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# The concept of thromboinflammation underlying thrombotic complications, tumor progression and metastasis in gynecological cancer patients

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**Abstract**

The results of recent studies show that tumor biology, coagulation activation, and inflammatory reactions profoundly contribute to the thrombosis pathogenesis in cancer as well as tumor progression, metastasis, and developing chemoresistance. Cancer is an independent predictor of thrombosis. During carcinogenesis, tumor cells express proinflammatory cytokines, proangiogenic and procoagulant factors, and also stimulate other cells to express various components promoting emerging thromboinflammation. The discovery of neutrophil extracellular traps (NETs) provides an opportunity to take a new look at biology and a role neutrophils may play in thromboinflammation and tumorigenesis. The close interplay between tumor cells, tumor-associated neutrophils and NETs as well as other players in the tumor microenvironment underlies activation of thromboinflammation in cancer patients not only resulting in thrombus formation, but also promoting tumor growth and dissemination.

**Keywords:** thromboinflammation, NETosis, neutrophil extracellular traps, NETs, neutrophils, chemoresistance, thrombosis

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# Концепция тромбовоспаления как основы тромботических осложнений, прогрессии опухоли и метастазирования у онкогинекологических больных

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**Резюме**

Результаты исследований последних лет показывают, что в патогенез тромбоза при раке, а также в прогрессию опухоли, метастазирование и формирование химиорезистентности большой вклад вносят биология опухоли, активация свертывания и воспаления. Рак является независимым предиктором тромбоза. Опухолевые клетки в процессе канцерогенеза экспрессируют провоспалительные цитокины, проангиогенные и прокоагулянтные факторы, а также стимулируют другие клетки к экспрессии различных компонентов, способствуя развитию тромбовоспаления. Открытие внеклеточных ловушек нейтрофилов (англ. neutrophil extracellular traps, NETs) дает возможность по-новому взглянуть на биологию нейтрофилов и их участие в тромбовоспалении и опухолевом процессе. Тесное взаимодействие между опухолевыми клетками, опухоль-ассоциированными нейтрофилами и NETs с участием других игроков микроокружения опухоли лежит в основе активации тромбовоспаления у онкологических пациентов, что не только приводит к тромбообразованию, но и способствует росту и диссеминации опухоли.

**Ключевые слова:** тромбовоспаление, нетоз, внеклеточные ловушки нейтрофилов, NETs, нейтрофилы, химиорезистентность, тромбоз

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## Introduction / Введение

For almost 150 years, there has been known the close connection between cancer and thrombosis. In the last 20 years, the international community focused significant attention on the problem of cancer-associated thrombosis. The relevant mechanisms and biomarkers have been extensively investigated, and new risk assessment scales for cancer-associated thrombosis as well as a search for new therapeutic targets is underway. Besides that thromboembolic complications the cause a direct harm to cancer patients, cancer-associated thrombosis hinders proper antitumor therapy. Patients on long-term anticoagulant

therapy after a thrombosis episode often cannot undergo surgical intervention due to high risk, nor can they receive several effective chemotherapy agents with prominent procoagulant effects. Moreover, prolonged use of anticoagulants increases the risk of bleeding in cancer patients. Although oral anticoagulants, Xa inhibitors approved for use in patients with cancer-associated thrombosis, demonstrated effectiveness and the opportunity for use as an alternative means to low molecular weight heparin, they, nevertheless, may result in increased risk of bleeding, especially in certain tumors, and interactions with antitumor agents.

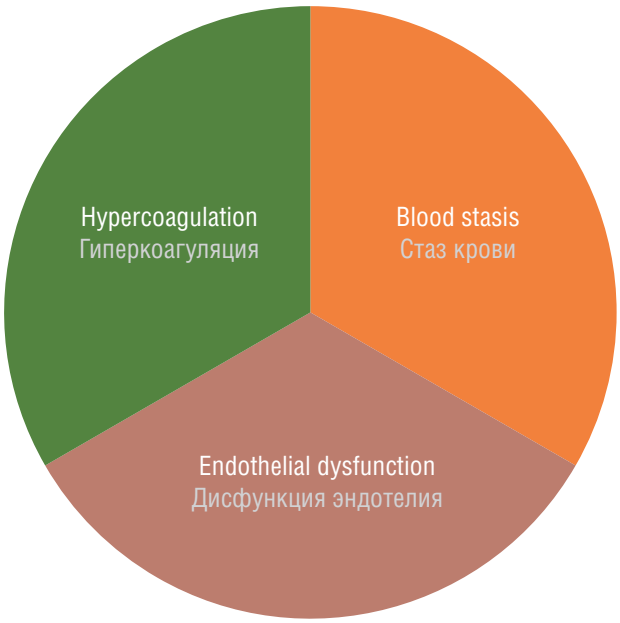
Traditionally, cancer-associated thrombosis has been viewed solely from the perspective of venous thromboembolism. However, recent studies demonstrated that oncological patients also have an increased risk of arterial thrombosis. Currently, cancer-related arterial thrombosis is a promising task for development focused on clarifying the underlying mechanisms and risk factors.

The increased risk of thrombosis observed in gynecological cancer patients has been traditionally explained by cancer potential to affect all components of Virchow's triad (hypercoagulation, stasis, and endothelial dysfunction). Numerous research results obtained in recent years allow us to describe thrombosis pathogenesis in cancer patients by another triad, namely, the thromboinflammation triad (**Fig. 1**) that will consist of tumor tissue-related biological properties and hemostasis activation as well as tumor-triggered inflammatory reactions. It is now evident that dysregulated hemostasis in cancer patients not only leads to thrombosis but also promotes tumor growth and metastasis spreading.

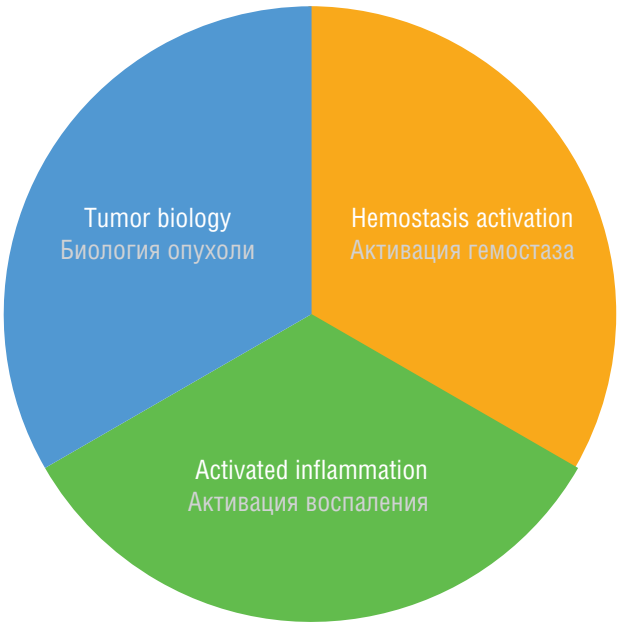
## Thromboinflammation: definition of concept / Тромбовоспаление: определение понятия

The concept of thromboinflammation is generally traced back to 2004 when V. Brinkmann and colleagues discovered neutrophil extracellular traps (NETs) and the process by which they are formed, known as NETosis [1]. The concept of thromboinflammation encompasses the mutual activation of the hemostasis system and inflammatory responses [2].

The process of thromboinflammation results from development and interaction between other simpler events in living organisms. In the early stages of animal evolution, responses to injury and infectious agents were unified. Such responses are the prototypes of modern thromboinflammatory reactions. For example, coagulation accounted not only for hemostasis after a blood vessel damage but also for inflammation and regeneration. In some invertebrates, coagulation still occurs in the hemolymph involving hemocytes. In more developed vertebrates, the latter represent predecessors of modern platelets. The external factor's influence results in initiating hemocyte-mediated hemolymph coagulation along with parallel pathogen




**Virchow's triad / Триада Вирхова**




**Thromboinflammatory triad / Триада тромбовоспаления**

**Figure 1.** Virchow's triad and thromboinflammation triad [drawn by authors].

**Рисунок 1.** Триада Вирхова и триада тромбовоспаления [рисунок авторов].

capture to limit their spread. This process is an early fundamental response that later divided into three systems: hemostasis, immunity, and inflammation. Today, in humans, thromboinflammation involves platelets, the hemostasis system, complement components, cells participating in inflammatory responses, leukocytes, neutrophils, the pro-inflammatory cytokines they release, complex process as well as NETs as one of the outcomes of multi-faceted events, and innate immune cells. Thromboinflammatory responses were identified in various diseases, including critical conditions such as sepsis and stroke.

**Neutrophils / Нейтрофилы**

Polymorphonuclear neutrophil is the most common type of leukocytes. The name of this cell type is accounted for by the lack of staining during laboratory diagnostics and observed lobed nuclear structure. Neutrophils are the primary cells of antimicrobial defense due to their powerful arsenal of antimicrobial granules. Tumor is a sort of non-healing wound. Among the many components of tumor microenvironment, neutrophils and their products play a crucial role in tumor progression, immune evasion, and metastasis [3].

Neutrophils destroy pathogens using a combination of mechanisms such as oxidative burst, phagocytosis, release of antimicrobial substances, and NETs. The latter is the major player in thromboinflammation leading to dysregulation of all hemostatic components.

Neutrophils are recruited to the site of inflammation via 3 stages: activation, adhesion, and extravasation mediated by chemokines and selectins [4]. NETosis is induced by various agents and pro-inflammatory mediators, including chemokines, which are abundantly produced in tumor tissue microenvironment. Recent studies demonstrated that neutrophils exhibit neutrophil adaptive (memory-like) responses. For example, the use of BCG (Bacillus Calmette-Guérin) promotes development of adaptive response in native neutrophils [5], leading to the reprogramming of neutrophil transcriptome, epigenetic modifications, and release of pro-inflammatory mediators. Upon repeated insult, neutrophils are rapidly attracted and activated resulting in stronger immune response.

Platelets activate tumor cells, which in turn activate platelets, creating a vicious cycle of cancer-associated thrombosis. Additionally, platelets stimulate neutrophils to release NETs, which intensifies subsequent thromboinflammatory reactions, tumor progression as well as developing metastases [2]. NETs are the key players in thromboinflammation. All types of thrombi in cancer patients contain NETs, indicating that thromboinflammation is an integral part of thrombosis pathogenesis [6].

**Neutrophil extracellular traps / Внеклеточные ловушки нейтрофилов**

Neutrophils represent the source of extracellular traps formed via a complex cascade of reactions known as NETosis. NETs consist of decondensed DNA strands, proteins, and histones. DNA strands create a network structure wherein the other components of NETs are "trapped." The damaging effects on tissues primarily result from neutrophil elastase (NE), myeloperoxidase (MPO), and cathepsin G contained inside NETs [2, 7]. NETosis can vary in intensity, being either physiological or excessive. The latter contributes to pathological thrombosis, hemorrhages, acute inflammation, and tissue destruction [8]. The involvement of NETs in the pathogenesis of various conditions has already been established for autoimmune diseases such as psoriasis, systemic lupus erythematosus, and rheumatoid arthritis, as well as atherosclerosis, vasculitis, cancer, etc. [9].

**Proinflammatory cytokines / Провоспалительные цитокины**

Interleukin (IL) concentrations are significantly elevated in cancer patients, particularly those with venous thrombosis. Studies demonstrated that interleukins, especially IL-8 in the context of its overexpression in non-small cell lung cancer, directly affect NETosis magnitude [10, 11]. Tumor cells actively secrete proinflammatory cytokines. NETs promote cytokine production in macrophages [12]. Cytokines, in turn, participate in NETosis. *In vitro* studies demonstrated that IL-1β induces NETs formation. In this case, NETosis was not suppressed by the interleukin-1 receptor antagonist (IL-1RA) [13].

Interleukin-8 is secreted by macrophages, endothelial cells, and epithelial cells expressing Toll-like receptors (TLRs) [13]. IL-8 facilitates neutrophil recruitment to the site of inflammation and subsequent NETosis. Malignant cells in various tumors (nasopharyngeal carcinoma, hepatocellular carcinoma, prostate cancer, colorectal cancer) increase IL-8 concentration [14]. The plasma IL-8 level in patients with ovarian tumors is significantly reduced during or after chemotherapy using paclitaxel, suggesting that IL-8 is a promising marker in cancer treatment. IL-8 binds to neutrophil membrane IL-8-R1/2 receptors to govern neutrophils to tumors [15, 16]. High levels of circulating IL-8 have been described in cancer patients [17]. IL-8 promotes tumor growth and invasion, the formation of *de novo* tumor vasculature, and metastatic spread [18]. A more malignant phenotype with a worse prognosis is observed in tumors that produce large amounts of IL-8 [19].

IL-1 and IL-6 activate megakaryopoiesis and increase platelet level. IL-2 reduces the secretion of platelet alpha granules, whereas interferon gamma (IFN-γ) and IL-1 enhance the release of dense granules. The

thrombomodulin–protein C–protein S pathway is suppressed by IL-1 and tumor necrosis factor alpha (TNF-α). Endothelial cells and monocytes release large amounts of tissue factor (TF) in response to TNF-α and IL-6 [20, 21]. IL-1, TNF-α, and IFN-γ trigger endothelial cells to release plasminogen activator inhibitor-1 (PAI-1) [1, 22].

**Structural components of neutrophil extracellular traps / Структурные компоненты внеклеточных ловушек нейтрофилов**

Thromboinflammation transits from a normal response to a pathological process upon excessive NETosis resulting either from enhanced NETs synthesis or its failed clearance. During inflammation, circulating exogenous and endogenous DNases break down NETs followed by release of histone-proteases associated with DNA to unveil their proteolytic properties. Such histone-proteases degrade the extracellular matrix, damage the endothelium, and harm other cells [23]. After histone-caused endothelial damage, the endothelium begins to release $H_2O_2$, which repeatedly triggers NETosis.

NETs influence all components of the hemostatic system [24]. Hemostasis is activated through both intrinsic and extrinsic pathways. NETs-contained DNA, along with TF, acts as a cofactor in thrombin-dependent activation of factor XI, participating in activation of extrinsic pathway [25]. NETs DNA also facilitates activation of intrinsic pathway on negatively charged surfaces by activating factor XII [26]. NETs histones activate platelets in conjunction with thrombin [27]. Histone H4, by binding to prothrombin, triggers its activation.

NETs components hinder fibrinolysis through several mechanisms. The stabilization of fibrin protofibrils occurs through histone-related lateral aggregation. Both non-covalent and covalent bonds with histones further enhance fibrin thickening. Plasmin is unable to fully carry out fibrinolysis due to NETs DNA integration into the fibrin matrix. Histones act as targets that inhibit plasmin activity by occupying plasminogen fibrin-binding sites [6, 28]. Additionally, NETs DNA disrupts tPA-mediated (tissue plasminogen activator, tPA) plasminogen-to-plasmin conversion by forming PAI-1 and tPA complexes [29].

NETs via histones alter function of key anticoagulants. Activated protein C (APC) is inactivated by neutrophil oxidase and elastase. Histones counter interaction between antithrombin, thrombomodulin, and thrombin [30].

Endothelial activation triggered partially by NETs components leads to von Willebrand factor (vWF) release. Upon exocytosis, vWF attracts a great number of platelets to the site of endothelial damage promoting microthrombus formation. Consequently, NETs interfere with the normal functioning of the ADAMTS-13/vWF axis.

Thus, excessive NETosis in various conditions including cancer patients leads to complete hemostasis dysregulation.

**Antiphospholipid antibodies / Антифосфолипидные антитела**

Increasing number of studies demonstrate the link between circulating antiphospholipid antibodies (aPL) and thromboinflammatory processes. S. Yalavarthi et al. described NETosis induced by anticardiolipin antibodies (aCL) as a novel thrombosis mechanism in antiphospholipid syndrome (APS) [31]. Supporting the hypothesis that aPL activate neutrophils for subsequent NETosis, it was demonstrated that neutrophils isolated from APS patients enhanced spontaneous NETs release. Additionally, a positive correlation was found between lupus anticoagulant (LA), anti-$\beta_2$-glycoprotein 1 IgG antibodies (a$\beta_2$-GP1), IgG aCL and circulating MPO-DNA complexes *in vivo*. Using various laboratory methods, $\beta_2$-GP1 was detected on neutrophil surface underlies that a$\beta_2$-GPI binds to neutrophils to trigger NETosis [6].

Molecules released during NETosis can be recognized by the immune system as autoantigens. This creates a vicious cycle of autoimmune reactions, leading to further antigen release [32]. NETosis *per se* contributes to developing thrombotic events and promotes further aPL production. These two events, mutually reinforcing each other, contribute to emerging prothrombotic state in cancer patients.

**Von Willebrand factor and ADAMTS-13 metalloproteinase / Фактор фон Виллебранда и металлопротеиназа ADAMTS-13**

The regulation of microthrombus formation in human involves the large multimeric glycoprotein vWF released by the endothelium upon injury. The primary function of this multimer is to recruit, activate and aggregate platelets on the collagen matrix in the subendothelial layer leading to thrombus formation and bleeding cessation. Additionally, vWF is involved in inflammatory responses, tumor growth, angiogenesis, and metastasis; vWF level is markedly elevated in various malignant neoplasms (**Fig. 2**).

The metalloproteinase ADAMTS-13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13) is the key factor regulating vWF multimer quantity. vWF accumulation and decline in ADAMTS-13 levels lead to emergence of vWF-platelet aggregates and fibrin deposition in the microvascular network, the phenomenon known as cancer-associated microangiopathy network. This process is known as the phenomenon of cancer-associated microangiopathy [33].

According to the data, increased vWF concentrations

and/or decreased ADAMTS-13 levels have been associated with poorer survival outcomes in colorectal cancer [34], head and neck tumors [35], lung cancer [36], and Waldenström's macroglobulinemia [37]. The mechanism leading to decreased plasma ADAMTS-13 levels in cancer patients is not fully understood. Various oncogenes regulate expression of extracellular proteases, which may directly impair enzyme function.

Congenital and acquired ADAMTS-13 deficiency as well as a decrease in vWF level and activity are potential markers of microthrombosis risk. During growth and invasion, tumor cells disrupt the integrity and activate endothelial cells leading to release of high amounts of vWF multimers and triggers ADAMTS-13 activation. During massive endothelial activation, ADAMTS-13 is actively consumed followed by a decrease in both its level and activity. A direct correlation between the degree of endothelial activation and tumor growth exists. While tumor tissue grows, the magnitude of ADAMTS-13 consumption elevates. A similar scenario occurs in other conditions accompanied by endothelial dysfunction such as systemic inflammatory diseases, sepsis, and disseminated intravascular coagulation (DIC) syndrome. vWF multimers during absolute or relative (in the presence of circulating inhibitors) ADAMTS-13 deficiency trigger platelet activation and aggregation, leading to the formation of mixed tumor-platelet thromboemboli.

Von Willebrand factor facilitates adhesion of tumor cells to the endothelium and their transit through blood vessel wall, thereby promoting metastasis [36]. In *in vitro* studies, melanoma cells intrinsically activated the endothelium and stimulated vWF multimer release leading to subsequent platelet aggregation and thrombosis [38]. Studies demonstrated that in cancer, a decrease in ADAMTS-13 concentration with excessive vWF release leads to thrombosis. This situation can potentially be corrected by using recombinant ADAMTS-13 (rADAMTS-13) [38].

ADAMTS-13 activity is reduced by NETs, which bind to vWF through electrostatic interactions between free DNA and the A1 domain recruiting more neutrophils to the site [6, 39, 40], that may be prevented by heparin [41]. Apart from this, NETs DNA occupies glycoprotein Iba (GPIba) binding sites in vWF A1 domain [20, 42].

Positively charged NE fragments may result in binding to vWF, a key mediator in recruiting platelets and leukocytes to the endothelium. The interaction with vWF recruits more leukocytes to the activated endothelium [20]. Experiments demonstrated that activated platelets stimulate NETosis only in the presence of vWF [43, 44].

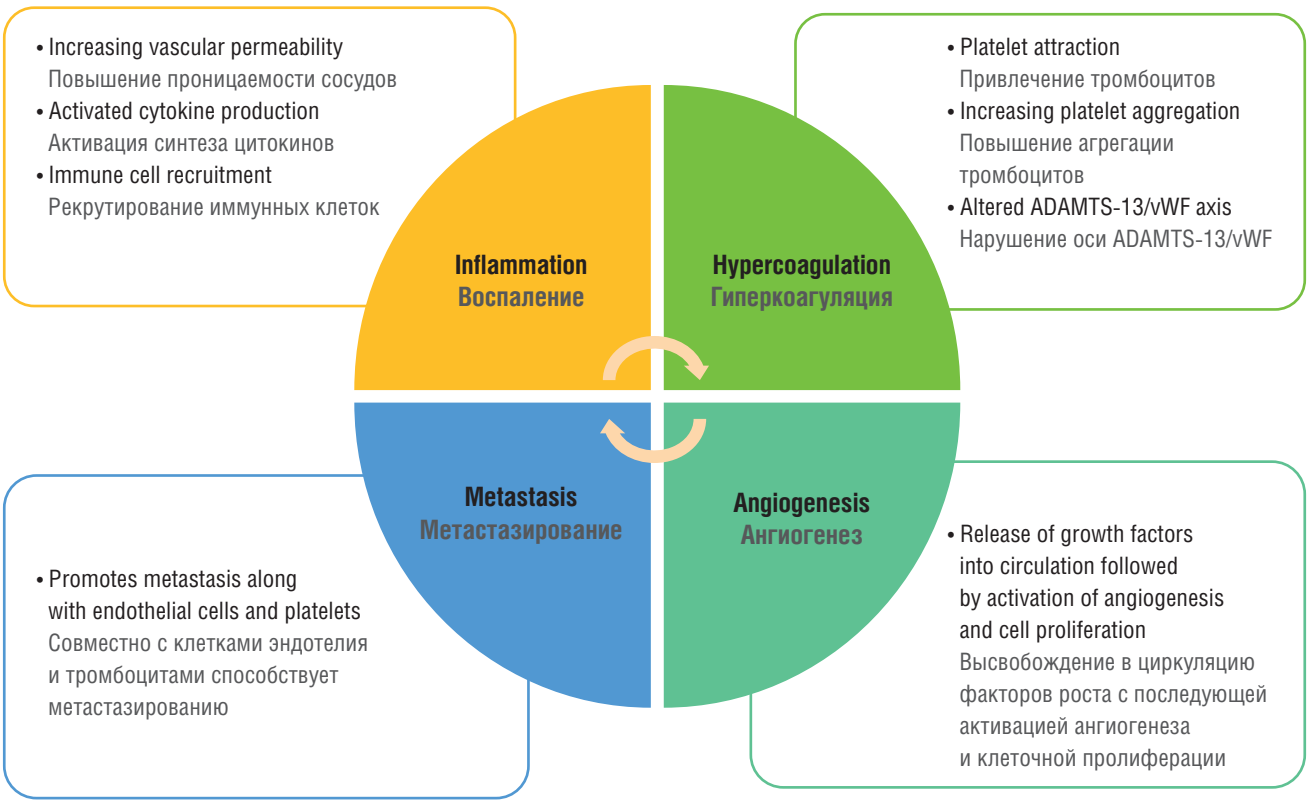



**Figure 2.** Von Willebrand factor in the pattern of thromboinflammation concept in cancer [drawn by authors].

**Рисунок 2.** Фактор фон Виллебранда в структуре концепции тромбовоспаления при раке [рисунок авторов].

A decrease in ADAMTS-13 concentration and activity as well as elevated vWF level and activity are universal microthrombosis mechanisms in sepsis and DIC syndrome [45]. NETs affect the activity of ADAMTS-13 and vWF. Activated neutrophils and NETs via factors such as proteases, peptides, cytokines, and reactive oxygen species modify the structure and conformation of ADAMTS-13 binding sites.

Peptidyl arginine deiminase 4 (PAD4) participates in NETosis and protein citrullination. PAD4 is found in leukocyte nucleus. Citrullination ensures conversion of protein arginine residues into citrulline residues acted upon by PAD4, which removes protein charge [46–49]. After neutrophils become recruited and stimulated, NADPH oxidase is phosphorylated, reactive oxygen species are synthesized, and histones undergo citrullination. PAD4 inhibition lowers NETosis magnitude by preventing histone H3 citrullination and subsequent NETs synthesis [50]. Mice lacking PAD4 are unable to undergo chromatin decondensation and subsequent NETosis [49, 51].

Peptidyl arginine deiminase 4 is also an integral NETs component that participates in NETs formation by converting arginine residues in histones to citrulline [52] and decondensing chromatin. PAD4 is able to citrullinate ADAMTS-13 in plasma by modifying arginine residues and, thereby altering its structure as well as activity [20, 53].

NETs contain alpha-defensins, also known as human neutrophil peptides (HNPs), which participate in immune responses *in vivo*. Due to their ability to activate platelets [54] and reduce fibrinolysis, they exhibit procoagulant properties [55]. HNPs bind to vWF A2 domain, thereby modulating the ADAMTS-13/vWF axis. Studies demonstrated elevated plasma HNPs levels in patients with acute thrombotic thrombocytopenic purpura (TTP) [20, 56].

One of NETs proteases is myeloperoxidase, which catalyzes the synthesis of hypochlorous acid from $H_2O_2$ and $Cl^-$. Hypochlorous acid oxidizes methionine to methionine sulfoxide. This occurs at ADAMTS-13 cleavage site within vWF A2 domain and in ADAMTS-13 by affecting function of the ADAMTS-13/vWF axis [57–59]. MPO–$H_2O_2$–$Cl^-$ system during NETosis may result in imbalanced ADAMTS-13/vWF axis and microvascular thrombosis [20]. Both plasmin and NE cleave ADAMTS-13 in plasma *in vitro*. Research has demonstrated the contribution of NETosis and thromboinflammation to extensive microthrombosis in patients with acute forms of TTP, who exhibit elevated plasma concentrations of NETs components, including DNA-histone complexes and MPO, along with reduced platelet counts [20, 60].

Pro-inflammatory cytokines regulate the release of endothelial vWF multimers and their cleavage into smaller fragments [20, 61]. IL-6 inhibits cleavage of vWF multimers by the ADAMTS-13. The IL-6/IL-6 receptor complex, TNF-α, and IL-8 enhance release of vWF multimers [62].

In DIC syndrome associated with sepsis, low-molecular-weight ADAMTS-13 isoforms are detected [56]. The decrease in ADAMTS-13 level and activity during excessive NETosis facilitates circulation of vWF multimers, which recruit and activate more neutrophils and platelets. Administering DNase I or recombinant ADAMTS-13 may provide a potential option to break this vicious cycle [20].

### Thromboinflammation and chemotherapy resistance / Тромбовоспаление и резистентность к химиотерапии

Tumor tissue has long been considered the primary source of circulating plasma free DNA (cfDNA) in cancer patients. During tumor progression, cfDNA resembles DNA from NETs, suggesting that NETosis may underlie chemoresistance [63].

Experiments with $PAD4^{+/+}$ mice bearing lung tumors using platinum-based chemotherapeutic agents were associated with cfDNA release and thrombus formation not observed in $PAD4^{-/-}$ mice, suggesting that an increase in cfDNA and thrombin levels during platinum-based chemotherapy is directly related to PAD4 and NETosis confirmed by other studies (**Fig. 3**) [49, 64, 65]. It is NETosis, rather than apoptosis or necrosis that promotes blood plasma cfDNA levels [65]. In $PAD4^{+/+}$ mice undergoing chemotherapy, DNase administration reduced the risk of thrombus formation, an effect not observed in $PAD4^{-/-}$ mice [66]. Tumor-associated neutrophils, acted upon by granulocyte colony-stimulating factor (G-CSF) trigger NETosis [64]. Hence, the results of such studies establish a link between tumor progression, neutrophil count, and increased blood plasma levels of G-CSF and cfDNA in cancer patients [66].

Neutrophils have long been associated with poor response to immune checkpoint inhibitor therapies. Recent studies demonstrated that NETosis indeed underlies the poor response to chemotherapy [67]. In the case of immune checkpoint inhibitor therapy for pancreatic adenocarcinoma, NETosis shields tumor cells from CD8+ T-cells action [49, 68].

By enveloping the tumor cell and preventing contact with CD8+ T-cells and natural killer cells, NETs mechanically protect the tumor *in vitro*. This protective barrier can be disrupted in experiments by administering DNase 1. However, supraphysiological DNase 1 concentrations are required for NETs degradation [49, 69, 70]. Additionally, the effectiveness of thrombolysis is enhanced when blood clots are simultaneously treated with DNase and tPA [49, 71].

The role of NE, matrix metalloproteinase (MMP) MMP-9, cathepsin G, programmed cell death ligand 1

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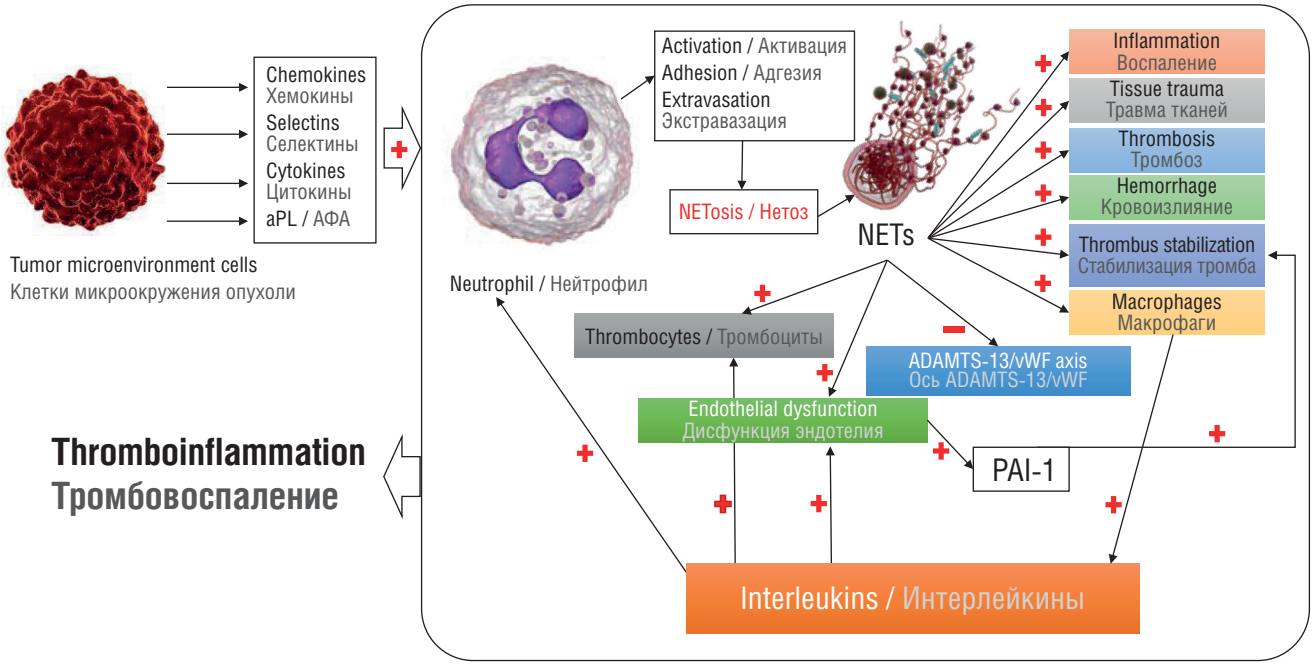


**Figure 3.** Integral concept of thromboinflammation in cancer [drawn by authors].

***Note:*** *aPL – antiphospholipid antibodies; NETs – neutrophil extracellular traps; vWF – von Willebrand factor; PAI-1 – plasminogen activator inhibitor-1.*

**Рисунок 3.** Интегральная концепция тромбовоспаления при раке [рисунок авторов].

***Примечание:*** *АФА – антифосфолипидные антитела; NETs – внеклеточные ловушки нейтрофилов; vWF – фактор фон Виллебранда; PAI-1 – ингибитор активатора плазминогена-1.*

(PDL-1), and carcinoembryonic antigen cell adhesion molecule 1 (CEACAM1) in emerging chemoresistance has now been established [49, 72]. MMP-9 is a metalloproteinase that degrades the extracellular matrix (ECM) [73]. Studies demonstrated tumor chemoresistance and ECM degradation associated with elevated MMP-9 expression in gastric cancer [74]. MMP-9 also contributes to tumor neoangiogenesis and reduces intra-tumoral perfusion of chemotherapeutic agents [49, 75]. One of NETs components, NE, promotes tumor growth by influencing the epithelial-mesenchymal transition, which transforms the tumor cell into a mesenchymal phenotype [72, 76]. Compared to rental cells, mesenchymal phenotype cells have a greater capacity for migration and apoptosis [49, 77]. The transmembrane glycoprotein CEACAM1 also found in NETs takes part in T-cell pool depletion and activation of tumor cell adhesion and migration [49, 78]. The programmed cell death protein 1 (PD-1) membrane receptor normally regulates T-cell antitumor activity. T-cell depletion occurs through the interaction between PD-1 and PDL-1 (NETs component) which inevitably leads to arising resistance to immunotherapy [79–81]. The involvement of neutrophils and NETs in formation of chemoresistance is multifaceted and requires further investigation, as do the potential pathways to overcome this resistance.

The link between neutropenia and improved survival prognosis has long attracted attention but lacked a logical explanation. This phenomenon can now be accounted for by understanding the mechanisms of thromboinflammation. In this context, neutropenia not only appears to be a marker of effective chemotherapy but also confirms the existence of NETs-dependent chemoresistance mechanisms.

## Conclusion / Заключение

Overall, thromboinflammation *per se* and NETosis in particular are specific mechanisms whose significance in clinical oncology is only now being explored. Both clinical and basic research data presented here confirm a need for further investigation of thromboinflammation. The relevance of thromboinflammation and hemostasis disorders in cancer patients is driven by the necessity to improve the principles of complication prevention and predictionof disease progression. The molecular mechanisms of cancer-associated thrombosis, tumor progression, and metastasis in gynecologic oncology patients, taking into account new findings on thromboinflammation in oncogynecology as well as laboratory diagnostics and therapy remain highly relevant issues for modern medicine.

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