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REVIEW

Neutrophil Extracellular Traps (NETs) in Sterile Inflammatory Diseases

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Abstract: Neutrophil Extracellular Traps (NETs) are fibrous web-like structures released by neutrophils in response to pathogenic infections or inflammatory stimuli. Composed of decondensed chromatin DNA, histones, and granular proteins, NETs primarily function to eliminate pathogens through physical entrapment and biochemical cytotoxicity. However, they may also contribute to the pathogenesis of inflammatory diseases. While NETs played an important role in pathogen defense, their non-specific components can also damage surrounding tissues, exacerbating inflammation. The role and mechanisms of NETs in various diseases have been well-documented, including autoimmune diseases, cancer, and infectious diseases. This review aims to elaborate on the mechanisms by which NETs mediate sterile inflammation.

Keywords: neutrophils, extracellular traps, autoimmune diseases, sterile inflammation, immune checkpoint inhibitors, ICIs

Introduction

Neutrophils are an essential type of innate immune cell that respond rapidly to pathogen invasion. Despite their short lifespan and limited biosynthetic capacity, neutrophils play a defensive role through phagocytosis of microorganisms, the release of lytic enzymes from granules, or the production of extracellular traps (NETs).[1,2] The concept of NETs was first introduced in 2004 by Volker Brinkmann et al. This is a NET-like structure formed by nucleic acids, where a DNA-based framework anchors protein granules such as elastase, cathepsin G, and myeloperoxidase. This structure facilitates the capture and elimination of pathogens,[3] but their excessive release is also a potential factor contributing to inflammation and tissue damage.

Indeed, NETs have recently been found to play a central role in the pathogenesis of various sterile inflammatory diseases. Sterile inflammation is an inflammatory response triggered by non-infectious factors (eg, physical/chemical stimuli, tissue injury, or immune dysregulation). Similar to infectious inflammation, it activates non-immune cells (eg, epithelial/endothelial cells) and recruits innate immune cells (eg, neutrophils, dendritic cells, and macrophages), promoting the release of cytokines/chemokines and subsequently triggering adaptive immune responses.[4] Here, we provide an overview of recent evidences elucidating the mechanisms by which NETs, released during neutrophil activation, contribute to sterile inflammatory diseases. We also discuss how targeting the formation and degradation of NETs may help mitigate the onset and progression of these diseases.

Mechanisms and Signaling Pathways of NETs Formation

NETs are produced by activated neutrophils through a programmed cell death pathway known as NETosis, which is distinct from apoptosis and necrosis. In vivo, NETosis can be triggered by various stimuli, including pathogens, immune

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complexes, autoantibodies, platelets, cytokines, and chemokines such as interleukin 8 (IL-8) and TNF. In vitro experiments commonly induce NETosis using phorbol 12-myristate 13-acetate (PMA), which mimics the activation of protein kinase C (PKC) by diacylglycerol, as well as calcium ionophores.[5] NETosis can be categorized into lytic NETosis, vital NETosis, and mitochondrial NETosis [Figure 1 and Table 1].

Lytic NETosis

When neutrophils are stimulated, various receptors such as Fcγ receptors (FcγR), Toll-like receptors (TLRs), damage-associated molecular pattern (DAMP) receptors, complement receptors (eg, C5aR), and A1 or A3 adenosine receptors become activated. This activation leads to an increase in intracellular calcium ion concentration, which in turn activates PKC and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase. These enzymes act on mitochondria, promoting the production of reactive oxygen species (ROS). The activation of ROS not only interacts with neutrophil elastase (NE) and myeloperoxidase (MPO) to permeabilize the nuclear membrane and further facilitate chromatin decondensation but also activates receptor-interacting protein kinase 3 (RIPK3) and mixed lineage kinase domain-like protein (MLKL), thereby promoting programmed cell death. Elevated intracellular calcium ions can also bind to calcium-dependent peptidylarginine deiminase 4 (PAD4), which is localized in the nucleus. This interaction disrupts the electrostatic forces of DNA, promoting chromatin unwinding. It mediates protein citrullination and/or histone carbamylation, facilitating chromatin decondensation.[6,7] The rupture of the nuclear membrane is mediated by cyclin-dependent kinases 4/6 (CDK4/6), retinoblastoma protein phosphorylation (Rb-P), and nuclear lamina B (lamin B). The DNA fragments released from the nucleus are modified by NE and MPO before entering the cytoplasm. Furthermore, lytic NETosis can be promoted by caspases 4/5 or caspase 11 activated by lipopolysaccharides (LPS), leading to the formation of pore-forming protein gasdermin D (GSDMD). GSDMD forms pores in the cytoplasmic and nuclear membranes, causing membrane rupture and facilitating the release of chromatin and proteins into the extracellular space.[8] Consequently, this process is often accompanied by neutrophil death.

Vital NETosis

Unlike lytic NETosis, the formation of vital NETs does not result in neutrophil death and requires a shorter time. Additionally, the NADPH oxidase complex is not essential for this process.[9] Neutrophils are stimulated by platelets,

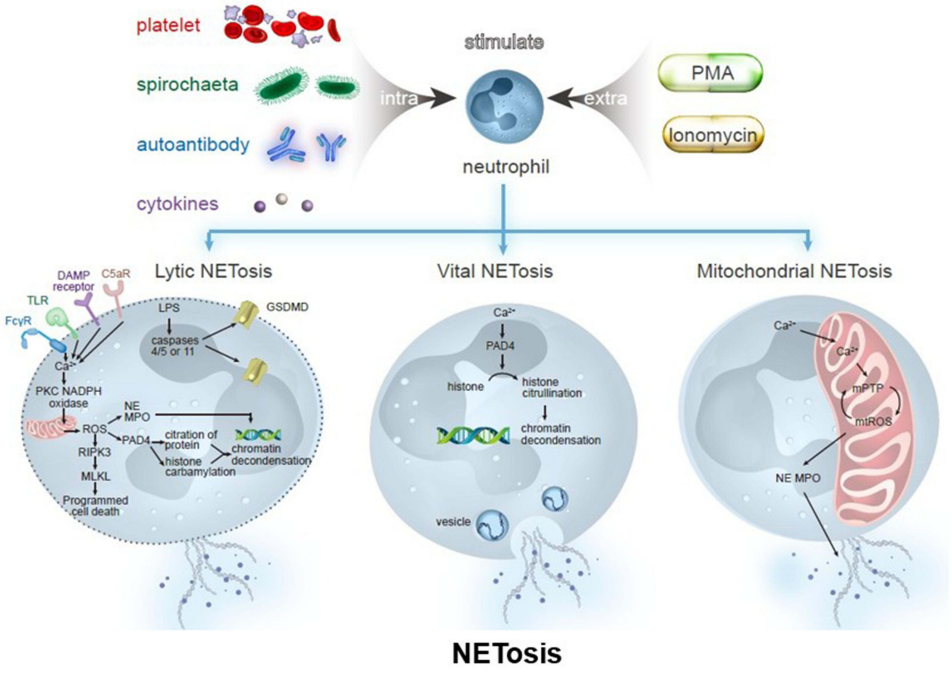

Figure 1 NETosis. Neutrophils trigger NETosis after being stimulated by platelets, pathogens, autoantibodies, cytokines, etc. in vivo and by PMA and ionomycin in in vitro experiments. NETosis could be further subdivided into Lytic NETosis, Vital NETosis, and mitochondrial NETosis according to different mechanisms of generating NETs.

Table 1 Tissue-Specific Mechanisms of NETs in Sterile Inflammatory Diseases

Disease	Key Effector Cells	Pathogenic Pathways	Clinical Biomarkers
Atherosclerosis	Neutrophils, Macrophages	- NETs promote plaque instability (matrix degradation, proinflammatory cytokine release) - oxLDL-triggered NETosis	- Elevated serum MPO-DNA complexes - Coronary NET deposition correlates with thrombosis risk
Type 1/2 Diabetes	Hyperglycemia-activated neutrophils	- Mitochondrial ROS-driven NETosis - NETs damage pancreatic β-cells and vascular endothelium	- Increased plasma cfDNA levels - NETs correlate with glomerular fibrosis in diabetic nephropathy
Neutrophilic Asthma	Airway neutrophils, Epithelial cells	- NETs activate TLR4/IL-36R → IL-8 release - Synergy with eosinophils worsens inflammation	- Increased NET components in sputum - Elevated peripheral NET markers in severe asthma
Gout	MSU crystal-activated neutrophils	- NLRP3 inflammasome activation → NET release - NETs entrap crystals to amplify joint inflammation	- Elevated NET-DNA complexes in synovial fluid - Positive correlation with tophus formation
Rheumatoid Arthritis (RA)	Neutrophils, Synovial fibroblasts	- PAD4-mediated citrullinated antigen formation - NETs activate autoreactive B cells and osteoclasts	- Elevated anti-citrullinated protein antibodies (ACPA) - High NET remnants in synovial fluid
Systemic Lupus Erythematosus (SLE)	Low-density granulocytes (LDGs), pDCs	- Mitochondrial NETs activate type I interferon pathway - Anti-NET antibodies promote immune complex deposition	- Elevated anti-dsDNA antibodies - Renal NET deposition correlates with lupus nephritis activity
Antiphospholipid Syndrome (APS)	Anti-β2GPI antibody-activated neutrophils	- NETs expose phospholipid antigens → prothrombotic state - Complement activation exacerbates vascular injury	- Elevated serum anti-NET antibodies - Impaired NET degradation increases thrombosis risk
Idiopathic Inflammatory Myopathy (IIM)	Myositis-associated neutrophils, Fibroblasts	- NETs activate TLR9-miR-7-Smad2 → pulmonary fibrosis - Elevated NETs in MDA5+ patients	- Serum NET remnants correlate with ILD severity - NET infiltration in muscle biopsies
Psoriasis	Skin neutrophils, Keratinocytes	- NETs activate AIM2 inflammasome → IL-1β release - MMP-9-mediated angiogenesis	- Elevated NET markers in lesions - PASI score positively correlates with NET levels
Immune Checkpoint Inhibitor Myocarditis	Cardiac-infiltrating neutrophils, T cells	- NETs activate cGAS-STING → cardiomyocyte apoptosis - PD-1 blockade exacerbates NETosis	- Plasma cfDNA levels correlate with myocarditis grade - NET deposition in cardiac tissue

microbes, or complement proteins,[10,11] followed by activation of intracellular calcium ions, which helps activate PAD4. This induces histone H3 citrullination, weakening the electrostatic forces between histones and DNA, leading to chromatin condensation. The DNA-protein complexes are encapsulated in vesicles and expelled into the extracellular space to assemble into NETs.[12]

Mitochondrial NETosis

In exploring the formation process of mitochondrial NETosis, researchers first observed that the lipopolysaccharides (LPS) of gram-negative bacteria could promote eosinophils to release mitochondrial DNA via a ROS-dependent

mechanism by activating interleukin 5 (IL-5) or interferon-γ (IFN-γ). The structures formed by extracellular mitochondrial DNA and granular proteins can bind to and kill bacteria.[13] S. Yousefi's demonstrated that neutrophils pre-stimulated with granulocyte/macrophage colony-stimulating factor (GM-CSF) for 20 minutes, followed by stimulation with LPS or C5a for 15 minutes, produced NETs containing mitochondrial DNA but not nuclear DNA. Subsequent inhibition of ROS revealed that NETs release was blocked, indicating that the formation of mitochondrial NETs is ROS-dependent.[14] Other studies have shown that NETs can simultaneously contain both nuclear and mitochondrial DNA, although the proportions of the two vary.[11]

The mechanism of NETs formation can be classified into NADPH oxidase-dependent and NADPH oxidase-independent typies. NADPH oxidase-dependent NETosis was the first to be discovered. In 2004, A. Zychlinsky et al demonstrated that NETosis induced by staphylococcus aureus or PMA depends on ROS production by NADPH oxidase. Furthermore, adding exogenous ROS to neutrophils from patients with chronic granulomatous disease can also promote NETs formation.[10] The primary mechanism of NADPH oxidase activation is related to PKC-mediated phosphorylation of its subunits, facilitating the assembly of the active enzyme on the membrane.[15] Other kinases, including c-Raf, MEK, Akt, and ERK, along with PKC, contribute to the activation of NADPH oxidase during Helicobacter pylori-induced NETosis. NETosis induced by the parasitic Entamoeba histolytica also depends on the activation of the c-Raf-MEK-ERK kinase cascade; however, PKC is not involved in this process.[16,17] A bidirectional regulatory mechanism exists between mtROS and NADPH oxidase-derived ROS, mediated by synergistic amplification via distinct signaling cascades. Dikalova et al first demonstrated the positive regulatory role of mtROS on NADPH oxidase activation in endothelial cells. Their study revealed that mtROS, through protein kinase C (PKC)-dependent signaling, directly stimulates the NADPH oxidase system, establishing a self-reinforcing positive feedback loop of oxidative stress.[18] Subsequent research by Nina Vorobjeva's team further elucidated the complexity of this regulatory network. They identified that activation of the G protein-coupled receptor (GPCR) by the peptide chemoattractant N-formylmethionyl-leucyl-phenylalanine (fMLP) triggers dual signaling modalities: (1) mobilization of intracellular calcium stores leading to Ca^{2+}flux, and (2) calcium-independent activation of the PI3K pathway. These parallel pathways collectively induce mtROS bursts, which subsequently amplify NADPH oxidase activation. This mechanism highlights mitochondria as critical signaling hubs for integrating immune responses during innate immunity.[19] Heather Parker's team demonstrated that calcium ion carriers can induce NETs formation independently of NADPH oxidase activation. Upon activation, calcium ions can enter neutrophils, regulated by small conductance potassium channel member 3 (SK3).[20] The influx of Ca^{2+} activates PAD4, facilitating H3 citrullination, which weakens the electrostatic interactions between histones and DNA, leading to chromatin decondensation and NETs formation.[12,21] The release of mitochondrial DNA (mtDNA) can trigger mtROS production, further activating NE and MPO, thereby promoting NETs formation.[22]

Mechanisms of NETs in Sterile Inflammatory Diseases

In various sterile diseases, neutrophils are induced by different factors to form NETs. The components of NETs can directly damage host cells. For instance, in patients with SLE and asthma, the matrix metalloproteinase 9 (MMP9) found in NETs can initiate apoptotic cascades, directly harming endothelial cells. Additionally, NETs can interact with TLRs to activate other immune cells, including B cells, T cells, dendritic cells (DCs), and macrophages, further amplifying the inflammatory response. In autoimmune diseases, the DNA and histones in NETs can bind to autoantibodies, forming immune complexes that deposit in tissues, exacerbating local inflammation. Moreover, NETs play a crucial role in cytokine secretion. They promote the release of pro-inflammatory cytokines such as IL-1β, IL-8, IL-6, and Tumor Necrosis Factor-alpha (TNF-α), creating a local inflammation amplification effect [Figure 2].

The Role of NETs in Atherosclerosis

Cardiovascular diseases remain the leading cause of death worldwide.[23] Atherosclerosis progresses through three stages: fatty streaks, atherosclerotic lesions, and the formation of atherosclerotic plaques. This process is driven by lipid-mediated chronic inflammation, in which immune cells play a significant role.[24] Giugliano, G. found that an increase in the total white blood cell count and neutrophil count is positively correlated with the development of atherosclerotic disease and serves as a predictive marker for cardiovascular risk in coronary artery disease patients.[25] In a mouse model

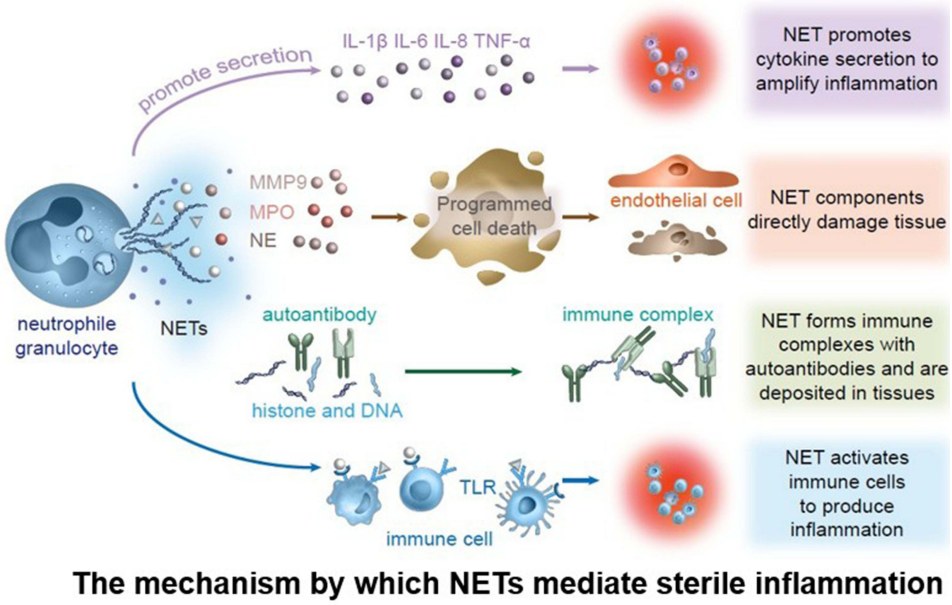

Figure 2 The mechanism by which NETs mediate sterile inflammation. NETs cause the occurrence of sterile inflammation and amplify the inflammation itself through ways such as damaging tissues with their own components, stimulating the production of inflammatory factors, forming complexes with autoantibodies, and activating immune cells.

with apolipoprotein E deficiency, the size of atherosclerotic plaques was found to correlate closely with the number of neutrophils in the peripheral blood. Furthermore, both Franck G. and Megens R.T.A. discovered NETs in atherosclerotic plaques from patients.[26,27] Neutrophils produce large amounts of ROS through NADPH oxidase and MPO, which are key triggers for NETs formation.[28] A study using an atherosclerotic mouse model showed that cholesterol crystals are engulfed by macrophages, triggering an inflammatory response that releases cytokines including IL-1β, an important inducer of NETs. Cholesterol crystals can also directly induce NETosis. When neutrophils from human peripheral blood interact with cholesterol crystals, ROS are generated, and NE translocates to the nucleus, which is a potential intracellular mechanism for signaling NETosis. Similarly, using NADPH oxidase inhibitors or inhibitors of NE and PR3 in vitro can block ROS-dependent NETs formation and the cholesterol crystal-induced NE translocation to the nucleus.[29] Grégory Franck's study also demonstrated that Peptidyl arginine deiminase-4(PAD4) inhibition by chlorimidazole can not only reduce NETosis and the recruitment of neutrophils and macrophages to the arteries but also reduce the size of atherosclerotic lesions and delay carotid artery thrombosis.[30] Enzymes in formed NETs, such as NE and MPO, can degrade the extracellular matrix, leading to tissue damage. Matrix metalloproteinase (MMPs) can also degrade the fibrous cap of plaques, thus promoting plaque instability and rupture, highlighting the important role of NETs in the progression of atherosclerotic diseases.

The Role of NETs in Diabetes

Type 1 diabetes (T1D) is an autoimmune disease caused by the immune destruction of insulin-producing β-cells in the pancreas, leading to elevated blood glucose levels. While T1D is primarily associated with autoantigen-reactive T cells as the pathogenic effector cells, abnormalities in other immune cells, including neutrophils, are also characteristic of T1D development.[31] Studies have shown that in newly diagnosed T1D patients, the count of circulating neutrophils is often reduced below the normal range. This decline in neutrophil count is not due to neutrophil death or targeting by anti-neutrophil antibodies but is a result of neutrophils migrating from the circulation to infiltrate the pancreas.[32,33] Under hyperglycemic conditions, neutrophils produce more superoxide[34] and cytokines.[35] Siu Ling Wong's research showed that, compared to healthy controls, diabetic patients have upregulated expression of PAD4 protein in their neutrophils, which facilitates chromatin decondensation. Increased NETosis in type 2 diabetes is driven by pro-inflammatory factors. Agostina Carestia's study found elevated plasma IL-6 and TNF-α in diabetic patients, associated with increased

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NETosis.[36] Moreover, neutrophils from type 2 diabetes patients can elevate basal calcium levels, promote ROS production, and PAD4-mediated citrullination of chromatin, leading to NETs formation.[37] Formed NETs can induce sterile inflammation, promote endothelial cell dysfunction related to diabetes, and activate the NOD-like receptor thermal protein domain associated protein 3 (NLRP3) inflammasome, damaging glomerular endothelial cells, leading to diabetic nephropathy.[38]

The Role of NETs in Bronchial Asthma

In both metabolic disorders and respiratory diseases, NETs mediate target organ damage through activation of pattern recognition receptors (PRRs): NLRP3 inflammasome activation drives tissue injury in diabetic microvascular complications, while triggering exaggerated inflammatory responses in airway epithelial cells in asthma models. Bronchial asthma is a chronic airway disease affecting nearly 300 million people worldwide. While lymphocytes, mast cells, eosinophils, and basophils play key roles in the pathogenesis of asthma, the pathophysiological role of neutrophils in asthma has only recently begun to be recognized.[39] Seung Hyun Kim's research found that compared to aspirin-tolerant asthma patients, those with aspirin-exacerbated asthma showed increased ROS production, upregulation of CD11b expression, and the release of CXCL8 and MMP9 in circulating polymorphonuclear leukocytes (PMNs).[40,41] NETs were found in bronchial biopsies from asthma patients,[42] where they can promote the secretion of IL-1 and IL-8 by human airway epithelial cells, regulating inflammation.[43] Additionally, formed NETs can activate the toll-like receptor 4(TLR4)/NF-κB pathway, triggering airway and alveolar epithelial cells to express more neutrophils, amplifying the inflammatory response.[41] X A Han's study found that inhibiting the phosphorylation of Mixed lineage kinase domain-like (MLKL) to reduce NETs release could improve neutrophilic inflammation in asthma.[44] Therefore, targeting NETs may provide new therapeutic approaches for treating asthma.

The Role of NETs in Gout

Gout is a metabolic disease characterized by acute arthritis triggered by the deposition of monosodium urate (MSU) crystals in the joints, marked by severe pain and intermittent attacks. Unlike RA, a chronic autoimmune disease presenting with symmetric polyarticular inflammation and progressive joint destruction accompanied by serum anti-CCP antibody positivity, the role of NETs in the pathogenesis of gout is complex and paradoxical.[45] NETs can alleviate inflammation by clearing MSU crystals but may also exacerbate tissue damage due to excessive release. Studies indicate that aggregated NETs (aggNETs) can encapsulate MSU crystals while rapidly sequestering pro-inflammatory cytokines and chemokines, including IL-6, TNF, IL-1β, and IL-8, and degrade inflammatory mediators, preventing neutrophil aggregation and thereby mitigating the escalation of acute inflammatory responses.[46] However, most of this experimental evidence derives from in vitro or acute gout models, and their role in chronic gout patients remains underexplored. Regarding the pathogenicity of NETs, they can release pro-inflammatory mediators (eg, IL-1β) and tissue-damaging enzymes, contributing to tissue injury. Additionally, NETs may promote bone erosion in gout patients by suppressing osteoblast activity and enhancing osteoclast function.[47] However, some studies suggest that the pathogenic effects of NETs depend on factors such as their quantity and duration of persistence. The role of NETs in gout is dualistic—capable of both alleviating acute inflammation and promoting chronic damage. The net effect may depend on the disease stage, the extent of NET formation, and the local microenvironment. Further research is needed to elucidate the precise regulatory mechanisms of NETs and explore their potential as therapeutic targets in gout management.

The Role of NETs in Systemic Autoimmune Diseases

NETs are composed of intracellular components that, when expelled from the body, are exposed to the immune system, which suggests that NETs play a role in autoimmunity and autoinflammation. In autoimmune diseases, an excessive production or inadequate clearance of NETs may significantly contribute to autoimmune conditions reactions.

Rheumatoid Arthritis (RA)

RA is the most common autoimmune disease that primarily affects synovial joints, accompanied by extra-articular manifestations such as rheumatoid nodules, pulmonary involvement, vasculitis, and systemic comorbidities.[48,49] The risk

of developing RA is primarily linked to seropositivity for autoantibodies that share common epitopes with anti-citrullinated peptide (ACPA) autoantibodies and anti-IgG autoantibodies, exhibiting a heritability of 40–66% in seropositive patients.[50] ACPA binds to citrulline on various self-proteins, including vimentin, α-enolase, fibronectin, fibrinogen, histones, and type II collagen, creating immune complexes that lead to inflammation and bone destruction.[51] Neutrophils are the primary source of citrullinated antigens, producing PAD4, which catalyzes the conversion of arginine to citrulline. PAD4 can regulate the activity of antithrombin and chemokines by promoting the release of NETs. Elevated levels of citrullinated antithrombin in the synovial fluid of patients can result in abnormal fibrin deposition and angiogenesis.[6,52,53] Therefore, elevated levels of NETs can be detected in the blood circulation of RA patients.[53] In the synovium, NETs activate rheumatoid arthritis synovial fibroblasts (FLS), which are crucial cells for joint damage. NETs containing citrullinated peptides are internalized by FLS via the RAGE-TLR9 pathway, and arthrogenic NETs are loaded into FLS MHC II and presented to T cells, establishing a link with adaptive immunity.[54] NE in NETs also plays a significant role in fostering cartilage damage and synovial inflammation.[55] In summary, NETs play a crucial role in initiating and sustaining self-antigen exposure, inducing inflammatory responses and adaptive immune responses in the synovium, lungs, and other organs of RA patients.

Systemic Lupus Erythematosus (SLE)

SLE is an idiopathic autoimmune disease marked by the production of autoantibodies against nucleic acids and other related nuclear component proteins.[56] Clinical manifestations are diverse and frequently affect various organs, such as the kidneys, synovial joints, skin, lungs, heart, and blood vessels. More than half of SLE patients will experience cardiac involvement, which includes pericarditis, myocarditis, heart valve issues, and endocardial lesions, primarily presented as non-bacterial warty endocarditis or Libman-Sacks endocarditis. In the past decade, people have uncovered the connection between SLE and neutrophils, monocytes, macrophages, dendritic cells, and others. They have come to understand that SLE may represent an imbalance between innate and adaptive immunity caused by genetic or environmental factors factors.[57,58] Compared to healthy individuals, SLE patients exhibit compromised phagocytic clearance function of neutrophils, reduced cell proliferation ability, and abnormal oxidative processes metabolism.[59,60] In SLE, a distinct neutrophil subset termed low-density granulocytes (LDGs) exhibits proinflammatory properties and pathogenic potential, containing a higher proportion of immature neutrophils compared to conventional neutrophils. Compared to normal neutrophils, LDGs exhibit a stronger spontaneous NETosis propensity, relying on mitochondrial ROS rather than the NOX2 pathway, and generate NETs containing oxidized mitochondrial DNA.[61] The CD10+ mature subset of LDGs demonstrates enhanced NETosis efficiency, with its activity significantly correlated with SLE disease activity.[62] This distinct NETosis mechanism establishes LDGs as a primary source of pathological NETs in autoimmune diseases.[63] In SLE, LDGs lack immunosuppressive functions but are instead associated with increased type I interferon production, endothelial damage, enhanced NET formation, dysregulated biomechanical properties, and impaired phagocytic capacity.[60,62,64] Studies have found that the level of LDG in the blood circulation of SLE patients increases. Extracting LDG from SLE patients for in vitro culture reveals that the ability to form NETs is enhanced, indicating that LDG is in an activated state in these patients. LDG spontaneously releases oxidized mtDNA-rich NETs in a manner dependent on mitochondrial-derived superoxide, thereby increasing the potential for pro-inflammatory effects and interference.[60] Furthermore, NETs formed by LDG contain higher levels of self-modified antigens and immunostimulatory molecules compared to NETs from normal-density neutrophils.[62,65,66] Simultaneously, LDG can also directly damage endothelial cells by triggering the programmed cell death cascade of MMP9 produced by NETs. Additionally, the protein modification driven by NETs can promote the pro-atherosclerotic process and facilitate the early occurrence of vascular events.[61,67] In the serum of SLE patients, production of NETs was not only increased but the ability to degrade them was also reduced. Abdul Hakkim's research revealed that the sera of some SLE patients contained specific DNaseI inhibitors: high titers of anti-DNA antibodies, which can bind to NETs and protect them from DNaseI degradation.[68,69] In summary, increased NETs formation and decreased NETs degradation can lead to elevated levels of these structures, heightened exposure to modified self-antigens, and greater tissue damage. Additionally, as NETs accumulate in tissues, they can activate B cells and plasmacytoid dendritic cells via TLRs and other intracellular sensors, further enhancing inflammatory signaling pathways. Immunostimulatory molecules like IL-33, High mobility group protein B1 (HMGB1),

and Antibacterial protein ll-37 amide (LL37) bound to DNA in NETs further enhance this signaling.[66,70–72] Furthermore, evidence of neutrophil infiltration forming NETs has been detected in the kidneys, skin, and placenta of SLE patients, supporting the existence of this phenomenon in vivo.

Antineutrophil Cytoplasmic Antibody (ANCA)-Associated Vasculitis (AAV)

AAV is a disease characterized by the infiltration of inflammatory cells into the vascular wall and perivascular area, resulting in vascular damage, which includes fibrin deposition, collagen fiber degeneration, and necrosis of endothelial cells and myocytes. It is also referred to as vasculitis. AAV is a specific type in which the presence of ANCA in the serum impacts small blood vessels throughout the body, alongside the presence of ANC in the serum. AAV encompasses microscopic polyangiitis (MPA), where antibodies typically bind to perinuclear MPO, granulomatosis with polyangiitis (GPA), where antibodies generally attach to cytoplasmic neutrophil membrane-bound proteinase 3 (PR3), eosinophilic granulomatosis with polyangiitis (EGPA), and drug-induced AAV. In patients with AAV, neutrophils exhibit an enhanced capability to synthesize NETs,[73] Once synthesized, ANCA can bind to activated neutrophils and NETs to form immune complexes, which further enhance neutrophil activity through Fcγ receptor activation. Studies have also demonstrated that DNA released from NETs contains immunostimulatory sequences (eg, CpG motifs) that can directly activate B cells and plasma cells, promoting the formation of autoantibodies against neutrophil proteins. Furthermore, NET-associated DNA can activate B cells via TLR9 signaling, thereby accelerating antibody production.[74,75] The release of histone metalloproteinases in NETs can also further damage endothelial cells, leading to increased vascular inflammation.[73] In summary, there is substantial evidence that NETs are associated with the pathogenesis of AAV and are anticipated to serve as potential biomarkers in immune regulatory responses.[72]

Antiphospholipid Antibody Syndrome (APS)

APS is a non-inflammatory autoimmune disease characterized by recurrent arterial and venous thrombosis, habitual miscarriage, thrombocytopenia, and persistently high to moderate titers of antiphospholipid antibodies, which is more prevalent among young women. Results from the 2023 APS Clinical Trials Alliance and the International Network Clinical Database and Repository indicated that 45% of patients with positive antiphospholipid antibodies had elevated levels of anti-NETs IgG/IgM.[76] The serum and IgG from APS patients can directly promote the formation of NETs, and the NETs degradation capacity in these patients is also diminished,[77,78] so the levels of free DNA and NETs residues in the circulatory system increase. At the same time, the number of LDGs in APS patients rises, and this type of neutrophil is prone to NETosis.[79] He Meng's study revealed that APS mice treated with IgG exhibited characteristics of excessive thrombosis, and the administration of deoxyribonucleotidase or neutrophil-depleting antibodies could diminish the thrombosis in APS mice to the level observed in the control group.[80] Although the role of NETs in mammalian reproduction has not yet been clearly defined, Sinuhe Hahn discovered that a significant number of NETs were detectable in the intervillous space of the placenta in cases of preeclampsia, indicating that NETs may have a function in preeclampsia.[81]

Idiopathic Inflammatory Myopathies (IIMs)

IIM is a group of inhibitory myopathies characterized by chronic inflammation of skeletal muscle and skin, primarily manifested by muscle weakness, with symmetrical progressive muscle weakness being the most prominent. It can also cause damage to the skin, joints, lungs, heart, and gastrointestinal tract tract.[72,82] Recent studies have demonstrated that NETs play a pivotal regulatory role in both interstitial lung disease and muscle damage associated with IIMs. S. Zhang found that DNase I activity was decreased in patients with IIMs, particularly those with interstitial pneumonia, suggesting that abnormal regulation of NETs may play a role in the disease activity of IIMs.[83] The serum levels of NETs in patients with rapidly progressive interstitial pneumonia who tested positive for anti-melanoma differentiation-associated gene 5 (MDA5) were elevated, and anti-MDA5Ab+ serum could stimulate more normal neutrophils to form NETs vitro.[84–86] Ma et al found that neutrophil extracellular traps (NETs) can accelerate the proliferation of lung fibroblasts in a TLR9-dependent manner.[86] The NETs-DNA complex, by activating the TLR9-miR-7-Smad2 signaling axis, not only promotes fibroblast activation and leads to interstitial lung disease,[87] but also upregulates the expression of major histocompatibility complex class I (MHC-I) in muscle tissue, enhancing the immune attack of CD8+ T cells on

muscle cells.[88] More notably, NETs inhibit the regenerative ability of muscle satellite cells by releasing mtROS. Animal models have shown that the clearance of NETs can increase the efficiency of muscle regeneration by 2.3 times.[89]

Psoriasis (PSO)

PSO is an autoimmune skin disease marked by epidermal hyperplasia resulting from the excessive proliferation of keratinocytes (KCs), increased endothelial cells, and the infiltration of leukocytes (such as DCs, T cells, and especially) PMNs).[78] Blood analysis of patients with psoriasis (PSO) and healthy controls revealed elevated levels of TNF-α, HMGB1, and lipocalin 2 (LCN2) in the serum of PSO patients, which are inducers of NETs formation.[90] The formed NETs can stimulate KCs to produce high levels of inflammatory mediators Interleukin 36 Gamma (IL-36γ) and LCN2. Activated IL-36γ can induce the expression of TLR4, while endogenous neutrophil-derived TLR4 ligands synergize with IL-36γ to induce the production of both LCN2 and IL-36γ through the NF-kB pathway. In turn, upregulated LCN2 can regulate the formation of NETs and the migration of neutrophils, enhancing and maintaining inflammation response.[90] At the same time, NETs can activate the Absent in melanoma 2 (AIM2) inflammasome, which is deleted in KC, through the p38-MAPK signaling pathway. Activated AIM2 not only enhances the production of IL-1β via the classical inflammatory pathway, but also stimulates the production of IFN-γ through the X-linked inhibitor of apoptosis protein (XIAP), mediating the immune response of KCs.[91] These findings are consistent with the broader biological characteristics of NETs, which serve as platforms for sustained inflammation and participate in pathological processes across various tissues - ranging from autoimmune diseases to chronic inflammatory disorders. Importantly, these observations suggest that targeting NET formation (eg, through PAD4 inhibition) or downstream effector molecules (AIM2/XIAP) may offer stratified therapeutic strategies. Of particular note, the p38-MAPK-AIM2 axis may represent a "psoriasis-specific vulnerability point", as NETs in other dermatological conditions (such as atopic dermatitis) primarily activate alternative pathways (eg, TLR9).

NETs in Cancer-Associated Sterile Inflammation

NETs play a dual role in cancer-associated sterile inflammation. On one hand, NETs promote tumor progression through multiple mechanisms. The NE and MMP-9 released from NETs can hydrolyze ECM to release pro-angiogenic factors like VEGF, thereby promoting tumor angiogenesis. Studies have demonstrated that MMP-9 bound to NETs exhibits 3–5 times higher pro-angiogenic activity compared to its free form.[92] Additionally, NET-DNA can form a physical barrier that impedes contact between tumor cells and cytotoxic NK cells or CD8+ T cells, while also facilitating metastatic niche formation through circulating tumor cell entrapment. Notably, in pancreatic cancer models, NETs were shown to reduce tumor-infiltrating CD8+ T cells by 40% while increasing Treg proportion, thereby shaping an immunosuppressive microenvironment.[93] On the other hand, NETs also demonstrate antitumor potential. In melanoma models, high concentrations of NETs exhibited direct cytotoxicity, inducing necrosis in 30–40% of tumor cells. BCG-induced NETs were found to significantly enhance TH1 cytokine expression and boost antitumor immunity.[94] NET-targeting therapeutic strategies (eg, PAD4 inhibitors, DNase I) have shown promising results in preclinical studies, with DNase I combined with anti-PD-1 increasing treatment response rates from 20% to 55% in pancreatic cancer models. However, clinical translation faces several challenges, including standardization of NETs detection, dose-dependent effects, and potential infection risks from systemic inhibition. Future research should focus on developing humanized NETs reporting systems and optimizing targeted delivery technologies to overcome these obstacles for clinical application of NETs-targeted therapy in comprehensive cancer treatment.

Role of NETs in Immune-Related Adverse Events (irAEs)

Immune checkpoint inhibitors (ICIs) have provided insights for treating various cancers, but the number of irAEs that have followed has also increased. Researchers are eager to explore the pertinent aspects of irAEs to avoid adverse events or to predict them in advance for prevention. Since peripheral blood samples are less invasive and easier to obtain than other types of samples, some studies aim to investigate the relationship between neutrophil changes and irAEs by analyzing blood biomarkers to indicate prognosis. For patients with irAEs, the neutrophil-to-lymphocyte ratio (NLR) serves as a significant biological indicator of the body's immune status: patients whose NLR increases and then decreases

quickly tend to have better progression-free survival and overall survival compared to those who maintain high levels.[95,96] Neutrophils are the source of NETs. An increasing number of people have recognized the role of NETs in irAEs and are investigating the relationship between NETs and irAEs. Immune checkpoint inhibitor-associated myocarditis (ICIAM) is a serious irAE. Although uncommon, many cases are fulminant and fatal. Other cardiovascular toxicities include pericarditis, vasculitis, arrhythmias, and possible complications atherosclerosis.[97–99] Xiaohong Xie analyzed blood samples from patients with myocarditis and found that the NLR increased compared to baseline during myocarditis occurred.[100] In the PD-1 inhibitor-induced mouse myocarditis model, there was an increase in MPO and Ly6G fluorescence co-localization signals at the myocardial infiltration site, and myocardial RTFQ-PCR also indicated a significant rise in neutrophil chemokines. Further investigation revealed the key pathway of myocardial damage associated with the activation of the NETs-NLRP3 inflammasome axis.[101] Ludwig T. Weckbach found that targeting midkine (MK), a cytokine that mediates NETs formation in vitro, can not only attenuate NETs formation and polymorphonuclear neutrophil (PMN) infiltration in vivo but also reduce fibrosis and maintain contractile function during experimental autoimmune myocarditis (EAM). These studies suggest that NETs promote the formation of ICIAM, and drugs that block NETs formation are anticipated to become a new strategy for treatment of ICIAM.[102] Yifan Zhou's team confirmed the enrichment of neutrophils and IFN-γ + CD4 + Th1 cells in CD11c-Cre + Stat3f/f mice during αCTLA-4 treatment, and the irAEs model also indicated that immune-related colitis was influenced by neutrophil activation.[103] However, the relationship between other irAEs and NETs still needs further study.

Potential Therapeutic Strategies Targeting NETs

The above article discusses the role of NETs in sterile inflammation. To better control inflammation occurrence and reduce tissue damage, targeted therapy for NETs shows promising development potential [Table 2]. First, inhibiting NETs formation is crucial. Recent literature indicates that targeting PAD4 to inhibit NETs formation has protective effects in mouse models of lupus, diabetes, and atherosclerosis, without any significant adverse events.[104–106] PAD4 is a nuclear promoter of neutrophil histone H3 citrullination, which aids in depolymerizing chromatin and exacerbates NETs formation. Wong's study found that the inhibition of PAD4 by chloramine can reduce reticulocytes and enhance wound healing in diabetic mice. Unlike the enhanced citH3 signaling pathway observed in wild-type mice, no changes in citH3 were detected in Padi4-/- mice, and wound healing was expedited.[37] Jason S. Knight et al also found that PAD

Table 2 NETs Inhibitors: Mechanisms and Therapeutic Potential

Inhibitor Name	Mechanism of Action	Experimental Models	Advantages	Challenges	Future Directions
PAD4 Inhibitors (eg, Cl-amidine)	Inhibits PAD4 enzymatic activity, preventing histone citrullination and NET formation	Lupus mouse models (MRL/lpr)	Significantly reduces renal, cutaneous, and vascular inflammation; improves multi-organ damage	Potential off-target effects; long-term safety unknown	Optimize selectivity; develop higher-specificity PAD4 inhibitors
DNase I	Degrades DNA backbone of NETs, disrupting NET structures	Mice, human cells, snake venom models	Direct NET clearance; clinically approved for cystic fibrosis treatment	Short half-life; does not inhibit NET formation; may interfere with physiological DNA repair	Improve delivery systems (eg, liposomal encapsulation, rectal administration); combine with other inhibitors
STING Inhibitors (eg, H-151)	Blocks cGAS-STING pathway, reducing NET-induced inflammatory cytokine release	Mouse acute lung injury model	Suppresses NET-associated innate immune hyperactivation	May compromise antiviral immunity; requires specificity validation	Develop tissue-specific STING inhibitors; explore synergies with other NET-targeting agents

(*Continued*)

Table 2 (Continued).

Inhibitor Name	Mechanism of Action	Experimental Models	Advantages	Challenges	Future Directions
Anti-IL-6 Antibodies (eg, Tocilizumab)	Neutralizes IL-6 signaling, attenuating NET-driven inflammation	Mouse colitis model	Targets key inflammatory mediator; FDA-approved for autoimmune diseases	Risks of systemic immunosuppression; no direct NET inhibition	Combine with NET-specific inhibitors to minimize systemic effects
Functionalized Nanosheets	Scavenges ROS, inhibits NETosis, and promotes NET degradation	Mouse asthma model	Multifunctional (antioxidant + anti-NET); localized delivery reduces toxicity	Long-term safety of nanomaterials unclear; requires improved targeting	Develop biodegradable nanocarriers; expand to other NET-related pathologies
Anti-Midkine Antibodies	Blocks Midkine-mediated neutrophil recruitment and NETosis	Mouse myocarditis model	Specifically inhibits NET-associated cardiac injury	High antibody production costs; human efficacy unverified	Explore small-molecule Midkine inhibitors; test combination immunotherapies
NETosis Signaling Inhibitors (eg, MEK/ERK inhibitors)	Inhibits Raf-MEK-ERK pathway to suppress NET formation	Human neutrophils	Targets critical signaling axis; potential synergy with antimicrobial therapies	Affects other cellular functions (eg, T-cell activation)	Develop neutrophil-specific kinase inhibitors; optimize therapeutic windows
Necroptosis Inhibitors (eg, Necrostatin-1)	Inhibits MLKL phosphorylation, blocking necroptotic NETosis pathway	Mouse asthma model	Reduces NET release without impairing apoptotic clearance	Ineffective against pre-formed NETs; NETosis subtype roles unclear	Combine with DNase I for dual NET formation/clearance targeting
Mitochondrial Antioxidants (eg, MitoTEMPO)	Scavenges mitochondrial ROS, inhibiting oxidative stress-driven NETosis	Hypertensive mouse models	Targets NET generation at source; improves vascular function	Limited tissue penetration; may disrupt physiological ROS signaling	Develop neutrophil mitochondrial-targeted delivery platforms
Anti-GSDMD Antibodies	Inhibits gasdermin D pore formation, blocking non-canonical inflammasome-mediated NETosis	Mouse sepsis models	Precisely inhibits specific NETosis pathway; reduces pyroptosis	Ineffective against alternative NETosis pathways; antibody stability issues	Explore small-molecule GSDMD inhibitors; investigate disease-specific NETosis mechanisms

inhibitors can reduce the formation of NETs while protecting the vascular system, kidneys, and skin from damage in various lupus models. However, no human clinical trials have been publicly conducted yet, though they may potentially advance to Phase I studies for inflammatory skin diseases in the future.[107] MPO and NE are both crucial components in the formation of NETs. NE inhibitors, such as sivelestat, can significantly reduce the occurrence of spontaneous insulitis and autoimmune diabetes when administered to diabetic mice in the early stages. Tu et al's study demonstrated that BP-PGA50 nanosheets can effectively inhibit the activation of Toll-like receptor 9 (TLR9), a key signaling pathway driving aberrant neutrophil responses. By blocking TLR9 signaling, these functionalized nanosheets significantly reduce NETosis formation and alleviate inflammatory responses in the nasal mucosa and lungs of mouse models, offering a novel therapeutic strategy for severe neutrophilic inflammation in diseases such as chronic rhinosinusitis, asthma, and chronic obstructive pulmonary disease.[108] The mechanistic advantage lies in the fact that, unlike broad-spectrum anti-inflammatory drugs, BP-PGA50 nanosheets specifically inhibit TLR9-mediated pro-inflammatory signaling, thereby minimizing off-target effects. Furthermore, by controlling excessive NETs release, they prevent tissue damage and

autoantigen exposure, consequently ameliorating chronic inflammation and autoimmune exacerbations. However, while demonstrating remarkable efficacy in animal models, human trials have not yet been conducted. Given the growing research interest in nanomaterial-based therapies for respiratory diseases, BP-PGA50 nanosheets could potentially be developed for either inhalation or systemic administration routes. Nevertheless, rigorous evaluation of their biocompatibility and long-term safety remains imperative before clinical translation.

Secondly, for the existing NETs, the use of DNase 1 to degrade them can also minimize tissue damage.[109,110] DNase1 is primarily produced by the pancreas and kidneys and is the predominant nuclease found in blood and other bodily fluids. Su-Bin Kwak discovered that DNase 1's ability to degrade NETs can significantly lower the mortality rate in a mouse model of LPS-induced shock.[111] Furthermore, the breakdown of NETs can enhance the inflammatory response and tissue damage in SLE and RA patients, hinder tumor cell migration, and alleviate symptoms of acute lung injury.[68,112,113] However, in some SLE patients, serum contains high-titer anti-DNA antibodies that bind to NETs and form immune complexes, thereby protecting NETs from DNase I-mediated degradation and contributing to significant interindividual variability in DNase I therapeutic efficacy. The randomized, double-blind, placebo-controlled Phase 2 clinical trial (NCT03277638) titled "A Study of DNase I in Patients With Lupus Nephritis" demonstrated no significant difference in renal remission rates between the DNase I and placebo groups. However, this study represents the first clinical validation of DNase I's therapeutic potential in lupus nephritis while simultaneously revealing the limitations of monotherapy. These findings suggest that optimization of drug delivery methods or combination therapy targeting protein components of NETs may be required when administering DNase I. Furthermore, Zuo et al identified substantial NET accumulation in the lungs of severe COVID-19 patients, but observed limited clinical efficacy of DNase I treatment - a phenomenon potentially attributable to the protein components of NETs that confer resistance to enzymatic degradation.[114,115] Simultaneously, inhibiting inflammatory factors downstream of NETs plays a crucial role in preventing the NET-induced cascade reaction. Following the formation of NETs, there may be an increase in inflammasomes and cytokines. Tongtong Lin's study revealed that the impact of oxaliplatin-induced peripheral neuropathy can be mitigated by inhibiting NLRP3.[116] Different patients should receive a multi-target combined intervention of NETs tailored to their specific physical conditions to explore the potential of inhibiting NETs in treating inflammation.

Conclusion

NETs play a dual role in sterile inflammation, acting as both defenders against tissue damage and drivers of pathological inflammation in autoimmune, cardiovascular, and metabolic diseases. The dysregulated release of NETs contributes to organ damage by promoting cytokine storms, autoantibody production, and endothelial dysfunction. Emerging therapeutic strategies—such as PAD4 inhibitors, DNase I, and targeted ROS scavengers—show promise in mitigating NET-mediated injury in preclinical models. However, challenges remain in achieving specificity, minimizing off-target effects, and preserving host defense mechanisms.

Future Research Directions

Although significant progress has been made in understanding the role of neutrophil extracellular traps (NETs) in sterile inflammation, there are still some areas that need to be explored in depth to promote clinical translation. Firstly, it is necessary to clarify the precise regulatory threshold of NETs in tissue repair and injury, especially the potential pro-metastatic risk that may occur after peptidylarginine deiminase 4 (PAD4) inhibition. There are also controversies regarding the standardization of NETs detection. Therefore, it is urgent to establish cross-platform comparable quantitative criteria for NETs. Meanwhile, the development of humanized NETs models is highly anticipated to overcome translational bottlenecks such as differences in TLR9 signaling pathway responsiveness in mouse models. Secondly, the clinical translation path still needs to be optimized. The development of biomarkers can focus on the dynamic monitoring of circulating NETs (such as citrullinated histone H3-DNA complexes). Moreover, when exploring the synergistic effects between NETs-targeted drugs and existing therapies, the challenge of dosage timing needs to be addressed. Finally, some hypotheses about NETs need to be verified. For example, whether the epigenetic information carried by NETs is involved in disease recurrence or trained immunity. With the continuous in-depth research on NETs, we have gained a preliminary

understanding of their role in sterile inflammatory diseases. As an emerging field, NETs are gradually demonstrating great potential and broad prospects.

Disclosure

The authors report no conflicts of interest in this work.

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