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The Multifaceted Role of Neutrophil Extracellular Traps in Pancreatic Cancer: From Pathogenesis to Therapeutic Implications

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Abstract

Neutrophil Extracellular Traps (NETs) have emerged as central regulators of Pancreatic Ductal Adenocarcinoma (PDAC) progression, serving as a mechanistic nexus linking inflammation, fibrosis, immunosuppression, and thrombosis. In PDAC, NETs are hyperactivated through multiple pathways, including the CXCL8-CXCR2 axis and Reactive Oxygen Species (ROS) signaling. They actively promote tumor invasion, metastatic spread, and the formation of immunosuppressive and pro-thrombotic microenvironments. Key mechanisms involve NET-mediated exclusion of cytotoxic T cells, arginine depletion via associated Arginase-1 (ARG1), and provision of a scaffold for coagulation activation. This review aims to synthesize current evidence and propose the concept of a self-amplifying «NETs-CAF-Immune suppression» cycle that drives PDAC aggressiveness. We further highlight NETs as a promising therapeutic target, with interventions aimed at inhibiting NET formation or enhancing their clearance holding potential to simultaneously mitigate metastasis, overcome immunosuppression, and reduce thrombotic risk. The ultimate goal is to provide a framework for integrating NET-targeting strategies into combination therapies to improve outcomes for PDAC patients.

Keywords: Neutrophil extracellular traps; Pancreatic ductal adenocarcinoma; Tumor microenvironment; Immunosuppression; Cancer-associated thrombosis.

Introduction

Neutrophil Extracellular Traps (NETs) are web-like structures composed of decondensed chromatin (nuclear or mitochondrial DNA) decorated with histones, granular proteins such as Myeloperoxidase (MPO) and Neutrophil Elastase (NE), and cytosolic antimicrobial peptides [1,2]. Initially described as a host defense mechanism to ensnare and kill pathogens, NET formation (NETosis) is now recognized as a double-edged sword, playing significant roles in sterile inflammatory diseases, autoimmune disorders, and cancer [1,2]. In the context of oncology, NETs have emerged as critical modulators of the Tumor Microenvironment (TME), influencing cancer initiation, progression, metastasis, and associated complications such as thrombosis [1,3]. Among various malignancies, Pancreatic Ductal Adenocarcinoma (PDAC) stands out due to its exceptionally aggressive nature, characterized by a dense, fibroinflammatory stroma, early metastatic dissemination, and profound resistance to therapy. A growing body of evidence

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positions NETs as central players in orchestrating the hostile TME of PDAC, contributing to its dismal prognosis [4-6]. This review provides a comprehensive synthesis of the current knowledge on the biological characteristics of NETs, their intricate mechanisms of action within the PDAC ecosystem, their role in Cancer-Associated Thrombosis (CAT), and their emerging potential as prognostic biomarkers and therapeutic targets. Despite rapidly accumulating evidence implicating Neutrophil Extracellular Traps (NETs) in Pancreatic Ductal Adenocarcinoma (PDAC) progression, the field remains fragmented, with individual studies focusing on isolated aspects such as thrombosis, immune suppression, or metastasis. A unified framework integrating NET induction, molecular composition, and downstream pathological consequences is still lacking. Moreover, whether NETs function as passive byproducts of inflammation or as active drivers of tumor evolution remains an open and clinically relevant question. In this review, we synthesize current mechanistic and clinical evidence to delineate the multifaceted roles of NETs in PDAC and propose conceptual models that may guide future translational investigations (Figure 1).

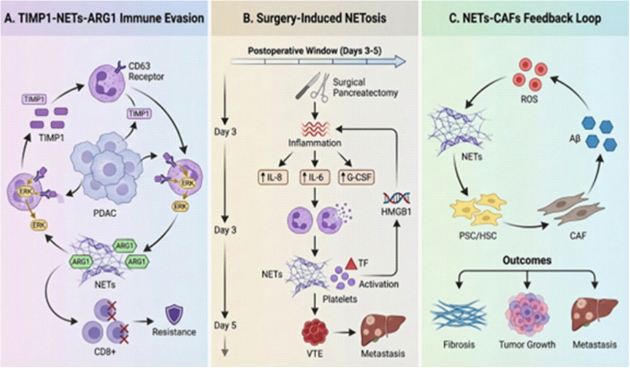

Figure 1: Schematic illustration of three interconnected mechanisms by which Neutrophil Extracellular traps (NETs) promote Pancreatic Ductal Adenocarcinoma (PDAC) progression. **(A)** Tumor-derived TIMP1 binds to the CD63 receptor on neutrophils and activates ERK signaling, inducing PAD4-dependent NET formation. NET-associated arginase 1 (ARG1) generates a localized arginine-depleted microenvironment that suppresses CD8$^+$ T cell proliferation and effector function, thereby promoting immune evasion and resistance to immune checkpoint blockade. **(B)** Surgical pancreatectomy induces a systemic inflammatory response characterized by elevated IL-8, IL-6, and G-CSF during the postoperative window (days 3–5), leading to widespread NETosis. Released NETs activate platelets and Tissue Factor (TF), increasing the risk of venous thromboembolism (VTE), while NET-associated HMGB1 contributes to the establishment of a pro-metastatic niche in distant organs such as the liver. **(C)** NETs establish a positive feedback loop with Cancer-Associated Fibroblasts (CAFs). NET-derived DNA activates pancreatic stellate cells (PSCs) or Hepatic Stellate Cells (HSCs), promoting their differentiation into CAFs. Activated CAFs secrete Amyloid Beta (Aβ), which enhances Reactive Oxygen Species (ROS) production and further stimulates NET formation, collectively driving stromal fibrosis, tumor growth, and metastatic dissemination.

Mechanisms of NET formation and induction in pancreatic cancer

NETosis is an active, regulated form of cell death distinct from apoptosis and necrosis. It can be triggered by a diverse array of stimuli, including pathogens, inflammatory cytokines, immune complexes, and, notably, cancer cells [1]. The process involves chromatin decondensation, which is critically dependent on the enzyme Peptidylarginine Deiminase 4 (PAD4). PAD4 catalyzes the citrullination of histones (converting arginine to citrulline), neutralizing their positive charge and weakening their binding to negatively charged DNA, thereby facilitating chromatin unraveling [7,8]. Concurrently, the granules rupture, releasing their contents, and the nuclear and granular membranes disintegrate. Finally, the cell membrane ruptures, expelling the DNA-protein meshwork into the extracellular space [2]. Autophagy has also been implicated as a key pathway for NET formation, particularly in response to certain stimuli [9].

In PDAC, the TME is replete with factors that potently induce NETosis. Pancreatic cancer cells themselves are a major source of NET-inducing signals. They secrete a plethora of chemokines and cytokines that recruit and activate neutrophils. A key mediator is interleukin-8 (CXCL8), which is upregulated in PDAC cells and can be further induced by chemotherapy like gemcitabine [10]. IL-8 signals through the CXCR1/2 receptors on neutrophils to drive NET formation, a process termed «chemoNETosis» that contributes to chemoresistance [10]. Similarly, cancer cell-derived CXCL1 is a potent neutrophil chemoattractant, and its secretion is significantly amplified in PDAC cells with loss of the tumor suppressor KDM6A, leading to increased Tumor-Associated Neutrophils (TANs) and NETs [11].

Beyond chemokines, other tumor-derived proteins directly trigger NETosis. Tissue inhibitor of Metalloproteinases-1 (TIMP1), often associated with poor prognosis, has been shown to directly induce NET formation in primary human neutrophils via interaction with its receptor CD63 and subsequent activation of the ERK signaling pathway [12]. The receptor tyrosine kinase DDR1, activated by collagen in the dense PDAC stroma, drives a signaling cascade (DDR1/PKCθ/SYK/NF-κB) that results in CXCL5 production, neutrophil recruitment, and NET formation [13]. Furthermore, cancer cell-derived Large Extracellular Vesicles (lEVs) deliver the CYBA protein to neutrophils, leading to a rapid increase in intracellular Reactive Oxygen Species (ROS) and subsequent NETosis via the CYBA-ROS-citH3 pathway [14].

The surgical intervention itself, pancreatectomy, is a potent inducer of NETs. The inflammatory response to surgery leads to a postoperative surge in NET markers (cell-free DNA and citrullinated histone H3) in plasma, peaking around days 3-4 [15]. This increase is driven by elevated levels of NET-inducing cytokines such as IL-8, IL-6, and Granulocyte Colony-Stimulating Factor (G-CSF). Notably, robotic (minimally invasive) pancreatectomy was associated with a reduction in postoperative NETs compared to the open approach, and complications like pancreatic leak further exacerbated NET formation [15]. This surgery-induced NETosis is believed to create a pro-metastatic environment, potentially contributing to postoperative recurrence [15,16].

Other components of the TME also contribute. Cancer-Associated Fibroblasts (CAFs) have been shown to induce NET formation both within the tumor and systemically. This process is driven by CAF-derived Amyloid β via a ROS-mediated pathway [17]. Additionally, the Receptor for Advanced Glycation End products (RAGE) enhances autophagy, which in turn promotes NET formation in the setting of PDA [9]. Platelets, often activated in cancer, can prime neutrophils and enhance NET release in response to tumor signals [18]. This complex network of inducers ensures a sustained presence of NETs within the PDAC TME.

However, it should be noted that most studies linking PDAC-derived factors to NETosis rely on correlative clinical data or in vitro stimulation assays. Direct in vivo evidence demonstrating that specific tumor-derived mediators are both necessary and sufficient to drive NET formation remains limited. In addition, the relative contribution of tumor-intrinsic signals versus systemic inflammatory cues, particularly in advanced-stage disease, has not been fully disentangled.

Pro-tumorigenic functions of NETs in pancreatic cancer progression and metastasis

NETs are not inert structures; they actively remodel the TME to foster tumor growth, invasion, and dissemination through multiple direct and indirect mechanisms.

Direct effects on cancer cells: Promoting invasion and EMT

NETs directly interact with pancreatic cancer cells to enhance their aggressive phenotype. Exposure of PDAC cells to NETs or NET components induces Epithelial-to-Mesenchymal Transition (EMT), a key program for cellular invasion and metastasis. This is characterized by loss of epithelial markers (e.g., E-cadherin) and gain of mesenchymal markers (e.g., vimentin, N-cadherin) [16,19]. NETs promote cancer cell migration and invasion in vitro, and this effect is mediated through specific signaling pathways. One major pathway involves the High-Mobility Group Box 1 (HMGB1) protein, a component of NETs. HMGB1 released from NETs can potentiate the malignancy of cancer cells [16]. Another critical pathway is the IL-1β/EGFR/ERK axis. NETs stimulate the secretion of IL-1β, which in turn activates the Epidermal Growth Factor Receptor (EGFR) and downstream ERK signaling in cancer cells, driving EMT, migration, and invasion [19]. Furthermore, NETs can activate a CCDC25-ITGB1-ILK (integrin-linked kinase) signaling complex in PDAC cells upon physical interaction, stimulating cytoskeletal dynamics, EMT, and invasive capacity [20].

Remodeling the tumor microenvironment and stroma

The dense, fibrotic stroma of PDAC is a major barrier to drug delivery and a facilitator of tumor progression. NETs actively participate in stromal activation. DNA released from NETs has been shown to activate Pancreatic Stellate Cells (PSCs), the principal source of Cancer-Associated Fibroblasts (CAFs) and Extracellular Matrix (ECM) deposition [21]. In murine models, deficiency in Padi4 (and thus impaired NET formation) led to decreased pancreatic stromal activation, reduced tumor growth, and improved survival [21]. In the context of liver metastasis, NETs promote the accumulation and activation of CAFs in metastatic foci. NETs enhance the migration of hepatic stellate cells (liver-resident fibroblast precursors) in vitro, and inhibition of NETs with DNase I reduces CAF accumulation and liver micrometastasis in vivo [22]. This suggests NETs help create a supportive «soil» in distant organs for metastatic «seeds» to thrive. Emerging evidence supports the existence of a self-sustaining NETs–CAF positive feedback loop that perpetuates fibrosis and metastatic niche formation in PDAC (Figure 2C). The proposed NETs–CAF positive feedback loop provides an attractive conceptual framework linking inflammation, fibrosis, and tumor progression. Nevertheless, most supporting evidence derives from preclinical models, and its spatial and temporal dynamics in human PDAC remain poorly defined. Whether NET-driven stromal remodeling precedes tumor invasion or predominantly reinforces established metastatic niches warrants further investigation.

Facilitating metastatic spread

NETs contribute to multiple steps of the metastatic cascade. They can degrade the extracellular matrix via associated proteases like MMP-9, facilitating local invasion and intravasation of cancer cells [2]. Within the circulation, NETs may physically entrap Circulating Tumor Cells (CTCs), potentially protecting them from shear stress and immune surveillance while also concentrating pro-metastatic factors around them [2]. At the site of a distant organ (e.g., liver or lung), NETs play a crucial role in promoting extravasation and colonization. In experimental models of inflammation-associated liver metastasis, NETs were observed around metastatic tumors and were found to enhance the extravasation of cancer cells [16]. The formation of a pre-metastatic niche is also influenced by NETs. In pre-metastatic liver biopsies from PDAC patients, enrichment of NETs was a distinguishing feature of patients who later developed liver metastasis [23]. Furthermore, tumor-secreted mesothelin reprograms macrophages to secrete S100A9, which in turn recruits neutrophils to the lungs and stimulates NET formation, thereby supporting pulmonary metastasis [24,25].

Impairing anti-tumor immunity & driving immunosuppression

One of the most significant roles of NETs in PDAC is the establishment of an immunosuppressive TME. PDAC is notoriously a «cold» tumor, resistant to immunotherapies like checkpoint blockade. NETs contribute to this resistance through several mechanisms. They can directly impair the function of cytotoxic T cells and Natural Killer (NK) cells [3]. NETs have been shown to exclude CD8+ T cells from the tumor parenchyma, creating an immune-privileged zone for cancer cells [26]. This exclusion is mediated, in part, by IL-17, which recruits neutrophils and triggers NET formation [26].

NETs also modulate the phenotype and function of other innate immune cells, particularly macrophages. In PDAC, NETs suppress the recruitment of macrophages with an anti-tumor (M1-like) phenotype. Depletion of NETs (via DNase I or PAD4 knockout) in murine models resulted in an increase in total macrophages (F4/80+) within the TME, with a shift towards a more stimulatory phenotype (increased CD80, decreased protumor marker CD206) [27]. This suggests NETs actively maintain a macrophage population that is ineffective at mounting an anti-tumor response. Moreover, NETs create a metabolic barrier to T cell function. In human PDAC, NET-associated Arginase 1 (ARG1) is cleaved and activated by cathepsin S, creating a microdomain of arginine depletion that suppresses T lymphocyte proliferation. Neutralizing ARG1 with a specific monoclonal antibody restored T cell function and enhanced the efficacy of checkpoint inhibitors in preclinical models [28].

NETs further contribute to an immunosuppressive milieu by promoting the recruitment and function of Myeloid-Derived Suppressor Cells (MDSCs). Surgery- or chemotherapy-induced gut dysbiosis and barrier dysfunction can lead to bacterial translocation, triggering the formation of immunothrombosis (composed of NETs and platelets) in the liver sinusoids. Alarmins like HMGB1 and S100A8/A9 released from these structures recruit MDSCs, creating a systemic immunosuppressive state [29]. Intra-tumoral administration of CHST15 siRNA, which remodels stroma and diminishes NETs, was shown to reduce MDSCs both locally and in tumor-draining lymph nodes, subsequently enhancing tumor-infiltrating T cells [30]. Tumor-derived TIMP1 has emerged as a potent inducer of NET formation, linking oncogenic signaling to metabolic immune suppression through NET-associated ARG1 (Figure 2A). While NET-associated ARG1 has been proposed as a major mediator of T cell dysfunction, it remains unclear whether ARG1 alone is sufficient to account for the profound immune suppression observed in PDAC. NETs are complex structures enriched in proteases, histones, and oxidized DNA, each of which may independently impair T cell activation. Dissecting the relative contribution of ARG1-dependent metabolic deprivation versus ARG1-independent mechanisms will be critical for the rational design of NET-targeted immunotherapeutic strategies.

NETs and Cancer-Associated Thrombosis (CAT) in pancreatic cancer

Patients with PDAC have one of the highest risks of Venous Thromboembolism (VTE) among all cancers, a major cause of morbidity and mortality [31,32]. NETs are now established as a critical driver of this hypercoagulable state, forming a vicious cycle with tumor progression [33].

Mechanisms of NET-Mediated hypercoagulability

NETs provide a potent prothrombotic scaffold. The extruded DNA and histones possess strong positive charges that can directly activate platelets and the contact pathway of coagulation (via factor XII) [34]. Histones are cytotoxic to endothelial cells, causing damage and exposure of subendothelial procoagulant tissue [2]. NET components also display Phosphatidylserine (PS) on their surface, providing a catalytic surface for the assembly of tenase and prothrombinase complexes, dramatically accelerating thrombin generation [35].

NETs interact synergistically with other prothrombotic factors in PDAC. They can bind to and concentrate Tissue Factor (TF), the primary initiator of coagulation in vivo. Tumor-derived, TF-positive Microparticles (MPs) adhere to NETs at the site of thrombosis, and TF carried by these MPs is essential for promoting deep vein thrombosis in mouse models [36]. NETs also stimulate platelet activation and aggregation. The DNA and histones within NETs, along with RAGE signaling, are necessary for inducing NET-associated platelet aggregation [37]. This activation leads to further release of procoagulant factors and stabilization of the thrombus.

Clinical evidence strongly supports this mechanistic link. Patients with pancreatic (and lung) cancer who experience VTE have significantly higher plasma levels of the NET biomarker citrullinated Histone H3 (H3Cit) compared to those without VTE or patients with other cancer types [38]. In mouse models bearing human pancreatic tumors, thrombi from tumor-bearing mice contained increased levels of neutrophil markers (Ly6G), H3Cit, and cell-free DNA. Importantly, either neutrophil depletion or administration of DNase I to degrade NETs reduced thrombus size specifically in tumor-bearing mice, confirming the causal role of NETs in cancer-associated thrombosis [38,39].

The vicious cycle: Thrombosis fuels cancer progression

The relationship between NETs, thrombosis, and cancer is bidirectional and self-reinforcing. The proinflammatory and procoagulant environment of the growing tumor induces NETosis, which promotes thrombosis. Conversely, thrombi and the associated inflammatory response can further stimulate NET release and create a niche that supports tumor cell survival and proliferation. For instance, platelets activated within a thrombus can release growth factors that stimulate cancer cells. This creates a «vicious cycle» where NET formation contributes to both PDAC progression and the accompanying hypercoagulability, each exacerbating the other [33,40]. Postoperative systemic NETosis represents a critical yet underappreciated driver of both venous thromboembolism and early metastatic relapse following pancreatectomy (Figure 2B). Although accumulating clinical data support a strong association between NET biomarkers and cancer-associated thrombosis, causality remains difficult to establish in patients. Importantly, whether targeting NETs can effectively reduce thrombotic risk without compromising host defense or postoperative wound healing has not been systematically evaluated. These unresolved issues underscore the need for carefully designed perioperative clinical trials incorporating NET-specific biomarkers.

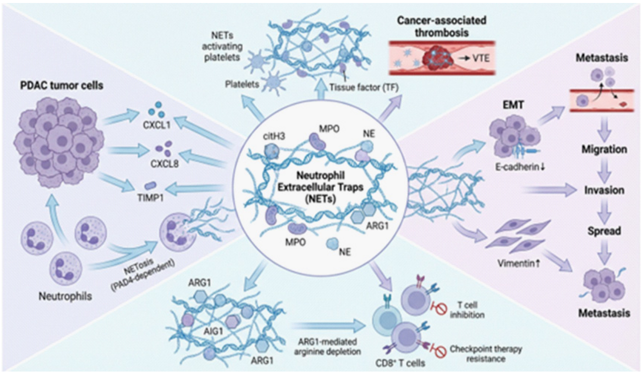

Figure 2: Integrated overview of the multifaceted functions of Neutrophil Extracellular Traps (NETs) within the Pancreatic Ductal Adenocarcinoma (PDAC) microenvironment. PDAC tumor cells secrete chemokines and cytokines, including CXCL1, CXCL8 (IL-8), and TIMP1, which recruit and activate neutrophils to undergo PAD4-dependent NETosis. NETs consist of extracellular DNA decorated with Citrullinated Histone H3 (citH3), Myeloperoxidase (MPO), Neutrophil Elastase (NE), and Arginase 1 (ARG1). NETs promote cancer-associated thrombosis by activating platelets and concentrating Tissue Factor (TF), facilitating venous thromboembolism. Concurrently, NETs drive Epithelial–Mesenchymal Transition (EMT) in tumor cells, characterized by downregulation of E-cadherin and upregulation of vimentin, thereby enhancing tumor cell migration, invasion, and metastatic spread. In addition, NET-associated ARG1 induces arginine depletion, leading to $CD8^+$ T cell dysfunction and resistance to immune checkpoint therapy. Collectively, NETs act as central regulators linking inflammation, immune suppression, thrombosis, and metastasis in PDAC.

NETs as prognostic biomarkers in pancreatic cancer

Given their central role in tumor biology, NETs and related signatures have significant prognostic value in PDAC.

Histological and circulating NET markers

The presence of tumor-infiltrating NETs, as detected by immunohistochemistry for citrullinated Histone H3 (citH3) in combination with neutrophil markers (CD15 or MPO), is a strong independent predictor of poor survival. In resected PDAC patients, high levels of intratumoral NETs were significantly associated with worse Overall Survival (OS) and Recurrence-Free Survival (RFS) [41]. Incorporating NET status into the traditional TNM staging system improved the predictive accuracy for patient survival [41]. Similarly, in Pancreatic Neuroendocrine Tumors (pNETs), the presence of neutrophil extracellular traps was an independent prognostic factor for worse recurrence-free survival [42].

Circulating NET markers also hold prognostic potential. Elevated plasma levels of NET components (e.g., MPO-DNA complexes, cell-free DNA, citH3) correlate with disease stage, metastatic burden, and poor outcomes [23,38]. A combination of plasma TIMP1 and NET markers (DNA-bound MPO) with the standard biomarker CA19-9 allowed for improved identification of prognostically distinct PDAC patient subgroups [12]. Furthermore, a postoperative surge in NET markers is associated with surgical complications like pancreatic leak and may predict early recurrence [15].

Gene expression signatures

Bioinformatics analyses of NET-related genes have led to the development of prognostic signatures. Consensus clustering of NETosis-related genes in PDAC cohorts has identified subtypes with distinct survival outcomes. Signatures enriched in integrin-actin cytoskeleton and EMT signaling are associated with very poor survival, while those related to cell death signaling correlate with better outcomes [20]. Other studies have constructed multi-gene risk scoring models based on NETosis-related genes (e.g., a 6-gene model) that effectively stratify patients into high- and low-risk groups with significant differences in survival [43]. Multi-omics integration, including single-cell RNA-seq, has further refined prognostic models, identifying factors like TLR2 expression as potent indicators of immune context and survival [44].

Targeting NETs: A novel therapeutic strategy for pancreatic cancer

The detrimental roles of NETs in PDAC progression, metastasis, thrombosis, and immunosuppression make them an attractive therapeutic target. Several strategies to inhibit NET formation or degrade existing NETs are under investigation.

Inhibiting NET formation

PAD4 inhibitors: Since histone citrullination by PAD4 is crucial for NETosis, pharmacological inhibition of PAD4 is a logical approach. Chloroquine (CQ) and its derivative Hydroxychloroquine (HCQ), FDA-approved anti-malarial drugs, have been identified as NET inhibitors. Recent mechanistic studies show that CQ/HCQ directly inhibit PAD4 enzyme activity, independent of their known autophagy-inhibitory effects [7]. In preclinical PDAC models, HCQ reduced metastatic tumor burden and prolonged survival, partly through inhibition of Myeloperoxidase (MPO) function [8]. More importantly, HCQ treatment reduced hypercoagulability, platelet aggregation, and circulating tissue factor in murine models, and correlative data from a clinical trial suggested a reduction in perioperative VTE rates [37].

Targeting inducing pathways: Blocking the upstream signals that drive NETosis is another strategy. Neutralizing antibodies against CXCL1/CXCR2 or IL-8/CXCR1/2 axis can inhibit neutrophil recruitment and NET formation induced by tumor cells [10,11]. The CXCR1/2 inhibitor navarixin, when combined with gemcitabine, suppressed chemoNETosis and restored chemosensitivity in PDAC models [10]. Inhibition of DDR1 or TIMP1 signaling could also indirectly reduce NET generation [12,13].

Other inhibitors: Metformin, a common diabetes drug, has been shown to inhibit obesity-promoted pancreatic carcinogenesis by suppressing NET formation [45]. The Src kinase inhibitor dasatinib reduces NETosis by inhibiting the RAF/MEK/ERK pathway and intracellular ROS production, showing efficacy in models of acute inflammatory injury [46]. Targeting CD53 with a neutralizing antibody inhibited NET formation via the PI3K/AKT pathway and alleviated injury in acute pancreatitis models [47].

Degrading existing NETs

DNase I: This enzyme degrades the DNA backbone of NETs, dismantling their structure. DNase I treatment has shown efficacy in multiple preclinical models: it reduced thrombus size in tumor-bearing mice [38], suppressed liver metastasis and micrometastasis [22], and improved vascular perfusion in distal organs affected by tumor-induced NET accumulation [48]. It also shifted the macrophage population in the TME towards a more anti-tumor phenotype [27]. However, systemic DNase I lacks targeting specificity. Innovative delivery systems, such as biomimetic cellular nanovesicles engineered to target inflamed lungs (e.g., for acute lung injury), are being developed to enhance precision [49].

Heparin and histone-binding agents: Unfractionated heparin can bind to histones, neutralizing their cytotoxic and procoagulant effects. It has been shown to inhibit NET-promoted cancer cell migration, invasion, and angiogenesis [40]. Other histone-binding molecules like polysialic acid show similar potential.

Combination therapies

The most promising applications of NET-targeting agents may be in combination with existing therapies.

With chemotherapy: Inhibiting NETs can overcome chemoresistance. As described, blocking the IL-8/CXCR1/2 axis or using PAD4 inhibitors enhances the efficacy of gemcitabine-based regimens [8,10]. The traditional Chinese medicine formula Pi Ji Pills was found to enhance gemcitabine efficacy by dual mechanisms involving PI3K/AKT pathway blockade and NETs inhibition [50].

With immunotherapy: NETs are a major barrier to immunotherapy in PDAC. Strategies that degrade NETs (DNase I) or inhibit their formation (PAD4 inhibitors, IL-17 blockade) have been shown to synergize with immune checkpoint inhibitors (anti-PD-1, anti-CTLA-4). This combination improves CD8+ T cell infiltration and function, leading to better tumor control [26,28,51]. Exenatide, a GLP-1 agonist, was found to enhance anti-PD-1 therapy by attenuating NET formation through reduction of ROS in neutrophils [51].

With anticoagulation: Targeting NETs offers a potential avenue for safer antithrombotic prophylaxis in cancer patients, as it may disrupt cancer-promoting thrombosis without causing significant bleeding risks associated with conventional anticoagulants. The use of HCQ for this purpose is being explored [37]. Collectively, current evidence positions NETs as central regulators at the intersection of inflammation, immunity, thrombosis, and stromal remodeling in PDAC. However, a major conceptual challenge lies in distinguishing whether NETs serve as initiating drivers of tumor progression or as amplifiers of an already established malignant ecosystem. Resolving this question will be essential for determining the optimal timing and patient population for NET-targeted interventions.

Conclusion

Neutrophil extracellular traps have evolved from being viewed as a simple antimicrobial defense to recognized as master regulators of the tumor microenvironment in pancreatic ductal adenocarcinoma. Through a complex interplay with cancer cells, stromal components, and immune cells, NETs drive key hallmarks of PDAC: they promote cancer cell invasion and EMT, activate stromal fibroblasts, facilitate metastasis at multiple steps, and establish a profoundly immunosuppressive milieu. Furthermore, NETs are a primary mechanistic link between PDAC and its life-threatening complication, cancer-associated thrombosis, engaging in a vicious cycle that fuels both processes. The clinical relevance of NETs is underscored by their utility as independent prognostic biomarkers, detectable both within tumors and in circulation.

This comprehensive understanding has opened a new frontier in PDAC therapy. Targeting NETs—either by preventing their formation with PAD4 inhibitors like hydroxychloroquine, blocking key induction pathways (e.g., CXCR1/2), or degrading existing structures with DNase I—represents a promising strategy with multimodal benefits. These approaches hold potential not only to inhibit tumor growth and metastasis but also to alleviate hypercoagulability and, most importantly, to reverse immunosuppression and sensitize «cold» PDAC tumors to immunotherapy. While challenges remain, including optimizing delivery, identifying patient subsets most likely to benefit, and integrating NET-targeting agents into combination regimens, the evidence strongly supports the continued investigation of NETs as a pivotal therapeutic axis in the fight against this devastating disease. The journey from mechanistic insight to clinical translation for NET-targeted therapies is underway, offering a glimmer of hope in improving the outcomes for patients with pancreatic cancer. Future studies integrating spatial transcriptomics, single-cell profiling, and longitudinal clinical sampling will be instrumental in elucidating the dynamic roles of NETs during PDAC initiation, progression, and therapeutic response. Importantly, translating NET-targeted strategies into clinical benefit will require a nuanced understanding of their context-dependent functions, balancing anti-tumor efficacy with preservation of essential innate immune defenses.

Author declarations

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