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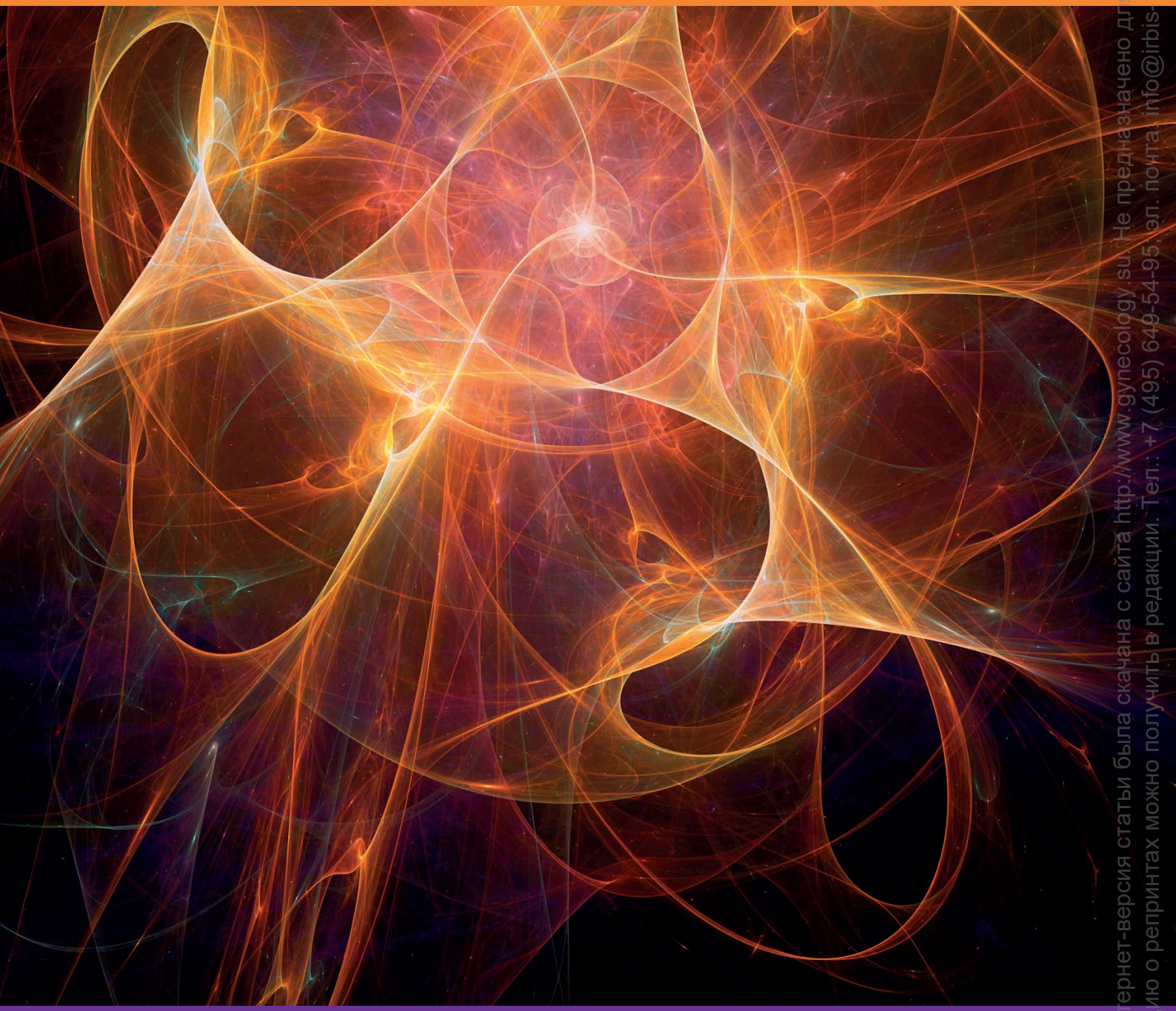

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Thromboinflammation in oncogynecological patients

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Abstract

Studies of the pathogenesis of thrombosis and inflammation and their contribution to tumor progression and metastasis in cancer patients, initiated many decades ago, have been continued to this day. At the same time, thrombosis and inflammation are inextricably linked to each other. One of the central places in thromboinflammation is held by the loss of normal antithrombotic and anti-inflammatory function in endothelial cells, which leads to dysregulated coagulation, imbalanced the complement system, platelet activation and recruitment of leukocytes in the microvasculature. In turn, tumor cells affect the hemostasis by releasing procoagulant substances, activating fibrinolysis, proteolysis, increasing platelet activation and aggregation, releasing adhesion molecules, secreting pro-inflammatory and pro-angiogenic cytokines. Future research aims to advance an understanding of thromboinflammation in oncology, particularly focusing on the role of platelets beyond hemostasis and thrombosis, as well as some new players in the process. In the future, the main attention will be paid to investigating molecular mechanisms that regulate cancer-related thromboinflammation, providing insights into mechanisms underlying both inflammation and thrombosis as pathogenetic components in cancer patients. Altogether, it will provide an opportunity to create new, modern strategies to treat cancer patients.

Keywords: cancer, thrombosis, inflammation, metastasis, thromboinflammation

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Тромбовоспаление у онкологических больных

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Резюме

Исследования патогенеза тромбоза и воспаления и их вклад в прогрессию опухоли и метастазирование у онкологических больных, начатые много десятилетий назад, продолжаются и в наши дни. При этом тромбообразование и воспаление неразрывно связаны друг с другом. Одно из центральных мест в тромбовоспалении занимает потеря нормальной антитромботической и противовоспалительной функций клетками эндотелия, что приводит к нарушению регуляции коагуляции, дисбалансу в системе комплемента, активации тромбоцитов и рекрутированию лейкоцитов в микроциркуляторном русле. Опухолевые клетки сами влияют на систему гемостаза путем высвобождения прокоагулянтных субстанций, активации фибринолиза, протеолиза, повышая активацию и агрегацию тромбоцитов, выделяя молекулы адгезии, секретируя провоспалительные и проангиогенные цитокины. Современные исследования направлены на углубление понимания патогенеза тромбовоспаления в онкологии с особым акцентом на роль тромбоцитов, а также ряда новых участников процесса. Основное внимание уделяется изучению молекулярных механизмов, регулирующих тромбовоспаление при раке, обеспечивая понимание механизмов как воспаления, так и тромбоза как составных частей патогенеза у онкологических больных. Все это даст возможность для создания новых, современных стратегий терапии онкологических больных.

Ключевые слова: рак, тромбоз, воспаление, метастазирование, тромбовоспаление

Для цитирования: Слуханчук Е.В., Бицадзе В.О., Солопова А.Г., Хизроева Д.Х., Гри Ж.-К., Элалами И., Панкратьева Л.Л., Цибизова В.И., Унгиадзе Д.Ю., Ашрафян Л.А., Макацария А.Д. Тромбовоспаление у онкологических больных. *Акушерство, Гинекология и Репродукция.* 2022;16(5):611–622. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2022.355.

Introduction / Введение

It has long been known that thrombosis complicates the oncological process. The relationship between cancer and thrombosis is a two-sided interplay [1] because activated coagulation in cancer contributes to tumor progression (**Fig. 1**). Thrombosis may be the first symptom of an oncological process. Unfortunately, a diagnostic search initiated immediately after thrombosis if it took place, does not always enhance survival, because, by

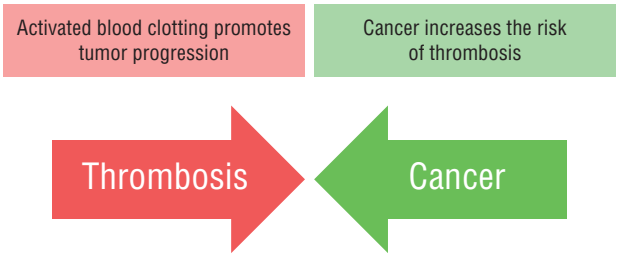

Figure 1. A relationship between thrombosis and cancer [drawn by authors].

Рисунок 1. Взаимосвязь тромбоза и рака [рисунок авторов].

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Highlights

What is already known about this subject?

- The relationship between thrombosis and cancer has long been known. In recent years, our knowledge has expanded regarding the main risk factors and pathogenetic mechanisms of cancer-related thrombosis.
- Recently, the term thromboinflammation has entered the researchers' lexicon. It was actively used by scientists during the last COVID-19 pandemic being also relevant in relation to the oncological process.

What are the new findings?

- The article presents all up-to-date detailed data on the process of thromboinflammation in cancer patients, outlining their clinical significance, including that in relation to developing new strategies for treatment of both thrombotic complications in cancer and progression and metastasis.

How might it impact on clinical practice in the foreseeable future?

- Owing to accumulated and expanded knowledge in this area, familiarization of a wide range of researchers and physicians along with investigated thromboinflammation will allow to develop new therapeutic approaches in the present and future, which will help reduce cancer-related mortality.

Основные моменты

Что уже известно об этой теме?

- Взаимосвязь тромбоза и рака известна давно. За последние годы расширились наши знания в отношении основных факторов риска, основных патогенетических механизмах тромбоза при раке.
- В последнее время в лексикон исследователей устойчиво вошёл термин «тромбовоспаление». Его активно использовали ученые в течение прошедшей пандемии COVID-19, актуален он и в отношении онкологического процесса.

Что нового дает статья?

- Подробно представлены все последние новые данные, касающиеся процессов тромбовоспаления у онкологических пациентов, обозначена их клиническая значимость, в том числе и в отношении разработки новых стратегий терапии как тромботических осложнений при раке, так и прогрессирования и метастазирования.

Как это может повлиять на клиническую практику в обозримом будущем?

- Благодаря накоплению и расширению знаний в этой области, ознакомлению широкого круга исследователей и врачей с изучаемыми процессами тромбовоспаления, в настоящем и будущем удастся разработать новые подходы к терапии, что поможет снизить смертность от онкологических заболеваний.

this time point, tumors usually might have metastasized [2]. Armand Trousseau was the first researcher who identified the link between cancer and thrombosis. The Trousseau phenomenon implies emergence appearance of thrombophlebitis in malignant neoplasms. Moreover, it was Dr. Trousseau who also reported about the relationship between idiopathic venous thrombosis and occult cancer [3].

In his study, one of the scientific leaders in the area, Cihan Ay, revealed the "Rule 1/5" [4] showing that every fifth case of thrombosis is associated with an oncological process. At the same time, one in five cancer patients has thrombotic complications. Apart from venous thrombosis and thromboembolism discussed most often, other thrombotic complications are noted in cancer patients, such as arterial thrombosis, endocarditis, disseminated intravascular coagulation (DIC), and migratory superficial thrombophlebitis (Trousseau's syndrome) [4].

Thrombosis risk factors in cancer patients / Факторы риска тромбоза у онкологических больных

Among the thrombosis risk factors, unavoidable cues, e.g., patient-associated risk factors, such as hereditary thrombophilia should be distinguished [5]. However, in the same cancer patient, thrombotic risk changes in developing disease due to change in external and internal factors, namely: stage of the disease, surgery, duration and type of anesthesia, chemotherapy, hormonal therapy, age, presence of central venous catheters, immobilization, infections, as in the case of the last COVID-19 pandemic, when the risk of thrombotic complications in cancer patients increased remarkably [4]. Cancer increases the risk of thrombosis by 4–7-fold; in some tumors, it rises the risk by 28-fold accounted for by organ-specific location. For instance, for tumors of the ovaries, brain, pancreas, and stomach, the risk of thrombosis is higher than that for tumors of the breast, head and neck, esophagus, and prostate. Oncohematological patients with lymphoma and leukemia have a high risk of thrombosis [6]. Thrombotic risk is affected by tumor extent and histological type, e.g., lung squamous cell carcinoma is less thrombogenic than lung adenocarcinoma. In the presence of metastases, the risk of thrombosis is higher than for confined tumor. Tumor metastasis and progression increases an initial risk of thrombosis by 4–12-fold [7].

Noteworthy is the section on risk factors associated with ongoing cancer therapy. Chemotherapy is of particular importance in increasing the risk of thrombosis [8]. In a large retrospective study conducted with oncological patients of various nosologies during chemotherapy, it was shown that the risk of thrombotic complications was progressively increased. Extremely high risk was noted for tumors of the pancreas, stomach, and lungs. No plateau or reduced risk during the 12-month follow-up period was observed [9].

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Pathogenesis of cancer-associated thrombosis / Патогенез рак-ассоциированного тромбоза

In the pathogenesis of cancer-associated thrombosis, three groups of cofactors may be distinguished: environmental, tumor-associated and patient-associated factors [7] (**Fig. 2**). It is known that tumor cells can disturb the hemostatic balance by producing procoagulant substances, due to profibrinolytic, proteolytic and proaggregant activity, by expressing adhesion molecules, secreting pro-inflammatory and pro-angiogenic cytokines [10]. Also, new players in the process have now been identified [11] (**Fig. 3**).

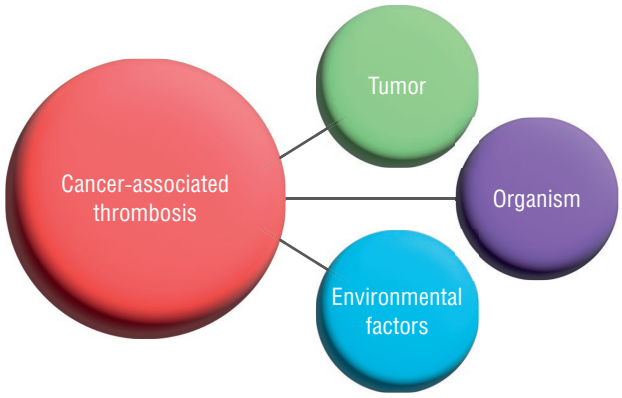

Figure 2. Players of cancer-associated thrombosis pathogenesis [drawn by authors].

Рисунок 2. Участники патогенеза рак-ассоциированного тромбоза [рисунок авторов].

The tumor cell expresses a procoagulant, a cysteine protease, which directly activates factor X, independently of factor VII, and activates platelets. Some tumor cells activate factor X due to sialic acid fragments of mucin produced by adenocarcinomas [12].

The tissue factor (TF) is a vascular cell transmembrane glycoprotein of the subendothelial layer, normally lacking contact with blood, which may occur in case of damage to the vessel or TF release stimulated by inflammatory triggers [13]. Pancreatic adenocarcinoma, ovarian tumor, tumor microenvironment cells as well as monocytes can independently express TF, including TF-rich microparticles [14]. TF acts to activate factors X and IX followed by the thrombin formation and, ultimately, a fibrin thrombus. In addition to the prothrombogenic effect, angiogenesis, metastasis, and tumor progression are associated with TF [5]. Studies have demonstrated a relationship between TF level and the degree of tumor differentiation. Moreover, TF was higher in poorly differentiated tumors [14].

In the blood plasma of oncological patients, the level of thrombin-generated biomarkers such as D-dimer and fragments of prothrombin 1+2, coagulation factors V, VIII, IX, and XI is markedly increased paralleled with deficiency of natural anticoagulants – antithrombin III, protein C, and protein S. Tumor cells secrete both urokinase plasminogen activator (uPA) and tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) [15].

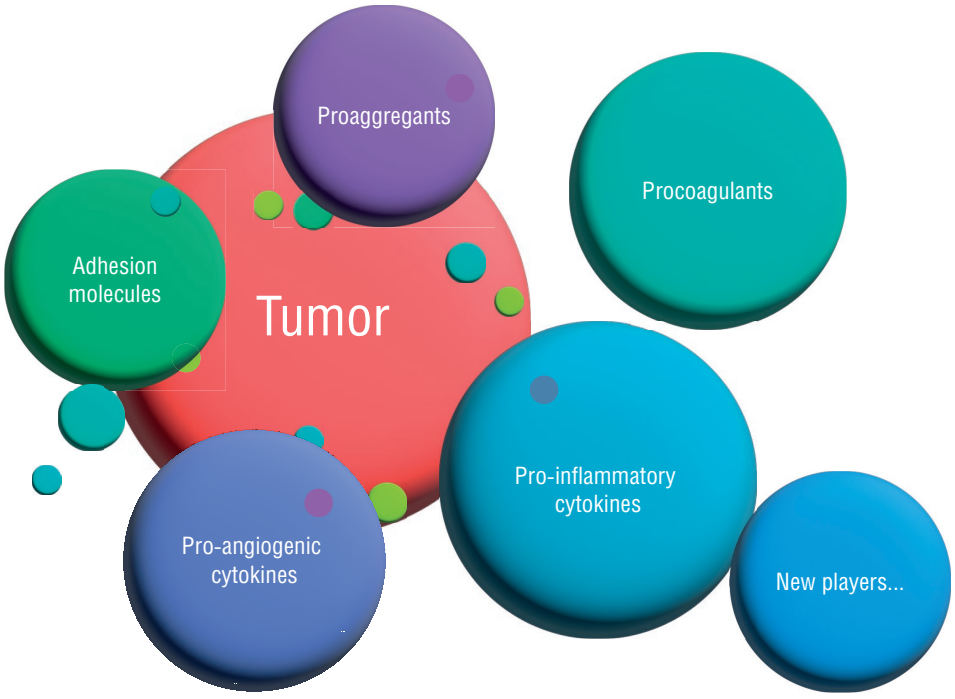

Figure 3. Tumor-associated factors in the pathogenesis of cancer-associated thrombosis [drawn by authors].

Рисунок 3. Опухоль-ассоциированные факторы патогенеза рак-ассоциированного тромбоза [рисунок авторов].

PAI-1 is the main inhibitor of fibrinolysis so that its serum increase reduces fibrinolytic activity by elevating risk of thrombosis. The related studies have demonstrated an increased expression of PAI-1 by pancreatic tumor cells concomitant with patient prothrombotic status. It has also been shown that during courses of bevacizumab chemotherapy, the concentration of PAI-1 increases, whereas elevated risk of thrombosis is leveled out with PAI-1 inhibitors [16].

The tumor may secrete pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1), vascular endothelial growth factor (VEGF), and granulocyte-macrophage colony-stimulating factor (GM-CSF). Interacting with other cells, tumor stimulates production of pro-inflammatory cytokines by endothelial cells and leukocytes. Pro-inflammatory cytokines stimulate PAI-1 production, promote tissue factor expression by endothelium and monocytes, and reduce the production of endothelial cell thrombomodulin, a natural anticoagulant. They damage endothelial cells and form a prothrombotic base on the vessel interface [12].

The tumor cell also affects the hemostasis system by interacting with immune cells – macrophages and monocytes. Leukocytosis is characteristic of cancer patients, which magnitude reflects disease prognosis [17] and risk of thrombosis [18]. In cancer, large number of leukocytes, mainly mature neutrophils are found in the circulation.

Tumor cells promote thrombocytosis and trigger platelet aggregation, secrete thrombopoietin to stimulate megakaryocyte differentiation, proliferation, and platelet production. Tumor cells can directly activate platelets and enhance thrombogenesis involving podoplanin (PDPN), which increased expression by tumor cells, is associated with a high risk of thrombosis. Lectin-like platelet C-2 (CLEC-2) receptor, interacting with tumor podoplanin, enhances the prothrombotic state and increases the risk of metastasis [19]. Tumor cells can also indirectly activate platelets by enhancing endothelial cell release of extracellular matrix proteins and TF, creating an active surface for platelet adhesion and subsequent thrombogenesis. Gas6 is a vitamin K-dependent receptor ligand of the tyrosine kinase family, present in both tumor and endothelial cells. Gas6 enhances secretion of endothelial prostaglandin E2 resulting in platelet activation and thrombosis.

Activated platelets release into own alpha-granules pro-angiogenic factors such as VEGF, epidermal growth factor (EGF), fibroblast growth factor (FGF), transforming growth factor-beta (TGF-β), insulin-like growth factor-1 (IGF-1), and platelet-associated microparticles (PMPs), bear several membrane receptors and proteins, including P-selectin and integrins, which contain growth factors, cytokines, and pro-inflammatory molecules [20]. PMPs also promote the chemotaxis of various hematopoietic cells. Platelets are the first cells to encounter tumor cells in the bloodstream, and facilitate a multi-faceted metastasis spreading [21].

Platelets previously known as players solely in hemostasis system now are considered to act differently because they were recently placed in one row with most critical players of immune response [22]. Platelets are essential participants in anti-infective immunity and are involved in the pathogenesis of autoimmune and chronic inflammatory diseases [23]. Thrombocytopenia, which develops in patients with oncological diseases, is accounted for by not only chronic DIC course but also extensive immunothrombosis reactions. The term immunothrombosis was first proposed by B. Engelmann and S. Massberg to refer to the internal effector pathway of innate immunity triggered by pathogens and damaged cells, which results in decreased spread and survival of newly invading pathogens [24]. The interest to platelets is also related to the fact that they can be a new target for developing anti-inflammatory therapy with promising outcome.

Tumor-secreted microparticles are small membrane vesicles originated from tumor cells [23]. The procoagulant activity of microparticles is related to an active TF and phosphatidylserine located on relevant surface, providing a negatively charged platform for the cascade of hemostasis reactions [25]. Sources of microparticles can also be presented by cancer-related activated endothelial cells and monocytes [26]. Inflammatory cytokines expressed by tumor cells lead to activated endothelial cells and monocytes, stimulating production of TF-containing microparticles [23].

Podoplanin is a mucin-type transmembrane glycoprotein that activates platelets via CLEC-2 receptors [27]. Podoplanin is involved at various stages of the metastatic cascade: exit of tumor cells through the basement membrane, penetration into the connective tissue, epithelial-mesenchymal transition, and entry into the bloodstream through degradation of the blood vessel-coupled basement membrane [22] (**Fig. 4**).

Malignant cells suppress immune cell attacks by activating and aggregating platelets involving podoplanin [28]. Platelet aggregation promotes adhesion of tumor cells and formation of emboli in the microvasculature, with further extravasation from the blood vessel [29, 30].

The relationship between podoplanin expression and the number of intratumoral intravascular platelet

aggregates has been proven in the study assessing podoplanin in primary brain tumors showing that its expression was associated with markedly increased risk of thrombosis [31]. Another study showed that decreased surface CLEC-2 receptor level in platelets led to reduced thrombosis, and inoculation of unchanged platelets leveled out the effect. At the same time, the podoplanin level in the vascular wall correlated with the severity of thrombosis [32].

Tumor cells, platelets, cytokines, chemokines, and other agents interact with leukocytes and form neutrophil extracellular traps (NETs) [33] serving as activated neutrophil derivatives and consisting of DNA strands, histones, and antimicrobial proteins that can capture and detain diverse pathogens until their destruction [34]. The process of NETs formation is called NETosis. Neutrophils synthesize NETs either due to ejection of the entire nucleus (suicidal NETosis) or parts of the nucleus without altering cell membrane integrity (vital NETosis). The type of NETosis depends on the stimulating agent. Suicidal NETosis requires several hours to produce NETs, whereas time frame for vital NETosis is shorter. In suicidal NETosis, chromatin decondensation occurs, the nuclear envelope dissolves, and the cell contents are released through cell membrane rupture. Vital NETosis results in no neutrophil destruction [35]. The structures secreted in NETs are represented by DNA strands intertwined in a network with 24 types of proteases and histones such as peptidyl arginine deiminase 4 (PAD4), neutrophil elastase (NE), myeloperoxidase (MPO), and cathepsin G [36]. Tumor cells change the way neutrophils function and promote NETosis. NETs, in turn, decorate tumor cells, making them inaccessible to T-cells and NK-cells (natural killer cells) [37].

Chemokines secreted by tumor cells comprise one of the factors stimulating NETosis [38] that was modeled before and demonstrated in one of the studies using, e.g., the chemokine receptors CXCR1 (C-X-C Motif Chemokine Receptor-1) and CXCR2 (C-X-C Motif Chemokine Receptor-2) [37]. CXCR1 and CXCR2 agonists are significant mediators of cancer-induced NETosis so that NETs cover tumor cells and protect them from immune cell cytotoxicity [39]. Tumor cells protected from cytotoxicity with NETs successfully metastasize while using PAD4 inhibitors, which reduce NETosis intensity and lowers metastasis.

A multi-layered mechanism was uncovered for the NETs histone-related effect on hemostasis (**Fig. 5**).

Histones as a part of NETs, activate endothelial cells, leading to release of von Willebrand factor (vWF) followed by triggered release of platelet inorganic polyphosphates, exposure of membrane-bound phosphatidylserine, causing activation of factor V, thereby increasing activity of the prothrombinase complex, and interfere with thrombomodulin-mediated protein C activation [40]. The most prominent procoagulant effect display histones H3 and H4. In turn, NETs are the basis for direct platelet aggregation and activation. Once at the injury site, NETs attract several proteins and coagulation factors involved in thromboses, such as vWF, factor XII, fibrinogen, and fibronectin [41].

Massive neutrophil activation during the cytokine storm along with release of a large NETs number and uncontrolled course of thromboinflammatory processes depends on the developing endotheliopathy in COVID-19 [38].

Studies show that the increased neutrophil activity and NETs number in the placenta increases dramatically with developing of pregnancy complications such as preeclampsia (PE), miscarriage, and poor pregnancy outcome due to the development of autoimmune states [42, 43]. Pregnancy may exacerbate the pro-inflammatory status, which causes increased activation of neutrophils, which is more pronounced in patients with PE [44]. Studies have shown that neutrophil activation through the complement cascade contributes to developing PE-like states or is characteristic of fetal loss [45]. The latter is corroborated by recent reports showing that antiphospholipid antibodies causing NETosis are frequently detected in case of recurrent fetal loss [42].

The von Willebrand factor is a multi-functional acute phase glycoprotein that plays one of the main roles in primary hemostasis. Sometimes, it is located within multimers inside Weibel-Palade bodies in endothelial

Figure 4. Podoplanin and platelets [drawn by authors].
Note: *CLEC-2 – C-type lectin-like receptor-2.*

Рисунок 4. Подопланин и тромбоциты [рисунок авторов].
Примечание: *CLEC-2 – лектиноподобный рецептор-2 С-типа тромбоцитов.*

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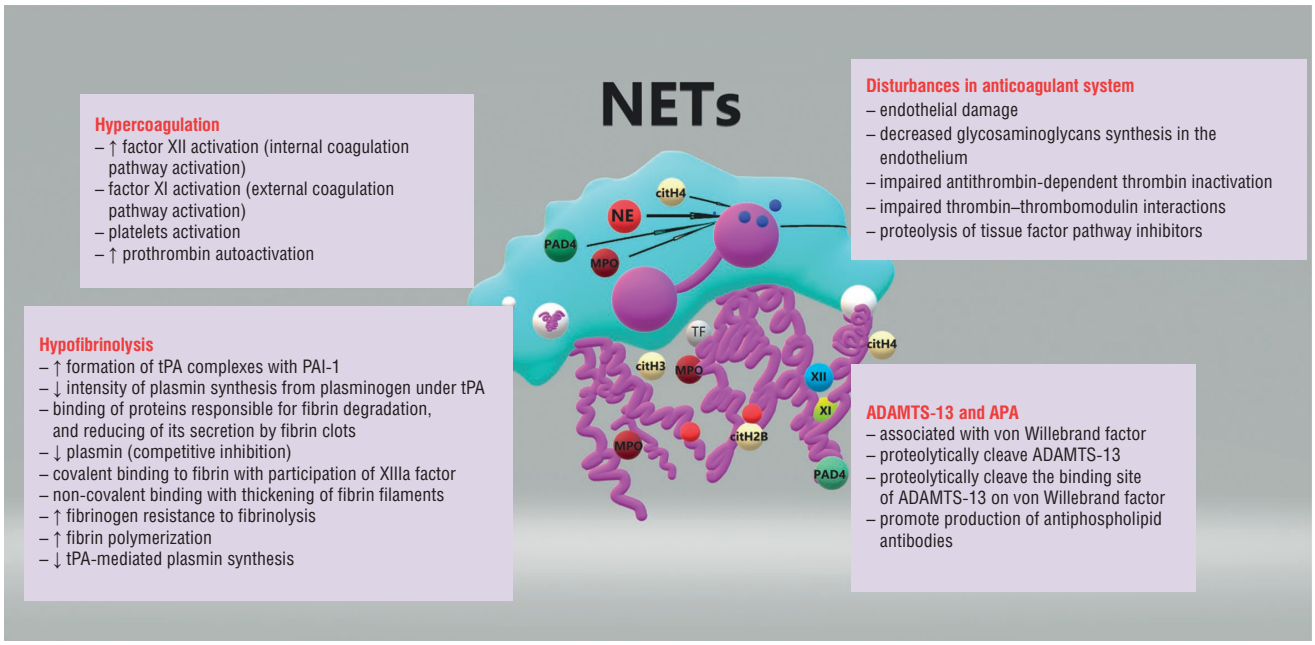

Figure 5. NETs multicomponent influence on hemostasis [drawn by authors].

Note: *NETs – neutrophil extracellular traps; tPA – tissue plasminogen activator; PAI-1 – plasminogen activator inhibitor-1; PAD4 – peptidyl arginine deiminase 4; NE – neutrophil elastase; MPO – myeloperoxidase; citH4 – citrullinated histone H4; citH2B – citrullinated histone H2B; ADAMTS-13 – a disintegrin and metalloprotease with thrombospondin type 1 motif; APA – antiphospholipid antibodies; TF – tissue factor.*

Рисунок 5. Многокомпонентное влияние NETs на гемостаз [рисунок авторов].

Примечание: *NETs – внеклеточные ловушки нейтрофилов; tPA – тканевой активатор плазминогена; PAI-1 – ингибитор активатора плазминогена-1; PAD4 – пептидил-аргинин деиминаза 4; NE – эластаза нейтрофилов; MPO – миелопероксидаза; citH4 – цитрулированный гистон H4; citH2B – цитрулированный гистон H2B; ADAMTS-13 – дизинтегрин-подобная металлопротеаза с мотивом тромбоспондина 1; АФА – антифосфолипидные антитела; TF – тканевой фактор.*

cells. Exocytosis begins in response to various endogenous stimulants, such as inflammatory cytokines, histamine, thrombin, fibrin, or exogenous desmopressin. The vWF multimers show a great potential to associate with platelets. They are highly thrombogenic, therefore undergoing enzymatic degradation into smaller fragments that exhibit less thrombogenicity until entering the bloodstream. Multimer trimming occurs due to metalloprotease ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) after binding to the A2 region of the vWF domain. Platelets and factor VIII activate this process. One of the factors in the pathogenesis of thrombosis during oncological diseases is tumor cell-dependent endothelial activation, which leads to released von Willebrand factor multimers, activated ADAMTS-13 followed by ADAMTS-13 pool exhaustion due to its active consumption (**Fig. 6**).

NETs contain PAD4, an enzyme capable of modifying arginine in other proteases. An increased PAD4 concentration during tumor growth affects ADAMTS-13 by altering its structure, reducing affinity to the vWF A2 domain, thereby lowering ADAMTS-13 activity [46] (**Fig. 7**). Under SARS-CoV-2-mediated endothelial damage, as a vivid example of immunoinflammation, ADAMTS-13 is consumed by excessive amounts of vWF and accumulation of its ultra-high molecular weight multimers, which, together with platelets, lead to microthromosis and multiple organ failure.

All noted above does not fully reflect the complete picture of cancer-coupled hemostasis changes. Tumor cells express specific adhesion molecules (E-selectin, P-selectin, ets.), which ensure attachment to the blood vessel wall and interaction with the endothelium, platelets, and leukocytes [47, 48]. Studies have shown that in cancer patients P-selectin is a high risk marker of thrombosis [48].

Damage-associated molecular patterns (DAMPs) are a heterogeneous group of molecules (histones, acute phase proteins, etc.) that are released by tumor cells during death events. DAMPs have a significant influence on the hemostasis activation [49].

Over the past decades, knowledge on the thrombosis pathogenesis in cancer has been profoundly deepened, many mechanisms, and factors have been identified. One recent study has hypothesized that the underlying mechanism in each case that controls thrombosis may depend on the tumor type. For example, lung tumor

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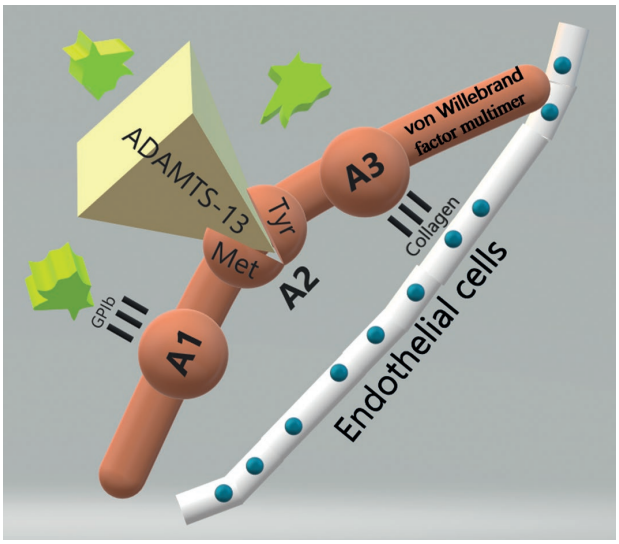

Figure 6. Interaction of ADAMTS-13 metalloprotease and von Willebrand factor [drawn by authors].

Note: *GP1b – glycoprotein 1b; A1, A2, A3 – domains of von Willebrand factor multimer; ADAMTS-13 – a disintegrin and metalloprotease with thrombospondin type 1 motif; Met – methionine amino acid; Tyr – tyrosine amino acid.*

Рисунок 6. Взаимодействие металлопротеазы ADAMTS-13 и фактора фон Виллебранда [рисунок авторов].

Примечание: *GP1b – гликопротеин 1b; A1, A2, A3 – домены мультимера фактора фон Виллебранда; ADAMTS-13 – дизинтегрин-подобная металлопротеаза с мотивом тромбоспондина 1; Met – аминокислота метионин; Tyr – аминокислота тирозин.*

granulocyte colony-stimulating factor (G-CSF) leads to increased neutrophil count and related NETs release, which increase thrombosis in patients with lung cancer. Thrombocytosis is the leading mechanism in ovarian cancer, with interleukin-6 (IL-6) stimulating hepatocytes to express thrombopoietin, increasing platelet production and thrombosis.

Pancreatic tumor cells release tissue factor and microvesicles (TF + MV) into the bloodstream, promoting thrombosis [50]. Brain tumor cells can release podoplanin-containing microvesicles (PDPN+MV) that activate circulating platelets and increase thrombosis in patients with brain cancer [2].

Not only in non-infectious inflammatory and oncological diseases but also in severe infections, including new coronavirus infection COVID-19 and sepsis, the systemic inflammatory response is accompanied by the production of a large NETs number and the activation of many pathways noted above, with subsequent endothelial damage, intravascular coagulation, and organ dysfunction, which evidence about common features in underlying pathogenetic mechanisms [51]. Since the COVID-19 pandemic start, many publications have appeared (description of clinical cases and review

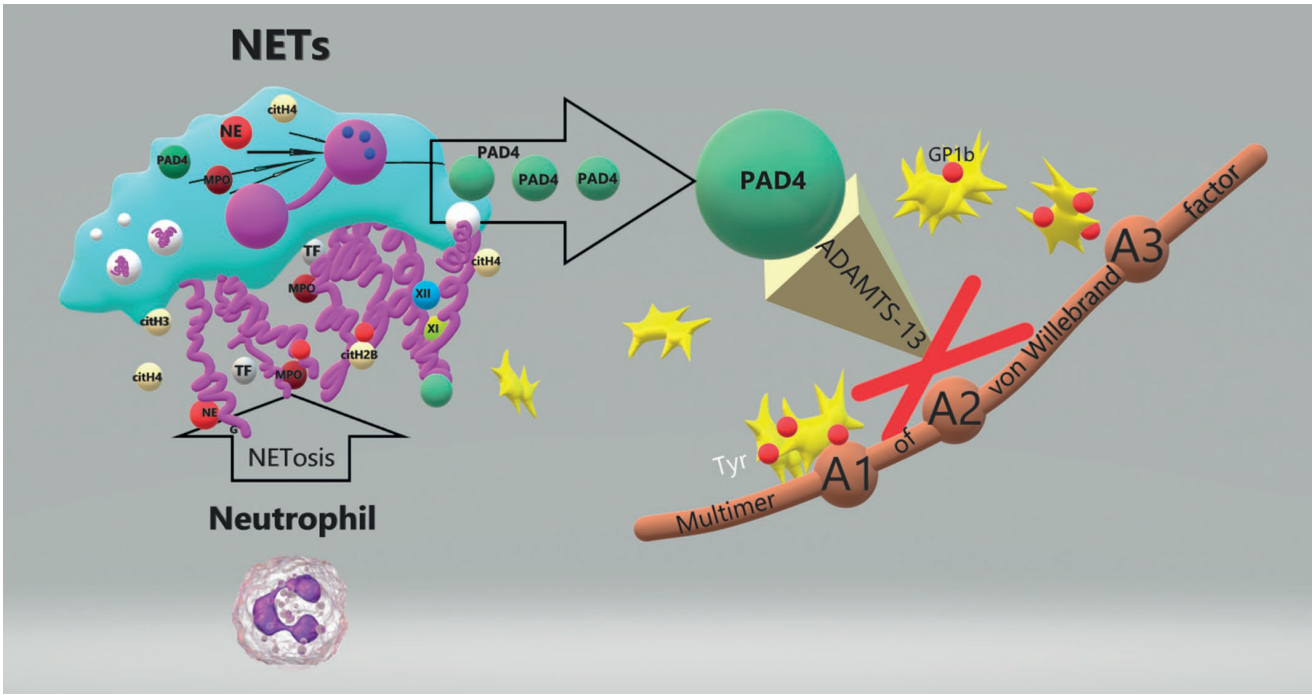

Figure 7. NETs effect on ADAMTS-13 activity [drawn by authors].

Note: *NETs – neutrophil extracellular traps; PAD4 – peptidyl arginine deiminase 4; GP1b – glycoprotein 1b; A1, A2, A3 – domains of von Willebrand factor multimer; ADAMTS-13 – a disintegrin and metalloprotease with thrombospondin type 1 motif; Tyr – tyrosine amino acid; NE – neutrophil elastase; MPO – myeloperoxidase; citH4 – citrullinated histone H4; citH2B – citrullinated histone H2B; TF – tissue factor.*

Рисунок 7. Влияние NETs на активность ADAMTS-13 [рисунок авторов].

Примечание: *NETs – внеклеточные ловушки нейтрофилов; PAD4 – пептидил-аргинин деиминаза 4; GP1b – гликопротеин 1b; A1, A2, A3 – домены мультимера фактора фон Виллебранда; ADAMTS-13 – дизинтегрин-подобная металлопротеаза с мотивом тромбоспондина 1; Tyr – аминокислота тирозин; NE – эластаза нейтрофилов; MPO – миелопероксидаза; citH4 – цитрулированный гистон H4; citH2B – цитрулированный гистон H2B; TF – тканевой фактор.*

articles) devoted to impaired hemostasis and thrombosis. Decompensation of the systemic inflammatory response and a prothrombotic state is now recognized as the pivotal pathogenetic arms of severe COVID-19 course [52]. Regarding COVID-19 it is worth noting that the terms thrombosis, endothelial dysfunction, and immunothrombosis have been increasingly more often associated with its pathogenesis.

NETs are one of the causes for developing severe COVID-19 [53]. Histones, the main NETs components, have a cytotoxic effect, induce cell damage being detected within thrombi along with platelets in the lungs of infected subjects [54]. Excessive neutrophil activation and NETs production contribute to acute lung tissue injury, microthrombosis, hemorrhage, and pulmonary insufficiency. Chromatin networks disrupt the alveolar-capillary barrier, leading to endothelial damage and hemorrhage [55].

The common features in the pathogenetic mechanisms between acute infectious process and tumor growth allow to advance the understanding of cancer-linked pathogenesis after the last pandemic.

Conclusion / Заключение

Cancer-associated thrombosis is a special type of prothrombotic condition. Moreover, risk assessment, monitoring, and management should be carried out considering the existing knowledge about etiopathogenesis. Inflammation and thrombosis play an essential role in tumor progression and metastasis in cancer patients. Coronavirus infection has become a vivid example of severe conditions caused by immunothrombosis. The main arms in the pathogenesis of severe COVID-19 are presented by intravascular coagulation along with increased thrombin generation, endotheliopathy in parallel with cytokine storm, NETosis, as well as activation of platelets and the complement system. Altogether, it opens up new horizons for developing modern innovative strategies for treating cancer patients.

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References / Литература:

1. Fernandes C.J., Morinaga L.T., Alves J.L. et al. Cancer-associated thrombosis: the when, how and why. *Eur Respir Rev*. 2019;28(151):180119. https://doi.org/10.1183/16000617.0119-2018.
2. Hisada Y., Mackman N. Cancer-associated pathways and biomarkers of venous thrombosis. *Blood*. 2017;130(13):1499–506. https://doi.org/10.1182/blood-2017-03-743211.
3. Trousseau A. Phlegmasia alba dolens. *Clinique medicale de l'Hotel-Dieu de Paris*. 1865;3:94.
4. Ay C., Pabinger I., Cohen A.T. Cancer-associated venous thromboembolism: burden, mechanisms, and management. *Thromb Haemost*. 2017;117(2):219–30. https://doi.org/10.1160/TH16-08-0615.
5. Noble S., Pasi J. Epidemiology and pathophysiology of cancer-associated thrombosis. *Br J Cancer*. 2010;102 Suppl 1(Suppl 1):S2–9. https://doi.org/10.1038/sj.bjc.6605599.
6. Wun T., White R.H. Venous thromboembolism (VTE) in patients with cancer: epidemiology and risk factors. *Cancer Invest*. 2009;27 Suppl 1:63–74. https://doi.org/10.1080/07357900802656681.
7. Ma S.-N., Mao Z.-X., Wu Y. et al. The anti-cancer properties of heparin and its derivatives: a review and prospect. *Cell Adh Migr*. 2020;14(1):118–28. https://doi.org/10.1080/19336918.2020.1767489.
8. Lyman G.H., Eckert L., Wang Y. et al. Venous thromboembolism risk in patients with cancer receiving chemotherapy: a real-world analysis. *Oncologist*. 2013;18(12):1321–9. https://doi.org/10.1634/theoncologist.2013-0226.
9. Lyman G.H. Venous thromboembolism in the patient with cancer: focus on burden of disease and benefits of thromboprophylaxis. *Cancer*. 2011;117(7):1334–49.https://doi.org/10.1002/cncr.25714.
10. Wun T., White R.H. Epidemiology of cancer-related venous thromboembolism. *Best Pract Res Clin Haematol*. 2009;22(1):9–23. https://doi.org/10.1016/j.beha.2008.12.001.
11. Falanga A., Marchetti M. Venous thromboembolism in the hematologic malignancies. *J Clin Oncol*. 2009;27(29):4848–57. https://doi.org/10.1200/JCO.2009.22.8197.
12. De Cicco M. The prothrombotic state in cancer: pathogenic mechanisms. *Crit Rev Oncol Hematol*. 2004;50(3):187–96. https://doi.org/10.1016/j.critrevonc.2003.10.003.

13. Abdel-Razeq H., Mansour A., Saadeh S.S. et al. The application of current proposed venous thromboembolism risk assessment model for ambulatory patients with cancer. *Clin Appl Thromb Hemost*. 2018;24(3):429–33. https://doi.org/10.1177/1076029617692880.
14. Hamada K., Kuratsu J., Saitoh Y. et al. Expression of tissue factor correlates with grade of malignancy in human glioma. *Cancer*. 1996;77(9):1877–83. https://doi.org/10.1002/(SICI)1097-0142(19960501)77:9<1877::AID-CNCR18>3.0.CO;2-X.
15. Dai H., Zhou H., Sun Y. et al. D-dimer as a potential clinical marker for predicting metastasis and progression in cancer. *Biomed Rep*. 2018;9(5):453–7. https://doi.org/10.3892/br.2018.1151.
16. Chen N., Ren M., Li R. et al. Bevacizumab promotes venous thromboembolism through the induction of PAI-1 in a mouse xenograft model of human lung carcinoma. *Mol Cancer*. 2015;14:140. https://doi.org/10.1186/s12943-015-0418-x.
17. Granger J.M., Kontoyiannis D.P. Etiology and outcome of extreme leukocytosis in 758 nonhematologic cancer patients: a retrospective, single-institution study. *Cancer*. 2009;115(17):3919–23. https://doi.org/10.1002/cncr.24480.
18. Blix K., Jensvoll H., Brækkan S.K., Hansen J.-B. White blood cell count measured prior to cancer development is associated with future risk of venous thromboembolism – the Tromsø study. *PLoS One*. 2013;8(9):e73447. https://doi.org/10.1371/journal.pone.0073447.
19. Shindo K., Aishima S., Ohuchida K. et al. Podoplanin expression in cancer-associated fibroblasts enhances tumor progression of invasive ductal carcinoma of the pancreas. *Mol Cancer*. 2013;12(1):168. https://doi.org/10.1186/1476-4598-12-168.
20. Mukai M., Oka T. Mechanism and management of cancer-associated thrombosis. *J Cardiol*. 2018;72(2):89–93. https://doi.org/10.1016/j.jjcc.2018.02.011.
21. Peterson J.E., Zurakowski D., Italiano J.E. et al. VEGF, PF4 and PDGF are elevated in platelets of colorectal cancer patients. *Angiogenesis*. 2012;15(2):265–73. https://doi.org/10.1007/s10456-012-9259-z.
22. Quintanilla M., Montero-Montero L., Renart J., Martín-Villar E. Podoplanin in inflammation and cancer. *Int J Mol Sci*. 2019;20(3):707. https://doi.org/10.3390/ijms20030707.
23. Aharon A., Brenner B. Microparticles, thrombosis and cancer. *Best Pract Res Clin Haematol*. 2009;22(1):61–9. https://doi.org/10.1016/j.beha.2008.11.002.
24. Engelmann B., Massberg S. Thrombosis as an intravascular effector of innate immunity. *Nat Rev Immunol*. 2013;13(1):34–45. https://doi.org/10.1038/nri3345.
25. Geddings J.E., Mackman N. Tumor-derived tissue factor–positive microparticles and venous thrombosis in cancer patients. *Blood*. 2013;122(11):1873–80. https://doi.org/10.1182/blood-2013-04-460139.
26. Zarà M., Canobbio I., Visconte C. et al. Molecular mechanisms of platelet activation and aggregation induced by breast cancer cells. *Cell Signal*. 2018;48:45–53. https://doi.org/10.1016/j.cellsig.2018.04.008.
27. Lowe K.L., Navarro-Nunez L., Watson S.P. Platelet CLEC-2 and podoplanin in cancer metastasis. *Thromb Res*. 2012;129 Suppl 1:S30–7. https://doi.org/10.1016/S0049-3848(12)70013-0.
28. Lee H.-Y., Yu N.-Y., Lee S.-H. et al. Podoplanin promotes cancer-associated thrombosis and contributes to the unfavorable overall survival in an ectopic xenograft mouse model of oral cancer. *Biomed J*. 2020;43(2):146–62. https://doi.org/10.1016/j.bj.2019.07.001.
29. Stone R.L., Nick A.M., McNeish I.A. et al. Paraneoplastic thrombocytosis in ovarian cancer. *N Engl J Med*. 2012;366(7):610–8. https://doi.org/10.1056/NEJMoa1110352.
30. Seyfried T.N., Huysentruyt L.C. On the origin of cancer metastasis. *Crit Rev Oncog*. 2013;18(1–2):43–73. https://doi.org/10.1615/critrevoncog.v18.i1-2.40.
31. Riedl J., Preusser M., Nazari P.M.S. et al. Podoplanin expression in primary brain tumors induces platelet aggregation and increases risk of venous thromboembolism. *Blood*. 2017;129(13):1831–9. https://doi.org/10.1182/blood-2016-06-720714.
32. Payne H., Ponomaryov T., Watson S.P., Brill A. Mice with a deficiency in CLEC-2 are protected against deep vein thrombosis. *Blood*. 2017;129(14):2013–20. https://doi.org/10.1182/blood-2016-09-742999.
33. Efrimescu C.I., Buggy P.M., Buggy D.J. Neutrophil extracellular trapping role in cancer, metastases, and cancer-related thrombosis: a narrative review of the current evidence base. *Curr Oncol Rep*. 2021;23(10):118. https://doi.org/10.1007/s11912-021-01103-0.
34. Martins-Cardoso K., Almeida V.H., Bagri K.M. et al. Neutrophil extracellular traps (NETs) promote pro-metastatic phenotype in human breast cancer cells through epithelial–mesenchymal transition. *Cancers (Basel)*. 2020;12(6):1542. https://doi.org/10.3390/cancers12061542.
35. 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;21(1):145. https://doi.org/10.1186/s13058-019-1237-6.
36. Brinkmann V., Reichard U., Goosmann C. et al. Neutrophil extracellular traps kill bacteria. *Science*. 2004;303(5663):1532–5. https://doi.org/10.1126/science.1092385.
37. Teijeira Á., Garasa S., Gato M. et al. CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. *Immunity*. 2020;2(5):856–71.e8. https://doi.org/10.1016/j.immuni.2020.03.001.
38. Zuo Y., Yalavarthi S., Shi H. et al. Neutrophil extracellular traps in COVID-19. *JCI Insight*. 2020;5(11):e138999. https://doi.org/10.1172/jci.insight.138999.
39. Nie M., Yang L., Bi X. et al. Neutrophil extracellular traps induced by IL8 promote diffuse large B-cell lymphoma progression via the TLR9 signaling. *Clin Cancer Res*. 2019;25(6):1867–79. https://doi.org/10.1158/1078-0432.CCR-18-1226.
40. Yang D., Liu J. Neutrophil extracellular traps: A new player in cancer metastasis and therapeutic target. *J Exp Clin Cancer Res*. 2021;40(1):233. https://doi.org/10.1186/s13046-021-02013-6.
41. Thalin C., Hisada Y., Lundstrom S. et al. Neutrophil extracellular traps: villains and targets in arterial, venous, and cancer-associated thrombosis. *Arterioscler Thromb Vasc Biol*. 2019;39(9):1724–38. https://doi.org/10.1161/ATVBAHA.119.312463.
42. Giaglis S., Stoikou M., Grimolizzi F. et al. Neutrophil migration into the placenta: Good, bad or deadly? *Cell Adh Migr*. 2016;10(1–2):208–25. https://doi.org/10.1080/19336918.2016.1148866.
43. Marder W., Knight J.S., Kaplan M.J. et al. Placental histology and neutrophil extracellular traps in lupus and pre-eclampsia pregnancies. *Lupus Sci Med*. 2016;3(1):e000134. https://doi.org/10.1136/lupus-2015-000134.
44. Osorio Y., Bonilla D.L., Peniche A.G. et al. Pregnancy enhances the innate immune response in experimental cutaneous leishmaniasis through hormone-modulated nitric oxide production. *J Leukoc Biol*. 2008;83(6):1413–22. https://doi.org/10.1189/jlb.0207130.
45. Hahn S., Lapaire O., Than N.G. Biomarker development for presymptomatic molecular diagnosis of preeclampsia: feasible, useful or even unnecessary? *Expert Rev Mol Diagn*. 2015;15(5):617–29. https://doi.org/10.1586/14737159.2015.1025757.
46. Lam F.W., Cruz M.A., Parikh K., Rumbaut R.E. Histones stimulate von Willebrand factor release in vitro and *in vivo*. *Haematologica*. 2016;101(7):e277–9. https://doi.org/10.3324/haematol.2015.140632.
47. Meier T.R., Myers D.D., Wrobleski S.K. et al. Prophylactic P-selectin inhibition with PSI-421 promotes resolution of venous thrombosis without anticoagulation. *Thromb Haemost*. 2008;99(2):343–51. https://doi.org/10.1160/TH07-10-0608.
48. Ay C., Simanek R., Vormittag R. et al. High plasma levels of soluble P-selectin are predictive of venous thromboembolism in cancer patients: results from the Vienna Cancer and Thrombosis Study (CATS). *Blood*. 2008;112(7):2703–8. https://doi.org/10.1182/blood-2008-02-142422.
49. Hernandez C., Huebener P., Schwabe R.F. Damage-associated molecular patterns in cancer: a double-edged sword. *Oncogene*. 2016;35(46):5931–41. https://doi.org/10.1038/onc.2016.104.
50. Tang M., Jiang L., Lin Y. et al. Platelet microparticle-mediated transfer of miR-939 to epithelial ovarian cancer cells promotes epithelial to mesenchymal transition. *Oncotarget*. 2017;8(57):97464–75. https://doi.org/10.18632/oncotarget.22136.
51. Hindilerden F., Yonal-Hindilerden I., Akar E., Kart-Yasar K. Covid-19 associated autoimmune thrombotic thrombocytopenic purpura: Report of a case. *Thromb Res*. 2020;195:136–8. https://doi.org/10.1016/j.thromres.2020.07.005.
52. Giamarellos-Bourboulis E.J., Netea M.G., Rovina N. et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. *Cell Host Microbe*. 2020;27(6):992–1000.e3. https://doi.org/10.1016/j.chom.2020.04.009.
53. Middleton E.A., He X.Y., Denorme F. et al. Neutrophil extracellular traps contribute to immunothrombosis in COVID-19 acute respiratory distress

syndrome. *Blood*. 2020;136(10):1169–79. https://doi.org/10.1182/blood.2020007008.
54. Ashar H.K., Mueller N.C., Rudd J.M. et al. The role of extracellular histones in influenza virus pathogenesis. *Am J Pathol*. 2018;188(1):135–48. https://doi.org/10.1016/j.ajpath.2017.09.014.
55. Gould T.J., Lysov Z., Liaw P.C. Extracellular DNA and histones: double-edged swords in immunothrombosis. *J Thromb Haemost*. 2015;13 Suppl 1:S82–91. https://doi.org/10.1111/jth.12977.

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