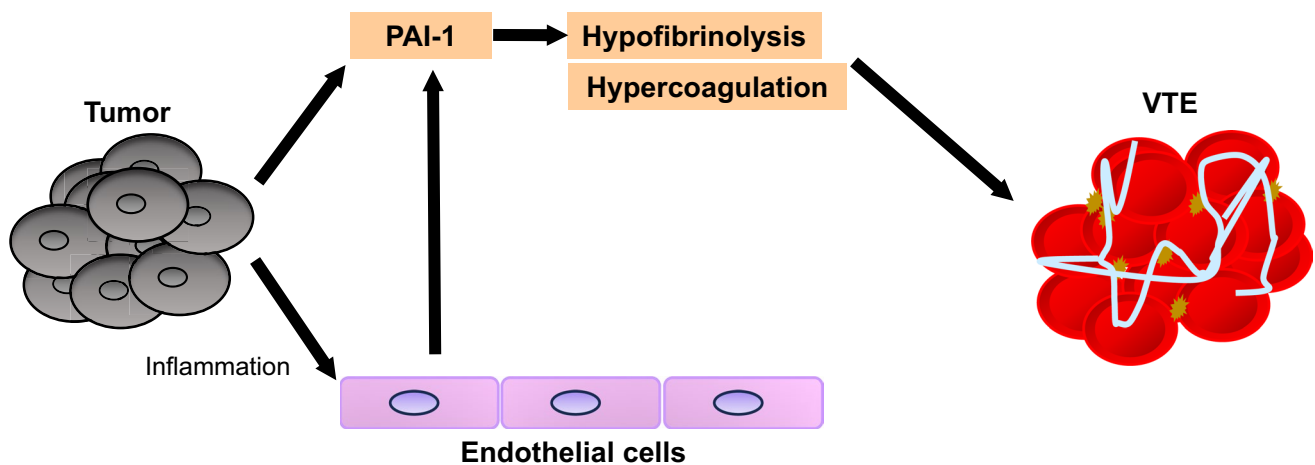


Fig. 3 Suggested pathways of hypofibrinolysis-mediated cancer-associated VTE. Tumor-derived plasminogen activator inhibitor-1 (PAI-1) inhibits plasminogen activators including tissue plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA) and therefore reduces the generation of plasmin, resulting in hypofibrinolysis.

This enhances clot strength leading to thrombosis formation. Tumor may enhance PAI-1 expressions of host endothelium via chronic inflammatory stimuli, leading to hypofibrinolysis

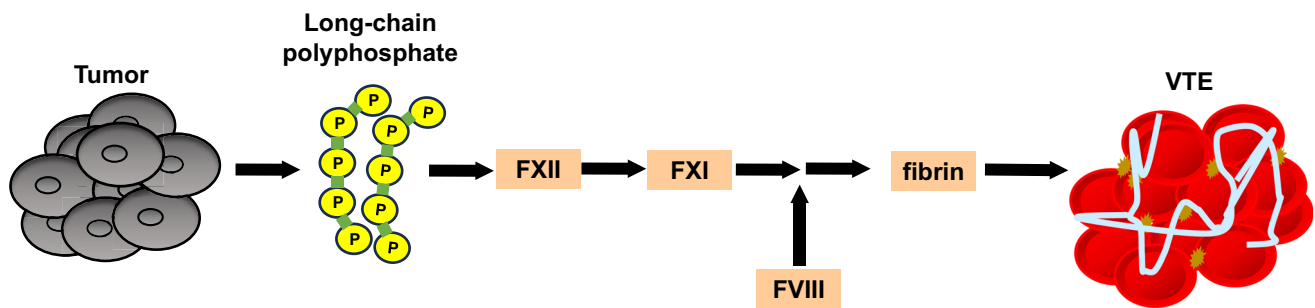


Fig. 4 Suggested pathways of intrinsic coagulation pathway-mediated cancer-associated VTE. Certain types of cancer cells produce long-chain polyphosphates which can activate factor XII (FXII). Activated

FXII further activates factor XI (FXI) and triggers the intrinsic coagulation pathway in the presence of activated factor VIII (FVIII), leading to thrombosis formation

coagulation cascade may be useful for VTE prophylaxis in certain types of cancer. Drugs targeting FXII or FXI are especially attractive because decreases in the plasma levels of these factors are not associated with increased bleeding risk. Additionally, high plasma level of FVIII is a risk factor for VTE in patients with cancer [100–102]. Gathering large-scale epidemiological data regarding the incidence of cancer in patients with hemophilia A and conducting preclinical studies using FVIII-deficient mice with cancer may clarify the precise association between FVIII and cancer-associated VTE.

Von Willebrand factor (VWF)

VWF is a large multimeric glycoprotein that plays an essential role in primary hemostasis [103]. VWF mediates platelet adhesion to the subendothelial collagen matrix and platelet interactions under high-shear conditions. VWF is synthesized in endothelial cells and megakaryocytes and stored in large multimeric forms in the Weibel–Palade bodies (WPB) of endothelial cells and alpha granules of platelets [104]. Besides hemostasis, VWF plays an important role in inflammation [105, 106]. Increased levels of plasma VWF have been documented in patients with cancer and are correlated with advanced cancer stage and poor

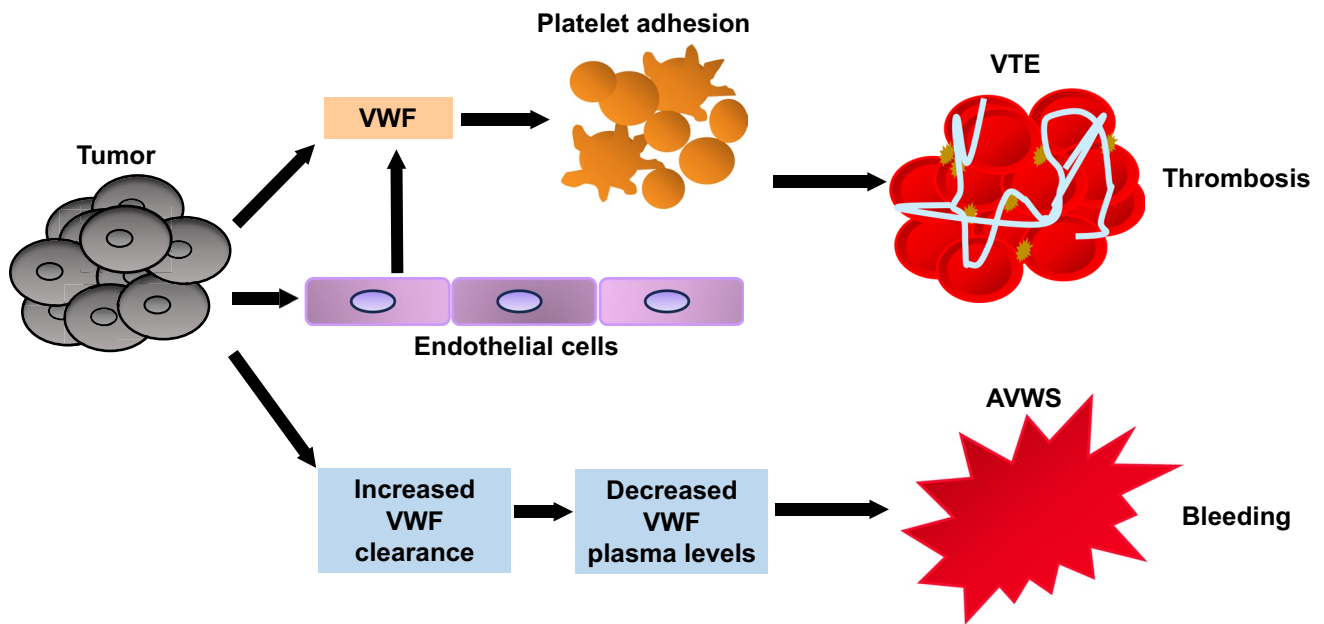


Fig. 5 Suggested pathways of VWF-mediated cancer-associated VTE and bleeding. Tumor cells induce endothelial cells to release von Willebrand factor (VWF); certain tumor cells have the capacity for de novo expression of VWF, increasing platelet adhesion and activation,

leading to thrombosis formation. VWF is also associated with severe bleeding in certain types of malignancy, called acquired von Willebrand syndrome (AVWS). In AVWS, increased VWF clearance from plasma and decreased VWF levels are observed

prognosis [107, 108]. Additionally, high plasma VWF levels are an independent risk factor for VTE in patients with cancer [109, 110]. Tumor cells can induce endothelial cells to release VWF; certain tumor cells have the capacity for de novo expression of VWF, thereby increasing thrombotic tendency (Fig. 5).

VWF is also associated with severe bleeding in certain malignancies, known as acquired von Willebrand syndrome (AVWS). In AVWS, reduced VWF activity increases the bleeding tendency. The mechanisms of cancer-associated AVWS are heterogenous but ultimately result in increased VWF clearance from plasma and decreased VWF levels (Fig. 5) [111]. Cancer is a major underlying cause of AVWS, and most AVWS cases occur in patients with hematological malignancies [112, 113]. Lymphoproliferative disorders are the most common causes of AVWS, accounting for approximately 50% of all AVWS cases [112]. VWF plays different roles depending on the type of cancer, and the use of chemotherapeutic drugs may compromise its regulation. A better understanding of the role of VWF in cancer will enhance the development of novel strategies for cancer treatment and VTE prophylaxis.

Conclusions

Multiple pathways leading to VTE in cancer patients have been postulated, and these pathways seem to differ between cancer types. Additionally, patient characteristics and chemotherapy may further modify coagulation status. The development of reliable, cancer-type-specific biomarkers for VTE prediction and evidence-based safe anticoagulants that confer a low risk of bleeding is necessary for the optimal management of cancer-associated thrombosis.

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Data availability The datasets generated in the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of interest KT is a member of Medicinal Biology of Thrombosis and Hemostasis established by Nara Medical University and Chugai Pharmaceutical Co., Ltd.

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