Where cancer meets thrombosis: thrombo-inflammatory landscape of cancer-associated thrombosis

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ABSTRACT

Cancer-associated thrombosis (CAT) is a major contributor to morbidity and mortality among patients with cancer, significantly impacting both treatment strategies and overall quality of life of patients. The pathogenesis of thrombosis in cancer is multifactorial, involving intricate interactions between both host immune responses and tumor-derived factors. This review highlights several key immune-thrombotic pathways implicated in the development of cancer associated thrombosis including neutrophil activation and NETosis, monocyte/macrophage-mediated coagulation, and tumor-induced endothelial activation via inflammatory cytokines. A deeper understanding of these mechanisms is essential for refining risk stratification, developing targeted prophylactic strategies, and improving therapeutic management of cancer-associated thrombosis.

Key words: cancer; thrombosis; thrombo-inflammation.

Introduction

Cancer-associated thrombosis (CAT), encompassing venous thromboembolism (VTE) and arterial thromboembolism (ATE), remains a leading cause of morbidity and mortality among cancer patients.[1] The incidence of VTE, including deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with cancer is increased 4-fold to 9-fold compared to the general population.[2-4] Data from a Danish Cancer Registry study observed that cancer patients with VTE had a 2.2-fold increase in mortality in comparison to patients with cancer, but without VTE.[5] This is important because while 5% to 20% of patients with cancer develop VTE, around 20% to 30% of all VTE cases occur in cancer patients.[6,7]

The pathogenesis of the CAT is complex and multifactorial. Notably, the incidence of CAT varies widely by tumor characteristics, cancer-directed therapies, and patient specific factors. Among malignancies, pancreatic and brain cancers have the highest rate of VTE observed with incidences up to 26%, while lung cancer showed the highest rate of ATE of 8.3%.[7,8] Several other factors influence CAT, including need for surgical intervention, which increases the risk of VTE by 2-fold for postoperative thrombosis up to 7 weeks, in comparison to non-cancer patients.[9] The patient's personal history of VTE, presence of an underlying inherited thrombophilia and age are additional risk factors.[10]

Despite significant advances in thromboprophylaxis and therapeutic anticoagulation, CAT continues to present complex challenges. Numerous cancer-specific mechanisms of thrombosis have been identified. These mechanisms can be broadly categorized into host-derived cellular responses and tumor-derived procoagulant factors. This review summarizes the relationship between immune effector cells (i.e., neutrophils and monocytes) and inflammatory cytokines and the development of venous thromboembolism in cancer (Figure 1).

Leukocyte counts

Among the earliest indicators that thrombosis in cancer is related to inflammatory milieu was the observation that white blood cell (WBC) count is often elevated in patients with cancer, which was later shown to be an independent predictor of throm-

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bosis.[11] Numerous studies have linked leukocytosis with malignancy including a large retrospective study which found extreme leukocytosis in 20% of patients with nonhematologic cancer, 69% of which though to be related to myeloid growth factors.[12] The relationship between leukocytosis at the time of diagnosis and development of VTE was best classified by Khorana *et al.*, noting a 2.2-fold increased risk of VTE in patients with a leukocytosis with a WBC count (>11×10^9 cells/L) compared with patients with lower leukocyte count.[13] This was later replicated in multiple other studies.[14,15] A prospective, multicenter observational study by Conolly *et al.* looked at the association of leukocytosis, VTE, and mortality during the course of chemotherapy and found that leukocytosis was associated with increased risk for VTE with a hazard ratio (HR) of 2.1 (95% confidence interval [CI]: 1.3-3.4, p=0.003), and associated with early mortality with a HR of 2.2 (95% confidence interval 1.5-3.3, p<0.0001).[16] In the Tromsø study, patients with WBC counts above the 80th percentile (≥8.6×10^9/L), experienced a significantly higher risk of developing VTE after being diagnosed with an underlying malignancy compared to those with lower WBC counts (HR 2.36, 95% CI: 1.44-3.87). No association was found between WBC count and VTE in patients who remained cancer-free, suggesting a specific link between pre-cancer leukocytosis and subsequent cancer-associated VTE risk.[15]

The mechanism by which leukocytosis mediated VTE in cancer patient occurs is complex. It is thought that different subtypes of white blood cells play a crucial role in CAT, particularly neutrophils, and monocytes. Neutrophils are believed to enhance thrombosis through the generation of neutrophil extracellular traps (NETs),[17] while monocytes result in the initiation of coagulation through the expression of the procoagulant protein tissues factor.[18,19]

The 4T1 mammary carcinoma mouse model studies have shown that tumor associated leukocytosis, particularly neutrophilia, was driven by tumor-secreted granulocyte colony stimulating factor (G-CSF). Importantly, the neutralization of the G-CSF with antibodies abolished neutrophilia in mice with the 4T1 tumors, while an injection of recombinant G-CSF into tumor free mice increased the number of circulating neutrophils.[20] This series of experiments among others hypothesized and showed that tumor-derived G-CSF is a driver of neutrophilia, which plays an integral role in the establishment in CAT.[21] Similar to the mouse models, studies have shown that in humans, elevated level of G-CSF and extreme leukocytosis are seen in patient with underlying solid malignancies.[22-24]

Neutrophils and NETs

Neutrophil extracellular traps (NETs) are externalized nucleosomes composed of extracellular chromatin fibers, histones, and neutrophil granule constituents. They are released by neu-

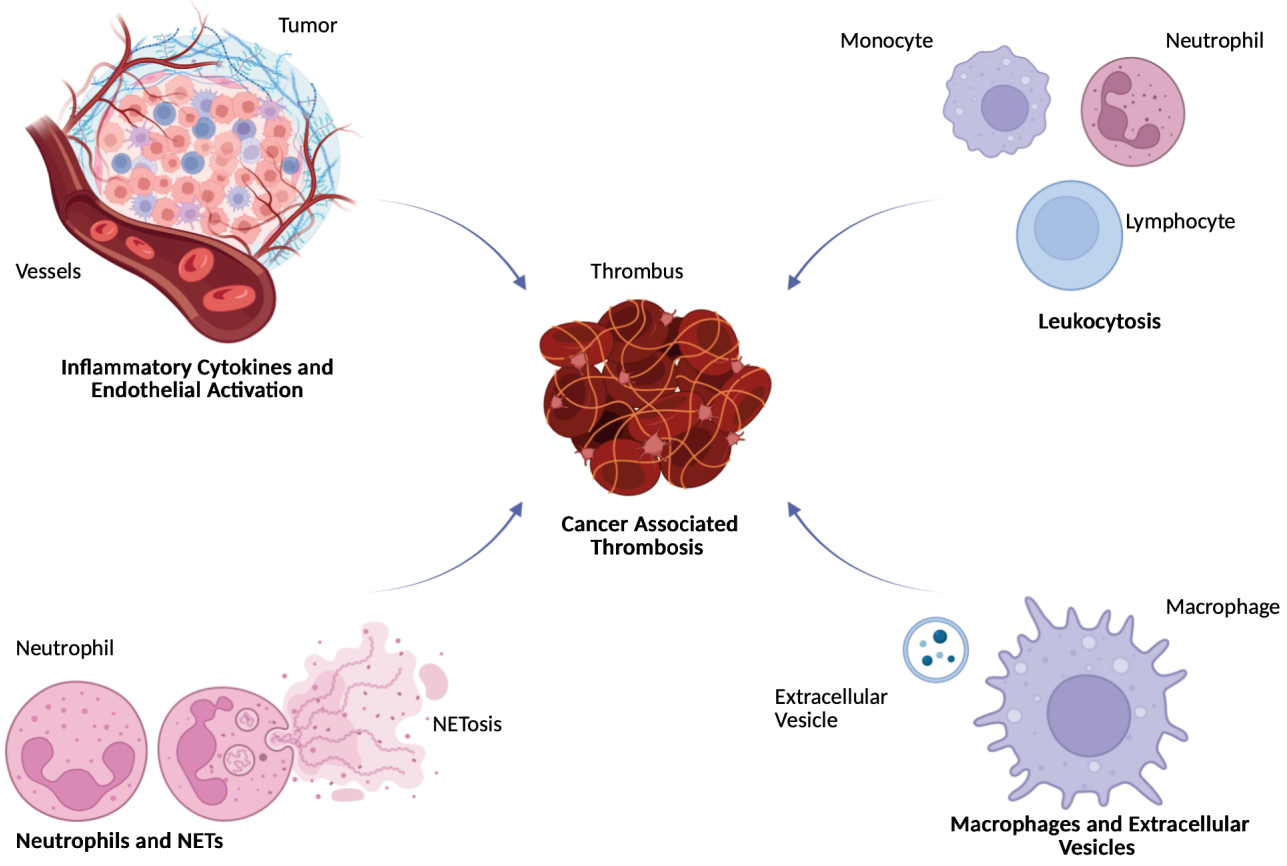

Figure 1. Pathways that contribute to cancer associated thrombosis.

trophils stimulated by microbes, reactive oxygen species, proinflammatory agents or platelets.[17,25] Historically, NETs were primarily known for their role in counteracting bacterial infections as part of the innate immune response. However, more recently, NETs were also found to play a key role in initiation of thrombosis through capturing platelets and extracellular vesicles.[26-28]

NETs promote thrombus formation by facilitating fibrin deposition and trapping red blood cells, resulting in the presence of extracellular DNA markers.[27] Studies in mice have shown that extracellular chromatin originating from neutrophils was a structural part of a thrombus. It was observed that both DNA chromatin and histones contributed to the pathogenesis of VTE formation in mice.[25,27,28] *In vitro* studies demonstrated that the perfusion of blood over NETs in chambers resulted in the formation of a red thrombus in a NET-dependent matter. The destruction of the NETs by DNAse-1 prevented recruitment of platelets and red blood cells. Similar findings were also reported with NETs and histones providing a scaffold for the formation of a thrombus, through platelet adhesion, activation, aggregation, along with red blood cell requirement and fibrin deposition.[27]

NETs are believed to play a role in CAT. Elevated G-CSF levels in cancer are thought to contribute to NETosis.[29] In female BALB/c mice that were injected with 4T1 breast cancer cells demonstrated increased levels of plasma DNA, circulating neutrophils and myeloperoxidase. The tumor bearing-mice were also found to exhibit accelerated thrombosis compared to the tumor free animals when subjected to models that promoted venous and arterial thrombosis, which was reversed when treated with recombinant human DNase. Interestingly, it was seen that administration of 4T1-derived exosome, which induced NET formation in mice previously treated with G-CSF, also accelerated *in vivo* venous thrombosis in G-CSF treated-mice. It was proposed that tumor-derived exosomes, induced the formation of NET in neutrophils and CAT through the activity of G-CSF.[21]

Although there has been a variety of biomarkers that have been used to assess the formation of NETs, citrullinated histone H3 (H3Cit) and H3Cit-DNA complexes remain the most specific biomarker for NETs.[30] While other biomarkers such as myeloperoxidase DNA, neutrophil elastase, cell free DNA (cfDNA) and nucleosome have been assessed, they have not been found to be specific to NET Formation.[4] NET formation is catalyzed by peptidyl-arginine deiminase 4 (PAD4), which enables the chromatin de-condensation, causing Histone 3 to be citrullinated (H3Cit).[31] H3Cit and H3Cit-DNA complexes in particular were also noted to be increased in patients with cancer in comparison to healthy subjects with no underlying malignancy.[32-34]

Circulating markers have been used to detect NETs in patients with CAT. Thalin *et al*. identified H3Cit and DNA in arterial microthrombi in cancer patients, while Oklu *et al.* observed H3Cit-DNA complexes in VTE in cancer patients.[4] Mauracher *et al*. suggested that NET biomarker formation, particularly H3CIT is associated with CAT and indicated a role of NET in pathogenesis of CAT. This was seen as patients with elevated H3Cit levels above the 75th percentile had a higher cumulative incidence of VTE in comparison to patients with levels below the cutoff, with a 2-year risk of 14.5 %. In fact, that same study showed that an increase in H3Cit level by a 100 mg/mL^{-1} it was associated with a 13% relative increase in VTE risk even after adjustment for multiple factors including high and very high risk VTE tumor sites and D-dimer levels (HR 1.13, 95% CI 1.04-1.22).[35] Conversely, a recent study did not find any difference in the levels of H3Cit in thrombi from patients with cancer compared with thrombi from patients without cancer.[36] In addition to the above, while the previously mentioned study also reported plasma levels cfDNA and nucleosomes were associated only with VTE in the high-risk period VTE (3-6 months after the diagnosis), another study failed to show that association.[37]

Measurement of H3CIT in plasma can be challenging due to instability in the plasma. Many antibodies used to detect intrapeptidyl citrulline have low specificity, especially when tested against semi-synthetic nucleosomes containing distinct histone H3 citrullinations. A more specific ELISA has been developed which utilizes highly specific monoclonal antibodies against semi-synthetic nucleosomes citrullinated at H3R2, H3R8, and H3R17 as a calibration standard that reported excellent quantification of H3CIT levels in human plasma samples.[38]

Cell-free DNA (cfDNA), the thrombogenic component of NETs, in patients with underlying malignancy has been associated with the development of VTE.[35] In a large cohort of over 4000 patients with cancer at Memorial Sloan Kettering, elevated levels of circulating cfDNA were independently associated with an increased risk of VTE even when adjusted for cancer stage.[39] Leukocytes, predominantly neutrophils, represent the major source of circulating cfDNA in patients with cancer, linking NET formation with the prothrombotic state observed in malignancy.[40]

Monocytes / macrophages

Elaboration or delivery of tissue factor (TF) is considered a fundamental event leading to thrombus formation. Activated monocyte/macrophages are characterized by the release highly procoagulant phosphatidylserine rich TF^{+} extracellular (EVs) which are known to modulate clot formation, structure and stability, suggesting unique contributions to thrombosis.[41] Interestingly, macrophages polarized through alternative activation, mainly involved in angiogenesis and tissue remodeling/repair, showed a significant increase in TF expression and release alongside EV production. The activity of TF in EV was also enhanced in alternatively polarized macrophages leading to a procoagulant phenotype, in contrast to macrophages activated by proinflammatory polarization.[42]

Recently, the role of macrophages and TF was reevaluated. EVs from interstitial macrophages from the lung in both metastatic and non-metastatic of mice and cancer patients were associated with increased risk of thrombosis.[43] The EV were secreted by the C-X-C motif chemokine 13 (CXCL13)-reprogrammed interstitial macrophages. It was shown that those EVs membranes contained activated and clustered form of integrin β_2 which dimerized with integrin α_X, also found on the same membrane, which led to an interaction with platelet-bound glycoprotein (GP)Ib and aggregation of platelets . Not only was EV-induced thrombosis decreased by blocking integrin β_2, but serum EV-β_2 levels were elevated in the plasma of patients with pancreatic ductal adenocarcinoma prior to thrombosis development compared with patients with no history of thrombosis.[43]

The tumor microenvironment plays an important role

through the immunomodulatory role of the tumor coagulome which interacts with a myriad of infiltrating cells resulting in prothrombotic stimuli. The interaction between the tumor microenvironment and the host vascular cells including endothelial cells, platelets and leukocytes are implicated in coagulopathy of malignancy. Tumor-associated macrophages represent a major cellular component of the tumor immune microenvironment and can adopt phenotypes that promote coagulation activation. Tumor associated macrophages, express coagulation signaling complexes including factor VII, TF, and factor X, which has been shown to increase thrombin generation, locally in the tumor microenvironment.[44,45] In addition, macrophage-derived cytokines and chemokines contribute to recruitment and activation of neutrophils and platelets, reinforcing a feed-forward loop between inflammation and thrombosis within the tumor microenvironment. Platelet activation in the tumor microenvironment can occur through direct activation by the tumor or through thrombin generation via cleavage of platelet thrombin receptors PAR1 and PAR4. Activated GpIIb-IIIa subsequently also binds prothrombin which promotes the activity of prothrombinase, further amplifying thrombin generation on the surface of the platelets.[44,46] Beyond their direct procoagulant activity, immune cells within the tumor microenvironment also promote thrombosis through the secretion of inflammatory cytokines that activate endothelial cells and amplify coagulation signaling.

Tumor inflammatory cytokines and endothelial activation

Thrombosis and malignancy are linked through multiple pathophysiological mechanisms, including a role by inflammatory cytokines and the activation of the endothelium. Numerous mediators have been linked to the process including C-Reactive Protein (CRP), Tumor Necrosis Factor-α (TNF-α), interleukin 6, and 1β (IL-1β), TF, fibrinogen, and soluble P- selectin, matrix metalloproteases-9 (MMP-9), and vascular endothelial growth factor (VEGF). These mediators are mainly secreted following the activation of monocytes, endothelial cells, or directly from tumor microenvironment.[47,48] In fact, it is thought that the increased production of these markers contributes to activation of host cells, including monocytes present in the tumor microenvironment, which further impacts cytokine release by the tumor cells themselves. This is seen in the case of TNF-α, IL-1β, and IL-6 in the induction of TF expression and activity.[47,48] Some of these cytokines and proteins have been linked to CAT and were found to be higher in cancer patient with VTE in comparison to patients with no VTE. [49] Some of those include:

Immune-mediated factors

TNF-α plays an important role in inducing procoagulant changes in the endothelial cells due to increased expression of TF and downregulation of thrombomodulin and tissue factor pathway inhibitor. It is thought that these changes in hemostatic balance, which are induced by inflammation, contribute to thrombosis.[50,51]

The inflammasome complexes, which are multiprotein complexes involved in the innate immune system, have been implicated in the development and propagation of VTE in general. Formed in the cytoplasm of immune cells in response to damage-associated molecular patterns, inflammasomes are thought to regulate venous thrombosis through the prothrombotic role of NLRP3. NLRP3 activation leads to caspase-1 activation, maturation and release of IL-1β and IL-18, and pyroptosis, which in turn increases recruitment of white blood cells and platelets, TF release from macrophages, and NETosis, hence linking inflammation with VTE. However, the role of inflammasomes has not been investigated in the setting of cancer associated thrombosis.[52]

Antiphospholipid antibodies presence is associated with a higher risk of VTE or ATE in cancer patients, particularly with the presence of a lupus anticoagulant or anti-β2-Glycoprotein antibodies. In comparison to non-cancer patients, the presence of a lupus anticoagulant in cancer patients was associated with a higher risk of composite ATE or VTE with a RR 5.3. On the other hand, anti-β2-GPI presence increased the risk of VTE as well with a RR 4.7.[53]

Conversely, multiple studies have not shown an association between inflammatory cytokines and thrombosis including a prospective study of patients with solid tumors that demonstrated no association of multiple interleukins and chemokine ligands with VTE, including IL-1β, IL-3, IL-4, IL-6, IL-8, IL-10, IL-11, or chemokine ligand 3 (CCL3).[54] Similarly, a prospective study on diffuse large B cell lymphoma patients showed no association VTE risk with IL-6, IL-10, or TNF-α.[55,56]

Conclusions

Cancer-associated thrombosis represents a prototypical example of immunothrombosis in which tumor biology and host inflammatory responses converge to promote coagulation activation. Increasing evidence suggests that leukocyte-driven mechanisms including NET formation, monocyte and macrophage–derived tissue factor activity, and cytokine-mediated endothelial activation fosters a prothrombotic microenvironment that extends beyond traditional tumor-derived procoagulant pathways. These processes not only amplify thrombin generation and platelet activation locally within the tumor microenvironment but may also contribute to systemic hypercoagulability observed in patients with malignancy. Despite advances in anticoagulant strategies, the persistent burden of cancer-associated thrombosis highlights the need for improved mechanistic understanding of thrombo-inflammatory pathways that link cancer progression with coagulation activation. Future studies integrating biomarkers of immunothrombosis, such as NET-derived components and other inflammatory mediators, may improve risk stratification and identify novel therapeutic targets aimed at disrupting the interplay between inflammation and thrombosis in cancer.

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