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Morphological Signatures of Neutrophil Extracellular Traps: From Ultra-Structural Organization to Tissue Remodeling and Pathophysiological Contexts

Firmas Morfológicas de las Trampas Extracelulares de Neutrófilos: Desde la Organización Ultraestructural hasta la Remodelación Tisular y los Contextos fisiopatológicos

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SUMMARY: Neutrophil extracellular traps (NETs) are web-like networks of decondensed chromatin fibers decorated with histones and neutrophil granular proteins that neutrophils release as part of the innate immune response. These structures, first observed by high-resolution electron microscopy as smooth DNA fibers, are pivotal in immobilizing pathogens. However, excessive NET formation is a double-edged sword. On one hand, NETs contribute to host defense; on the other, their accumulation can cause vessel occlusion, cytotoxicity to host cells, and persistent inflammation. This scientific review provides a comprehensive histological and pathological perspective on NETs, from their ultrastructural organization to their roles in tissue remodeling across various organ systems. We place a particular emphasis on reproductive tissues, where NETs have been implicated in conditions from infertility to pregnancy complications. Additionally, we explore NET-associated pathology in pulmonary diseases (e.g. acute respiratory distress syndrome and chronic airway diseases), vascular systems (atherothrombosis and immunothrombosis), and other contexts such as autoimmune disorders and cancer. We discuss how NETs are identified in tissue (e.g. by extracellular DNA co-localized with neutrophil enzymes), the morphological signatures they present (e.g. fibrillar chromatin networks or aggregated DNA-protein complexes), and how these structures drive tissue damage or remodeling. In conclusion, while NETs are essential for trapping microbes, their dysregulation leads to collateral damage in tissues. Understanding NET morphology in situ and its consequences provides insight into disease mechanisms and highlights potential therapeutic strategies to mitigate tissue injury while preserving host defense.

KEY WORDS: Neutrophil extracellular traps (NETs); Tissue remodeling; Pathophysiology.

INTRODUCTION

Neutrophils are the most abundant circulating leukocytes and are rapid first responders to infection or injury. They utilize several mechanisms to destroy microbes, including phagocytosis, degranulation, and the formation of neutrophil extracellular traps (NETs) (Wang *et al*., 2024b). NETs were first described in 2004 by Brinkmann *et al*. (2004) as extracellular fibrous networks of DNA studded with antimicrobial proteins. Morphologically, NETs consist of a scaffold of decondensed chromatin (nuclear or mitochondrial DNA) adorned with histones and neutrophil granule enzymes such as neutrophil elastase (NE), myeloperoxidase (MPO), cathepsin G, and others (Wang *et al*., 2024b). These web-like structures can ensnare bacteria, fungi, viruses and other pathogens, preventing their spread and facilitating their neutralization (Xuan *et al*., 2023). NET formation (often termed "NETosis") can occur via distinct pathways, a lytic process (suicidal NETosis) involving cell membrane rupture, and non-lytic "vital" NET release where neutrophils survive after expelling nuclear contents (Jorch & Kubes, 2017).

Physiologically, NET deployment represents a specialized form of neutrophil-mediated antimicrobial

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activity. However, in sterile inflammation or chronic disease, NETs can become pathogenic (Wang *et al*., 2024a). Excessive or persistent NET accumulation is linked to host tissue damage and dysfunction: NET components (e.g. proteases, cytotoxic histones) can injure endothelium and parenchymal cells (Wang *et al*., 2024a), and the DNA-rich webs can physically obstruct small vessels, contributing to microthrombosis (Wang *et al*., 2024a). NETs thus have a dual role, protecting the host but also promoting inflammation and thrombosis when dysregulated (Thakur *et al*., 2023). Intriguingly, one of the first pathological contexts in which NETs were implicated was in the female reproductive tract, when large numbers of NETs were observed in the intervillous spaces of preeclamptic placentas (Morawiec *et al*., 2025). Since then, NETs have been identified as important players in numerous conditions, ranging from pregnancy complications to autoimmune diseases and cancer metastasis (Thakur *et al*., 2023). In the following sections, we review the characteristic morphology of NETs at the ultrastructural and histological levels, and examine how these "toxic webs" contribute to tissue remodeling and pathology in reproductive organs, the lungs, the vasculature, and other systems.

Ultra-Structural Organization of NETs

Under electron microscopy, NETs appear as an intricate meshwork of fibers and globular domains. The core structural element is strands of decondensed chromatin. Early high-resolution scanning EM images showed NETs as smooth filaments of DNA extending tens of microns from neutrophils (Wang *et al*., 2024b). These chromatin filaments often exhibit beads-on-a-string morphology, where the "beads" correspond to clusters of histones and bound proteins. Indeed, NET fibers are richly decorated with histones (H1, H2A, H2B, H3, H4), which maintain association with DNA (Brinkmann *et al*., 2004). Attached to the DNA-backbone are numerous antimicrobial proteins released from neutrophilgranules, including serine proteases (NE, cathepsin G), MPO, defensins, lactoferrin, and calprotectin, among others (Wang *et al*., 2024b). This unique molecular composition, which depicts a neutrophil expelling a chromatin web coated with granule proteins and enzymes. Notably, NETs can form via different pathways which influence their ultrastructure. In "suicidal" NETosis, which takes several hours, the neutrophil undergoes membrane rupture: the nuclear envelope disintegrates, chromatin decondenses and mixes with cytoplasmic contents before bursting out of the cell (Jorch & Kubes, 2017). This results in extensive webs of DNA spreading outward from the lysed neutrophil remnants. In contrast, "vital" NET release occurs rapidly (within minutes) and does not lyse the cell: patches of the nuclear membrane vesiculate and DNA is externalized in a piecemeal fashion (Wang *et al*., 2024b). Vital NETs may appear as more localized fibrous expulsions, sometimes still attached to live neutrophils. Additionally, neutrophils stimulated under certain conditions (e.g. by GM-CSF plus C5a) can expel mitochondrial DNA to form NETs without using nuclear DNA (Jorch & Kubes, 2017). These mitochondrial NETs are often thinner and may be more fragmented. Despite these variations, a unifying morphological signature of all NETs is extracellular DNA-based fibers that form tangled networks and are studded with neutrophil-derived proteins. Their mesh-like architecture provides a physical trap for microbes, but in tissues it can also serve as a scaffold for protein and cell adhesion (for example, NET fibers readily bind platelets, red blood cells, and coagulation factors, promoting clot formation) (Wang *et al*., 2024a).

Extracellular traps can be morphologically classified into three main types: diffuse (*dif*NETs), elongated (sprNETs), and aggregated (*agg*NETs), each reflecting a distinct mode of chromatin organization and immune function. *dif*NETs consist of fine, loosely dispersed chromatin fibers forming a low-density, discontinuous mesh that appears as a hazy or cloud-like structure. This morphology is typical of early inflammatory stages, enabling broad antimicrobial coverage without disrupting tissue integrity (Manda *et al*., 2014). *spr*NETs display long, linear, or ribbon-like DNA filaments extending over several micrometers, often induced by crystalline or mechanical stimuli (Li *et al*., 2018). *agg*NETs, by contrast, form dense, multilayered clusters of extracellular DNA, generating compact macrostructures (>10 μm) commonly found in chronically inflamed tissues. These aggregates can trap inflammatory mediators and regulate local immune responses (Li *et al*., 2018). Together, these morphotypes demonstrate the structural plasticity of extracellular networks and their ability to adapt to diverse pathological contexts. Figure 1 depicts the morphology of the three network types, highlighting their distinct organization and spatial distribution.

Histological Identification of NETs

In tissue sections and clinical samples, NETs can be identified by their content of DNA and neutrophil-specific proteins. Histologically, NETs may be visualized as amorphous extracellular fibrillar material that is positive for DNA dyes (such as DAPI or hematoxylin) but lying outside of intact nuclei. However, routine H&E staining is not very specific, as NETs can resemble necrotic debris. Thus, immunofluorescence microscopy is considered the gold standard for NET detection (Zambrano *et al*., 2025). Co-localization of extracellular DNA with neutrophil granule enzymes (like MPO or NE) or with citrullinated histone H3

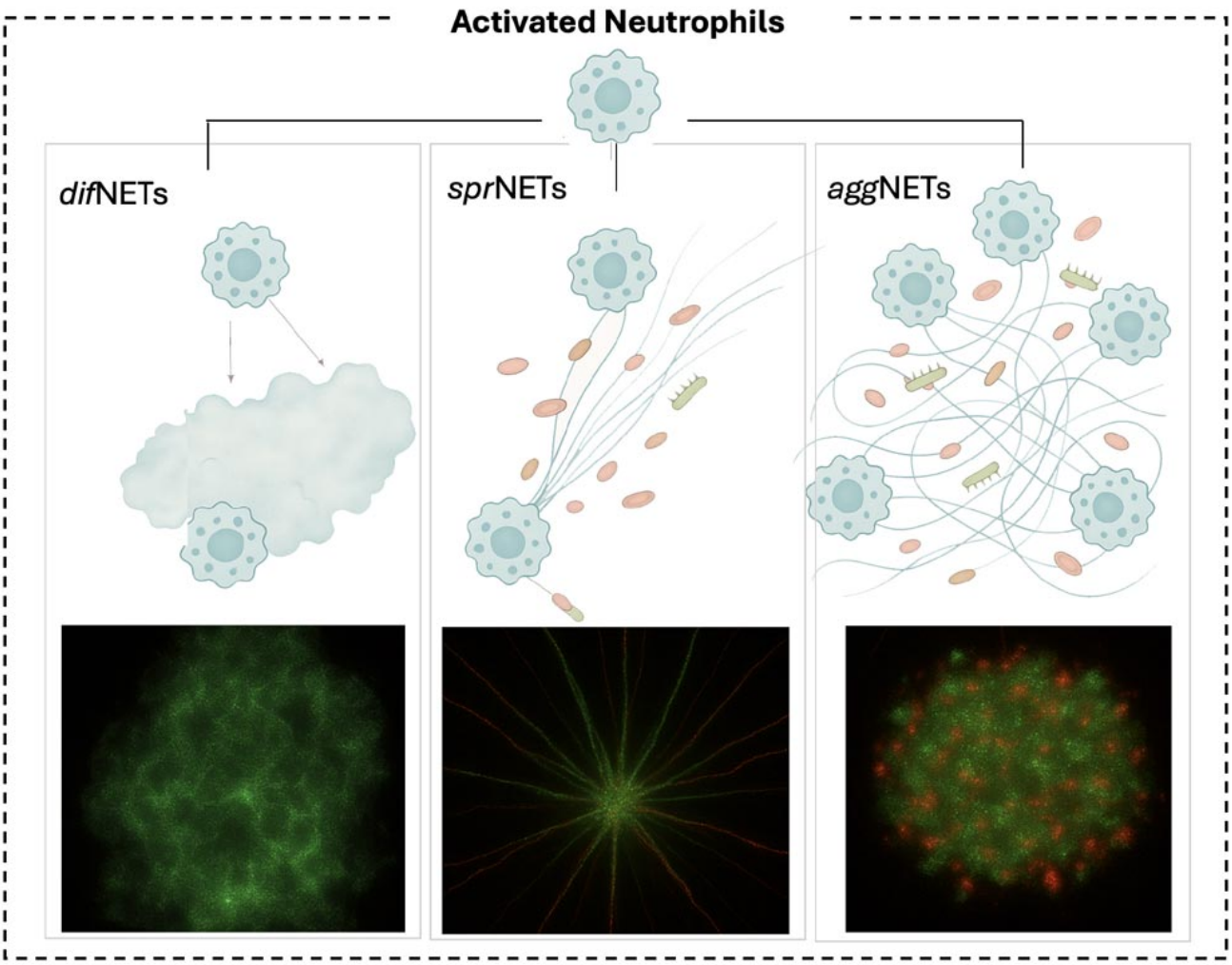

Fig. 1. Morphological phenotypes of neutrophil extracellular traps (NETs). Schematic and fluorescence micrographs depicting the three principal NET morphotypes released by activated neutrophils. Following activation, neutrophils undergo nuclear decondensation and chromatin extrusion, generating distinct NET structures. SprNETs exhibit elongated filamentous DNA strands forming open web-like networks; diffNETs display a cloud-like distribution of decondensed chromatin; and aggNETs consist of dense chromatin aggregates formed by overlapping NETs from multiple cells. Representative IA fluorescence images illustrate each phenotype.

(H3Cit) is typically used as a definitive signature of NETs (Morawiec *et al*., 2025). For example, in a tissue section, one might observe diffuse DNA staining in areas of inflammation, which co-localizes with MPO deposits, indicating that the DNA is of neutrophil origin (NETs) rather than from dead cells in general. Antibodies against H3Cit (a histone modification catalyzed by PAD4 during NETosis) are especially useful, as they mark decondensed chromatin associated with NET formation. Indeed, clinical studies have measured circulating complexes of MPO-DNA or H3Cit-DNA as surrogate markers of NET burden (Zambrano *et al*., 2025). Detection of such NET components can even have prognostic value; for instance, patients with certain cancers or autoimmune diseases show elevated NET markers in blood which correlate with disease activity (Morawiec *et al*., 2025).

On a pathology slide, NETs often manifest in areas of intense neutrophil infiltration. A classic example is in acute lung tissue damage: neutrophil-rich alveolar capillaries in severe COVID-19 or influenza infection contain stringy extracellular DNA/MPO deposits corresponding to NETs, frequently entwined with fibrin in microthrombi (Enomoto, 2022). In such cases, immunohistochemistry for NE or CitH3 highlights a network extending beyond neutrophil cell bodies, confirming NET structures. Likewise, in thrombi retrieved from patients (e.g. cerebral or coronary thromboemboli), immunostaining has demonstrated NET components woven through the fibrin/platelet matrix (Essig *et al*., 2020). Such histological evidence indicates NETs are not merely in solution but form actual structural scaffolds within tissues and clots.

It should be noted that sample processing can affect NET visualization. Because NET DNA is susceptible to nuclease digestion, improper handling may lead to under-detection. Specialized fixation methods or NET-preserving stains (e.g. picogreen for DNA alongside MPO immunostain) help preserve the delicate NET structures. Emerging techniques like in situ zymography (to detect NET-associated proteases) and machine-learning image analysis are also being applied to identify NETs in histopathology specimens (Zambrano *et al*., 2025). In summary, a combination of DNA dyes and neutrophil-specific markers is required to confidently identify NETs in tissue. The presence of extracellular chromatin decorated with neutrophil enzymes is the defining histological signature of NETs, distinguishing them from other forms of cell death debris. Table I provides examples of how NETs are detected and what morphological features they exhibit in different tissues and disease contexts.

Pathophysiological Contexts: NETs in Tissue Remodeling and Disease

Excessive NET formation has been implicated in a wide spectrum of diseases. Here, we discuss how NET-associated structures contribute to tissue remodeling and pathology in several organ systems, with an emphasis on reproductive tissues, as well as pulmonary, vascular, and other contexts. NETs can drive tissue remodeling both by direct degradation of tissue components (via neutrophil proteases and oxidants on the NET) and by triggering dysregulated repair processes (fibrosis, abnormal angiogenesis, etc.). In each context, we highlight morphological evidence of NETs and their pathological consequences.

NETs in Reproductive Tissues

In pregnancy and placental pathologies, the female reproductive tract is a notable site of NET-associated pathology. In preeclampsia, a pregnancy complication characterized by placental dysfunction and maternal hypertension, NETs have been found in abundance within the intervillous space of affected placentas (Morawiec *et al*., 2025). Histologically, these NETs appear as fibrillary extracellular DNA networks in the maternal blood spaces of the placenta. Their presence correlates with inflammation and excessive placental damage (Giaglis *et al.*, 2016). It is hypothesized that placental ischemia or micro-debris can trigger neutrophils to release NETs, which then trap circulating platelets and red cells, contributing to intervillous thromboses and impaired maternal-fetal exchange. In fact, elevated levels of NET components (circulating cell-free DNA, MPO-DNA complexes) have been detected in the blood of women with preeclampsia (Sur Chowdhury *et al*., 2016). This suggests that NET formation is systemically increased and may exacerbate endothelial injury in the mother as well (Morawiec *et al*., 2025). Apart from preeclampsia, NETs are implicated in other pregnancy-related disorders: for example, chronic NET activity has been linked to recurrent miscarriage, preterm labor, and premature rupture of membranes (Aslanian-Kalkhoran *et al*., 2024). In these conditions, NETs at the maternal-fetal interface or in decidual tissues could induce

Table I. Morphological classification of neutrophil extracellular traps (NETs) across tissue contexts.

Morphological Type	Key Characteristics	Representative Tissues / Pathologies	citation
Diffuse extracellular traps	Dispersed, fine chromatin fibers (<100_nm) decondensed from neutrophil nuclei, forming non-continuous, low-density webs; decorated with histones (H1–H4), neutrophil elastase (NE), and myeloperoxidase (MPO). Provide a high local concentration of antimicrobial proteins at infection sites without large aggregates.	Observed in early infection zones and acute inflammation (bacterial sepsis, early gout flares, influenza, cystic fibrosis sputum, and systemic lupus erythematosus).	(Manda *et al*., 2014)
Elongated extracellular traps	Linear or ribbon-like DNA-protein filaments, often exceeding tens of micrometers; result from specific crystalline or mechanical stimuli (e.g., calcium pyrophosphate dihydrate, cholesterol, silica). Associated with NADPH oxidase or PADI4 activity and histone citrullination.	Prominent in pseudogout (CPPD), atherosclerotic plaques (cholesterol crystals), and pulmonary silicosis, forming extended extracellular DNA fibers in tissue interstitium.	(Brinkmann et al., 2004; Manda *et al*., 2014)
Aggregated extracellular traps	Dense, multilayered clusters of intertwined NETs forming compact macrostructures (>10__m); appear when neutrophil density is high. Capable of proteolytic degradation of cytokines and DAMPs, shifting inflammation toward resolution. Contain oxidized histones, NE, MPO, and calprotectin.	Found in chronic gouty tophi, pancreatitis (ductal calcium carbonate aggNETs), and silicosis nodules. Functionally associated with inflammation resolution and tissue occlusion.	(Li *et al.*, 2018)

local inflammation and extracellular matrix breakdown (e.g. degrading fetal membrane integrity), thereby precipitating complications. The hormonal milieu may also modulate NET formation; interestingly, progesterone has been reported to inhibit full NET release despite inducing histone citrullination, potentially as a protective mechanism during pregnancy (Giaglis *et al*., 2016). Understanding NETs in placental pathology has diagnostic potential, one study suggests that NET biomarkers might serve as early indicators of pregnancy complications (Morawiec *et al*., 2025).

In endometriosis and gynecological disorders, NETs have also been observed in non-pregnant reproductive tissues. Endometriosis, a disease where endometrial tissue grows outside the uterus, is marked by pelvic inflammation. NETs are increasingly recognized in endometriosis lesions and fluids. In patients with endometriosis, neutrophils in the peritoneal cavity release NETs at a significantly higher rate than in healthy individuals (Berkes *et al*., 2014). Researchers found abundant NET structures in the peritoneal fluid of endometriosis patients, whereas healthy controls had only scant NET formation (Morawiec *et al*., 2025). This NET accumulation likely contributes to the chronic inflammatory microenvironment and may promote fibrotic adhesions typical of endometriosis. Elevated circulating NET markers are also reported in women with endometriosis (Munrós *et al*., 2019), supporting a systemic pro-NETosis tendency. The presence of NETs in endometriotic tissue can directly damage cells and may expose nuclear antigens to the immune system, possibly linking to the autoimmune features of endometriosis. Other gynecological conditions have NET involvement as well. In cervicitis (inflammation of the cervix, often due to infection), local NET release could help trap pathogens but also cause collateral tissue damage in the cervical epithelium. There is emerging evidence that premature ovarian failure and certain ovarian pathologies might involve aberrant neutrophil activation and NET release in ovarian stroma, disrupting the tissue architecture (though this is an area of ongoing research). Furthermore, NETs have been linked to gynecologic cancers: for instance, in ovarian cancer, NETs can form a pro-tumor microenvironment. NET fibers have been found within ovarian tumor histology, and in vitro studies show NETs can stimulate ovarian cancer cell invasion (Morawiec *et al*., 2025). Overall, in reproductive tissues, NETs serve as a common thread linking infection, sterile inflammation, and even malignancy, often correlating with tissue remodeling processes such as decidual necrosis, fibrosis, or neoangiogenesis in lesions.

NETs in Pulmonary System

The lung is another organ where NETs play paradoxical roles in disease. Neutrophils are key effectors in pulmonary inflammation, and their NETs can either contain infections or inflict damage on delicate gas-exchange surfaces.

In conditions like acute respiratory distress syndrome (ARDS), whether due to severe infections (pneumonia, COVID-19) or other insults – NETs are abundantly present in the affected lung tissue. Autopsy studies of severe COVID-19 pneumonia have confirmed extensive NET deposition in the lungs, especially in areas of diffuse alveolar damage (DAD) (Enomoto, 2022). NETs are found lining alveolar walls and occluding microvessels; they are often associated with hyaline membranes and fibrin clots in alveolar capillaries, indicating involvement in microthrombosis and immune-driven coagulation (Enomoto, 2022). Morphologically, immunostaining reveals networks of extracellular DNA co-localized with neutrophil elastase within alveoli, and electron microscopy shows NET fibers entwined with platelet-fibrin aggregates in capillaries. These NETs contribute to the severe tissue damage observed in ARDS lungs – neutrophil proteases and histones on NETs can destroy the pulmonary endothelium and epithelium, leading to alveolar wall necrosis, edema, and hemorrhage (Scozzi *et al*., 2022). In ARDS patients, lung neutrophils exhibit an enhanced ability to form NETs, correlating with worse pathological changes like alveolar wall destruction and interstitial edema (Xuan *et al*., 2023). Clinically, high levels of NET markers (e.g. MPO-DNA) in the blood or bronchoalveolar lavage of ARDS patients are associated with more severe oxygenation impairment and outcomes (Obermayer *et al*., 2021; Inui *et al*., 2025). These findings have driven interest in therapies targeting NETs in acute lung injury; for example, trials of inhaled DNase (to dismantle NETs) in COVID-19 were explored to reduce ventilatory failure (Gregoire *et al*., 2025), though results have been mixed.

In severe asthma, especially neutrophilic subtypes of asthma, NET formation in the airways has been linked to disease severity. Sputum from asthmatics often contains high levels of extracellular DNA, and severe asthmatics have elevated sputum NET components (NE-DNA, CitH3) that correlate inversely with lung function (FEV?) (Xuan *et al*., 2023). This suggests persistent NET presence is associated with airflow obstruction. Notably, neutrophils from patients with steroid-resistant asthma release excessive NETs, and those NETs have been shown to carry IL-17A (a key cytokine in neutrophilic asthma) (Xuan *et al*., 2023). IL-17A-enriched NETs can directly stimulate airway structural cells, promoting fibrotic changes and mucus hypersecretion in the bronchial wall (Ntinopoulou *et al*., 2023). Thus, NETs might drive airway remodeling (subepithelial fibrosis, goblet cell hyperplasia) that characterizes chronic asthma damage. In chronic obstructive pulmonary disease (COPD), chronic

neutrophilic inflammation similarly leads to NET accumulation in the bronchial mucus, which can perpetuate inflammation and proteolytic lung tissue destruction (emphysema).

A striking example of pathological NET accumulation is seen in cystic fibrosis (CF). CF patients' airways are clogged with viscous DNA-rich sputum, much of it derived from NETs released by the massive neutrophil influx in response to chronic infection. The prolonged survival and activation of neutrophils in CF lung tissue leads to excessive NET production (Gray *et al*., 2018). NET DNA and proteases increase sputum viscosity and cause chronic bronchial obstruction. Histologically, CF airways show NETs intermingled with mucus and bacteria, forming tenacious biofilms. These NETs also damage airway epithelium and drive bronchiectasis by digesting structural proteins. Therapeutically, recombinant human DNase I (dornase alfa) is used in CF specifically to degrade NET DNA in airway secretions, which thins the mucus and improves lung function (Xuan *et al*., 2023). This is a direct example of targeting NETs to mitigate tissue damage. In sum, across chronic lung diseases, NETs serve as mediators of ongoing inflammation and tissue remodeling – they can induce necrosis of epithelial cells, impair ciliary function, and stimulate fibroblast activity, thereby linking persistent inflammation to structural changes in the lungs.

NETs in the Vascular System

Neutrophils and NETs have emerged as significant contributors to vascular pathology, particularly in thrombosis and atherosclerosis. The vasculature is both a highway for NETs (since neutrophils often release NETs in blood or endothelium) and a target of NET-induced injury (endothelial damage, clot formation, etc.).

In Thrombosis and Immunothrombosis, NETs can act as a scaffold for thrombus formation. In conditions of intravascular inflammation (sepsis, trauma, or autoimmune flares), NET release within blood vessels promotes a form of immune-driven thrombosis often termed immunothrombosis. Structural analysis of thrombi retrieved from patients (for example, large-vessel clots in stroke or heart attack) has demonstrated that neutrophils and NETs are substantial constituents of the thrombus architecture[30]. NET fibers, studded with platelets and coagulation factors, weave through the fibrin matrix, increasing the structural stability and size of clots (Essig *et al*., 2020). Moreover, NET components like tissue factor (externalized on NETs) can trigger the coagulation cascade, while NET histones and proteases inhibit natural anticoagulants, tipping the hemostatic balance towards thrombosis. Clinically, elevated NET markers are associated with deep vein thrombosis and pulmonary embolism, and animal models show NET inhibition (via DNase or histone neutralization) can reduce thrombus size (Carminita *et al*., 2021). In microvascular thrombosis (as seen in disseminated intravascular coagulation or severe COVID-19), NETs have been observed in occlusive platelet-rich microthrombi, contributing to organ damage. Endothelial cells exposed to NETs become injured and pro-coagulant, further propagating clotting (Martinod & Wagner, 2014). Thus, morphologically, one finds NET deposits in affected vessels, and functionally, NETs bridge inflammation and thrombosis in vascular pathology (Thakur *et al*., 2021).

In atherosclerosis, chronic inflammation of arteries in atherosclerosis also involves NETs. Neutrophils infiltrate atherosclerotic plaques and can release NETs therein, especially in regions of plaque instability. NETs have been demonstrated to play a pivotal role in the development of atherosclerotic lesions (Yuan *et al*., 2025). In plaques, NET-derived proteases (NE, MPO) degrade the fibrous cap and extracellular matrix, potentially weakening the plaque and making it prone to rupture. NET histones can kill endothelial and smooth muscle cells, exacerbating endothelial erosion and exposing thrombogenic material (Tang *et al*., 2024). Additionally, NETs provide a sticky network that can trap oxidized LDL and cholesterol crystals, amplifying local inflammation. Indeed, cholesterol crystals themselves can induce neutrophils to undergo NETosis, linking hyperlipidemia to NET release in plaques. Plaque analyses have revealed citrullinated histones and DNA co-localized with neutrophil markers, indicating in situ NET formation. The presence of NETs in plaques is associated with plaque instability and thrombosis, for example, aspirated material from sites of plaque rupture in myocardial infarction often contains NETs. NETs thus connect to the concept of "atherothrombosis," where an inflamed, NET-rich plaque is more likely to trigger an occlusive clot. From a remodeling perspective, NET enzymes also stimulate macrophages and endothelial cells to produce pro-inflammatory cytokines (Tang *et al*., 2024), sustaining the cycle of inflammation and hindering resolution of the plaque. In diabetes-accelerated atherosclerosis, NETosis is often increased, and diabetic mice show larger atherosclerotic lesions partly due to NET-mediated inflammation (Cao *et al*., 2024). Therefore, NETs in the vascular system exemplify how innate immune effectors can drive both acute events (thrombosis) and chronic remodeling (plaque growth and instability).

Other Pathophysiological Contexts

Beyond the reproductive, pulmonary, and vascular systems, NETs influence a variety of other pathological contexts. In autoimmune and inflammatory diseases, NETs are heavily implicated in the pathogenesis of systemic

autoimmune disorders. In diseases like systemic lupus erythematosus (SLE) and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, NETs serve as a source of autoantigens and inflammatory stimuli. Excessive NET accumulation in tissues can lead to exposure of nuclear antigens (DNA, histones) that drive autoantibody production. Evidence suggests that in such conditions, NETs act as autoantigens, triggering the production of anti-DNA and anti-histone antibodies and causing immune-complex deposition (Wang *et al*., 2024a). For instance, in the kidneys of patients with lupus nephritis, immunofluorescence often shows extracellular DNA and neutrophil enzymes (NETs) depositing in glomeruli, coinciding with sites of immune complex injury. NET components (like H3Cit and LL37) have been found in these immune complexes, implicating NETs in tissue damage. Furthermore, impaired clearance of NETs (due to deficiencies in DNases or complement regulators) is linked to autoimmune pathology – SLE patients frequently have a reduced ability to degrade NETs, allowing them to persist and fuel inflammation. NETs can also directly injure tissues in autoimmunity: NET histones are cytotoxic and can kill endothelial or epithelial cells, contributing to vasculitis and organ damage (Wang *et al*., 2024a). In rheumatoid arthritis, neutrophils in the synovial fluid release NETs that contain citrullinated proteins, which may drive anti-citrullinated protein antibody (ACPA) production and joint inflammation. Thus, morphologically, many autoimmune lesions show signs of NETosis – e.g. fibrillary DNA in inflamed synovium or vessel walls – and these structures help propagate chronic inflammation. NETs also promote sterile inflammation in conditions like gout (neutrophils cast NETs in response to urate crystals) and pancreatitis, linking innate immune responses to tissue injury in the absence of infection.

In cancer, NETs have garnered attention as facilitators of cancer progression and metastasis. Tumors often induce a systemic pro-NETotic state (through granulocyte colony-stimulating factor and other cytokines). In the context of cancer, NETs create a pro-tumorigenic microenvironment. Morphologically, NETs have been observed within tumor stroma and especially at the invasive front of tumors, where they may aid tumor cell migration. For example, in breast cancer and ovarian cancer, researchers have found NET structures in histological sections of tumor tissue, sometimes in association with clusters of tumor cells (Morawiec *et al*., 2025). These NETs can act as physical snares that capture circulating tumor cells, helping them establish metastases at distant sites (Wang *et al*., 2024a). NETs also carry proteases like NE that can degrade the extracellular matrix and promote tumor invasion. In addition, NETs sequester and activate growth factors – for instance, NET elastase can cleave and activate TGF-b or IL-8, which then support tumor growth and angiogenesis (Morawiec *et al*., 2025). A notable role of NETs is in cancer-associated thrombosis: cancer patients often have heightened NET levels, and NETs form a scaffold for tumor cell-platelet clots, contributing to the high incidence of venous thrombosis in cancer (Wang *et al*., 2024a). Clinically, high levels of NET markers (like MPO-DNA complexes) have been correlated with poor prognosis in cancer patients (Taifour *et al*., 2023). NETs can enable immune evasion by shielding tumor cells from cytotoxic lymphocytes or by inducing an immunosuppressive milieu (for example, NETs can induce death of T cells and promote M2 macrophage polarization). Thus, in cancer pathology, NETs represent a bridge between inflammation and malignancy – their presence in tissues often signals aggressive disease and remodeling of tissue architecture to favor tumor spread (such as increased matrix degradation and formation of metastatic niches).

CONCLUSION

Neutrophil extracellular traps have emerged as critical mediators at the interface of immunity, tissue homeostasis, and pathology. From a morphological standpoint, NETs are defined by extracellular chromatin fibers studded with neutrophil-derived proteins – a structure exquisitely suited to ensnare microbes, but equally capable of ensnaring host tissues in collateral damage. We have discussed how NETs are identified histologically and their ultrastructural makeup, and then examined their roles across various organ systems. In reproductive tissues, NETs contribute to conditions like preeclampsia and endometriosis, where their presence heralds inflammation-driven tissue injury and remodeling. In the lungs, NETs can both save and suffocate – they trap pathogens y*et al*so damage alveolar-capillary barriers and instigate fibrosis. In the vasculature, NETs create a physical and biochemical scaffold for thrombosis and accelerate atherogenic processes. Beyond these, NETs serve as agents of autoimmune activation and tumor progression, indicating their far-reaching impact on human disease. A unifying theme is that NETs contribute to tissue remodeling, whether it is placental villous destruction, airway wall thickening, capillary obliteration, or plaque destabilization, the enzymes and oxidants delivered by NETs, along with their pro-inflammatory DNA-protein complexes, drive changes in tissue structure and function.

From a clinical perspective, recognizing NETs' morphological signatures in diseased tissue has important implications. It enables pathologists to identify NET-driven injury (for example, staining for citrullinated histone H3 in a biopsy can reveal occult NETosis). It also opens avenues for therapy: drugs that target NET formation (PAD4 inhibitors, NADPH oxidase inhibitors) or that enhance NET

clearance (like DNase) are being investigated to treat diseases ranging from ARDS to lupus. The challenge moving forward is to selectively inhibit the harmful effects of NETs while preserving their antimicrobial benefit. Ongoing research aims to unravel the triggers and regulators of NETosis in different tissues – why, for instance, the placenta in preeclampsia becomes a nidus of NET release, or how tumors co-opt neutrophils to form NETs that aid metastasis. As our understanding deepens, it is conceivable that NET-oriented diagnostics and therapeutics will become part of routine care (e.g. measuring NET biomarkers to predict disease flares, or using NET inhibitors to prevent organ damage). In conclusion, NETs are a striking example of the body's own defenses turning into structural mediators of disease. By appreciating their morphological signatures, from the ultra-structural webs visible on electron micrographs to the histological patterns in patient tissues, scientists and clinicians can better grasp how innate immunity shapes pathology, especially in reproductive health, pulmonary disease, vascular disorders, and beyond. This knowledge ultimately guides us toward interventions that quell the destructive potential of NETs while harnessing their protective power.

LEVIMAN, B.; MUÑOZ-CARO, T.; PRADO-SANHUEZA, A.; RIVERA-CONCHA, R. & ZAMBRANO, F. Firmas morfológicas de las trampas extracelulares de neutrófilos: desde la organización ultraestructural hasta la remodelación tisular y los contextos fisiopatológicos. *Int. J. Morphol., 43(5)*:1603-1611, 2025.

RESUMEN: Las trampas extracelulares de neutrófilos (NETs, por sus siglas en inglés) son redes similares a telarañas compuestas por fibras de cromatina descondensada decoradas con histonas y proteínas granulares neutrofílicas, que los neutrófilos liberan como parte de la respuesta inmune innata. Estas estructuras, observadas por primera vez mediante microscopía electrónica de alta resolución como fibras de ADN lisas, son fundamentales para inmovilizar patógenos. Sin embargo, la formación excesiva de NETs es un arma de doble filo. Por un lado, las NETs contribuyen a la defensa del hospedador; por otro, su acumulación puede causar oclusión vascular, citotoxicidad hacia las células del propio organismo e inflamación persistente. Esta revisión científica ofrece una perspectiva histológica y patológica integral sobre las NETs, desde su organización ultraestructural hasta sus funciones en la remodelación tisular en diversos sistemas orgánicos. Se pone especial énfasis en los tejidos reproductivos, donde las NETs se han implicado en condiciones que van desde la infertilidad hasta complicaciones del embarazo. Asimismo, se explora la patología asociada a NETs en enfermedades pulmonares (por ejemplo, síndrome de dificultad respiratoria aguda y enfermedades crónicas de las vías respiratorias), en el sistema vascular (aterotrombosis e inmunotrombosis) y en otros contextos como enfermedades autoinmunes y cáncer. Se discute cómo se identifican las NETs en el tejido (por ejemplo, mediante ADN extracelular co-localizado con enzimas neutrofílicas), las firmas morfológicas que presentan (por ejemplo, redes fibrilares de cromatina o complejos agregados de ADN-proteína) y cómo estas estructuras impulsan el daño o la remodelación tisular. En conclusión, aunque las NETs son esenciales para atrapar microbios, su desregulación conduce a daño colateral en los tejidos. Comprender la morfología de las NETs in situ y sus consecuencias proporciona información clave sobre los mecanismos de enfermedad y revela posibles estrategias terapéuticas para mitigar la lesión tisular preservando al mismo tiempo la defensa del hospedador.

KEY WORDS: Trampas extracelulares de neutrófilos (NETs); Remodelación tisular; Fisiopatología.

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