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REVIEW

Aberrant Factors of Fibrinolysis and Coagulation in Pancreatic Cancer

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Abstract: Aberrant factors associated with fibrinolysis and thrombosis are found in many cancer patients, which can promote metastasis and are associated with poor prognosis. The relationship between tumor-associated fibrinolysis and thrombosis is poorly understood in pancreatic cancer. This review provides a brief highlight of existing studies that the fibrinolysis and coagulation systems were activated in pancreatic cancer patients, along with aberrant high concentrations of tissue plasminogen activator (t-PA), urine plasminogen activator (u-PA), D-dimer, fibrinogen, or platelets. These factors cooperate with each other, propelling tumor cell shedding, localization, adhesion to distant metastasis. The relationship between thrombosis or fibrinolysis and cancer immune escape is also investigated. In addition, the potential prevention and therapy strategies of pancreatic cancer targeting factors in fibrinolysis and coagulation systems are also been discussed, in which we highlight two effective agents aspirin and low-molecular weight heparin (LMWH). Summarily, this review provides new directions for the research and treatment of pancreatic cancer.

Keywords: fibrinolysis, thrombosis, pancreatic cancer, immune escape

Introduction

Pancreatic cancer is the fourth leading cause of cancer-related death in men and fifth in women in the United States from 2013 to 2017.[1] Its prognosis remains very poor with a five-year net survival of less than 10%.[2] Several reasons are responsible for this poor prognosis, including poor early diagnosis, a high rate of relapse after curative surgery, and strong resistance to chemotherapy and radiotherapy. Venous thrombosis has been identified as the second leading cause of death in patients with cancer, inferior only to the progression of cancer.[3]

Pancreatic cancer has the highest risk of venous thromboembolism (VTE).[4] In systematic analysis, thromboembolic event in patients with pancreatic cancer predicted excess premature (3 months) mortality,[5] and symptomatic VTE is an independent risk factor for death.[6] However, anticoagulation is not associated with longer survival[6] and should not be used to extend the survival of patients with cancer in the absence of other indications.[7] This suggested that thrombosis is a late event in the process of cancer. Control of thrombosis cannot impede cancer progression. Interestingly, the fibrin degradation product, D-dimer, could be found in resectable pancreatic cancer without thrombosis and is associated with poor prognosis in these patients.[8] D-dimer is the product of secondary fibrinolysis, which aims to disintegrate the thrombus and maintain patency of the vascular

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system. This suggested that the pathological state of thrombosis already exists, although the thrombus has not yet formed in patients with pancreatic cancer.

Primary hyperfibrinolysis is uncommon in the setting of solid tumors and only isolated cases of primary fibrinolysis have been reported in metastatic prostate cancer[9,10] and breast cancer,[11] which can be reversed by anti-tumor therapy.[11] Although it was not reported in pancreatic cancer so far, factors associated with primary hyperfibrinolysis, such as tissue plasminogen activator (t-PA)[12] and urine plasminogen activator (u-PA),[13] were found at high concentrations in tissue homogenates and sera of patients with pancreatic cancer patients. This indicated that plasminogen was more likely to be activated because of these high concentrations of plasminogen activator, which would lead to a fibrinolysis cascade in pancreatic cancer.

Understanding the aberrant factors associated with tumor-associated thrombosis and fibrinolysis has generated novel hypotheses regarding the mechanisms involved in pancreatic ductal adenocarcinoma (PDAC) growth and dissemination. We will initially review studies identifying the factors associated with the clotting and bleeding system in PDAC and speculate how these two distinct systems might be related to one another and promote metastasis of PDAC. We will then discuss potential strategies to target the molecules associated with the clotting and bleeding system in pancreatic cancer and the development of new directions for the research and treatment of PDAC.

Correlation Between Factors of the Fibrinolysis System and Tumor Cells Free from Their Original Site

The Activation of t-PA and u-PA in Patients with Pancreatic Cancer

The fibrinolytic system is a highly regulated enzymatic process that prevents the unnecessary accumulation of intravascular fibrin and enables the removal of thrombi, which is more appropriately referred to as the plasminogen activator system. In humans, t-PA and u-PA are the two activators of this system. High u-PA expression in tumor tissues[14–16] and increased plasma levels of uPA[17] have long been noted in colonic cancer, lung cancer, basal cell carcinoma, endometrial cancer, and cervical cancer. The overexpression of u-PA in tumor tissue or increased u-PA levels in serum have strong independent prognostic value in terms of relapse-free and/or overall survival in patients with breast, colorectal, esophageal, gastric, hepatocellular, prostate cancer, sarcoma, head and neck squamous cell carcinoma.[17–25]

In pancreatic cancer, the importance of the plasminogen activator system has also been demonstrated.[13,26–30] The first study on u-PA in pancreatic cancer was conducted in 1993, which showed that 78% of pancreatic cancers overexpressed u-PA and this overexpression correlated with decreased survival.[31] Ten years later, these results were confirmed by another study, which showed a higher rate of u-PA expression, with 93% in archival paraffin sections. The u-PA staining was also found in pancreatic intraepithelial neoplasia (Pan IN) lesions, but not in normal tissue,[29] which indicated that u-PA was an early event in the malignant transformation of pancreatic cancer. Furthermore, in situ hybridization experiments revealed the presence of u-PA mRNA, not only in the cytoplasm of tumor cells but also in the vessels of the tumor stroma,[29] which suggested that u-PA should be detectable via serum analysis. Indeed, u-PA overexpression in tumor tissue correlated with the serum levels of u-PA in patients with pancreatic or biliary cancer.[30] In summary, overexpression of u-PA correlates closely with the rapid progression, invasiveness, and short overall survival of pancreatic cancer.

t-PA is one of the better studied compounds of the fibrinolysis pathway, which has been detected in multiple tumors, such as ovarian cancer,[32] lung cancer,[33] breast cancer,[34] glioma,[35] hepatocellular cancer,[36] laryngeal tumors,[37] malignant melanoma,[38] prostate cancer,[39] gastric cancer,[40] and colonic cancer.[41] However, t-PA antigen levels in cancer tissue varied in different tumor types. t-PA levels were significantly lower in non-small cell lung cancer, gastric cancer, and colonic cancer than in normal tissue; However, t-PA levels were significantly higher in patients with breast carcinoma compared with that in the control group. The significance of t-PA for prognosis is also controversial, some studies showed that overall survival was significantly worse for patients with tumors showing tPA in the lowest quartile of activity in primary breast cancer;[42,43] however, others showed that no significance was found in gastric cancer,[40] hepatocellular carcinoma (HCC).[36]

Although the value of t-PA varied in many cancers, multiple studies showed that t-PA was overexpressed in pancreatic cancer tissue.[12,44,45] The mean t-PA concentration in tissue homogenates gradually increased in cases with a normal pancreas, chronic pancreatitis, and

pancreatic cancer.[12] Additionally, t-PA plays an important role in the growth, invasion and angiogenesis of pancreatic tumor cells.[44] Increasing tissue homogenate t-PA concentrations were associated with blood vessel infiltration, and t-PA concentrations were higher in sera than in tissue homogenates in patients with pancreatic cancer.[12] In addition, vulnerability to t-PA increased in patients with pancreatic cancer,[46] which might explain the higher incidence of hemorrhage after surgery in pancreatic cancer (9.9%; 42/423),[47] but was only 1.3 (4/316) in patients with lung cancer after surgery.[48]

Tumor Cells are Freed from Their Original Site Through the Fribrinosis System

The plasminogen-plasmin system, also known as the fibrinolysis system, has been reported to be associated with various processes of tumor development, proliferation, invasion, and tumor angiogenesis.[14,49,50] The overexpression of t-PA and u-PA in tumor cells locally activated plasminogen to plasmin, which in turn activates latent metalloproteinases, latent growth factors, and the degradation of extracellular matrix (ECM) proteins, such as laminin and fibronectin.[51,52] It is believed that the resulting proteolysis of ECM frees the cell from its adhesion site allowing cell migration, which is manifested as invasion at local sites, and as metastasis at distant sites via circulating tumor cells (CTC) migrating to the blood system. Therefore, it was hypothesized that the u-PA system could be responsible for CTC generation and D-dimer production. Previous studies showed that D-dimer was an essential accompaniment of CTCs in gastric cancer[53] and metastatic breast cancer.[54,55] Plasma u-PA was highly associated with CTCs in early breast cancer and u-PA overexpressed in CTC_EP (epithelial phenotype), but not in CTC_EMT (epithelial to mesenchyme transition phenotype).[55] These results indicated that the CTC_EP cells that overexpressed u-PA become detached from the lesion and invade directly to the blood system.

In pancreatic cancer, high concentrations of D-dimer,[8,56] uPA,[30] and tPA[12] were found in plasma and were associated with reduced survival in pancreatic cancer and predict non-resectability. Although the relationships among D-dimer, u-PA, t-PA, and CTCs remain unknown, studies have shown that t-PA and u-PA could promote metastasis by activating plasminogen in pancreatic cancer.[57] t-PA binds to Annexin II, which is overexpressed in pancreatic cancer and accelerates cell surface conversion of plasminogen to plasmin.[58,59] Disruption of the t-PA/annexin II interaction using a specific hexapeptide significantly decreased the invasive capacity of pancreatic cancer cells (SK-PC-1) in vitro.[45] Meanwhile, u-PA binds to its receptor (u-PAR) to activate plasminogen.[60] Importantly, both u-PAR and u-PA are highly expressed in human pancreatic cancer tissues, and the expression of u-PAR always correlated with the expression of its ligand u-PA. Furthermore, suppression of the u-PAR–u-PA system prevented invasion,[61] and upregulation of the u-PAR–u-PA system promoted EMT and metastasis in pancreatic cancer.[13]

Therefore, we speculated that activation of the fibrinolysis system comprises the first step for local invasion and distant metastasis in pancreatic cancer (Figure 1). From this hypothesis, we suggested that CTCs would be detected in patients with pancreatic cancer. Most patients of pancreatic cancer have no symptoms at the early stage and lack an effective early detection method; therefore, detecting CTCs might be an effective method to detect pancreatic cancer earlier, especially in cases with a high risk of developing pancreatic cancer. Furthermore, cancer tissues are difficult to access because of their deep and hidden site; thus, detection of CTCs might help to clarify the diagnosis and guide therapy although there still remain a number of challenges to the routine implementation of CTCs in the clinical management of pancreatic cancer.[62]

The Coagulation System and the Anchoring/Adherence of Tumor Cells

Abnormality of Platelets and Fibrinogen in Pancreatic Cancer

Coagulation is a dynamic system, representing a balance between clotting and bleeding that is always maintained in normal physiology and is generally altered under disease conditions. About 60–100% of patients with malignant neoplasia were found to have hemostatic alterations, as detected by laboratory tests, including those without thrombotic manifestations. These changes comprise different levels of blood coagulation abnormalities, such as shortened activated partial thromboplastin time, thrombocytosis, elevated levels of circulating blood coagulation proteins [fibrinogen, factor V, VIII, IX, and X], and increased concentrations of fibrin or fibrinogen, or both, degradation products.[63]

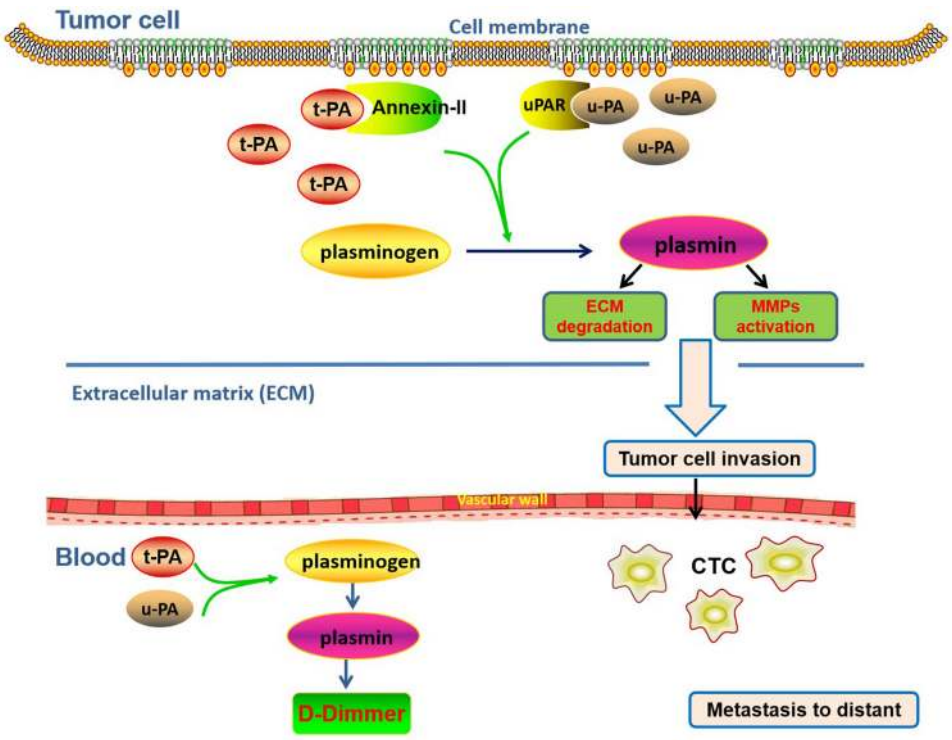

Figure 1 The diagram of the plasminogen activator system associated with local invasion and distant metastasis in pancreatic cancer. In this system, t-PA and u-PA are overexpressed in tumor cells; (t-PA)-(annexin II) binding and (u-PA)-(u-PAR) binding can both activate plasminogen to plasmin, which in turn activates MMPs and ECM degradation; the resulting proteolysis of ECM frees the cells from their original site allowing cell invasion, which is manifested as metastasis at distant sites via CTC migrating to the blood system; high concentration of D-dimer in plasma is an essential accompaniment of CTCs.

It was reported that a long duration of thrombocytosis was a major risk factor for thrombosis.[64] The prevalence of thrombocytosis was 11.4% in gastric cancer,[65] 32% in lung cancer,[66] and 8% in rectal cancer,[67] and predict worse prognosis in non-small cell lung cancer (NSCLC)[68] and gastric cancer.[69] Also, high plasma fibrinogen levels (≥400 mg/dL) were another important risk factor for thrombosis, which were found in 45.8% (55/120) of small-cell lung cancer,[70] in 34% (34/100) of ovarian cancer,[71] and in 56.7% (68/120) of renal cell carcinoma (levels ≥343 mg/dL).[72] High plasma fibrinogen was also considered as a poor prognosis factor and predicted shorter survival.

In advanced pancreatic cancer, VTE represents a frequent complication, with an estimated incidence between 12.1% and 42%. Symptomatic VTE was an independent risk factor for death.[6] Many factors associated with thrombosis had existed in patients with pancreatic cancer without VTE. Thrombocytosis was reported in 15.2% (19/125) of pancreatic cancer.[73] It was higher in patients with pancreatic cancer with T3 and T4 tumor than in patients with T1–2 tumors.[74] Furthermore, a higher concentration of platelets was associated with a worse prognosis and a high risk of developing distant organ metastasis in pancreatic cancer.[73,75] The other factor associated with thrombus, high plasma fibrinogen level, was found in 32.8% (39/119) of postoperative patients with resectable pancreatic cancer and in 24.8% (31/125) of patients with stage I–IV disease.[73] Similarly, plasma fibrinogen levels ≥400 mg/dL were independent predictors of poor progression-free survival (PFS) and OS in locally advanced pancreatic adenocarcinoma.[73,76] Notably, both platelet and fibrinogen levels were simultaneously and significantly elevated in the plasma of patients with pancreatic cancer. There was also a significant correlation between higher fibrinogen/platelet levels and distant organ metastasis ($p < 0.05$, respectively).[73] Therefore, we suggested that high levels of fibrinogen and platelets in patients with pancreatic cancer would help the CTCs anchor and adhere to the vascular wall, promoting the formation of blood clots with cancer cells, and thus resulting in distant metastasis.

Tumor Cells Anchor/Adhere Though Platelets and Fibrinogen

Following their entrance into the circulation, CTCs must adhere to the microvasculature of a target organ prior to growth.[77] Obviously, adhesion or anchoring to the

microvasculature is the key step in hematogenous metastasis. Platelets express a number of cell-surface receptors for adhesion and aggregation, including the glycoprotein (GP) Ib-IX-V complex, which serves as a receptor for von Willebrand factor (vWF), and GP IIb-IIIa integrin, which binds to fibrinogen and fibronectin.[78,79] They might also contribute to the physical interaction between CTCs and vascular endothelial cells by supporting the stable adhesion to endothelium and/or transmigration of tumor cells out of the vasculature.

The molecular coordination between platelets and tumor cells adhered to the vascular wall, which supported metastasis from the bloodstream, is well described.[80] The platelet membrane glycoprotein (GP) $\alpha_{IIb}ß_3$ complex,[81] GP α_{Ib},[82] and GP VI[83] facilitate platelet adhesion and aggregation to tumor cells, thus promoting metastatic seeding. P-selectin, a platelet surface protein, is known to bind to CD24 on tumor cells, causing their adherence to endothelial cells, and mediate adhesion of leukocytes, platelets and cancer cells in inflammation, thrombosis, cancer growth and metastasis.[84,85] P-selectin-mediated adhesion of cancer cells to immobilized platelets under dynamic flow conditions[86] and immobilized platelets support cancer cell tethering, rolling, and firm adhesion under dynamic flow conditions via P-selectin and GPαIIbß3.[87]

However, in pancreatic cancer, there are still many opportunities for research into the role of platelets. Platelets adhere to vWF through the platelet receptor GPIb/IX/V complex bound to endothelial cells. This interaction is responsible for the tethering, rolling, and activation of platelets that eventually become firmly adhered, leading to thrombus formation.[88] Recently, a novel molecule, vimentin, was found to be expressed on the platelet surface and serve as an adhesive receptor for vWF.[89] In pancreatic cancer, there was a 3-fold increase in vimentin expression compared with that in other tumors, and a more specific antigenic isoform of vimentin was found at 5–10 fold higher levels in pancreatic cancer.[90] Therefore, we hypothesized that the pancreatic cancer cells in circulating blood were also combined with the vWF molecule by vimentin. This suggested that platelets enriched around circulating pancreatic cancer cells because vWF molecule captured CTCs to adhere to the capillary wall, as well as captured the platelets. Pancreatic cancer cells would tightly adhere together by the platelets that were around them, making it easier to form a thrombus. Meanwhile, platelets form a protective network, which impedes natural killer cell-mediated elimination of tumor cells.[91]

Fibrinogen acts as a "molecular bridge" between specific receptors on tumor cells and the vascular endothelium or adherent platelets and leukocytes to promote cancer cell metastasis. Although fibrinogen deficiency was found to have no effect on the time required for the formation of palpable tumors and tumor growth, it markedly reduced the incidence of spontaneous macroscopic metastases in the lung and regional lymph nodes.[92] Fibrinogen appears to facilitate metastasis by enhancing the sustained adherence and survival of individual tumor cell emboli in the vasculature of target organs.[93]

It has been demonstrated that fibrinogen binding to intercellular adhesion molecule-1 (ICAM-1) on endothelial cells could mediate the attachment of leukocytes and platelets.[94] Tumor-derived ICAM-1 serves as an important docking point for tumor infiltration of immune cells that functionally promote pancreatic cancer cell metastasis.[95] Interestingly, expression of ICAM-1 was increased by five-fold in surgical specimens from patients with pancreatic cancer compared with healthy controls, and this increased level of ICAM-1 correlates with increased nodal metastasis, advanced tumor stage, and shorter survival time.[96] However, the normal human pancreas expresses low levels of ICAM-1.[97] This indicated that ICAM-1 might be a promising target for therapy and could play an important role in pancreatic cancer progression and metastasis. Therefore, we postulated that high fibrinogen levers in patients with pancreatic cancer might promote CTC adhesion and immobilization to the endothelium through ICAM-1.

In summary, a high concentration of platelets and fibrinogen might work together to help the adhesion of CTCs to the vascular wall in pancreatic cancer, which is shown in a diagram in Figure 2.

Platelets and Immune Escape in Pancreatic Cancer

Tumor cell adhesion via platelet receptors leads to platelet activation and release of secondary mediators to create a positive feedback activation mechanism. Once activated, platelets change shape and degranulate to release high local concentrations of soluble factors, including transforming growth factor-β (TGF-β), platelet-activating factor (PAF), histamine, 5-HT, and serotonin, which act as signals for target cells, including cells of the innate and adaptive immune systems.[98] Lam et al recently reviewed the interaction of platelets with other immune cells.[99]

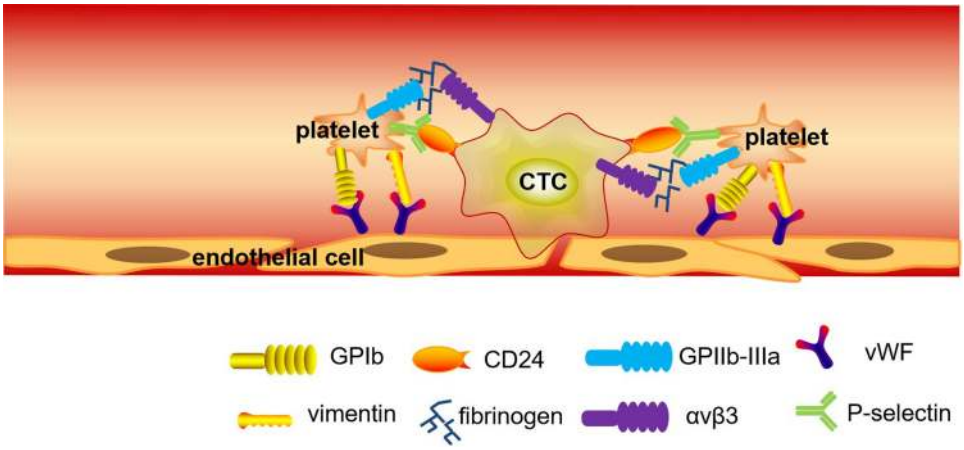

Figure 2 The diagram of the aberrant coagulation system associated with the anchoring and adherence in pancreatic cancer. In this system, platelets express a number of cell-surface receptors for adhesion and aggregation, including the GP Ib-IX-V complex and vimentin for vWF binding, the GP IIb-IIIa integrin for binding to fibrinogen and fibronectin, and the P-selectin for binding to CD24 on CTCs, supporting their adherence to endothelial cells, thus causing thrombosis and metastasis in pancreatic cancer; Fibrinogen acts as a "molecular bridge" between specific receptors on CTCs and the vascular endothelium or adherent platelets and leukocytes to promote cell metastasis.

A previous study demonstrated that TGF-β from platelets diminished natural killer (NK) cell granule mobilization, downregulated NKG2D receptor on the NK cells, and interferon-γ (IFN-γ) secretion.[100] Moreover, tumor cell coating by platelets might cause the transfer of MHC class I onto the tumor cell surface, resulting in impaired cytotoxicity and IFN-γ production by NK cells.[101] In other words, downregulation of NKG2D in NK cells and the "pseudonormal" phenotype of platelet-coated tumor cells impairs NK cell tumor immune surveillance by disturbing "induced self" and "missing self" tumor cell recognition and elimination.[102] Apart from NK cells, TGF-β from platelets could completely block T cell proliferation, blastogenesis, and IFN-γ production. T cell immunity against cancer was subverted by platelets via the glycoprotein A repetitions predominant (GARP)-TGF-β axis. Furthermore, anti-platelet agents can enhance the antitumor effect of immunotherapy with adoptive T cell transfer.[103]

Lam recently reviewed the interaction of platelets with neutrophils.[99] A previous study showed that activated platelets present high mobility group box 1(HMGB1) to neutrophils, promoting the extrusion of neutrophil extracellular traps (NETs),[104] which was able to trap CTCs, thus promoting early adhesion of tumor cells to distant organ sites in a lung cancer model.[105] Although platelet-mediated tumor immune escape has been demonstrated in many tumor models, little research has been done in pancreatic cancer. Recently, Boone et al showed that NETs could be detected in both human and murine pancreatic tumors,[106] suggesting that infiltrating neutrophils release NETs into the tumor microenvironment. Genetic ablation of the receptor for advanced glycation end products (RAGE) resulted in a decreased propensity for the NET formation and decreased serum DNA (one of the compositions of NETs). RAGE is a class III MHC protein receptor and mediates platelet–neutrophil interactions, which is increasingly expressed on the surface of activated platelets. HMGB1 binds to activated platelets via RAGE in platelet-rich human coronary artery thrombi.[107] Interestingly, circulating HMGB1 is elevated in pancreatic cancer, which has been shown to stimulate NET formation;[108,109] therefore, we hypothesized that NETs might be found in the blood system, where they trap cancer cells to protect them from NK cells, thus promoting metastasis in patients with pancreatic cancer.

In addition, fibrinogen helps platelets to adhere to tumor cells, and platelets in turn promote more fibrinogen to aggregate around tumor cells by forming thrombin. Their mutual facilitation protects tumor cells from NK cytotoxicity.[91,110] However, the exact mechanisms of how platelet activation and fibrin clotting mediates immune escape still need to be defined in pancreatic cancer.

Prevention and Therapy of Cancer Targeting the Factors in Thrombosis or Fibrinolysis

As it is well known, classical anti-platelet/anti-thrombotic agents include aspirin and low-molecular-weight heparin (LMWH). Currently, LMWH was suggested as the standard of care. The American Society of Clinical Oncology (ASCO) recommendations propose unfractionated heparin,

fondaparinux or LMWH as a first-line treatment, unless contraindicated due to high bleeding risk or active bleeding.[111] However, little clinical information is available regarding other anti-platelet agents in cancer, but some of them may be beneficial for cancer patients. In other words, these drugs are in the preclinical stage or different phases of clinical trials, and part of them may be available in the market in the near future. Studies pointed out that targeting specific molecules on platelet membranes, such as protease-activated receptor 4 (PAR-4),[112] glycoprotein (GP) GPIIb-GPIIIa complex,[81,113–115] the GPIb-V-IX complex,[116] GPVI,[83] integrins α6ß1 and αIIbß3,[117] and p-selectin,[118,119] showed a significant experimental anti-metastatic effect. Interestingly, these molecules all mediated the characteristic of platelet adhesion, which further confirmed the importance of platelet adhesion in tumor cell metastasis. In Heyu Ni group's review, P-selectin inhibitors, GPVI and GPIbα antagonists are under development.[120] Other emerging anti-platelet agents include those targeting platelet-activating receptors and inhibitory receptors, anti-coagulants and plant-based food products (eg anthocyanins) may also have anti-tumor effects. Interestingly, Heyu Ni et al comprehensively characterized these new agents that may affect tumor metastasis and tumorigenesis in Table 1, which will certainly advance our knowledge for tumor treatment.[120] It is also possible that platelet inhibitors could have other antitumor mechanisms, such as blocking angiogenesis and immune-suppressive prostaglandins,[121] which would contribute to their antitumor activity. Another review paper by Nikolaos Arkadopoulos's group highlights the family of Novel Oral Anticoagulants (NOACs), including dabigatran etexilate, rivaroxaban, apixaban and edoxaban, each one with their own special pharmacokinetics and pharmacodynamics, which were detailedly summarized in Table 3.[111] However, the use of NOACs for VTE prophylaxis is certainly debatable. The potential drug interactions with chemotherapeutic components, GI abnormalities, and hepatic and renal insufficiency remain significant determinants of NOACs administration,[122–124] which indicate NOACs' limited bioavailability and the main reason not carried out in clinical. Here, we will highlight aspirin and LMWH, whose molecular mechanisms, efficiency and benefits for patients have been well discussed.

Aspirin

Aspirin, an antithrombotic drug, has become the focus of intense research on cancer prevention and outcome. Some of these studies have shown a favorable effect, while others failed to find any significant decrease in cancer incidence. These studies have been reviewed.[125] Furthermore, regular use of aspirin reduces the long-term risk of several cancers and the risk of distant metastasis.[126]

In pancreatic cancer, evidence from 15 clinical studies or analyses that aspirin has chemo-preventive effects is somewhat controversial: Five trials endorsed the protective effect of aspirin, one indicated a harmful effect, and the others revealed no significant correlation.[127] Among the studies that showed a protective effect, all of them indicated that long-term aspirin use, or use for 5 to 10 years or more in the past, was associated with reduced risk of cancer incidence.[128] Furthermore, this trend of decreasing risk with duration of use was evident.[129] In addition, high-dose aspirin, rather than low-dose aspirin, might be associated with a decreased risk for pancreatic cancer, especially for Americans.[130] Further efforts should be made to explore the chemo-preventive effects as well as the dose, frequency, and duration of aspirin use for better clinical practice. A previous meta-analysis of 20 studies conducted a decade ago estimated that individuals with diabetes have a two-fold greater relative risk (RR) of pancreatic cancer compared with individuals without diabetes.[131] Therefore, the combination of metformin and aspirin could provide additive and possibly synergistic effects for the prevention and treatment of pancreatic cancer.[132,133] Prospective clinical trials are urgently required, whose results might form a milestone for the prevention of pancreatic cancer in patients with diabetes.

The therapeutic effects of aspirin in pancreatic cancer involve multiple molecular targets, including: suppressing sustained cell survival and proliferation (eg, via COX, IKBKB, and PRKA), attenuating genome instability and mutations, regulating the cancer immune and inflammatory profile, anti-tumor angiogenesis, and impeding the accommodation of cancer cells to the microenvironment. An animal study showed that aspirin strongly inhibited the formation of metastasis via inhibition of αvβ1/β3 integrins and p-selectin in an orthotopic model of pancreatic cancer.[134] Inhibition of platelets by aspirin could affect their ability to induce cell proliferation through the modulation of the c-MYC oncoprotein in pancreatic cancer.[135] Furthermore, activated platelet-derived TGF-β1 resulted in a reduction of cisplatin sensitivity in pancreatic cancer cells through stimulating PI3K/AKT and MEK/ERK signaling.[136] This suggested that inhibition of platelet

activation could reverse the resistance to cisplatin in pancreatic cancer.

Low-Molecular Weight Heparin (LMWH)

In 1992, Green et al found that LMWH could reduce mortality in patients with cancer.[137] Thereafter, a number of data showed the potential anti-metastatic activity of heparin and LMWH via in vitro and in vivo studies.[138–143] These in vitro studies showed that heparin or LMWH treatment attenuated tumor metastasis in mice by inhibiting P-selectin-mediated interactions of platelets with carcinoma cell-surface mucin ligands, which reinforced the importance of adherence between the cancer cells and platelets.

In patients with advanced pancreatic cancer, the in vitro study showed that dalteparin could decrease serum-mediated induction of cancer cell invasion.[144] Sulfated non-anticoagulant heparins (S-NACHs) distinctly increased tumor necrosis, enhanced gemcitabine response in mouse pancreatic cancer models,[145] and inhibited pancreatic cancer cell adhesion and metastasis in human umbilical cord vessel segments and in a mouse model.[146] Clinical data showed that nadroparin[147] and dalteparin[144] could prevent thromboembolic events in patients with advanced pancreatic cancer receiving chemotherapy;[144] however, the survival data were not analyzed.

von Delius et al reported that treatment with LMWH did not produce a survival difference in 213 patients with advanced pancreatic adenocarcinoma. However, in the subgroup with metastatic pancreatic adenocarcinoma, treatment with LMWH was a survival advantage for patients. The median survival was 6.6 months and 3.8 months for the LMWH group and the non-LMWH group, respectively.[148] Another study, which involved 69 patients with advanced pancreatic cancer with a follow-up time of less than 25 months, showed that the addition of LMWH to chemotherapy significantly improved the response to the chemotherapy (response rate: 58.8% vs 12.1%, $p = 0.0001$) and prolonged survival (13.0 vs 5.5 months, $p = 0.0001$) patients with advanced pancreatic cancer.[149] However, another prospective clinical study, which was conducted in 312 patients with pancreatic cancer, with a follow-up time up to 60 months, did not show a significant difference in progression-free survival (4.99 vs 5.42 months, $p = 0.64$) or overall survival (8.51 vs 8.02 months, $p = 0.44$) in these patients receiving chemotherapy together with LMWH or without LMWH. However, the overall cumulative incidence rate of symptomatic VTEs was lower in the patients with APC that received chemotherapy with LMWH than in those not receiving LMWH (6.4% vs 15.1%). The numbers of major bleeding events were similar between the two groups (7/160 vs 5/152, $P = 1.0$).[150] Then, inconsistent survival data in these studies might be caused by differences between the number of enrolled patients and the follow-up duration.

One meta-analysis showed that the use of prophylactic LMWH did not have a discernible effect on overall survival in patients with solid malignancy without VTE.[151] The result was confirmed by the most recent meta-analysis,[152] which was the second update by Cochrane in 2016. It showed that primary thromboprophylaxis with LMWH significantly reduced the incidence of symptomatic VTE in patients with ambulatory cancer treated with chemotherapy. Therefore, LMWH as an agent to prevent metastasis and improve the survival duration requires further investigation.

Concluding Remarks

Increased attention has focused on the effect of activation of the fibrinolysis and coagulation systems in cancer. Our review showed that the fibrinolysis and coagulation systems were activated in patients with pancreatic cancer, manifested as high concentrations of t-PA, u-PA, D-dimer, fibrinogen, or platelets. These factors cooperate with each other and encourage cancer immune escape to achieve local invasion and distant metastasis. Prevention and treatment of cancer metastasis by the agents of aspirin and LMWH targeting molecules of these two systems have been well discussed. However, other novel anti-platelet/anti-thrombotic agents are still in the preclinical stage or different phases of clinical trials, but some of them may be beneficial for cancer patients and available in the market in the near future.

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Disclosure

The authors report no conflicts of interest for this work.

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