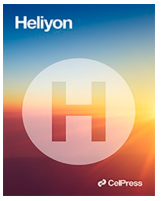
Heliyon 10 (2024) e38831

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Review article

Blood hypercoagulability and thrombosis mechanisms in cancer patients -A brief review

Qiongle Peng [a,**], Jinmei Zhu [b], Yanhu Zhang [c], Yanping Jing [a,d,*]

[a] Department of Blood Transfusion, Affiliated Hospital of Jiangsu University, No. 438 Jiefang Road, Zhenjiang, 212000, PR China
[b] School of Medicine, Jiangsu University, No. 301 Xuefu Road, Zhenjiang, 212013, PR China
[c] School of Mechanical Engineering, Jiangsu University, No. 301 Xuefu Road, Zhenjiang, 212013, PR China
[d] School of Life Sciences, Jiangsu University, No. 301 Xuefu Road, Zhenjiang, 212013, PR China

ARTICLE INFO

Keywords:
Malignant tumor
Hypercoagulability
Thrombosis
Coagulation function
Potential mechanisms

ABSTRACT

Patients with malignant tumors are prone to present hypercoagulability of blood and form thrombosis, and its pathogenesis is complex involving various factors from clinical and histopathological to genetic influences. Current studies on the potential mechanism of blood hypercoagulability in patients with malignant tumors focus on the following aspects but are not limited: (1) tumor cells release coagulant-promoting substances, (2) tumor cells interact with the fibrinolytic system, (3) tumor cell-mediated platelet activation, (4) tumor-associated complement activation, and (5) genetic factors and clinical factors. Especially, the pathogenesis of blood hypercoagulability is in-depth analyzed covering tumor cells' release of procoagulant substances, the interplay of cancer cells and fibrinolytic system, platelet activation mediated by cancer cells, cancer-associated complement activation, and the action of genetic and clinical factors. We review the pathogenesis of blood hypercoagulability in patients with malignant tumors, which will assist in the research and development of new drugs and providing theoretical support for the formulation of the best treatment plan for patients, to prolong the survival of patients.

1. Introduction

Blood hypercoagulability in cancer patients refers to the abnormal enhancement of blood coagulation function in cancer patients, being prone to lead to an increased risk of thrombosis, which increases the incidence of cardiovascular events and other complications [1]. Venous thromboembolism (VTE), including deep venous thrombosis (DVT) and pulmonary embolism (PE), is the most common manifestation of cancer-related hypercoagulability [2]. Thromboembolic disease and hemorrhagic disease induced by blood hypercoagulability are some of the important causes of death in patients with malignant tumors. Enough research, including clinical and laboratory examination, histological examination, and pharmacological analysis have proved that cancer patients are prone to blood hypercoagulability since Armand Trousseau discussed the relationship between thrombus and cancer [3]. Further studies support the interaction of tumor cells with the blood coagulation system in various ways, such as fibrin formation and fibrinolysis increasingly with metastases [4], hemostatic proteins and reactions interdigitating the tumor growth and dissemination [5], microparticles shedding of

* Corresponding author. Department of Blood Transfusion, Affiliated Hospital of Jiangsu University, No. 438 Jiefang Road, Zhenjiang, 212000, PR China.
** Corresponding author.
E-mail addresses: pengxiaoman@ujs.edu.cn (Q. Peng), jingyanping@ujs.edu.cn (Y. Jing).

https://doi.org/10.1016/j.heliyon.2024.e38831
Received 14 June 2024; Received in revised form 28 September 2024; Accepted 30 September 2024
Available online 1 October 2024

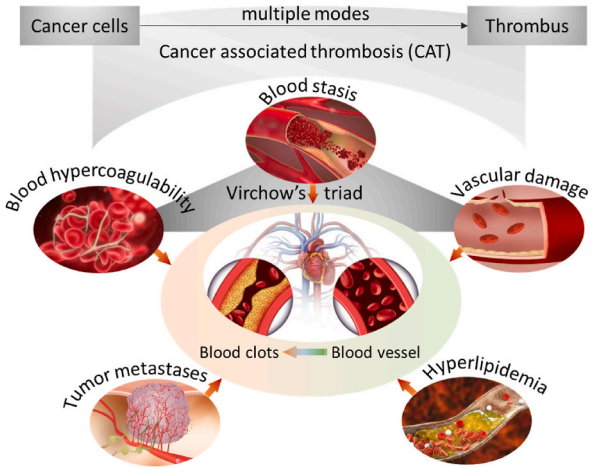


Fig. 1. Sketchy illustration of cancer-associated thrombosis after Virchow's triad. In particular, blood hypercoagulability relates to malignant tumor, pregnancy and perinatal period, estrogen therapy, inflammatory intestinal disease, sepsis, and history of thrombus. Circulatory stagnation mainly includes left ventricular insufficiency, inactivity or paralysis, venous insufficiency or varicose veins, tumor-oppressed veins, obesity, or pregnancy. The derived factors of vascular damage include trauma or surgery, heart valve disease or replacement, atherosclerosis, and indwelling catheter.

tumor cells [6], and/or immune response to delimit tumor growth [7].

The blood hypercoagulability of cancer patients can be caused by a variety of factors, including the procoagulant released by the cancer itself, the effect of the tumor on vascular endothelial cells and platelets, and the treatment received by the patient (e.g., chemotherapy or radiotherapy) [8]. These factors may lead to the abnormal enhancement of blood coagulation function. Blood hypercoagulability seriously affects the health of cancer patients, including increasing the risk of thrombosis, cardio-cerebrovascular events, and other complications [9]. Therefore, preventing and treating blood hypercoagulability are fairly important for cancer patients. Preventing thrombosis includes active control of tumor growth and metastasis, rational use of anticoagulants, strengthening physical exercise, and rehabilitation nursing of patients [10]. Nowadays, the relationship between cancer and blood hypercoagulability is still being explored. It is of great clinical significance to clarify the pathogenesis of blood hypercoagulability in patients with cancer and reduce the occurrence of thrombus and hemorrhagic well. Despite this, antiplatelet agents and anticoagulants become fundamental for the prevention and treatment of thrombosis with side bleeding [11]. The research of blood hypercoagulability and thrombosis mechanisms has thus far been covered by broader reviews highlighting advances in the interaction of tumor cells with the blood coagulation system [1,12–16], we dedicate this review to the blood hypercoagulability and thrombosis mechanisms in cancer patients following the fundamental hypercoagulability of cancer patients, perioperative monitoring, and pathogenesis of blood hypercoagulability.

2. Blood hypercoagulability of cancer patients

2.1. Clinical symptoms of hypercoagulability

The blood circulation of malignant tumors is abundant and easily causes the blood in a hypercoagulable state, which induces the blood clots formation in the host associated with worsened survival and a variety of cancer health-related outcomes [17]. A thrombus is a small mass formed by blood flow on the surface of the peeling or repair of blood vessels in the cardiovascular system. Blood hypercoagulability relates to local poor blood circulation, and easily leads to local tissue swelling symptoms and limb cyanosis [18].

The thrombus consists of insoluble fibrin, deposited platelets, accumulated white blood cells, and trapped red blood cells in variable flow-dependent patterns [19]. The common substances that would induce thrombosis include fibrinogen deposits, prothrombin and fibrinolysis system, cancer cells, and red blood cells [20]. Fibrinogen deposits that are formed in the blood vessels of cancer patients can activate platelets in the blood and coagulation factors in plasma, which then cause thrombosis [21]. Prothrombin being activated in the blood of cancer patients and binding to fibrin to form a prothrombin fibrinolysis system causes fibrin, platelets, and other cellular components in the blood deposited in the formed clot, resulting in cancer thrombus [22]. Cancer cells secrete a variety of substances that stimulate blood vessels to proliferate vascular endothelial cells, promote platelet aggregation, accelerate blood coagulation, and eventually lead to cancer thrombus [14]. Red blood cells may also appear in the blood of cancer patients, such as leukemic patients, the proliferation of leukemic cells in the bone marrow, and secret platelets, which squeeze red blood cells into peripheral blood vessels and lead to cancer thrombus [23].

2.2. Biomedical insights on hypercoagulability

The systems of coagulation, anticoagulation, and fibrinolysis in the normal body are in dynamic balance. In some abnormal cases, this balance is broken. When the blood clotting function is weakened and the anticoagulation function is enhanced, the body is in a hypocoagulable state and is prone to hemorrhagic diseases [24]. When the blood clotting function is enhanced and the anticoagulant function is weakened, the body is in hypercoagulability, thrombotic diseases are easy to occur [25]. In the case of breast cancer, a kind of malignant tumor in women, the blood circulation is abundant and prone to cause the blood to be in a hypercoagulable state. The high blood coagulation may lead to a decrease in blood fluidity and cause blood clots in many places [26]. With the deepening of research, the mechanisms of blood hypercoagulability or hypocoagulation in clinical patients are fairly complex [27], coupled with the imbalance of the fibrinolysis system, a series of complex diseases can be secondary [28,29].

2.3. Hypercoagulable thrombosis

Blood hypercoagulability is termed as prethrombotic state, in which the body coagulation, anticoagulation, and fibrinolysis are imbalance because of some physiological and pathological factors, all kinds of blood cells and vascular endothelial cells in the blood are easy to agglomerate into lumps to form thrombosis [30]. Cancer cells in the blood of cancer patients form the thrombus by coagulating with other cells or from themselves, this thrombus is termed as cancer-associated thrombosis (CAT), which display serious complications of malignant tumor patients, and the fatality rate is fairly high [31]. Cancer patients are prone to venous thromboembolism (VTE) under hypercoagulability. The previous study on colorectal cancer indicated that the incidence of postoperative VTE in patients with malignant tumors was higher and lasted for more than one month, which was related to their hypercoagulability [32]. The cancer-associated thrombosis after Virchow's triad form the complex map to correlate the between the blood hypercoagulability and malignant tumor, pregnancy and perinatal period, estrogen therapy, intestinal disease, and history of thrombus (Fig. 1). The incidence of cerebral venous thrombosis and visceral thrombosis (VT) are particularly high in patients with myeloproliferative tumors (Myeloproliferative neoplasms, MPNs). SVT includes Budd-Chiari syndrome and portal vein thrombosis [1]. In addition, transitional thrombophlebitis, arterial thrombosis, disseminated intravascular coagulation and nonbacterial thrombotic endocarditis (NBTE) are all classified as complications of hypercoagulability in cancer patients [33]. Once thrombus occurs in cancer patients, it is difficult to control spontaneously, and they usually need thrombolytic therapy by injection of drugs (alteplase, urokinase for injection, etc.), as well as surgery (interventional therapy, endovascular stent implantation) [34]. The treatment will carry a huge financial burden and strongly weaken the quality of life and living standards of patients.

3. Perioperative monitoring of hypercoagulability

Blood hypercoagulability and thrombosis in cancer patients leads to morbidity and death. Predicting the risk of thrombosis and cardiovascular complications to be one of the fundamental challenges in modern medicine. The monitoring of blood hypercoagulability was summarized into three categories, i.e., clinical and laboratory examination, histological detection, and pharmacological analysis.

3.1. Clinical and laboratory examination

Laboratory tests such as thromboelastogram (TEG), viscoelastic hemostatic assays, rotational thromboelastometry, and blood coagulation function indexes can indicate the patients with malignant tumors are in a state of blood hypercoagulability [35,36]. In the results of low-cost TEG tests, the blood reaction time (R-value) and clotting time (K value) of cancer patients were significantly shorter than those of benign disease patients, while the maximum amplitude (MA), coagulation rate (α-angle) and coagulation comprehensive index (CI) were significantly increased [37,38]. In the detection of coagulation function, the prothrombin time (PT) was shortened, fibrinogen (FIB) and D-dimer were significantly increased, the activated partial thromboplastin time (APTT) and the thrombin time (TT) also prolonged slightly [39]. A retrospective analysis of patients with musculoskeletal tumors indicated that the TEG parameters of the patients significantly deviated from the normal value, and the blood showed hypercoagulability [40]. However, routine clotting tests do not provide enough information, mainly because they measure the time when blood clotting begins, rather than assessing the production of total thrombin [10]. Blood hypercoagulability refers to the state in which blood is prone to coagulate through the activating process of coagulation factors. The increase of blood coagulation especially pancreatic cancer, gastric cancer, breast cancer, and bronchial cancer, is because of the release of procoagulant factors in cancer cells [41]. In addition, thrombocytopenia or increased platelet viscosity in pregnancy, surgery, postpartum, high-fat diet, smoking, and coronary atherosclerosis could also increase blood coagulation and the possibility of thrombosis [42]. In addition, the congenital genetic defects that lead to congenital deficiency of anticoagulants, such as antithrombin, protein C, or protein S, lead to damage of natural anticoagulant pathways and are prone to thrombosis [11]. Inflammatory cytokines produced after trauma, surgery, or disease can contribute to the appearance of a procoagulant state. Inflammatory cytokines activate the endothelial cells of blood vessels and express adhesion molecules, which further bind to white blood cells in the blood and to promote blood coagulation on the surface of the blood vessels [21]. Bound white blood cells damage the endothelium by producing oxygen-free radicals and releasing hydrolases, thereby enhancing the formation of local blood clots, these inflammation mechanisms are closely linked to blood coagulation [43]. Patients with hypercoagulable blood have a high risk of thrombosis and should be actively prevented and clinically treated with antithrombotic and anticoagulant therapy in time after laboratory examination.

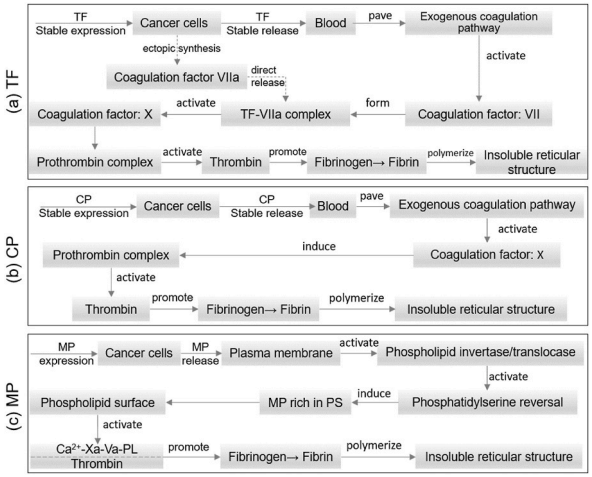


Fig. 2. Critical activities of the procoagulant substances released by tumor cells in the formation of insoluble reticular structures. Procoagulants released by tumor cells play an important role in the formation of fibrinolytic structures. These substances can activate or regulate a variety of active systems related to coagulation and fibrinolysis (e.g., TF, CP, and MP), thereby affecting the formation and dissolution of the fibrin network.

3.2. Histopathological examination

The medical examination is also an important basis for the diagnosis of a hypercoagulability, including a heart function test, blood test, and blood biochemical examination. In addition, biopsy of diseased tissue is sometimes used to detect hypercoagulable conditions. Suppurative inflammation occurs in and around the intima of the portal vein, including thrombosis and pus. If the pipe wall is damaged, it may bleed. In the tissue anatomical observation of malignant tumor patients, it was found that the thrombus of platelet and fibrin in blood vessels increased abnormally, and the immunohistochemistry of fibrin around tumor cells showed an increase of platelet clot and fibrin coagulation products [44]. Romans et al. reviewed the pathological tissues of many patients with parathyroid tumors and concluded that immunohistochemical analysis is of value in the auxiliary diagnosis of malignant tumors [45]. Histological examination provides evidence for blood hypercoagulability and plays a critical role in clinical diagnosis.

Hypercoagulable thrombosis is the classical complication of cardiovascular diseases to cause of death, which raises worldwide attention to the health-care challenge before the multiple cancer-specific mechanisms [1]. Pharmacological analysis reflects the use of anticoagulants or antiplatelet drugs in cancer patients to achieve a positive effect [46], indicating that cancer patients present blood hypercoagulability. The pharmacological analysis is not yet sufficient to successfully pave the way for the treatment of most cancers, effective intervention including the physical scale in hypercoagulability is necessary to assist treatment for cancer patients. The oral anticoagulants of myeloproliferative neoplasms (MPN) patients reduced tumor metastasis and improved prognosis [47]. It is unknown to what extent potential malignant tumors (MPN) contribute to immunosuppression and susceptibility to infection [48]. The recurrence rate of VTE was fairly low and there was no complication of massive hemorrhage [49].

The increase of platelet agglutination and procoagulant factors in the blood, which is prone to thrombosis and embolism, causes the hypercoagulable state. The hypercoagulablility is the common state in patients with nephrotic syndrome. There are many reasons for causing hypercoagulable state, and promote platelet aggregation and procoagulant factors are the most critical. Patients with hypercoagulability also have symptoms, such as venous congestion, hyperlipidemia, an increase in low-density lipoprotein, and hypoproteinemia, blood concentration, and an increase of blood viscosity [50]. From a pathological point of view, the use of hormones and diuretics can also cause an increase in the level of plasma fibrinogen and a significant increase in the content of fibrin and fibrinogen degradation products, leading to a hypercoagulable state in patients [42]. Anticoagulant drugs are usually used to improve the prevention of hypercoagulability and hypercoagulable states in patients. In general, patients with plasma albumin below 20 g/L or 25 g/L are at risk of venous thrombosis and require anticoagulant drugs [51]. The most commonly used anticoagulant drugs are heparin and urokinase, which play an anticoagulant effect mainly by activating antithrombin activity [52]. Therefore, pharmacological analysis is an important basis for detecting, tracking, and monitoring the hypercoagulable state of patients in the clinic, and is also the basic information support for further diagnosis and treatment.

4. Pathogenesis of blood hypercoagulability

The pathogenesis of blood hypercoagulable state in patients with malignant tumors is fairly complex, involving various factors ranged from clinical intervention to genetic influence. The hemostatic elements cover three aspects, i.e., coagulation, fibrinolysis, and plates in the whole tumor progression of cellular transformation, proliferation, survival of tumor cells, and angiogenesis. After that, the influence mechanisms were discussed as follows in a regular view of biomedical insights.

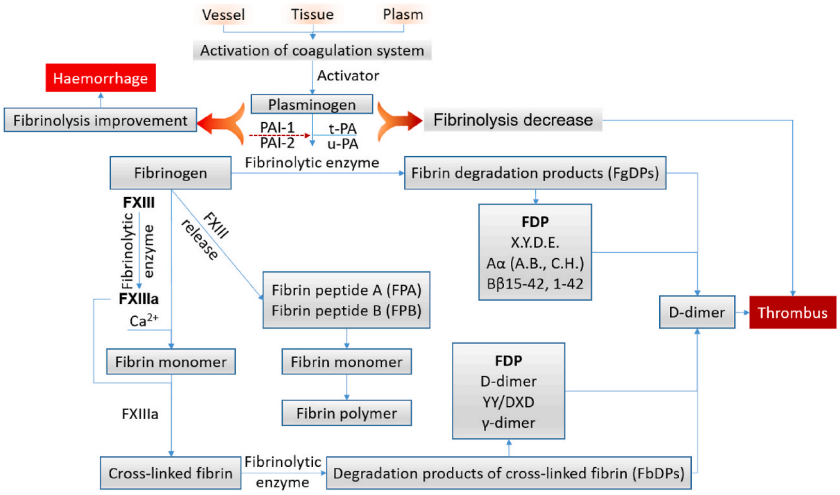


Fig. 3. Illustration of hemorrhage and thrombus diseases within the complex internal circulation and competition mechanisms. Hemorrhagic and thrombotic diseases have a highly complex physiological and pathological basis in complex internal circulation and competitive mechanisms. These diseases are closely related to the imbalance between coagulation and anticoagulation, fibrinolytic and antifibrinolytic systems in the body.

4.1. Tumor cells release procoagulant substances

The procoagulant substances released by tumor cells include tissue factors (Tissue factor, TF), cancer promoters (Cancer procoagulant, CP), and particles (Microparticle, MP). TF is the most classic coagulant is tissue factor that is stably expressed on the surface of tumor cells and actively released into the blood to initiate the exogenous coagulation pathway [6]. Firstly, TF activates and interacts with coagulation factor VII to form TF- VII complex. The TF- VII complex further activates the coagulation factor X. Factor V, $Ca^{2+,}$ and phospholipid (PL) to form the prothrombin complex, which could activate thrombin, transform fibrinogen into fibrin, and polymerize into insoluble reticular structure [53]. In addition, some tumor cells could synthesize VII an ectopic and directly release TF-VII a complex [54]. CP is a kind of tumor cell product independent of the coagulation factor system. The mechanism of activating blood coagulation by CP is similar to that of TF. CP directly activates the coagulation factor X without the participation of the coagulation factor VII [55]. Krause and Frost determined two CP binding sites on Fibronectin (FN), as a substance connecting cells and stroma, and playing a role in promoting tumor metastasis, and proved that CP can also interact with FN [56]. Therefore, CP may be one marker for early diagnosis of tumors. MP is a kind of phospholipid vesicle with a diameter of 0.1–1 μm, which can form and is released by the cell membrane of a variety of cells, mostly from platelets [57]. In patients with malignant tumors, tumor cells can also release MP, and the level of MP in tumor patients is much higher than the normal level. Under certain pathological conditions or apoptosis initiation, phospholipid invertase and translocase on the plasma membrane are activated, and phosphatidylserine (PS) reverses from endoplasmic to ectoplasmic, and MP is also released into the blood with the reversal of PS. The MP is rich in PS and provides a rich phospholipid surface for the formation of the Ca^{2+}-Xa-PL complex and the activation of thrombin. TF is highly expressed on the surface of MP, and both of them promoted the coagulation cascade amplification reaction [58]. The abovementioned typical mechanisms are summarized in Fig. 2.

4.2. Interplay of cancer cells and fibrinolytic system

Fibrin is a component of the extracellular matrix (ECM) that acts as a transport barrier in the tumor core by contracting blood vessels and forming clots [59]. Fibrinolysis is the physiological process of maintaining a hemostatic balance by counteracting excessive thrombosis through dissolving fibrin to maintain vascular potency [60]. The malignant cells are prone to invade and travel within the bloodstream to distant sites, and the tumor cells will accumulate in normal tissue in a clonogenic way. Tumor cells interact with the fibrinolytic system by expressing the receptors related to the fibrinolytic system. Plasminogen receptor S100A10 can bind to Annexin A2 (ANXA2) to form a tetramer, which regulates the formation and destruction of plasmin [61]. Other plasminogen receptors include cytokeratin, integrin, histone H2B [62], and α-enolase [63,64], which could recruit macrophages to move to the tumor site, and tumor cells are more likely to proliferate and metastasize with the participation of macrophages [65]. Tumor cells also increase tissue-type plasminogen activator (tPA) (an activator released from endothelial cells), urokinase-type plasminogen activator (uPA), and its receptor uPAR to interact with each other. These pathways affect tumor occurrence and development by regulating the tumor microenvironment [66]. The plasminogen activator inhibitor (PAI-1, and PAI-2) and activated protein inhibitor (PAI-3) also affect the action of plasminogen activators (tPA or uPA) [67]. The fibrinolytic components regulate multiple biological processes ranging from cell migration, tissue remodeling, and modulation of various growth factors and cytokines, to regulation of immune response and chemotaxis [60]. In a variety of pathological conditions, including cancer, fibrin can directly deregulate the fibrinolysis system. However, because of the role of plasmin in key physiological processes such as tissue remodeling and thrombolysis, the therapeutic

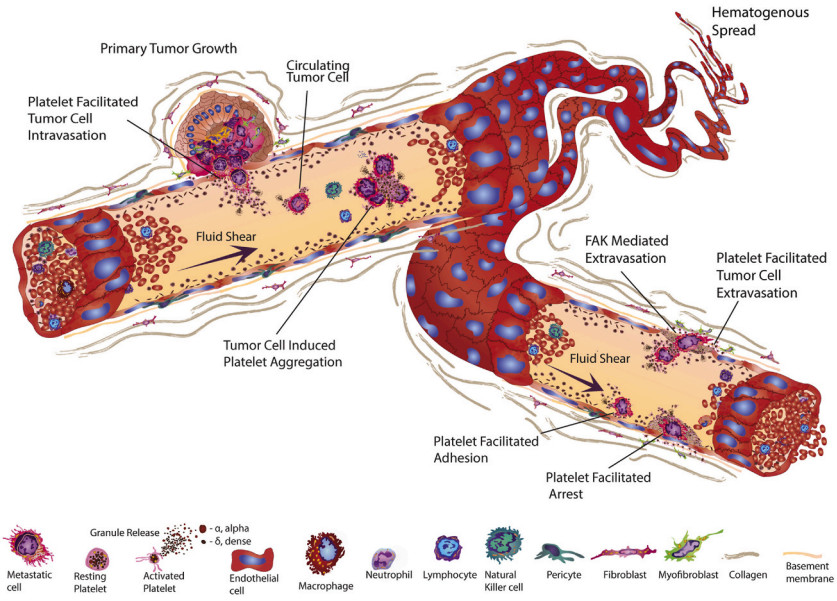


Fig. 4. Platelet activation releases growth factors and small molecules that facilitate tumor growth and invasion [73]. Once tumor cells enter the bloodstream, platelet-tumor cell aggregates form and platelets protect tumor cells. Additionally, platelets stimulate and aid cancer cell adhesion and extravasation, supporting cancer cell transmigration and metastasis formation. Interactively, tumor cells mediate platelet activation, leading to platelet aggregation and granule release. Activated platelets are capable to extravasate into the tumor microenvironment via focal adhesion kinase to fuel tumor growth.

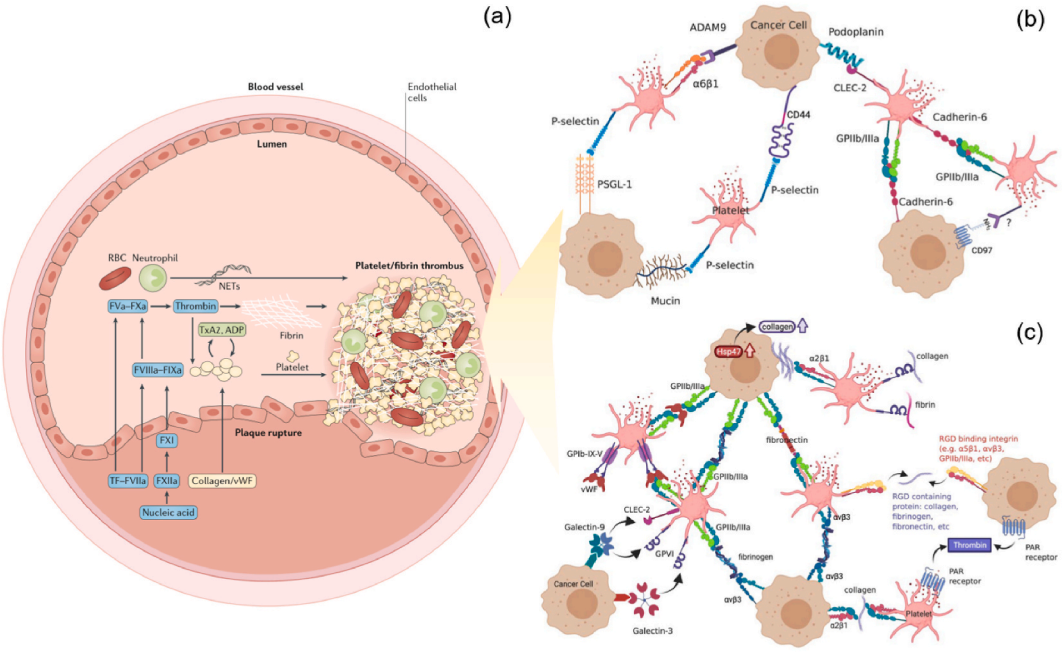


Fig. 5. Platelet in the formation of an occlusive arterial thrombosis (a) [11] and two modes of platelet-cancer cell interplay [119]: (b) direct surface receptor interactions, and (c) extracellular protein-mediated platelet.

target of plasmin is not always feasible in clinical environments [68]. Blocking plasmin activity may lead to systemic diseases. The components of the fibrinolytic system present a critical role in the processes of cell migration, tissue remodeling, regulation of various growth factors and cytokines, regulation of immune response, and chemotaxis. There is plenty encouraging preclinical evidence that targets key carcinogenic components of targeted fibrinolytic systems having potential therapeutic benefits, although they have not been involved in the alternations from lab to bed due to the limited number of clinical trials. One illustration of hemorrhage and

thrombus diseases within the complex internal circulation and competition mechanism is shown in Fig. 3.

4.3. Platelet activation mediated by cancer cells

Metastasis is a pathological process during tumor cells use the bloodstream to colonize distant organs, exploiting hemodynamics to arrest and successfully grow upon extravasation [69]. The bloodstream ecosystem interacts with blood components efficiently advance their way to metastasis [70,71]. Platelet promote metastatic progression [72] by protecting circulating tumor cells from destruction by shear forces, mediate immune evasion, favor adhesion and extravasation at distant sites, facilitate neo-angiogenesis, and sustain a tumor-prone inflammation [73]. Procoagulant platelets deliver large amounts of immune checkpoint molecules to malignant tumors and misguide immune cell responses, thus promoting tumor progression [74]. Circulating tumor cells can quickly bind, activate and aggregate circulating platelets in the blood, which provides a physical barrier to facilitate intravascular arrest and survival [75], as well as successful extravasation and metastatic growth [76] (See Fig. 4).

The results of platelet count in patients with malignant tumors are basically at a high level, which is closely related to the thrombopoietin factors released by tumor cells. The most common thrombopoietin factor is plasminogen activator inhibitors (TPO), which is far from the relationship with the tumor. Only some liver and ovarian cancers can produce TPO [77]. However, soluble mediators such as ADP, Thromboxin A2 (TXA2), Toll-like receptor 4 (TLR4) and high mobility group protein B1 (HMGB1) released by tumor cells can activate platelets locally [78]. Interleukin-1 (IL-1), IL-6, and other cytokines are expressed in tumor patients, which can promote thrombosis and affect platelet function and count in the presence of TPO. Tumor cells usually invade blood vessels for metastasis, natural killer cells (Natural killer cell, NK cells) can attack these cancer cells entering blood vessels, and only a few cancer cells can escape this attack and transfer to all parts of the body with blood circulation [79]. The increased platelets in cancer patients wrap the cancer cells in thrombus and prevent NK cells attack [80]. However, for the normal body, platelets can release angiogenic factors and stimulate angiogenesis, which has a positive effect on normal bodies. Type IV collagen exposed on tumor vessels has been shown to promote platelet recruitment in the tumor microenvironment and is considered being a marker of angiogenesis in breast cancer [81]. Platelets have a positive effect on the normal body in cancer progression, and inflammation has been obtained sufficient attention. The different interactive mechanisms of platelet activation and thrombo-inflammation in cancer have been reviewed [82]. The approved insights light the processes of tumor cells' active platelets, platelets influence tumor growth, and the potential pathways of platelet-cancer cell interplay (Fig. 5). Despite the complex mechanisms of the platelets interacting with tumor cells are on the way, the interaction between cancer cells and platelets is an important area in cancer research. Platelets not only participate in hemostasis and coagulation, but also play an important role in the progress and metastasis of tumors. Cancer cells can activate platelets through multiple mechanisms such as direct cell-cell contact, secretion of soluble factors, and modification of surface proteins. Further, platelet activation can promote tumor metastasis, promote angiogenesis, and affect the tumor microenvironment.

4.4. Cancer-associated complement activation

Cancer-associated complement is a kind of innate immune molecule, which participates in immune response and inflammation, inhibits microbial infection and the clearance of apoptotic cells through classical pathway, bypass pathway, and mannose-binding lectin pathway [83]. Cancer transformation is usually accompanied by an increase in the ability of malignant cells to activate complement [84]. The inhibition mechanism of complement activation enables cancer cells to escape from complement-mediated elimination and hinders the clinical efficacy of monoclonal antibody-based cancer immunotherapy. In the past, it was believed that complement activation is the host's defense mechanism against cancer, and cancer cells resist complement attack by overexpressing CRPs. The view of complement activation as an anti-tumor defense mechanism cannot be ignored from two aspects, (i) the complement system participates in immune surveillance against malignant cells and (ii) complement-dependent cytotoxicity of therapeutic monoclonal antibodies [85]. Studies have pointed out that complement mediates thrombosis in patients with malignant cancers, despite the specific mechanism is not clear [30]. One instance is that thrombin plays a role in the cleavage of complement C5 to allergic toxin C5a, regulating vascular endotheliogenesis and mediating TF expression. In addition, compliment C3 can activate platelets and cause blood hypercoagulability [47].

The membrane attack complex (Membrane attack complex, MAC) is the final substance formed by the three pathways of the complement system MAC cannot only lyse infected cells but also kill cancer cells and inhibit cancer growth, while complement regulatory proteins (Complement regulatory proteins, CRPs) prevent the complement over-activation and reduce the efficiency of MAC production [86]. The results of a mouse model of non-small cell lung cancer showed that inhibition of CRP by immunomodulators could slow down cancer growth in mice, further confirming that the complement system is involved in the regulation of cancer growth [87]. The expression of complement protein C1q affects angiogenesis, tumor progression, and metastasis [88], and it also favors trophoblast invasion of maternal decidua [89] and promotes angiogenesis in wound healing [90]. As an activator of the classical pathway, C1q is also detected in the stroma and vascular endothelium of tumor specimens, confirming that it plays the exert functions unrelated to complement activation [83]. The complement system is one of the inflammatory mechanisms activated in the tumor microenvironment, regulating anti-tumor mechanisms (complement-dependent cytotoxicity and therapeutic phagocytosis), promoting immunosuppression and tumor growth and invasiveness, especially targeting leukocytes and cancer cells through allergic toxins [91]. Literate reviewed the complex mechanisms of activation (classical, lectin, and alternative pathways) and regulation of the complement cascade (avoiding host tissue damage). At present, anti-platelet aggregation drugs play an important role in antithrombotic treatment. P2Y1 and P2Y12 belong to the P2Y receptor family and are located on the surface of platelets. ADP is released after vascular injury and binds to the P2Y1 receptor, triggering an increase in calcium ion levels and promoting platelet aggregation. ADP

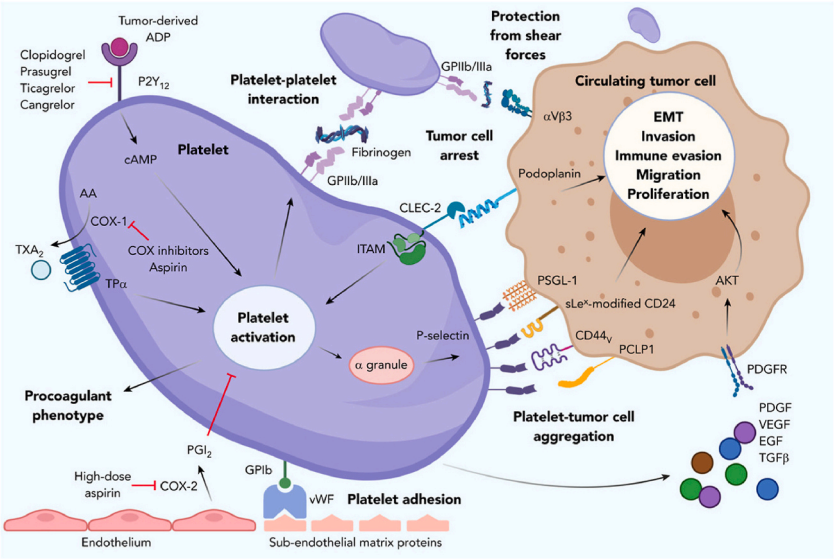


Fig. 6. Analysis of anti-platelet pharmacokinetic mechanism of interaction between platelets and cancer cells [92]. Paracrine interactions between platelets and cancer cells are associated with enhanced spread, survival and extravasation of cancer cells at distant metastatic sites. Signals from platelets are also thought to confer epigenetic changes, including upregulation of cancer proteins in circulating tumor cells, and the secretion of effective growth factors may play a role in promoting mitosis, angiogenesis and metastatic growth. The abbreviations are referred as follows. AA: arachidonic acid; ADP: adenosine diphosphate; AKT: also known as PKB, Protein kinase B; cAMP: cyclic adenosine monophosphate; CD44v: CD44 variant; CLEC-2: C-type lectin-like receptor 2; COX: Cyclooxygenase; EGF: epithelial growth factor; EMT: epithelial-mesenchymal transition; PCLP1: podocalyxin-like protein 1; PDGF: platelet-derived growth factor; PDGFR: PDGF receptor; PSGL-1: P-selectin glycoprotein ligand-1; TPα: thromboxane receptor α; TGFβ: transforming growth factor β; TXA2: thromboxane A2; vWF: von Willebrand factor; VEGF: vascular endothelial growth factor.

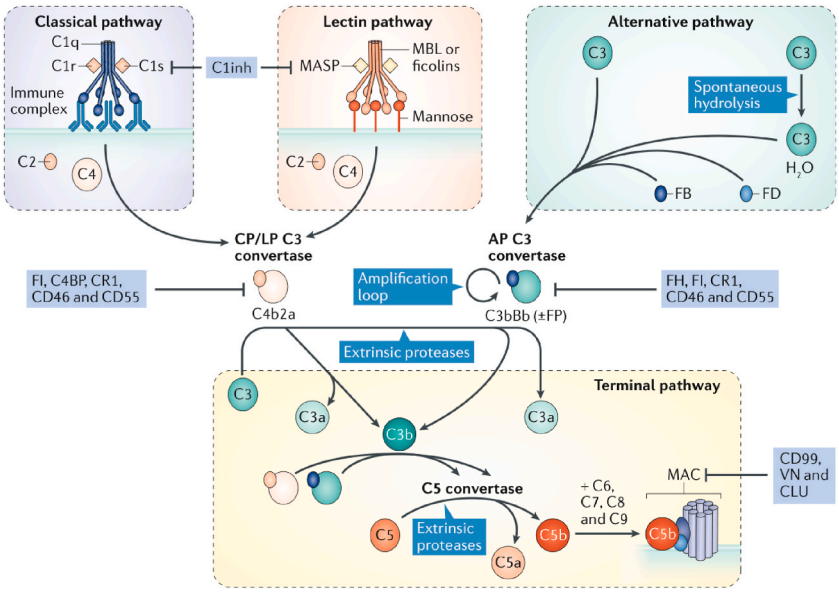


Fig. 7. Mechanisms of activation (classical, lectin, and alternative pathways) and regulation of the complement cascade (avoiding host tissue damage) [120].

then binds to the P2Y12 receptor, causing it to block the action of adenylate cyclase and reduce intracellular cyclic adenosine, accelerating the continued aggregation of platelets. One critical illustration of the complex mechanisms is shown in Fig. 6 [92].

4.5. Intervention of antiplatelet agents

Platelets not only play an important role in hemostasis, but also participate in the formation of the cancer microenvironment and the growth and metastasis of tumors. Platelets protect circulating tumor cells from attack by the immune system and promote the adhesion and dissemination of tumor cells. Several epidemiological studies have shown that long-term low-dose aspirin use is associated with a reduced risk of multiple cancers (such as colorectal cancer [93,94], gastric cancer [95], breast cancer [96], etc.). Especially for colorectal cancer, aspirin is considered to have a good preventive effect [97]. Aspirin mainly reduces the production of thromboxane A2 by inhibiting cyclooxygenase-1 (COX-1), thereby inhibiting platelet aggregation [98]. In addition, aspirin may also play an anti-cancer role by inhibiting COX-2-mediated inflammatory responses, regulating immune responses, and inducing apoptosis of tumor cells. Some animal experiments have shown that anti-platelet drugs can reduce the incidence of tumor metastasis. For example, aspirin has been shown to inhibit metastasis in breast, lung and other cancers in mouse models [99]. Clinical research is also exploring the potential of antiplatelet drugs in reducing the risk of cancer metastasis. However, due to the complex conditions of cancer patients, the use of drugs needs to consider multiple factors (such as bleeding risk, patient's overall health status, etc.), so further large-scale, randomized controlled trials are needed to verify the effectiveness and safety of these drugs. Although antiplatelet drugs have shown potential in preventing cancer, long-term use may increase the risk of bleeding, especially in elderly patients [100]. Therefore, balancing the potential benefits and risks of drugs is a key challenge in clinical application. Future research may pay more attention to the differences in the role of anti-platelet drugs in different types of cancer and how to individualized treatment based on patients 'genetic characteristics and pathological status [92] (Fig. 7).

4.6. Action of genetic and clinical factors

Three typical clinical symptoms (i.e. venous thromboembolism, arterial thrombosis, and malignant tumors) in terms of common clinical manifestations and related diseases. Hypercoagulability is usually associated with the development of venous thromboembolism, including deep vein thrombosis and pulmonary embolism. The level of coagulation factors in the blood of such patients usually increases, and indicators such as fibrinogen and D-dimer are abnormal [101]. Hypercoagulable states are also associated with arterial thrombosis, such as coronary artery disease, stroke, etc. This is usually related to factors such as rupture of atherosclerotic plaques and increased platelet aggregation. Cancer patients are usually in a hypercoagulable state because tumor cells can secrete procoagulant substances and induce host cells (e.g. monocytes and endothelial cells) to express more coagulation factors, increasing the risk of thrombosis [102]. Moreover, the above symptoms may have a certain probability of transformation process patterns, which brings the complex things and causes in clinical diagnosis and intervention. Routine tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer level, fibrinogen concentration, etc. are the basis for assessing hypercoagulability [103]. Specific coagulation factors or genetic testing may be needed for specific causes. With the deepening of research, more and more new biomarkers (such as circulating tumor DNA [104], microsomes [105], and tissue factor-positive particles [106]) have been proposed to assess hypercoagulability, but the clinical application of these markers is still under study. In terms of treatment strategies and clinical management, anticoagulant therapy is the main intervention for hypercoagulability states. Commonly used drugs include warfarin, low molecular weight heparin, direct oral anticoagulants, etc [107]. With the in-depth understanding of the causes and mechanisms of hypercoagulable states, treatment is becoming increasingly personalized, especially in complex cases such as tumor-associated thrombus and inherited hypercoagulable states both in genetic and clinical aspects.

Genetic variation in the 3 ′-untranslated region (3′-UTR) of the prothrombin gene can lead to the increase in prothrombin. The activated protein C (Activated protein C, APC) inhibits the activity of clotting factor V and coagulation factor VIII, but the Factor V Leiden mutation (FVL) of clotting factor V loses the arginine residue acting site of APC, hinders the inactivation of factor V by APC and promotes blood coagulation [108]. Thrombomodulin can help activate Protein C (PC), the mutation of the thrombomodulin coding gene also leads to the imbalance of the anticoagulant system and the hypercoagulable state of blood [109]. In addition to the above common genetic factors, the role of different genes in different cancers is also closely related to blood hypercoagulability. The mutation of the breast cancer susceptibility gene *BARC1/2* not only increases the risk of breast cancer but also has an important impact on the malignant degree and prognosis of patients [110]. P53 gene inactivation and K-RAS gene activation lead to increased TF expression in colorectal cancer patients [111]. Micro ribonucleic acid-338-5p (miR-338-5p) negatively regulates the zinc finger E-box binding homeobox 2 (ZEB2). The down-regulated expression of miR-338-5p leads to the increase of ZEB2 levels in patients with gastric cancer, which is related to the worse survival status of cancer patients [112]. The decrease of PC activity in primary thrombocytopenia and true polycythemia is related to the mutation of the JAK2V617F gene [113]. Activated protein C resistance (factor V Leiden mutation)-gene mutation encoding factor V protein, factor V can be activated normally, but it can resist the degradation of activated protein C, thus affecting the process of blood clot formation [114]. Antithrombin III deficiency or dysfunction-Antithrombin III inhibits blood coagulation by inhibiting coagulation factors Xa, IXa, and XIa, as well as thrombin [115]. Hereditary or acquired antithrombin deficiency can lead to the formation of blood clots.

Clinical factors involve many aspects, including anti-cancer therapy, cancer characteristics, and patient factors. Usually, the use of anticancer drugs can lead to blood hypercoagulability, radiotherapy, surgery, and other abnormal hemorheology, promote the formation of hypercoagulability. The patients with head and neck cancer are counted in the incidence of hypercoagulability after free skin flap repair [116]. Some cancers are prone to thrombosis, such as acute promyelocytic leukemia. A common complication is

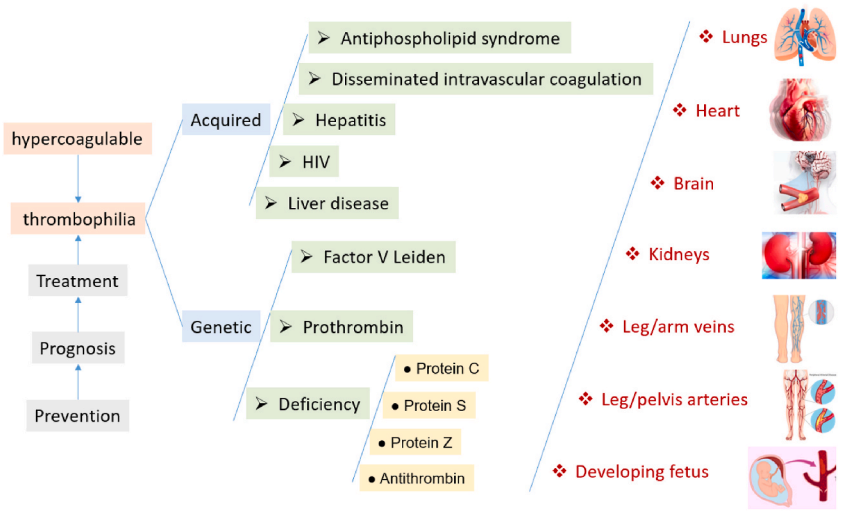


Fig. 8. Thrombophilia is a hypercoagulable condition of inherited (genetic) or acquired tendency to form blood clots in arteries and veins. The various hypercoagulable diseases occur at the different locations in the body of human beings. The dimensional intervention sketches including prevention, prognosis, and treatment are critical for the health maintenance and disease management related to blood hypercoagulability.

disseminated intravascular coagulation (DIC). Hematological malignancies such as Hodgkin's lymphoma (HL), Non-hodgkin's lymphoma (NHL), and Multiple myeloma (MM) have much higher risk of thrombosis than non-hematological malignancies [117]. In non-hematological malignant cancers, pancreatic cancer, gastric cancer, ovarian cancer, lung cancer, renal adenocarcinoma, uterine cancer, and malignant brain cancers are prone to thrombosis [118]. Patients with long-term bedridden, advanced age, obesity, and a history of thrombosis are risk factors for blood hypercoagulability. Furthermore, patients with infection, heart disease, and respiratory diseases have an increased risk of thrombosis [47]. Future research may further explore the association between hypercoagulability and prognosis of different diseases to optimize treatment decisions (Fig. 8). With the development of molecular biology technology, the diagnosis and treatment of hypercoagulable states are moving in a more precise direction. For example, anticoagulation treatment options based on patient's specific genotype may become a hot topic for future research. How to balance thrombus prevention and bleeding risk in long-term anticoagulation therapy remains a major challenge in clinical management, especially in the elderly and patients with multiple comorbidities. To sum up, research on the pathogenesis of blood hypercoagulability is still developing, and more basic research and clinical trials are needed in the future to further clarify its pathological mechanism and optimize diagnosis and treatment strategies.

5. Conclusions and challenges

A variety of mechanisms promote the formation of blood hypercoagulability in patients with malignant cancers, increase the risk of thrombosis and hemorrhagic diseases, and promote the occurrence and development of cancers. In addition, this hypercoagulability supports the cancer immune escape and interferes with immunotherapy. The investigation of the pathogenesis of blood hypercoagulability in patients with cancer will provide an important theoretical basis for clinically reasonable anticoagulant therapy. Hitherto, the formation mechanism of blood hypercoagulability in patients with cancer remains to be further studied. However, with the continuous attention by scholars and the maturity of various technologies, the mechanism of blood hypercoagulability will be more prefect and can be effectively used in the treatment of cancer patients. Additionally, new targetable approaches are longing for effective advances in clinical treatment and early prediction of cancers. There is a high degree of empiricism in the modeling of thrombosis, and physics based on experimental observations may provide useful strategies for predicting thrombosis and growth. A sequential work-up combining assessment of clinical pretest probability is necessary for hypercoagulable thromboembolism using clinical testing and pharmacological imaging. Especially, evidence-based exercise guidance for cancer patients is on the way to efficient and effective diagnosis and treatment.

CRediT authorship contribution statement

Qiongle Peng: Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization. **Jinmei Zhu:** Writing – review & editing, Writing – original draft. **Yanhu Zhang:** Writing – review & editing, Writing – original draft. **Yanping Jing:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

This research was funded by the Science and Technology program (No. jdfyRC2017003) and the "Beigu Talent" Youth Program (No. BGYCB202203) of the Affiliated Hospital of Jiangsu University, the Medical Teaching and Research Collaborative Project (JDYY2023004) of Jiangsu University, and the Jiangsu Society of Blood Transfusion (No. JS2022036).

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