Neutrophil extracellular traps in thrombosis of hematologic malignancies: Underlying mechanisms and therapeutic opportunities (Review)

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Abstract. Patients with cancer, particularly those diagnosed with hematological malignancies, exhibit thrombus incidence rates that exceed those observed in the general population by a substantial margin, and this elevated risk is associated with worse clinical outcomes. Neutrophil extracellular traps (NETs), which are web-like structures released by neutrophils as part of their innate immune repertoire, drive coagulation and vascular occlusion by supplying a physical scaffold, recruiting procoagulant factors, and cleaving tissue factor pathway inhibitors. In hematological malignancies, emerging evidence points to NET overproduction and dysregulation as key drivers of thrombosis, representing a previously underappreciated mechanistic axis. The present review focuses on the molecular mechanisms by which NETs promote thrombosis, specifically on thrombosis associated with hematological malignancies (such as myeloproliferative neoplasm, acute myeloid leukemia, Hodgkin lymphoma, multiple myeloma and acute lymphoblastic leukemia), and also explores the clinical translation potential of NET-related therapies. The present study offers a potential basis for refining current approaches to coagulation risk reduction in patients with hematological malignancies.

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Contents

1. Introduction

Patients with cancer face a substantially elevated risk of venous thromboembolism (VTE), with incidence rates 4-7-fold higher than those observed in the normal population (1,2). Furthermore, the coexistence of VTE further worsens the clinical outcomes of patients with cancer (3). While thrombotic complications have historically been associated mainly with solid tumors, hematological malignancies have typically been characterized by bleeding tendencies and overt disseminated intravascular coagulation (DIC). However, contemporary data indicate that the incidence of VTE in patients with hematological malignancies is comparable to that observed in patients with solid tumors at high risk of thrombosis (4). The high incidence of thrombosis is closely related to the hypercoagulable state of the tumor itself, treatment-related factors (such as chemotherapy and central venous catheterization), and the patient's own factors (such as advanced age and long-term bed rest) (5). Additionally, a common treatment course for patients with hematological malignancies consists of aggressive chemotherapy followed by hematopoietic stem cell (HSC) transplantation. This regimen frequently causes long-lasting and severe pancytopenia (4). Given these challenges, there is a paucity of accumulated clinical expertise concerning the prevention and treatment of thrombotic events in individuals with hematological malignancies.

Through the extrusion of neutrophil extracellular traps (NETs), which are thread-like structures composed of chromatin, neutrophils are able to eliminate invading microbes (6). NET formation leads to a unique cell death process called NETosis (7). Previous studies have shown that intravascular NETs promote coagulation and thrombosis by activating the clotting cascade and interacting with platelets, playing a key role in immunothrombosis (8-11). Excessive immunothrombosis triggers thromboinflammation, driven by endothelial dysfunction, dysregulated coagulation, complement activation, platelet activation and leukocyte recruitment (12). In sterile inflammation, such as in hematological malignancies, NET-mediated thrombosis can cause tissue ischemia. For example, the Jak2V617F mutation in myeloproliferative neoplasms (MPNs) was shown to increase thrombosis by enhancing NET formation (13). Disrupting NETs [for example with deoxyribonuclease (DNase)] can reduce clotting and thrombotic events (14). Understanding the mechanisms of thromboinflammation is crucial, as current anticoagulants only partially prevent thrombosis while increasing bleeding risk, particularly in thrombocytopenic hematological malignancies (15). The present review explores the role of NETs in thrombosis and potential therapeutic strategies.

2. Formation of NETs

Beyond their well-established role in entrapping and neutralizing a wide spectrum of pathogens (including bacteria, fungi, viruses and parasites), NETs also help confine microbial dissemination to local sites (6). However, excessive or dysregulated NET formation can drive immune-related diseases (16). Structurally, NETs consist of a DNA scaffold associated with antimicrobial proteins such as myeloperoxidase (MPO), neutrophil elastase (NE), defensins, cathepsin G, lactoferrin, matrix metalloproteinase-9, pentraxins, peptidoglycan-recognizing proteins and LL-37 (a 37-amino acid peptide) (6,17).

NETs are activated through diverse pathways, including protein kinase C (PKC) activation [such as phorbol 12-myristate 13-acetate (PMA)-induced reactive oxygen species (ROS) production], microbial stimuli (bacterial/viral pathogens) and immunological/tumor-related factors (including immune complexes, chemokines, complement components and damage-associated molecular patterns). Notably, stimulus-specific variations in NET protein composition may lead to functional heterogeneity, warranting further investigation (9).

Several reported mechanisms contribute to the induction of NET formation in individuals with hematological malignancies. In a previous study on $CD5^+$ B-cell chronic lymphoblastic leukemia, Sangaletti *et al* (18) observed that splenic neutrophils from lpr/lpr/$Sparc^{-/-}$ mice enhanced the generation of B-cell activating factors, resulting in a more notable tendency toward NET formation. Previous research has shown that, in patients with MPNs, platelets rapidly adhere to and stimulate neutrophils, thereby driving NET production (19). Increased interleukin (IL)-8 in patients with diffuse large B-cell lymphoma (DLBCL) was demonstrated to interact with C-X-C motif chemokine receptor 2 (CXCR2) expressed on neutrophils, leading to NET induction through the coordinated action of the Src, p38 and ERK pathways. In a DLBCL mouse model, the use of corresponding inhibitors was shown to eliminate NETosis triggered by C-X-C motif chemokine ligand (CXCL)1/CXCL2 within neutrophils (20); NETosis triggered by tumor necrosis factor (TNF) together with interferon-γ (IFN-γ) has been widely reported in classical Hodgkin lymphoma (cHL) (18,21). These findings suggest that hematological malignancies and infection-induced NETs share various upstream triggers while also being driven by their respective tumor-related stimuli.

3. Release pathways of NETs

Upon activation, neutrophils adhere to vascular endothelial cells (ECs) and transfer their granular components (such as MPO and elastase) into the nucleus, where they work in concert with peptidylarginine deiminase (PAD)4 to promote chromatin decondensation (22,23). Stimulus-dependent NETosis occurs via two pathways: Suicidal (membrane rupture) or vital (intact membrane), both releasing chromatin-bound granular proteins extracellularly (24-26). The vital NETosis or alternative pathway is caused by pathogens, including bacteria, fungi, viruses and protozoa (24,27). NETs can be rapidly secreted within minutes of stimulation, while maintaining anucleate phagocytes that remain functional and retain the ability to clear microbes and respond to chemotactic signals (24). The classic suicidal NETosis pathway is triggered by inflammatory mediators (such as IL-8 and TNF-α), platelet activation, autoantibodies, or cholesterol crystals (24,27). The generation of ROS by reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase serves as an essential prerequisite for this distinct cell death mechanism (28). Following neutrophil activation (3-8 h, membrane rupture enables extracellular NET extrusion, culminating in lytic cell death (Fig. 1).

4. Mechanisms of NETs in thrombosis promotion

The concept of 'immunothrombosis', which was introduced by Engelmann and Massberg (15), describes the physiological antimicrobial function of NET-mediated thrombosis. However, dysregulated NET formation drives pathological thrombosis (Fig. 2). Emerging research has established NETs as pivotal mediators in venous thrombosis, fundamentally advancing the current understanding of thrombotic pathogenesis (29,30).

In addition to mediating antimicrobial activity, NETs contribute to thrombosis by supplying a scaffold that facilitates a potent cohesive reaction (8). NETs harbor a range of prothrombotic molecules (such as anionic DNA scaffold, cathelicidin, MPO, histones H3/H4 and NE). Each of these components contributes to clot formation by engaging separate mechanisms, namely platelet activation and aggregation, thrombin synthesis, and tissue factor (TF) export (10,11,31-33). NETs possess the ability to trigger the coagulation cascade. Circulating cell-free DNA (cfDNA) triggers the intrinsic coagulation cascade by activating FXII, a plasma serine protease (34). This event sets off sequential activation of multiple coagulation factors, leading ultimately to fibrin deposition and thrombus formation. As factors that inhibit coagulation, TF pathway inhibitors (TFPIs) can be cleaved by NEs bound to NETs. Therefore, TF increases and supports exogenous coagulation pathways (35). NETs can also interact with platelets. Histones are the most abundant proteins in NETs. Previous studies have

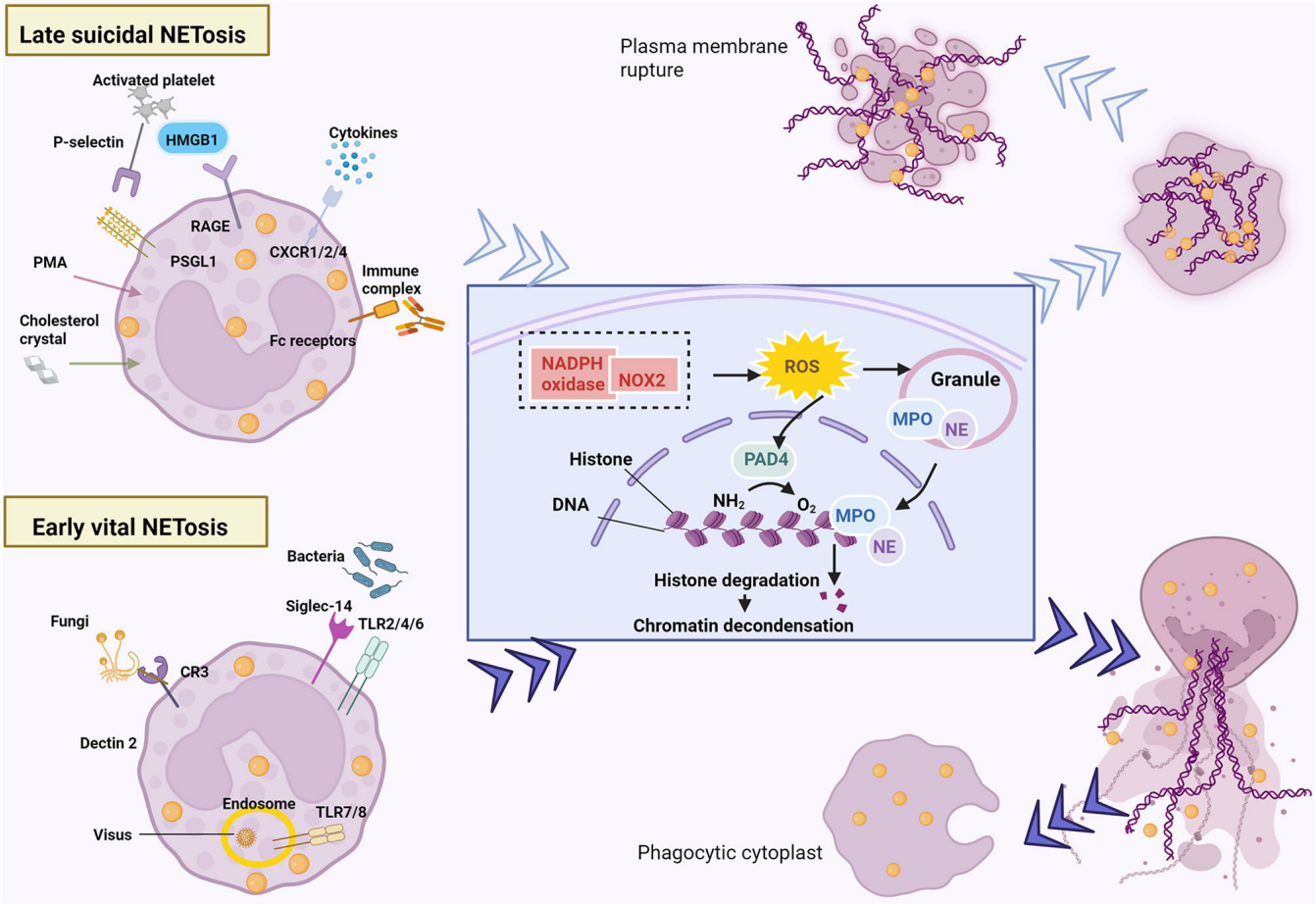

Figure 1. Mechanisms of NET formation and release: Pathways and triggers. NET formation is triggered by PKC activators, and microbial (bacterial, fungal, viral), immune and tumor-related stimuli, resulting in chromatin lysis and nuclear membrane rupture through peptidylarginine deiminase 4, either dependently or independently of nicotinamide adenine dinucleotide phosphate oxidase-mediated reactive oxygen species production. NET-forming neutrophil cell death are divided into 'vital NETosis' (rapid release, cell survival) and 'suicidal NETosis' (lytic cell death), which are triggered by pathogens and inflammatory stimuli, respectively. Figure created with BioRender.com. NET, neutrophil extracellular trap; PKC, protein kinase C; CXCR1/2/4, C-X-C chemokine receptors 1, 2 and 4; HMGB1, high mobility group box 1; MPO, myeloperoxidase; NADPH, nicotinamide adenine dinucleotide phosphate; NE, neutrophil elastase; NOX2, NADPH oxidase 2; PAD4, peptidylarginine deiminase 4; PMA, phorbol 12-myristate 13-acetate; PSGL1, P-selectin glycoprotein ligand-1; RAGE, receptor for advanced glycation end products; ROS, reactive oxygen species; Siglec-14, sialic acid-binding immunoglobulin-like lectin 14; TLR2/4/6, Toll-like receptors 2, 4 and 6; TLR7/8, Toll-like receptors 7 and 8.

shown that histone H3 can activate platelets (8,36). Activated platelets release platelet factor 4, platelet activating factor and von Willebrand factor (vWF), all of which act as soluble mediators that promote NET generation (37). NETs bind to platelet-secreted vWF, and this interaction serves to augment platelet adhesion and aggregation, along with the production of fibrin and subsequent thrombosis (32,38), thereby establishing a self-amplifying cycle wherein platelets are activated by NETs. In addition, NET-derived PAD4 is capable of citrullinating a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13). This post-translational modification diminishes the activity of the enzyme, which in turn facilitates the assembly of ultra-large vWF-platelet strings and promotes microvascular thrombus formation following vascular damage (38).

In summary, NETs promote thrombosis through multiple mechanisms. To establish an integrated molecular framework linking these mechanisms to hematological malignancies, a three-tiered model is proposed, as illustrated in Fig. 3. In the upper tier, disease-specific triggers [Jak2V617F signaling in MPN, inflammatory cytokines in multiple myeloma (MM)/acute myeloid leukemia (AML), and the inflammatory microenvironment in HL] activate NADPH oxidase-dependent ROS production via distinct proximal mechanisms. In the middle tier, this ROS production drives PAD4-mediated histone citrullination and NET release. In the lower tier, NETs promote thrombosis via the FXII-driven intrinsic pathway, NE-mediated TFPI cleavage to facilitate the extrinsic TF pathway, and histone-induced platelet/vWF activation that creates a positive feedback loop. This framework distinguishes disease-specific heterogeneity from a unifying prothrombotic mechanism downstream of NETosis, highlighting that therapeutic targeting of the downstream NETosis pathway could offer broad antithrombotic benefit across multiple hematologic cancers.

5. NET-related thrombosis in hematological malignancies

VTE, a serious complication in hematological malignancies, significantly increases morbidity and mortality with varying risk across cancer types. Emerging evidence associated NETs to thrombotic events in MPN, HL, chronic myeloid leukemia,

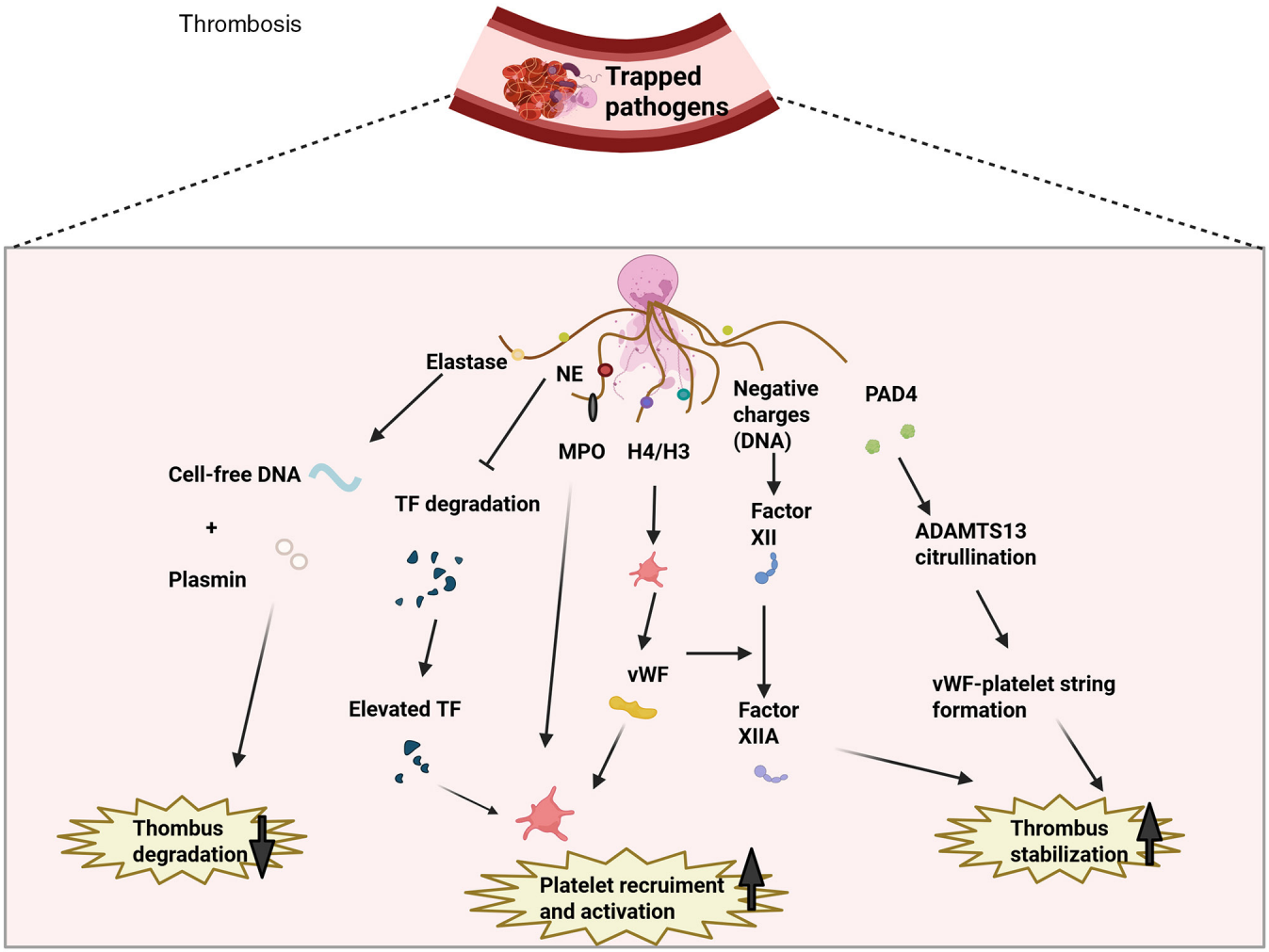

Figure 2. NET constituents trigger thrombotic processes. Through their components (such as DNA, histones, myeloperoxidase, and neutrophil elastase), NETs can activate factor XII, bind to von Willebrand factor, and promote tissue factor release, leading to thrombin production and platelet activation, resulting in thrombosis and stabilization. Figure created with BioRender.com. NET, neutrophil extracellular trap; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif 13; DNA, deoxyribonucleic acid; Factor XII, coagulation factor XII; Factor XIIa, activated coagulation factor XII; H3, histone H3; H4, histone H4; MPO, myeloperoxidase; NE, neutrophil elastase; NETs, neutrophil extracellular traps; PAD4, peptidylarginine deiminase 4; TF, tissue factor; vWF, von Willebrand factor.

acute lymphoblastic leukemia (ALL) and AML. Deciphering the NET-thrombosis interplay in these malignancies may reveal novel therapeutic approaches to reduce thrombosis risk and improve outcomes. Based on the unified molecular framework described in Fig. 3, the following subsections will elaborate, by disease type, the evidence for each molecular pathway in different hematological malignancies.

MPN. MPN is a clonal disorder originating from HSCs, marked by the overproliferation of one or more myeloid lines in the bone marrow (BM) (39). In a previous European collaborative study on low-dose aspirin, the cumulative incidence of fatal and nonfatal thrombosis in patients with polycythemia vera (PV) was 5.5% (40). The Gruppo Italiano Studio Paliticemia conducted a study involving 1,213 patients and reported that 19% of them experienced thrombotic events (41). Patients with essential thrombocythemia (ET) experience thrombotic complications at a rate of 2-4% per patient each year, a frequency that parallels the 2.33 events per person-year observed in primary myelofibrosis (PMF) (42). Both a prior history of thrombosis and the Jak2V617F mutation serve as important predictors of thrombotic risk, with established value in clinical risk assessment (36,43). However, there is still a lack of biomarkers for predicting the risk of thrombosis in an individual, especially in younger age groups. The high incidence, complex management and high mortality of thrombus make it a worthy clinical concern in patients with MPN (44). It is necessary to identify new risk factors for thrombosis.

Multiple studies have examined the procoagulant role of NETs among patients with MPN. Using a murine MPN model driven by the Jak2V617F mutation, Wolach *et al* (13) observed increased NET formation and a predisposition to spontaneous thrombosis in lung tissues. Ruxolitinib, which targets JAK2 and is already in clinical use, was found to abrogate NET production and attenuate thrombosis through suppression of JAK-STAT signaling. Additionally, PAD4 was found to be essential for Jak2V617F-induced NET production and thrombotic events *in vivo*. In summary, that study suggested that Jak2V617F may promote thrombosis in MPN by enhancing NET formation. According to previous research, essential

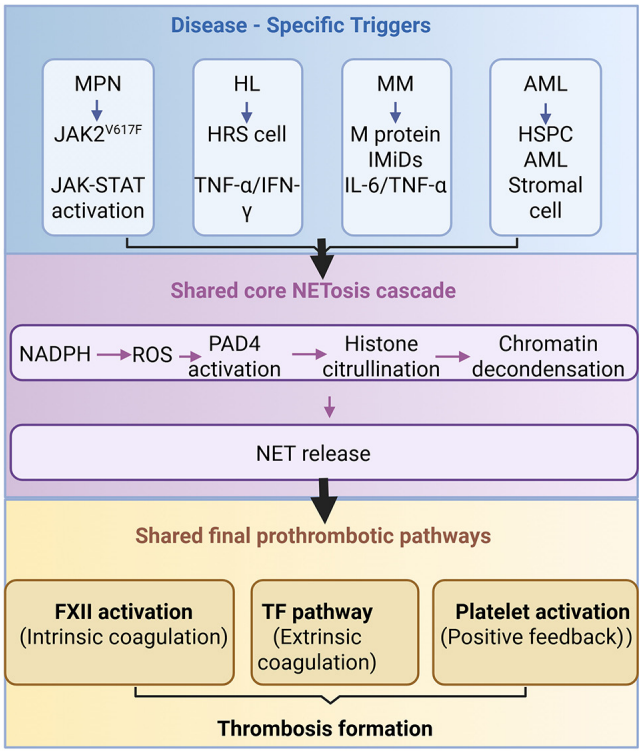

Figure 3. Molecular framework of NET-driven thrombosis in hematological malignancies. Disease-specific triggers in MPN, MM, HL and AML activate NADPH oxidase-dependent reactive oxygen species production via distinct proximal mechanisms, leading to PAD4-mediated histone citrullination, chromatin decondensation and NET release. Released NETs promote thrombosis by activating the FXII-driven intrinsic pathway, and by facilitating the extrinsic TF pathway through neutrophil elastase-mediated cleavage of TF pathway inhibitor. Furthermore, histones within NETs induce platelet activation and von Willebrand factor release, establishing a positive feedback loop that amplifies thrombosis. Figure created with BioRender.com. NET, neutrophil extracellular trap; MPN, myeloproliferative neoplasm; MM, multiple myeloma; HL, Hodgkin lymphoma; AML, acute myeloid leukemia; NADPH, nicotinamide adenine dinucleotide phosphate; PAD4, peptidylarginine deiminase 4; FXII, coagulation factor XII; TF, tissue factor; JAK-STAT, Janus kinase-signal transducer and activator of transcription; HRS, Hodgkin and Reed-Sternberg; TNF-α, tumor necrosis factor-α; IFN-γ, interferon-γ; IMiDs, immunomodulatory drugs; HSPC, hematopoietic stem and progenitor cell; IL-6, interleukin-6; ROS, reactive oxygen species.

thrombocythemia-associated thrombosis arises in part from hyperactivation of platelets and white blood cells, a state that is itself closely associated with whether the patient harbors a JAK2 mutation. Among individuals harboring the Jak2V617F mutation or having experienced prior thrombotic events, the levels of TF, P-selectin and vWF were all higher than in those without a history of thrombosis (45,46). Suppressing the JAK-STAT pathway reduces the release of pro-adhesive and procoagulant P-selectin and vWF, as well as the pro-inflammatory cytokine IL-6 (47). Therefore, it can be hypothesized that JAK2 mutations activate platelets through NETs, promote the elevation of TF and vWF, and induce high expression of P-selectin in platelets, thereby increasing thrombotic events in patients with MPN. Ruxolitinib suppresses NET-induced thrombosis by restricting the secretion of IL-6. This hypothesis is presented in Fig. 4. MPO-DNA is a specific marker of NETs that can be measured in plasma. Guy *et al* (48) found that the MPO-DNA concentration in patients with MPN exhibiting thrombosis was significantly higher than that in the control group, supporting the pathogenic role of NET formation in thrombosis. Notably, these patients with MPN had a history of thrombosis, particularly portal vein thrombosis. However, no differences were found when comparing patients with MPN with thrombosis with those without thrombosis. According to Marin Oyarzún *et al* (49), only nucleosome levels were elevated. However, nucleosomes lack specificity as NET biomarkers, as they can also be generated through other cell death processes such as apoptosis or necrosis.

Meanwhile, the aforementioned studies have yielded some conflicting findings. In a study by Guy *et al* (48), 52 patients with newly diagnosed MPN and 54 healthy controls (free of prior thrombotic bleeding episodes) were examined. Neutrophils isolated from the MPN group exhibited a greater propensity for NET formation compared with those obtained from healthy subjects. However, two separate studies conducted by Wolach *et al* (13) and Marin Oyarzún *et al* (49) failed to demonstrate that the presence of Jak2V617F in unstimulated neutrophils leads to increased NETosis. The reasons for these discrepancies may be attributed to differences in patient inclusion criteria, treatment status, sample size and MPN subtype heterogeneity across the studies. First, regarding treatment-related confounding, in the two studies by Wolach *et al* (13) and Marin Oyarzún *et al* (49), the majority of enrolled patients were undergoing cytoreductive regimens along with JAK inhibitor therapy. These interventions exert myelosuppressive effects and increase the risk of opportunistic infections, leading to neutropenia and altered neutrophil functional status, thereby affecting NET release. Second, regarding cohort characteristics, according to Guy *et al* (48), half of the patients enrolled in their study had experienced prior thrombotic events. Relative to the data obtained from the other two aforementioned studies, this observation highlights the association between NET release and thrombosis. Third, regarding sample size limitations, the sample sizes of the aforementioned studies were relatively limited (each study included <70 cases), which may be insufficient to detect true intergroup differences, and limits the statistical power of multivariable and subgroup analyses. Fourth, regarding MPN subtype heterogeneity, MPN encompasses three main subtypes, namely PV, ET and PMF, each with distinct disease characteristics. Patients with PV frequently present with erythrocytosis and elevated blood viscosity; patients with ET are characterized by megakaryocyte hyperplasia and thrombocytosis; and patients with PMF exhibit more pronounced BM fibrosis and an inflammatory cytokine storm. These subtype differences may lead to heterogeneity in baseline NETosis levels and their contribution to thrombotic risk. However, due to the limited sample sizes of the aforementioned studies, no subtype-stratified analyses were performed. Differences in the proportions of MPN subtypes included across studies may also represent an important source of result variability.

Although the aforementioned studies show minor discrepancies in their results, they all consistently demonstrate that NETs promote thrombosis in MPN. Future larger-scale and more precisely stratified studies are needed to further strengthen this preliminary evidence (Table I).

AML. Thrombosis incidence in AML ranges from 2.09 to 8.60% across studies, with variations attributed to diagnostic

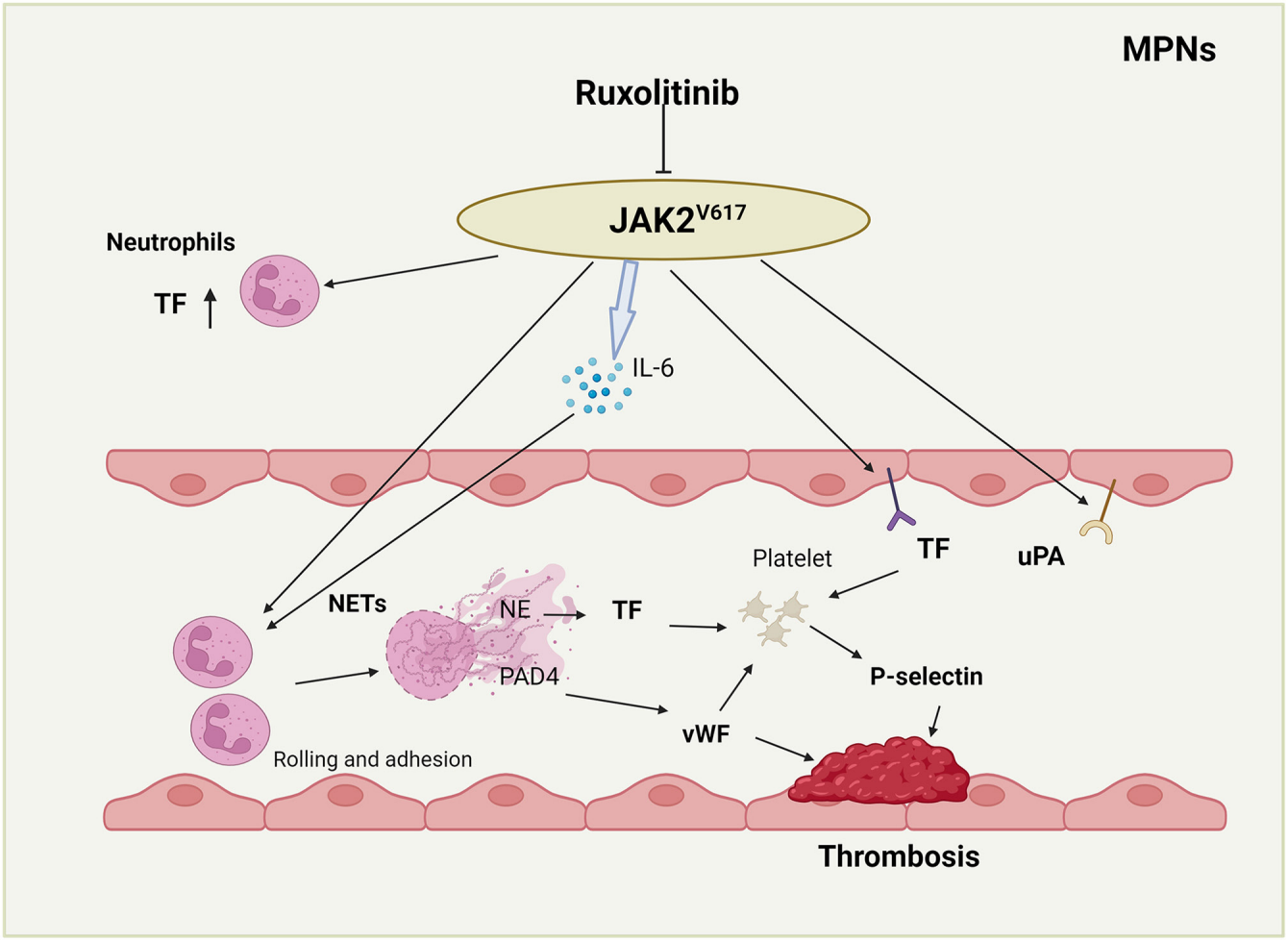

Figure 4. Mechanism of thrombosis in myeloproliferative neoplasms. The JAK2 V617F mutation significantly elevates the levels of tissue factor, P-selectin, von Willebrand factor, IL-6 and other prothrombotic factors. Both JAK2 V617F mutation and IL-6 further enhance the production of these markers by promoting neutrophil extracellular trap formation, thereby contributing to thrombotic events. Figure created with BioRender.com. IL-6, interleukin-6; TF, tissue factor; NETs, neutrophil extracellular traps; MPN, myeloproliferative neoplasm; NE, neutrophil elastase; PAD4, peptidylarginine deiminase 4; vWF, von Willebrand factor; uPA, urokinase-type plasminogen activator.

methods and patient populations (50-52). While disease aggressiveness correlates with VTE risk and poorer outcomes (53), thrombocytopenia in patients with AML has limited their inclusion in thrombosis trials, resulting in scarce management guidelines. This evidence gap underscores the need for an improved mechanistic understanding of thrombosis in AML.

According to previous studies, NET-TF interplay serves as a key driver of thrombus formation. Hell *et al* (54) conducted a study on 28 patients with malignant diseases accompanied by overt DIC (ISTH score >5), including 15 patients with AML. The authors defined plasma DNA and nucleosomes as parameters related to NETs formation, and measured TF activity in microvesicles (MV-TF) as well as other conventional coagulation indicators. The results showed that NETs-related parameters were closely associated with changes in MV-TF and conventional coagulation parameters. Doubling in plasma DNA levels was linked to a 7.6% decrease in fibrinogen, a 41% increase in D-dimer, a 15.3% reduction in platelets and a 3.9% shortening in prothrombin time. A 10% increase in nucleosomes was associated with a 3.1% decrease in fibrinogen, a 112.7% increase in D-dimer, a 5.0% reduction in platelets and a 1.0% shortening in prothrombin time. Furthermore, upon administration of chemotherapy to patients with AML, NETs parameters and MV-TF activity significantly decreased (nucleosomes and MV-TF activity returned to normal levels after 1 week and 1 month, respectively), and coagulation indicators improved. According to these findings, NETs and TF-carrying MVs are interconnected, and this association may explain why thrombosis frequently complicates AML. Ostafin *et al* (55) conducted a study on 45 children with leukemia (including 33 patients with ALL, 8 patients with AML and 4 patients with T-cell ALL). During the progression of acute leukemia in children, unlike in adults, neutrophils demonstrate a compromised ability to extrude NETs. Consequently, infectious complications become more probable, whereas thrombotic risk is not similarly elevated. The currently available research is limited, and therefore larger multicenter studies with bigger sample sizes are needed for further validation (Table I).

The progression of AML is associated with inflammatory signaling in the BM (56). Various effector cells drive inflammation, including malignant clonal cells and stromal cells. High levels of pro-inflammatory cytokines, including IL-1β, TNF, IL-6, CXCL8, IFN-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF), are generated by

Table I. Summary of studies of NETs associated with thrombosis in hematologic malignancies.

Disease	Study design	Sample size	Sample source	NET markers	Key finding	(Refs.)
MPN	Case-control	52 MPN, 54 controls	Human plasma	MPO-DNA	MPO-DNA was elevated in patients with MPN and thrombosis vs. controls	(48)
	Case-control (human) + Animal model (mouse)	Human: NR (patients with MPN vs. controls); Mouse: NR	Human neutrophils and mouse neutrophils and lungs	CitH3	Jak2V617F mice showed increased NETs and thrombosis, which ruxolitinib reduced *in vitro* and *in vivo*	(13)
	Cross-sectional	66 patients with MPN	Human plasma	Nucleosome levels	Nucleosome levels were not associated with thrombosis or activation markers, suggesting limited predictive value in MPN	(49)
AML	Cross-sectional (with healthy controls)	15 AML (overt DIC), 28 controls	Human plasma	Plasma DNA and nucleosome	Overt DIC in cancer was largely mediated by NETs and TF-carrying MVs	(54)
	Case-control	45 leukemic children, 28 healthy controls	Human neutrophils	Extracellular DNA	Neutrophils in childhood acute leukemias have impaired NET release, increasing infection risk rather than thrombosis risk	(55)
HL	Cross-sectional	32 HL (12 NS-cHL 20 non-NS-cHL[a])	Formalin-fixed paraffin-embedded tissue	CitH3 and MPO	NETs promoted the formation of NS-cHL immune thrombus	(21)
MM	Case-control	38 MM, 19 MGUS, 34 controls	Human platelet-free plasma	cfDNA	Hypercoagulability in patients with MGUS and MM may be attributed to the activity of NETs	(77)
ALL	Case-control	29 acute leukemia (7 ALL), 48 controls	Human plasma	Histone-DNA, cfDNA, elastase	NET markers were higher in acute leukemia; associated with factor XIIa activation	(84)
	Case-control (with longitudinal follow-up)	17 ALL, 14 healthy controls	Human plasma	cfDNA	cfDNA contributed to increased thrombogenic potential	(85)

[a]Non-NS-cHL included 5 mixed-cellularity, 5 lymphocyte-rich, 1 lymphocyte-depleted, 4 nodular lymphocyte-predominant, and 5 other/unclassified cases. MPN, myeloproliferative neoplasm; MPO, myeloperoxidase; CitH3, citrullinated histone H3; NR, not reported; AML, acute myeloid leukemia; DIC, disseminated intravascular coagulation; NETs, neutrophil extracellular traps; TF, tissue factor; MVs, microvesicles; HL, Hodgkin lymphoma; NS-cHL, nodular sclerosis classical Hodgkin lymphoma; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; cfDNA, cell-free DNA; ALL, acute lymphoblastic leukemia.

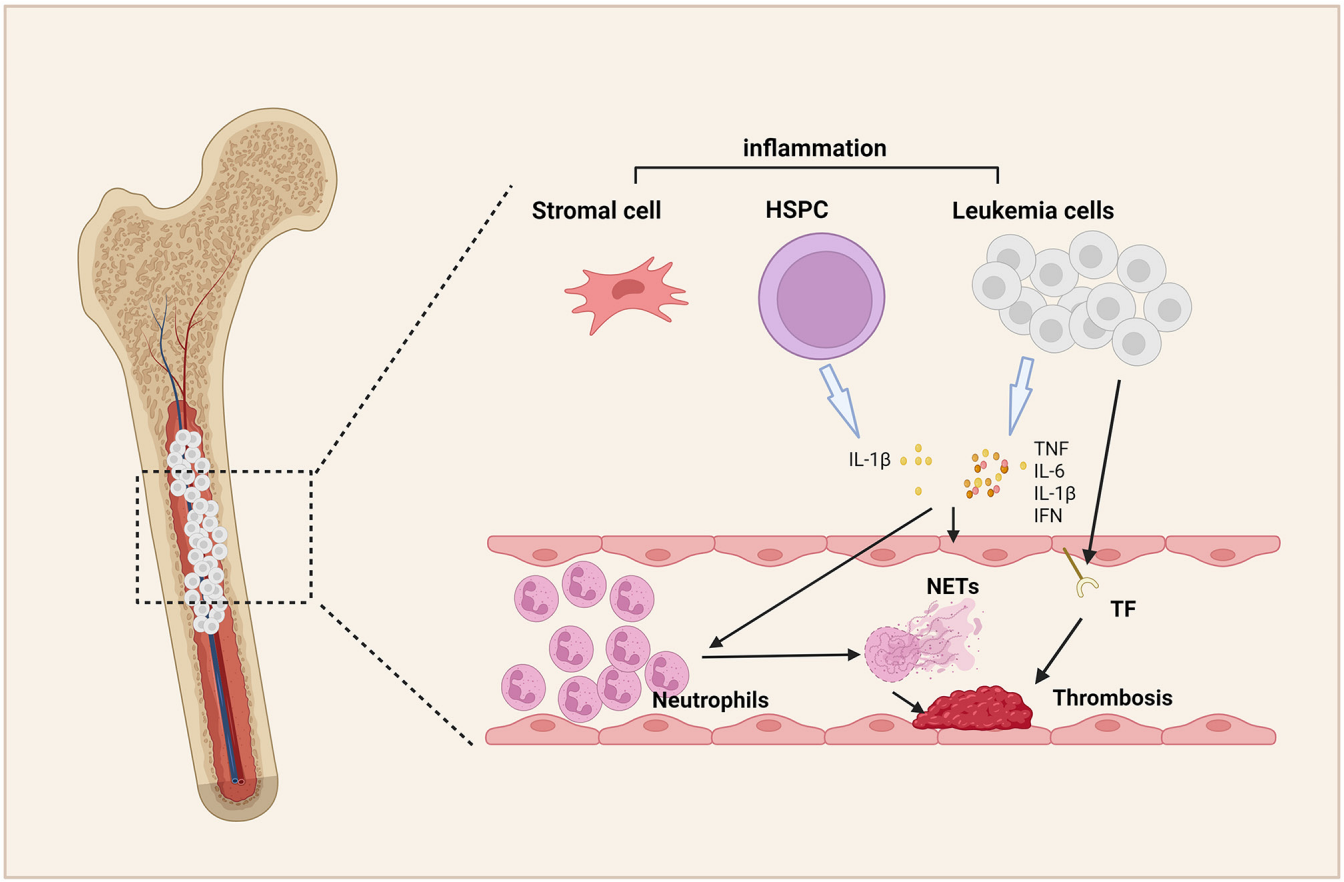

Figure 5. Mechanism of thrombosis in acute myeloid leukemia. Different effector cells, including leukemia, stromal and clonal hematopoietic stem and progenitor cells, drive tumor-associated bone marrow inflammation, inducing neutrophils to produce neutrophil extracellular traps and thereby promoting thrombus formation. Figure created with BioRender.com. HSPC, hematopoietic stem and progenitor cell; TNF, tumor necrosis factor; IL, interleukin; IFN, interferon; NETs, neutrophil extracellular traps; TF, tissue factor.

leukemia cells (57-59). Enhanced innate signaling in clonal hematopoietic stem and progenitor cells (HSPCs) leads to elevated secretion of IL-1β (60,61). Through this process, routine hematopoiesis becomes impaired, and the stability of the stem cell niche is undermined, thereby favoring disease progression. Meanwhile, inflammatory cytokines trigger the classic suicidal NETosis pathway in neutrophils, promoting NADPH oxidase-derived ROS-dependent NET release, thereby further contributing to thrombus formation. This working hypothesis is presented in Fig. 5.

HL. In the German Hodgkin Study Group trials (n=5,773), patients with HL showed a 3.3% thrombosis incidence (193 events) (62). Given the significant mortality impact of thrombosis in this curable malignancy, improved risk prediction is clinically crucial. Current tools such as the Khorana score inadequately predict VTE risk in HL (63), highlighting the need for refined risk assessment to guide timely thromboprophylaxis and improve outcomes.

Francischetti *et al* (21) analyzed 32 cases of cHL, among which, 75% (9 out of 12) of the nodular sclerosis (NS) subtype exhibited NET formation associated with fibrosis. Histones and elastase, two key NET components, can stimulate TF production within the endothelium. Through subsequent interaction with FVIIa, this response may activate the extrinsic arm of the coagulation system (64). Consequently, immunohistochemistry was used to measure TF expression, revealing 100% positivity (12/12) in the NS subtype. Through the combined action of NETs and TF, ECs become activated, which in turn fosters a reciprocal cycle linking coagulation and inflammation. This cycle emits signals that draw lymphocytes and neutrophils to the site (64-67). Hodgkin Reed-Sternberg (HRS) cells in NS cHL express PAR-2, indicating their tumorigenic and inflammatory phenotype. These events plausibly participate in fostering an inflammatory tumor microenvironment, operating via pathways that bear conceptual resemblance to immunothrombosis (15) (Fig. 6). In summary, these data provide the first evidence that NETs promote immunothrombosis and tumor growth in NS cHL. Future studies should explore the potential of targeting NETs and the PAR/protease axis. Such approaches may offer a way to retard the progression of cHL (Table I). In the aforementioned study (21), no NET formation was observed in patient samples of 5 mixed-cellularity, 5 lymphocyte-rich, 1 lymphocyte-depleted and 4 nodular lymphocyte-predominant HL cases. Thus far, the presence or absence of NETs in these HL subtypes has not been addressed by subsequent investigations.

MM. VTE occurs in >10% of patients with MM, driven by disease-specific factors (such as M-protein hyperviscosity, proinflammatory cytokines, newly diagnosed disease, renal impairment, and chromosome 11 abnormalities) (4,68-71)

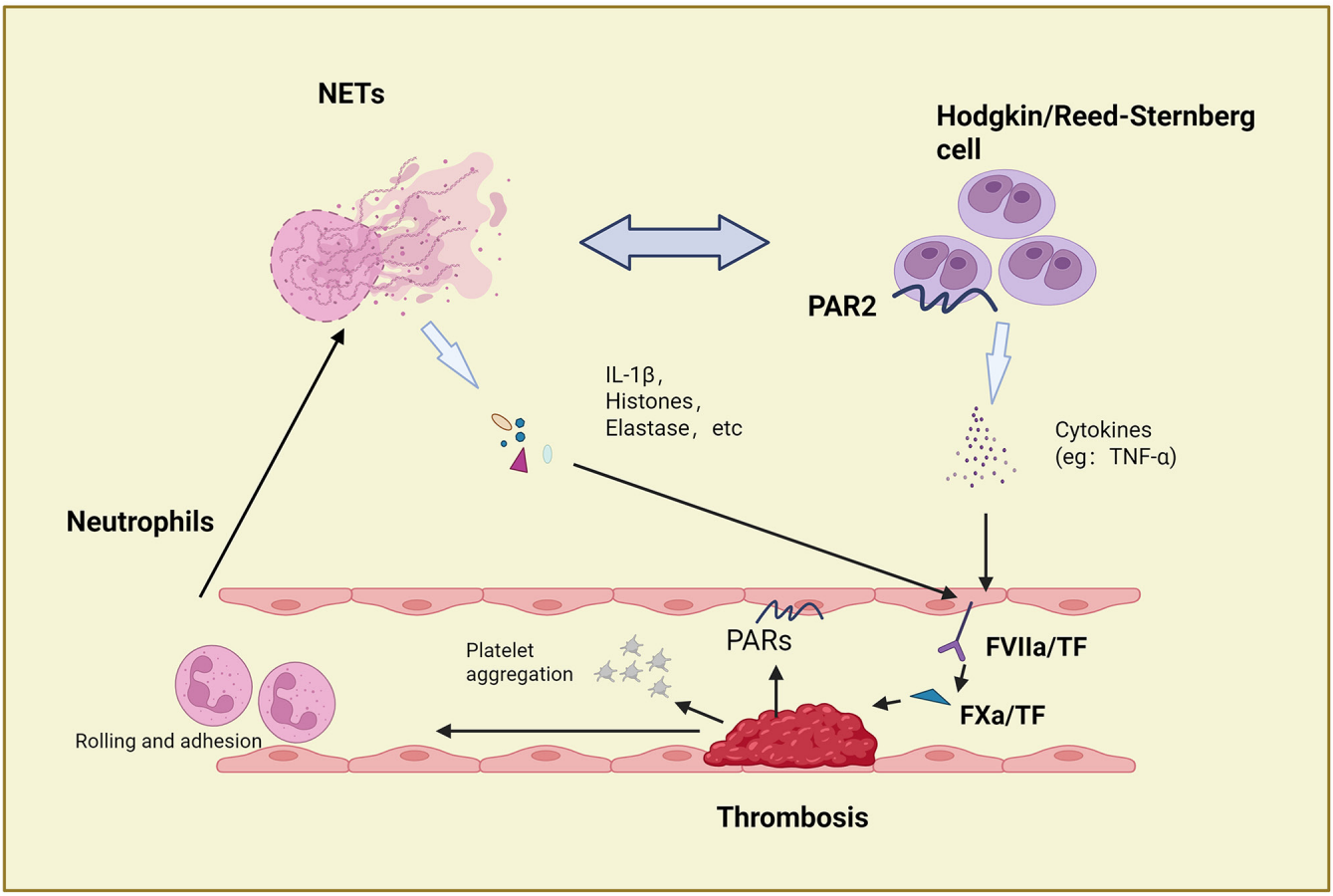

Figure 6. Mechanism of thrombosis in nodular sclerosis classical Hodgkin lymphoma. HRS cells recruit neutrophils to the tumor microenvironment by secreting cytokines such as TNF-α to activate endothelial cells. Under sustained stimulation by HRS-derived IL-8 and interferon-γ, neutrophils are induced to produce NETs. The elastase and tissue factor components of NETs establish a positive feedback loop via the PAR-2/MAPK pathway, which further promotes HRS cells to secrete pro-inflammatory factors such as IL-6 and IL-8, while simultaneously activating the coagulation system to facilitate thrombus formation. Figure created with BioRender.com. HRS, Hodgkin and Reed-Sternberg; TNF-α, tumor necrosis factor-α; IL, interleukin; NETs, neutrophil extracellular traps; PAR-2, protease-activated receptor 2; MAPK, mitogen-activated protein kinase; PARs, protease-activated receptors; FVIIa, activated coagulation factor VII; FXa, activated coagulation factor X; TF, tissue factor.

and hemostatic alterations (including elevated FVIII, vWF, fibrinogen, and thrombin generation) (72-74). Despite existing International Myeloma Working Group and European risk stratification guidelines (2014-2015) (75,76), current models cannot reliably distinguish between low-, intermediate- and high-risk patients, and validated predictive biomarkers remain lacking, thus highlighting the need for deeper mechanistic insights to improve VTE risk assessment in MM.

In a previous study by Nielsen *et al* (77), 38 patients diagnosed with MM, 19 patients with monoclonal gammopathy of undetermined significance (MGUS) and 34 healthy subjects were enrolled. The hypercoagulable state of the patients was assessed through coagulation analysis. The results revealed that both patients with MM and MGUS exhibited increased TG and procoagulant phospholipid activity, and all patients with MM showed an increase in MV-TF. Additionally, plasma levels of cfDNA, employed as a proxy indicator of NET generation, were assessed. Patients with MM exhibited markedly elevated cfDNA concentrations, and, in certain individuals, these values ranged from 5 to 10-fold above those observed in the control group. The authors suggested that the hypercoagulability observed in patients with MM may be attributed to the production of NETs. However, since the study was limited by a small sample size, this hypothesis remains to be validated (Table I).

MM progression is associated with tumor-related tissue inflammation (78). Myeloma cells can autonomously secrete IL-6 and TNF-α, while mesenchymal stromal cells and osteoblasts also secrete IL-6 (79,80). Additionally, immunoglobulin-specific mechanisms contribute to VTE through inflammatory cytokine effects and acquired activated protein C resistance (81). Massive deposition of M-protein on the vascular endothelium triggers inflammatory responses. The hypercoagulable state in MM arises not only from the disease itself but also from therapeutic interventions. The use of immunomodulatory drugs (IMiDs), such as lenalidomide, promotes the release of inflammatory cytokines and induces stress and injury in ECs (82). It can be hypothesized that these inflammatory cytokine effects, in addition to sustaining tumor growth, may partially promote thrombosis by stimulating NET formation. This working hypothesis is presented in Fig. 7.

ALL. The California Cancer Registry analyzed 2,482 cases of ALL from 1993 to 1995, accounting for 4.5% of the cohort (51). Ziegler *et al* (50) studied 185 cases of ALL and found a thrombosis incidence of 2.09%. Adolescents with ALL face

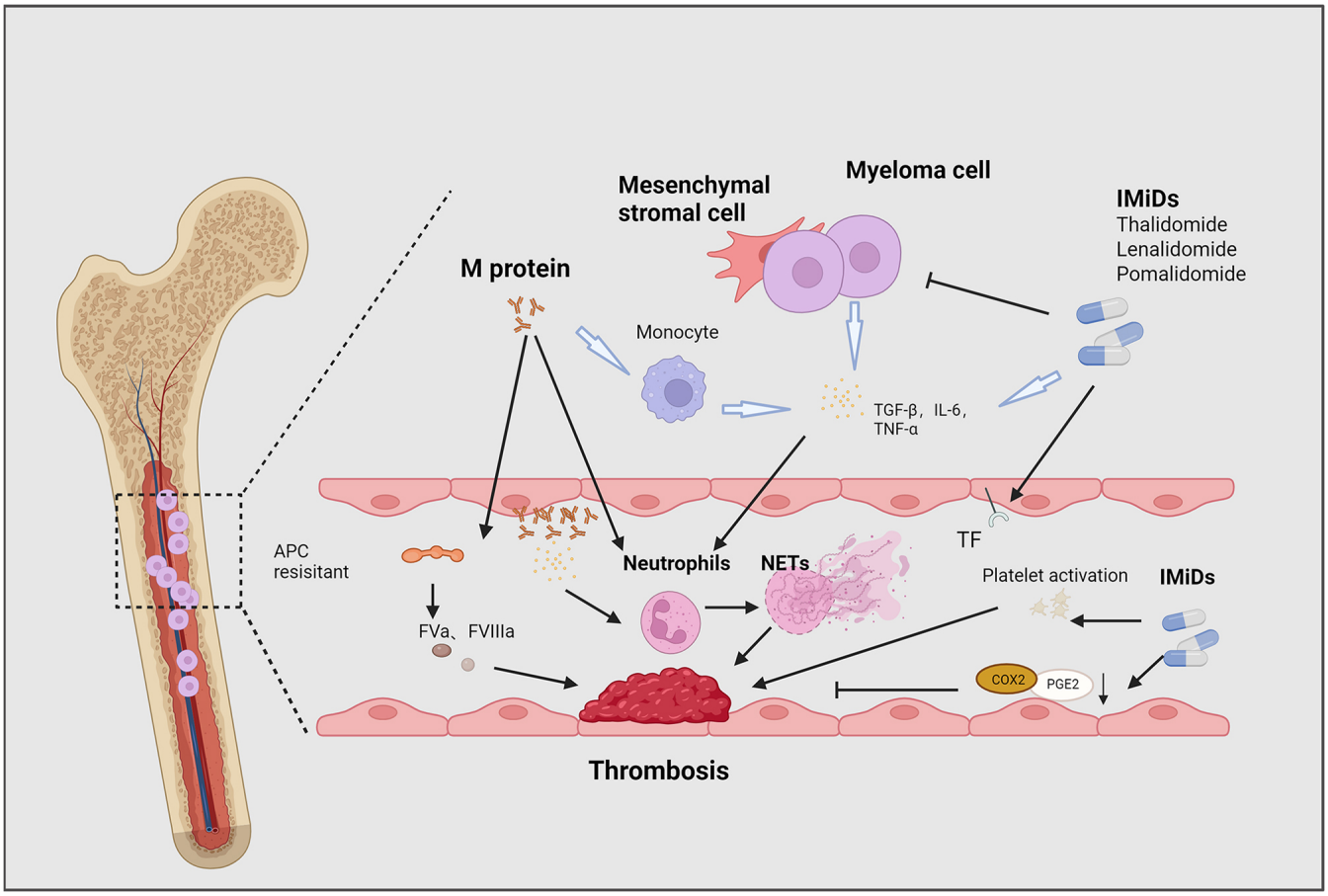

Figure 7. Mechanism of thrombosis in multiple myeloma. Myeloma cells, mesenchymal stromal cells and M protein collectively stimulate the formation of a tumor-associated inflammatory microenvironment. IMiDs can alter the balance between procoagulant and anticoagulant proteins on EC surfaces, including upregulating tissue factor expression, while suppressing cyclooxygenase-2 and prostaglandin E2 synthesis. These effects simultaneously increase EC stress and injury. Collectively, these mechanisms promote neutrophil extracellular trap formation, ultimately contributing to venous thromboembolism. Figure created with BioRender.com. IMiDs, immunomodulatory drugs; EC, endothelial cell; APC, activated protein C; NETs, neutrophil extracellular traps; TGF-β, transforming growth factor-β; IL, interleukin; TNF-α, tumor necrosis factor-α; TF, tissue factor; COX2, cyclooxygenase-2; PGE2, prostaglandin E2; FVIIIa, activated coagulation factor VIII; Fva, activated coagulation factor V.

an elevated thrombotic risk compared with other age groups. A meta-analysis comprising 17 prospective studies (1,752 participants) reported that 5.2% of pediatric patients with ALL experienced thrombotic complications (83). VTE occurrence, meanwhile, elevates the likelihood of mortality within the first year by 40% (51). The incomplete understanding of ALL-associated thrombosis mechanisms and the absence of standardized thromboprophylaxis underscore the need for personalized prevention strategies tailored to patient-specific risk profiles.

Kim *et al* (84) examined 29 adult patients with acute leukemia (mean age, 50 years, among whom, 7 had ALL). The authors found increased levels of both factor XIIa and extracellular trap markers, specifically histone-DNA complex and cell-free dsDNA, and noted a strong correlation between these measurements. These results offer a previously unrecognized mechanistic explanation for the fact that adult patients with ALL are prone to thrombotic events. NETs may activate factor XII, thus triggering the intrinsic clotting cascade and resulting in a prothrombotic state along with increased thrombotic risk. To investigate the link between coagulation parameters and NET formation in pediatric ALL, Kumar *et al* (85) performed a research study where the authors measured NET-related markers, including circulating cfDNA, nucleosomes and citrullinated H3Cit, as well as endogenous thrombin potential (ETP) in 17 patients and a control group. The results showed that, with the exception of cfDNA, the concentrations of H3Cit and nucleosomes in plasma remained comparable to those observed in the control group at all the measured time points during treatment. Subsequent treatment of plasma samples with DNase I only revealed a significant reduction in ETP. cfDNA is considered to elevate the likelihood of thrombotic events. The above study also faced limitations due to its relatively small sample size, which restricted the ability to assess the associations among thrombin generation, NETs and clinical thrombosis (Table I). Therefore, future research should expand the sample size of patients with ALL and conduct multicenter studies to validate the association between NET markers and thrombosis. A concurrent in-depth investigation of the differences in NET formation and thrombotic risk mechanisms between pediatric and adult ALL would be of great importance.

Notably, four common issues emerge from the literature on the aforementioned diseases (1), including i) sample size: The majority of studies are single-center exploratory analyses (n<50), lacking multicenter, prospective, large-cohort

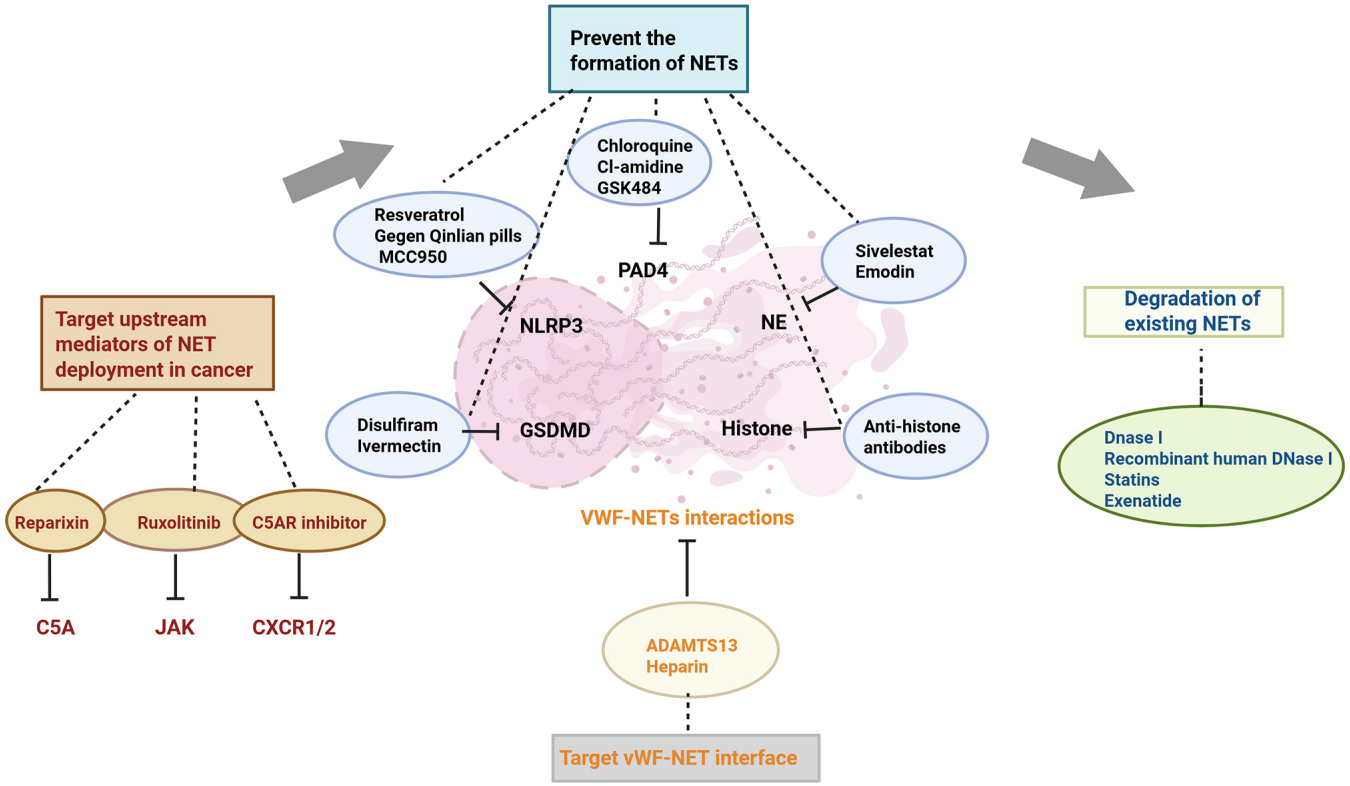

Figure 8. Targeting NETs in thrombotic processes. It has been reported that the mechanism of action of drugs targeting NETs to improve thrombus involves various aspects, including inhibiting formation, increasing degradation, targeting upstream mediators of cancer-associated NET formation and targeting vWF-NET interface. Figure created with BioRender.com. NETs, neutrophil extracellular traps; C5A, complement component 5a; CXCR1/2, C-X-C chemokine receptors 1 and 2; NLRP3, NLR family pyrin domain-containing 3; PAD4, peptidylarginine deiminase 4; GSDMD, gasdermin D; NE, neutrophil elastase; vWF, von Willebrand factor; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif 13.

validation (n>200), as well as prospective stratification by treatment stage (newly diagnosed, post-chemotherapy, or post-transplantation) and disease subtype; ii) NET marker standardization: cfDNA and nucleosomes are easily measurable but lack specificity; MPO-DNA and H3Cit exhibit high specificity, yet their detection methods (ELISA, immunofluorescence, and flow cytometry) have not been standardized. At the same time, as NET research has advanced, the understanding of traditional indicators has evolved. Free plasma DNA and nucleosomes have been discussed as non-exclusive indicators of NET formation, since they can likewise derive from other modes of cell death, namely cancer-associated or treatment-induced apoptosis and necrosis (49). To the best of our knowledge, no study has to date performed a parallel comparison of the predictive efficacy of cfDNA, nucleosomes, MPO-DNA and H3Cit for thrombotic events within the same cohort, nor has a unified positive threshold been established. In future research, a combined detection strategy is recommended, and the specificity of plasma markers should be verified whenever possible by immunocytochemistry or flow cytometry to guarantee the robustness of the findings; iii) therapeutic confounding: The majority of studies have not adequately controlled for or performed stratified analyses on the direct effects of cytoreductive therapy, JAK inhibitors, IMiDs, asparaginase or GM-CSF on NETosis. An ideal study design should involve dynamic sample collection before treatment (baseline), during treatment (acute phase) and after treatment (remission phase) to distinguish the contributions of the disease itself vs. therapeutic interventions to NET formation; and iv) lack of causal validation: Existing studies are predominantly correlational in nature and lack causal chain validation (such as using PAD4 inhibitors, DNase I or PAD4-knockout mice in disease models to demonstrate that NETs lead to thrombosis). Furthermore, *in vitro* experiments often employ non-physiological strong stimuli such as PMA to induce NETosis, which may differ mechanistically from NETosis induced by tumor-related stimuli *in vivo* (characterized by low-concentration, chronic stimulation).

6. Novel therapies for NET-associated thrombosis

In hematological malignancies, the development of thrombosis typically is associated with worse prognosis. As one of the emerging mechanisms of thrombosis, NETs may be potential intervention targets for the treatment of hematological malignancies (Fig. 8).

Preventing the formation of NETs

Preclinical evidence. Therapeutic targeting of NET formation pathways, particularly through PAD inhibition, has shown promising antithrombotic effects in preclinical studies. *In vivo*, PAD gene deletion and inhibition of NET formation resulted in similar phenotypes in various disease models (9). Previous studies have examined Cl-amidine, a comparatively new PAD-targeting agent, in diverse inflammatory disease settings, including atherosclerosis (86), lupus, diabetes mellitus and endometritis (87-89). Knight *et al* (86) reported that, in

atherosclerotic mice, pharmacologically targeting NET formation with Cl-amidine was shown to lessen both atherosclerotic plaque load and arterial thrombotic events. Novotny *et al* (90) treated mice with arterial thrombosis with Cl-amidine and showed inhibition of NET formation, reduced thrombosis and reduced disease-associated tissue damage. Additionally, two more specific PAD4 inhibitors, GSK199 and GSK484, have been reported to suppress NET production in models of arthritis, heparin-induced settings and a murine coronavirus system (91-93). Previous studies on GSK484 intervention showed significant inhibition of thrombosis. In addition, an important aminoquinoline compound, chloroquine, is extensively employed in treating diverse illnesses, including malaria, lupus erythematosus and rheumatoid arthritis, and additionally functions as a PAD4 inhibitor (94). Dyer *et al* (95) found that hydroxychloroquine (HCQ) could reduce deep vein thrombotic burden in traumatized mice. Notably, Petri *et al* (96) found that it inhibited thrombosis in patients with systemic lupus erythematosus (SLE). Thrombosis occurred in 38 (5.1%) of 739 patients with SLE. Patients with mean HCQ blood levels ≥1,068 ng/ml had 69% fewer thrombotic events (P=0.024). However, published reports describing other PAD inhibitors in human applications are lacking, despite that the fact that these agents possess the capacity to modulate thrombosis.

The assembly process of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome also requires PAD4 (97). NLRP3, a multimeric protein complex, recognizes endogenous or pathogen-associated signals and stimulates the secretion of pro-inflammatory cytokines (98). Activation of NETosis requires the involvement of the NLRP3 inflammasome. Gegen Qinlian pills (99) and resveratrol (100) have been shown to reduce thrombosis by inhibiting NLRP3 signaling or downregulating NLRP3 expression, respectively. MCC950, a synthetic compound, represents the most powerful selective NLRP3 inhibitor yet described (101) and was demonstrated to ameliorate thrombin-induced platelet aggregation (102). Therefore, inhibiting NETosis through NLRP3 targeting could open novel avenues for antithrombotic therapy.

The release of NETs following NLRP3 inflammasome activation is orchestrated by gasdermin D (GSDMD), a protein known for its pore-forming activity in pyroptosis (103,104). Approved as a therapy for alcohol use disorder, disulfiram, which inhibits GSDMD and exerts its clinical effect through suppression of aldehyde dehydrogenase (105), has been shown to downregulate innate immunity and the complement/coagulation pathways (106). Another GSDMD-targeting agent, ivermectin, was found to diminish microclot development via interference with SARS-CoV-2 binding to fibrinogen, a finding supported by molecular docking and dynamics simulations (107).

Approved drugs with indirect NET effects. Therapeutic targeting of NET-associated cytotoxic components shows clinical potential. Sivelestat, an inhibitor of NE, has received regulatory approval in Japan and South Korea as a therapy for acute respiratory distress syndrome (108). Zhou *et al* (109) demonstrated that NETs induce endothelial cytotoxicity and procoagulant transformation, effects attenuated by 25% with Sivelestat treatment. Zhang *et al* (110) demonstrated that NETs trigger endothelial procoagulant activation through vWF/plasminogen activator inhibitor-1 (PAI-1) release, a process inhibited by Sivelestat to potentially enhance fibrinolysis. Meanwhile, the NE inhibitor α-1 antitrypsin (prolastin-C) is under clinical evaluation for bronchiectasis (NCT05582798). Prolastin-C represents the sole NET-formation inhibitor currently in clinical trials. Meanwhile, histones drive endothelial dysfunction and prothrombotic responses (111), with anti-histone antibodies showing efficacy in reducing pulmonary microthrombi in murine trauma models (112), supporting histone targeting as a viable therapeutic strategy.

N-acetylcysteine (NAC) is a drug with antioxidant, expectorant and anti-inflammatory effects. The dependence of NETosis on ROS has led to the observation that NAC inhibits NET formation *in vitro* (113). NAC has been explored as a potential therapy for various thrombotic conditions, including thrombotic thrombocytopenic purpura (NCT01808521). In that phase I clinical trial, the treatment was administered as an initial intravenous injection of 150 mg/kg over 60 min. If this dose was tolerated, it was then followed by a 17-h intravenous infusion at the same dose. According to Craver *et al* (19), NAC prolonged the survival of Jak2V617F mice while leaving both blood cell parameters and spleen enlargement unaffected. NAC was shown to decrease thrombus formation when tested in an animal model of acute pulmonary thrombosis. Analysis of *in vitro* platelet activation revealed that NAC decreased the formation of platelet-leukocyte aggregates in Jak2V617F mice (19). Additionally, NAC suppressed NET generation in primary human neutrophils derived from patients with MPN and from healthy individuals (19). These findings demonstrate that NAC exerts antithrombotic effects in Jak2V617F mice. Furthermore, they provide a preclinical rationale for continued evaluation of NAC as a potential agent to lower thrombotic risk in MPN.

Other promising therapeutic targets. Drugs targeting molecules such as EPCR, BTK, SIRT and NADPH have demonstrated potential in inhibiting NET formation and ameliorating thrombosis (19,114-123) (Table II). However, clinical trials for these drugs have not yet been initiated.

Degradation of existing NETs

Approved drugs with indirect NET effects. DNase I is a recognized substance capable of degrading the main chain of NETs (32). The use of exogenous DNase has been applied across multiple disease settings, demonstrating reductions in measurable biomarkers and associated improvements in outcomes, including the reversal of coagulopathy and thrombotic burden, as well as decreased cancer growth and metastasis. Pulmozyme®, an inhaled formulation of DNase I, has received Food and Drug Administration approval as a therapy for cystic fibrosis (NCT00843817) with the aim of alleviating disease manifestations (124). Inhaled DNase I does not readily reach the circulation. Consequently, its activity against NETs found in the vasculature outside the lungs is suboptimal (106). DNase I was shown to inhibit thrombosis in preclinical mouse and baboon models (32,34,125). In a murine cancer model, recombinant human DNase I was found to decrease thrombosis occurrence while exhibiting no hemorrhagic adverse effects (126).

In addition, statins could reduce the levels of macrophages, neutrophils and NETs in a murine model of venous thrombosis, and decrease thrombus burden through profibrinolytic, anticoagulant and antiplatelet effects (127). As a GLP-1 agonist,

Table II. Summary of reported NET-targeting drugs that inhibit thrombotic effects.

Intervention and potential role in hematologic malignancies	Target	Therapeutic agent	Study stage	Mechanism	(Refs.)
Prevent the formation of NETs	PAD4	Chloroquine	Preclinical (murine pancreatic cancer model) Correlative human serum	Reduced thrombus burden	(95)
			Clinical (systemic lupus erythematosus patients)	A 13% lower rate of thrombotic events was observed per 200-ng/ml rise in the most recently measured hydroxychloroquine level	(96)
		Cl-amidine	Preclinical (murine atherosclerosis model)	Reduced NET release in mice lessened atherosclerosis and thrombosis	(86)
			Preclinical (murine myocardial infarction model)	NET elimination reduced arterial clotting and minimized harm	(90)
		GSK484	Preclinical (murine coronavirus infection model)	Achieved a 31% reduction in NETs and a 93% reduction in pulmonary thrombi	(92)
			Preclinical (murine heparin-induced thrombocytopenia model)	Abrogated NETosis and sharply reduced clotting	(93)
	GSDMD	Disulfiram	Preclinical (SARS-CoV-2-infected golden hamsters)	Downregulated innate immune and complement/ coagulation pathways	(106)
		Ivermectin	Preclinical (molecular docking and dynamics simulations)	Hindered SARS-CoV-2 SP attachment to fibrinogen and lowered the incidence of microscopic clots	(107)
	Neutrophil elastase	Sivelestat	Preclinical (*in vitro* human umbilical vein endothelial cells)	Neutralized NET cytotoxicity to protect ECs and reduce PCA, highlighting their importance in preventing thrombosis in atherosclerosis	(109)
			Preclinical (murine ischemia-reperfusion model)	Blocked the procoagulant state as well as vWF and PAI-1 secretion	(110)
		Emodin	Preclinical (zebrafish model)	Achieved a higher level of thrombosis suppression	(138)
	NLRP3	Gegen Qinlian pills	Preclinical (murine carrageenan-induced thrombosis model)	Provided defense against thrombosis triggered by carrageenan	(99)
		Resveratrol	Preclinical (rat venous thrombosis model)	Diminished the severity of venous thrombosis	(100)
		MCC950	Preclinical (4T1 tumor-bearing mice)	Reduced thrombosis	(102)
	Histone	Anti-histone antibodies	Preclinical (murine trauma model)	An anti-histone antibody could reduce microvascular thrombosis and protect mice from histone-induced lethality	(112)
	EPCR	Activated protein C	Preclinical (rabbit *in vivo* stent implantation)	Inhibited platelet or neutrophil adhesion in a simulated stent environment	(114)
	Mitochondrial oxidative stress	MitoQ	Preclinical (mouse embryonic fibroblasts)	Inhibited platelet activation steps by reducing ROS levels	(115)
	NADPH/SHP2	Kaempferol	Preclinical (murine collagen-induced platelet activation model)	Suppressed collagen-induced platelet activation	(116)

Table II. Continued.

Intervention and potential role in hematologic malignancies	Target	Therapeutic agent	Study stage	Mechanism	(Refs.)
	SYK COVID-19	Fostamatinib	Preclinical (signaling network analysis)	Prevented COVID-19-induced NETosis and controlled platelet hyperactivation	(117, 118)
	Phosphoinositide 3-kinase	Salvianolic acid A	Preclinical (murine arterial thrombosis model)	Inhibited platelet activation and arterial thrombosis	(119)
	Nrf2	Taxifolin	Preclinical (thrombo-inflammatory mouse model)	Suppressed autoantibody generation, curtailed pro-inflammatory cytokine release, and reduced the occurrence of venous thrombi	(120)
	SIRT1	Resveratrol	Preclinical (BDNFMet/Met mice and/or Met allele-transfected cells)	Blocked clot development while normalizing coagulation parameters and platelet marker levels	(139)
	BTK	PRN473	Preclinical (healthy donors and XLA platelets; IVC stenosis and *Salmonella* infection mouse models)	Reduced venous thrombosis formation	(121)
	Other promising therapeutic targets	Itaconate (4-OI)	Preclinical (murine SARS-CoV-2 infection model)	Inhibited TF-dependent thrombin generation	(123)
		Lactoferrin	Preclinical (*in vitro* anticoagulation experiments)	LF-LR, a lactoferrin-derived peptide (sequence LRPVAAEIY), showed anti-clotting activity	(122)
		NAC	Preclinical (murine MPN model; human neutrophils from patients with MPN)	Decreased clot development and suppressed the formation of thrombin-triggered platelet-leukocyte aggregates	(19)
Degradation of existing NETs		DNase I	Preclinical (baboon and mouse thrombosis models)	Suppressed thrombus growth	(32, 124, 125)
		Recombinant human DNase I (rhDNase I)	Preclinical (tumor-bearing mice)	Decreased clot development without inducing major hemorrhage	(126)
		Statins	Preclinical (murine IVC ligation stasis VT model)	Reduced venous thrombus burden, platelet aggregation, and clot stability.	(127)
		Exenatide	Preclinical (murine cremaster artery laser injury model)	Inhibited thrombus formation.	(128)

NETs, neutrophil extracellular traps; PAD4, peptidylarginine deiminase 4; GSDMD, gasdermin D; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SP, spike protein; ECs, endothelial cells; PCA, procoagulant activity; vWF, von Willebrand factor; PAI-1, plasminogen activator inhibitor-1; NLRP3, NLR pyrin domain-containing protein 3; EPCR, endothelial protein C receptor; ROS, reactive oxygen species; NADPH, nicotinamide adenine dinucleotide phosphate; SHP2, Src homology 2 domain-containing phosphatase 2; SYK, spleen tyrosine kinase; COVID-19, coronavirus disease 2019; Nrf2, nuclear factor erythroid 2-related factor 2; SIRT1, sirtuin 1; BDNF, brain-derived neurotrophic factor; BTK, Bruton's tyrosine kinase; XLA, X-linked agammaglobulinemia; TF, tissue factor; LF-LR, lactoferrin-derived peptide; NAC, N-acetylcysteine; MPN, myeloproliferative neoplasm; DNase I, deoxyribonuclease I; rhDNase I, recombinant human deoxyribonuclease I; IVC, inferior vena cava; VT, venous thrombosis.

Table III. Summary of reported drugs targeting upstream regulators and NET-associated pathways.

Intervention and potential role in hematologic malignancies	Target	Therapeutic agent	Study stage	Mechanism	(Refs.)
Target upstream mediators of NET deployment in cancer	CXCR1/2	Reparixin	Preclinical (murine sepsis model)	Reduced thrombosis, lung injury, and mortality	(132)
	C5AR	C5AR inhibitor	Preclinical (murine kidney injury model)	Prevented immunothrombosis	(133)
Target the vWF-NET interface	vWF-NET interactions	ADAMTS13	Preclinical (murine thrombosis model)	Reduced cerebral infarct sizes in a thrombosis.	(137)
		Heparin	Preclinical (baboon thrombosis model)	Inhibited thrombosis by activation of antithrombin.	(32)

NET, neutrophil extracellular trap; CXCR1/2, C-X-C chemokine receptors 1 and 2; C5AR, complement component 5a receptor; vWF, von Willebrand factor; ADAMTS13, a disintegrin and metalloproteinase with thrombospondin type 1 motif 13.

exenatide exhibits multiple activities: It reduces circulating NET marker concentrations (128), inhibits platelet aggregation *in vitro* and suppresses thrombus formation *in vivo*, suggesting its potential to reduce NET-associated thrombosis (129).

Targeting upstream mediators of NET formation in cancer Preclinical evidence. Targeting the upstream mediators of cancer NET formation also has the potential to ameliorate coagulation. Previous research has shown that CXCR2 has a promoting effect on tumorigenesis (130). Furthermore, CXCR2 can bind to IL-8 to recruit and activate neutrophils and promote NET formation (131). Alsabani *et al* (132) found that NET formation was associated with fibrin deposition (r=0.702) and lung injury (r=0.692) in a mouse model of sepsis. The application of the CXCR1/2 inhibitor reparixin was demonstrated to inhibit NETs and thrombosis, thereby reducing multiorgan injury and mortality.

Approved drugs with indirect NET effects. Complement component 5a (C5A) promotes NET formation, whereas complement component 5a receptor 1 (C5AR1) blockers are authorized for use in anti-neutrophil cytoplasmic antibody-related small-vessel vasculitis (133). Zhao *et al* (134) found that inhibiting the C5A/C5AR axis resolves cholesterol crystals and attenuates renal vascular thrombosis in mice. Although the role of this axis in malignancy remains unclear, its inhibition may slow disease progression in animal models by targeting NETs (Table III).

Targeting the vWF-NET interface Preclinical evidence. NETs function as a scaffold, which facilitates the adherence of platelets and red blood cells, and also serves to concentrate clotting-relevant proteins. Interactions with NETs can be mediated in several ways. Under inflammatory conditions, ultra-large vWF fibers are formed, which are anchored to the endothelial lining and serve as intermediaries that facilitate NET-driven remodeling of fibrin networks. Finally, the fibers exert a procoagulant effect by stabilizing the thrombus (135). Grässle *et al* (37) reported that heparin interferes with DNA-vWF binding, thereby blocking adhesion to white blood cells. Fuchs *et al* (32) found that heparin prevented the formation of blood clots in baboons by affecting the binding of NETs to fibrin chains. Similarly, vWF can be lysed by the metalloproteinase ADAMTS13, which has been shown to improve ischemic brain injury *in vivo* (136). Denorme *et al* (137) observed that ADAMTS13 broke down TPA-resistant clots in a concentration-responsive manner in a murine stroke model, reducing the area of cerebral infarction. In summary, interfering with the vWF-NET interface may serve as a promising strategy for developing antithrombotic treatments (Table III).

In conclusion, directing therapeutic efforts toward NETs may offer a viable approach to address thrombosis in the context of hematological malignancies. However, these are frequently complicated by cytopenias and coagulation disorders, which may predispose patients to bleeding complications and platelet-related safety risks following NET-targeted therapies. Although no adverse effects on platelet counts or organ function were observed in NAC-treated MPN mouse models, future investigations should prioritize the assessment of these potential risks. Furthermore, given that monotherapy may not adequately mitigate thrombotic risk, the combination of NET-targeted agents with conventional anticoagulants warrants exploration as a promising approach. The two modalities are mechanistically complementary, potentially exerting synergistic antithrombotic effects by targeting distinct steps in thrombus formation. However, concurrent administration of two antithrombotic agents may also increase bleeding risk, particularly in patients with thrombocytopenia. The efficacy and safety of such combination therapy require systematic evaluation in future animal studies.

7. Conclusion and future perspectives

Thrombosis remains a life-threatening complication in hematological malignancies, with emerging evidence implicating NETs as key mediators through multiple prothrombotic mechanisms. While the involvement of NETs in hypercoagulability across MPN, AML, MM, HL and ALL is established,

their disease-specific mechanisms require further elucidation. Current NET-targeting strategies, including formation inhibition, degradation enhancement and mediator blockade, show preclinical promise but demand rigorous clinical validation, particularly regarding bleeding risks in patients with thrombocytopenia.

Critical challenges persist in NET quantification and biomarker development. Future directions should prioritize i) standardized NET detection assays, ii) mechanistic studies on NET-driven thrombosis, iii) therapeutic optimization through targeted NETosis inhibition or combination approaches and iv) integration of NET biomarkers into risk stratification models. Addressing these priorities through collaborative research will accelerate the translation of NET-focused strategies into clinical practice, offering novel avenues for thrombosis management in hematological malignancies.

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Availability of data and materials

Not applicable.

Authors' contributions

KL and ZM designed, conducted the literature review and drafted the manuscript. QC, YS and JM contributed to supervision, funding acquisition, and manuscript writing, review and editing. LY contributed to the conceptualization of the review, as well as manuscript, writing, review and editing. CW contributed to the study design, supervision, funding acquisition, conceptualization, project administration, and manuscript writing, review and editing. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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