Hemostasis and tumor immunity

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Abstract

Significant data have accumulated demonstrating a reciprocal relationship between cancer and the hemostatic system whereby cancer promotes life-threatening hemostatic system dysregulation (e.g., thromboembolism, consumptive coagulopathy), and hemostatic system components directly contribute to cancer pathogenesis. The mechanistic underpinnings of this relationship continue to be defined, but it is becoming increasingly clear that many of these mechanisms involve crosstalk between the hemostatic and immune systems. This is perhaps not surprising given that there is ample evidence for bidirectional crosstalk between the hemostatic and immune systems at multiple levels that likely evolved to coordinate the response to injury, host defense, and tissue repair. Much of the data linking hemostasis and immunity in cancer biology focus on innate immune system components. However, the advent of adaptive immunity-based cancer therapies such as immune checkpoint inhibitors has revealed that the relationship of hemostasis and immunity in cancer extends to the adaptive immune system. Adaptive immunity-based cancer therapies appear to be associated with an increased risk of thromboembolic complications, and hemostatic system components appear to regulate adaptive immune functions through diverse mechanisms to affect tumor progression. In this review, the evidence for crosstalk between hemostatic and adaptive immune system components is discussed, and the implications of this relationship in the context of cancer therapy are reviewed. A better understanding of these relationships will likely lead to strategies to make existing adaptive immune-based therapies safer by decreasing thromboembolic risk and may also lead to novel targets to improve adaptive immune-based cancer treatments.

KEYWORDS

cancer, hemostasis, immune system, thromboembolism, tumor

Essentials

- A bidirectional link between hemostasis and cancer has been recognized for decades.
- The mechanisms linking hemostasis and cancer include innate and adaptive immunity.
- Hemostatic system components limit adaptive antitumor immunity through multiple mechanisms.
- Therapies that promote adaptive antitumor immunity appear to increase thromboembolic risk.
The association of venous thromboembolism (VTE) with cancer was first described more than a century ago by Dr. Armand Trousseau and is referred to as “Trousseau syndrome.” Studies spanning the past 5 decades have shown that the association of cancer and hemostasis is bidirectional. Cancer not only causes hemostatic system dysregulation, but hemostatic system components are actively involved in cancer pathogenesis. Many malignant cell types express tissue factor (TF), the primary cell associated initiator of thrombin generation. TF expression by tumor cells has been linked to more advanced disease and a worse prognosis for multiple cancers. More recent data have shown that tumor cells and/or stromal cells in the microenvironment are also capable of secreting hemostatic proteases, including factor VII and factor X. Therefore, the tumor microenvironment has the necessary “tools” to initiate signaling events through protease activated receptors (PARs) and to generate thrombin. Consistent with this, TF has been implicated in cancer progression through mechanisms linked to both hemostatic system activation as well as signaling mechanisms independent of hemostasis. Thrombin has been shown to promote multiple aspects of cancer pathogenesis, including tumorogenesis, angiogenesis, and metastases. Thrombin-mediated cleavage of the seven-transmembrane receptor, PAR-1, which is up-regulated in many malignant cell types, has been implicated in promoting oncogenic gene up-regulation, subendothelial matrix adhesion, self-sufficient growth signals, resistance to apoptosis, and unlimited replication potential. PAR-1 expressed by tumor stromal cells has also been implicated in tumor progression. Thrombin-mediated activation of platelets, fibrinogen, and factor XIII constitute indirect mechanisms by which thrombin further enhances pro-tumorigenic phenotypes, including metastasis, and immune cell evasion. Several of the mechanisms coupling hemostatic system components to cancer progression have been shown to involve innate immune cells (e.g., macrophages, natural killer cells). However, the role of interplay between hemostatic system components and adaptive immunity in cancer pathogenesis represents a relatively new area of exploration. The role in the hemostatic factors in adaptive immunity has become of significant importance because of the implementation of immune checkpoint inhibitor (ICI) therapies. Malignant tumors can be recognized by adaptive immune system components, and cytotoxic T cells are capable of killing cancer cells. However, malignant tumors rapidly evolve multiple mechanisms to shut down adaptive immune mechanisms and create T-cell exhaustion in the tumor microenvironment. ICI therapies are promising anticancer strategies to reinvigorate the immune compartment that reached clinical practice over the past decade. Broadly speaking, the mechanism of action of these therapies involves blocking the interaction of regulatory immune receptors (e.g., programmed cell death protein 1, programmed death ligand 1 [PD-L1], and cytotoxic T lymphocyte-associated protein 4) with their ligands, thereby promoting an adaptive antitumor immune response. Similarly, chimeric antigen receptor (CAR) T-cell therapy has become a widely used strategy to manipulate the immune system to target “liquid” tumors (i.e., leukemia and lymphoma). Here, cytotoxic T cells engineered to express a T-cell receptor capable of recognizing tumor antigens are introduced into patients.

Although adaptive immune-based therapies have improved outcomes for numerous patients with a variety of malignancies, growing evidence indicates that the use of these therapies may be associated with a high risk of coagulation disorders, particularly VTE. Taken together, these clinical observations suggest that the reciprocal bidirectional link between hemostasis and immunity in cancer pathogenesis extends beyond innate immunity to include adaptive immunity. The goals of this manuscript are to (1) review the data linking adaptive immunity-based cancer therapies to hemostatic system deregulation and thrombosis and (2) discuss the mechanistic underpinnings of the reciprocal relationship between the hemostatic and immune systems in cancer progression, including relatively recent data indicating that hemostatic system components regulate the adaptive immune response in cancer. Note that for the purposes of this review, the term “hemostasis” is broadly used to describe all components of the hemostatic system, including cellular (e.g., platelets, endothelial cells) and protein components.

Hemostatic System Components Regulate Innate and Adaptive Tumor Immunity in the Context of Cancer Pathogenesis

Substantial evidence has accumulated supporting the view that the hemostatic and immune systems represent an integrated unit involved in wound healing and host defense. This view is supported by an impressive and growing body of evidence indicating that there is bidirectional crosstalk between the hemostatic and immune systems at multiple levels. Given the importance of both innate and adaptive immune functions in the pathogenesis of cancer, it is perhaps not surprising that these areas of critical crosstalk between hemostasis and immunity also affect cancer pathogenesis. The reciprocal nature of the crosstalk between hemostasis and immunity means that immune dysregulation in cancer not only leads to thromboembolic complications, but also that alterations in immune functions driven by hemostatic system components directly affect cancer pathogenesis.

To date, most of the studies examining the interplay of hemostasis and immunity on cancer pathogenesis have focused on innate immune system components. For example, platelets and fibrinogen have been shown to promote the metastatic potential of circulating tumor cells by impeding the clearance of micrometastases by natural killer (NK) cells. One mechanism coupling platelets to metastasis involves the local release of transforming growth factor-β1 from α granules, a key immune modulator that downregulates NK cell functions. Platelets also have been shown to transfer major histocompatibility class I molecules to the surface of circulating tumor cells, thereby making them less likely to be targeted by NK cells.
Platelets rapidly adhere to embolic tumor cells and promote that extravasation of metastatic tumor cells into the parenchyma of target organs.\(^{25}\) In addition to providing a suitable microenvironment to a metastatic tumor cell, extravasation could also protect the malignant cell from circulating immune surveillance mechanisms.

The platelet/fibrinogen axis has also been shown to drive pathological innate immune functions important in intestinal tumorigenesis. Pharmacological platelet inhibition was shown to significantly limit tumorigenesis in a murine model of inflammation-driven adenoma formation.\(^{26}\) Mechanistic studies suggested that platelets and/or platelet-derived soluble factors promote tumorigenesis in the colon by creating an immunosuppressive microenvironment by regulating the development of myeloid-derived suppressor cells.\(^{26}\) Fibrinogen has also been linked to intestinal tumorigenesis via mechanisms involving innate immunity independently of its role in platelet aggregation. These studies showed that fibrinogen-driven leukocyte interactions were shown to support the local secretion of key inflammatory cytokines known to play a role in colon cancer progression (i.e., interleukin-6 [IL-6], tumor necrosis factor-α, IL-1β). These fibrinogen-driven inflammatory events led to rapid alterations in colonic epithelial cells, including phosphorylation of the transcription factors cJun and p65.\(^{27}\)

More recent studies have shown a link between hemostatic system components and adaptive immunity in cancer pathogenesis. Refer to Figure 1A for a graphical summary of the potential mechanisms linking hemostatic system components to adaptive tumor immunity reviewed here. Analyses of syngeneic transplantable pancreatic cancer cells in mice revealed that tumor-derived PAR-1 expression promotes tumor growth in this context by a mechanism linked to downregulation of adaptive immune clearance mechanisms. Genetic deletion of tumor cell-associated PAR-1 essentially eliminated the ability of these cells to form tumors in immunocompetent mice, but tumor growth was restored in immunodeficient NSG mice, or by depletion of CD8+ T cells.\(^{28}\) Thrombin-mediated activation of PAR-1 expressed by pancreatic cancer cells was shown to upregulate expression of Csf2 (granulocyte macrophage colony stimulating factor), and Ptgs2 (prostaglandin-endoperoxide synthase 2), both of which have been linked to immunosuppressive functions.\(^{29}\) Overexpression of Csf2 and Ptgs2 in PAR-1-deleted pancreatic cancer cells partially restored tumor growth. These studies suggest that, at least in some contexts, thrombin-mediated activation of tumor cell-associated PAR-1 triggers transcriptional changes that contribute to the immunosuppressive tumor microenvironment, thereby promoting tumor growth. These studies also suggest the intriguing possibility that available inhibitors of PAR-1 (e.g., vorapaxar) could be used to stimulate an adaptive immune response in some cancers, such as pancreatic adenocarcinoma. However, further study will be needed to better determine which malignancies could potentially benefit from such therapy. Previous studies in mice showed that genetic deletion of PAR-1 resulted in larger and more aggressive tumors in two distinct murine models of spontaneous prostate cancer and intestinal adenoma formation.\(^{30}\) Better defining which cancers are dependent on PAR-1 for escape from tumor immunity will be

**FIGURE 1** Graphical summary of the proposed mechanistic crosstalk between adaptive immunity and hemostasis in cancer. (A) Thrombin-mediated activation of tumor cell-associated PAR-1 and factor Xa-mediated activation of TAM-associated PAR-2 downregulate T-cell effector functions, limiting adaptive tumor immunity. Thrombin-mediated activation of T cell-associated PAR-1 has been linked to upregulation of T-cell effector functions in other contexts, but whether this pathway plays a role in adaptive tumor immunity remains to be determined. See text for details. (B) Upregulation of adaptive tumor immunity could promote thrombosis through multiple mechanisms. Killing of tumor cells could result in release of TF-expressing microvesicles. T cell activation has been shown to result in upregulation of monocyte/macrophage TF expression in vitro. Whether this mechanism is relevant in the context of cancer remains to be determined. Increased circulating levels of IL-8 have been associated with an increased incidence of thrombosis in patients receiving ICI therapy. IL-8 has been shown to promote NETosis in myeloid derived suppressor cells (MDSC), providing a potential link between IL-8 and thrombosis. See text for details.
an important step in determining which cancers could benefit from drugs targeting PAR-1.

A role for hemostatic system components in adaptive tumor immunity was also indicated by studies in mice showing that factor Xa (FXa) secreted by myeloid cells in the tumor microenvironment promotes evasion from adaptive tumor immunity. FXa was mechanistically coupled to evasion of adaptive immune clearance mechanisms by activation of PAR-2. These studies also showed that treatment of tumor bearing mice with the FXa inhibitor, rivaroxaban, enhanced the antitumor immune response generated by ICI therapy. Consistent with these results, recent clinical analyses suggested a link between the use of FXa inhibitors and improved outcomes in patients receiving ICI therapy. This retrospective study analyzed 280 patients with metastatic melanoma receiving ICI therapy. Of these, 76 were treated concomitantly with anticoagulation with 29 receiving heparins, 20 receiving vitamin K antagonists, and 27 receiving small-molecule FXa inhibitors (rivaroxaban, edoxaban, or apixaban). Anticoagulation was not associated with a significant increase in bleeding complications in these patients. There was no difference in response to therapy in comparisons of those patients receiving ICI therapy together with anticoagulation versus those receiving ICI therapy alone. However, when the authors stratified the patients by the class of anticoagulant administered, a different picture emerged. Patients receiving FXa inhibitors had a significantly better response to ICI therapy than those not receiving any anticoagulant. Interestingly, patients receiving vitamin K antagonists had a similar response to therapy as those patients receiving no anticoagulation, but patients receiving heparins had a worse response than those not receiving any anticoagulation.

Although the results of this clinical analysis are intriguing and suggest that FXa inhibitors could augment antitumor immunotherapy, they must be interpreted with caution. The study was entirely retrospective in nature. Prospective randomized trials are needed to definitively determine if the combination of a FXa inhibitor and ICI therapy is superior to ICI therapy alone and is safe. Moreover, additional mechanistic studies are needed to explain why a small-molecule FXa inhibitor would be superior in this context relative to other anticoagulants that would also target FX. One possibility is that this class of FXa inhibitors is better able to enter the tumor microenvironment relative to heparins, which are rather large molecules. Another possible explanation is that patients receiving heparins in this study tended to have more severe thromboembolic complications (e.g., pulmonary embolism) than patients receiving a FXa inhibitor (e.g., atrial fibrillation), which could have contributed to the worse outcome seen in the heparin treated cohort. That vitamin K antagonists (VKAs) were not beneficial is harder to explain because VKAs target FX in addition to FII, FVII, and FIX. However, VKAs also limit the vitamin K-dependent anticoagulants, protein C and protein S, and can have off-target effects.

Another intriguing explanation for these findings comes from studies showing that thrombin promotes T-cell effector functions. Thrombin has been shown to promote T-cell proliferation and cytokine production at physiological concentrations. Previous studies of primary human T cells showed that thrombin acts in synergy with the T-cell receptor to increase cytokine production (i.e., interferon γ). These same authors showed that thrombin promotes T-cell motility. More recent studies have shown that PAR-1 signaling accelerates TCR-induced calcium mobilization and facilitates polarized secretion of cytotoxic granules at the immunological synapse in human T cells. Consistent with a role for the thrombin/PAR-1 axis in T-cell effector functions, these authors showed that CD8+ T cells deficient in PAR-1 have impaired clearance of lymphocytic choriomeningitis virus in vivo. Together, these studies implicate CD8+ T-cell-associated PAR-1 as a relevant thrombin target, and strongly suggest that thrombin promotes crucial T-cell effector function. Therefore, it is conceivable that anticoagulant strategies that significantly limit prothrombin synthesis or thrombin functions could limit an adaptive immune-driven antitumor response. One could hypothesize that anticoagulants that specifically target FXa and are small enough to enter the tumor microenvironment create a favorable balance of diminished PAR-2 activation relative to diminished local thrombin generation, thereby favoring the adaptive antitumor immune response. Conversely, anticoagulants that are incapable of entering the tumor microenvironment or also significantly impact prothrombin synthesis could lead to impaired T-cell activation and a poor antitumor response. Additional mechanistic studies, particularly in animal models, are needed to better define the role thrombin and FXa in adaptive antitumor immunity.

### 3 | ADAPTIVE IMMUNE DIRECTED CANCER THERAPY AND THROMBOEMBOLISM

There is growing recognition that adaptive immune based cancer therapies appear to be associated with a relatively high risk of thromboembolism. Several retrospective studies have shown a strong correlation between ICI treatment and thrombotic complications. The majority of thromboembolic events reported in patients receiving ICI therapies are VTE, but arterial thromboembolism (ATE) has also been reported. The rates of VTE and ATE in these studies range from ~12% to 25% and 2% to 6%, respectively. A retrospective review of 2854 patients receiving ICI therapy demonstrated an absolute risk of VTE of 13.8% at 1 year. The patients in this study had a variety of malignancies, but the majority were diagnosed with non-small cell lung cancer (NSCLC; 28%) and melanoma (28%). The risk of VTE was estimated as 4-fold higher after starting ICI versus before ICI therapy. Traditional risk factors for VTE, including a higher Khorana risk score, history of hypertension, and history of previous VTE, all correlated with a higher VTE risk with ICI therapy. Note that the five variables of the Khorana score include primary tumor site, body mass index, white blood cell count, platelet count, and hemoglobin level or use of erythropoiesis-stimulating agents.

A retrospective cohort study of 1686 patients receiving ICI therapy for a variety of cancers demonstrated an overall incidence of VTE of 24%. The patients who suffered VTE in this cohort also had worse survival relative to those without VTE. Because of the retrospective
nature of this study, it is unclear what treatment, if any, these patients received for VTE. A correlation between VTE and poor survival was also shown in a retrospective analysis of 228 patients with melanoma receiving ICI therapy. Here, the cumulative incidence of VTE and ATE were 16.2% and 6.1%. These authors also observed an increased incidence of VTE in patients receiving dual ICI therapies relative to those receiving single agents. Moreover, patient with thromboembolism had a 2-year survival of 50.8% compared with 71.3% for patients without thromboses. Notably, all the patients in this study had stage III or IV disease, with the majority having stage IV disease (81%).

Hemostatic derangements have also been observed in patients receiving CAR immunotherapies. A retrospective review of 127 patients with B-cell leukemia or lymphoma receiving CAR therapies noted bleeding and thrombotic complications in ~10% and 6% of patients, respectively. An ~10% incidence of VTE within 60 days of initiating CAR-T cell therapy was observed in a retrospective analysis of 91 patients with non-Hodgkin lymphoma or multiple myeloma. However, another retrospective study observed a much lower risk of thrombosis (~2%) with CAR therapy, but the patients in this study had high rate of pharmacological thromboprophylaxis. Other therapies can accompany CAR-T, such as radiotherapy, which can also contribute to thrombotic risk.

Although the data suggesting that adaptive immunity-based cancer therapies carry a high risk of thrombosis is compelling, two critical related questions remain unanswered: (1) Are these therapies inherently more thrombogenic than traditional chemotherapy and/or the cancer itself? (2) Are there unique mechanism(s) coupling adaptive immune-based cancer therapies to thrombosis that are not at play with other cancer therapies or cancer in general? As previously discussed, cancer is a well-recognized thrombophilic state. Because there are no prospective studies directly comparing adaptive immune-based therapies to traditional chemotherapy, it is difficult to determine to what degree adaptive immunity-based therapies add to the risk of thrombosis already associated with cancer and cancer therapy in general. The overall incidence of VTE in cancer has been estimated at 4%–20%, and varies depending on the type of malignancy, stage of the disease, therapy, and host factors. These numbers are comparable to the incidence of VTE reported with ICI and CAR therapies. Many of the patients receiving ICI therapy have advanced-stage disease, which also correlates with an increased risk of thrombosis for many cancers. For example, melanoma represents one particular malignancy that is often highly responsive to ICI therapy. A retrospective analysis of 290 patients with stage IV melanoma observed a cumulative incidence of VTE of 25%. All these events occurred during chemotherapy treatment. This is comparable to the cumulative incidence of VTE of 16.2% observed in patients with advanced-stage melanoma receiving ICI therapy noted previously. The question of whether ICI therapy represents a unique thrombogenic risk has also been called into question in a study of patients with NSCLC. Here, a retrospective analysis of a series of 593 patients with NSCLC receiving ICI were shown to have a cumulative incidence of VTE of 14.8%. Here, VTE did not correlate with overall survival. There was a trend toward diminished progression-free survival in patients who developed thromboses, but this did not reach statistical significance. The authors concluded that VTE incidence in this cohort of patients receiving ICI therapy was comparable to that observed with patients treated with chemotherapy. Together, the conflicting conclusions reviewed here speak to the limitations of the retrospective studies of ICI therapies and thrombosis conducted thus far. Although these studies have been informative, they lack the proper control groups necessary to definitively determine the relative contribution of ICI to thrombotic risk. It remains to be determined if adaptive immune-based therapies are inherently more prothrombotic than malignancy itself and/or traditional cancer therapies.

The potential mechanism(s) coupling adaptive immunity-based therapies to thrombosis remain poorly defined. In fact, it remains to be determined if immune-based cancer therapies promote thromboembolism through unique mechanisms, or if the prothrombotic risk apparently associated with these therapies simply represents an extension of the well-established thromboembolic risk associated with malignancy and cancer treatment in general. A straightforward explanation for the apparent thrombotic risk associated with immune based cancer therapies is that T cell-mediated lysis of tumor cell results in rampant release of tumor cell-associated TF expressing microvesicles. ICI therapy has also been implicated in increasing TF expression in tumor associated macrophages. A study of patients with NSCLC receiving ICI therapy showed that hemostatic system dysregulation was associated with high PD-L1 expression. Moreover, in vitro studies showed that T-cell activation induced TF expression in monocytes expressing high levels of PD-L1, suggesting that these cells could represent another source of TF in the context of ICI therapy. Activation of inflammatory pathways and release of proinflammatory cytokines may contribute to VTE in the context of adaptive immune-based cancer therapies. Cytokine release syndrome and subsequent hemostatic system derangements appears to be especially important in the context of CAR T therapies. A link between immunoregulatory pathways and thrombosis is also suggested by analyses of a large cohort of patients receiving ICI therapy, where it was shown that the patients who went on to developed VTE had higher pretreatment levels of myeloid-derived suppressor cells (MDSCs), IL-8, and soluble vascular cell adhesion protein 1. Notably, these biomarkers are completely distinct from the biomarkers shown to be associated with VTE in other studies of cancer-associated thrombosis (e.g., TF-expressing microvesicles, elevated D-dimer, soluble P-selectin). It is also notable that cancer-associated MDSCs have been shown to secrete FX. Furthermore, IL-8 has been linked to the generation of neutrophil extracellular traps by MDSCs, which have also been shown to have procoagulant properties. Taken together, these results suggest that the mechanisms driving VTE in ICI therapy are distinct from those associated with cancer and cancer therapy in general and are related to alterations in immune functions. Refer to Figure 1B for a pictorial summary of the potential
mechanisms linking adaptive immune-driven anticancer therapy to thromboembolism.

The available evidence supports the view that adaptive immune-based cancer therapies are associated with a significant risk of thromboembolism, particularly VTE. Whether this thrombophilia is driven by unique mechanism(s) linked to upregulation of adaptive immune functions represents an extension of the more well-established link between malignancy and thrombosis, or some combination of the two remains to be definitively determined. More mechanistic studies, particularly analyses in animal models, will help answer this critical question. Current practice for thromboprophylaxis of patients with cancer involves a risk assessment to determine which patients would most benefit from prophylactic anticoagulation, weighing the potential for bleeding complications against the perceived thrombotic risk. A mechanistic understanding of what is driving thrombosis in these contexts could lead to a better risk assessment of which patients need thromboprophylaxis, as well as novel therapies to prevent thrombosis. Understanding why patients who develop VTE appear to have a worse prognosis could also lead to further improvements in adaptive immunity-based cancer therapies.

4 | CONCLUSIONS AND FUTURE DIRECTIONS

The available evidence strongly supports the conclusion that bidirectional crosstalk between the hemostatic and immune systems directly contributes to cancer pathogenesis. Previous studies in this regard focused largely on components of the innate immune system. More recent studies strongly suggest that this relationship extends to adaptive immune system components as well. Adaptive immunity-based cancer therapies, particularly ICI treatment, appear to carry a significant risk of thromboembolism, and thrombotic complications appear to lead to worse outcomes for these patients. Moreover, growing evidence indicates that tumor cell- and host-derived hemostatic system components play crucial roles in regulating the adaptive immune response, particularly in the context of ICI therapy. Understanding the mechanistic interplay between the hemostatic and adaptive immune system in cancer is of major clinical importance. Such an understanding would likely lead to better methods for identifying which patients are at risk for thromboembolism in the context of adaptive immune-based cancer therapies, allowing for better tailoring of pharmacological thromboprophylaxis therapy. Such an understanding is also likely to lead to novel targets for preventing thrombosis in these patients. Moreover, the available data suggest that understanding the bidirectional crosstalk between the hemostatic and adaptive immune systems at play in ICI therapy could lead to novel strategies to further improve the adaptive anti-cancer immune response.

AUTHOR CONTRIBUTIONS

R. C. and J. S. P. researched the paper and wrote the paper.

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The authors have nothing to disclose.

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