Journal of Clinical and Cellular Immunology
ISSN: 2155-9899
OPEN ACCESS Freely available online
Perspective

Neutrophil Extracellular Trap Formation and Its Role in Endothelial Injury and Thromboinflammation in Sepsis

Samuel Okoye*

Department of Experimental Immunology and Critical Care Medicine, West African Institute of Health Sciences, Lagos, Nigeria

DESCRIPTION

Sepsis is a life-threatening condition characterized by dysregulated host responses to infection leading to widespread inflammation, organ dysfunction, and high mortality. Neutrophils are central effector cells in the early immune response, traditionally known for phagocytosis and microbial killing. However, a distinct antimicrobial mechanism involving the release of neutrophil extracellular traps has been increasingly recognized as a contributor to both pathogen control and host tissue injury. While neutrophil extracellular traps can immobilize and neutralize pathogens, excessive or uncontrolled formation contributes to endothelial damage, microvascular thrombosis, and multi-organ dysfunction. This article examines the biological mechanisms of neutrophil extracellular trap formation and their role in thromboinflammatory processes during sepsis.

The innate immune system provides rapid defense against invading microorganisms through coordinated actions of immune cells and soluble mediators. Among these cells, neutrophils represent the most abundant circulating leukocytes and serve as first responders during infection. Upon detection of pathogens, neutrophils migrate rapidly to affected tissues, where they execute antimicrobial functions through phagocytosis, degranulation, and production of reactive oxygen species. In addition to these classical functions, neutrophils can undergo a specialized form of cell death resulting in the release of chromatin structures decorated with antimicrobial proteins. These structures, known as neutrophil extracellular traps, consist of decondensed Deoxyribonucleic Acid (DNA) fibers associated with histones, neutrophil elastase, myeloperoxidase, and other granule-derived enzymes. Their primary function is to immobilize and kill pathogens extracellularly, preventing dissemination of infection.

Neutrophil extracellular trap formation, often referred to as Neutrophil Extracellular Trap (NET) formation, is triggered by a variety of stimuli including bacterial components, fungal elements, viral particles, immune complexes, and inflammatory cytokines. Activation of intracellular signaling pathways leads to chromatin decondensation, breakdown of nuclear membranes, and release of nuclear material into the extracellular space. This process can occur in response to both infectious and sterile inflammatory signals. Reactive oxygen species production plays a critical role in NET formation. Activation of Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase leads to generation of superoxide and downstream oxidants, which contribute to enzymatic activation and chromatin remodeling. Neutrophil elastase translocates to the nucleus during activation and facilitates histone degradation, enabling chromatin decondensation. Myeloperoxidase further modifies chromatin structure and enhances extracellular trap formation.

While NETs provide antimicrobial benefits, their dysregulated formation can have harmful consequences for host tissues. In sepsis, excessive NET release contributes to widespread endothelial injury. Endothelial cells line the interior surface of blood vessels and regulate vascular tone, permeability, and hemostasis. Exposure to NET-associated components such as histones and proteases induces endothelial activation and injury. Histones released during NET formation possess cytotoxic properties and can directly damage endothelial membranes. These proteins interact with cell surfaces, leading to calcium influx, membrane disruption, and cell death. Endothelial injury results in increased vascular permeability, allowing plasma components to leak into surrounding tissues and contributing to edema and organ dysfunction.

In addition to direct cytotoxicity, NETs promote a pro-thrombotic state within the microcirculation. Histones and DNA structures provide a scaffold for platelet adhesion and activation. Platelets interact with NET components through specific receptors, leading to aggregation and thrombus formation. This process contributes to microvascular occlusion and impaired tissue perfusion. Coagulation pathways are closely linked to inflammatory responses in sepsis. NET formation enhances activation of the intrinsic and extrinsic coagulation cascades. Tissue factor expression is increased on endothelial cells and monocytes in response to inflammatory mediators. Simultaneously, natural anticoagulant mechanisms are impaired, leading to a procoagulant state.

Correspondence to: Samuel Okoye, Department of Experimental Immunology and Critical Care Medicine, West African Institute of Health Sciences, Lagos, Nigeria, E-mail: samuel.okoye@waihs.edu.ng

Received: 01-Sep-2025, Manuscript No. JCCI-25-42581; **Editor assigned:** 03-Sep-2025, PreQC No. JCCI-25-42581 (PQ); **Reviewed:** 17-Sep-2025, QC No. JCCI-25-42581; **Revised:** 24-Sep-2025, Manuscript No. JCCI-25-42581 (R); **Published:** 01-Oct-2025, DOI: 10.35248/2155-9899.25.16.785

Citation: Okoye S (2025). Neutrophil Extracellular Trap Formation and Its Role in Endothelial Injury and Thromboinflammation in Sepsis. J Clin Cell Immunol. 16:785.

Microvascular thrombosis is a hallmark of severe sepsis and contributes significantly to organ dysfunction. Occlusion of small blood vessels limits oxygen delivery to tissues, resulting in ischemia and cellular injury. Organs such as the kidneys, liver, lungs, and brain are particularly vulnerable to these effects due to their high metabolic demands. The lungs are frequently affected in sepsis-associated acute respiratory failure. NET accumulation within pulmonary microvasculature and alveolar spaces contributes to impaired gas exchange. Damage to alveolar epithelial cells and endothelial barriers leads to pulmonary edema and reduced oxygenation capacity. These changes are characteristic of acute respiratory distress syndrome, a severe complication of sepsis.

However, in sepsis, these regulatory mechanisms may become overwhelmed or impaired. Persistent infection and continuous inflammatory stimulation lead to sustained neutrophil activation. As a result, NET accumulation exceeds clearance capacity, contributing to progressive tissue injury. Pathogen-specific interactions also influence NET dynamics. Certain bacteria produce nucleases that degrade NETs, enhancing their survival. Conversely, some pathogens are particularly susceptible to NET-mediated killing, highlighting the dual role of these structures in host-pathogen interactions.

CONCLUSION

Neutrophil extracellular trap formation represents a critical mechanism in host defense but also contributes significantly to endothelial injury and thromboinflammation in sepsis. Excessive NET release leads to vascular damage, microthrombosis, and multi-organ dysfunction. Understanding the regulation of NET formation and its pathological consequences provides important insight into sepsis progression and supports the development of targeted therapeutic strategies aimed at improving clinical outcomes in critically ill patients.