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Research Progress on Neutrophil Extracellular Traps in Gastric Cancer Postprint

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Abstract

In recent years, neutrophil extracellular traps (NETs) have received increasing attention in cancer research, particularly regarding their mechanisms of action and clinical significance in gastric cancer. This article systematically and comprehensively explores the research advances of NETs in gastric cancer, including the mechanisms of NETs formation, their role in the gastric cancer microenvironment, and their impact on gastric cancer initiation, progression, and metastasis. By reviewing relevant literature, it summarizes the important role of NETs in gastric cancer immune evasion, inflammatory responses, and their interactions with tumor cells. This article demonstrates that during the initiation and progression of gastric cancer, NETs not only promote tumor cell proliferation and metastasis, but are also closely associated with poor prognosis in gastric cancer patients. Furthermore, NETs affect the therapeutic efficacy of gastric cancer by inducing an immunosuppressive environment and enhancing drug resistance in cancer cells. This article can serve as a valuable reference for the diagnosis and treatment of gastric cancer and provide insights for further in-depth research on NETs in gastric cancer.

Full Text

Review and Monograph: Research Progress of Neutrophil Extracellular Traps in Gastric Cancer

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Abstract

In recent years, neutrophil extracellular traps (NETs) have garnered increasing attention in cancer research, particularly regarding their mechanisms and clinical significance in gastric cancer. This paper systematically and comprehensively explores the research progress of NETs in gastric cancer, including the formation mechanisms of NETs, their role in the gastric cancer microenvironment, and their impact on the occurrence, development, and metastasis of gastric cancer. By reviewing relevant literature, we summarize the crucial roles of NETs in gastric cancer immune evasion, inflammatory response, and interactions with other tumor cells. Our analysis indicates that NETs not only promote tumor cell proliferation and metastasis during gastric cancer progression but are also closely associated with poor prognosis in gastric cancer patients. Additionally, NETs affect treatment outcomes by inducing an immunosuppressive environment and enhancing cancer cell drug resistance. This review provides a reference for the diagnosis and treatment of gastric cancer and offers insights for further research on NETs in gastric cancer.

Keywords: Gastric cancer; Neutrophil extracellular traps; Gastric cancer metastasis; Mechanism of action; Review

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Gastric cancer (GC) ranks among the leading causes of cancer incidence and mortality worldwide, with over 968,000 new cases and more than 660,000 deaths reported in 2022 alone [1]. China accounts for 44% of the global GC burden [2]. Established risk factors include *Helicobacter pylori* infection, age, smoking, high salt intake, and low consumption of fruits and vegetables. With an estimated 50% of the global population infected with *H. pylori*, this represents a serious worldwide health challenge [3], and epidemiological studies consistently indicate that *H. pylori* infection will remain the primary risk factor for GC for decades to come [4].

Although substantial research has improved GC treatment and overall survival rates, cases with distant metastasis and drug resistance remain common. Consequently, a deeper understanding of GC progression mechanisms and identification of novel therapeutic targets are urgently needed. Recent studies increas-

ingly demonstrate that neutrophil extracellular traps (NETs) play important roles in GC development and progression [4-8]. Compared with traditional markers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), NETs exhibit higher sensitivity and specificity for GC diagnosis [8], suggesting their potential as novel biomarkers to significantly improve early diagnosis and prognostic assessment. As research into NETs' mechanisms in GC deepens, modulating or blocking NETs formation has emerged as a promising therapeutic strategy through pharmacological inhibition of neutrophil activation or degradation of NETs components. This review systematically examines NETs formation mechanisms in GC and their roles in tumor progression and therapy, aiming to provide a theoretical foundation for further research and therapeutic development.

1. Basic Structure and Formation Mechanisms of NETs

NETs represent a novel form of neutrophil death distinct from traditional apoptosis or necrosis, primarily functioning to prevent pathogen invasion. First observed by Takei et al. [9] using phorbol myristate acetate (PMA) stimulation, NETs are extruded from activated neutrophils into the extracellular space as three-dimensional mesh-like structures composed of decondensed chromatin and various granule proteins, including a DNA backbone and proteases such as matrix metalloproteinase-9 (MMP-9), neutrophil elastase (NE), cathepsin G (CG), and myeloperoxidase (MPO) [10]. Recent research confirms NETs generation in multiple tumor types, suggesting their involvement in tumor initiation and progression [11].

NETs formation occurs through two primary mechanisms: suicidal and non-suicidal NETosis (Figure 1 [Figure 1: see original paper]). In suicidal NETosis, PMA binding to its receptor triggers neutrophil membrane rupture, releasing decondensed chromatin and associated proteins. In contrast, non-suicidal NETosis preserves neutrophil viability and phagocytic function without cell lysis [12-13]. Additionally, mitochondria can trigger NETs formation [14]. Both pathways involve key steps with mitochondrial reactive oxygen species (ROS) and peptidylarginine deiminase 4 (PAD4). ROS and PAD4 can transform NETs from protective innate immune factors to destructive agents [15]. For instance, ROS facilitates NE and MPO translocation to the nucleus, promoting chromatin decondensation [16]. Li et al. [17] demonstrated that PAD4 plays a crucial regulatory role, as PAD4-deficient mice cannot produce NETs and are thus susceptible to bacterial infection. Appropriate PAD4 activation is essential for maintaining gastrointestinal homeostasis, while its dysregulation may promote inflammation and tissue damage [15].

NETs represent a double-edged sword. While they can form barriers that prevent lesion spread or isolate necrotic areas from healthy tissue, excessive formation or inadequate clearance may promote inflammation, autoimmune reactions, vascular disease, thrombosis, and ischemia-reperfusion injury, thereby facilitating cancer development [18]. Currently, NETs are most commonly detected

by fluorescence microscopy identifying specific markers such as citrullinated histone H3 (CitH3) or complexes of MPO, NE, and DNA (e.g., MPO-DNA, NE-DNA). These markers enable researchers to identify and quantify NETs formation. However, technological advances have introduced newer methods such as flow cytometry and mass spectrometry for more precise investigation of NETs formation mechanisms and their roles in various pathological states [19]. Furthermore, developing drugs that specifically regulate NETs formation and clearance has become a research hotspot, aiming to reduce their potential harm.

2. Role of NETs in Gastric Cancer Development and Immunotherapy

The link between cancer cells and NETs was first identified in Ewing' s sarcoma, where NETs correlated with poor prognosis [20]. Subsequent research demonstrates increased NETs formation in multiple malignancies, including gastric, liver, breast, colorectal, head and neck, and ovarian cancers [21-24]. Both in vivo and in vitro studies confirm significantly elevated NETs numbers and components—such as cell-free DNA (CFDNA), nucleosomes, histones, NE, CitH3, and MPO-DNA complexes—in gastric cancer tissues compared with normal tissues, with expression positively correlating with TNM stage [5-6,8,25]. Moreover, MPO-DNA or NE-DNA complexes appear more conducive to NETs formation than CFDNA alone [26].

In GC mouse models, high triggering receptor expressed on myeloid cell 1 (TREM1) expression closely correlates with NETs formation. Specifically, TREM1 deficiency ($TREM1^{-}/^{-}$) inhibits NETs formation, evidenced by reduced H3Cit expression and decreased serum dsDNA and MPO-DNA levels. Concurrently, TREM1 deficiency promotes pro-inflammatory M1 macrophage polarization while reducing pro-tumorigenic M2 polarization, thereby hindering tumor progression. Treatment with the NETs-degrading enzyme DNase-1 partially reverses tumor growth and NETs formation in $TREM1^{+}/^{+}$ mice, demonstrating NETs' important role in TREM1-mediated GC progression. These findings suggest TREM1 may promote GC development by inhibiting M1 polarization while facilitating NETs-mediated M2 polarization, revealing its potential as a tumor initiator [27].

Additionally, IL-8 and its receptors CXCR1 and CXCR2 show significantly elevated expression in GC mouse models. Treatment with DNase I or anti-CXCR2 antibodies markedly reduces CXCR1/2 and CitH3 colocalization, decreases NE-DNA levels, and delays tumor progression. These results indicate that the IL-8-CXCR1/2 axis in the GC microenvironment may accelerate tumor progression by promoting NETs formation. Conversely, high NETs expression upregulates transcription factor IIB-related factor 1 (BRF1) and cyclin p21/p27 expression in GC cells, further driving tumor progression [28]. Thus, the GC microenvironment promotes NETs formation, while high NETs expression reciprocally accelerates malignant GC development. Li et al. [29] validated this bidirectional mechanism using an LPS-induced NETs model and BALB/c nude mouse

subcutaneous tumor models, demonstrating that rapid GC cell proliferation creates a post-ischemia hypoxic microenvironment where high mobility group box 1 (HMGB1) translocates from nucleus to cytoplasm and promotes NETs formation through the TLR4/p38 MAPK signaling pathway in neutrophils. Furthermore, in GC patients undergoing radical surgery, low-density neutrophils isolated from peritoneal lavage fluid more readily form NETs that effectively capture GC cells and influence their behavior [30-31].

Collectively, current research demonstrates that NETs play crucial roles in GC progression through multiple signaling pathways and molecular mechanisms intimately intertwined with the gastric cancer microenvironment (Figure 2 [Figure 2: see original paper]). These findings provide novel therapeutic insights, suggesting that targeting NETs formation or related pathways may open new avenues for GC treatment.

Immune checkpoint inhibitors (ICIs) have achieved major advances in GC treatment. Primary clinical indicators for selecting suitable patients include PD-L1/PD-1 expression, microsatellite instability (MSI), mismatch repair (MMR) gene status, Epstein-Barr virus (EBV) positivity, and tumor mutation burden (TMB). Li et al. [32] identified seven NETs-related risk genes in GC and established a NETs scoring system. Their results showed that low NETs scores correlate with enhanced stem cell characteristics and lower differentiation levels, features typically associated with MSI-H, high TMB, and immune activity. High TMB usually accompanies more neoantigens, increasing T cell recognition of cancer cells and correlating with better ICI treatment outcomes. Further analysis revealed that GC patients with low NETs scores exhibit higher immunogenicity, suggesting greater potential for triggering effective immune responses and positive reactions to ICIs. Conversely, high NETs scores often indicate lower immunogenicity and potentially poorer ICI responses. Additionally, the signature gene C5AR1 plays a key role in promoting GC cell growth and metastasis and may be involved in NETs formation [33]. These findings emphasize NETs' important role in GC development and progression and suggest they may regulate patient responses to ICIs by influencing key indicators such as immunogenicity and TMB.

3. Role of NETs in Gastric Cancer Metastasis

NETs promote gastric cancer metastasis by capturing circulating tumor cells and serving as "carriers" and "armor" that facilitate transport and protect GC cells [5,25,34]. Epithelial-mesenchymal transition (EMT) is a critical prerequisite for cancer cell dissemination, with E-cadherin and vimentin as key EMT markers [35]. E-cadherin is a transmembrane glycoprotein mediating cell-cell adhesion and maintaining epithelial characteristics, while vimentin is highly expressed in mesenchymal cells and positively correlates with metastatic potential. Studies show that NETs-containing culture medium stimulates GC cells to suppress E-cadherin expression while enhancing vimentin expression, thereby promoting GC cell migration and invasion [25].

Furthermore, NETs promote metastasis by stimulating angiogenesis. Research demonstrates that NETs concentration-dependently stimulate high ANGPT2 expression in human umbilical vein endothelial cells (HUVECs), with maximal effect at 0.4 g/mL [36]. ANGPT2 plays an important role in angiogenesis and vascular stability; its high expression disrupts vascular integrity and promotes VEGF-driven vascular sprouting and chemotactic migration, thereby participating in GC metastasis. Moreover, high ANGPT2 expression correlates with advanced GC stage, poor survival prognosis, and tumor burden. Notably, patients with high ANGPT2 expression show lower tumor immune dysfunction and rejection scores, suggesting potential benefits from immunotherapy [36].

GC mouse models have further elucidated how NETs promote tumor growth and metastasis by activating specific signaling pathways. Under NETs stimulation, the NET-DNA receptor CCDC25 translocates from nucleus to cytoplasm in HUVECs, activating the AKT/mTOR signaling pathway to promote HUVEC proliferation, migration, and tube formation, ultimately driving tumor growth. Notably, CCDC25 knockout significantly inhibits NETs-mediated metastatic potential, demonstrating its key role in NETs-driven metastasis. Drug sensitivity analysis reveals that GC patients with low CCDC25 expression respond better to various chemotherapeutic agents and immune inhibitors, whereas those with high CCDC25 expression show significantly enhanced lung and liver metastasis [7,37]. Additionally, LPS-induced NETs mouse models show marked CD31 upregulation, further supporting that NETs accelerate tumor growth through angiogenesis rather than by directly increasing GC cell proliferation [29]. These findings indicate that NETs' role in GC progression extends beyond promoting tumor cell migration and invasion to include supporting overall tumor growth and metastasis through angiogenesis.

Postoperative abdominal infectious complications (AIC) influence GC cell behavior. Under these conditions, co-cultured GC cells show increased SMYD2 expression upon TGF-β stimulation, which positively correlates with NETs formation markers MPO-DNA and CitH3, as well as with the metastasis marker vimentin. Conversely, SMYD2 expression negatively correlates with E-cadherin expression, suggesting SMYD2 may promote EMT and cancer cell invasion by suppressing E-cadherin [34]. TGF-β induces LIF expression through Smad2/3 complex activation, promoting NETs formation [38], while NETs enhance SMYD2 ac4C modification and stability by increasing NAT10 mRNA and protein expression, thereby further augmenting GC cell migration and invasion [39]. These studies demonstrate that SMYD2 participates in NETs formation through multiple pathways in the GC microenvironment, and NETs reciprocally enhance SMYD2' s role in GC metastasis.

Growing evidence supports NETs' ability to influence tumor development by regulating RNA expression. A comprehensive analysis of differentially expressed genes in NETs-treated GC cells revealed that RNA interference against NEAT1 inhibits NETs-induced AGS cell invasion and metastasis [4]. Furthermore, NETs in GC promote tumor proliferation, adhesion, migration,

and invasion through multiple inflammatory signaling pathways including the IL-8-CXCR1/2 axis [28], platelet TLR4-ERK5 axis [43], and TLR4/9-COX2 axis [21]. NETs components also play critical roles in GC metastasis. For example, integrin-αv\$ 1$and MMP-9 capture and activate TGF-$\$, inducing EMT in cancer cells and promoting metastasis while also contributing to chemotherapy resistance [44]. Experimental evidence shows that NETs deficiency, PAD4 knockout, or treatment with DNase I or NE inhibitors significantly reduces spontaneous lung and liver metastasis in tumor-bearing mice [45]. This strongly indicates that NETs and their components promote metastasis through multiple pathways in the GC microenvironment, and that targeting NETs formation or function may be an effective strategy to hinder GC metastasis. Table 1 summarizes NETs formation and progression-related targets in GC.

4. NETs Involvement in GC-Associated Thrombosis

Hypercoagulability is a common complication in GC patients and a significant cause of mortality [46]. This prothrombotic state closely correlates with the procoagulant activity (PCA) exhibited by GC cells in their microenvironment, which activates the coagulation system through multiple pathways, promoting tumor growth and metastasis while increasing thromboembolic complications [47]. NETs play an important role in this process, particularly through their components' effects on the coagulation system. NETs-derived CFDNA directly promotes coagulation factor activation through the intrinsic pathway, forming blood clots. Additionally, NETs histones induce platelet and red blood cell activation, accelerating coagulation. This dual action facilitates both thrombus initiation and progression [5].

In GC patients, NETs and MPO-DNA released by neutrophils positively correlate with thrombin-antithrombin complex (TAT) and D-dimer levels [5], indicating that NETs formation closely associates with coagulation activation and may promote hypercoagulability. Moreover, NETs stimulate thrombin and fibrin generation in normal human plasma, and DNase I-mediated NETs degradation significantly prolongs fibrin formation time, confirming NETs' key role in GC-associated hypercoagulability [48]. In vitro studies by Li et al. [6] demonstrated that GC-NETs treatment of normal platelets or endothelial cells (ECs) significantly increases plasma fibrin formation and TAT complex levels, suggesting GC-induced NETs may elevate venous thromboembolism risk. Although NETs degradation reduces fibrin formation, some platelet adhesion persists even after DNase I treatment, implying that other NETs-secreted proteins such as histones and NE may also contribute to platelet hypercoagulability [6].

NETs induce phosphatidylserine (PS) exposure on platelet and HUVEC membranes. This negatively charged phospholipid exhibits procoagulant activity, providing a surface for coagulation factors and enhancing PCA. CitH3-DNA levels closely correlate with platelet and endothelial activation markers and may induce platelet network formation through p-selectin/PSGL-1 interactions [49].

In certain malignancies, NETs induce EC dysfunction and apoptosis, disrupting procoagulant-anticoagulant balance and promoting thrombosis [50]. In GC, NETs induce a procoagulant and pro-inflammatory phenotypic shift in ECs by downregulating tight junction proteins and upregulating functional tissue factor (TF) expression [6], thereby exacerbating coagulation risk. Additionally, *Fusobacterium nucleatum* may positively correlate with GC-NETs formation and increased platelet counts [51].

Despite numerous studies linking NETs to coagulation, most employ mouse models, and whether intact NETs directly activate the coagulation system remains controversial. Some research indicates that intact NETs may occlude small vessels, forming microthrombi lacking fibrin or von Willebrand factor [52], suggesting NETs may contribute to poor prognosis through mechanisms unrelated to coagulation, such as direct endothelial toxicity [49] or non-coagulant vascular occlusion [52]. These mechanisms may cause vascular dysfunction and local blood flow impairment, leading to adverse clinical outcomes even without obvious fibrin or von Willebrand factor involvement.

In summary, coagulation activation during GC progression represents a poor prognostic marker. Future research should further explore NETs markers' potential as reliable clinical prognostic tools and investigate their utility as novel therapeutic targets, particularly in advanced cancer patients.

5. Potential Therapeutic Value of NETs in Gastric Cancer

Drug resistance represents a major global concern in oncology, and NETs presence has been identified as both a partial cause of cancer resistance and an independent prognostic biomarker. DNase I is a potent inhibitor that reduces NETs formation by degrading DNA structures. Postoperative peritoneal lavage with 0.9% saline solution effectively inhibits peritoneal metastasis after radical GC surgery, likely by dramatically reducing intraperitoneal cancer cell numbers. However, extensive intraoperative lavage may also wash away substantial NETs, suggesting that clinical benefits may partially result from reduced peritoneal NETs. Adding DNase I to lavage fluid could further decrease NETs formation and potentially achieve similar clinical effects more efficiently, improving postoperative lavage efficacy while reducing peritoneal metastasis [53].

Salvia miltiorrhiza (Danshen) is a well-studied medicinal plant commonly used for advanced cancer patients with blood stasis syndrome. Research shows that diterpenoid tanshinones inhibit GC cell proliferation, induce apoptosis, and suppress tumor invasion and metastasis [54]. Active components such as salvianolic acid B (Sal B) and 15,16-dihydrotanshinone I (DHT I) significantly reduce CitH3 levels by inhibiting MPO and NADPH oxidase activity. This inhibition effectively prevents neutrophil migration to metastatic sites, reducing NETs formation and suppressing cancer cell dissemination [55]. Additionally, approaches including vitamin C [56], probiotic supplementation [57], *H. pylori* eradication [58], and NE or PAD4 inhibitors show promise in preventing NETs release and

potentially inhibiting GC progression. However, since NETs are essential components of innate immunity, inhibiting or disrupting their formation may impair immune function and increase infection risk—a significant cause of mortality in cancer patients. Therefore, achieving targeted DNase I delivery and controlled release for local NETs degradation is crucial [59]. In summary, targeted NETs inhibition offers new strategies and combination therapy options for GC prevention and treatment.

Despite multiple therapeutic options, cancer remains a leading cause of mortality. NETs not only eliminate pathogenic microorganisms but also actively participate in cancer development and progression. Through multiple mechanisms—including promoting tumor cell migration and invasion, enhancing local inflammatory responses, and facilitating thrombosis—NETs create a favorable environment for tumor development. This review summarizes NETs' roles and mechanisms in GC and explores therapeutic targets for inhibiting or degrading NETs overexpression, providing potential directions for novel anticancer therapies. However, since NETs are vital to innate immunity, developing treatments that accurately target NETs in gastric cancer without compromising normal immune function is essential. Future research should focus on elucidating NETs' specific mechanisms in GC and developing selective therapeutic strategies, representing an emerging hotspot in cancer therapy.

References

[1] BRAY F, LAUVERSANNE M, SUNG H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries[J]. CA Cancer J Clin, 2024, 74(3): 229-263. DOI: 10.3322/caac.21834.

[2] HE F F, WANG S M, ZHENG R S, et al. Trends of gastric cancer burdens attributable to risk factors in China from 2000 to 2050[J]. Lancet Reg Health West Pac, 2024, 44: 101003. DOI: 10.1016/j.lanwpc.2023.101003.

[3] BURUCOA C, AXON A. Epidemiology of *Helicobacter pylori* infection[J]. Helicobacter, 2017, 22(Suppl 1). DOI: 10.1111/hel.12403.

[4] LI C J, ZOU X M, CAI Q X, et al. Comprehensive expression profile analysis of neutrophil extracellular trap-affected genes in gastric cancer cells and the clinical significance of lncRNA NEAT1-related signaling[J]. Front Oncol, 2022, 12: 798531. DOI: 10.3389/fonc.2022.798531.

[5] YANG C F, SUN W Y, CUI W, et al. Procoagulant role of neutrophil extracellular traps in patients with gastric cancer[J]. Int J Clin Exp Pathol, 2015, 8(11): 14075-14086.

[6] LI J C, ZOU X M, YANG S F, et al. Neutrophil extracellular traps participate in the development of cancer-associated thrombosis in patients

with gastric cancer[J]. World J Gastroenterol, 2022, 28(26): 3132-3149. DOI: 10.3748/wjg.v28.i26.3132.

[7] YANG S F, SUN B S, LI J C, et al. Neutrophil extracellular traps promote angiogenesis in gastric cancer[J]. Cell Commun Signal, 2023, 21(1): 176. DOI: 10.1186/s12964-023-01196-z.

[8] ZHANG Y Y, HU Y Y, MA C, et al. Diagnostic, therapeutic predictive, and prognostic value of neutrophil extracellular traps in patients with gastric adenocarcinoma[J]. Front Oncol, 2020, 10: 1036. DOI: 10.3389/fonc.2020.01036.

[9] TAKEI H, ARAKI A, WATANABE H, et al. Rapid killing of human neutrophils by the potent activator phorbol 12-myristate 13-acetate (PMA) accompanied by changes different from typical apoptosis or necrosis[J]. J Leukoc Biol, 1996, 59(2): 229-240. DOI: 10.1002/jlb.59.2.229.

[10] JUNG H S, GU J, KIM J E, et al. Cancer cell-induced neutrophil extracellular traps promote both hypercoagulability and cancer progression[J]. PLoS One, 2019, 14(4): e0216055. DOI: 10.1371/journal.pone.0216055.

[11] MASUCCI M T, MINOPOLI M, DEL VECCHIO S, et al. The emerging role of neutrophil extracellular traps (NETs) in tumor progression and metastasis[J]. Front Immunol, 2020, 11: 1749. DOI: 10.3389/fimmu.2020.01749.

[12] ZHONG W T, WANG Q Y, SHEN X F, et al. The emerging role of neutrophil extracellular traps in cancer: from lab to ward[J]. Front Oncol, 2023, 13: 1163802. DOI: 10.3389/fonc.2023.1163802.

[13] SONG Y H, WANG Z J, KANG L, et al. PADs and NETs in digestive system: from physiology to pathology[J]. Front Immunol, 2023, 14: 1077041. DOI: 10.3389/fimmu.2023.1077041.

[14] YAZDANI H O, ROY E, COMERCI A J, et al. Neutrophil extracellular traps drive mitochondrial homeostasis in tumors to augment growth[J]. Cancer Res, 2019, 79(21): 5626-5639. DOI: 10.1158/0008-5472.CAN-19-0800.

[15] CHEN Y X, HAN L L, QIU X Y, et al. Neutrophil extracellular traps in digestive cancers: warrior or accomplice[J]. Front Oncol, 2021, 11: 766636. DOI: 10.3389/fonc.2021.766636.

[16] PAPAYANNOPOULOS V. Neutrophil extracellular traps in immunity and disease[J]. Nat Rev Immunol, 2018, 18(2): 134-147. DOI: 10.1038/nri.2017.105.

[17] LI P X, LI M, LINDBERG M R, et al. PAD4 is essential for antibacterial innate immunity mediated by neutrophil extracellular traps[J]. J Exp Med, 2010, 207(9): 1853-1862. DOI: 10.1084/jem.20100239.

[18] CASTANHEIRA F V S, KUBES P. Neutrophils and NETs in modulating acute and chronic inflammation[J]. Blood, 2019, 133(20): 2178-2185. DOI: 10.1182/blood-2018-11-844530.

[19] ZHANG Y J, SONG J J, ZHANG Y W, et al. Emerging role of neutrophil extracellular traps in gastrointestinal tumors: a narrative review[J]. Int J Mol Sci, 2022, 24(1): 334. DOI: 10.3390/ijms24010334.

[20] BERGER-ACHITUV S, BRINKMANN V, ABED U A, et al. A proposed role for neutrophil extracellular traps in cancer immunoediting[J]. Front Immunol, 2013, 4: 48. DOI: 10.3389/fimmu.2013.00048.

[21] TOHME S, YAZDANI H O, AL-KHAFAJI A B, et al. Neutrophil extracellular traps promote the development and progression of liver metastases after surgical stress[J]. Cancer Res, 2016, 76(6): 1367-1380. DOI: 10.1158/0008-5472.CAN-15-1591.

[22] DEMERS M, KRAUSE D S, SCHATZBERG D, et al. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis[J]. Proc Natl Acad Sci U S A, 2012, 109(32): 13076-13081. DOI: 10.1073/pnas.1200419109.

[23] MILLRUD C R, KÅGEDAL Å, KUMLIEN GEORÉN S, et al. NET-producing CD16high CD62Ldim neutrophils migrate to tumor sites and predict improved survival in patients with HNSCC[J]. Int J Cancer, 2017, 140(11): 2557-2567. DOI: 10.1002/ijc.30671.

[24] LEE W, KO S Y, MOHAMED M S, et al. Neutrophils facilitate ovarian cancer premetastatic niche formation in the omentum[J]. J Exp Med, 2019, 216(1): 176-194. DOI: 10.1084/jem.20181170.

[25] ZHU T, ZOU X M, YANG C F, et al. Neutrophil extracellular traps promote gastric cancer metastasis by inducing epithelial-mesenchymal transition[J]. Int J Mol Med, 2021, 48(1): 127. DOI: 10.3892/ijmm.2021.4960.

[26] YOO D G, FLOYD M, WINN M, et al. NET formation induced by *Pseudomonas aeruginosa* cystic fibrosis isolates measured as release of myeloperoxidase-DNA and neutrophil elastase-DNA complexes[J]. Immunol Lett, 2014, 160(2): 186-194. DOI: 10.1016/j.imlet.2014.03.003.

[27] YU C, ZHOU G Q, SHI Z L, et al. TREM1 facilitates the development of gastric cancer through regulating neutrophil extracellular traps-mediated macrophage polarization[J]. Dig Liver Dis, 2024, 56(7): 1237-1247. DOI: 10.1016/j.dld.2023.12.002.

[28] WANG Q L, ZHANG Y Y, DING W X, et al. Neutrophil extracellular traps induced by interleukin 8 via CXCR1/2 promote the progression of gastric carcinoma through transcription factor IIB-related factor 1 and cyclin[J]. Genes Dis, 2024, 11(2): 575-578. DOI: 10.1016/j.gendis.2023.03.025.

[29] LI J C, XIA Y, SUN B Y, et al. Neutrophil extracellular traps induced by the hypoxic microenvironment in gastric cancer augment tumour growth[J]. Cell Commun Signal, 2023, 21(1): 86. DOI: 10.1186/s12964-023-01112-5.

[30] KANAMARU R, OHZAWA H, MIYATO H, et al. Neutrophil extracellular

traps generated by low density neutrophils obtained from peritoneal lavage fluid mediate tumor cell growth and attachment[J]. J Vis Exp, 2018(138): 58201. DOI: 10.3791/58201.

[31] KUMAGAI Y, OHZAWA H, MIYATO H, et al. Surgical stress increases circulating low-density neutrophils which may promote tumor recurrence[J]. J Surg Res, 2020, 246: 52-61. DOI: 10.1016/j.jss.2019.08.022.

[32] LI M Z, ZHAO Z D, MAK T K, et al. Neutrophil extracellular traps-related signature predicts the prognosis and immune infiltration in gastric cancer[J]. Front Med, 2023, 10: 1174764. DOI: 10.3389/fmed.2023.1174764.

[33] ZHAO J, LI X Y, LI L M, et al. Identification of neutrophil extracellular trap-driven gastric cancer heterogeneity and C5AR1 as a therapeutic target[J]. Acta Biochim Biophys Sin, 2024, 56(4): 538-550. DOI: 10.3724/abbs.2023290.

[34] XIA X, ZHANG Z Z, ZHU C C, et al. Neutrophil extracellular traps promote metastasis in gastric cancer patients with postoperative abdominal infectious complications[J]. Nat Commun, 2022, 13(1): 1017. DOI: 10.1038/s41467-022-28492-5.

[35] NATALWALA A, SPYCHAL R, TSELEPIS C. Epithelial-mesenchymal transition mediated tumourigenesis in the gastrointestinal tract[J]. World J Gastroenterol, 2008, 14(24): 3792-3797. DOI: 10.3748/wjg.14.3792.

[36] YANG S F, ZOU X M, LI J C, et al. Immunoregulation and clinical significance of neutrophils/NETs-ANGPT2 in tumor microenvironment of gastric cancer[J]. Front Immunol, 2022, 13: 1010434. DOI: 10.3389/fimmu.2022.1010434.

[37] YANG L B, LIU Q, ZHANG X Q, et al. DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25[J]. Nature, 2020, 583(7814): 133-138. DOI: 10.1038/s41586-020-2396-9.

[38] ZHANG F B, YAN Y, CAO X G, et al. TGF-β-driven LIF expression influences neutrophil extracellular traps (NETs) and contributes to peritoneal metastasis in gastric cancer[J]. Cell Death Dis, 2024, 15(3): 218. DOI: 10.1038/s41419-024-06594-w.

[39] LIU D H, YANG X Y, WANG X Y. Neutrophil extracellular traps promote gastric cancer cell metastasis via the NAT10-mediated N4-acetylcytidine modification of SMYD2[J]. Cell Signal, 2024, 116: 111014. DOI: 10.1016/j.cellsig.2023.111014.

[40] XING L, WU S L, XUE S Y, et al. A novel neutrophil extracellular trap signature predicts patient chemotherapy resistance and prognosis in lung adenocarcinoma[J]. Mol Biotechnol, 2024. DOI: 10.1007/s12033-024-01170-1.

[41] FU Y F, TAO J X, GU Y N, et al. Multiomics integration reveals NETosis heterogeneity and TLR2 as a prognostic biomarker in pancreatic cancer[J]. NPJ Precis Oncol, 2024, 8(1): 109. DOI: 10.1038/s41698-024-00586-x.

[42] WANG Q, HUANG Y X, ZHU Y, et al. The m6A methyltransferase METTL5 promotes neutrophil extracellular trap network release to regulate hepatocellular carcinoma progression[J]. Cancer Med, 2024, 13(7): e7165. DOI: 10.1002/cam4.7165.

[43] REN J H, HE J Y, ZHANG H J, et al. Platelet TLR4-ERK5 axis facilitates NET-mediated capturing of circulating tumor cells and distant metastasis after surgical stress[J]. Cancer Res, 2021, 81(9): 2373-2385. DOI: 10.1158/0008-5472.CAN-20-3222.

[44] MOUSSET A, LECORGNE E, BOURGET I, et al. Neutrophil extracellular traps formed during chemotherapy confer treatment resistance via TGF-β activation[J]. Cancer Cell, 2023, 41(4): 757-775.e10. DOI: 10.1016/j.ccell.2023.03.008.

[45] RAYES R F, MOUHANNA J G, NICOLAU I, et al. Primary tumors induce neutrophil extracellular traps with targetable metastasis promoting effects[J]. JCI Insight, 2019, 5(16): e128008. DOI: 10.1172/jci.insight.128008.

[46] YANG C F, MA R S, JIANG T, et al. Contributions of phosphatidylserine-positive platelets and leukocytes and microparticles to hypercoagulable state in gastric cancer patients[J]. Tumour Biol, 2016, 37(6): 7881-7891. DOI: 10.1007/s13277-015-4667-5.

[47] ROSELL A, AGUILERA K, HISADA Y, et al. Prognostic value of circulating markers of neutrophil activation, neutrophil extracellular traps, coagulation and fibrinolysis in patients with terminal cancer[J]. Sci Rep, 2021, 11(1): 5074. DOI: 10.1038/s41598-021-84476-3.

[48] HEERINGA P, RUTGERS A, KALLENBERG C G M. The net effect of ANCA on neutrophil extracellular trap formation[J]. Kidney Int, 2018, 94(1): 14-16. DOI: 10.1016/j.kint.2018.03.010.

[49] CLARK S R, MA A C, TAVENER S A, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood[J]. Nat Med, 2007, 13(4): 463-469. DOI: 10.1038/nm1565.

[50] FOLCO E J, MAWSON T L, VROMMAN A, et al. Neutrophil extracellular traps induce endothelial cell activation and tissue factor production through interleukin-1α and cathepsin G[J]. Arterioscler Thromb Vasc Biol, 2018, 38(8): 1901-1912. DOI: 10.1161/ATVBAHA.118.311150.

[51] LIU C, ZHANG H, LI T P, et al. *Fusobacterium nucleatum* promotes megakaryocyte maturation in patients with gastric cancer via inducing the production of extracellular vesicles containing 14-3-3 [J]. Infect Immun, 2023, 91(8): e0010223. DOI: 10.1128/iai.00102-23.

[52] JIMÉNEZ-ALCÁZAR M, RANGASWAMY C, PANDA R, et al. Host DNases prevent vascular occlusion by neutrophil extracellular traps[J]. Science, 2017, 358(6367): 1202-1206. DOI: 10.1126/science.aam8897.

[53] KANAMARU R, OHZAWA H, MIYATO H, et al. Low density neutrophils (LDN) in postoperative abdominal cavity assist the peritoneal recurrence through the production of neutrophil extracellular traps (NETs)[J]. Sci Rep, 2018, 8(1): 632. DOI: 10.1038/s41598-017-19091-2.

[54] YU J R, LIU Y Y, GAO Y Y, et al. Diterpenoid tanshinones inhibit gastric cancer angiogenesis through the PI3K/Akt/mTOR signaling pathway[J]. J Ethnopharmacol, 2024, 324: 117791. DOI: 10.1016/j.jep.2024.117791.

[55] TAO L, XU M, DAI X J, et al. Polypharmacological profiles underlying the antitumor property of *Salvia miltiorrhiza* root (Danshen) interfering with NOX-dependent neutrophil extracellular traps[J]. Oxid Med Cell Longev, 2018, 2018: 4908328. DOI: 10.1155/2018/4908328.

[56] LI R, ZOU X M, ZHU T, et al. Destruction of neutrophil extracellular traps promotes the apoptosis and inhibits the invasion of gastric cancer cells by regulating the expression of bcl-2, bax and NF- B[J]. Onco Targets Ther, 2020, 13: 5271-5281. DOI: 10.2147/OTT.S227331.

[57] MANGROLIA U, OSBORNE J W. Probiotics in counteracting the role of neutrophils in cancer metastasis[J]. Vaccines, 2021, 9(11): 1306. DOI: 10.3390/vaccines9111306.

[58] VILLARROEL-ESPINDOLA F, EJSMENTEWICZ T, GONZALEZ-STEGMAIER R, et al. Intersections between innate immune response and gastric cancer development[J]. World J Gastroenterol, 2023, 29(15): 2222-2240. DOI: 10.3748/wjg.v29.i15.2222.

[59] NAGARAJU G P, SRIVANI G, DARIYA B, et al. Nanoparticles guided drug delivery and imaging in gastric cancer[J]. Semin Cancer Biol, 2020, 60: 312-321. DOI: 10.1016/j.semcancer.2020.01.006.

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