Research progress on neutrophil extracellular traps in sepsis-induced coagulopathy (Review)

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Abstract. Sepsis affects an estimated 166 million individuals globally with 21.4 million annual deaths and represents a notable public health challenge. Sepsis-induced coagulopathy (SIC) is a marked complication of sepsis, characterized by dysregulated hemostasis and microvascular thrombosis. Neutrophil extracellular traps (NETs) are pivotal mediators linking innate immunity to thrombo-inflammation in this process. The present review systematically examined the epidemiology and pathogenesis of SIC, the molecular mechanisms of NET release (suicidal, vital, mitochondrial and non-canonical pathways) and the mechanistic pathways by which NETs regulate SIC. NETs disrupt endothelial integrity, amplify platelet activation, propagate coagulation cascades and suppress fibrinolysis, thereby establishing a self-amplifying cycle that accelerates progression to disseminated intravascular coagulation and multiple organ failure. Furthermore, the present review highlighted current therapeutic strategies targeting NETs, including inhibition of NET synthesis, acceleration of NET clearance and disruption of platelet-neutrophil interactions. Elucidating the central role of NETs in SIC pathophysiology may facilitate the development of novel biomarkers and precision therapeutic interventions for this life-threatening condition.

Contents

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1. Introduction

Sepsis is defined as life-threatening organ dysfunction resulting from a dysregulated host response to infection (1). Its pathogenesis is complex and rapidly progressive, and it is associated with carrying a high risk of mortality. Clinically, sepsis manifests as hemostatic imbalance and fibrinolytic system dysfunction, with the increased generation of thrombin and fibrin within the vasculature, promoting microthrombus formation in small and medium-sized vessels that can ultimately progress to systemic hemorrhage, multiple organ failure and death (2,3). Although numerous randomized controlled trials have investigated the efficacy of anticoagulant therapy in sepsis, its effectiveness and the optimal timing of intervention remain controversial (4,5). Therefore, elucidating the pathophysiological mechanisms of sepsis-induced coagulopathy (SIC) is essential.

Neutrophil extracellular traps (NETs) are three-dimensional mesh-like scaffolds composed of a DNA backbone embedded with various antimicrobial proteins, playing a dual role in pathogen infection. Initially, NETs protect the host by confining pathogen dissemination and exerting direct antimicrobial effects (6,7). Conversely, excessive NET generation may hyperactivate the coagulation system, inhibit anticoagulant pathways, damage vascular endothelial cells (VECs) (8) and contribute to SIC through interactions with platelets (9-11). In severe cases, this may progress to disseminated intravascular coagulation (DIC), leading to widespread hemorrhage and organ dysfunction (12). The present review discuses: i) The epidemiology and pathogenesis of SIC; ii) NET production and the mechanistic pathways by which NETs regulate SIC; and iii) the target therapy of NETs in SIC, aiming to clarify the central role of NETs in SIC and identify potential therapeutic targets.

2. Epidemiology of sepsis

In 2017, epidemiological data indicated 48.9 million new sepsis cases globally, with 11 million related deaths,

accounting for 19.7% of total global mortality. Between 1990 and 2017, the incidence of sepsis decreased by 37.0% and related mortality rates decreased by 52.8% (13). However, the COVID-19 pandemic notably increased the global burden in 2021, with an estimated 166 million new cases (95% uncertainty interval 135-201 million) and 21.4 million related deaths (20.3-22.5 million), representing 31.5% of total mortality rates. Adults aged ≥70 years exhibited the highest mortality rates, with sepsis-related deaths in this age group increasing from 8.34 million in 2019 to 15.5 million in 2021 (13). Research has demonstrated a higher incidence of sepsis and mortality among males overall (14). Notably, in the specific context of postoperative sepsis, females exhibit higher incidence and mortality rates (15-17). The progression of sepsis can induce multiple organ dysfunction, increasing patient mortality, prolonging periods of hospitalization, hindering clinical recovery and imposing heavy economic burdens on society and families.

3. SIC

Pathogenesis of SIC. Coagulation dysfunction is a notable risk factors for adverse outcomes in sepsis (18). Globally, 24.0-60.0% of patients with sepsis develop SIC (19). This condition exhibits a high incidence and diverse manifestations, ranging from mild thrombocytopenia and hyperfibrinolytic states to overt DIC if left untreated, with doubling mortality rates (20). In the initial phase of septic shock, circulating inflammatory mediators damage VECs, activate the coagulation system and increase capillary permeability, resulting in fluid and protein leakage. The sympathoadrenal axis is activated, with catecholamines inducing systemic vasoconstriction to ensure blood supply to vital organs. At this stage, tissues may still receive adequate perfusion, and hemodynamic alterations remain insignificant (21,22). As the condition is aggravated however, the marked release of inflammatory mediators causes damages to VECs and even death, notably increasing capillary permeability with substantial fluid and protein leakage, resulting in severe tissue edema. Marked catecholamine release causes intense capillary constriction, leading to blood stagnation within the microcirculation and promoting extensive microthrombus formation. In the stage of microcirculatory failure, persistent hypoxia and inflammation cause extensive VEC death, and the microcirculation loses its autoregulatory capacity. Circulating blood volume becomes notably depleted, and tissue perfusion becomes markedly insufficient. Vascular responsiveness to catecholamines decreases, and blood pressure further declines. Blood flow becomes extensively stagnant within the microcirculation, with the coagulation system markedly activated while fibrinolysis is suppressed, leading to DIC and ultimately resulting in severe tissue hypoxia and organ failure (23-25).

Mechanistic pathways of the pathogenesis of SIC. The pathogenesis of SIC involves multiple regulatory pathways. i) Tissue factor (TF) activation; following lipopolysaccharide (LPS) binding to Toll-like receptor (TLR)-4 on VEC/monocytes, the rapid recruitment of myeloid differentiation primary response 88/TIR-domain-containing adapter-inducing interferon β subsequently activates the NF-κB/interferon regulatory factor 3 pathway. This leads to increased TF mRNA expression within 30 min. The newly expressed TF, a transmembrane glycoprotein, binds to coagulation factor VIIa (FVIIa) to form the TF-FVIIa complex, which subsequently activates coagulation factor X (FX) and factor IX (FIX), converting them to FXa and FIXa, respectively. FXa, with the assistance of FVa, converts prothrombin (FII) to thrombin (FIIa), which then converts fibrinogen to fibrin, ultimately forming a stable blood clot. Additionally, the TF-FVIIa complex inhibits fibrinolysis by activating thrombin-activatable fibrinolysis inhibitor (TAFI), thereby further promoting coagulation (26-28). ii) Platelet-endothelial-glycocalyx axis; inflammatory storms reduce endothelial glycocalyx thickness from 0.5 μm to <0.1 μm, exposing collagen-von Willebrand factor (vWF), and the platelet glycoprotein Ib-IX-V adhesion triggers immediate release of ADP, thromboxane A2 and platelet factor 4 (PF4), forming protein aggregates and generating primary thrombi within 30 sec (29,30). iii) Natural anticoagulant consumption; TNF-α and IL-6 inhibit the hepatic synthesis of antithrombin (AT) and protein C, while activated neutrophil elastase (NE) degrades TF pathway inhibitor (TFPI), reducing plasma AT activity (31-34). iv) Inflammation-complement-coagulation cross-talk; TNF-α and IL-6 upregulate hepatic FVII and FVIII synthesis via JAK/STAT, and complement C3a and C5a directly activate platelets and recruit leukocytes, while membrane attack complex perforates the endothelium, exposing procoagulant phospholipids and creating a positive feedback loop among inflammation-complement-coagulation (35-37). v) Mitochondria-reactive oxygen species (RO)-Ca^{2+} axis; ROS disrupts mitochondrial electron transport chains, reducing ATP by >50%, with Na^{+}/Ca^{2+} exchanger imbalance causing cytoplasmic Ca^{2+} overload, tripling the efficiency of Ca^{2+}-dependent thrombin complex assembly, and lactate accumulation with pH <7.2 further amplifies platelet deformation and aggregation (38,39). vi) NETs; the ROS-PAD4-histone citrullination pathway promotes NET release, directly providing TF and anionic scaffolds that accelerate thrombus formation (40-42) (Fig. 1).

4. NETs

Neutrophils, as critical components of the host immune system, participate in immune regulation against various microorganisms primarily through three mechanisms: Degranulation, phagocytosis and NET release. NETs are complex reticular structures composed of a DNA backbone, embedded with multiple proteins including citrullinated histone H3 (H3), NE, myeloperoxidase (MPO) and cathepsin G (43). In eukaryotes, DNA is tightly wound around octamers composed of two molecules each of H3, H2B, H2A and H4, forming nucleosome core particles. Histone citrullination reduces chromatin affinity for DNA, allowing released DNA to interact with bacteria, thereby mediating the antimicrobial activity of NETs (40,44).

Types of NET release

Suicidal NETosis. Suicidal NETosis is a NADPH oxidase (NOX)-dependent form of cell death distinct from apoptosis and necrosis (45) (Fig. 2). This type of NETosis is initiated by receptor activation (Toll-like receptors, Fc receptors or

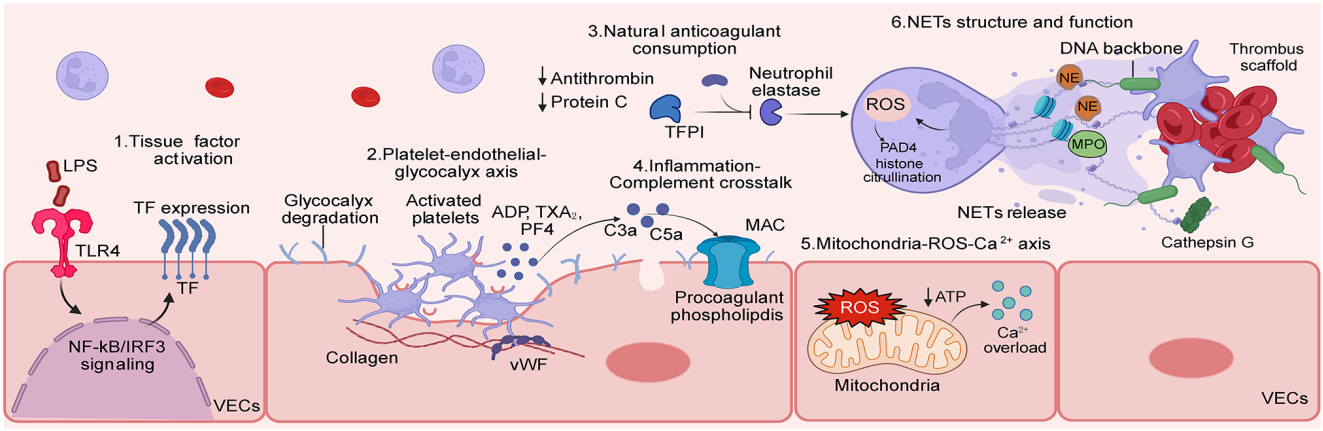

Figure 1. Mechanistic pathways of SIC pathogenesis. The pathogenesis of SIC involves six interconnected regulatory mechanisms. i) TF activation: Pathogen LPS binds to TLR4 on VECs, triggering MyD88/TRIF-dependent signaling and subsequent NF-0B/IRF3 pathway activation, leading to rapid TF expression and initiation of the extrinsic coagulation cascade. ii) Platelet-endothelial-glycocalyx axis: Inflammatory injury causes degradation of the endothelial glycocalyx layer, exposing subendothelial collagen and vWF. Activated platelets adhere via GPIb-IX-V receptors and release ADP, TXA_2 and PF4, promoting primary thrombus formation. iii) Natural anticoagulant consumption: Proinflammatory cytokines suppress hepatic synthesis of antithrombin and protein C, while NE degrades TFPI, resulting in diminished anticoagulant capacity. iv) Inflammation-complement-crosstalk: Complement activation generates C3a and C5a anaphylatoxins that activate platelets and recruit leukocytes, whereas MAC formation exposes procoagulant phospholipids, establishing a positive feedback loop among inflammation, complement and coagulation systems. v) Mitochondria-ROS-Ca^{2+} axis: Mitochondrial dysfunction induced by ROS causes ATP depletion and disruption of Na^+/Ca^{2+} homeostasis, resulting in cytoplasmic Ca^{2+} overload that enhances Ca^{2+}-dependent coagulation enzyme complex assembly. vi) NETs structure and function: The ROS-PAD4 signaling pathway drives histone citrullination and NET release, providing DNA backbone decorated with NE, MPO and cathepsin G that facilitate thrombus propagation. SIC, sepsis-induced coagulopathy; NE, neutrophil elastase; MPO, myeloperoxidase; PAD4, peptidylarginine deiminase 4; ROS, reactive oxygen species; TF, tissue factor; TFPI, TF pathway inhibitor; vWF, von Willebrand factor; VECs, vascular endothelial cells; LPS, lipopolysaccharide; TLR-4; TXA_2, thromboxane A_2; PF4, platelet factor 4; MAC, membrane attack complex; NET, neutrophil extracellular trap.

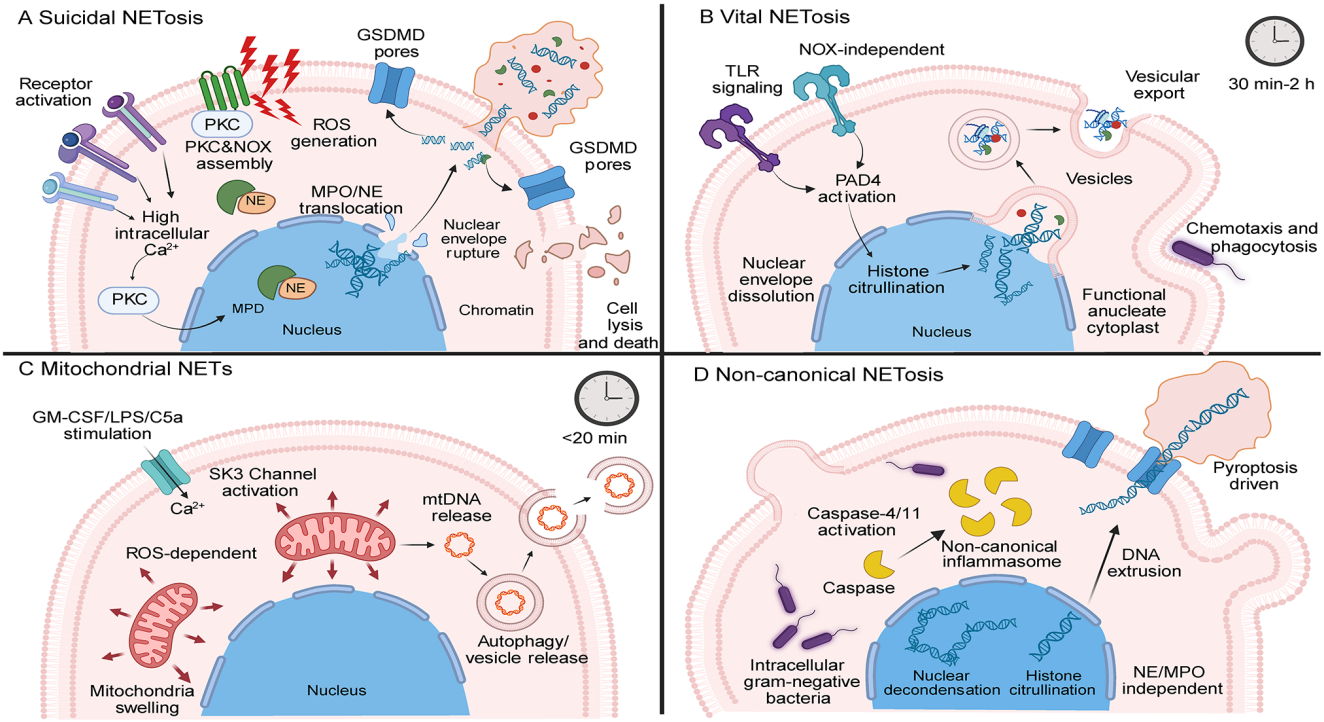

Figure 2. Molecular pathways of NET release. (A) Suicidal NETosis: Receptor activation elevates intracellular Ca^{2+}, stimulating PKC and NOX assembly to generate ROS. ROS-activated MPO promotes chromatin decondensation and nuclear envelope rupture, while NE translocates to the nucleus. Decondensed chromatin is expelled through GSDMD pores, resulting in neutrophil death. (B) Vital NETosis: TLR signaling activates PAD4 in a NOX-independent manner, inducing histone citrullination and nuclear envelope dissolution. DNA-protein complexes are packaged into vesicles and released extracellularly within 30 min-2 h. Neutrophils remain viable as anucleate cytoplasts with preserved chemotactic and phagocytic functions. (C) Mitochondrial NETs: GM-CSF/LPS/C5a stimulation activates SK3 channels, causing ROS-dependent mitochondrial swelling and mtDNA release. mtDNA-granule complexes are expelled via vesicles or autophagy within <20 min without compromising neutrophil viability. (D) Non-canonical NETosis: Intracellular Gram-negative bacteria trigger non-canonical inflammasome activation, with caspase-4/11 driving pyroptosis-dependent DNA extrusion through GSDMD. This pathway proceeds independent of NE and MPO. GSDMD, gasdermin D; MPO, myeloperoxidase; mtDNA, mitochondrial DNA; NE, neutrophil elastase; NOX, NADPH oxidase; PAD4, peptidylarginine deiminase 4; PKC, protein kinase C; ROS, reactive oxygen species; SK3, small conductance calcium-activated potassium channel 3; TLR, Toll-like receptor; NET, neutrophil extracellular trap; LPS, lipopolysaccharide; GM-CSF, granulocyte-macrophage colony stimulating factor.

complement receptors), leading to elevated intracellular Ca^{2+}. Increased Ca^{2+} stimulates protein kinase C and NOX activity, thereby generating ROS (46). Under the influence of ROS, activated MPO participates in chromatin decondensation and nuclear membrane rupture (47). The resulting proteins and DNA constitute the major components of NETs, further activating NE and promoting its nuclear translocation. Subsequently, nuclear membrane rupture occurs, and decondensed chromatin is released into the cytoplasm, it is subsequently expelled extracellularly through gasdermin D (GSDMD) pores or GSDMD-mediated membrane tearing, ultimately resulting in neutrophil death (48,49).

Vital NETosis. Vital NETosis is TLR-mediated, with peptidylarginine deiminase 4 (PAD4) and calpains synergistically promoting nuclear envelope dissolution (50). Unlike suicidal NETosis, vital NETosis is characterized by neutrophil survival following NET release. In this pathway, neutrophils respond to extracellular stimuli, triggering a series of reactions that initiate NET formation (51). In contrast to suicidal NETosis, this process does not require NOX complex assembly. Following the activation of PAD4, histone citrullination occurs, leading to chromatin decondensation. DNA-protein complexes are packaged into vesicles and expelled extracellularly within 30 min to 2 h, forming NETs (52,53). Neutrophils remain viable following NET release, and the formed anucleate cytoplasts retain chemotactic and phagocytic capabilities, enabling rapid pathogen restriction during early infection (54,55).

Mitochondrial NETs (mtNETs). mtNETs were first described by Yousefi *et al* (56), and are formed by the release of mitochondrial DNA (mtDNA) following Granulocyte-Macrophage Colony-Stimulating Factor pretreatment and LPS/C5a stimulation (57). Observed in activated neutrophils and post-trauma settings, their ROS-dependent formation involves calcium-induced SK3 signaling, leading to increased mitochondrial permeability, swelling and mtDNA release (58-60). mtDNA-granule protein complexes are expelled via vesicles or autophagy, while neutrophils maintain functionality; the entire release process is completed within 20 min (61).

Non-canonical NETosis. This type of NETosis is induced upon the detection of Gram-negative bacteria in the cytoplasm. It depends on non-canonical inflammasomes and exhibits key features of NETosis, including nuclear decondensation, DNA extrusion, DNA-MPO co-localization and histone citrullination (62,63). Non-canonical NET formation requires pyroptosis involvement, executed through caspase-4/11 and GSDMD, independent of NE and MPO.

Mechanisms involved in the regulation of SIC by NETs

NET-induced endothelial cell injury. VECs represent primary targets in sepsis, and VEC injury is a characteristic feature of SIC (64) (Fig. 3). During sepsis development, excessive neutrophil activation leads to NET release, promoting the transition of VECs to pro-inflammatory and procoagulant phenotypes. VECs amplify the inflammation-coagulation cross-talk through the secretion of IL-6, TNF-α, VEGF and other factors, providing an endothelial foundation for early microthrombus formation in SIC (8). Additionally, NETs disrupt the glycocalyx barrier on VEC surfaces, increasing vascular permeability, or inducing ferroptosis, thereby causing endothelial barrier collapse and resulting in microcirculatory flow disturbances (8,65). Folco *et al* (66) reported that NETs promote the time- and concentration- dependent expression of vascular cell adhesion molecule-1 and intercellular adhesion molecule-1 on human VECs, facilitating inflammatory cell recruitment on damaged endothelial surfaces and further promoting thrombus formation. NETs can also activate the cGAS-STING pathway in VECs and act on TLR2 on endothelial surfaces, thereby inducing endothelial injury and TF expression to promote coagulation (7). The activation of the pore-forming protein GSDMD is the core driver of NET release. Recent research has indicated that activation markers of the GSDMD-NET axis, MPO-DNA, are notably associated with the elevated expression of endothelial surface glycocalyx injury markers (syndecan-1, MMP-9) in patients with SIC (67). It has been found that direct VEC-neutrophil contact serves as the initiation platform for NETosis in sepsis, with integrin Mac-1 identified as the molecular switch. Blocking Mac-1 function notably inhibits the LPS induced increase in NETs and thrombus formation (68). Currently, research on the regulation of VEC function in SIC by NETs regulation of VECs remains limited, representing an area requiring further investigation.

NET-platelet interactions. In a previous study, in a model of sepsis induced by cecal ligation and puncture, platelet-specific STK10 deletion reduced P-selectin expression by ~50%, decreased peripheral platelet-neutrophil aggregates to 40% of the controls, reduced the pulmonary NET area by 60%, almost eliminated microvascular thrombi and increased 24-h mouse survival from 35 to 70%, confirming that STK10-regulated platelet-NET interaction is a notable pathway driving thromboinflammation in sepsis (69). Similarly, in another study, platelet-specific NLRP6 knockout activated intracellular NF-κB signaling, promoting platelet-neutrophil interactions and NET formation, exacerbating pulmonary and hepatic microvascular thrombosis (70). Although heparin and low-molecular-weight heparin are commonly used pharmacological thrombo-prophylactic agents in Critical Care Medicine settings (e.g., intensive care units), heparin-induced thrombocytopenia (HIT) is a marked adverse reaction characterized by thrombocytopenia, paradoxical hypercoagulability and severe thrombotic complications. Without timely intervention, up to 50% of patients progress to overt thrombosis (71). A study in 2019 revealed that NETs are the mechanistic link between HIT and thrombosis. HIT immune complexes (IgG-heparin-PF4) activate neutrophils through FcγRIIA receptors, triggering NETosis and subsequent thrombus formation. Notably, this NET-mediated procoagulant cascade is independent of platelet activation and aggregation (72). Subsequent mechanistic research demonstrated that targeting neutrophil-derived ROS completely blocked NETosis and thrombosis in an *ex vivo* human whole blood HIT model. Furthermore, the pharmacological or genetic inhibition of NOX2 activity eliminated thrombosis in a murine HIT model without improving thrombocytopenia. These findings indicate that NOX2-mediated NET formation is an intervenable prothrombotic target in HIT, operating independently of platelet count recovery (73). Therefore, HIT therapeutic strategies have shifted from simply changing anticoagulant medications to precisely blocking NETosis, providing novel molecular leverage points for

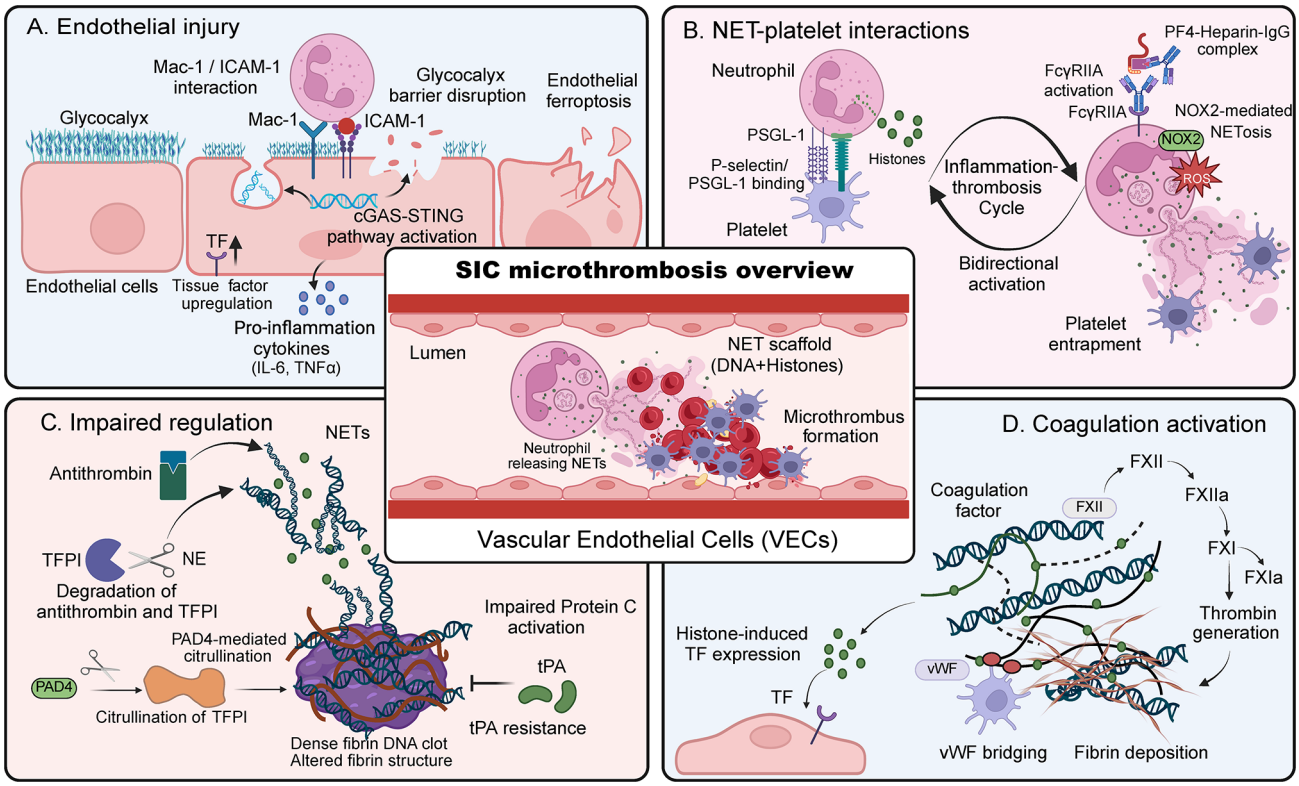

Figure 3. Mechanisms of NET regulation in SIC. Central panel: Schematic overview of SIC microthrombosis, illustrating NET release from neutrophils within the vascular lumen, formation of NET scaffolds (DNA and histones), and subsequent microthrombus formation on VECs. (A) Endothelial injury: NETs disrupt the endothelial glycocalyx barrier and induce endothelial ferroptosis, leading to barrier collapse. Mac-1/ICAM-1 interactions between neutrophils and VECs facilitate neutrophil adhesion and NETosis. NET-derived DNA activates the cGAS-STING pathway in VECs, while pro-inflammatory cytokines IL-6 and TNF-α and TF upregulation promote a procoagulant endothelial phenotype. (B) NET-platelet interactions: P-selectin/PSGL-1 binding initiates bidirectional activation between platelets and neutrophils. The PF4-heparin-IgG complex activates neutrophils via FcγRIIA, triggering NOX2-mediated NETosis and establishing an inflammation-thrombosis cycle. NETs reciprocally entrap platelets, amplifying thrombotic responses. (C) Impaired regulation: NET-associated NE degrades AT and TFPI, while PAD4-mediated citrullination inactivates TFPI. NETs impair protein C activation and confer resistance to tPA, resulting in dense fibrin-DNA clots with altered fibrin structure that resist fibrinolysis. (D) Coagulation activation: NETs activate the intrinsic coagulation pathway through FXII activation, leading to downstream activation of FXI and thrombin generation. Histone-induced TF expression on VECs initiates the extrinsic pathway. NETs provide scaffolds for vWF bridging and fibrin deposition, promoting clot formation. SIC, sepsis-induced coagulopathy; AT, antithrombin; cGAS-STING, cyclic GMP-AMP synthase-stimulator of interferon genes; FcγRIIA, Fc gamma receptor IIA; FXII, coagulation factor XII; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; Mac-1, macrophage-1 antigen; NET, neutrophil extracellular trap; NOX2, NADPH oxidase 2; PAD4, peptidylarginine deiminase 4; PF4, platelet factor 4; PSGL-1, P-selectin glycoprotein ligand-1; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; TNF-α, tumor necrosis factor-alpha; VECs, vascular endothelial cells; vWF, von Willebrand factor; NE, neutrophil elastase.

precision diagnosis and treatment. NETs and platelets exhibit bidirectional regulatory mechanisms in immunothrombosis; platelets trigger NETosis through P-selectin/PSGL-1, TLR and HMGB1 signaling axes, whereas the DNA-histone scaffold of NETs reciprocally activates platelets, provides anchoring sites for coagulation factors and amplifies the inflammation-thrombosis positive feedback. The future development of specific inhibitors targeting key nodes of NETs-platelet interactions (such as PAD4, GSDMD and P-selectin) is required in order to achieve multi-target synergistic intervention, breaking the vicious cycle of inflammation-thrombosis and providing novel strategies for the precision treatment of thrombotic diseases (74).

NETs and the coagulation cascade. NETs provide scaffolds for platelets, erythrocytes and procoagulant factors, thereby obstructing vessels (75). NET-derived proteases and histones exert cytotoxic effects on VECs through TF, while coagulation factors such as prothrombin, fibrinogen and factor X deposit in complexes formed between platelets and NETs, promoting thrombus formation (76). In the extrinsic pathway, extracellular histones, a key structural component of NETs, increase TF expression at both VEC surfaces and increase mRNA levels, while suppressing thrombomodulin expression. Similarly, NET-associated proteases (such as NE and proteinase 3) can also upregulate TF expression (77). Mature IL-1α in NETs (activated by proteinase G) stimulates VECs, further increasing TF expression and reinforcing the prothrombotic effects of NETs in sepsis (66). In the intrinsic coagulation pathway, NETs promote thrombin generation through the activation of coagulation factors XII and XI, and stimulate fibrin generation through binding to coagulation factor XII, thereby promoting coagulation (78). Histone 4 and DNA can increase the expression of hepatocyte nuclear factor 4α mRNA and TF mRNA, thereby inducing the transcription of procoagulant factors (79). The DNA backbone of NETs activates coagulation factor XII independently of platelets, and together with coagulation factor XI, they promote the coagulation cascade and thrombin formation (80). Furthermore, NETs stabilize thrombus formation by linking vWF and TFPI, thereby stabilizing thrombus formation (81).

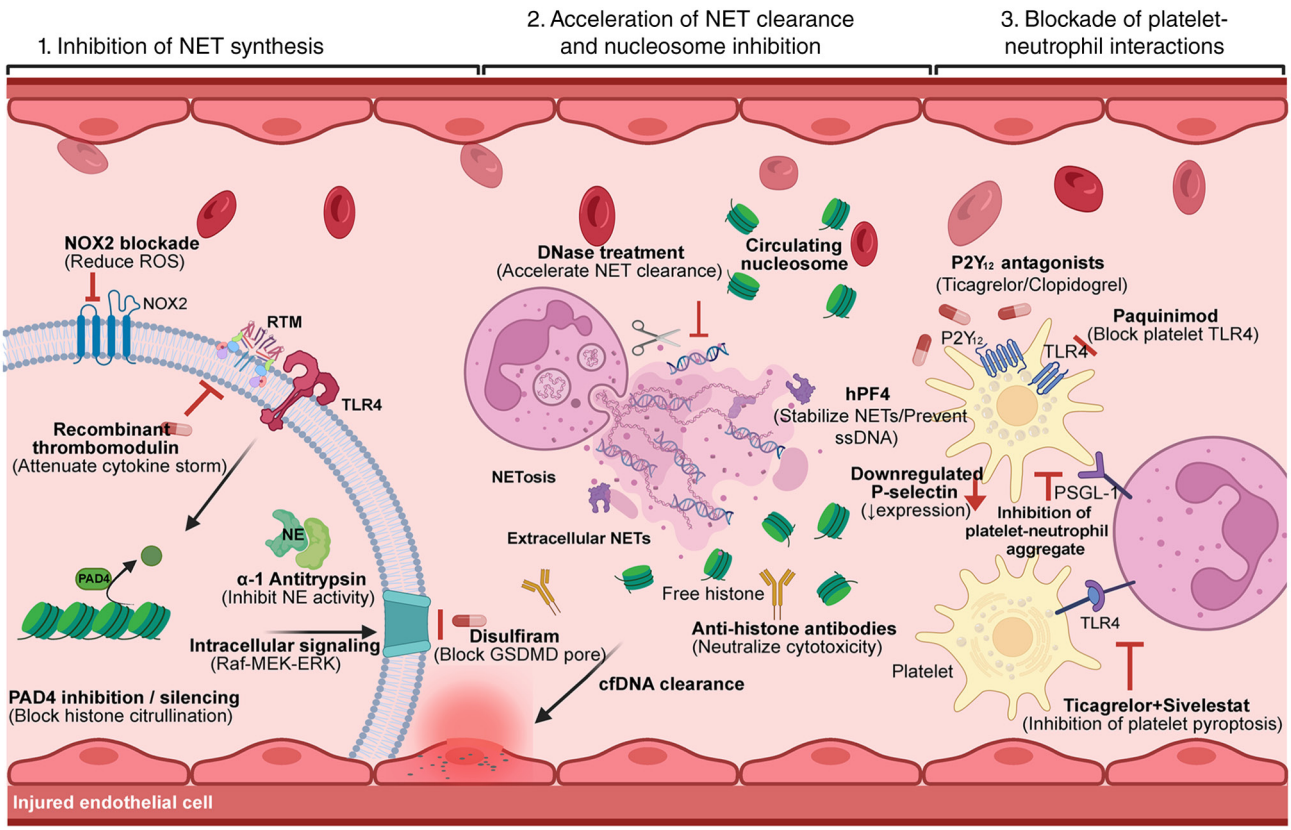

Figure 4. Therapeutic strategies targeting NETs in sepsis-induced coagulopathy. The diagram illustrates three major therapeutic approaches: 1) Inhibition of NET synthesis: Multiple targets block NET formation at different stages, NOX2 blockade reduces ROS generation; RTM attenuates cytokine storm via TLR4 signaling inhibition; αAAT inhibits NE activity; PAD4 inhibition or gene silencing prevents histone citrullination; and disulfiram blocks GSDMD pore formation to prevent NET extrusion. 2) Acceleration of NET clearance and nucleosome inhibition: DNase treatment accelerates NET degradation; anti-histone antibodies neutralize cytotoxicity of free histones; hPF4 stabilizes NETs and prevents ssDNA generation; and cfDNA clearance reduces circulating nucleosome levels. 3) Blockade of platelet-neutrophil interactions: P2Y$_{12}$ antagonists (ticagrelor/clopidogrel) downregulate P-selectin expression; paquinimod blocks platelet TLR4 signaling; and combined ticagrelor-sivelestat therapy inhibits platelet pyroptosis and platelet-neutrophil aggregate formation via PSGL-1 inhibition. AAT, α-1 antitrypsin; cfDNA, cell-free DNA; DNase, deoxyribonuclease; GSDMD, gasdermin D; hPF4, human platelet factor 4; NE, neutrophil elastase; NET, neutrophil extracellular trap; NOX2, NADPH oxidase 2; PAD4, peptidylarginine deiminase 4; PSGL-1, P-selectin glycoprotein ligand-1; ROS, reactive oxygen species; RTM, recombinant thrombomodulin; ssDNA, single-stranded DNA; TLR4, Toll-like receptor 4; NE, neutrophil elastase.

NETs and the anticoagulant system. The anticoagulant system comprises antithrombin, the protein C system and TFPI. Research has demonstrated that during sepsis, NETs can impair the anticoagulant system through their protein components by degrading antithrombin, inhibiting activated protein C generation and cleaving TFPI (82). It has been demonstrated that PAD4, a notable protein in NET synthesis, can cause the citrullination of arginine residues exposed on the TFPI surface, thereby impairing its anticoagulant function and reducing coagulation inhibition (83).

NETs and fibrinolytic system resistance. Laboratory findings in patients with sepsis have demonstrated that fibrinogen degradation products, D-dimer and the plasmin activation marker plasmin-α2 antiplasmin complex are only mildly elevated, indicating that SIC manifests as marked fibrinolysis suppression (84). Varjú *et al* (85) demonstrated that NETs and their components can directly participate in clot formation and alter fibrin structure within clots, enhancing mechanical resistance and reducing sensitivity to tissue-type plasminogen activator (tPA)-induced fibrinolysis, exerting antifibrinolytic effects. Mangold *et al* (86) further demonstrated that treatment with deoxyribonuclease (DNase) increased tPA-mediated fibrinolysis.

5. NET targeted therapeutic strategies for SIC

The precise regulation of NET formation and clearance represents a promising strategy for mitigating their deleterious effects in SIC. Potential anti-NET agents encompass anti-inflammatory/immunomodulatory agents (such as aspirin and cyclosporine A), anticoagulants (such as thrombomodulin, activated protein C) and nucleases (such as DNase) (87-90). These agents exert effects by inhibiting NET formation, degrading the DNA backbone of NETs or neutralizing NET-associated proteins (Fig. 4).

Inhibition of NET synthesis or acceleration of NET clearance. Key molecular targets include the Raf-MEK-ERK signaling cascade, the NOX2-ROS axis and chromatin decondensation enzymes critical in NETosis, such as NE, PAD4, MPO and histone deacetylases. Preclinical studies have demonstrated that DNase reduces sepsis-induced organ injury and bacterial dissemination, synergizing with standard antimicrobial therapeutics (91,92). α-1 antitrypsin inhibits NET formation by targeting NE, reducing MPO activity by 50% in lung, liver, kidney and heart tissues, thereby attenuating inflammation, coagulation and multi-organ injury in mice with sepsis (93).

Pharmacological inhibition of PAD4 (the master regulator of NET formation) similarly reduces NET release, ameliorates organ dysfunction and improves the survival rates of mice with sepsis, highlighting the therapeutic potential of PAD4-targeted strategies (94,95). Recombinant thrombomodulin inhibits LPS-induced NET formation in animal models, attenuates systemic cytokine storms (apart from IL-1β) and improves survival rates (96). GSDMD also represents an emerging target; disulfiram or GSDMD gene knockout eliminates NET formation, alleviates multi-organ dysfunction and reduces mortality in sepsis models (97).

Blockade of platelet-neutrophil interactions. $P2Y_{12}$ receptor antagonists (such as clopidogrel, prasugrel, ticagrelor, cangrelor) attenuate platelet-leukocyte cross-talk by down-regulating platelet P-selectin expression (98). The positive feedback loop between platelets and neutrophils (mediated through platelet pyroptosis and NET release) amplifies systemic inflammation in sepsis. The immunomodulator, paquinimod, antagonizes platelet TLR4, effectively inhibiting platelet pyroptosis, reducing NET formation, decreasing inflammatory burden and improving survival in mice with sepsis (99,100). Previously, researchers developed a combination of ticagrelor (antiplatelet agent) and sivelestat (NE inhibitor), which notably inhibited platelet and neutrophil synergy, thereby markedly reducing platelet aggregation, NET formation and release and improving thrombosis and mortality in mice with sepsis (101).

Inhibition of circulating nucleosome release. Circulating nucleosomes are established early biomarkers reflecting cellular damage and NETosis in sepsis. Nucleosome levels are higher in patients with sepsis than in healthy volunteers and associate with disease severity (102). Nucleosomes are the basic structural units of eukaryotic chromatin, composed of histones and DNA (103). In sepsis, neutrophil activation triggers the release of granule proteins and chromatin, leading to apoptosis, necrosis or pyroptosis (104,105), increasing extracellular nucleosome levels through the following pathways: i) The increased release of cell-free DNA (cfDNA), leading to biphasic nucleosome release (106,107); ii) suppressed or reduced DNase activity, resulting in inadequate nucleosome clearance (108,109); and iii) histone release inducing cytotoxicity, causing nucleosome cascade amplification (110). Therefore, neutralizing extracellular histones can reduce cytokine release, improve tissue perfusion and decrease mortality in experimental sepsis (111). In a previous study, following the administration of human PF4 to septic mice, PF4 was found to inhibit procoagulant and endothelial toxicity by physically cross-linking cfDNA/NETs, reducing generation of short-fragment, single-stranded DNA (112). Collectively, these findings establish a solid foundation for developing NET-targeted therapies for SIC and organ failure.

6. Conclusion

SIC is a notable pathophysiological process driven by complex interactions between dysregulated host immune responses and hemostatic system activation. As discussed in the present review, NETs serve as pivotal mediators bridging innate immunity and thrombo-inflammation in sepsis. Four distinct mechanisms of NET release, suicidal NETosis, vital NETosis, mitochondrial NETs and non-canonical NETosis, provide diverse pathways through which neutrophils contribute to SIC pathogenesis. NETs exacerbate SIC through multiple mechanisms, inducing VEC injury and barrier dysfunction, amplifying platelet-neutrophil interactions, activating both intrinsic and extrinsic coagulation cascades, impairing natural anticoagulant systems and promoting fibrinolytic resistance. These processes collectively drive microvascular thrombosis, tissue hypoperfusion and ultimately multiple organ failure. The identification of key molecular targets, particularly PAD4, GSDMD, NOX2 and components of the platelet-NET axis, has opened avenues for therapeutic intervention. Emerging strategies targeting NET formation, accelerating NET clearance or disrupting pathological platelet-neutrophil cross-talk exhibit notable potential in preclinical models. However, clinical translation requires further investigation to establish optimal timing, dosing and patient selection criteria. Future research is required to focus on developing specific biomarkers for NET burden, refining targeted therapies with favorable risk-benefit profiles, and conducting well-designed clinical trials to validate these approaches. Elucidating the complex regulatory networks governing NET-mediated coagulopathy will not only deepen the understanding of sepsis pathophysiology but may also pave the way for precision medicine strategies to improve outcomes in this life-threatening condition.

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Availability of data and materials

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Authors' contributions

HS and ZC conceived and organized the manuscript. JH and BZ wrote the manuscript. JH and MJ designed the study and YZ performed the literature search and the screening. JH, MJ, ZC, BZ, YZ and HS contributed to editorial changes in the manuscript. All authors read and approved the final version of the manuscript. Data authentication not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

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Competing interests

The authors declare that they have no competing interests.

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