УДК: 616-006.66
DOI: 10.52532/2663-4864-2025-2-76-280

THE ROLE OF NEUTROPHIL EXTRACELLULAR TRAPS IN THE DEVELOPMENT OF BREAST CANCER: A LITERATURE REVIEW

A.T. OMAR[1], N. A. KABILDINA[1], O. A. PONAMAREVA[1], E. V. KRUK[1], M. MARATKYZY[1]

[1]Karaganda Medical University, Karaganda, the Republic of Kazakhstan

ABSTRACT

Relevance: *Neutrophil extracellular traps (NETs) are extracellular networks released by neutrophils. They are extracellular strands of decondensed DNA fiber, combined with histones and proteins from neutrophil granules, which immobilize pathogens to facilitate their subsequent elimina-tion.*

NET formation (netosis) was first discovered as an immune response to bacterial infection. However, it has since been proven that netosis occurs abnormally in several other inflammatory conditions, including cancer.

Breast cancer (BC) is the most commonly diagnosed malignant disease in women. In this review, we will focus on the role of NETs in BC development and their potential use as diagnostic biomarkers and/or therapeutic targets in cancer.

The study aimed to *evaluate the role of NETs in the pathogenesis of breast cancer based on literature data.*

Methods: *The search in the Web of Science, PubMed, and Scopus databases for 2014-2024 revealed about 600 articles. Of these, 53 were analyzed following the inclusion and exclusion crite-ria.*

Results: *The NET role in tumor development is related to cancer immunoediting and the interaction between the immune system and cancer cells. NETs play a key regulatory role in the tumor microenvironment, contributing to the development of distant metastases and exacerbating the tumor's aggressiveness, thereby increasing its ability to invade. NETs play a significant role in regulating the tumor microenvironment. NETs also have an antitumor effect since their components directly kill cancer cells.*

NETs' production in cancer requires interaction between various cells and blood components, including platelets, leukocytes, metastatic tumor cells, and the primary tumor site.

Today, there are no generally accepted methods of using NETs to treat cancer. These treatment methods are under development, and work is underway to target various points and components of the NETs.

Conclusion: *In BC, netosis is associated with accelerated disease progression, metastasis, and complications. The study identifies potential NET-specific targets that should be investigated and used to develop treatment methods. A better understanding of the interaction between cancer and NETs will facilitate the development of precision treatments and diagnostics tailored specifically to NETs.*

Keywords: *breast cancer (BC), extracellular neutrophil traps (NETs).*

Introduction: Neutrophils are the most common leukocytes formed in the bone marrow. Neutrophils constitute the first line of defense against non-indigenous pathogens, utilizing the primary effector mechanisms of phagocytosis, degranulation, and neutrophil extracellular trap (NET) formation [1]. Neutrophil extracellular traps (NETs) are extracellular networks that are released by neutrophils and are extracellular strands of decondensed DNA fiber in combination with histones and granule proteins neutrophils, including matrix metalloproteinase (MMP), neutrophil elastase (NE), myeloperoxidase (MPO), cathepsin G, complement factors, and other enzymatically active proteases and peptides that immobilize pathogens to facilitate their subsequent elimination [2].

The NETs formation, known as NETosis, was first discovered as an immune response to bacterial infection. Histones and the released granular contents of neutrophils have antimicrobial properties, and the fibrous structure of the networks can physically capture and render harmless bacteria. However, it has since been proven that NETosis occurs abnormally in several other inflammatory conditions, including cancer. NETosis occurs when proteases enter the neutrophil nucleus, leading to chromatin decondensation through citrullination. These loosely bound filaments are eventually ejected from the cell, destroying it or leaving the membrane intact. The subsequent integrity of the membrane depends on the nature of the stimulus that provokes NETosis [3-6].

According to the data of the Global Cancer Observatory, 2,296,840 cases of breast cancer (BC) and 666,103 deaths from this disease were registered in the world in 2022. The incidence was 46.8 cases per 100,000 people, and the mortality was 12.7 deaths per 100,000. In Kazakhstan, the absolute number of BC cases amounted to 5,171 in 2022. The incidence was at 26.5 per 100,000, and the mortality was 5.4 per 100,000 [7, 8].

This review focuses primarily on the NET role in BC development. It is well established that NETs exhibit both antitumor and protumorigenic effects. This review en-

compasses the established and potential stimuli that contribute to oncogenic NETosis at the molecular level, and also describes the interactions between neutrophil species, other blood components, and the tumor cells themselves. The review also presents the consequences of NETosis and its role in the progression of BC. NET is further considered a diagnostic biomarker and/or a possible therapeutic target in malignant tumors.

The study aimed to evaluate the role of NETs in the pathogenesis of breast cancer based on literature data.

Methods: For this literature review, a systematic search of the scientific literature in the Web of Science, PubMed, and Scopus databases was conducted from January 2014 to January 2024. In exceptional cases, publications published earlier than 2014 were included in the review, as they represented basic research that had a significant impact on the development of the topic [9, 10].

The search was conducted using combinations of keywords and medical subject headings (MeSH terms), such as "breast cancer" and "neutrophil extracellular traps", as well as their synonyms and derivatives in English.

The following search strategy was used (example for PubMed):

(«breast neoplasms»[MeSH Terms] OR «breast cancer») AND ("neutrophil extracellular traps" OR "NETs")

Publications were included in the analysis according to the following inclusion criteria:

• articles published in peer-reviewed scientific journals;

• availability of the full version of the article in English;

• articles containing data from randomized controlled trials, cohort studies, meta-analyses, and systematic reviews;

• studies directly relating to the role of neutrophil extracellular traps (NETs) in BC pathogenesis, progression, or treatment.

Exclusion criteria included:

• incomplete publications, including conference abstracts, presentations, and short communications;

• articles describing only isolated clinical cases (case reports);

• publications in journals with a dubious scientific reputation, determined by the lack of indexing in leading databases and a low impact factor;

• articles with a citation index below the average for the subject (according to Scopus/Web of Science data at the time of search).

As a result of the initial search, about 600 publications have been identified. After applying the inclusion and exclusion criteria to the analysis, 53 of the most relevant sources were selected. A detailed selection scheme is presented in Figure 1. The selection of articles was carried out by two researchers. The level of convergence of views regarding the inclusion of articles was 98%. All disagreements were resolved through discussion and consensus.

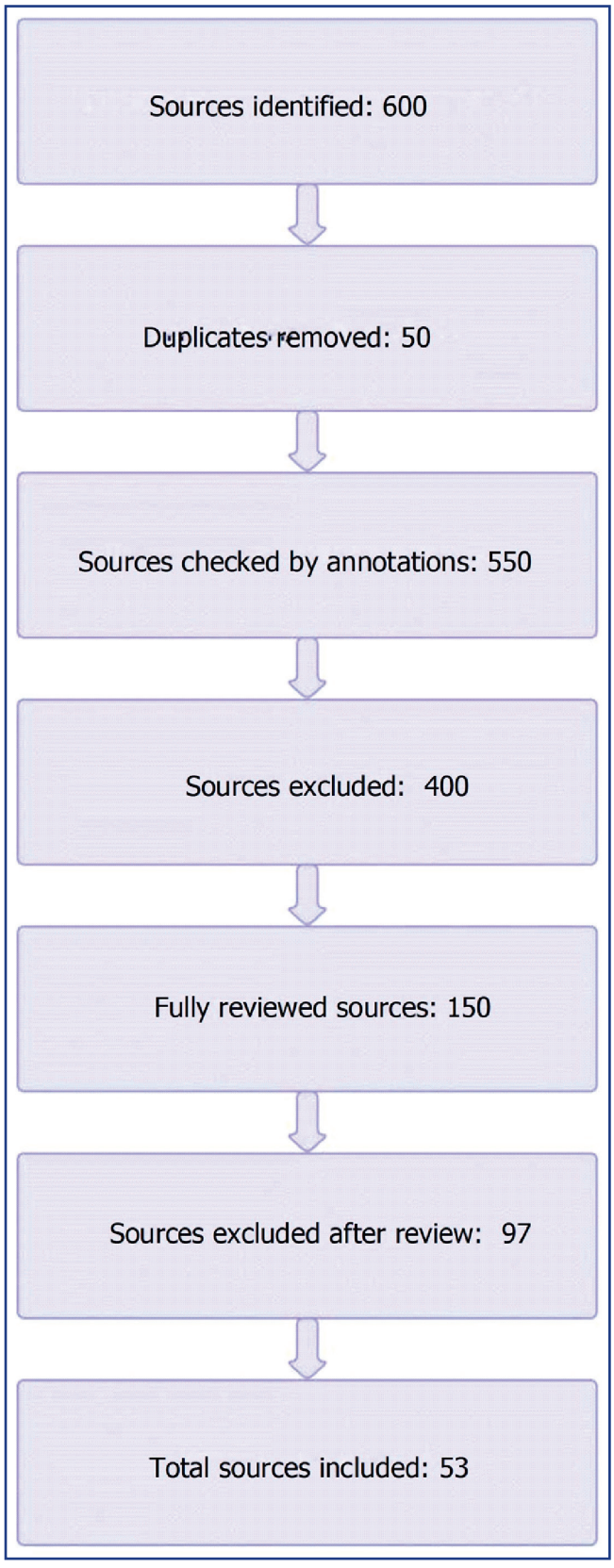

Figure 1 – Stages of selection of sources for the review

Results: In a scientific first, V. Brinkmann et al. reported on NETs in 2004, when electron microscopy was used to obtain images of activated neutrophils involved in antimicrobial processes [9]. An in vitro study of neutrophils activated with IL-8, phorbol-12-myristate-13-acetate (PMA)

showed the formation of distinctive extracellular fibers. This concept has been further confirmed in vivo, where these structures have been identified under infection conditions in both preclinical models and humans.

In 2012, M. Demers et al. were the first to report on the role of traps in oncological processes. In the main part, the authors studied melanoma B16F10 and leukemia AML. In this study, NET has been associated with tumor progression for the first time [10]. Later, several authors demonstrated that breast tumors generate neutrophils, which are predisposed to forming NETs. The number of traps increases with the progression of the tumor stage. NET was identified by an increase in plasma DNA content, as well as by immunofluorescence staining of extracellular histone and DNA around neutrophils. These markers represent the process of NETosis, in which neutrophils release decondensed enzymatic granules containing chromatin into the extracellular space, typically resulting in non-apoptotic cell death [11, 12].

The NETs' antitumor effect can theoretically be exerted by activating the immune system or directly destroying malignant cells. It has been shown that NETs components, such as NE and MPO in vitro, as well as histones, can destroy cancer cells, thereby blocking further cell growth and the development of distant metastases [13, 14].

Numerous studies have shown that granulocyte colony-stimulating factor (G-CSF) contributes to the production of NETs. Demonstration of NETs in mice with tumors has been made possible by tumor-derived neutrophil G-CSF priming, which can be neutralized by treating mice with an anti-G-CSF antibody. Additionally, neutrophils from mice treated with recombinant G-CSF were more predisposed to platelet formation when stimulated by platelet-activating factor in vivo. Thus, NETs have been shown to induce a prothrombotic state in the lungs of mice with a tumor and also participate in tumor growth [15, 16].

Several studies have shown higher preoperative levels of MPO-DNA, a well-known marker of systemic neutralization, in the serum of patients with metastatic cancer compared to healthy controls. These rates were associated with low disease-free survival and overall survival. NETs can promote the growth of stressed cancer cells by altering their bioenergetics, while inhibiting traps leads to the death of cancer cells. Thus, serum levels of MPO-DNA may represent a possible prognostic biomarker [17-19].

NETs have also been recognized as a crucial component of the dynamic tumor immune microenvironment (TIME), which can significantly contribute to the prevention of metastatic spread [20, 21]. Several factors have been identified that contribute to the formation of TIME. Among them are cancer-associated fibroblasts (CAFs), which are considered one of the most important protumor factors. Regarding the effect of NETs on CAFs, it has been reported that trap formation occurs in these fibroblasts within pancreatic ductal adenocarcinoma, thereby creating a protumor microenvironment [22]. However, due to the difficulty of converting normal fibroblasts into CAFs, further research is required to study the specific mechanisms mediated by NETs regulation.

Neutrophil elastase (NE), a key granular protein in reticulated microvesicles, has been shown to disrupt the extracellular matrix and activate the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K) pathway in cancer cells. Induction of the PI3K signaling pathway promotes the proliferation and migration of cancer cells [23, 24]. Another representative of granule proteins, a matrix metalloproteinase (MMP), has also been reported to promote tumor growth and metastasis through extracellular matrix proteolysis [25, 26].

Patients with malignant tumors show an increase in platelet activation [27]. NETs have been shown to contribute to the formation of arterial, venous, and cancer-related thrombosis [28, 29]. The traps induce intravascular activation of the coagulation cascade, which promotes primary tumor growth, cancer aggressiveness, progression, and metastasis. According to L.G. Lima et al., there is a significant correlation between the incidence of thromboembolic complications and a worsening of the prognosis of tumor diseases. These authors suggested that the traps collect on the scaffold with the thrombus and may play a crucial role in the pathogenesis of cancer, in conjunction with the hemostasis system [30]. Subsequently, H.S. Jung et al. demonstrated that NETs stimulate cancer-associated thrombosis, which correlates with a worse clinical outcome [31]. It is well known that the incidence of thromboembolic diseases is markedly dependent on the type of cancer. For example, patients with BC have a low incidence of thromboembolic complications, while patients with pancreatic cancer have a high incidence [32].

Methods to identify neutrophil extracellular traps: The detection of NETs in peripheral blood enables the separation of patients at higher risk of venous thromboembolism and metastasis. This is especially important in clinical practice for a personalized approach in the choice of treatment tactics. The traps can be used as a biomarker for risk stratification and treatment adaptation. However, as of today, the literature does not outline the reference values for the NET level. One of the available ways to determine in vivo networks is to measure the NETs components, such as circulating cell-free DNA, citrullinated histone H3 (citH3), NE, and MPO.

In the study of the blood of patients with established diagnoses of colorectal cancer and BC, freely circulating DNA was detected by quantitative analysis of nucleic acid staining [33]. A correlation was found between circulating DNA and the size of the breast tumor, as well as the degree of its malignancy. A disadvantage of this study was the lack of specificity in measuring NETosis. The elevation of DNA in blood serum can also be attributed to the consequences of cell necrosis and apoptosis. A solution in this situation

may be to measure the circulating MPO-DNA conjugates, which are more specific in NETs formation, compared to assessing cell-free DNA alone [34].

The most specific marker of traps is citrullinated histone H3 (citH3). It is formed during the NETs formation within PAD4-mediated citrullination and has an important predictive value. In patients with advanced cancer, high levels of citH3 are a significant indicator of short-term death, surpassing even those of critically ill patients without cancer [35].

Neutrophil derivatives - neutrophil elastase and myeloperoxidase - cannot be reliable and specific markers for NETs, since these enzymes are released during degranulation of neutrophils, regardless of the trap's formation. Additionally, in the study of seriously ill patients, no significant differences were found between these markers, regardless of whether a malignant tumor was present or absent [6].

From the above, it follows that citH3 is the most stable indicator of NETosis, as it is highly specific for netosis. The CitH3 may be effective in understanding the differences between other biomarkers associated with NETs. The CitH3 levels are also predictors of venous thromboembolism (VTE) risk in newly diagnosed patients, further supporting its diagnostic usefulness [35, 36].

Extracellular neutrophil traps and breast cancer: BC is one of the three most commonly diagnosed cancers worldwide [7, 36], as well as one of the most studied cancers. In the previously mentioned work, additional experiments by Demers et al. also studied the BC in a mouse model (4T1) for the first time, finding that in a mouse model of BC, the formation of NETs corresponded to cancer-associated thrombosis in the lung. The development of thrombosis in patients with BC is associated with an increased risk of death, both due to the thromboembolic complication itself and due to the progression of the malignant process, against which thrombosis may reflect a more aggressive course of the disease [10]. It was found that the release of cancerous extracellular chromatin networks (CECN) occurred due to high levels of *Padi4* gene expression in 4T1 BC cells of mice and PAD4-mediated traps. The deletion of Padi4 genes in mouse models significantly slowed the proliferation and migration of BC cells, indicating that PAD4-mediated NETs stimulate breast tumor growth and liver metastasis [37]. In addition, NETs have been shown to stimulate the prometastatic phenotype in human BC cells by inducing an epithelial-mesenchymal transition program [38].

It was also revealed that the activation of neutrophil lipopolysaccharides awakens dormant BC cells, leading to the production of NETs. The obtained NETs reconstruct laminin, utilizing MMP-9 and NE proteases. The reconstructed laminin further activates the signaling of integrin α3β1 to awaken BC cells. Inhibition of NETs formation via cleavage by DNase I or by inhibition of protein-dezincinase 4 prevents the activation of dormant cancer cells [40]. Besides, metastatic BC cells are also able to activate neutrophils, thereby promoting NET formation even in the absence of infection. Activation of neutrophils by cancer cells occurs through the secretion of G-CSF. Blocking the NETs formation by DNase I showed the prevention of lung metastasis in mice [41].

Therapeutic capacity of neutrophil extracellular traps: There are currently no approved medicines that target NETs. These treatments are under development. There are several ways to inhibit NETosis, each with different potential for clinical therapy. According to several studies, DNase I treatment disrupts networks, leading to the loss of reticular structure and a reduced ability to induce metastasis [41-43]. In addition, DNase I has been shown to reduce the tumor volume in rats when administered intramuscularly or intraperitoneally in combination with other proteases (papain, trypsin, and chymotrypsin). However, it is not known whether these effects were primarily due to inhibition of NETs [44].

Inhibition of trap components integral to NETosis, such as NE or PAD4, is likely to have similar off-target effects due to their involvement in other key pathways, potentially disrupting normal neutrophil function. Low-molecular-weight irreversible PAD4 inhibitors, Cl-amidin and F-amidine, are being actively studied as they inactivate the calcium-related PAD4. The disadvantage of these inhibitors is their lack of specificity and the potential for interaction with other enzymes within the PAD family. Lewis et al. synthesized two reversible inhibitors, GSK199 and GSK484, which overcome this obstacle. Both exhibit high specificity for PAD4 and inhibit NETosis in both mouse and human neutrophils. GSK484 has been shown to prevent tumor-associated renal dysfunction in mice, which NETs mediate. The inhibitory effects of GSK484 were as effective as DNase I [45].

Alternatively, there is an example of adaptations of FDA-approved drugs that contribute to the development of effective methods to combat NETs. For example, the inhibitory effect of aspirin on the network has yielded some promising results in animal models. M.J. Lapponi et al. showed that aspirin prevented NET-induced damage to the lung endothelium by inhibiting platelet activation and subsequent formation of NETs in mice. The authors found that aspirin treatment effectively suppressed NETs in human neutrophils in vitro, but led to an increase in bacteria in mice with aggravated infection in vivo, suggesting a loss of normal NET functionality [46]. There is evidence of a positive effect of aspirin in clinical practice. Thus, it was found that daily aspirin, regardless of the dose, can reduce the risk of cancer mortality and the development of distant metastases, in particular in adenocarcinomas, and that in patients with BC, aspirin affects the reduction of metastasis [47].

The FDA-approved hydroxychloroquine, originally used to treat malaria, was also found to inhibit NETosis. Although the mechanism underlying hydroxychloroquine's

inhibition of NETs is unclear, it may be related to autophagy inhibition [48-50]. A phase II clinical trial in patients with advanced pancreatic cancer had little clinical benefit. However, the authors suggest that combination therapy may be more effective than hydroxychloroquine monotherapy [51]. Additionally, the use of hydroxychloroquine as a neoadjuvant treatment in the early stages of the disease holds significant promise [52].

L. Yang et al. studied the therapeutic targets associated with NETs in the treatment of BC and revealed a potential specific mechanism of the effect of NETs on BC metastasis. The researchers demonstrated that the DNA components of NETs can function as a chemotactic factor, attracting BC cells and contributing to the development of liver metastases in patients with early-stage BC. It was assumed that the transmembrane protein CCDC25 could be a potential receptor for the DNA components of NETs in BC cells, by reading information from cell-free DNA. Activation of CCDC25 contributed to the improvement of cell motility by activating the ILK-B-PARVIN pathway. These results highlight the potential of using CCDC25 as a target for the development of a therapeutic strategy aimed at preventing cancer metastasis [53].

Discussion: The role of NETs in tumor development increasingly involves the cancer immunoediting and the interaction between the immune system and cancer cells. According to the accumulated evidence, NET awakens dormant cancer cells, thereby causing tumor recurrence, as well as its uncontrolled growth and spread [16]. NETs play a significant role in regulating the tumor microenvironment, particularly in the formation of distant metastases, by secreting matrix metalloproteinases and pro-inflammatory cytokines. Additionally, NET enhances the tumor's ability to invade and spread, contributing to its increased aggressiveness. The data obtained show that NET induces the epithelial-mesenchymal transition in tumor cells through the activation of the highly mobile group protein box 1, which also enhances their invasive properties. NET proteinases can also disrupt the extracellular matrix, promoting the extravasation of cancer cells. Moreover, the traps can capture and grip circulating cancer cells, thereby promoting metastasis. NET directly triggers the proliferation of tumor cells through their proteases or activating signals.

Studies have shown that in cancer, the formation of NETs is associated with a complex interaction between different cells and blood elements, including platelets, white blood cells, metastatic tumor cells, and the primary tumor. NETs contribute to the development of an inflammatory microenvironment, creating a vicious cycle: NETs enter the bloodstream, damage endothelial cells, which increases inflammation and activates platelets and neutrophils. This, in turn, can lead to additional release of NETs. Platelet activation induced by NETs may also contribute to several negative effects associated with late-stage metastatic BC, including VTE.

NETs also have an antitumor effect. Various NETs components, such as MPO or histones, have been shown to directly kill the cancer cells.

To date, the effect of NETs on the tumor process is being actively studied, and therapeutic strategies targeting NETs are being developed; however, they are still in the preclinical stage. It is worth noting that relevant work is underway aimed at various points and components of NETs [41-43, 53]. Each method has its advantages and disadvantages. The prognostic consequences of cancer-related NETosis are being studied in addition to the development of new therapeutics to improve the outcomes in patients with BC. Future research should focus on finding new specific targets for the prevention of concomitant complications, such as increased risk of venous thromboembolism and metastasis, which adversely affect the prognosis of patients with BC.

Conclusion: BC is the most commonly diagnosed malignant disease in women. Immunological experiments over the past two decades have addressed many important questions regarding the causal relationship between chronic inflammation and carcinogenesis.

Accordingly, there is now more and more evidence that NETs play a significant role in the formation of the inflammatory component of the tumor microenvironment and can contribute to the progression of cancer. The data presented in the review relate to both classical inducers of NETs and specific stimuli capable of triggering NETosis in malignant neoplasms, although the mechanisms of their action are still insufficiently studied. The review also examines the negative consequences triggered by NETs and identifies potential therapeutic targets associated with them, which are of interest for future preclinical and clinical studies. One of the next important steps is to determine the relationship between neutrophils, tumor cells, endothelial cells, platelets, and extracellular vesicles, as well as to define the impact of other components of the innate and adaptive immune system on cancer progression. NET-targeted therapy has shown success in preclinical models of cancer and may prove to be a valuable clinical goal in slowing or stopping the tumor progression in patients with BC.

A better understanding of the interaction between cancer and NETs will enable the development of precision diagnostic and therapeutic strategies focused on NETs. This will make it possible to identify the tumors with the potential for metastasis, carry out an early diagnosis, and provide more effective and personalized treatment for patients with BC.

References:

1. Teng T.S., Ji A.L., Ji, X.Y., Li Y.Z. Neutrophils and Immunity: From Bactericidal Action to Being Conquered // Journal of Immunology Research. – 2017. – Vol. 2017. – P. 1–14. https://doi.org/10.1155/2017/9671604

2. Papayannopoulos V. Neutrophil extracellular traps in immunity and disease // Nature Reviews Immunology. – 2018. – Vol. 18(2). – P. 134-147. https://doi.org/10.1038/nri.2017.105

3. Sur Chowdhury C., Giaglis S., Walker U. A., Buser A., Hahn S., Hasler P. Enhanced neutrophil extracellular trap generation in rheumatoid arthritis: analysis of underlying signal transduction pathways and potential diagnostic utility. // Arthritis research & therapy. – 2014. – Vol. 16(3). – P. 122. https://doi.org/10.1186/ar4579

4. Gray R.D., McCullagh B.N., McCray P.B. NETs and CF Lung Disease: Current Status and Future Prospects // Antibiotics (Basel). – 2015. – Vol. 4(1). – P. 62-75. https://doi.org/10.3390/antibiotics4010062

5. Jorch S.K., Kubes P. An emerging role for neutrophil extracellular traps in noninfectious disease // Nature medicine. – 2017. – Vol. 23(3). – P. 279-287. https://doi.org/10.1038/nm.4294

6. Wang Y., Xiao Y., Zhong L., Ye D., Zhang J., Tu Y., Bornstein S.R., Zhou Z., Lam K.S., Xu A. Increased neutrophil elastase and proteinase 3 and augmented NETosis are closely associated with β-cell autoimmunity in patients with type 1 diabetes // Diabetes. – 2014. – Vol. 63(12). – P. 4239-4248. https://doi.org/10.2337/db14-0480

7. International Agency for Research on Cancer (IARC). Cancer Today: Estimated number of new cases in 2022, worldwide, both sexes, all ages. Global Cancer Observatory. 2022. Дата обращения: 13.02.2024. Адрес доступа: https://gco.iarc.fr/today/en/dataviz/bars?types=0_1&mode=population&populations=900&sort_by=value1&key=total&cancers=20

8. International Agency for Research on Cancer (IARC). Cancer Today: Estimated number of new cases in 2022, Kazakhstan, both sexes, all ages. Global Cancer Observatory. 2022. Дата обращения: 13.02.2024. Адрес доступа: https://gco.iarc.fr/today/en/dataviz/bars?types=0_1&mode=population&populations=398&sort_by=value1&key=total&cancers=20

9. Brinkmann V., Reichard U., Goosmann C., Fauler B., Uhlemann Y., Weiss D.S., Weinrauch Y., Zychlinsky A. Neutrophil extracellular traps kill bacteria // Science. – 2004. – Vol. 303(5663). – P. 1532–1535. http://doi.org/10.1126/science.1092385

10. Demers M., Krause D.S., Schatzberg D., Martinod K., Voorhees J.R., Fuchs T.A., Scadden D.T., Wagner D.D. Cancers predispose neutrophils to release extracellular DNA traps that contribute to cancer-associated thrombosis // Proceedings of the National Academy of Sciences of the United States of America. – 2012. – Vol. 109(32). – P. 13076-13081. http://doi.org/10.1073/pnas.1200419109

11. Mouchemore K.A., Anderson R.L., Hamilton J. A. Neutrophils, G-CSF and their contribution to breast cancer metastasis // The FEBS journal. – 2018. – Vol. 285(4). – P. 665-679. https://doi.org/10.1111/febs.14206

12. Shao B.Z., Yao Y., Li J.P., Chai N.L., Linghu E.Q. The Role of Neutrophil Extracellular Traps in Cancer // Frontiers in Oncology. – 2021. – Vol. 11. – Art. no. 714357. https://doi.org/10.3389/fonc.2021.714357

13. Cedervall J., Hamidi A., Olsson A.K. Platelets, NETs and cancer // Thrombosis Res. – 2018. – Vol. 164 Suppl 1. – P. S148-S152. https://doi.org/10.1016/j.thromres.2018.01.049

14. Schedel F., Mayer-Hain S., Pappelbaum K.I., Metze D., Stock M., Goerge T., Loser K., Sunderkötter C., Luger T.A., Weishaupt C. Evidence and impact of neutrophil extracellular traps in malignant melanoma // Pigment Cell Melanoma Res. – 2020. – Vol. 33(1). – P. 63-73. https://doi.org/10.1111/pcmr.12818

15. Demers M., Wong S.L., Martinod K., Gallant M., Cabral J.E., Wang Y., Wagner D.D. Priming of neutrophils toward NETosis promotes tumor growth // Oncoimmunology. – 2016. – Vol. 5(5). – e1134073. https://doi.org/10.1080/2162402X.2015.1134073

16. Demkow U. Neutrophil Extracellular Traps (NETs) in Cancer Invasion, Evasion and Metastasis // Cancers. – 2021. – Vol. 13(17). – Art. no. 4495. https://doi.org/10.3390/cancers13174495

17. Yazdani H.O., Roy E., Comerci A.J., van der Windt D.J., Zhang H., Huang H., Loughran P., Shiva S., Geller D.A., Bartlett D.L., Tsung A., Sheng T., Simmons R.L., Tohme S. Neutrophil Extracellular Traps Drive Mitochondrial Homeostasis in Tumors to Augment Growth // Cancer Res. – 2019. – Vol. 79(21). – P. 5626-5639. https://doi.org/10.1158/0008-5472.CAN-19-0800

18. Park J., Wysocki R.W., Amoozgar Z., Maiorino L., Fein M.R., Jorns J., Schott A.F., Kinugasa-Katayama Y., Lee Y., Won N.H., Nakasone E.S., Hearn S.A., Küttner V., Qiu J., Almeida A.S., Perurena N., Kessenbrock K., Goldberg M.S., Egeblad M. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps // Sci. Transl. Med. – 2016. – Vol. 8(361). – P. 361ra138. https://doi.org/10.1126/scitranslmed.aag1711

19. Tohme S., Yazdani H.O., Al-Khafaji A.B., Chidi A.P., Loughran P., Mowen K., Wang Y., Simmons R.L., Huang H., Tsung, A. Neutrophil Extracellular Traps Promote the Development and Progression of Liver Metastases after Surgical Stress // Cancer Res. – 2016. – Vol. 76(6). – P. 1367-1380. https://doi.org/10.1158/0008-5472.CAN-15-1591

20. Gonzalez-Aparicio M., Alfaro C. Influence of Interleukin-8 and Neutrophil Extracellular Trap (NET) Formation in the Tumor Microenvironment: Is There a Pathogenic Role? // J. Immunol. Res. – 2019. – Vol. 2019. – P. 1-7. https://doi.org/10.1155/2019/6252138

21. Rayes R.F., Mouhanna J.G., Nicolau I., Bourdeau F., Giannias B., Rousseau S., Quail D., Walsh L., Sangwan V., Bertos N., Cools-Lartigue J., Ferri L.E., Spicer J.D. Primary tumors induce neutrophil extracellular traps with targetable metastasis promoting effect // JCI insight. – 2019. – Vol. 5(16). – Art. no. e128008. https://doi.org/10.1172/jci.insight.128008

22. Takesue S., Ohuchida K., Shinkawa T., Otsubo Y., Matsumoto S., Sagara A., Yonenaga A., Ando Y., Kibe S., Nakayama H., Iwamoto C., Shindo K., Moriyama T., Nakata K., Miyasaka Y., Ohtsuka T., Toma H., Tominaga Y., Mizumoto K., Hashizume M., Nakamura M. Neutrophil extracellular traps promote liver micrometastasis in pancreatic ductal adenocarcinoma via the activation of cancer-associated fibroblasts // Intl. J. Oncol. – 2020. – Vol. 56(2). – P. 596-605. https://doi.org/10.3892/ijo.2019.4951

23. DeSouza-Vieira T., Guimarães-Costa A., Rochael N.C., Lira M.N., Nascimento M.T., Lima-Gomez P. S., Mariante R. M., Persechini P. M., Saraiva E. M. Neutrophil extracellular traps release induced by Leishmania: role of PI3Kγ, ERK, PI3Kσ, PKC, and [Ca2+] // J. Leukocyte Biol. – 2016. – Vol. 100(4). – P.801-810. https://doi.org/10.1189/jlb.4A0615-261RR

24. Krotova K., Khodayari N., Oshins R., Aslanidi G., Brantly M.L. Neutrophil elastase promotes macrophage cell adhesion and cytokine production through the integrin-Src kinases pathway // Sci. Rep. – 2020. – Vol.10(1). – Art. no. 15874. https://doi.org/10.1038/s41598-020-72667-3

25. Boeltz S., Amini P., Anders H.J., Andrade F., Bilyy R., Chatfield S., Cichon I., Clancy D.M., Desai J., Dumych T., Dwivedi N., Gordon R. A., Hahn J., Hidalgo A., Hoffmann M.H., Kaplan M.J., Knight J.S., Kolaczkowska E., Kubes P., Leppkes M., Herrmann M. To NET or not to NET: current opinions and state of the science regarding the formation of neutrophil extracellular traps // Cell Death Different. – 2019. – Vol. 26(3). – P. 395-408. https://doi.org/10.1038/s41418-018-0261-x

26. Albrengues J., Shields M.A., Ng D., Park C.G., Ambrico A., Poindexter M.E., Upadhyay P., Uyeminami D.L., Pommier A., Küttner V., Bružas E., Maiorino L., Bautista C., Carmona E.M., Gimotty P.A., Fearon D.T., Chang K., Lyons S.K., Pinkerton K.E., Trotman L.C., Egeblad M. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice // Science (New York). – 2018. – Vol. 361(6409). – Art. no. 4227. https://doi.org/10.1126/science.aao4227

27. Stoiber D., Assinger A. Platelet-Leukocyte Interplay in Cancer Development and Progression // Cells. – 2020. – Vol. 9(4). – Art. no. 855. https://doi.org/10.3390/cells9040855

28. Almeida V.H., Rondon A.M.R., Gomes T., Monteiro R.Q. Novel Aspects of Extracellular Vesicles as Mediators of Cancer-Associated Thrombosis // Cells. – 2019. – Vol. 8(7). – Art. no. 716. https://doi.org/10.3390/cells8070716

29. Thålin C., Hisada Y., Lundström S., Mackman N., Wallén H. Neutrophil Extracellular Traps: Villains and Targets in Arterial, Venous, and Cancer-Associated Thrombosis // Arteriosclerosis Thrombosis Vasc. Biol. – 2019. – Vol. 39(9). – P. 1724-1738. https://doi.org/10.1161/ATVBAHA.119.312463

30. Lima L. G., Monteiro R.Q. Activation of blood coagulation in cancer: implications for tumour progression // Biosci. Rep. – 2013. – Vol. 33(5). – Art. no. e00064. https://doi.org/10.1042/BSR20130057

31. Jung H.S., Gu J., Kim J.E., Nam Y., Song J.W., Kim H.K. Cancer cell-induced neutrophil extracellular traps promote both hypercoagulability and cancer progression // PloS one. – 2019. – Vol. 14(4). – Art. no. e.0216055. https://doi.org/10.1371/journal.pone.0216055

32. Gervaso L., Dave H., Khorana A.A. Venous and Arterial Thromboembolism in Patients With Cancer: JACC: CardioOncology State-of-the-Art Review // JACC. CardioOncology. – 2021. – Vol. 3(2). – P. 173-190. https://doi.org/10.1016/j.jaccao.2021.03.001

33. Agassi R., Czeiger D., Shaked G., Avriel A., Sheynin J., Lavrenkov K., Ariad S., Douvdevani A. Measurement of circulating cell-free DNA levels by a simple fluorescent test in patients with breast cancer // Am. J. Clin. Pathol. – 2015. – Vol. 143(1). – P. 18-24. https://doi.org/10.1309/AJCPI5YHG0OGFAHM

34. Yoo D.G., Floyd M., Winn M., Moskowitz S. M., Rada B. NET formation induced by Pseudomonas aeruginosa cystic fibrosis isolates measured as release of myeloperoxidase-DNA and neutrophil elastase-DNA complexes // Immunol. Let. – 2014. – Vol. 160(2). – P. 186-194. https://doi.org/10.1016/j.imlet.2014.03.003

35. Thålin C., Lundström S., Seignez C., Daleskog M., Lundström A., Henriksson P., Helleday T., Phillipson M., Wallén H., Demers M. Citrullinated histone H3 as a novel prognostic blood marker in patients with advanced cancer // PloS one. – 2018. – Vol. 13(1). – Art. no. e0191231. https://doi.org/10.1371/journal.pone.0191231

36. Harbeck N., Gnant, M. Breast cancer // Lancet (London, England). – 2017. – Vol. 389(10074). – P. 1134-1150. https://doi.org/10.1016/S0140-6736(16)31891-8

37. Shi L., Yao H., Liu Z., Xu M., Tsung A., Wang Y. Endogenous PAD4 in Breast Cancer Cells Mediates Cancer Extracellular Chromatin Network Formation and Promotes Lung Metastasis // MCR. – 2020. – Vol. 18(5). – P. 735-747. https://doi.org/10.1158/1541-7786.MCR-19-0018

38. Martins-Cardoso K., Almeida V.H., Bagri K.M., Rossi M.I.D., Mermelstein C.S., König S., Monteiro R.Q. Neutrophil Extracellular Traps (NETs) Promote Pro-Metastatic Phenotype in Human Breast Cancer Cells through Epithelial-Mesenchymal Transition // Cancers. – 2020. – Vol. 12(6). – Art. no. 1542. https://doi.org/10.3390/cancers12061542

39. Albrengues J., Shields M.A., Ng D., Park C.G., Ambrico A., Poindexter M.E., Upadhyay P., Uyeminami D.L., Pommier A., Küttner V., Bružas E., Maiorino L., Bautista C., Carmona E.M., Gimotty P.A., Fearon D.T., Chang K., Lyons S.K., Pinkerton K.E., Trotman L.C., Egeblad M. Neutrophil extracellular traps produced during inflammation awaken dormant cancer cells in mice // Science (New York). – 2018. – Vol. 361(6409). – Art. no. eaao4227. https://doi.org/10.1126/science.aao4227

40. Park J., Wysocki R.W., Amoozgar Z., Maiorino L., Fein M.R., Jorns J., Schott A.F., Kinugasa-Katayama Y., Lee Y., Won N.H., Nakasone E.S., Hearn S.A., Küttner V., Qiu J., Almeida A.S., Perurena N., Kessenbrock K., Goldberg M.S., Egeblad M. Cancer cells induce metastasis-supporting neutrophil extracellular DNA traps // Sci. Transl. Med. – 2016. – Vol. 8(361). – Art. no. 361ra138. https://doi.org/10.1126/scitranslmed.aag1711

41. Tohme S., Yazdani H.O., Al-Khafaji A.B., Chidi A.P., Loughran P., Mowen K., Wang Y., Simmons R.L., Huang H., Tsung A. Neutrophil Extracellular Traps Promote the Development and Progression of Liver Metastases after Surgical Stress // Cancer Res. – 2016. – Vol. 76(6). – P. 1367–1380. https://doi.org/10.1158/0008-5472.CAN-15-1591

42. Leal A.C., Mizurini D.M., Gomes T., Rochael N.C., Saraiva E.M., Dias M.S., Werneck C.C., Sielski M.S., Vicente C.P., Monteiro R.Q. Tumor-Derived Exosomes Induce the Formation of Neutrophil Extracellular Traps: Implications For The Establishment of Cancer-Associated Thrombosis // Sci. Rep. – 2017. – Vol. 7(1). – Art. no. 6438. https://doi.org/10.1038/s41598-017-06893-7

43. Trejo-Becerril C., Pérez-Cardenas E., Gutiérrez-Díaz B., De La Cruz-Sigüenza D., Taja-Chayeb L., González-Ballesteros M., García-López P., Chanona J., Dueñas-González A. Antitumor Effects of Systemic DNAse I and Proteases in an In Vivo Model // Integr. Cancer Ther. – 2016. – Vol. 15(4). – P. NP35-NP43. https://doi.org/10.1177/1534735416631102

44. Lewis H.D., Liddle J., Coote J.E., Atkinson S.J., Barker M.D., Bax B.D., Bicker K.L., Bingham R.P., Campbell M., Chen Y.H., Chung C.W., Craggs P.D., Davis R.P., Eberhard D., Joberty G., Lind K.E., Locke K., Maller C., Martinod K., Patten C., Wilson D.M. Inhibition of PAD4 activity is sufficient to disrupt mouse and human NET formation // Nature Chem. Biol. – 2015. – Vol. 11(3). – P. 189-191. https://doi.org/10.1038/nchembio.1735

45. Cedervall J., Dragomir A., Saupe F., Zhang Y., Ärnlöv J., Larsson E., Dimberg A., Larsson A., Olsson A.K. Pharmacological targeting of peptidylarginine deiminase 4 prevents cancer-associated kidney injury in mice // Oncoimmunology. – 2017. – Vol. 6(8). – Art. no. e1320009. https://doi.org/10.1080/2162402X.2017.1320009

46. Lapponi M.J., Carestia A., Landoni V.I., Rivadeneyra L., Etulain J., Negrotto S., Pozner R.G., Schattner M. Regulation of neutrophil extracellular trap formation by anti-inflammatory drugs // J. Pharmacol. Experiment. Ther. – 2013. – Vol. 345(3). – P. 430-437. https://doi.org/10.1124/jpet.112.202879

47. Snoderly H.T., Boone B.A., Bennewitz M.F. Neutrophil extracellular traps in breast cancer and beyond: current perspectives on NET stimuli, thrombosis and metastasis, and clinical utility for diagnosis and treatment // Breast Cancer Res. – 2019. – Vol. 21(1). – Art. no. 145. https://doi.org/10.1186/s13058-019-1237-6

48. Boone B.A., Murthy P., Miller-Ocuin J., Doerfler W.R., Ellis J.T., Liang X., Ross M.A., Wallace C.T., Sperry J.L., Lotze M.T., Neal M.D., Zeh H.J. Chloroquine reduces hypercoagulability in pancreatic cancer through inhibition of neutrophil extracellular traps // BMC cancer. – 2018. – Vol. 18(1). – Art. no. 678. https://doi.org/10.1186/s12885-018-4584-2

49. Boone B.A., Orlichenko L., Schapiro N.E., Loughran P., Gianfrate G.C., Ellis J.T., Singhi A.D., Kang R., Tang D., Lotze M.T., Zeh H.J. The receptor for advanced glycation end products (RAGE) enhances autophagy and neutrophil extracellular traps in pancreatic cancer // Cancer Gene Ther. – 2015. – Vol. 22(6). – P. 326-334. https://doi.org/10.1038/cgt.2015.21

50. Murthy P., Singhi A.D., Ross M.A., Loughran P., Paragomi P., Papachristou G.I., Whitcomb D.C., Zureikat A.H., Lotze M.T., Zeh Iii H.J., Boone B.A. Enhanced Neutrophil Extracellular Trap Formation in Acute Pancreatitis Contributes to Disease Severity and Is Reduced by Chloroquine // Front. Immunol. – 2019. – Vol. 10. – P. 28. https://doi.org/10.3389/fimmu.2019.00028

51. Wolpin B.M., Rubinson D.A., Wang X., Chan J.A., Cleary J.M., Enzinger P.C., Fuchs C.S., McCleary N.J., Meyerhardt J.A., Ng K., Schrag D., Sikora A.L., Spicer B.A., Killion L., Mamon H., Kimmelman A.C. Phase II and pharmacodynamic study of autophagy inhibition using hydroxychloroquine in patients with metastatic pancreatic adenocarcinoma // O oncologist. – 2014. – Vol. 19(6). – P. 637-638. https://doi.org/10.1634/theoncologist.2014-0086

52. Boone B.A., Bahary N., Zureikat A.H., Moser A.J., Normolle D.P., Wu W.C., Singhi A.D., Bao P., Bartlett D.L., Liotta L.A., Espina V., Loughran P., Lotze M.T., Zeh H.J. Safety and Biologic Response of Preoperative Autophagy Inhibition in Combination with Gemcitabine in Patients with Pancreatic Adenocarcinoma // Ann. Surg. Oncol. – 2015. – Vol. 22(13). – P. 4402-4410. https://doi.org/10.1245/s10434-015-4566-4

53. Yang L., Liu Q., Zhang X., Liu X., Zhou B., Chen J., Huang D., Li J., Li H., Chen F., Liu J., Xing Y., Chen X., Su S., Song E. DNA of neutrophil extracellular traps promotes cancer metastasis via CCDC25 // Nature. – 2020. – Vol. 583(7814). – P. 133–138. https://doi.org/10.1038/s41586-020-2394-6

АҢДАТПА

СҮТ БЕЗІ ҚАТЕРЛІ ІСІГІНІҢ ДАМУЫНДАҒЫ ЖАСУШАДАН ТЫС НЕЙТРОФИЛЬДІ ТҰЗАҚТАРДЫҢ РӨЛІ: ӘДЕБИЕТКЕ ШОЛУ

Ә.Т. Омар[1], Н.А. Кабилдина[1], О.А. Понамарева[1], Е.В. Крук[1], М. Маратқызы[1]

[1]«Қарағанды медицина университеті» КЕАҚ, Қарағанды, Қазақстан Республикасы

Өзектілігі: *Нейтрофильді жасушадан тыс тұзақтар (НЖТТ) – нейтрофилдер шығаратын жасушадан тыс торлар. Олар гистондар және нейтрофилді түйіршік ақуыздарымен біріктірілген деконденсацияланған ДНҚ талшығының жасушадан тыс жіптері болып табылады, олар патогендерді кейіннен жоюды жеңілдету үшін иммобилизацияланады.*

НЖТТ түзілуі (нетоз) алғаш рет бактериялық инфекцияға иммундық жауап ретінде анықталды. Алайда, содан бері нетоздың қалыптан тыс бірқатар басқа қабыну жағдайларында, соның ішінде қатерлі ісіктерде болатындығы дәлелденді.

Сүт безінің қатерлі ісігі (СБҚІ) – әйелдер арасындағы қатерлі ісіктерден ең жиі қойылатын диагнозы. Бұл мақалада НЖТТ-нің СБҚІ дамуындағы рөліне, НЖТТ-ны ықтимал диагностикалық биомаркерлер және/немесе қатерлі ісікке арналған клиникалық емдік мақсаттар ретінде пайдалануға назар аударамыз.

Зерттеудің мақсаты *– әдебиет деректері негізінде сүт безі қатерлі ісігінің патогенезіндегі NSCLC рөлін бағалау.*

Әдістері: *2014-2024 жылдар аралығында келесі мәліметтер базасында іздеу жүргізілді: Web of Science, Pubmed, Scopus. 600-ге жуық мақала табылды, қосу және алып тастау критерийлеріне сәйкес 53 мақала талданды.*

Нәтижелері: *Ісіктің дамуындағы НЖТТ рөлі-қатерлі ісіктің иммунередактациясы және иммундық жүйе мен қатерлі ісіктің жасушаларының өзара әрекеттесуі. НЖТТ ісік микроортасында, алыс метастаздардың дамуында негізгі реттеуші рөл атқарады, ісіктің агрессивтілігін күшейтеді, қатерлі ісіктің таралуын және инвазия қабілетін арттырады. НЖТТ сонымен қатар ісікке қарсы әсері де анықталған: тұзақтардың компоненттері қатерлі жасушаларды тікелей жояды.*

Қатерлі ісік кезіндегі НЖТТ өндірісі тромбоциттер, лейкоциттер, метастатикалық ісік жасушалары және бастапқы ісік аймағының өзін қоса алғанда, әртүрлі жасушалар мен қан компоненттері арасындағы өзара әрекеттесуді қамтиды.

Қазіргі уақытта НЖТТ көмегімен қатерлі ісік ауруын емдеудің жалпы қабылданған әдістері жоқ. Бұл емдеу әдістері даму сатысында, НЖТТ-нің әртүрлі нүктелері мен компоненттеріне бағытталған жұмыстар жүргізілуде.

***Қорытынды:** сүт безі қатерлі ісігінде нетоз аурудың жедел дамуымен, метастазбен және асқынулармен байланысты. Мақалада НЖТТ-ге тән ықтимал мақсаттар анықталған, оларды зерттеу және емдеу әдістерін әзірлеу үшін пайдалану керек. Қатерлі ісік пен НЖТТ арасындағы өзара әрекеттесуді жақсырақ түсіну НЖТТ-ге бағытталған дәл емдеу мен диагностиканы жасауға мүмкіндік береді.*

***Түйінді сөздер:** сүт безі қатерлі ісігі, жасушадан тыс нейтрофильді тұзақтар.*

АННОТАЦИЯ

РОЛЬ ВНЕКЛЕТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК В РАЗВИТИИ РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ: ОБЗОР ЛИТЕРАТУРЫ

***А.Т. Омар*[1], *Н.А. Кабилдина*[1], *О.А. Понамарева*[1], *Е.В. Крук*[1], *М. Мараткызы*[1]**

[1]НАО «Медицинский университет Караганды», Караганда, Республика Казахстан

***Актуальность:** Нейтрофильные внеклеточные ловушки (ВНЛ) — это внеклеточные сети, высвобождающиеся нейтрофилами. Они представляют собой внеклеточные нити из деконденсированного ДНК-волокна в комплексе с гистонами и белками гранул нейтрофилов, которые иммобилизуют патогены для облегчения их последующей элиминации.*

Образование ВНЛ (нетоз) впервые было обнаружено как иммунный ответ на бактериальную инфекцию. Однако с тех пор было доказано, что нетоз происходит аномально и при ряде других воспалительных состояний, включая рак.

Рак молочной железы (РМЖ) является наиболее часто диагностируемым злокачественным заболеванием у женщин. В этом обзоре мы сосредоточимся на роли ВНЛ в развитии РМЖ, на использовании ВНЛ в качестве потенциальных диагностических биомаркеров и/или клинических терапевтических мишеней при раке.

***Цель исследования** – оценить роль внеклеточных нейтрофильных ловушек в патогенезе рака молочной железы на основе данных литературы.*

***Методы:** Поиск в базах данных Web of Science, Pubmed, Scopus за 2014-2024 гг. выявил около 600 статей. Проанализировано 53 публикации согласно критериям включения и исключения.*

***Результаты:** Роль ВНЛ в развитии опухоли- иммунноредактирование рака и взаимодействие между иммунной системой и раковыми клетками. ВНЛ являются регуляторами микроокружения опухоли, участвуют в распространении опухоли и в развитии отдаленных метастазов, способствуют повышению агрессивности опухоли и усиливают способность к инвазии. ВНЛ играют значимую роль в регуляции микроокружения опухоли, а также оказывают противоопухолевое действие, поскольку компоненты ВНЛ напрямую убивают раковые клетки.*

Продукция ВНЛ при раке включает взаимодействие между различными клетками и компонентами крови, включая тромбоциты, лейкоциты, метастатические опухолевые клетки и сам участок первичной опухоли.

В настоящее время нет общепринятых способов лечения рака с использованием ВНЛ. Данные методы лечения находятся на стадии разработки, ведутся работы по нацеливанию на различные точки и компоненты ВНЛ.

***Заключение:** Нетоз при РМЖ связан с ускоренным прогрессированием заболевания, метастазированием и осложнениями. В работе определены потенциальные специфичные для ВНЛ цели, которые следует исследовать и использовать для разработки методов лечения. Лучшее понимание взаимодействия между раком и ВНЛ позволит разработать прецизионные методы лечения и диагностики, нацеленные на ВНЛ.*

***Ключевые слова:** рак молочной железы (РМЖ), внеклеточные нейтрофильные ловушки (ВНЛ).*

***Research transparency:** The authors are fully responsible for the content of this article.*
***Conflict of Interests:** The authors declare no conflict of interests.*
***Funding:** The authors declare no funding for the study.*
***Authors Contribution:** conceptualization, writing – Original Draft Preparation – A.T. Omar, N.A. Kabildina; project administration – N.A. Kabildina, O.A. Ponamareva; investigation – A.T. Omar, M. Maratkyzy; validation – E.V. Kruk*

Information about the Authors:
A.T. Omar (corresponding author) – teacher-researcher (postdoctoral fellowship) of the Department of Oncology and Radiation Diagnostics, Karaganda Medical University; oncologist, chemotherapist, "Multidisciplinary Hospital No. 3 of Karaganda" UZKO, Karaganda, Kazakhstan, tel.: +77477043103, email: omar.aigerim30@gmail.com, ORCID: 0009-0003-1021-6964;
N.A. Kabildina – Candidate of Medicine, Professor, Head of the Department of Oncology and Radiation Diagnostics, Karaganda Medical University, Karaganda, Kazakhstan, tel.: +77015338259, email: nailyakabildina@mail.ru, ORCID: 0000-0002-5616-1829;
E.V. Kruk – Candidate of Medicine, Associated Professor, Department of Oncology and Radiation Diagnostics, Karaganda Medical University, Karaganda, Kazakhstan, tel.: +77059656551, email: kostrova@qmu.kz, ORCID: 0000-0003-0995-1235;
O.A. Ponamareva – Candidate of Medicine, Head of the Department of Biomedicine, Karaganda Medical University, Karaganda, Kazakhstan, tel.: 87017714620, email: Ponamareva@qmu.kz, ORCID: 0000-0002-0222-5794;
M. Maratkyzy – Associated Professor, Department of Oncology and Radiation Diagnostics, Karaganda Medical University, Karaganda, Kazakhstan, tel.: 87001425730, email: sanjarik1616@mail.ru , ORCID: 0000-0003-4787-2175.

***Address for Correspondence:** A.T. Omar, Karbyshev St. 4, apt. 78, Karaganda 100026, the Republic of Kazakhstan.*