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Cancer progression and tumor hypercoagulability: a platelet perspective

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Abstract

Venous thromboembolism, which is common in cancer patients and accompanies or even precedes malignant tumors, is known as cancer-related thrombosis and is an important cause of cancer- associated death. At present, the exact etiology of the elevated incidence of venous thrombosis in cancer patients remains elusive. Platelets play a crucial role in blood coagulation, which is intimately linked to the development of arterial thrombosis. Additionally, platelets contribute to tumor progression and facilitate immune evasion by tumors. Tumor cells can interact with the coagulation system through various mechanisms, such as producing hemostatic proteins, activating platelets, and directly adhering to normal cells. The relationship between platelets and malignant tumors is also significant. In this review article, we will explore these connections.

Keywords Cancer · Platelets · Coagulation · VTE · PD-L1

Introduction

Cancer and cardiovascular disease are diseases with intricate pathophysiology and the most common causes of death; prevalence is steadily increasing worldwide [1, 2]. Although venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is common in the general population, it is especially common in cancer patients, and is accompanied by or can occur prior to malignant tumors [3]. Research indicates that the annual incidence rate of venous thromboembolism (VTE) in cancer patients is 0.5%, compared to 0.1% in the general population[4]. Active cancer accounts for 20% of the total VTE incidence [5, 6]. Furthermore, cancer-associated thrombosis (CAT) is a significant contributor to mortality in cancer patients [7, 8]. Compared with non-malignant tumor patients, cancer patients have a nine-fold increased risk of developing VTE [9]. The high incidence of VTE in cancer patients arises from a complex interplay between acquired and genetic factors that perturb the delicate balance of hemostasis, ultimately culminating in thrombosis [10]. In the general population, numerous genetic factors associated with VTE have been identified, including mutations in genes related to anticoagulation (SERPINC1, PROC, and PROS1), as well as various genetic polymorphisms [11]. Common factors contributing to the high incidence of VTE in cancer patients include advanced age, reduced mobility, and various cancer treatments such as surgery, radiotherapy, and chemotherapy. During the development of cancer, tumor cells release inflammatory cytokines and pro-angiogenic/procoagulant factors that stimulate stromal cells to express prothrombotic components, thereby promoting blood clotting [12, 13]. Table 1 provides a comprehensive overview of the factors that predisposed patients to thrombosis. Furthermore, cancer patients undergoing immune checkpoint therapy are highly susceptible to developing CAT and exhibit elevated mortality rates [14–16]. The inherent heterogeneity

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Table 1 Cancer and thrombosis risk factor overview [22–32]

Tumor related factors	
Cancer Type and Location	Certain cancers like pancreatic, stomach, and brain are more thrombogenic
Histological stage	Advanced stages often carry a higher risk
Stage of cancer	Patients of distant metastases usually carries a higher risk
Tumor Secretions	Some tumors release substances that increase coagulability
Patient-related factors	
Comorbidity	Conditions like obesity, cardiovascular disease, or previous thrombosis
Genetic Predispositions	Certain genetic mutations increase thrombosis risk
Age	Older patients generally have a higher risk
Varicose Veins	Can predispose to superficial venous thrombosis which may lead to deep vein thrombosis
Treatment related factors	
Surgical treatment	Surgical treatments increase the risk of thrombosis
Central Venous Catheters	Used for treatment can increase risk
Adjunct Therapies	Erythropoietin and Transfusions
Immobility	Due to hospitalization or illness can lead to stasis and clot formation
Pharmacological Interventions	Chemotherapy (e.g., thalidomide, platinum-based drugs)
Hormone Therapy	Altering blood clotting and hormone levels(e.g., tamoxifen)
Lifestyle and External Factors	
Smoking	Increases the risk of thrombosis
Nutrition	Poor diet may contribute to higher risk
Physical Activity	Sedentary lifestyle can increase risk

and biological characteristics of tumors may also contribute to an increased susceptibility to VTE [17], such as glioblastoma multiforme (GBM), pancreatic cancer, gastric cancer, and lung cancer carry a significantly higher risk of VTE due to the unique tumor mechanism that induces a hypercoagulable state in the body [18]. VTE is an independent predictor of reduced survival in cancer patients, meaning that the presence of VTE may indicate tumor progression, tumor treatment failure, and some underlying cancers [14, 19–21]. Gene mutations in tumor cells, particularly those affecting TP53, KRAS, EGFR, PTEN and IDH1 genes, can have an impact on hemostasis by inducing the expression of tumor tissue factor (TF) and vascular endothelial growth factor (VEGF), as well as promoting thrombosis through the release of pro-inflammatory cytokines and extracellular vesicles [13].

Platelets are enucleated cells released from the membrane processes of mature megakaryocytes (pro-platelets), which contribute to the formation of clots and, if maladjusted, may lead to thrombosis [33]. With the development of platelet biology, we have a new understanding of platelet formation, function, and signaling (Fig. 1). Despite numerous hypotheses, the etiology underlying the high prevalence of venous thrombosis in cancer patients remains uncertain. Tumor cells can interact with the hemostatic system in a myriad of ways, including the production of hemostatic proteins such as TF and thrombin, activation of platelets, and direct adhesion to normal cells like endothelial cells, monocytes, and platelets [34, 35]. In this review, our objective is to provide a concise overview of the pivotal role that platelets play in hemostasis and thrombosis, as well as to examine the intricate interplay between tumors and platelets, the current state of research, and the possibility of future treatment of tumors.

Tumor progression with platelet aggregation and activation

While platelets can have a positive impact on the behavior of cancer cells, the physiology and phenotype of platelets are also subject to influence by tumor cells [36]. In fact, several studies have revealed that tumor cells can regulate the RNA profile, number, and functionality of platelets. Cancer patients often exhibit activated clotting pathways that lead to a four-fold increased risk of thrombosis [37]. Professors Levin and Conley found that at least 40% of their hospitalized cancer patients had thrombocytosis [38]. Since then, a growing number of studies have reported a significant link between thrombocytosis and solid tumors, with a prevalence of 4–55% at the time of initial diagnosis [39–42]. As described in a review study of 3,654 patients with stage I-III breast cancer, 6.5% of these patients were diagnosed with inflammatory breast cancer (IBC), this study concluded that thrombocytosis, which is more prevalent in IBC patients, was associated with lower overall survival in these subjects, but not in non-IBC patients

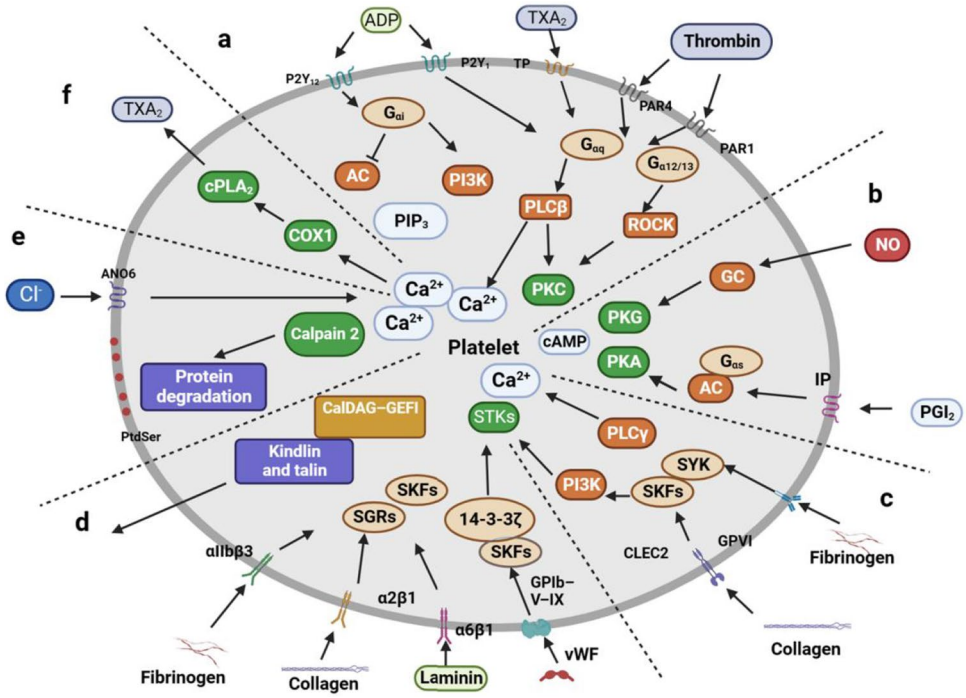

Fig. 1 Main signal events and responses in the process of platelet activation (**a**) The release of ADP and thromboxane A2(TXA2) activates purine receptors P2Y12, P2Y1, TXA2 receptors (TP) and platelet activation. P2Y12 inhibits AC but stimulates phosphoinositide 3 kinase (PI3Ks) via GαI protein. The P2Y1 and TP signals activate the GαQ protein, which stimulates phospholipase C β (PLC β) to release Ca2 + into the cytoplasm, leading to protein kinase C (PKC) activation and downstream signaling events. The TP receptor also activates Gα12 and 13 proteins, leading to the activation of rho-associated protein kinase (ROCK) and contributing to platelet shape change and diffusion.thrombin activates platelets by binding to GαQ-coupled receptors PAR1 and PAR4. **b** Platelet inhibition is achieved through nitric oxide (NO) and prostaglandin I2 (PGI2) IP receptor-mediated activation of guanylate cyclase (GC) and adenylate cyclase (AC), leading to protein kinase G (PKG) and protein kinase A (PKA) activation. **c** Enhance platelet activation. GPVI and type c lectin-like receptor 2 (CLEC2) induce strong signals through the protein tyrosine kinase pathway, resulting in the release of Ca2 + into the cytoplasm. **d** Platelet activation is initiated by the interaction between adhesion receptors (integrin α6β1, α2β1, αIIbβ3 and glycoprotein Ib-V-IX complex) and their ligands, such as collagen and von Willebrand factor. This involves signal transduction through small G protein regulators (SGRs), src family kinases (SFKs) and serine/threonine protein kinases (STKs).The conformational changes of integrins, such as αIIbβ3, involve a pathway downstream of PLC, PKC and PI3K that leads from low to high affinity. This pathway includes CalDAG-GEFI (a guanosine nucleotide exchange factor regulated by Ca2 + and diacylglycerol), SGRs (RAS3A and RAP1B), as well as signaling molecules connected to the cytoskeleton (kindlin and talin subtypes). **e** Platelet membrane swelling and exposure of phosphatidylserine (PtdSer) occur through high Ca2 + mobilization agonists mediated by the ion channel anooctamin6 (ANO6), while calpain-2 mediates intracellular protein degradation. **f** The activation of Ca2 + -dependent and protein kinase-dependent cytoplasmic phospholipase A2 (cPLA2) and cyclooxygenase 1 (COX1) mediates the release of TXA2

[43]. Tumor cells have the ability to increase thrombin production through direct and indirect mechanisms. To proliferate and foster metastasis, these cells concurrently manipulate platelet behavior by enhancing the synthesis and/or secretion of various compounds that incite platelet activation and aggregation [44–46]. The initial observation that tumor cells can induce platelet activation is based on a co-culture system, wherein tumor-induced platelet aggregation (TCIPA) is mitigated following the introduction of direct thrombin inhibitors[47]. Despite TCIPA being characterized by a heightened platelet count and conventional platelet activation, contemporary studies have demonstrated alterations in platelet derivatives within cancer patients. It's been discovered that EGFRvIII-mRNA can be isolated from the platelets of glioma patients, and PCA3-mRNA resides in the platelets of those with prostate cancer [48]. Furthermore, aberrant fusions of specific EML4-ALK genes have been detected in the platelets of patients suffering from non-small cell lung cancer [49]. Dysexpression of platelet protein can also be used as a diagnostic marker and prognostic factor. It has been reported that platelet concentrations of vascular endothelial growth factor (VEGF) are higher in cancer patients than in healthy individuals, including lung cancer patients [50, 51], Liver Cancer [52, 53] and colorectal cancer [54]. Furthermore, malignant tumor cells exhibit heightened thrombin production compared to benign tumors, underscoring thrombin's role as a potent platelet activator with significant pro-coagulant attributes [55]. Previous research has also indicated that the rise in thrombin levels is related

to the tumor's location, with lung cancer demonstrating a more significant increase compared to brain and pancreatic cancers [56]. Previous research has demonstrated that TF plays a crucial role in initiating platelet activation and aggregation, with TF being expressed on the cell membranes of various cancer cells [57]. Extracellular vesicles (EVs), a diverse collection of cell-derived membrane structures including exosomes, microvesicles, and apoptotic bodies, are released by cells and significantly contribute to blood coagulation, thereby facilitating the direct generation of thrombin in cancer patients. Numerous studies have identified that EVs can express TF, linking it to thrombin production across different types of cancer [58]. Furthermore, activated host cells, such as monocytes and cancer cells, can release EVs that bear transferrin on their surface, further enhancing platelet activation [59–61]. Infact, it is reported that transferrin potentiates thrombin/FXIIa and blocks AT's inactivation effect on coagulation proteases inducing activation coagulation and platelet[62]. EVs are also exposed to negatively charged phospholipids, such as phosphatidyl serine (PS), on adventitia lobules [63], is an effective substance to promote coagulation. Circulating TF and EVs are good biomarkers of thrombosis and disseminated intravascular coagulation (DIC) in different diseases [64, 65].

Mechanisms of cancer-induced coagulation

Platelets are closely related to the blood hypercoagulable state, which is an important cause of cancer-related venous thrombosis and and tumors may affect the blood hypercoagulable state in many ways [66]. Existing studies have found that, tumor-derived G-CSF induces neutrophilia, triggering NET release and promoting thrombosis in murine model[67] and tumor-derived IL-6 induces thrombopoietin (TPO) expression in hepatocytes, and cancer cells have the ability to generate thrombin as well, promoting thrombosis and increasing the risk of thrombotic events in cancer patients[68–70]. Studies have found that about 5% of patients with idiopathic venous thromboembolism show latent malignant tumors, which are found within one year after the diagnosis of venous thromboembolism [71]. Previous studies have shown that 10%–57% of cancer patients have a high platelet count, which is associated with a poor prognosis [72]. Many cancer types, such as adenocarcinoma, ovarian cancer, brain cancer, gastric cancer, colon cancer, and lung cancer, have a higher risk of developing VTE, while in cancer types such as breast and prostate cancer, the risk of VTE is lower, indicating that there may be specific VTE pathways in different cancer types (Table 2). Additionally, cancer patients often exhibit a hypercoagulable state at the time of diagnosis, with a higher prevalence

Table 2 Primary Thrombogenic Mechanisms in various cancer types

Tumor type	Primary Thrombogenic Mechanisms	Reference
Lung	Neutrophils and neutrophil extracellular traps (NETs), Leukocytosis	[80–82]
Ovary	Thrombocytopenia	[70, 83–85]
Brain	$PDPN1^+$ MVs	[86, 87]
Colorectum	Leukocytosis	[88–93]
Pancreas	$TF1^+$ MVs	[61, 94–96]

of certain prothrombotic gene mutations compared to the general population [73, 74]. This suggests a strong correlation between blood status and tumor growth, with potential implications for the role of blood coagulation gene polymorphisms in cancer development. Upon activation of prothrombin, thrombin is generated, which subsequently triggers fibrinogenesis and platelet activation to maintain hemostasis. In addition to its hemostatic function, thrombin, especially through its interaction with the receptor PAR1, is also thought to affect key mechanisms of tumor initiation, including cell survival, proliferation, and adhesion [75, 76]. Previous studies have found that F7rs510317A alleles are associated with an increased risk of breast cancer [77]. This allele is also linked to an elevation in the levels of FVII, the activating enzyme in the exogenous coagulation pathway, within circulation [78, 79].

As mentioned earlier, cancer patients with VTE have a more aggressive underlying cancer phenotype, disease progression, and treatment failure, and tumors may affect the blood hypercoagulable state in many ways (Fig. 2). Platelets play a crucial role in coagulation, indicating their close association with tumor progression. Markers of platelet activation and coagulation have been identified in primary tumor tissues [97].

FVII is structurally expressed in cancer cells under hypoxic conditions, and forms a complex with TF (TF/FVIIa) to enhance blood clotting activity. FX plays a pivotal role in both endogenous and exogenous coagulation pathways. Tumor cells produce a thrombin called a cancer coagulant, which activates FX [98]. Tissue factor pathway inhibitor (TFPI) is known to modulate the activity of transferrin, which triggers the exogenous coagulation pathway and represents the most extensively studied coagulation factor in the context of malignant tumors [99, 100]. TF is the center of current thrombosis models: exposed when injured. Following oncogene induction, expression of TF in tumor tissue is related to cell survival, proliferation, invasion, angiogenesis, and metastasis, and generally related to poor prognosis in different tumor types. As previously mentioned, TF interacts with plasma coagulation factors to facilitate the generation of thrombin, which exerts pleiotropic effects on various cellular processes. Thrombin

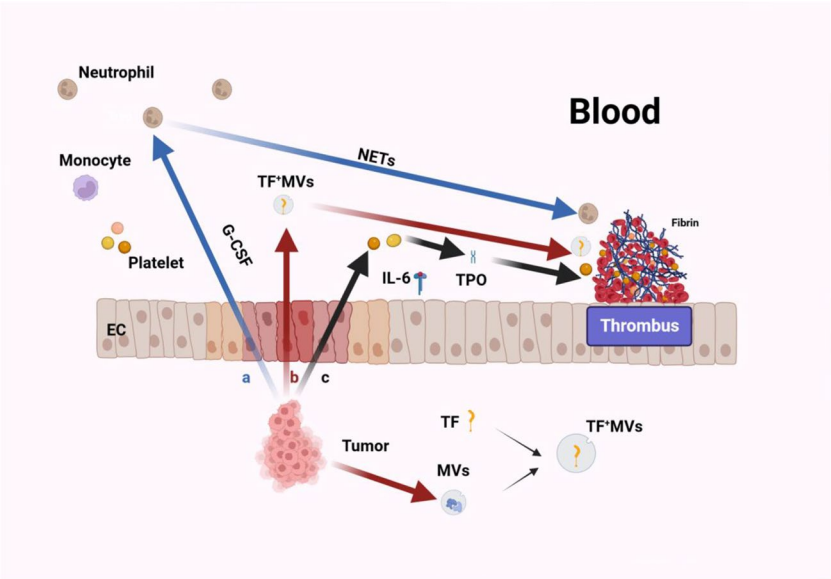

Fig. 2 Partial pathways of tumor affecting thrombosis (**a**) Tumor-derived G-CSF induces neutrophilia, triggering NET release and promoting thrombosis. **b** Tumor cells release $TF1^{+}$MVs, causing thrombosis in tumor patients through circulation. **c** Tumor-derived IL-6 induces TPO expression in hepatocytes, promoting thrombosis and increasing the risk of thrombotic events in cancer patients

contributes to thrombosis by cleaving fibrinogen and activating protease activated receptors (PARs), which mediate a variety of cellular effects. However, when considering the biological function of the thrombin-PAR axis, it remains challenging to determine how this pathway specifically contributes to both blood coagulation and tumor progression. Studies have demonstrated that thrombin activates human platelets via PAR-1 and PAR-4, leading to the secretion of a diverse array of molecules, which facilitates the formation of thrombus [101, 102].

In cancer, transferrin is often structurally overexpressed and can act locally or remotely, and is carried by tumor-derived extracellular vesicles and released into the circulation [18]. In tumor tissue, blood coagulation can be activated by destruction of the blood vessel wall, leading to bleeding and intravascular coagulation, or extravascular coagulation due to increased vascular permeability and plasma extravasation [103]. In addition, the entry of metastatic cancer cells into the circulation and the recruitment/activation of inflammatory cells (immune thrombosis) may further amplify these processes.

Some biomarkers have been shown to be associated with the occurrence of VTE in cancer (Table 3). Parameters such as increased white blood cell and platelet count and decreased hemoglobin have been shown to be good predictors of the risk of venous thromboembolism in cancer patients. In addition, the increased concentrations of prothrombin fragments 1–2, soluble P-selectin, coagulation factor VIII, and D-dimer are closely bound up with an increased incidence of cancer VTE. In an extensive synthesis of eighteen studies incorporating thirty-six biomarkers, D-dimer levels and epidermal growth factor receptor (EGFR) mutations emerged as the paramount predictors for thromboembolic incidents.[104].

Role of platelets in cancer-related thrombosis

The role of platelets in CAT is increasingly recognized. Platelet-cancer cell interactions are involved in the regulation of cancer-associated thrombosis [110]. A noteworthy

Table 3 Selected biomarkers of coagulation / fibrinolysis and their relationship with hemostasis[61, 105–109]

Marker	Link to coagulation
Determination of thrombin production by specific substrate	Thrombin activity
Thrombin-antithrombin (TAT) complex	
Prothrombin 1–2 fragment (F1 + 2)	
$TF+^{ve}$ microparticles	
D-dimar	Fibrin degradation products
Soluble P-selectin	Biomarkers of platelet activation
Citrulline histone H3	Biomarkers of NETosis

clinical study has shown that patients with high-grade gliomas (HGGs) who exhibit a low platelet count — accounting for 25% of the participants — are at a heightened risk for VTE [86]. This discovery is particularly surprising when contrasted with the commonly observed phenomenon of elevated platelet counts in patients with solid tumors, suggesting a unique aspect of HGG biology. Moreover, the expression of P-selectin on the surface of activated platelets, and its release as soluble P-selectin into the circulation, has been identified as a contributory factor in thrombosis development [111–113]. Elevated levels of P-selectin might result in decreased platelet counts due to its role in augmenting platelet adhesion, potentially leading to enhanced platelet consumption [114, 115]. This theory is corroborated by the observation of increased soluble P-selectin levels in individuals with conditions that lead to platelet depletion before thrombotic events, such as disseminated intravascular coagulation, heparin-induced thrombocytopenia, and thrombotic thrombocytopenic purpura (TTP) [116]. Furthermore, the formation of nodules targeted by prothrombin activity is noted in specific pathological conditions characterized by extensive coagulation activity, including VTE in ovarian cancer [117], highlighting the involvement of podoplanin (PDPN) [87, 118]. PDPN induces platelet aggregation in a CLEC-2-dependent manner within human glioblastoma cells (LN319) [119], and PDPN expression is negatively correlated with platelet count, but positively correlated with D-dimer level [87]. These findings suggest that tumors may release PDPN1-containing microvesicles, which can activate circulating platelets and lead to an increased risk of venous thromboembolism in cancer patients (Fig. 2).

Activated platelets interact with the coagulation system directly or indirectly through MPs or secretory factors. Once activated, expression of anionic phospholipids on the procoagulant surface is involved in thrombin production, fibrin formation, and clotting [120]. In addition, the interaction between platelets and neutrophils leads to the formation of NETs. NETs can be formed without infection, such as in cancer and autoimmunity, and can promote thrombosis [121]. Activated platelets are involved in cancer-related thrombosis by providing procoagulant surfaces, releasing inflammatory molecules, and interacting with monocytes and neutrophils [120].

In cancer patients, platelets play a crucial role not only in the development of arterial thrombosis but also significantly contribute to venous thrombosis [122, 123]. Thrombocytosis is common in cancer patients, especially in gastrointestinal, lung, breast, and ovarian cancer [104]. Previous studies have found that individuals with elevated platelet counts prior to cancer diagnosis have a higher frequency of VTE compared to individuals with lower platelet counts [83], and similar results were observed when measuring platelet counts in cancer patients [84, 85]. The reduction of VTE in patients with multiple myeloma who are treated with thalidomide or lenalidomide and low-dose aspirin is comparable to that achieved by low molecular weight heparin, indicating the involvement of platelets in VTE development among these patients [124]. In addition, use of aspirin was associated with reduced edge of venous thromboembolism in patients with ovarian cancer, but not in patients with breast cancer [125, 126]. Many studies have measured the biomarkers of platelet activating factor [123]. In general, these biomarkers are increased in cancer patients, but only a limited number of studies have determined whether they can predict venous thromboembolism in this group of patients. A recent study failed to find a link between various platelet activation markers, including PF4 and VTE, in patients with various cancer types [127]. However, a pancreatic cancer study found that increased PF4 levels were associated with an approximately three-fold increase in VTE risk [128]. This disparity highlights the significance of examining distinct cancer categories.

The role of platelets in thrombosis has also been investigated in murine cancer models. A study employing a syngeneic orthotopic model of pancreatic cancer has demonstrated that clopidogrel can mitigate the binding of tumor-derived microvesicles to sites of thrombosis [129]. We have observed that TF1 microvesicles are capable of activating platelets via thrombin, while clopidogrel can effectively mitigate the augmented effect of exogenous TF1 microvesicles on thrombosis in murine models [130]. Collectively, these fundamental and clinical investigations propose that the administration of antiplatelet agents may serve as a preventive measure against venous thromboembolism in select cancer patients [123].

Numerous platelet receptors and signaling pathways, in addition to the release of platelet agonists by malignant cells, are implicated in TCIPA [131–133]. At the same time, the specific mechanism of platelet aggregation in malignant tumor cells is related to the type of cancer cell [132]. Several cancer cell lines, including melanoma, are capable of producing ADP [133], glioblastoma [134], breast cancer [135, 136], lung cancer [137], pancreatic ductal adenocarcinoma [138], and TCIPA induced by fibrosarcoma [137]. The activation of the P2Y12 receptor initiates a positive feedback mechanism in ADP-induced platelet activation, leading to the release of more ADP, ATP, and calcium from dense granules [139]. In human MCF-7 breast cancer cells, the reduction of ADP levels and the inhibition of the ADP receptor P2Y12 were found to diminish platelet activation and aggregation [136].

Platelets in the tumor microenvironment and interaction with PD-L1

Further clinical retrospective studies provide additional evidence that platelets present in the TME contribute to chemotherapy resistance and are associated with early disease

recurrence and poor survival outcomes [140]. GPIbα platelet markers were detected in 59% of HER2-negative breast cancer biopsies and were significantly associated with reduced efficacy of neoadjuvant therapy. Circulating platelets are not mere pliable sacs summoned by VWF to impede damaged blood vessels and avert hemorrhage [141]. Platelets indeed express PD-L1, which facilitates direct interaction with T cells and may have an impact on the efficacy of immune checkpoint therapy [142]. Studies have shown that the proliferation and activity of T cells bound to platelets decreased [143]. This may be linked to the significantly reduced efficacy of immune checkpoint therapy utilizing PD-1 antibodies, indicating the direct involvement of platelets in cancer-related immune evasion. In addition to the aforementioned tumor-promoting effects, there is compelling evidence that thrombin cleaves platelet glycoprotein A (GARP) repeats, resulting in the liberation of TGF-β derived from platelets [144, 145]. Activated platelets can also trigger innate immune responses by recruiting neutrophils and inducing reticulocytosis, thereby unleashing a cascade of physiological events [146]. Neutrophils can block the function of cytotoxic T cells through the expression of inducible nitric oxide synthase (iNOS) and production of nitric oxide (NO) [147]. In addition, the presence of PD-L1 on neutrophils is associated with initiating T cell apoptosis through interference induced activation of T cells and subsequent interaction with PD-1 [148].

Tumor patients exhibiting a procoagulant state, who subsequently develop CAT, manifest significant tumor progression, limited treatment efficacy and poor overall survival. Current evidence from in vitro and in vivo studies suggests that the procoagulant environment not only facilitates tumor immune evasion but also impedes immunotherapeutic interventions. Revealing the intricate mechanisms by which endothelial cells orchestrate inflammation and thrombosis is pivotal in devising innovative strategies to augment the potency of immune checkpoint inhibition and targeted therapy (Fig. 3). A combined approach targeting both tumor-mediated coagulation and tumor-induced immune evasion

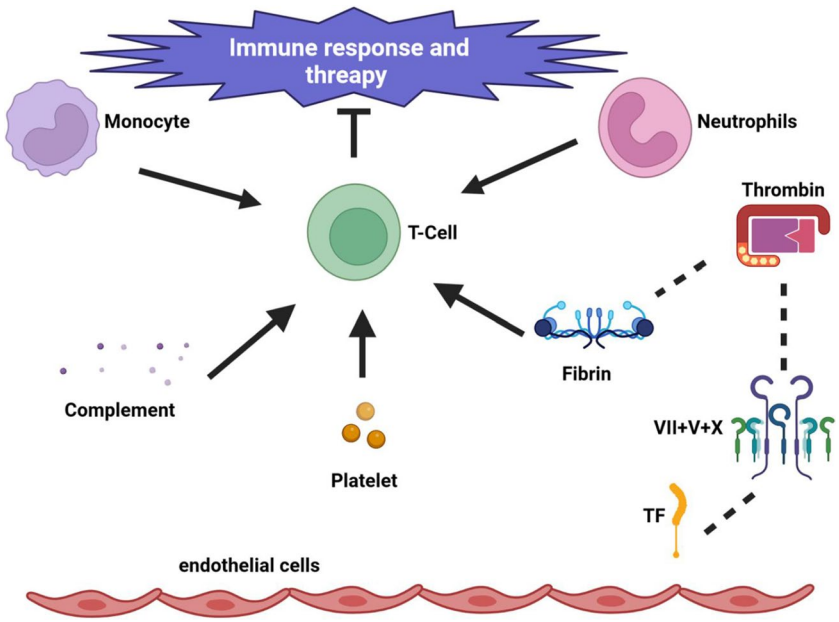

Fig. 3 Interaction between cancer-associated immune thrombosis and immune checkpoint inhibition Immune thrombosis associated with cancer is formed by the interaction of a variety of cells. Activation of plasma coagulation and complement factor, as well as TF released by endothelial cells, platelets, monocytes and neutrophils can modify T cell responses in relation to immune checkpoint inhibition

Table 4 Immune thrombosis inhibitors

Medicine	Targets		Reference
M7824	Fusion protein against PD-L1 and TGF- β	Cancer	[151]
Caplacizumab	Nano-body antagonizes VWF A1 domain	Thrombocytopenic purpura (TTP)	[149, 152]
Eculizumab	Anti-C5 monoclonal antibody	Atypical haemolytic uraemic syndrome(aHUS); Paroxysmal nocturnal hemoglobinuria (PNH)	[153, 154]
IPH5401	Anti-C5a receptor antibody	Cancer	[155]
Recombinant ADAMTS13	Cutting and inactivating VWF	TTP	[156]
Low molecular weight heparin(LMWH)	Activate antithrombin III and inhibit thrombin activation	Venous thromboembolism; Cancer	[157]

has been postulated to potentially bestow clinical benefits upon cancer patients. In view of the intricacy of the tumor microenvironment, targeted therapies aimed at specific pathways may augment response rates and ameliorate adverse effects (Table 4). Inhibition of the hypercoagulable state can be accomplished by administering anti-VWF nanoparticles that obstruct the A1 domain, thereby impeding VWF-mediated platelet binding. Alternatively, recombinant disintegrin and metalloproteinase member 13 (ADAMTS13) with thrombin reactive protein type 1 motif can cleave and inactivate VWF to provide a therapeutic option for supporting immune checkpoint inhibition [149]. In addition, the investigation of platelet mRNA analysis or detection of cancer cell activation induced by platelets is also being explored for diagnostic and monitoring purposes related to tumor development [150].

Therapeutic perspectives targeting tumor progression

Platelets are critical not only for hemostasis and coagulation but also, as extensive research has shown, in tumor progression, including aspects like invasion and exosmosis, closely linking them to CAT. This means that this property of platelets could be used for anti-tumor therapy. Integrin αIIbβ3, which is highly expressed in platelets and their progenitors, plays a pivotal role in platelet function, hemostasis, and arterial thrombosis, as well as in tumor progression, including cell proliferation and metastasis [158]. The binding of abciximab to integrin αIIbβ3 creates steric hindrance, preventing fibrinogen and other ligands from interacting with the integrin, thus interfering with platelet aggregation and thrombosis [159]. Caplacizumab, a humanized immunoglobulin fragment, specifically targets the A1 domain of vWF, disrupting the interaction between vWF and the platelet receptor GP1b- α [160]. This action prevents platelet adhesion, a critical step in the formation of microvascular thrombosis, and has been shown to normalize platelet counts in preclinical studies [160, 161]. Currently approved for the treatment of acquired TTP [162–164], but there is no relevant research in the field of cancer. The combination of antitumor drugs with Caplacizumab may be a potential treatment to reduce the occurrence of CAT and improve the prognosis of tumor patients, which needs further research to prove. Whilding et al. constructed αVβ3 specific CAR T cells and evaluated their antitumor function in vitro and in vivo preclinical models. These αVβ3-CAR T cells rapidly and specifically targeted αvβ3-positive tumor cells, secreting IFN-γ and IL-2. In a mouse xenograft model of metastatic A-375 melanoma, the intervention led to the complete eradication of melanoma lesions and long-term tumor-free survival. Integrins are also used to generate specific, controllable, and improved cytotoxicity of CAR-T therapies [165]. These studies illustrate the potential of the integrin family in anti-cancer and prevention of CAT.

Targeted drug delivery has become a new therapeutic strategy for cancer treatment. The tumor microenvironment is highly acidic compared to normal tissues, so Ph-sensitive nanosystems have been developed based on this difference. Drug release is activated in response to the acidic microenvironment and can enhance the therapeutic effects of cancer therapy. Crucially, platelets present promising avenues for targeted drug delivery. Nanocarriers can be engineered with peptides, enzymes, and antibodies [166]. For instance, a dual-targeted delivery system, consisting of paclitaxel-supported PEGylated-polylactic acid nanoparticles and cyclic peptides, is designed to selectively bind to the platelet-derived PDGF/PDGβ, offering improved treatment options for multiple myeloma [167].

Liposomes have been extensively studied as drug delivery systems, and many liposomal nanomedicines have been approved for clinical use [168]. Exosomes, which are biological extracellular vesicles, transmit signals through ligands or adhesion molecules on their membranes and have shown significant potential for targeted cancer drug delivery due to their origin from tumor cells [169]. Additionally, virus simulation systems are being developed for cancer diagnosis and targeted therapy. These systems mimic viruses in structure but lack genetic material, allowing them to be ingested by host cells without causing infection. Importantly, nanocarriers can be functionalized with small molecules, aptamers, and antibodies that possess high specificity and affinity [168]. There's growing evidence that these platelet-targeted drug delivery systems can enhance the efficacy of cancer treatments while minimizing potential side effects.

Conclusion and future prospects

Cancer-related venous thromboembolism is a well-known disease, but little is known about the potential biological mechanism of linking tumors to thrombosis [170]. Platelets play an important role in the process of blood coagulation. From a clinical point of view, platelet therapy may reduce the incidence of CAT and the rate of tumor progression. The use of some antiplatelet drugs may have a certain effect on the treatment of tumors (Table 5). Patient-related factors (including acquired and genetic determinants), cancer biology, and antineoplastic therapy are thought to play a synergistic role in venous thrombosis [11]. It is worth noting that the hemostatic system in cancer patients not only causes thrombosis, but also contributes to the growth and spread of tumors, suggesting cancer-related coagulation disorders may not be an accidental phenomenon [171].

In view of the adverse effects of venous thromboembolization on the prognosis of patients, disease prevention in cancer patients is important. It has been difficult to identify

Table 5 Commonly used and potential antiplatelet drugs [172–177]

Target	Drugs	Inhibition mechanism	Platelet function testing
Current target			
COX1	Aspirin and NSAIDs	Block the formation of TXA2 (autocrine)	LTA, PFA-100
P2Y12	Clopidogrel and prasugrel	Irreversible inhibition of ADP receptor (autocrine)	LTA, PAGT, VP
	ticagrelor	Reversible inhibition of ADP receptor (autocrine)	LTA, PAGT, VP
Integrin αIIbβ3	Abciximab, eptifibatide and tirofiban	Inhibition of integrin αIIbβ3 aggregation	LTA, PAGT
PAR1	Vorapaxar	Block thrombin receptor	LTA, PAGT
Potential target			
Factor Xa or thrombin		Inhibition of coagulation	TEM, Blood clotting test
GPIb-V–IX		Hinder vWF adhesion	PFA-100, microfluidics
GPVI and CLEC2	revacept	Block ITAM-like signal receptor	LTA, microfluidics
PI3Kβ and PDI		Inhibition of integrin αIIbβ3 aggregation	LTA, microfluidics
PAR1 and PAR4	pepducins	Block thrombin receptor	LTA, PAGT

LTA light transmission aggregometry, *PDI* protein disulfide isomerase, *TEM* thrombo-elastometry, *TKI* tyrosine kinase inhibitor, *VP* VASP phosphorylation, *PAGT* platelet aggregation test

coagulation and fibrinolysis biomarkers. There is a strong correlation between TF and primary tumor types, while fibrinolysis is more closely related to the cellular composition of the TME [178], which requires exploration of the kinetics of coagulation and fibrinolysis simultaneously [8]. It was recently reported that longitudinal evaluation of D-dimer significantly improved the estimation of VTE risk in cancer patients [179]. Functional analysis of thrombin production is also used in the early diagnosis of postoperative recurrence of breast cancer [180]. Because studies in the general population have shown that venous thromboembolism is hereditary, genetic markers, especially genetic polymorphisms, are attractive candidates for predicting cancer-related venous thromboembolism. In addition, given the role of hemostatic components in cancer development, these genetic markers may also predict cancer susceptibility and/or progression [11].

Thrombosis in tumor patients may be different from VTE in the general population. According to tumor models, some biological mechanisms are more related than others. In terms of the susceptibility and progression of cancer, the few studies so far have mainly focused on oral squamous cell carcinoma, breast cancer, and gastrointestinal cancer. Twelve and nine genetic polymorphisms related to cancer susceptibility and progression have been reported. It is worth noting that most of these variants have not been confirmed as predictors of cancer-related venous thromboembolism [3]. However, according to rare data, hemostatic gene polymorphisms seem to have an impact on cancer occurrence, which seems to be specific to cancer models, but may also may be related to tumor staging. Taking into account thrombus prevention, cancer screening, prognostic assessment, and the development of potential antineoplastic therapy targeting coagulation, the scientific basis of these observations requires further investigation [11].

Blood coagulation is closely related to cancer, and platelets are an important player in blood clotting. The development of strategies that selectively target blood coagulation and simultaneously affect complement factors and the inflammatory response may promote anti-tumor effects. Further research is needed to fully understand the interaction of these pathways in the TME. Targeted coagulation, as a bridge between innate and acquired immune systems, may provide a new strategy to overcome drug resistance to checkpoint inhibition [181, 182]. Specifically, targeted platelets may provide a novel idea for the treatment of tumors and tumor-related embolism in the future.

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Declarations

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