

Neutrophil Extracellular Trap Formation in Systemic Disorders: Contemporary Clinical Therapeutic Perspectives

Sofia Lindholm*

Department of Clinical Immunology, Northern European Institute of Medical Sciences, Helsinki, Finland

DESCRIPTION

Neutrophils are among the earliest circulating leukocytes recruited to sites of microbial invasion and tissue injury. For many years their biological function was considered primarily limited to phagocytosis, release of antimicrobial granules, and production of reactive oxygen species. Continued investigation has demonstrated that these cells possess additional mechanisms capable of controlling microorganisms while influencing communication with surrounding tissues. One of the most significant discoveries has been the identification of neutrophil extracellular traps, commonly referred to as Neutrophil Extracellular Traps (NETs). These web-like structures consist of decondensed chromatin associated with antimicrobial proteins released into the extracellular environment. Under physiological conditions, NET formation contributes to microbial containment and removal of harmful agents. When regulation becomes disturbed, excessive or persistent NET production may participate in tissue injury involving the cardiovascular system, kidneys, lungs, joints, skin, nervous system, and additional organs. Increasing knowledge regarding NET biology has encouraged development of therapeutic strategies directed toward restoring physiological cellular balance while preserving normal host defense.

Neutrophils originate from hematopoietic stem cells within the bone marrow through a tightly regulated developmental process influenced by growth factors, cytokines, and stromal cell interactions. Mature neutrophils enter the circulation in large numbers and continuously patrol blood vessels before migrating into tissues following appropriate biological signals. Their short lifespan is balanced by continuous production within the bone marrow, allowing rapid replacement during infection or tissue injury. Although circulating neutrophils appear morphologically similar, recent molecular investigations demonstrate substantial functional diversity among distinct neutrophil populations.

NET formation represents a specialized cellular response initiated after recognition of microorganisms, activated platelets, immune complexes, crystalline particles, cytokines, and endogenous molecules released by injured tissues. Several

intracellular signaling pathways converge to promote chromatin decondensation, disintegration of nuclear membranes, mixing of nuclear material with cytoplasmic granule proteins, and eventual release of extracellular chromatin networks. These structures trap microorganisms, concentrating antimicrobial enzymes around invading pathogens while reducing microbial dissemination.

The molecular composition of NETs extends beyond deoxyribonucleic acid. Histones, neutrophil elastase, myeloperoxidase, cathepsin G, lactoferrin, defensins, matrix metalloproteinases, and additional antimicrobial proteins become incorporated within extracellular chromatin fibers. This complex molecular organization allows simultaneous mechanical trapping of microorganisms and localized delivery of antimicrobial compounds. Under physiological conditions, circulating deoxyribonucleases gradually degrade extracellular chromatin, limiting prolonged tissue exposure to potentially damaging components.

Two principal mechanisms of NET formation have been described. In one pathway, neutrophils undergo a specialized form of cellular death accompanied by chromatin release after membrane rupture. An alternative pathway permits release of extracellular chromatin while preserving cellular membrane integrity and selected biological functions. Living neutrophils capable of continued migration and phagocytosis after partial chromatin release have been identified in experimental investigations. The relative contribution of these mechanisms depends upon the activating stimulus and local tissue environment.

Reactive oxygen species generated through nicotinamide adenine dinucleotide phosphate oxidase contribute substantially to many forms of NET formation. Oxidative signaling promotes activation of intracellular enzymes responsible for chromatin modification and nuclear membrane disruption. Peptidylarginine deiminase 4 catalyzes citrullination of histone proteins, reducing their affinity for deoxyribonucleic acid and facilitating chromatin decondensation. Pharmacological inhibition of these molecular pathways has therefore become an important area of therapeutic investigation.

Correspondence to: Sofia Lindholm, Department of Clinical Immunology, Northern European Institute of Medical Sciences, Helsinki, Finland, E-mail : sofia.lindholm@neims-finland.edu

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Platelets actively participate in regulation of NET formation. During vascular injury or microbial infection, activated platelets establish direct contact with neutrophils through adhesion molecules and soluble mediators. These interactions stimulate chromatin release while coordinating responses involving endothelial cells and coagulation pathways. Appropriate communication supports vascular protection; however, persistent activation may contribute to thrombus formation and microvascular injury during chronic systemic disorders.

Endothelial cells lining blood vessels influence neutrophil recruitment and NET formation through expression of adhesion molecules, chemokines, and cytokines. Activated endothelial cells promote neutrophil attachment, migration across the vascular wall, and localized activation within affected tissues. NET components may subsequently modify endothelial function, creating bidirectional communication that affects vascular permeability, coagulation, and tissue oxygenation. Balanced regulation of these interactions remains essential for preservation of vascular integrity.

Cellular metabolism has emerged as another important determinant of NET biology. Activation increases glucose utilization, glycolytic activity, mitochondrial function, and amino acid metabolism to satisfy energy requirements associated with chromatin remodeling and enzyme release. Variations in oxygen availability, nutrient concentrations, and metabolic disorders influence these pathways while modifying neutrophil responsiveness. Targeting metabolic regulation may therefore provide additional opportunities for selective therapeutic intervention.

Extracellular vesicles released during neutrophil activation contribute to intercellular communication. These membrane-bound particles transport proteins, lipids, messenger ribonucleic

acid, and micro ribonucleic acid capable of influencing macrophages, endothelial cells, fibroblasts, platelets, and lymphocytes. Vesicle composition varies according to activating stimuli, suggesting that extracellular vesicles participate in coordination of biological responses beyond direct NET formation.

Continued investigation into neutrophil extracellular trap formation is expanding understanding of cellular communication, vascular biology, tissue homeostasis, metabolic regulation, and molecular defense mechanisms. These scientific developments are expected to support increasingly selective therapeutic strategies capable of restoring physiological neutrophil activity while preserving essential antimicrobial protection. Ongoing collaboration among laboratory researchers, clinicians, pharmaceutical scientists, and biomedical engineers will remain essential for translating these discoveries into practical clinical applications that improve long-term outcomes for individuals affected by chronic systemic disorders.

CONCLUSION

Continued investigation into epigenetic regulation is expanding understanding of cellular adaptation, tissue homeostasis, molecular communication, and biological plasticity. These scientific advances are expected to support increasingly selective therapeutic strategies capable of restoring balanced cellular function while preserving essential physiological processes. Ongoing collaboration among molecular biologists, clinicians, bioinformaticians, and pharmaceutical scientists will remain essential for transforming epigenetic discoveries into effective clinical applications that improve long-term outcomes for individuals affected by chronic tissue disorders.