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PERSPECTIVES OF USING THE EXTRACELLULAR NEUTROPHIL TRAP LEVELS IN COLORECTAL CANCER: A LITERATURE REVIEW

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ABSTRACT

Relevance: *This literature review evaluates an alternative type of neutrophil immune response – the ability for NETosis or forming neutrophil extracellular traps (NETs). NETs influence the processes of carcinogenesis and cancer metastasis and play a role in the formation of tumor microenvironment and tumor-associated inflammation. The study of netosis has provided a deeper understanding of the mechanisms of intercellular interactions of the tumor microenvironment. NETs can also potentially become prognostic markers and predictors of complications of antitumor treatment of various cancers, including colorectal cancer (CRC).*

The study aimed to *summarize and systematize the current information on NETs and the impact of this phenomenon on the course of CRC and metastasis, as well as identify potential clinical points for using this marker in oncological practice.*

Methods: *The articles were searched and selected in Pubmed, Web of Science, Scopus, and RSCI databases by keywords among articles published in the past 10 years.*

Results: *NETs play an important role in the immune response to tumor niches and the metastasis of various solid tumors. There are data on the possibility of using NETs as a prognostic marker in various oncologic diseases. Experimental and clinical studies showed a potential relationship between NET levels and chemotherapy resistance and the impact of chemotherapy on the incidence of various complications. Chemotherapy with 5-Fluorouracil, according to the results of experimental studies, significantly increases the formation of NETs. The influence on the mechanism of NET release showed limited clinical efficacy of chemotherapy in CRC patients with PIK3CA mutation.*

The phenomenon of NETs is still poorly understood, and more studies are needed to widely implement this indicator into routine practice; however, research in this direction has the potential to have broad prospects for clinical application.

Conclusion: *Advances in immunology and the discovery of the netosis process have led to a deeper understanding of the mechanisms of interactions in the tumor microenvironment. Studying this process may make it possible to control or predict cancer progression and complications of antitumor treatment.*

Keywords: *neutrophil extracellular traps (NETs), netosis, colorectal cancer (CRC), oncology, immunology, biomarkers.*

Introduction: Colorectal cancer (CRC) is among the leading nosologies in the structure of cancer incidence worldwide and in Kazakhstan. CRC ranks 3rd-4th in prevalence, counting for 10% of all detected malignant neoplasms, and 2nd in mortality worldwide (ceding only to breast cancer and lung cancer in these indicators) [1, 2].

In metastasis, tumor cells exhibit certain characteristics, including increased expression of cell adhesion molecules, chemokine receptors, and strengthening of cytoskeletal changes that promote migration in response to chemotactic signals to distant organs [3].

According to the literature, up to 25% of all tumors could result from chronic inflammation, likely to generate chemoattractants that promote tumor cell proliferation, adhesion, and migration. Neutrophils play a key role in the immune response process and, according to some studies, accumulate in the pre-metastatic organs in increased numbers [4, 5].

Apart from the well-known phagocytosis mechanism, neutrophils can form sticky, web-like structures from decondensed chromatin filaments, containing an abundance of histones and proteins from neutrophil granules called the neutrophil extracellular traps (NETs). Studies suggest that NETs play a role in carcinogenesis and cancer metastasis [6].

For example, D. Lin et al. showed a connection between the formation of NETs in the vessels of the microcirculatory bed under the influence of systemic inflammation with the subsequent capture of cancer cells in the process of netosis in both the liver and lungs [7]. Intravascular neutrophil extracellular traps can increase vascular permeability, promoting the extravasation of immune and tumor cells from blood vessels to organs, thus providing the basis for hematogenous metastasis.

Some studies have also shown that body stress due to surgical treatment can contribute to cancer spread, possibly associated with an inflammatory process [8].

In addition, staining of tissue samples from patients with CRC using immunohistochemical methods revealed the presence of NETs in both the primary tumor and regional affected lymph nodes [9].

Based on these data, it can be assumed that NETs potentially play a role in the provision of proliferative signals and may be involved in colon cancer metastasis.

The study aimed to summarize and systematize the current information on NETs and the impact of this phenomenon on the course of CRC and metastasis, as well as identify potential clinical points for using this marker in oncological practice.

Materials and methods: We searched and selected articles published in the past 10 years using keywords in Pubmed, Web of Science, Scopus, and RSCI databases. We selected and analyzed 50 articles and generalized the relevant data in a review.

Results:

Molecular mechanisms of formation of neutrophil extracellular traps.

The process of NETs formation is known as netosis. Initially, netosis was called a new type of protective neutrophil death, but later, it was found that pathogenic stimulation can also cause viable and rapid production of NETs without affecting neutrophil viability [10].

In a further study of the mechanisms of netosis in order to clarify the mechanism of NETs formation, M. Ravindran et al. suggested two ways of netosis formation:

1) NADPH-oxidase (NOX)-dependent and lytic formation of NETs;

2) NADPH-oxidase (NOX)-independent nonlytic formation of NETs [11].

The first NOX-dependent lytic mechanism of netosis begins with recognizing pathogens or activating various receptors, including Toll-like receptors (TLRs), antibody fragment receptors, complement receptors, and others. Activation of these receptors eventually leads to the formation of reactive oxygen species that can stimulate the PAD4 enzyme, which leads to the decondensation of nuclear chromatin. Besides, the neutrophil granule protein myeloperoxidase promotes the translocation of neutrophil elastase into the nucleus, which promotes chromatin decondensation, nuclear membrane destruction, and chromatin release into the cytosol, where cytosol and granule proteins are attached to the DNA. Ultimately, NETs are released with the membrane destruction followed by neutrophil death [12].

Several studies found that the formation of NETs can occur independently of cell death, which was later specified as *the vital* or *nonlytic* mechanism of netosis. As a rule, this mechanism is characterized by the lack of participation in the NOX pathway and does not lead to oxidant formation (reactive oxygen species, ROS) [13].

The main difference between the lytic and nonlytic mechanisms of netosis is that nonlytic netosis occurs within minutes of stimulation without forming reactive oxygen species, while lytic netosis requires several hours of stimulation and ROS formation. The netosis nonlytic mechanism is activated by bacteria, platelet bacterial products, or complement proteins [10].

In both mechanisms of netosis, the chromatin decondensation and translocation of neutrophil granule elastase occur similarly. However, chromatin "encrusted" by bactericidal proteins is released by rupture of the nuclear envelope rather than by apparent destruction of the nuclear membrane. Nuclear membrane rupture and vesicle-mediated extracellular transport of NETs occur independently of plasma membrane disintegration [14, 15].

Scientists have connected the NETs formation with the pathogenesis of many gastrointestinal tract diseases, including inflammatory bowel disease, liver disease, and acute pancreatitis [16, 17]. Over the years, NETs have been associated with various types of cancer, suspecting their involvement in tumor growth or destruction, depending on the type of cancer, the state of the immune system, or the tumor microenvironment [18-20].

Consequently, NETs and their role in the immune response are also the object of active study in a wide range of nosologies, including cancer diseases.

The role of NETs in the microtumor microenvironment.

The tumor microenvironment is a complex environment that includes an extracellular matrix, microcirculation vessels, inflammatory factors, and immune cells, in which tumor cells proliferate and gain the ability for metastatic growth [21].

One microenvironment component is tumor-infiltrating immune cells such as neutrophils, which are involved in various stages of tumor genesis and can be divided into N1/N2 subtypes according to different functions and phenotypes. In light of the rapid growth of tumors and subsequent local necrosis caused by insufficient blood supply or treatment, a large number of inflammatory factors and damaging molecular patterns are discharged [22]. Neutrophils are mobilized into the tumor microenvironment under the influence of various pro-inflammatory factors, such as the cytokines CXCL1, IL-8/CXCL8, and CXCL12, complement proteins C3a and C5a, and lipid metabolism metabolites LTB4 [23-24]. These pro-inflammatory factors induce the formation of NETs to a certain extent. Besides, damaging molecular factors produced by necrotic cells in the microtumor environment induce TLR activation-dependent netosis. Clinical methods of treatment, such as radiotherapy and chemotherapy, can directly or indirectly induce netosis, which contributes to resistance to therapy [25-26].

NETs networks can promote tumor progression by inhibiting the proliferation, activation, and function of CD8+ T cells and NK cells. In addition, NETs can carry the programmed cell death ligand-1 (PD-L1) from the neutrophils surface, which is involved in immune regulation as an inhibitory component in the immune microenvironment. Based on this, inhibition of netosis can be an addition to immunotherapy. Besides, NETs can promote tumor growth, change the metabolism of tumor cells, and promote tumor metastasis by capturing cancer cells or directly binding to nucleic acid receptors on the tumor cell surface [27, 28].

Summarizing all aforesaid information, NETs play an important role in carcinogenesis and forming the tumor microenvironment, potentially impacting the clinical aspects, such as immunotherapy of malignant tumors.

The role of NETs in the pathogenesis of various types of cancer.

Elevated NETs levels in blood plasma have been observed in patients with various types of cancer, including lung, pancreatic, and bladder cancer [17-20, 29].

According to experimental studies, it was assumed that cancer cells can independently induce the NETs for-

mation, which in turn promotes further adhesion and growth of cancer cells in breast cancer metastases to the lungs. A higher level of netosis was also revealed in breast cancer metastases to the liver, and NETs level in blood serum showed the prognostic value of this indicator as a risk factor for liver metastases in patients with early stages of breast cancer. It was also found that the CCDC25 transmembrane protein of breast cancer cells can recognize distant NETs and attract the tumor cells in response to this [28].

In vitro experiments have shown that NETs can induce invasion and migration of breast cancer cells and subsequent digestion of NETs by DNase I-coated nanoparticles, as well as reduce metastasis of breast cancer cells to the lungs in mice [30].

The NETs formation is observed in pneumonia caused by exposure to smoke or nasal instillation of lipopolysaccharide in animal models. The NETs-related proteases, neutrophil elastase, and matrix metalloproteinase 9 can break down basal laminin and thus promote the growth of "dormant" cancer cells by activating alpha-3 beta-1 integrin signals. NETs can act as a trap to capture the circulating cancer cells in the microcirculatory bed of organs distant from the primary tumor focus. In a mouse model of sepsis, circulating lung carcinoma cells have been reported to be retained by NETs in liver microcirculation vessels and cause metastatic lesions following injection of tumor cells. Besides, treatment with DNase or a neutrophil elastase inhibitor showed a trend towards a reduced risk of cancer metastases spread. The neutrophil subpopulation with high CD16 counts and low CD62 counts has a higher ability to produce NETs, and in patients with squamous cell carcinoma of the head and neck, this subpopulation shows better survival. Another study showed that tumors can release granulocytic colony-stimulating factors into the bloodstream and promote the accumulation of intra-tumoral NETs and tumor growth, stimulating the circulating neutrophils [31].

The blood samples analysis revealed elevated levels of NETs in patients with gastric cancer (GC). The results indicate a higher diagnostic value of NETs compared to such tumor markers as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9).

These data indicate the key role of NETs in the GC carcinogenesis. Another study reported that low-density neutrophils (LDNs) from postoperative lavage generate huge NETs in vitro culture. Moreover, the co-transfer of peritoneal LDNs with human GC cells enhances the peritoneal metastatic spread in vivo [32].

Indicatively, detecting NETs levels at an early stage of tumor development or premetastatic stage can help predict the severity of disease progression, and targeting the impact on NETs with specific inhibitors could potentially help to control the tumor growth and synergized with other antitumor treatments [27, 28, 33, 34].

The role of DNase and PAD4 inhibition on NETs levels in various cancer types.

Given the role of NETs in cancer progression and metastasis, the possibilities of blocking the process of netosis have been studied. The most convenient target for that is the extracellular part of DNA. The use of DNase enzymes led to a decrease in netosis. There is also data on the reduction of lung metastases in mouse models using these drugs [29].

Currently, DNases are applied in a fairly limited number of cases; for example, inhaled forms of DNases are used for cystic fibrosis and help reduce sputum viscosity through NET destruction. The DNase preparations are not recommended for systemic use due to marked toxicity during parenteral use [35].

The potential use of DNase preparations is limited due to a small amount of available data. But despite this, there are studies on the use of DNase in thrombosis associated with cancer [36, 37], and there are data on the successful local use of DNase in cancer, in particular, based on the data obtained by researchers from Spain who used this drug on urothelial bladder cancer cells in vitro [38].

Inhibition of PAD4 in experimental models also demonstrated the interruption of the netosis process. For example, prostaglandin E2 and chlorine inhibit tumor-induced netosis, reducing cancer patients' blood clots [39].

It is worth noting that no drugs would have a selective effect on NETs without affecting the immune system in the form of excessive immunosuppression or immune stimulation, and the issue of developing such drugs remains open.

Involvement of NETs in CRC progression and metastatic spread.

Several studies have confirmed that patients with CRC can excrete elevated levels of NETs in vivo and in vitro, which are mainly scattered in the primary tumor foci and along the CRC tumor margin [9, 40].

Despite the widespread use of chemoradiotherapy and screening programs for early detection of CRC, about half of patients who undergo therapeutic resolution resection develop metastatic disease. Accumulated data suggest that preoperative systemic inflammation may be involved in CRC recurrence after the surgical resection. In addition, several mouse models and human observational studies have demonstrated the potential prognostic value and association of NETs with the progression of CRC. Recurrence and metastasis may be associated with NETs production due to perioperative systemic inflammation, such as sepsis or NETs production in a surgical wound [41].

Several mechanisms have been proposed that can trigger the formation of NETs in the CRC microenvironment. For example, polyphosphate (polyP) expressed by CD68+ mast cells has been shown to stimulate neutrophils to form NETs in CRC ex vivo. Activation of the mutated KRAS gene regulates the oncogenic malignant transformation followed by the proliferation of cancer cells through activation of the RAS/MAPK signaling pathway, which occurs in 40-50% of CRC cases. Malignant cells can secrete exosomes to control the cellular microenvironment, and studies have shown that CRC cells with the KRAS mutation can transfer this mutation to neutrophils via exosomes, which induces neutrophil mobilization and subsequent formation of NETs by increasing interleukin-8 (IL-8) levels both in vivo and in vitro. The production of elevated levels of IL-8 and the formation of NETs may stimulate CRC cell

proliferation and ultimately worsen the course and prognosis in that category of patients [40, 42].

Effect of IL-8 and the microtumor environment on netosis in CRC.

It is known that IL-8, through its CXCR1 and CXCR2 receptors, attracts neutrophils and other myeloid leukocytes to the site of infection. IL-8 acts as a multifaceted chemotactic stimulus used by the tumor to simultaneously induce transmigration and angiogenesis. IL-8 released by tumor cells can also promote their survival and proliferation by activating the autocrine system, promoting the angiogenesis and tumor infiltration of neutrophils.

In some studies, IL-8 has been shown to promote angiogenesis and cancer metastasis by directly stimulating the formation of NETs through activation of the Src, ERK, and p38 signaling pathways. NETs can directly stimulate the TLR9 pathways, affecting cancer progression. The myeloid suppressor cells expressing CXCR1 and CXCR2 are also stimulated by IL-8. This increases the NET levels, which, in turn, can capture the tumor cells [43].

R.F. Rayes et al. found that serum levels of IL-8 and its receptor CXCR2 have been significantly elevated at different stages of CRC compared to normal samples. Secreted IL-8 significantly stimulates proliferation, penetration, and migration and enhances the angiogenesis around the tumor. Moreover, IL-8-stimulated neutrophils secreted by NETs contribute to further invasion and proliferation of CRC [44].

It has been established that the formation of NETs not only enhances the proliferation of CRC cells but also stimulates the process of metastatic spread. NETs promote the adhesion of circulating tumor cells to the hepatic or pulmonary endothelial surface and thus enhance the migration of CRC cells to major vital organs and prognostically significant areas of the body, such as the liver, lungs, and peritoneal cavity. According to population studies, about 25-30% of patients with colon cancer develop concomitant liver metastases, and most of them have a significant elevation of NETs formation [45-49].

NETS are not cytotoxic for CRC cells captured in the liver. However, they can increase their malignant potential by stimulating the tumor production of IL-8, which, in turn, stimulates the formation of even more NETs, creating a vicious cycle provoking the progression of liver metastases [45]. In addition, the NETs-associated cell adhesion molecule 1 (CEACAM1), bound to carcinoembryonic antigen (CEA), has been shown to stimulate the movement of CRC cells to the liver both in vitro and in vivo [46].

Alongside the anatomical and above-mentioned immunological prerequisites for CRC metastasis to the liver, dysregulation of the intestinal microbiota also plays an important role in the progression process. Numerous studies have found a relationship between certain strains of intestinal bacteria (e.g., pks + E. coli and Bacteroides fragilis) and the occurrence of CRC, and intestinal bacteria translocation is commonly observed during the CRC progression. The intestinal microbiota forms the tumor microenvironment through direct contact with immune cells or through its functional metabolites. However, the question of how the intestinal microbiota contributes to CRC metastasis remains controversial. Meanwhile, recent studies have revealed the spread of bacteria from the intestinal lumen to the liver, suggesting intestinal microbiota's role in forming tumor niches. Protumor pre-metastatic niches in the liver are characterized by infiltration of immunosuppressive cells and reinforcement of pro-inflammatory immune responses [47].

Discussion: The study of NETs is one of the promising areas of oncology and immunology, which pushes us to look for clinical points of application for the phenomenon of netosis and the regulation of the activity of this process. Given their role in carcinogenesis and metastasis, NETs may play a role in personalizing treatment based on NETs levels and influence the course of systemic therapy for CRC.

According to the results of experimental studies conducted by L. Basyreva et al. [48], during prolonged incubation of whole blood with free 5-fluorouracil (5-FU) at certain concentrations, the chemotherapy drug has contributed to a significant NETs release (the maximum number of NETs was formed at a concentration of free 5-FU of 0.1 μg/ml during incubation from 2 to 3 hours). The authors considered an increase in the number of NETs combined with an unchanged total number of leukocytes to be a manifestation of vital netosis. The authors suggest that the release of mitochondrial DNA forms NETs, and neutrophils retain the nucleus and remain alive. It is reported that about 3% of the cells could generate more than one NETs from a single cell. In this experimental work, it was also demonstrated that the application of 5-FU coated with composite polymer nanoparticles significantly reduces netosis.

In the studies of Mousset et al. [25, 50], the following hypothesis has been expressed: strategic exposure to NETs is a promising direction for identifying combination therapies that can help counter resistance or increase the effectiveness of chemotherapy, as well as limit the complications caused by that type of treatment. In this experimental work on mouse models, the elevation of renal parameters levels, such as creatinine and urea, was noted during treatment with cisplatin, which may suggest the development of acute kidney injury. In the course of the experimental work, the studied mice showed an increase of the neutrophils levels that form NETs in the kidneys of mice treated with cisplatin, and that NETs targeting not only restored the sensitivity of cancer cells to chemotherapy but also significantly improved the kidney function. According to the authors, these findings are consistent with the results of similar studies and may confirm that the side effects of chemotherapy in the form of acute kidney injury are partially mediated by NETs generated in response to treatment.

In the work of Li Y. et al., the role of NETs in the course of chemotherapy for CRC was studied. These researchers studied treatment using a glutaminase inhibitor (CB-839), which inhibits the NETs formation, and 5-FU chemotherapy in CRC with PIK3CA mutation, which is found in 30% of patients. The researchers chose this molecular type of tumor because, in previous experimental work, the infiltration of the tumor with NETs was significantly lower [49].

The combination of NETs inhibitors and 5-FU induces IL-8 expression in tumor cells, which attracts neutrophils to the tumor niche. This combination also increases the level of reactive oxygen species in neutrophils, inducing the formation of NETs. The NETS-bound cathepsin G (CG) enters the cancer cells via the receptor for advanced glycation end (RAGE), after which CG can break down the sequestration protein 14-3-3ε, releasing the active Bcl-2-associated protein X (Bax), which in turn activates the apoptosis pathway.

Thus, in the context of CRC, NETs have shown a synergizing role in conjunction with antitumor chemotherapy. Thus, A. Mousset et al. mentioned the previous phase 2 clinical trials using this drug regimen, which did not have positive results [51] since the study sample did not have objective answers, despite the positive relationship between the NETs level elevation and prolongation of progression-free survival in tumor biopsies after conducted treatment.

Accordingly, the complexities of converting promising pre-clinical results into successful clinical outcomes highlight the need to consider factors such as patient heterogeneity, tumor-specific characteristics, and sample size.

One of the other clinically relevant treatment-limiting side effects of chemotherapy is chemotherapy-induced peripheral neuropathy. In the course of research conducted by C.Y. Wang et al., mice treated with oxaliplatin chemotherapy have been shown to have NETs accumulation in the dorsal radicular ganglia and extremities, which disrupts the microcirculation. In turn, inhibition of NETs formation successfully counteracted the chemotherapeutic hyperalgesia and restored the peripheral microcirculation [52].

A. Mousset et al. concluded that a combination of control of NETs levels and a targeted effect on their formation in the blood can potentially:

1. Reduce the serious side effects of anticancer therapy in the conditions, such as acute kidney injury, chemotherapy-induced neuropathy, and potentially gastrointestinal complications, all of which may be a reason for discontinuation of systemic therapy;

2. Predict the development of chemoresistance;

3. Reduce the time spent on chemotherapy and influence the effectiveness of treatment [25, 51].

In summary, it should be highlighted that despite the relevance of netosis, this phenomenon is still poorly understood. In order to extend our understanding of the role of NET formation, more experimental studies are necessary. The number and quality of clinical studies of this phenomenon in malignant neoplasms at the moment may not be enough for the widespread introduction of NETs as a marker for the prognosis of the course of cancer or its treatment. However, considering the promising results of the existing work, research in this direction could potentially have broad prospects for clinical application.

Conclusion: The development of immunology and the discovery of the process of netosis made it possible to better understand the mechanisms of intercellular interactions of the tumor microenvironment. A thorough study of each step of this process can help to find the leverages and targets to control and prevent tumor progression. Also, the NETs levels can potentially become the markers for prognosis of the course of cancer and perhaps even be a predictor of complications of antitumor treatment. The future outlook and lack of studies on this phenomenon are considered topical issues in immunology and oncology.

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АҢДАТПА

КОЛОРЕКТАЛЬДЫ ҚАТЕРЛІ ІСІККЕ ЖАСУШАДАН ТЫС НЕЙТРОФИЛЬДІ ТҰЗАҚ ДЕҢГЕЙЛЕРІН ҚОЛДАНУ КЕЛЕШЕГІ: ӘДЕБИЕТКЕ ШОЛУ

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Сәйкестік: *Бұл жұмыста нейтрофилдердің иммундық реакциясының балама түрі-нетозға қабілеттілік немесе жасушадан тыс «тұзақтардың» пайда болуын (ЖТТ) бағалауға бағытталған зерттеу ұсынылған. ЖТТ қатерлі ісік канцерогенезі мен метастаз процесіне әсер етеді, ісік микроортасының және ісікпен байланысты қабынудың қалыптасуында рөлі атқарады. Нетоз процесінің зерттелуі ісік микроортасының жасушааралық өзара әрекеттесу механизмдерін тереңірек түсінуге мүмкіндік берді. ЖТТ сонымен қатар әртүрлі онкологиялық аурулардың, сондай-ақ әсіресе колоректальды қатерлі ісіктің болжамды белгілері болуы мүмкін, тіпті ісікке қарсы емдеудің асқынуларының болжаушысы болуы мүмкін.*

Зерттеудің мақсаты *– бұл әдебиет шолу ЖТТ бойынша актуальды мәлімет жүйелеуге және жалпылауға, және осы феноменның тоқ және тік ішек обыры ағымына әсер етуіне арналған. Осы маркердің онкологиялық практикада потенциалдық клиникалық қолдануын анықтау үшін жасалынған.*

Әдістері: *Pubmed, Web of Science, Scopus, РИНЦ базаларының ішінен түйін сөздер бойынша ізделу және талдау жасалынды; осы әдебиет шолына кейінгі 10 жылдың көлемінде кірген жұмыстар алынды.*

Нәтижелері: *ЖТТ ісіктік ойықша иммундық реакцияны қалыптастыруда және әртүрлі солидті ісіктердің метастаз беру процесінде маңызды рөл атқарады. ЖТТны әртүрлі онкологиялық ауруларда болжамды маркер ретінде пайдалану мүмкіндігі туралы деректер бар. Сондай-ақ, эксперименттік және клиникалық зерттеулер жүргізілді, олар ЖТТ деңгейлерінің ықтимал байланысын және химиотерапияға төзімділіктің қалыптасуын, сондай-ақ химиотерапияның әртүрлі асқынуларының жиілігіне әсерін көрсетті. Эксперименттік жұмыстардың нәтижелері бойынша 5-фторурацилмен химиотерапиясы ЖТТ түзілуін едәуір арттырады. ЖТТ босату механизміне әсері PIK3CA мутациясы бар колоректальды обыр бар пациенттерде химиотерапия жүргізуде шектеулі клиникалық тиімділікті көрсетті.*

ЖТТ феномені әлі де жақсы зерттелмеген және бұл көрсеткішті күнделікті тәжірибеге енгізу үшін көбірек зерттеулер жүргізу қажет; дегенмен, осы бағыттағы зерттеулер клиникалық қолдану үшін келешекте үлкен нәтижелерге ие болуы мүмкін.

Қорытынды: *Иммунологияның дамуы және нетоз процесінің ашылуы ісік микроортасындағы өзара әрекеттесу механизмдерін тереңірек түсінуге мүмкіндік берді. Бұл процессті зерттеу онкологиялық аурулардың дамуын және ісікке қарсы емдеудің асқынуларын бақылауға немесе болжауға мүмкіндік береді.*

Түйінді сөздер: *жасушадан тыс нейтрофильді тұзақтар, нетоз, колоректальды қатерлі ісік, онкология, иммунология, биомаркерлер.*

АННОТАЦИЯ

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ УРОВНЕЙ ВНЕКЛЕ-ТОЧНЫХ НЕЙТРОФИЛЬНЫХ ЛОВУШЕК ПРИ КОЛОРЕКТАЛЬНОМ РАКЕ: ОБЗОР ЛИТЕРАТУРЫ

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Актуальность: *В данной работе представлена оценка возможности альтернативного вида иммунного ответа нейтрофилов – способности к нетозу, или же образованию «внеклеточных ловушек» (ВНЛ). ВНЛ оказывают влияние на процессы канцерогенеза и метастазирования рака, играют роль в формировании опухолевого микроокружения и опухоль-ассоциированного воспаления. Изучение нетоза позволило глубже понять механизмы межклеточных взаимодействий опухолевого микроокружения.ВНЛ также потенциально могут стать маркерами прогноза течения и предикторами осложнений противоопухолевого лечения различных онкологических заболеваний, в том числе колоректального рака (КРР).*

Цель исследования *– обобщение и систематизация актуальной информации по внеклеточным нейтрофильным ловушкам, их влиянию на течение и процесс метастазирования колоректального рака и возможности применения в клинической практике.*

Методы: *Произведен поиск и отбор статей в базах данных Pubmed, Web of Science, Scopus, РИНЦ по ключевым словам исследования; в обзор были включены статьи давностью не более 10 лет.*

Результаты: *ВНЛ играют важную роль в иммунном ответе на опухолевые ниши и процесс метастазирования различных солидных опухолей. Имеются данные о возможномсти использования ВНЛ в качестве прогностического маркера при различных*

онкологических заболеваниях. Экспериментальные и клинические исследования показали потенциальную взаимосвязь уровней ВНЛ и формирования резистентности к химиотерапии, а также влияние химиотерапии на частоту различных осложнений. Химиотерапия 5-Фторурацилом, по результатам экспериментальных работ выраженно повышает образование ВНЛ. Влияние на механизм высвобождения ВНЛ показало ограниченную клиническую эффективность при проведении химиотерапии у пациентов с КРР с мутацией PIK3CA.

Феномен ВНЛ все еще недостаточно изучен, и необходимо проведение большего количества исследований для широкого внедрения этого показателя в рутинную практику, однако исследования в данном направлении потенциально могут иметь широкие перспективы для клинического применения.

***Заключение:** Развитие иммунологии и открытие процесса нетоза позволило глубже понять механизмы взаимодействий в опухолевом микроокружении. Изучение этого процесса может позволить контролировать либо прогнозировать прогрессирование онкологических заболеваний и осложнений противоопухолевого лечения.*

***Ключевые слова:** внеклеточные нейтрофильные ловушки (ВНЛ), нетоз, колоректальный рак (КРР), онкология, иммунология, биомаркеры.*

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