ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих рецензируемых журналов и изданий ВАК

2021 • том 15 • № 6

OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2021 Vol. 15 No 6

www.gynecology.su

ISSN 2313-7347 (print)
ISSN 2500-3194 (online)

Научный обзор | Review article

https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.274

Platelets, thrombo-inflammation and cancer

Ekaterina V. Slukhanchuk[1,2], Viktoria O. Bitsadze[1], Jamilya Kh. Khizroeva[1], Maria V. Tretyakova[1], Antonina G. Solopova[1], Vsevolod N. Galkin[3], Andrey S. Shkoda[4], Valentina I. Tsibizova[5], Valery I. Linnikov[6], Ismail Elalamy[1,7,8], Jean-Christophe Gris[1,9], Benjamin Brenner[10], Alexander D. Makatsariya[1]

[1]Sechenov University; 2 bldg. 4, Bolshaya Pirogovskaya Str., Moscow 119991, Russia;

[2]Petrovsky National Research Centre of Surgery; 2 Abrikosovskiy Lane, Moscow 119991, Russia;

[3]City Clinical Oncological Hospital № 1, Moscow City Healthcare Department; 17/1 Baumanskaya Str., Moscow 105005, Russia;

[4]Vorokhobov City Clinical Hospital № 67, Moscow City Healthcare Department; 2/44 Salyama Adilya Str., Moscow 123423, Russia;

[5]Almazov National Medical Research Centre, Health Ministry of Russian Federation; 2 Akkuratova Str., Saint Petersburg 197341, Russia;

[6]Saint Paul German Medical and Diagnostic Center; 68/2 Novoselskogo Str., Odessa 65023, Ukraine;

[7]Medicine Sorbonne University; 12 Rue de l'École de Médecine, Paris 75006, France;

[8]Hospital Tenon; 4 Rue de la Chine, Paris 75020, France;

[9]University of Montpellier; 163 Rue Auguste Broussonnet, Montpellier 34090, France;

[10]Rambam Academic Hospital; 8 Aliya-ha-Shniya Str., Haifa 31096, Israel

Corresponding author: *Ekaterina V. Slukhanchuk, e-mail: ekaterina@ginekologhirurg.ru*

Abstract

It has long been recognized a crucial role played by platelets in thrombosis and hemostasis. Along with that, laboratory and clinical data suggest that platelets contribute to tumor progression and metastasis through a variety of interactions with cancer cells. During oncological process, the platelet function becomes modulated via their activation and increased aggregation being one of the risk factors for developing thrombosis in cancer patients. The platelets per se enhance tumor cell dissemination, activate endothelial cells, and attract immune cells to the primary and metastatic tumor sites. In this review, we summarize the current knowledge about the complex interactions between platelets and tumor cells, as well as cells of the microenvironment, and discuss the development of new antitumor agents aimed at various arms in platelet functioning.

Keywords: platelets, thrombosis, metastasis, tumor, tumor growth, tumor progression

For citation: Slukhanchuk E.V., Bitsadze V.O., Khizroeva J.Kh., Tretyakova M.V., Solopova A.G., Galkin V.N., Shkoda A.S., Tsibizova V.I., Linnikov V.I., Elalamy E., Gris J.-C., Brenner B., Makatsariya A.D. Platelets, thrombo-inflammation and cancer. *Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction*. 2021;15(6):755–776. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.274.

Тромбоциты, тромбовоспаление и онкологический процесс

Е.В. Слуханчук[1,2], В.О. Бицадзе[1], Д.Х. Хизроева[1], М.В. Третьякова[1], А.Г. Солопова[1], В.Н. Галкин[3], А.С. Шкода[4], В.И. Цибизова[5], В.И. Линников[6], И. Элалами[1,7,8], Ж.-К. Гри[1,9], Б. Бреннер[10], А.Д. Макацария[1]

[1]ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет); Россия, 119991 Москва, ул. Большая Пироговская, д. 2, стр. 4;

[2]ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского»; Россия, 119991 Москва, Абрикосовский пер., д. 2;

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[3]ГБУЗ «Городская клиническая онкологическая больница № 1 Департамента здравоохранения города Москвы»; Россия, 105005 Москва, Бауманская ул., д. 17/1;

[4]ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы»; Россия, 123423 Москва, ул. Саляма Адиля, д. 2/44;

[5]ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения Российской Федерации; Россия, 197341 Санкт-Петербург, ул. Аккуратова, д. 2;

[6]Немецкий лечебно-диагностический центр Святого Павла; Украина, 65023 Одесса, ул. Новосельского, д. 68/2;

[7]Медицинский Университет Сорбонны; Франция, 75006 Париж, Улица медицинского факультета, д. 12;

[8]Госпиталь Тенон; Франция, 75020 Париж, Китайская улица, д. 4;

[9]Университет Монпелье; Франция, 34090 Монпелье, ул. Огюста Бруссоне, д. 163;

[10]Академический госпиталь Рамбам; Израиль, 31096 Хайфа, ул. Алия-а-Шния, д. 8

Для контактов: *Екатерина Викторовна Слуханчук, e-mail: ekaterina@ginekologhirurg.ru*

Резюме

Всем давно известна важная роль, которую тромбоциты играют в тромбозе и гемостазе. Лабораторные и клинические данные указывают на то, что кроме этого тромбоциты способствуют прогрессии опухоли и ее метастазированию путем многообразных взаимодействий с опухолевыми клетками. На фоне онкологического процесса происходит модуляция функции тромбоцитов, повышение их активации и агрегации, что является одним из факторов риска тромбозов у онкологических больных. Сами тромбоциты усиливают диссеминацию опухолевых клеток, активируют эндотелиальные клетки, привлекают иммунные клетки к первичным и метастатическим участкам опухоли. В обзоре мы обобщаем текущие знания о сложных взаимодействиях между тромбоцитами и опухолевыми клетками, а также клетками микроокружения, обсуждаем вопросы разработки новых противоопуолевых агентов, направленных на различные звенья функционирования тромбоцитов.

Ключевые слова: тромбоциты, тромбоз, метастазирование, опухоль, опухолевый рост, прогрессия опухоли

Для цитирования: Слуханчук Е.В., Бицадзе В.О., Хизроева Д.Х., Третьякова М.В., Солопова А.Г., Галкин В.Н., Шкода А.С., Цибизова В.И., Линников В.И., Элалами Э., Гри Ж.-К., Бреннер Б., Макацария А.Д. Тромбоциты, тромбовоспаление и онкологический процесс. *Акушерство, Гинекология и Репродукция.* 2021;15(6):755–776. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2021.274.

Highlights

What is already known about this subject?

- It has long been recognized a crucial role played by platelets in thrombosis and hemostasis. It has been proven that platelets contribute to tumor progression and metastasis through a variety of interactions with tumor cells.
- During oncological process, the platelet function becomes modulated, their activation and increased aggregation being one of the risk factors for developing thrombosis in cancer patients. Platelets are able to enhance tumor cell dissemination, activate endothelial cells, and recruit immune cells to primary and metastatic tumor sites.

What are the new findings?

- The review summarizes current knowledge about interactions between platelets, tumor as well as microenvironmental cells. The issues related to development of new anticancer agents aimed at various stages of platelet functioning are discussed.

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

- The development of new therapeutic agents aimed at potential platelet targets is a promising area of anticancer therapy able not only to retard tumor progression and metastasis, but also alleviate the associated risks of thrombotic complications in cancer patients.

Основные моменты

Что уже известно об этой теме?

- Тромбоциты играют важную роль в тромбозе и гемостазе. Доказано, что они способствуют прогрессии опухоли и ее метастазированию путем многообразных взаимодействий с опухолевыми клетками.
- На фоне онкологического процесса происходит модуляция функции тромбоцитов, повышение их активации и агрегации, что является одним из факторов риска тромбозов у онкологических больных. Тромбоциты усиливают диссеминацию опухолевых клеток, активируют эндотелиальные клетки, привлекают иммунные клетки к первичным и метастатическим участкам опухоли.

Что нового дает статья?

- Обобщены текущие знания о взаимодействиях между тромбоцитами, опухолевыми клетками, клетками микроокружения. Обсуждаются вопросы разработки новых противоопухолевых агентов, направленных на различные звенья функционирования тромбоцитов.

Как это может повлиять на клиническую практику в обозримом будущем?

- Разработка новых терапевтических агентов, направленных на возможные тромбоцитарные мишени, является перспективным направлением противоопухолевой терапии, способной не только затормозить прогрессирование опухоли и метастазирование, но и снизить сопутствующие риски тромботических осложнений у онкологических пациентов.

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Introduction / Введение

A tumor develops due to uncontrolled cell division, their growth, and spread during metastasis. For many years, cancer biology has focused on tumor cells, tumor suppressor genes, and oncogenes, and this has contributed to our understanding of the underlying mechanisms of oncogenesis and associated cellular signaling pathways. In recent years, there has been progressively accumulated more evidence that tumor progression and metastasis depend not only on tumor cells but also on a cellular and molecular crosstalk with various components of the tumor microenvironment.

Since the mid-19th century, the relationship between cancer and thrombosis has been studied [1]. The risk of venous thromboembolic complications in cancer patients is increased by 7-fold [2]. Thrombotic complications in cancer indicate the active participation of platelets and factors they release in the tumor progression while enhancing the blood procoagulant activity. Currently, experimental and clinical data indicate the relationship between platelets and angiogenesis, tumor progression, and metastasis through platelets interacting with both tumor cells and its microenvironment.

The tumor microenvironment consists of the extracellular matrix (ECM), cytokines, growth factors, adhesion molecules, and various cellular components such as fibroblasts, immune cells, adipocytes, pericytes, epithelial cells, and lymphatic endothelial cells, and platelets [3]. The tumor microenvironment provides the necessary environment, nutrients, and blood supply, promoting the proliferation of tumor cells.

Platelets are small, nucleus-free structures formed from megakaryocytes in the bone marrow. Circulating in the blood, they play an essential role in the process of thrombosis and hemostasis. In case of vascular injury, subendothelial matrix proteins are found in the circulating blood; von Willebrand factor (vWF) binds to endothelial collagen as well as platelet glycoproteins GPIbα, and this is generally an essential stage in platelet activation and adhesion and thrombogenesis. Platelets express several surface integrins, which interact with ligands such as fibrinogen, vitronectin, collagen, fibronectin, and laminin to promote platelet attachment to the vascular wall. The platelet secretory granules contain several bioactive plasma proteins (coagulation factors, fibrinogen, vWF), regulatory factors, and secondary mediators such as adenosine diphosphate and triphosphate (ADP/ATP) and serotonin. All of them are released upon platelet activation, thereby enhancing the prothrombotic effect, stimulating the attraction of circulating platelets to the site of injury [4]. The concentration of platelets at the site of damaged vessel promotes their own aggregation as well as activation of the blood coagulation cascade via thrombin and active coagulation factors. Due to thrombin action, soluble fibrinogen is converted to fibrin, which per se enhances platelet activation and aggregation. The activated platelets expose phosphatidylserine (PS), facilitating the recruitment of the prothrombinase complex and the platelet surface interaction with the coagulation cascade factors [5].

Thrombosis and thrombo-inflammation in cancer patients / Тромбоз и тромбовоспаление у онкологических пациентов

Statistics data indicate that the incidence rate for deep vein thrombosis and thromboembolism in cancer patients reaches around 500 per 100,000 per year, compared with 70–130 per 100,000 per year in the general population [6]. Thromboembolic complications are the second leading cause of death in cancer patients. There has been shown the association between thrombocytosis and poor survival, increased risk of tumor metastasis, and venous thromboembolism (VTE) in a wide variety of cancers, including colorectal cancer, breast, lung, kidney, and stomach tumors [2, 7, 8].

Thrombocytosis / Тромбоцитоз

Thrombocytosis has traditionally been considered as a reaction to the paraneoplastic process and a reflection of a parallel inflammatory process with pathological cytokine production. In many studies, thrombocytosis is a predictor of distant metastases, particularly in colorectal cancer [9]. Several researchers have proposed a molecular mechanism for the development of thrombocytosis associated with the ability of certain tumor cell types to produce thrombopoietin (TPO). This key cytokine stimulates differentiation and proliferation of megakaryocytes and, as a result, platelet production. Elevated plasma TPO levels have been observed in cancer patients with reactive thrombocytosis [10].

Interestingly, in many cases, in the presence of high plasma TPO titers, high concentrations of interleukin IL-6 were also observed, whereas both parameters are associated with a poor prognosis [11]. In mouse models of colorectal and ovarian cancer, the inflammatory response of tumor and immune cells has been shown to include the production of IL-6, which can stimulate platelet production by enhancing hepatocyte TPO secretion, which is abrogated in IL-6 deficient mice.

Ovarian tumor cells can secrete functionally active TPO, directly activating platelet synthesis in the bone marrow [12]. In addition, an increased platelet marker expression in cancer patients, including CD40 and beta-thromboglobulin was found [13]. P-selectin is exposed on the surface of activated platelets, and its serum soluble isoform concentration is increased, which is combined with an increased risk of VTE in cancer patients. In addition, the concentration of CD63-positive platelet-derived microparticles (PMPs) is often increased as well [14] (**Fig. 1**).

Tumor cell-induced platelet activation / Активация тромбоцитов, индуцированная опухолевыми клетками

Tumor cells can directly activate platelets and increase blood clotting. Tumor cell-induced platelet activation and platelet aggregation (TCIPA) have been found *in vitro* in neuroblastoma, small cell lung tumor, fibroblastoma, kidney, stomach, breast, melanoma, and colorectal cancer [15, 16]. TCIPA was first identified in 1968 [17].

Podoplanin was proposed as a key regulator of this process being a transmembrane sialomucin-like type I glycoprotein located on the surface of many tumor cells, including squamous cell carcinoma, seminoma, and brain tumors. Its upregulated expression by tumor cells is associated with a high risk of thrombosis. Platelet aggregation was increased in podoplanin-positive squamous cell tumors in mice, which showed lower survival. Expression of podoplanin by human brain tumors is also associated with increased platelet aggregation, hypercoagulation, and a high risk of VTE [18].

CLEC-2, a C-type lectin-like receptor-2 of platelets, for the first time was discovered in 2006 [19] and is considered as an important platelet receptor, which is activated by the snake venom toxin rhodocytin and podoplanin. Suppressed CLEC-2 function in mice with lung tumor significantly reduces thrombogenesis and metastasis after injection of B16F10 melanoma cells, which probably suggests that the interaction between CLEC-2 and tumor podoplanin may also enhance thromboembolism, TCIPA, and metastasis [20].

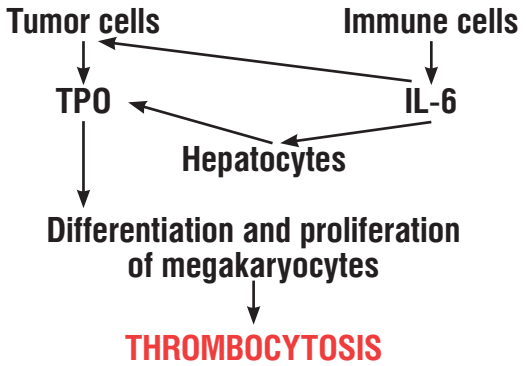

Figure 1. Thrombocytosis and neoplastic process [drawn by authors].

Note: *TPO – thrombopoietin; IL-6 – interleukin-6.*

Рисунок 1. Тромбоцитоз и опухолевый процесс [рисунок авторов].

Примечание: *TPO – тромбопоэтин; IL-6 – интерлейкин-6.*

Tumor cells can also induce indirect platelet activation by enhancing the release of ECM proteins and tissue factor (TF) from endothelial cells, creating an active surface for platelet adhesion and subsequent thrombogenesis. It is the increased concentration of tissue factor that accounts for developing thrombosis during chemotherapy in some types of tumors.

Possible mechanisms also include platelet-dependent thrombin formation and subsequent activation of the PAR (protease-activated receptor), phospholipase C (PLC) activation, depletion of calcium stores, and activation of guanosine-5'-triphosphate(GTP)ase Rap1b. Suppression of PLC in platelets can prevent TCIPA, contributing significantly to inositol triphosphate (IP3)-dependent calcium release and diacylglycerol (DAG)-mediated signaling in this process [21]. IP3-dependent calcium release triggers the PS (phosphatidylserine) action on the platelet surface, activating the prothrombinase complex. It has been shown that the concentration of PS-positive platelets is significantly higher in blood samples from cancer patients, which is combined with a shortened blood clotting time and increased prothrombinase activity [14].

Cancer-associated thrombosis can be triggered without tissue factor involvement. Gas6 is a vitamin K-dependent acts as a receptor-ligand of the tyrosine kinase family, including Tyro3, Axl, and Mer (TAM), found in both tumor and endothelial cells. Even though Gas6 regulates the inflammatory responses of immune and endothelial cells, modeled venous thrombosis associated with lung cancer showed that Gas6 enhances the secretion of endothelial prostaglandin E2 (PGE2) resulting in platelet activation and venous thrombosis [22]. The interaction of platelets with T-cells also enhances the pro-inflammatory-procoagulant state and promotes the development of thrombosis in patients with lung cancer [23] (**Fig. 2**).

Thrombo-inflammation / Тромбовоспаление

The inflammation leads to increased vWF level released from activated platelets and endothelial cells, as shown in postoperative prostate cancer patients.

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Interestingly, down regulated or suppressed androgen receptor function in tumor cells can induce TCIPA *in vitro*. As a result, the loss of androgen receptors accounts for the increased thrombogenicity. In contrast, androgen receptor-rich prostate cancer cells cannot induce TCIPA [24]. A. Mitrugno et al. reported that FcgRIIa (Fc-gamma receptor IIa) expressed on human platelets can promote platelet activation induced by prostate cancer P3 cells able to directly induce ADP release [25]. This cross-interaction of platelets and tumor cells is triggered by the direct interaction of platelet FcgRIIa with tumor-induced immunoglobulin G.

Neutrophil extracellular traps / Внеклеточные ловушки нейтрофилов

In cancer patients, there was an increased formation of neutrophil extracellular traps (NETs), an increased serum histone concentration, and deoxyribonucleic acid (DNA). NETs synthesis is associated with an increased incidence of cancer-associated thrombosis and multiple organ failure. In cancer patients with thrombosis and increased TF level, extracellular vesicles and citrullinated histone H3 were reported. In an *in vivo* experiment, suppression of TF, decreased neutrophil count or the introduction of deoxyribonuclease I (DNase I) in mice reduced the incidence of venous thrombosis [26]. These results suggest that systemic therapy with DNase I disrupting NETs may be effective against cancer-associated thrombosis. A growing body of evidence indicates that monocytes, macrophages, and endothelial cells can also expose their granular and nuclear contents

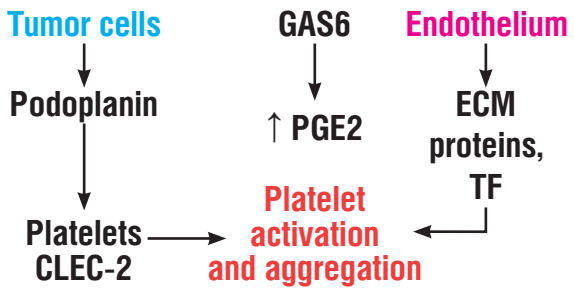

Figure 2. Platelet activation and aggregation under tumor growth [drawn by authors].

Note: *PGE2 – prostaglandin E2; TF – tissue factor; ECM – extracellular matrix; GAS6 – growth arrest specific 6; CLEC-2 – C-type lectin-like receptor-2.*

Рисунок 2. Активация и агрегация тромбоцитов в условиях опухолевого роста [рисунок авторов].

Примечание: *PGE2 – простагландин E2; TF – тканевой фактор; ECM – внеклеточный матрикс; GAS6 – специфическая задержка роста 6; CLEC-2 – лектиноподобный рецептор-2 С-типа.*

to expulsion, and in some cases, activated platelets contribute to this process [27]. Procoagulant tumor cells can also release extracellular traps [28].

Platelet effect on tumor vasculature formation / Влияние тромбоцитов на формирование сосудистой сети опухоли

Angiogenesis / Ангиогенез

After reaching a certain size, tumors begin to stimulate angiogenesis, a regulated process associated with cell migration towards pro-angiogenic signals due to pro-angiogenic vascular endothelial growth factor (VEGF). Mural cells, pericytes, and smooth muscle cells are then recruited into the vessel thus formed [29].

Alpha-granules of platelets are the primary storage of angiogenic factors that simultaneously control hemostasis and angiogenesis in the tumor microenvironment. Each platelet contains 50 to 80 alpha-granules. The synthesis and accumulation of proteins contained in granules occurs even at the stage of megakaryocytes or via endocytosis in megakaryocytes and platelets [30].

Platelet-derived growth factor (PDGF) is a family of peptide growth factors that act through surface tyrosine kinase receptors (platelet-derived growth factor receptor, PDGFR) by stimulating growth, proliferation, and differentiation. Their potential is also associated with the tumor invasiveness and metastatic activity.

Activated platelets release pro-angiogenic factors such as VEGF, epidermal growth factor (EGF), fibroblast growth factor (bFGF), transforming growth factor-beta (TGR-β), insulin-like growth factor 1 (IGF-1), as well as anti-angiogenic factors such as angiopoietin-1 (ANGPT1), sphingosine 1-phosphate (S1P), thrombospondin-1 (TSP1), platelet factor 4 (PF4), and endostatin [31]. Depending on the type of external stimulus, platelets can selectively release these factors to stimulate or suppress vasculogenesis in a growing tumor. For instance, platelets stimulated with ADP can release VEGF, but not endostatin, whereas stimulation with thromboxane A2 (TxA2) causes a more significant release of endostatin than VEGF *in vitro*. ADP-stimulated platelets promote capillary formation from human umbilical vein endothelial cells (HUVEC), whereas TxA2-stimulated platelets suppress this process [32].

Platelets are the primary source of VEGF in blood plasma. Tumor cells can also secrete VEGF. Platelets collected from cancer patients selectively absorb and store VEGF in alpha-granules. Depending on the setting, tumor cells can stimulate the release of VEGF accumulated

in platelets and regulate its local concentration in the tumor microenvironment. Tumor IL-6 increases VEGF expression in megakaryocytes and, consequently, in platelet alpha-granules. Altogether, it indicates about multilayered interaction between platelets and tumor cells in regulating angiogenesis [33].

The models demonstrated the ability of platelets to attract cells bone marrow-derived cells to sites of neovascularized hypoxic tissues. This process was triggered by the contents of platelet granules including growth factors and cytokines [34]. A breast cancer xenograft model showed that platelets store cytokines released by human breast cancer cells and deliver them to inactive tumors, thereby ensuring tumor growth and angiogenesis [35].

Tumor-derived VEGF triggers endothelial cell activation, vWF release, platelet aggregation, thereby unfolding a coagulation cascade in melanoma patients. The release of vWF is accompanied by locally suppressed proteolytic activity and expression of the vWF-cleaving protease ADAMTS-13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13). VEGF also upregulates TF level in the endothelium, which enhances platelet and thrombin formation [36].

The accumulation of activated platelets was observed on the fibrinogen/fibrin-coated endothelial surface. This temporary fibrin matrix supported the viability of endothelial cells and facilitated their migration [37].

Platelets contain and secrete a small number of anti-angiogenic factors, including endostatin and platelet factor 4 [31]. PF4 is a member of the chemokine family (CXCL4) being released from alpha-granules in response to platelet activation after blood vessel damage. After release, PF4 interacts with heparin-like molecules on the surface of endothelial cells, suppressing the local action of antithrombin and promoting enhanced coagulation processes. It is also able to bind to heparin and neutralize the anticoagulant activity of the latter. PF4 and its recombinant form rHuPF4 bind to sites of active angiogenesis *in vivo,* which allows to hope for the use of the recombinant form as a potential antitumor agent [38].

Platelets may be able to regulate angiogenesis independently of their granular content via triggering angiogenesis by directly interacting with endothelial cells. The monoclonal antibody c7E3 Fab (abciximab, ReoPro), which inhibits the integrin αIIbβ3 function on platelet surface, reduces the activity of angiogenetic processes *in vitro* [39]. Recent studies have shown that platelet tetraspanin promotes the formation of endothelial colony-forming tubular structures. The function of tetraspanin is associated with the laminin-specific integrin α6β1, and its blockade in both platelets and endothelial cells weakens the influence of platelets on the formation of endothelial tubular structures [40].

Activated platelets secrete PMPs – microvesicles ranging in size from 0.05 to 1 mm, which on their surface membrane contain several receptors and proteins, including P-selectin and integrins; they contain growth factors, cytokines, and pro-inflammatory molecules. PMPs also contribute to the chemotaxis of various hematopoietic cells. An increased PMPs concentration has been found in the blood plasma of cancer patients. PMPs exert angiogenic properties comparable to platelets. Platelets and PMPs contain different types of miRNA. The transfer of PMP-specific miRNA let-7a or miR-27b into endothelial cells can suppress thrombospondin-1 (TSP1) expression, thereby enhancing the platelet-dependent formation of endothelial tubular structures [41] (**Fig. 3**).

Lymphangiogenesis / Лимфангиогенез

During embryogenesis, platelets support the separation of the circulatory and lymphatic systems by interacting with podoplanin (PDPN) at the lympho-venous junction. In a mouse model with CLEC-2 deficiency, lymphatic vessels were filled with blood, resulting in embryonic death [42]. Experimentally, injection of B16F10 melanoma cells with CLEC-2 deficiency also led to filling the lymphatic vessels with blood [43]. Further research is needed to identify causes allowing CLEC2 platelets to regulate partition of the lymphatic and blood vessels during tumor growth.

Vascular mimicry / Сосудистая мимикрия

Vascular mimicry promotes tumor metastasis, often seen in patients with aggressive tumor types such as melanoma and cholangiocarcinoma. Vascular mimicry reflects tumor potential or tumor stem cells to form vascular networks to acquire oxygen and essential nutrients, regardless of the intensity of angiogenesis. Unlike other types of angiogenesis, platelets suppress vascular mimicry, which indicates that platelets can coordinate the process of vascularization [44].

Angioprotective effect / Ангиопротективный эффект

In addition to their key role in angiogenesis, platelets regulate the integrity of tumor vessels in primary tumors, thereby preventing tumor hemorrhage. Studies by B. Ho-Tin-Noe et al. showed that preserving tumor vascular integrity results from the secretion of platelet granules

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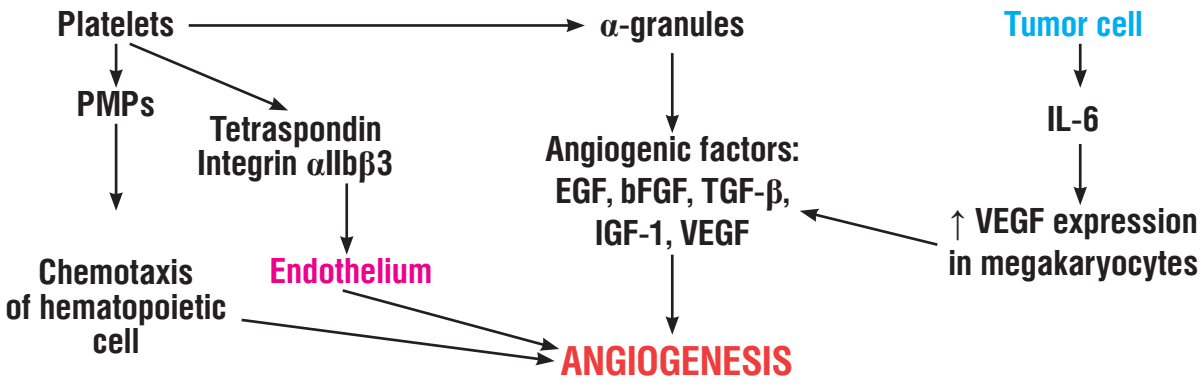

Figure 3. Platelets and angiogenesis during tumor growth [drawn by authors].

Note: *PMPs – platelet microparticles; IL-6 – interleukin-6; VEGF – vascular endothelial growth factor; EGF – epidermal growth factor; bFGF – basic fibroblast growth factor; TGF-β – transforming growth factor beta; IGF-1 – insulin-like growth factor 1.*

Рисунок 3. Тромбоциты и ангиогенез в процессе опухолевого роста [рисунок авторов].

Примечание: *PMPs – микрочастицы тромбоцитов; IL-6 – интерлекин-6; VEGF – фактор роста эндотелия сосудов; EGF – эпидермальный фактор роста; bFGF – основной фактор роста фибробластов; TGF-β – трансформирующий фактор роста бета; IGF-1 – инсулиноподобный фактор роста 1.*

containing serotonin and ANGPT, which counteract tumor cell-derived VEGF [45]. By maintaining vascular integrity, platelets resist tissue damage caused by tumor invading immune cells. It has been hypothesized that the destruction of tumor vessels may have beneficial effects by facilitating the efficient delivery of chemotherapeutic agents into tumor cells [46]. Recent studies have shown that the integrity of tumor vessels depends on the platelet-specific glycoprotein VI (GPVI) receptor, which blockage in primary prostate and breast tumors has been shown to increase the effectiveness of chemotherapy [47].

Depending on the stage of the disease, platelets can promote neovascularization and cause vascular stabilization by maintaining the vascular integrity. Growing tumors require neovascularization. Platelets are the primary cellular regulators of this process. Angiogenesis is an essential target of research that led to the development of antiangiogenic drugs. However, the effectiveness of antiangiogenic therapy is often limited by several factors expressed by tumors of various cell types. Hence, platelets regulate tumor angiogenesis, making them a potential target for an alternative antiangiogenic strategy.

Platelets and metastasis / Тромбоциты и метастазирование

Tumor cells separated from the primary tumor can migrate and colonize being far from it, forming secondary tumors – metastases. Once in the vascular or lymphatic system, they are exposed to oxidative stress, the cytotoxic effect of immune cells, which significantly reduces their number.

Platelets are the first cells to meet tumor cells in the bloodstream, also facilitating metastasis in various ways. G.J. Gasic et al. showed that thrombocytopenia with decreased number of metastases, whereas administration of platelets to mice with thrombocytopenia restores the ability to form metastases [17]. Later studies showed that disruption of megakaryopoiesis and platelet production reduces the intensity of metastasis in mouse models [48].

Antineoplastic immunity / Противоопухолевый иммунитет

Of all tumor cells that enter the bloodstream, only their small number subsequently form metastatic foci. Most tumor cells die to natural killer (NK) cell cytotoxic activity. Platelets, interacting with tumor cells, physically protect them from being recognized by the immune cells. Studies in mice with thrombocytopenia showed that platelets affect the lysis of tumor cells by NK cells, and this hypothesis was later confirmed by J.S. Palumbo et al. in mice lacking fibrinogen or Gaq protein and mutant platelets. In both cases, tumor cell survival was greatly reduced. These studies suggest that activated platelets along with fibrinogen (or fibrin), can envelop tumor cells thereby protecting from induced NK cells [49]. Other studies have shown that platelets show their prometastatic effects within the first hour after tumor cells enter the bloodstream, whereas NK cell antimetastatic effects emerge 1–6 hours after the

appearance of tumor cells [50]. While interacting with tumor cells, transfer major histocompatibility complex (MHC) class I molecules onto their own surface, thereby reducing NK cell-coupled antitumor inhibitory effect *in vitro* [51]. Platelet-mediated release of Natural Killer Group 2D (NKG2D) ligands can also suppress the cytotoxic effect of NK cells [52]. Platelets store a marked amount of TGF-β in α-granules (by 50–100 times more than other blood cells) and release it into the vascular lumen as well as sites of tumor microenvironment during tumor progression and metastasis. It was shown that platelet TGF-β down modulates NKG2D on NK cells while interacting with tumor cells, thereby reducing antitumor immunity [53].

Suppression of NKG2D correlates with elevated TGF-β levels in patients with colorectal cancer and lung cancer. TGF-β receptor – glycoprotein A repeat predominant protein (GARP) activates the latent form of platelet TGF-β. Using the TGF-β-GARP complex, platelets can directly inhibit T-lymphocyte function *in vitro* and *in vivo*. The release of TGF-β and lactate by platelets can inhibit the activity of both CD4+ and CD8+ T-cells [54]. Interestingly, thrombin cleaves platelet-bound GARP, thereby activating latent TGF-β [55]. TGF-β inhibitors that block peptides and aptamers are currently undergoing clinical trials in patients with solid tumors [56]. Transferring T-cells to stimulate the immune system has been proposed as a potentially promising new approach in anticancer therapy [57]. Suppression of TGF-β uptake by platelets may also be a potential antitumor strategy (**Fig. 4**).

Reprogramming of a tumor cell / Перепрограммирование опухолевой клетки

Epithelial-mesenchymal transition (EMT) is an important process of cell development, including in tumor progression. Epithelial tumor cells change their morphology, lose contact with the basement membrane and form a layer of primary mesenchymal cells through EMF. The EMT process can be reversible; primary mesenchymal cells can also be converted to epithelial cells and vice versa. EMF is supported by immune and stromal cells, as well as cells in the tumor microenvironment. Factors involved in the regulation of EMF include TGF-β, hepatocyte growth factor (HGF), EGF receptor, and transcription factors (ZEB1/2, Snail, Twist, and Tiam1). Processes similar to EMF occur during intravascular transit of tumor cells when platelets interact with them, at which point the platelets release EMF inducers. In tumor cells, after interaction with platelets, mesenchymal markers are activated, such as the snail family transcription repressor-1, vimentin, N-cadherin, fibronectin, and matrix metalloproteinase-2 (MMP-2), whereas epithelial markers (E-cadherin, claudin-1) are suppressed [58]. Activated platelets, releasing TGF-β from alpha-granules, switch tumor cells to the prometastatic EMT phenotype. Platelet TGF-β and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) trigger the EMT phenotype and metastasis *in vivo*. In this regard, suppressing NF-kB signaling to tumor cells or decreasing TGF-β expression in platelets reduces metastasis [58] (**Fig. 4**).

The ECM components secreted by the tumor or microenvironmental cells are actively involved in EMT. Collagen and heat shock protein 47 (Hsp47), a chaperone promoting collagen secretion and deposition, are expressed during the EMF. Expression of Hsp47 induces mesenchymal phenotypes and enhances platelet accumulation, leading to tumor cell colonization. The depletion of the platelet pool prevents such events. Thus, it is believed that Hsp47 promotes the colonization of tumor cells by increasing their interaction with platelets. Accordingly, blockade of the GPVI collagen receptor and 2β1 integrin on the platelet surface can prevent Hsp47-induced platelet-tumor cell interaction, emphasizing that such platelet receptors exert a crucial role in the EMT [59]. During the cultivation of MCF7 breast cancer cells with platelets, the EMT process was associated with platelets and tumor integrin α2β1, which led to the activation of the Wnt-β-catenin signaling pathway [60]. During systemic inflammation, extravascular platelets-fibrin conglomerates activate inflammatory cells by interacting with integrin αMβ2, which leads to the release of various cytokines and growth factors, thereby further supporting EMT [61].

Members of the cathepsin family are proteases secreted by various tumor cells. Cathepsins are mainly localized in endosomal or lysosomal vesicles and are also secreted as soluble exoenzymes. They cleave ECM components around tumor cells and activate or deactivate surface receptors via proteolysis. The cathepsin K isoform can induce platelet aggregation and maintain interaction with EMF-like tumor cells being triggered by cathepsin-mediated cleavage of the platelet PAR receptor. A joint aggregation of platelets and tumor cells promotes the exposure of P-selectin, activation of CD44, and an increase in the level of growth factors [62].

PMPs also modulate the EMF. The cultivation of ovarian cells with PMPs increases the intensity of the EMF. Upregulated expression or complete suppression of

PMP-specific miRNA-939 can enhance or suppress EMF. The uptake of PMP/miRNA-939 by tumor cells is regulated by type A2IIA secretory phospholipase (sPLA2-IIA), which indicates an essential role of PMPs in interactions between platelets and tumor cells [63] (**Fig. 4**).

Interaction of tumor cells with vascular endothelium / Взаимодействие опухолевой клетки с эндотелием сосудов

Platelets are essential in tethering tumor cells to the vascular endothelium, thereby enhancing extravasation and metastasis occurring with aid of platelet integrin αIIbβ3 and P-selectin. Thus, a genetic defect (deficiency) or blockade of integrin β3 and P-selectin can reduce the colonization of tumor cells [64]. P-selectin also binds mucins and the P-selectin glycoprotein ligand-1 (PSGL-1) on the surface of tumor cells, mediating the interaction between platelets, leukocytes, and endothelium [65].

Von Willebrand factor on the activated surface of endothelial cells can also promote the recruitment of aggregates of tumor cells with platelets since hereditary deficiency or antibody-mediated blockade of GPIba (vWF receptor binding on platelet surface) suppresses TCIPA, as well as the interaction between platelet-tumor cell conglomerates and endothelial cells, and subsequent metastasis [66].

Tumor integrin αVβ3 supports the interaction of tumor cells with platelets, the vascular wall, thereby facilitating metastasis. On tumor cells, αVβ3 integrin is located nearby nectin-like molecule 5 (NECL5) that interacts with CD226 on the platelet surface, providing adhesion for tumor cells to the vascular endothelium [67]. Studies have shown that integrin αVβ3 from breast cancer cells can bind to platelet autotaxin, which is deposited in α-granules and secreted into the vasculature upon platelet activation [68]. This process promotes early bone tumor cell colonization and the progression of skeletal metastases in mice (**Fig. 4**).

Not all types of tumor cells attach to the endothelium and platelet aggregates; some require no platelets for this, e.g., liver tumor cells and leukemia cells. Studies in mouse models showed that therapy with the thrombin inhibitor hirudin disrupted the interaction between tumor cells and platelets. However, therapeutic intervention did not affect the adhesion of tumor cells to the endothelium [69].

Extravasation of tumor cells / Экстравазация опухолевых клеток

After tumor cell tethering to the endothelium, they migrate through it with the formation of metastases. The types of extravasation differ according to various types of blood vessels. It is essential to understand that the molecular mechanisms of extravasation depend on the vessel types while creating differentiated therapeutic approaches to prevent metastasis. Platelets can contribute to the retraction of endothelial cells and paracellular migration of tumor cells, although in many cases, this process can occur without platelets being involved. Platelets can damage the endothelial layer with the subsequent release of necroptosis inducers that damage the ECM, which contributes to the extravasation of tumor cells.

Molecules stored in platelet α- and δ-granules can regulate vascular permeability. After platelet activation, degranulated serotonin, VEGF, platelet-activating factor (PAF), thrombin, ATP/ADP, HGF, fibrinogen are released, which can increase vascular permeability and promote the migration of tumor cells. Studies have shown that the extravasation of tumor cells in mice was significantly lower in the case of strongly suppressed secretion of platelet δ-granules and moderately for α-granules [70] (**Fig. 4**).

ATP obtained from platelets weakens intercellular interactions in the endothelium and an increased permeability due to activated P2Y2 and P2Y1 purinergic receptors on the surface of endothelial cells [71]. Recently, a novel molecular mechanism has been identified that further supports ATP-mediated effects in cancer cell metastasis. Galectin-3, which is expressed on the surface of colon and breast tumor cells, has been shown to interact with the platelet-specific GPVI receptor. This receptor-ligand mediated cell-cell interaction enhances platelet activation and degranulation (ATP secretion), which increases tumor cell extravasation. The impaired release of δ-granules and apyrase-mediated impairment of ATP function in platelets significantly suppress tumor cell migration, indicating platelet-derived nucleotide essential role [70, 72].

The PAF secreted by platelets affects some tumor cells by interacting with their receptors (PAF-R). Interaction with the receptor activates tumor growth, promotes VEGF expression. The beneficial effect of the antioxidant-rich Mediterranean diet on cancer risk has been linked to its PAF-suppressing activity [73].

Serotonin is a biogenic monoamine derived from tryptophan. Serotonin synthesis occurs in enterochromaffin cells located in the gastrointestinal tract. After entering the blood, platelets quickly absorb it into δ-granules. Local accumulation of serotonin affects vascular tone. Circulating tumor cells increase

plasma serotonin concentration by blocking serotonin receptors or calcium channels; they effectively suppress metastasis, indicating a role for serotonin in tumor progression. However, the role of platelet serotonin in tumor progression, including the stage of extravasation, has not yet been investigated.

Activated platelets release lysophosphatidic acid (LPA) from their alpha-granules, promoting tumor cell invasion and affecting endothelial permeability. In the study with mice lacking alpha-granules, metastatic processes were reduced [74]. Blocking platelet activation leads to lowered serum LPA level. Autotaxin is a secreted glycosylated enzyme lysophospholipase D (LPD), responsible for regulating basal blood LPA level (**Fig 4**).

ADAM-9 belongs to the disintegrin and metalloproteinase family (ADAM), which regulate receptors. Interestingly, this proteinase can promote tumor cell migration and metastasis with or without MMP involvement. The interaction of platelet α6β1 with a disintegrin-cysteine-rich ADAM-9 tumor cell domain triggers platelet activation, α-granule release, and P-selectin exposure, which increases tumor cell extravasation [75]. The interaction of platelets with tumor cells mediated by platelet toll-like receptor 4 (TLR4) and tumor high-mobility group box 1 protein (HMGB1) also leads to the release of α-granules and the exposure of P-selectin [76].

To effectively penetrate the subendothelial layer, tumor cells must damage the basement membrane. Platelets accumulate and release several exoenzymes, such as MMP, platelet hyaluronidase-2, and heparanase, which destroy the collagen-rich components of the ECM. After platelet depletion, the extracellular activity of MMP decreases, and, as a result, the intensity of metastasis declines, as shown in mice. This underlines the contribution of MMP platelet derivatives to the destruction of the basement membrane [77] (**Fig. 4**).

Tumor metastasis, the metastatic niche /
Метастазирование опухоли, метастатическая ниша

Tumor ECM components stimulate the micro-environment of cells in distant organs to receive tumor cell screenings. After metastasis of cells and the formation of tumor masses in distant organs, the so formed metastatic niches recruit pro-inflammatory immune cells from the circulation.

Platelets are involved in different stages of forming metastatic niche: they can support adhesion of cancer cells and attraction of granulocytes to the early metastatic niche. Platelets can release various chemokines that stimulate the recruitment of host cells to build the tumor microenvironment. Later, platelets also release pro-angiogenic factors, stimulating angiogenesis, creating an immune cell-rich microenvironment around developing metastases, thereby supporting the proliferation and survival of tumor cells.

Tumor cells release angiogenic growth factors. VEGF from tumor cells alters the microenvironment in distant organs. VEGF supports the inflammatory response and also increases the concentration of cyclooxygenase (COX) and PGE2. Some ECM components, integrin receptors, and VEGF receptors are recognized as the primary regulators of organ-specific tropism of tumor cells and niche formation [78].

In the process of metastasis, monocytes and macrophages are attracted to the metastatic niches for maintaining the processes of screening out tumor cells therein. Platelet-secreted chemokines – motif ligand CXC (CXCL) 5 and CXCL7 have been shown to promote the early stages of metastatic niche formation by activating the granulocyte C-X-C chemokine receptor 2 (CXCR2). After the interaction of tumor cells and platelets, chemokines are released from granules that attract granulocytes to platelet and tumor cell conglomerates [79] (**Fig. 4**).

Aggregates of platelets with fibrin also create some matrix for metastatic screening. TF released by tumor cells triggers a coagulation cascade with thrombin formation, platelet activation, and fibrin formation. TxA2 stimulates macrophage infiltration and cytokine release. The experimental model of B16F10 melanoma cell metastases by S. Lucotti et al. showed that the platelet-specific COX-1/TxA2 pathway triggers the formation of aggregates between platelets and tumor cells, endothelial activation, adhesion of tumor cells to the endothelium, and recruitment of monocytes and macrophages, thereby promoting the formation of a premetastatic niche in the lung [80] (**Fig. 4**).

On the other hand, immune cells and granulocytes can also cause the death of metastatic tumor cells depending on the stage of the tumor process and the environment. Human prostate cancer cells 3 (PC3) derivatives and MDA-MB-231 breast cancer cells with a low metastatic potential recruit prometastatic Gr+ myeloid cells and create a microenvironment resistant to metastasis by inducing TSP1 secretion which prevents lung metastasis [81]. In contrast, platelet TSP1 has the opposite effect on bone metastasis. In the microenvironment of bone tissue, TSP1/TGF-β regulates premetastatic niche formation and bone metastasis [82] (**Fig. 4**).

Promising platelet-associated targets for anticancer therapy / Тромбоцит-ассоциированные перспективные мишени противоопухолевой терапии

Since the 1990s, when it was first shown that acetylsalicylic acid has a positive effect on some forms of cancer, in the platelet arm there has been an active search for targets of anticancer therapy. The adhesion, activation, and aggregation of platelets affect all stages of tumor progression. Integrins, glycoproteins, and many other signaling receptors on the platelet surface are actively involved in these events.

Integrins / Интегрины

Platelets express integrins α2β1, α5β1, and α6β1 for binding to collagen, fibronectin, and laminin, respectively. Integrin α2β1 together with GPVI comprises a direct pathway for platelet interaction with subendothelial matrix collagen. It has been shown that the blockade of platelet integrin α2β1 prevents the interaction of platelets with tumor cells and tumor metastasis.

In models of metastatic tumors – melanoma B16F10 and MC38 of the colon, it was shown that platelet integrin α6β1 promotes metastasis by binding to ADAM-9 of tumor cells. Blockade of α6 integrin by the GoH3 antibody suppresses platelet-tumor cell interactions *in vitro* as well as tumor metastasis *in vivo*. Genetic or antibody-mediated blocking of α6 integrin function in mice did not alter the course of hemostasis responses or platelet counts. Antibodies did not affect tumor metastasis when administered to mice with α6β1 platelet integrin deficiency [75]. Also, α6β1 is present on the surface of other cells, e.g., tumors, endothelial and pericytes. Recent research by A. De Archangelis et al. showed that α6 integrin deficiency in mouse intestinal epithelium leads to disrupted integrity of hemidesmosomes and development of colitis and colorectal cancer [83]. α6 integrin deficiency in mice and humans leads to skin and mucosal diseases such as pyloric atresia and epidermolysis bullosa. Therefore, before using an integrin blockade strategy, it is worth assessing the severity of its potential adverse reactions *in vivo*.

Integrin αIIbβ3 is the main platelet integrin, widely represented on the cell surface. After binding to the ligand upon agonist stimulation, it shifts from inactive conformation to active form and regulates platelet aggregation, thrombosis, and hemostasis. The latter allows integrin αIIbβ3 to bind fibrinogen and vWF and

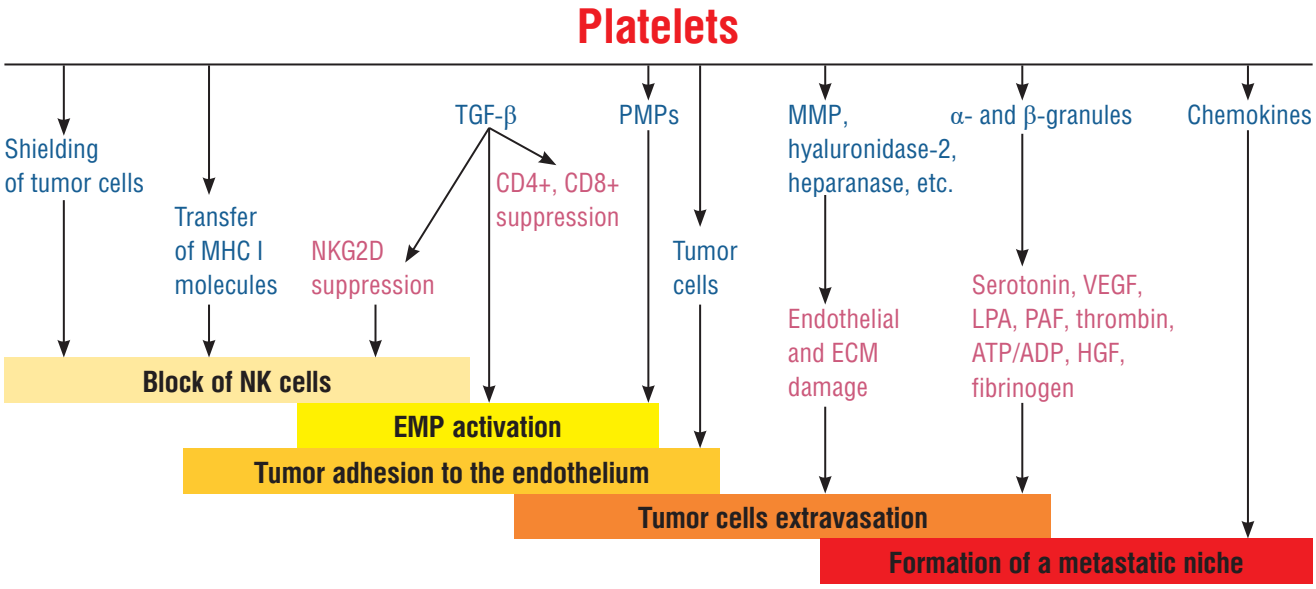

Figure 4. Platelets and metastatic stages [drawn by authors].

Note: *MHC I – class I of major histocompatibility complex; NK-клетки – natural killer cells; NKG2D – natural killer group 2D; PMPs – platelet microparticles; MMP – matrix metalloproteinases; BKM – extracellular matrix; VEGF – vascular endothelial growth factor; LPA – lysophosphatidic acid; PAF – platelet-activating factor; HGF – hepatocyte growth factor; ЭМП – epithelial-mesenchymal transition.*

Рисунок 4. Тромбоциты и этапы метастазирования [рисунок авторов].

Примечание: *MHC I – класс I главного комплекса гистосовместимости; NK-клетки – клетки естественных киллеров; NKG2D – группа естественных киллеров 2D; PMPs – микрочастицы тромбоцитов, MMP – матриксные металлопротеиназы; BKM – внеклеточный матрикс; VEGF – фактор роста эндотелия сосудов; LPA – лизофосфатидная кислота; PAF – фактор активации тромбоцитов; HGF – фактор роста гепатоцитов; ЭМП – эпителиально-мезенхимальный переход.*

platelets [84]. αIIbβ3 integrin antagonists are already being used in the treatment of patients with the acute coronary syndrome. Integrilin, a potent αIIbβ3 blocker, has been shown to inhibit metastatic processes [85]. The αIIβ subunit deficiency in mouse experiments leads to lowered intensity of the early metastasis stages [86]. The expression of integrin αIIbβ3 is not specific solely to platelets; it is also found on the surface of breast tumor cells [87].

Integrilin can suppress the function of integrin αVβ3; this integrin is also expressed on the surface of tumor cells and endothelial cells, macrophages, and in small amount on the platelet surface. Integrin β3 was chosen as one of the targets for anticancer therapy. Side effects from blocking αIIbβ3 integrin function are displayed as bleeding up to profuse manifestation. It is possible to overcome the side effects by creating specific inhibitors that target only the active form of integrins. A strategy based on creating antibodies against the active form of integrins can dramatically reduce the risk of bleeding [88].

The GP (glycoprotein) Ib-V-IX complex is a multifunctional receptor on the surface of platelets that simultaneously interacts with multiple ligands, including vWF, thrombin, factor XI, factor XII, P-selectin, and is involved in platelet adhesion on the surface of the damaged vessel and their aggregation. This receptor complex is composed of the four membrane glycoproteins: GPIbα, GPIbβ, GPIX, and GPV. In genetically modified GPIbα/IL4-R mice, when IL4-R replaces the extracellular domains of GPIbα, S. Jain et al. showed that removal of various binding sites, including vWF located in GPIbα, reduces metastasis [89]. More recent studies by L. Erpenbeck et al. showed that administration of antibodies (p0p3/p0p4) directed against the vWF binding site on GPIbα suppressed tumor metastasis in mouse models. However, administration of such antibodies leads to severe thrombocytopenia, which probably accounts for the major effect [90].

Recently, the role of GPIbα has been further analyzed using the YQ3 antibody, which blocks the GPIbα–vWF interaction explicitly. The authors showed interactions between platelets and tumor cells, endothelium, and TCIPA *in vitro* while using antibodies were suppressed, and metastasis was also suppressed *in vivo*. At the same time, YQ3 antibodies did not induce platelet activation and consumption, nor lead to the development of thrombocytopenia or thrombocytopenia in mouse models [66].

GPIbα function has also been studied in the context of thrombus inflammation and carcinogenesis. The interaction of platelets and Kupffer cells includes the binding of hyaluronan to CD44 and early platelet activation in the liver, which contributes to non-alcoholic steatohepatitis (NASH) and, as a result, malignant liver tumors. Genetic deficiency or blockade of GPIbα function by the p0p6 antibody, previously described as an inhibitor of GPIbα and GPIX, suppresses pathological disorders that cause the NASH. This process did not depend on the interaction between GPIbα and vWF, P-selectin, or integrin αMβ2 [91].

Glycoprotein VI (GPVI) is the ITAM (immunoreceptor tyrosine-based activation motif) signaling receptor being activated by collagen, laminin, and fibrin to regulate diverse physiological processes in platelets, including adhesion, activation, aggregation, and procoagulant activity. A soluble form of GPVI has been developed and clinically tested in patients with thrombotic diseases. The mechanism of action was to disrupt the GPVI interaction between platelets and collagen, thereby suppressing thrombogenesis [92]. Recently, GPVI has been shown to promote platelet adhesion to colon and breast tumor cells. The interaction of platelets with tumor cells leads to platelet activation, as well as tumor cell extravasation and metastasis [72].

In addition to collagen, GPVI can bind to other ECM components such as fibrin, fibronectin, vitronectin, adiponectin, MMP13, and histones. Interactions with fibrin promote blood clot growth. Genetic deficiency or antibody-mediated GPVI suppression can lead to intratumoral bleeding [47]. However, studies show that potential therapeutic strategies based on selectively blocked GPVI function or its interaction with such ligands in some cancer types may pave the way for new cancer treatments while maintaining normal hemostasis.

C-type lectin-like receptor-2 / Лектиноподобный рецептор-2 С-типа

C-type lectin-like receptor-2 (CLEC-2) is mainly expressed in megakaryocytes, platelets, dendritic cells, and Kupffer cells. The genetic or pharmacological blockade of CLEC-2 in mouse affected no platelets and hemostasis. It has been shown that the effect on the CLEC-2 function in oncological diseases effectively reduces hematogenous metastasis, the rate of cancer-associated thrombosis, and severity of thrombus inflammation [20].

Aberrant O-glycosylation was found in podoplanin (PDPN) of tumor origin. The LpMab-2 antibody can recognize this region and effectively suppress the PDPN-CLEC-2 interaction in the tumor microenvironment.

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Therefore, the LpMab-2 antibody is a potential tool for selectively targeting PDPN-positive tumor cells; it can suppress thrombogenesis in tumor vessels without affecting normal cells in lymphatic vessels [93]. Another functional blocking monoclonal antibody (mAb, SZ168) directed against the extracellular domain of human PDPN is also effective in slowing down metastatic processes [94].

PDPN domains that induce platelet aggregation (platelet aggregation-inducing domains, PLAG), which were recently identified, are functionally associated with CLEC-2. This interaction promotes platelet aggregation and the formation of tumor emboli. The use of anti-PLAG-neutralizing antibodies effectively blocks PDPN-mediated tumor growth and metastasis [95]. In addition to blocking antibodies, some CLEC-2 binding molecules can also interfere with CLEC-2-PDPN interactions. Thus, a potentially effective anticancer therapy strategy is to selectively block CLEC-2 function on the platelet surface or disrupt PDPN-CLEC-2 interactions.

Cyclooxygenases / Циклооксигеназы

Thromboxane A2 is an active metabolite of arachidonic acid, formed due to thromboxane synthase activity. It is involved in a variety of biological processes, including platelet aggregation and vasoconstriction. TxA2 secretion during platelet activation enhances platelet aggregation and thrombogenesis due to its interaction with the thromboxane receptor (TR) and induces various paracrine effects in surrounding cells. Acetylsalicylic acid irreversibly inhibits the enzymatic activity of cyclooxygenases (COXs), which are involved in the metabolism of arachidonic acid to produce TxA2. The binding of acetylsalicylic acid covalently alters the COX-1 and COX-2 isoforms through acetylation at serine residues 529 and 516, respectively. Although platelets always express a standard COX-1 level, the expression of COX-2 is dramatically increased during the inflammatory response and tumor growth [96].

Recently, there have been emerged more data indicating that thromboxane A2 plays a vital role in carcinogenesis; many authors suggest using TxA2 as one of the cancer markers as well as a therapeutic agent, which suppression lowers proliferation and activates apoptosis.

The antitumor effects of acetylsalicylic acid were first identified by G.J. Gasic et al. in 1973 [97]. Aspirin-pretreated platelets can effectively suppress tumor-induced platelet aggregation. The effect of acetylsalicylic acid on cancer has been also investigated by G.A. Kune et al. in a clinical setting. A lower incidence rate of colorectal cancer has been found among patients taking drugs containing acetylsalicylic acid [98]. In patients with early stages of colorectal cancer, daily use of lysine acetylsalicylate (160 or 300 mg) has been shown to benefit relapses [99].

In a randomized clinical trial, acetylsalicylic acid was administered to patients with adenomatous polyps. Polyps were mainly detected in the epithelium of the large intestine, and the size of polyps in patients in the experimental vs. placebo group decreased while taking acetylsalicylic acid [100]. In Lynch syndrome, a non-polyposis colorectal cancer, regular acetylsalicylic acid use (600 mg) has also been shown to reduce the risk of developing the disease [101]. M. Frouws et al. demonstrated that regular use of acetylsalicylic acid (≤ 100 mg) significantly improved survival in patients with gastrointestinal cancers, including esophageal, hepatobiliary, and colorectal cancers [102]. According to them, acetylsalicylic acid therapy reduced the risk of developing malignant pancreatic diseases. Later P.M. Rothwell et al. summarized the data from the five large randomized clinical trials on daily acetylsalicylic acid intake (≥ 75 mg). These studies have shown that regular low-dose acetylsalicylic acid administration reduces the incidence of colorectal cancer both in women and men, smokers and nonsmokers [103]. They also demonstrated that at daily low-dose acetylsalicylic acid reduces metastasis spread. Similar data were obtained concerning malignant tumors of other localizations, such as mammary glands, lungs or the prostate gland.

How acetylsalicylic acid affects tumor progression and metastasis, whether these mechanisms are platelet dependent or not? The lifespan of human platelets is as few as 10 days; platelet turnover in the human body is very fast, so patients take acetylsalicylic acid every 24 hours. In case it is applied at a dose of 100 mg/day, it leads to the maximum acetylation in circulating platelets, which significantly reduces the concentration of TxB2, a product of the TxA2 metabolism. Acetylsalicylic acid has a short half-life (about 20 minutes) in the blood and is rapidly hydrolyzed to salicylic acid by enzymes found in the blood and liver. Its low dose can completely and irreversibly suppress the activity of COX-1 in platelets, which suggests about very rapid absorption by platelets. Unlike nucleated cells, protein synthesis in platelets is limited due to the lacked nucleus and residual RNA obtained from megakaryocytes.

Consequently, the effect of acetylsalicylic acid is more stable in platelets than non-nucleated cells, in

which acetylated new COXs quickly replace former counterparts within few hours due to de novo production. The activity of COX-1 is entirely blocked by acetylsalicylic acid, whereas acetylated COX-2 cans still form 15R-hydroxyeicosatetraenoic acid (15R-HETE) from arachidonic acid [104]. In addition, acetylsalicylic acid affects bone marrow megakaryocytes and may suppress COX-1 function in newborns [105]. In a study by S. Lucotti et al., it was shown that inoculating COX-1 +/+ vs. COX-1 –/– platelets led to increased number of B16F10 melanoma cells, which caused lung metastases in mice with thrombocytopenia [106]. This proves that acetylsalicylic acid has a platelet-dependent effect on various stages of metastasis, including tumor-induced platelet aggregation, activation of endothelial cells, adhesion of tumor cells to the endothelium, recruitment of monocytes/macrophages, and the formation of a premetastatic niche [106]. In general, these results suggest that the antimetastatic effect of acetylsalicylic acid may be associated mainly with the suppression of platelet COX-1 activity. Activated platelets, immune cells, and the tumor microenvironment can release various growth factors, cytokines, which also stimulate the expression of the COX-2 gene in tumor cells. In addition, activated platelets increase the expression of COX-2 in stromal cells by releasing IL-1β, PDGF, and TGF-β, leading to tumor progression. In general, these results indicate that platelets also affect oncogenesis and tumor progression due to direct effects on COX-2, whereas acetylsalicylic acid can counterbalance it.

P2Y12 purinergic receptor / Пуринергический рецептор P2Y12

The P2Y12 receptor is a purinergic Gi-linked ADP receptor expressed on the surface of platelets and regulates thrombus stability *in vivo*. Currently used P2Y12 inhibitors block the receptor either indirectly, e.g., members of the thienopyridine family (Ticlopidine, Clopidogrel, and Prasugrel) or directly, e.g., Ticagrelor and Cangrelor. The bioactive form of the thienopyridine derivative irreversibly suppresses the binding of ADP to the receptor, which leads to decreased platelet activation and aggregation, lowered activation and externalization of platelet integrins αIIbβ3 [107].

Studies in mice have shown that Clopidogrel at a dose of 8 mg/kg is able to suppress tumor development and metastasis in pancreatic tumors. This effect is probably associated with the complete suppression of ADP-induced platelet aggregation [108]. In breast cancer models, Ticagrelor (10 mg/kg) reduced the rate of metastasis and increased survival [109). Ticagrelor therapy was associated with decreased platelet aggregation with tumor cells in the lungs [109]. In ovarian cancer models, the deficiency of the P2Y12 receptor on the platelet surface or apiraza therapy suppressed the ADP-dependent interaction of platelets with tumor cells and the subsequent growth of the primary tumor [110].

Genetic P2Y12 deficiency also results in reduced lung metastases by Lewis lung carcinoma and B16F10 cells in mice. This effect was associated with the suppression of VEGFR1+ clusters of bone marrow cells and fibronectin deposition in the lungs. The result confirms the effectiveness of the new anticancer strategy. The pentapeptide called CREKA (Cysteine–Arginine–Glutamic acid–Lysine–Alanine) is directed against fibrin-fibronectin complexes in the tumor stroma and the vascular wall. The CREKA-Ticagrelor complex effectively suppresses platelet-induced migration of tumor cells and prevents the interaction between tumor cells and platelets, thereby suppressing metastasis [111].

In pancreatic adenocarcinoma, platelets have been shown to contribute to developing Gemcitabine resistance. Platelet-secreted nucleotides (ADP and ATP) are the main triggers for arising Gemcitabine resistance, which is fully blocked by Ticagrelor [112]. Isorapontigenin is a polyphenolic compound with antitumor and anti-inflammatory properties. It can selectively suppress ADP-induced platelet aggregation, activation and externalization of αIIbβ3 integrin, and granule secretion. Isorapontigenin increases the level of adenosine-3',5'-cyclic monophosphate (cAMP) and phosphorylation of vasodilator-stimulated phosphoprotein (VASP). The drug also affects phosphoinositide-3-kinase (PI3K) signaling pathways via the P2Y12 receptor. Clopidogrel enhances the antitumor and/or antimetastatic activity of chemotherapeutic agents such as 5-fluorouracil, Cyclophosphamide, and Mitoxantrone, but reduces the antitumor activity of Doxorubicin, Cisplatin, and Tamoxifen [113]. The molecular mechanisms for such differentiated effects are not fully understood. The P2Y12 receptor is expressed not only on platelets but also on other cells, such as osteoclasts. Bone loss (osteolysis) associated with tumor growth in mice is effectively controlled by Clopidogrel [114].

Proteinase-activated receptors and thrombin / Рецепторы, активируемые протеиназами, и тромбин

Thrombin receptors belongs to the PAR family of the four transmembrane GPCR receptors (G-protein-coupled receptors) activated by thrombin via the trypsin-like

enzymatic cleavage of relevant exodomain N-terminus. PARs are present in platelets, neutrophils, monocytes/macrophages, endothelial cells, and fibroblasts. Human platelets are mainly activated by thrombin through their action on the PAR1 and PAR4 isoforms, whereas mouse platelets express no PAR1, hence being activated via PAR3 and PAR4.

Thrombin receptors are an attractive target for the therapy of conditions mediated by platelet function. Targeting the platelet PAR1 receptors, thrombin-induced aggregation can be effectively suppressed. The PAR1 blocker Vorapaxar effectively reduces the risk of thrombosis in patients with myocardial infarction and stroke, but moderate to severe bleeding episodes have been reported afterwards [115]. Parmodulin reversibly affects the cytosolic portion of the PAR1 receptor, thereby inhibiting signaling through Gαq, but not Gα12/13. Parmodulin ML-161 has demonstrated antithrombotic and anti-inflammatory effects with a low risk of bleeding. Pepducin is a cell-penetrating fragment of the GPCR cytosolic portion that modulates the action of this receptor. PAR1 specific pepducin PZ-128 has been proposed as an effective antimetastatic agent and antiangiogenic inhibitor in mouse breast, lung, and ovarian tumors [116]. PZ-128 has already been tested in patients with coronary artery disease and has shown a lower bleeding risk compared with Vorapaxar. Thus, acting on PAR1 function in tumor progression and metastasis simultaneously suppresses function of platelets and tumor cells. The clinical applicability of Parmodulin and Pepducin is crucial for further *in vivo* studies.

Heparin prevents the formation of thrombin, thereby suppressing its activity. Heparin, unfractionated heparin (UFH), low molecular weight heparin (LMWH), and heparin derivatives are used to treat VTE. In addition, the effectiveness of these drugs in reducing the survival of tumor cells has been proven. Heparin inhibits angiogenesis, tumor cell proliferation, adhesion, migration, and invasion by suppressing heparanase, P- and L-selectin. In addition, heparin treatment suppresses tumor-induced neoangiogenesis and CXCL12/CXCR4 signaling pathways. Tinzaparin is LMWH synthesized by the enzymatic degradation of unfractionated porcine heparin. Sulfated non-anti-coagulant heparins (S-NACH) are also LMWH. All LMWHs effectively inhibit P-selectin-mediated cell adhesion and metastasis. Modified heparin with low anticoagulant activity reduces the adhesion of A375 melanoma cells to platelets by downregulating activation of αIIbβ3 integrins. Heparin can also disrupt the interaction between monocytes and α4β1 tumor cells with the vascular cell adhesion molecule 1 (VCAM1) [117]. Despite antitumor effects described for heparin and its derivatives, further clinical studies are needed to assess the potential efficacy of heparin in the absence of bleeding.

P-selectin / P-селектин

The prometastatic role of platelets has been discussed for a long time, particularly their ability to shield tumor cells, protecting them from the effects of NK cells, as well as facilitating tethering to the endothelium and extravasation by using P-selectin, a membrane glycoprotein. P-selectin is expressed on the surface of activated platelets and can bind to various human tumor cells. P-selectin secreted by endothelial cells is no less important and plays an essential role in metastasis spreading. It ensures the interaction of platelets with tumor cells and the vascular wall during tumor growth and metastasis. Thus, the blockade of P-selectin is a potential target for anticancer therapy. Rivipansel blocks several selectins *in vivo*, including P-, L- and E-selectins [118]. Chrysanlizumab a selective P-selectin blocking antibody [119]. Both drugs can be used for further research in tumor models.

A search for hemostasiological prognostic biomarkers of tumor growth / Поиск гемостазиологических прогностических биомаркеров опухолевого роста

It is possible to detect biomarkers from the blood of an oncological patient, which has excellent diagnostic and prognostic value. Tumor cells circulating in the blood and interacting with platelets as well as immune cells (circulating tumor cells, CTC) are actively used to assess the tumor landscape. Platelets can uptake and sequester CTC-specific proteins, mRNA, and tumor pro-oncogenic and angiogenic factors, leading to tumor-specific modification of the platelet proteome and transcriptome. It was shown that platelets from patients with glioma and prostate cancer were enriched with cancer-associated RNA biomarkers EGFRvIII (epidermal growth factor receptor, variant III) [120]. M. Best et al. identified over 5000 differentially expressed or mutated mRNAs in healthy individuals and cancer patients, including the expression of MET, HER2 (human epidermal growth factor receptor 2), and mutations in KRAS (Kristen retrovirus associated DNAS sequences), EGFR (epidermal growth factor receptor),

and PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha) [121]. These data were effectively used to identify a group of patients with metastatic tumors. During tumor progression, the platelet transcriptome changes dynamically over time. It has been suggested that the platelet mRNA profile can accurately distinguish and predict tumor progression [122].

Soluble P-selectin and blood clotting factors circulate at high concentrations in patients with solid cancer, determining the status of the tumor process and the risk of thrombotic complications. Studies have shown that high plasma concentrations of vWF, fibrinogen, and D-dimer have been associated with a poor prognosis in patients with tumors of the breast, colon, stomach, rectum, non-small cell lung cancer, ovarian and pancreatic tumors [123]. Other studies have shown that the concentrations of TF-positive microparticles are increased in the blood plasma from patients with tumors of the pancreas, colon, breast, ovaries, and non-small cell lung cancer [124]. Testing patients for these procoagulant factors can be effective in screening for an increased VTE risk. Assessing genomic profile of oncogenic mutations can also be helpful in predicting thromboembolic risks in patients with various tumor types.

The concentration of soluble glycoprotein VI (sGPVI) in plasma reflects the degree of platelet activation in thrombo-inflammatory diseases such as stroke, disseminated intravascular coagulation, arthritis, and sepsis. GPVI stabilizes the thrombus by interacting with fibrin and fibrinogen. The increased level of sGPVI in patients with sepsis is caused by fibrin-induced release of this receptor. Recent studies have shown that sGPVI concentration increases in the blood plasma of patients with breast tumors and colorectal cancer. In small cohorts in patients with colorectal cancer, sGPVI concentrations were increased and correlated with the disease stage [72]. Further studies are necessary to confirm diagnostic and prognostic value of sGPVI as a tumor-related marker.

Other therapy strategies / Другие стратегии терапии

Platelets can influence tumor growth and progression by enhancing the proliferation of tumor cells. G.M. Ibele et al., in their studies, have shown that platelets play an essential role in tumor growth because leukocytes exhibit more significant activity against tumor cells in the presence of platelets [125]. Another study showed that non-activated and thrombin-activated platelets have a cytotoxic effect on myeloid leukemia cells [126]. The cytotoxic effect on non-activated vs. thrombin-activated platelets was suppressed by esterase inhibitors. The cytotoxic effect of platelets is accounted for by a potential to secrete factors such as TNF (tumor necrosis factor), which induces apoptosis, as well as TNF-associated ligand TRAIL (tumor necrosis factor-related apoptosis inducing ligand), CD154, and Fas-L associated with TRAIL. The binding of Fas-L to the Fas receptor (Fas-R) activates the caspase-mediated apoptosis pathway in Fas-R expressing tumor cells [127].

Anoikisis is a programmed cell death that occurs when tumor cells detach from the surrounding extracellular matrix. Platelets cause resistance of tumor cells to anoikis. Platelets also enhance RhoA-MYPT1-PP1-mediated YAP1 dephosphorylation in tumor cells, thereby triggering the expression of the survival gene and suppressing apoptosis [128]. In addition, platelets have been shown to promote the proliferation of hepatocellular carcinoma cells by activating MAPK (mitogen-activated protein kinase) signaling and decreasing the number of apoptotic mediators [129]. The factors released by platelets enhance the proliferation of human cells and tumor cells in mouse ovarian tumors, which is promoted by the interaction between platelet-released TGF-β and its cognate receptor on tumor cells [130].

Genetically modified platelets expressing TRAIL can destroy tumor cells *in vitro* and significantly reduce the number of metastases formed. Q. Hu et al. used platelets with membrane-coated nanoparticles (PM-NV, platelet membrane-coated nanovehicles) to deliver intratumorally two antitumor therapeutic agents (TRAIL and Doxorubicin). PM-NV can efficiently deliver TRAIL to the tumor cell membrane for subsequent activation of the external signaling pathway of apoptosis [131]. A.-L. Papa et al. demonstrated modified human platelets (platelet traps) that retained platelet binding functions but could not become activated and aggregated. Their results showed that platelet traps could act as effective antimetastatic and antithrombotic therapy. In a rabbit model *in vivo*, it was shown that the preliminary administration of platelet traps suppresses thromboembolism; they also disrupt the interaction of platelets with tumor cells, followed lowering extravasation of tumor cells. In a mouse model of metastasis, the simultaneous injection of platelet traps and tumor cells resulted in the suppression of metastatic tumor growth [132].

Platelets have been proposed as drug carriers in many studies because platelets can easily absorb and store bioactive molecules in their secretory granules.

Doxorubicin has been loaded into platelets for the treatment of lymphoma. Doxorubicin was accumulated by platelets using TCIPA (tumour cell-induced platelet aggregation) and released into the medium in a pH-dependent manner. This study showed that platelets with fixed Doxorubicin reduced the side effects of extracellular Doxorubicin and increased therapeutic efficacy at the target organ level [133].

Platelet-mediated resistance to chemotherapy / Тромбоцит-опосредованная резистентность к химиотерапии

Tumor resistance to chemotherapy occurs when a tumor that initially responded to therapy suddenly begins to grow. Clinical studies have shown a relationship between platelet count and tumor resistance to chemotherapy. *In vitro* studies have demonstrated an association between thrombocytosis and tumor resistance to chemotherapy while using Paclitaxel and 5-fluorouracil in patients with colon and ovarian tumors [47]. In mouse breast and prostate tumors models, low platelet counts increased sensitivity to Doxorubicin and Paclitaxel [46]. Suppressed GPVI function led to developing intratumoral hemorrhages, which could improve the access of chemotherapeutic agents to tumor cells [47]. Platelets also promote ovarian tumor recurrence in mice after discontinuation of anti-angiogenic therapy with Bevacizumab or Pazopanib. Platelet FAK (focal adhesion kinase) plays an essential role in this process, as FAK-deficient platelets prevent recurrences. In this regard, combination therapy with a FAK inhibitor and Pazopanib/Bevacizumab can mitigate the adverse effects after discontinuation of anti-angiogenic drugs [134].

Several mechanisms have been proposed by which bioactive substances released by platelets can affect tumor resistance to chemotherapy, thereby counteracting the cytotoxic effects of certain drugs, such as Paclitaxel and 5-fluorouracil:

- growth factors and cytokines interfere with the effects of chemotherapeutic agents by shifting the balance from anti-apoptotic to pro-apoptotic genes;
- platelets activate regulators of cell progression, thereby causing blockage of cell cycle arrest caused by anticancer agents;
- platelets increase phosphorylation of DNA repair proteins, Chk1, BRCA1, and Mre11.

In addition, platelets have been shown to suppress the cytotoxic effects of the chemotherapeutic agent's Sorafenib and Regorafenib used in patients with hepatocellular carcinoma by activating the MAPK signaling pathway [135].

Conclusion / Заключение

The study on the interaction between tumor cells and platelets has been carried out for a long time and requires many further continuation. The emergence of tumor cells has a multifaceted effect on platelet function due to the presence of various mediators, cytokines, and other essential agents. Various signaling pathways are triggered simultaneously. Platelet activation leads to the release of growth factors, tumor neoangiogenesis and progression, as well as increased metastatic events. The interaction between platelets and tumor cells ensures their transformation with developing tolerance to immune cell effects, which facilitates metastasis. Development of new therapeutic agents acting on potential platelet targets is a promising area of anticancer therapy that can retard tumor progression and metastasis as well as reduce associated risks for emerging thrombotic complications in such patients.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 16.11.2021. **Revision received:** 06.12.2021.	**Поступила:** 16.11.2021. **В доработанном виде:** 06.12.2021.
Accepted: 20.12.2021. **Published online:** 21.12.2021.	**Принята к печати:** 20.12.2021. **Опубликована онлайн:** 21.12.2021.
Author's contribution	**Вклад авторов**
All authors contributed equally to the article.	Все авторы внести равный вклад в написание и подготовку рукописи.
All authors have read and approved the final version of the manuscript.	Все авторы прочитали и утвердили окончательный вариант рукописи.
Conflict of interests	**Конфликт интересов**
The authors declare no conflict of interests.	Авторы заявляют об отсутствии конфликта интересов.
Funding	**Финансирование**
The work was done at the authors' own funds.	Работа проведена на собственные средства авторов.
Provenance and peer review	**Происхождение статьи и рецензирование**
Not commissioned; externally peer reviewed.	Журнал не заказывал статью; внешнее рецензирование.

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About the authors:
Ekaterina V. Slukhanchuk – MD, PhD, Associate Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow Russia; Obstetrician-Gynecologist, Department of Abdominal Surgery and Oncology 2, Petrovsky National Research Centre of Surgery, Moscow, Russia. E-mail: ekaterina@ginekologhirurg.ru. ORCID: https://orcid.org/0000-0001-7441-2778.
Victoria O. Bitsadze – MD, Dr Sci Med, Professor of RAS, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0001-8404-1042. Scopus Author ID: 6506003478. Researcher ID: F-8409-2017.
Jamilya Kh. Khizroeva – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-0725-9686. Scopus Author ID: 57194547147. Researcher ID: F-8384-2017.
Maria V. Tretyakova – MD, PhD, Obstetrician-Gynecologist, Assistant, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-3628-0804.
Antonina G. Solopova – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-7456-2386. Scopus Author ID: 6505479504. Researcher ID: Q-1385-2015.
Vsevolod N. Galkin – MD, Dr Sci Med, Professor, Chief Physician, City Clinical Oncological Hospital № 1, Moscow, Russia. ORCID: https://orcid.org/0000-0002-6619-6179.
Andrey S. Shkoda – MD, Dr Sci Med, Professor, Chief Physician, Vorokhobov City Clinical Hospital № 67, Moscow, Russia. ORCID: https://orcid.org/0000-0002-9783-1796.
Valentina I. Tsibizova – MD, PhD, Obstetrician-Gynecologist, Research Laboratory of Operative Gynecology, Institute of Perinatology and Pediatrics; Physician, Department of Functional and Ultrasound Diagnostics, Almazov National Medical Research Centre, Saint Petersburg, Russia. ORCID: https://orcid.org/0000-0001-5888-0774.
Valery I. Linnikov – MD, PhD, Professor, Saint Paul German Medical and Diagnostic Center, Odessa, Ukraine. ORCID: https://orcid.org/0000-0001-6877-2777.
Ismail Elalamy – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Professor, Medicine Sorbonne University, Paris, France; Director of Hematology, Department of Thrombosis Center, Hospital Tenon, Paris, France. ORCID: https://orcid.org/0000-0002-9576-1368. Scopus Author ID: 7003652413. Researcher ID: AAC-9695-2019.
Jean-Christophe Gris – MD, Dr Sci Med, Professor, Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Professor of Haematology, Head of the Laboratory of Haematology, Faculty of Biological and Pharmaceutical Sciences, Montpellier University and University Hospital of Nîmes, France. ORCID: https://orcid.org/0000-0002-9899-9910. Scopus Author ID: 7005114260. Researcher ID: AAA-2923-2019.
Benjamin Brenner – MD, Dr Sci Med, Professor, Director of the Hematology and Bone Marrow Transplantation Institute; Director of the Department of Internal Medicine, Rambam Academic Hospital, Haifa, Israel.
Alexander D. Makatsariya – MD, Dr Sci Med, Academician of RAS, Professor, Head of the Department of Obstetrics and Gynecology, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0001-7415-4633. Scopus Author ID: 57222220144. Researcher ID: M-5660-2016.

Сведения об авторах:
Слуханчук Екатерина Викторовна – к.м.н., доцент кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия; врач акушер-гинеколог отделения абдоминальной хирургии и онкологии 2, ФГБНУ «Российский научный центр хирургии имени академика Б.В. Петровского», Москва, Россия. E-mail: ekaterina@ginekologhirurg.ru. ORCID: https://orcid.org/0000-0001-7441-2778.
Бицадзе Виктория Омаровна – д.м.н., профессор РАН, профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0001-8404-1042. Scopus Author ID: 6506003478. Researcher ID: F-8409-2017.
Хизроева Джамиля Хизриевна – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия. ORCID: https://orcid.org/0000-0002-0725-9686. Scopus Author ID: 57194547147. Researcher ID: F-8384-2017.
Третьякова Мария Владимировна – к.м.н., врач акушер-гинеколог, ассистент кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия. ORCID: https://orcid.org/0000-0002-3628-0804.
Солопова Антонина Григорьевна – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0002-7456-2386. Scopus Author ID: 6505479504. Researcher ID: Q-1385-2015.

Галкин Всеволод Николаевич – д.м.н., профессор, главный врач ГБУЗ «Городская клиническая онкологическая больница № 1 Департамента здравоохранения города Москвы», Москва, Россия. ORCID: https://orcid.org/0000-0002-6619-6179.

Шкода Андрей Сергеевич – д.м.н., профессор, главный врач ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы», Москва, Россия. ORCID: https://orcid.org/0000-0002-9783-1796.

Цибизова Валентина Ивановна – к.м.н., акушер-гинеколог НИЛ оперативной гинекологии Института перинатологии и педиатрии; врач отделения функциональной и ультразвуковой диагностики ФГБУ «Национальный медицинский исследовательский центр имени В.А. Алмазова» Министерства здравоохранения Российской Федерации, Санкт-Петербург, Россия. ORCID: https://orcid.org/0000-0001-5888-0774.

Линников Валерий Иванович – д.м.н., профессор, Немецкий лечебно-диагностический центр Святого Павла, Одесса, Украина. ORCID: https://orcid.org/0000-0001-6877-2777.

Злалами Исмаил – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия; профессор медицинского Университета Сорбонны, Париж, Франция; директор гематологии Центра Тромбозов, Госпиталь Тенон, Париж, Франция. ORCID: https://orcid.org/0000-0002-9576-1368. Scopus Author ID: 7003652413. Researcher ID: AAC-9695-2019.

Гри Жан-Кристоф – д.м.н., профессор кафедры акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский университет), Москва, Россия; профессор гематологии, зав. лабораторией гематологии факультета биологических и фармацевтических наук Университета Монпелье и Университетской больницы Нима, Франция. ORCID: https://orcid.org/0000-0002-9899-9910. Scopus Author ID: 7005114260. Researcher ID: AAA-2923-2019.

Бреннер Бенджамин – д.м.н., профессор, директор Института гематологии и трансплантации костного мозга; директор отдела внутренних болезней, Академический госпиталь Рамбам, Хайфа, Израиль.

Макацария Александр Давидович – д.м.н., профессор, академик РАН, зав. кафедрой акушерства и гинекологии Клинического института детского здоровья имени Н.Ф. Филатова ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0001-7415-4633. Scopus Author ID: 57222220144. Researcher ID: M-5660-2016.