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

АКУШЕРСТВО ГИНЕКОЛОГИЯ РЕПРОДУКЦИЯ

Включен в перечень ведущих рецензируемых журналов и изданий ВАК

2024 • том 18 • № 1

OBSTETRICS, GYNECOLOGY AND REPRODUCTION

2024 Vol. 18 No 1

https://gynecology.su

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

https://doi.org/10.17749/2313-7347/ob.gyn.rep.2024.489

The role of the microenvironment in tumor growth and spreading

Viktoria O. Bitsadze[1], Ekaterina V. Slukhanchuk[1], Antonina G. Solopova[1], Jamilya Kh. Khizroeva[1], Fidan E. Yakubova[1], Esmira A. Orudzhova[2], Natalia D. Degtyareva[1], Elena S. Egorova[1], Nataliya A. Makatsariya[1], Natalia V. Samburova[1], Vladimir N. Serov[3], Lev A. Ashrafyan[3], Zamilya D. Aslanova[1], Arina V. Lazarchuk[1], Ekaterina S. Kudryavtseva[1], Alina E. Solopova[1,3], Daredzhan L. Kapanadze[4], Jean-Christophe Gris[1,5], Ismail Elalamy[1,6,7], Cihan Ay[8], Alexander D. Makatsariya[1]

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

[2]Maternity Hospital No. 1 – Branch of Vorokhobov City Clinical Hospital No. 67, Moscow City Healthcare Department; 2/44 Salyama Adilya Str., Moscow 123423, Russia;

[3]Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Health Ministry of Russian Federation; 4 Academika Oparina Str., Moscow 117997, Russia;

[4]Center for Pathology of Pregnancy and Hemostasis; 78 Uznadze Str., Tbilisi 0179, Georgia;

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

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

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

[8]University of Vienna; 10 Universitätsring, Vienna 1010, Austria

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

Abstract

Introduction. The tumor microenvironment (TME) consisting of non-tumor cells and other components plays a crucial role in cancer development by promoting uncontrolled tumor growth.

Aim: to detail all the components in TME and their contribution to carcinogenesis by analyzing available publications.

Results. Currently, TME study is of great interest in the medical field. Its crucial role in the tumor initiation, progression, and spreading is emphasized. Several constituents have been identified in TME including cancer-associated fibroblasts, neutrophils, adipocytes, tumor vasculature, lymphocytes, extracellular matrix, dendritic cells, neutrophil extracellular traps, etc. Thromboinflammatory reactions are also considered an important TME element.

Conclusion. TME constituents can serve as new targets for both diagnostics and antitumor therapy.

Keywords: tumor microenvironment, TME, tumor progression, tumor growth, cancer, metastasis

For citation: Bitsadze V.O., Slukhanchuk E.V., Solopova A.G., Khizroeva J.Kh., Yakubova F.E., Orudzhova E.A., Degtyareva N.D., Egorova E.S., Makatsariya N.A., Samburova N.V., Serov V.N., Ashrafyan L.A., Aslanova Z.D., Lazarchuk A.V., Kudryavtseva E.S., Solopova A.E., Kapanadze D.L., Gris J.-C., Elalamy I., Ay C., Makatsariya A.D. The role of the microenvironment in tumor growth and spreading. *Akusherstvo, Ginekologia i Reprodukcia = Obstetrics, Gynecology and Reproduction.* 2024;18(1):96–111. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2024.489.

2024 • Vol. 18 • № 1
Obstetrics, Gynecology and Reproduction

Роль микроокружения в росте и распространении опухоли

В.О. Бицадзе[1], Е.В. Слуханчук[1], А.Г. Солопова[1], Д.Х. Хизроева[1], Ф.Э. Якубова[1], Э.А. Оруджова[2], Н.Д. Дегтярева[1], Е.С. Егорова[1], Н.А. Макацария[1], Н.В. Самбурова[1], В.Н. Серов[3], Л.А. Ашрафян[3], З.Д. Асланова[1], А.В. Лазарчук[1], Е.С. Кудрявцева[1], А.Е. Солопова[1,3], Д.Л. Капанадзе[4], Ж.-К. Гри[1,5], И. Элалами[1,6,7], Д. Ай[1,8], 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]Родильный дом № 1 – филиал ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы»; Россия, 123423 Москва, ул. Саляма Адиля, д. 2/44;

[3]ФГБУ «Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени академика В.И. Кулакова» Министерства здравоохранения Российской Федерации; Россия, 117997 Москва, ул. академика Опарина, д. 4;

[4]Центр патологии беременности и гемостаза; Грузия, 0179 Тбилиси, ул. Узнадзе, д. 78;

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

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

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

[8]Венский университет; Австрия, 1010 Вена, Universitätsring, д. 1

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

Резюме

Введение. Микроокружение опухоли (МОО) играет одну из самых важных ролей в онкогенезе. В его состав помимо опухолевых клеток входят и неопухолевые клетки и другие компоненты, стимулирующие и способствующие неконтролируемой пролиферации опухоли.

Цель: в статье подробно изложены все участники МОО и их вклад в онкогенез. Обзор основан на анализе предыдущих исследований по данной проблеме.

Результаты. Микроокружению опухоли в настоящее время уделяется большое внимание в литературе. Выделяют его особую роль в инициации, прогрессии опухоли и метастазировании. В исследованиях описаны различные компоненты МОО, такие как рак-ассоциированные фибробласты, нейтрофилы, адипоциты, сосудистая сеть опухоли, лимфоциты, внеклеточный матрикс, дендритные клетки, внеклеточные ловушки и другие. Важную роль отводят участникам реакций тромбовоспаления как неотъемлемой части МОО.

Заключение. Компоненты МОО могут выступать в роли новых мишеней как диагностики, так и противоопухолевой терапии.

Ключевые слова: микроокружение опухоли, МОО, прогрессия опухоли, рост опухоли, рак, метастазирование

Для цитирования: Бицадзе В.О., Слуханчук Е.В., Солопова А.Г., Хизроева Д.Х., Якубова Ф.Э., Оруджова Э.А., Дегтярева Н.Д., Егорова Е.С., Макацария Н.А., Самбурова Н.В., Серов В.Н., Ашрафян Л.А., Асланова З.Д., Лазарчук А.В., Кудрявцева Е.С., Солопова А.Е., Капанадзе Д.Л., Гри Ж.-К., Элалами И., Ай Д., Макацария А.Д. Роль микроокружения в росте и распространении опухоли. *Акушерство, Гинекология и Репродукция.* 2024;18(1):96–111. https://doi.org/10.17749/2313-7347/ob.gyn.rep.2024.489.

2024 • Том 18 • № 1
Акушерство, Гинекология и Репродукция

Highlights

What is already known about this subject?

- The tumor microenvironment (TME) includes cellular and acellular components, which together constitute a dynamic and complex environment primarily influencing on tumor behavior.
- TME includes blood vessels, immune cells, extracellular matrix, lymphocytes, fibroblasts, inflammatory cells, signaling molecules, and tumor stem cells.

What are the new findings?

- This review summarizes the data obtained published recently on TME, the contribution of each of the players to tumorigenesis, metastasis and tumor progression.

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

- TME constituents may represent new targets for development of both diagnostic strategies and new types of antitumor therapy.

Основные моменты

Что уже известно об этой теме?

- В состав микроокружения опухоли (МОО) входят клеточные и бесклеточные компоненты, составляющие в совокупности динамичную и сложную среду, оказывающую большое влияние на поведение опухоли.
- В состав МОО входят кровеносные сосуды, иммунные клетки, внеклеточный матрикс, лимфоциты, фибробласты, клетки-участники реакций воспаления, сигнальные молекулы, а также опухолевые стволовые клетки.

Что нового дает статья?

- Обобщена информация, полученная в результате исследований последних лет в этой области, посвященная составу МОО, вкладу каждого из участников в онкогенез, метастазирование и прогрессию опухоли.

Как это может повлиять на клиническую практику в обозримом будущем?

- Участники МОО могут являться новыми мишенями для разработки как диагностических стратегий, так и новых видов противоопухолевой терапии.

Introduction / Введение

The tumor microenvironment (TME) is a complex and dynamic environment consisting of both cellular and acellular components [1]. TME includes tumor-surrounding immune cells, blood vessels, extracellular matrix (ECM), fibroblasts, lymphocytes, inflammatory cells, and diverse signaling molecules [2]. Recent studies have shown that TME non-cancerous cells comprise about 50 % of tumor tissue and its metastases [3] and play a role at all stages of carcinogenesis, stimulating uncontrolled cell proliferation [4]. TME also contains tumor stem cells capable of self-reproduction and stimulation of carcinogenesis. Current studies have found isolated tumor stem cells in patients with breast, colon, lung, and brain cancer [5, 6]. TME contains a heterogeneous population of tumor and stromal cells involved in tumor progression. Cell-cell interactions are regulated by multilayered, dynamic network of cytokines, chemokines, and growth factors, as well as inflammatory and matrix remodeling enzymes [7]. TME components vary depending on cancer type and the individual patient characteristics [6].

Tumor microenvironment components / Состав микроокружения опухоли

Cellular components of tumor microenvironment / Клеточные компоненты микроокружения опухоли

Immune cells / Клетки иммунной системы

Immune cells are an important TME component that can either suppress or stimulate tumor growth. Infection-triggered inflammation is the underlying mechanism in formation of several tumor types, including colorectal cancer, hepatocellular carcinoma, and cervical cancer.

The immune cells are presented by innate and acquired immune cells. Macrophages, neutrophils, dendritic cells, and natural killer cells (NK-cells) belong to the innate immunity that comes into action immediately after interaction with an antigen. T-cells and B-cells belong to adaptive immunity, which arise in response to diverse antigens followed by subsequent formation of immunological memory [1].

The interaction between tumor cells and TME cells promotes the recruitment, activation, and reprogramming of immune and stromal cells in the extracellular space [8]. TME components and immune surveillance affect tumor progression. Assessment of immune TME has important prognostic implications and can complement tumor histopathological and molecular characteristics while assessing patient response to therapy [8, 9].

At the initial stages of tumorigenesis, malignant-specific T-cells are weak stimulators and targets for the immune response. Over time, such cells become resistant to and begin to suppress innate immune response [9].

T-lymphocytes / Т-лимфоциты

Each T-lymphocyte is equipped with a T-cell receptor that recognizes a specific antigen. Imposing immunosuppression involves compromised function and development of T-lymphocytes, which form a crucial TME component. While some T-cells promote carcinogenesis, others exert an antitumor effect [10, 11]. TME consists of distinct T-cell subsets, which infiltrate

2024 • Vol. 18 • № 1 Obstetrics, Gynecology and Reproduction

the invasive tumor margin and reside in draining lymphatic reservoirs.

In TME, cytotoxic CD8+ memory T-cells represent one of the most commonly found T-cell types, which exhibit cytolytic effects on tumor cells by sensing aberrant tumor antigens expressed on cancer cells and stimulating immune responses [12]. Notably, TME cytotoxic T-lymphocytes are associated with a beneficial prognosis in cancer patients. In addition to their role in tumor cell destruction, such T-cells also suppress angiogenesis via interferon-gamma (IFN-γ) production. TME CD4+ T helper 1 (Th1) cells accompany CD8+ T-cells by releasing IFN-γ and interleukin-2 (IL-2). Elevated Th1 cell level in TME is associated with beneficial prognosis in some tumor types.

Other CD4+ cell subsets such as Th2 cells secrete IL-4, IL-5, and IL-13 to assist B-cell response [9, 12]. On the other hand, Th17 cells produce IL-17A, IL-17F, IL-21, and IL-22 and promote tumor growth by stimulating inflammation [12]. Therefore, CD4+ T-cells differentiate into multiple subsets and participate in a wide range of TME immune responses.

Regulatory T-cells / Регуляторные Т-клетки

Three major types of TME immune landscape are distinguished. In the first type, immune-infiltrated TME and immune cells (e.g., cytotoxic T-cells) are distributed evenly suggesting about actively developing immune response. In the second type, immune cells are located on the tumor periphery, without penetrating the tumor. Finally, in the third type of tumor TME, no infiltration of immune cells was observed, indicating the lack of tumor immune response. In cancer patients, regulatory T-cells (T-regs) suppress the antitumor immune response by establishing immunosuppressive TME and promoting cancer progression.

Regulatory T-cells (T-regs) are essential for suppressing inflammatory responses and preventing autoimmune diseases [13]. T-regs are abundant in TME and facilitate tumor development and progression by attenuating antitumor immune responses. T-regs secrete IL-2, which modulates NK-cells. In addition, T-regs produce immunosuppressive cytokines such as IL-10 and transforming growth factor-beta (TGF-β) and mediate their immunosuppressive effects via cytotoxic T-lymphocyte antigen 4 (CTLA4). T-regs also facilitate tumor cell survival by secreting growth factors and interacting with stromal cells, fibroblasts, as well as endothelial cells. CD4+ T-cells expressing transcription factor forkhead box P3 (FOXP3) and CD25 represent T-regs exerting pro-tumorigenic effects acting as immunosuppressive cells. A high T-regs number in TME correlates with poor prognosis in various cancer types [14]. However, studies have shown that depletion of T-regs can lead to regression of metastatic foci in advanced melanoma. Depletion of T-regs and subsequent vaccination with tumor antigen can initiate antitumor CD4+ T-cell responses. T-regs may also suppress tumor growth in some B-cell cancers, and their presence in Hodgkin lymphoma correlates with a good prognosis, presumably due to directly suppressed tumor cell growth [15, 16].

Gamma-delta-T-lymphocytes / Гамма-дельта-Т-лимфоциты

Gamma-delta-T-lymphocytes (γδ-T-cells) are cytotoxic to a wide range of malignant T-cells, including tumor stem cells [17]. The effect of TME γδ-T-cells on disease prognosis is not fully elucidated.

B-lymphocytes / В-лимфоциты

B-cells are a type of specialized immune cells that play an essential role in antibody production, antigen presentation, and cytokine secretion. They are mainly found in lymph nodes and lymphoid structures close to TME as well as invasive margin of the tumor [18]. However, compared to T-lymphocytes, B-cells are relatively less abundant in TME. It has been observed that the infiltration of B-cells into TME is associated with a favorable prognosis in some types of breast and ovarian cancers [19].

Available publications suggest that B-cells may have contrasting effects on tumor-specific cytotoxic T-cell responses in mouse models. While some studies have reported that B-cells can suppress antigen-specific responses, recent data indicates that B-cells may also stimulate tumor growth in mouse models of skin cancer [20]. Specifically, regulatory B-cells (B-regs), also known as B10-cells [21], have been found to produce the immunosuppressive protein IL-10, which promotes tumor growth and suppresses tumor-specific immune responses in skin cancer. Furthermore, B-regs have also been found to promote lung metastasis in mouse breast cancer models. In addition, mouse lymphoma models showed that B-regs suppress the antitumor effect induced by anti-CD20 antibodies [22]. However, B-regs do not penetrate TME but rather impact other immune cells in the surrounding lymphoid tissue and modulate the activity of myeloid cells [20].

B-lymphocytes present in TME play a crucial role in regulating tumor cell survival and proliferation, additionally contributing to arising drug resistance and evasion of immune surveillance [23]. Controlling the B-cells in TME can aid in disrupting initiation of tumor-induced immunosuppression through TGF-β-dependent conversion of FOXP3+ T-cells.

NK- and NKT-cells / NK- и NKT-клетки

Cytotoxic lymphocytes, natural killer cells (NK-cells), and natural killer T cells (NKT-cells) are capable of infiltrating tumor stroma, without encountering the tumor cells. NK-cells are equipped to identify virus-infected host cells or tumor cells in the circulation. The presence of NK- and NKT-cells is believed to be an indicator of favorable prognosis for multiple cancer types such as colorectal, gastric, lung, kidney, and liver cancer. NK- and NKT-cells employ various receptors to recognize cellular targets and ignore healthy host cells. These receptors transduce signals during contact with TME cells, which in turn activate NK-cells. NK- and NKT-cells can detect changes in host tissues [24], leading to the subsequent activation of TME immune cells. Functionally, NK-cells can be bifurcated into two classes, namely antitumor defense cells and proinflammatory cells that secrete inflammatory cytokines. Although NK-cells are highly efficient in tumor cell lysis and can prevent metastasis, they are less effective against the tumor microenvironment.

Tumor-associated macrophages /
Опухоль-ассоциированные макрофаги

Tumor-associated macrophages (TAMs) are an essential part of TME [25]. TAMs always accompany tumor cells while they spread, invade, and metastasize [26]. Macrophages are crucial components of the innate immune system. In TME, TAMs, dendritic cells, and tumor-associated fibroblasts (TAFs) play a role in tumor progression [4]. Macrophages regulate immune responses via pathogen phagocytosis and antigen presentation. Moreover, macrophages are critical for tissue regeneration. Monocyte-derived macrophages can be divided into two types: pro-inflammatory M1 macrophages responsible for cell phagocytosis and immunosuppressive M2 macrophages, which promote regeneration. Despite that both macrophage types are found inside tumor tissue, TME stimulates growth of M2 macrophages due to hypoxia and cytokine secretion. In some tumor types, macrophages can comprise up to 50 % of the tumor mass. Research has revealed that TAMs in TME are associated with poor prognosis. Macrophages promote the extravasation of tumor cells to distant sites and suppress antitumor immune responses [4]. TAMs counteract antitumor therapy and decrease the effectiveness of radiation therapy, cytotoxic drugs, and checkpoint inhibitors. TAMs support tumor cell invasion by producing various molecules, which promote tissue remodeling, including vascular endothelial growth factor (VEGF), metalloproteinases (MMPs) MMP-9, and MMP-2, as well as pro-inflammatory molecules such as IL-1β, chemokine (C-X-C motif) ligand10 (CXCL10) and tumor necrosis factor-alpha (TNF-α). In addition, they also secrete growth factors and cytokines to promote tumor cell growth, spread, and survival [27]. TAMs express the vascular cell adhesion molecule 1 (VCAM-1) and can differentiate into inflammatory monocytes [28]. Macrophages are an important contributor to tumor angiogenesis. Tumor tissue recruits TAMs by releasing hypoxia-induced chemoattractants such as VEGF, endothelins, endothelial monocyte-activating polypeptide II (EMAP II), also known as AIMP1. Additionally, human macrophages were also identified to display a hypoxia-induced pro-angiogenic phenotype.

Dendritic cells / Дендритные клетки

Dendritic cells (DCs) play a critical role as antigen-presenting cells able to recognize, capture, and present antigens to T-cells in secondary lymphoid organs (e.g., lymph nodes), thereby bridging the innate and adaptive immune responses. In TME, DCs are necessary for antigen processing and presentation [29]. They migrate to the lymph nodes and initiate immune response by stimulating T- and B-cells [30]. However, the ability of TME DCs to stimulate an immune response against tumor-associated antigens is compromised by hypoxia and cytokine proinflammatory effects within TME.

Tumor-associated neutrophils /
Опухоль-ассоциированные нейтрофилы

The role of tumor-associated neutrophils (TANs) in the context of tumor progression and metastasis remains debated. Available studies indicate that neutrophils promote tumor growth in mouse cancer models due to their potential to activate angiogenesis [31], degrade the extracellular matrix components, and induce immunosuppression [32]. Furthermore, neutrophils have been identified as key contributors to metastasis, because they facilitate formation of premetastatic niches [33]. Despite these findings, it is noteworthy that neutrophils possess antitumor activity under certain conditions, e.g., immune- or cytokine-mediated activation. In such circumstances, neutrophils can directly [34] or indirectly suppress TGF-β to destroy tumor cells. It is also important to note about a multifaceted nature of neutrophil-released components, including neutrophil extracellular traps (NETs), which actively participate in both tumor growth and metastasis.

Stroma / Строма

Tumor cells are able to recruit supportive cells from the stroma of neighboring tissues to facilitate their growth. The stroma plays a crucial role in controlling carcinogenesis, tumor cell growth, metastasis, and invasion. Furthermore,

2024 • Vol. 18 • № 1 Obstetrics, Gynecology and Reproduction

the stroma promotes the growth of mesenchymal cells [35]. The composition of stromal cells can significantly vary depending on tumor type, including vascular endothelial cells, fibroblasts, adipocytes, and stellate cells. Once recruited to TME, stromal cells secrete a variety of factors that influence angiogenesis, proliferation, invasion, and metastasis. For the tumor cells to form a significant-sized tumor, they must penetrate other cellular spaces by disrupting the basement membrane and separating the tissue parenchyma from the epithelial compartment. During the invasion process, TME is regulated by tumor growth. The tumor-associated stroma provides a tumor with nutrients, oxygen, enzymes, and matrix-associated growth factors that promote tumor progression. Furthermore, stromal cells divide and differentiate into various cell lineages based on TME composition.

Adipocytes / Адипоциты

Adipocytes are specialized body cells that store excess energy in a form of fat and regulate energy balance. However, in some tumor types, adipocytes can promote tumor cell growth by releasing adipokines and providing fatty acids to tumor tissue. Adipocytes deeply impact on TME by secreting diverse agents such as metabolites, enzymes, hormones, growth factors, and cytokines. Tumor cells stimulate adipocytes to release free fatty acids, which they use for energy production, cell membrane formation, lipid bioactive molecules, and exosomes. Leptin, an important hormone produced by adipocytes, can promote tumor progression directly by influencing the proliferation of breast cancer cells and indirectly by activating macrophages. Additionally, adipocytes can modify the extracellular matrix (ECM) by secreting metalloproteases such as MMP-1, MMP-7, MMP-10, MMP-11, and MMP-14. Obesity is a major risk factor for cancer, and more than 40 % of cancer patients are obese.

Endothelial cells / Эндотелиальные клетки

The vascular endothelium comprises a thin monolayer of endothelial cells that form the inner lining of blood vessels. It serves a crucial role in maintaining the barrier between blood and tissue, facilitates the transport of water and nutrients, supports metabolism, transports immune cells, and contributes to neoangiogenesis. During the initial stage of tumor development, the cellular exchange of gases and nutrients occurs via a simple diffusion. However, as the tumor volume reaches 1–2 mm^3, hypoxia and acidosis develop within TME, resulting in *de novo* formation of blood vessels via neoangiogenesis.

Vascular endothelial growth factor (VEGF) is the main, but not the only stimulator of neoangiogenesis in TME. It is secreted by both malignant cells and proinflammatory leukocytes. During neoangiogenesis, growth factors in TME, such as fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), VEGF and chemokines, stimulate endothelial cells and their associated pericytes. Hypoxia in TME leads to the activation of hypoxia-inducible factors, transcription factors critical for coordinating cellular responses to low O_2 level.

Activation of neoangiogenesis occurs under hypoxic conditions, as well as when the intact endothelium senses an angiogenic signal from malignant or inflammatory cells. The *de novo* formed tumor vascular network has an aberrant structure, the blood vessels are heterogeneous, with an irregular, branching pattern and uneven lumen, and are leaky. The latter property elevates interstitial fluid pressure, causing uneven blood flow, oxygenation, and distribution of nutrients and drugs in TME. Altogether, these properties of *de novo* formed vasculature increase hypoxia in TME and facilitate metastasis.

In addition to angiogenesis, ECs play a role in promoting tumor cell spread, invasion, and metastasis. ECs undergo endothelial-mesenchymal transition and develop into tumor-associated fibroblasts (TAFs). The EC-to-TAF transition is accompanied by TGF-β and bone marrow-derived protein that leads to loss of intercellular connections, migration as well as loss of properties of endothelial cells. Tumor cells during metastasis spreading must first exits from the primary tumor site and enter the vascular system in a process known as intravasation. Blood vessels formed in TME are usually immature and have not proper intercellular connections, allowing tumor cells to easily extravasate.

Lymphatic endothelial cells / Лимфатические эндотелиальные клетки

Tumor cells stimulate lymphangiogenesis via VEGF-C or VEGF-D [37]. Tumor cells also penetrate existing lymphatic vessels, however, in the presence of high VEGF-C or VEGF-D concentrations, the number of lymphatic vessels, collecting lymphatic vessels, and lymph node hyperplasia increases. TME lymphatic endothelial cells and the lymphatic vessels they form favor tumor spread [38].

Tumor-associated fibroblasts / Опухоль-ассоциированные фибробласты

Tumor-associated fibroblasts (TAFs) are a major component of tumor stroma and play an important role in the interaction between tumor cells and TME. Tumor-associated fibroblasts can be derived from various progenitor cells such as endothelial cells, smooth muscle cells, myoepithelial cells, or mesenchymal stem cells.

When tissue is damaged, fibroblasts undergo a reversible transition to myofibroblasts, which actively participate in tissue regeneration. Activated myofibroblasts become capable of participating in TGF-β-related regeneration. Regenerative properties in this case include the ability to proliferate, secrete, and form the extracellular matrix. Thus, tumors are known as "wounds that never heal".

In TME, TAFs produce most of the extracellular components, including growth factors, cytokines, and extracellular matrix. TME fibroblasts secrete ECM components and ECM remodeling enzymes [39].

TAFs form TME in four main ways:

1. tumor proliferation and metastasis;
2. neoangiogenesis;
3. ECM remodeling;
4. immunosuppression.

In epithelial tumors, epithelial-mesenchymal transition is a critical step in metastasis [40, 41]. One way to control metastasis is secretion of TAF TGF-β, a growth factor required for EMT and angiogenesis. TGF-β released by fibroblasts triggers epithelial-mesenchymal transition in tumor cells and contributes to developing immunosuppressive microenvironment [39]. To facilitate tumor cell migration through TME, TAFs secrete MMP-3, which degrades E-cadherin, promoting tumor cell invasion. TAFs contribute to immunosuppression via production of immunomodulatory chemokines, cytokines and growth factors such as fibroblast-secreted protein-1 (FSP1), which is known to initiate metastasis in colon and breast cancer [40, 42]. TAFs promote tumor cell proliferation [40, 43]. TAFs secrete growth factors such as EGF, hepatocyte growth factor (HGF), insulin-like growth factor 1 (IGF1), VEGF and FGF, which are mitogenic for tumor cells. Fibroblast-produced chemokine CXCL12 promotes tumor cell growth and survival and also exerting chemoattractant effects favoring migration of other types of stromal cells and their precursors into TME.

In some types of cancer, TAFs are located scattered throughout the tumor mass, in others – surround the malignant cells with a dense stroma, limiting the effectiveness of anticancer drugs [39]. The effect of removing fibroblast marker – fibroblast activation protein-α (FAP)-positive cells in tumor-bearing mice was studied, with IFN-γ and TNF-α resulting in tumor necrosis. It was shown that FAP-positive TME cells are important mediators of immunosuppression [44].

Pericytes / Перициты

Perivascular stromal cells, known as pericytes is an integral component of the tumor vasculature, providing structural support to blood vessels [45]. Clinical studies in bladder cancer, colorectal cancer, and invasive breast cancer showed that low pericyte level in the vasculature predispose to poor prognosis and activation of metastasis. Studies in mouse models also revealed that pericyte depletion suppresses primary tumor growth but leads to elevated hypoxia [46] and metastasis.

Stellate cells (SCs) are quiescent stromal fibroblasts in the liver and pancreas. SCs transforming into myofibroblasts are activated during injuries. TGF- triggers SCs activation, after which they modify the ECM and begin to secrete proangiogenic factors such as VEGF-A and MMP-2 [47].

Tumor stem cells / Опухолевые стволовые клетки

Tumor stem cells interact with TME through activation of pathways such as Notch-1 and PI3K [48]. Tumor stem cells survive hypoxic conditions by promoting production of hypoxia-inducible factor-1 alpha (HIF-1α), VEGF, and proangiogenic factors. In some cases, stem cells induce immune tolerance in TME via production of anti-inflammatory cytokines [49].

TME protects tumor stem cells via TAFs and epithelial-mesenchymal transition (EMT). TAFs are active TME stromal components able to stimulate tumor progression via secretion of soluble factors, modulate ECM composition, and interact with other cell types. Moreover, these cells are capable of driving tumor-like behavior in TME through exosomes secretion, which ultimately stimulate cell migration [50]. In patients with prostate cancer, TAFs in TME promote the growth of tumor stem cells by enhancing cell proliferation and spheroid formation via paracrine signaling. In EMT, epithelial cells become fibroblast-mesenchymal cells [50]. In TME, higher invasiveness and cell motility, as well as turnover of ECM components, accompany EMT. TME protects tumor stem cells through EMT, allowing them to penetrate the basement membrane, migrate to distant sites, and form secondary tumors.

Typically, tumor cells are surrounded by a dense extracellular matrix composed of collagen, proteins, proteoglycans, and glycoproteins [50], and their increased ECM deposition may reduce the effectiveness of antitumor therapy.

TME plays a marked role in protecting tumor stem cells through angiogenesis [50]. The latter is a rapid event that occurs when endothelial cells and pericytes interact. Due to the high rate of cell proliferation and oxygen consumption, trophic deficiency and hypoxia may develop. Under hypoxic conditions, HIF-1α is activated and regulates alternative angiogenic signaling processes. Disorganized angiogenesis can result in insufficient blood flow to TME shaping a unique metabolic environment.

2024 • Vol. 18 • № 1 Obstetrics, Gynecology and Reproduction

The concentration of energy sources in tumor site leads to tumor cells switching to glycolysis for proliferation and enabling effect or functions such as IFN-γ release [51]. In TME, T-cells and glycolytic tumor cells upregulate expression of glucose transporters such as sodium/glucose cotransporter 1 (SGLT1) and facilitated glucose transporter member 1 (GLUT-1). Activated T-cells can uptake glucose from tumor environment without prominent competition from tumor cells.

Non-cellular components of the tumor microenvironment / Неклеточные компоненты микроокружения опухоли

Extracellular matrix / Внеклеточный матрикс

Extracellular matrix is a substrate that provides intercellular structural and biochemical scaffold consisting of water, proteins, proteoglycans, minerals [35], and macromolecules, such as glycoproteins, collagens, and enzymes, which affect cell adhesion, proliferation, and intercellular communication [41, 52]. The ECM exhibits the properties of a living cell [35], and its composition varies depending on the surrounding cells and the needs in specific tissue type. It undergoes remodeling when its primary components are modified and degraded by proteinases. The presence of ECM cell growth factors such as integrins allows tumor cells to interact with TME. The ECM also regulates production of vital proteins, including laminin, elastin, and collagen [41].

The ECM not only supports the physical structure of all TME cells but also affects tumor metastasis by influencing cell adhesion to the ECM. The properties of tumor cells are modulated by the ECM, which in turn affects their movement. Cells can migrate between low-to-high ECM areas due to adhesion gradient [41] that determines the rate at which tumor cells migrate from one area to another [35]. Too high ECM concentrations interfere with cell migration [53].

The ECM serves as a reservoir for transforming growth factor-beta [48], a protein that regulates various cellular processes, including nerve and epithelial cell growth, wound healing, and immune responses. Almost all human cells are sensitive to TGF-β that plays an important role in maintaining tissue homeostasis and preventing progression. [48]. However, due to genetic instability tumor cells can evade TGF-β-related suppressive effect in TME. They can inactivate the TGF-β receptors, and thereby escape its influence [41]. Additionally, tumor-produced TGF-β enhances immune tolerance and avoids immune surveillance. Tumor-associated TGF-β also promotes recruitment of stromal cells such as myofibroblasts and osteoclasts, which in turn promotes carcinogenesis.

The ECM composition and biomechanical characteristics affect integrin signaling, which in turn influences cancer-causing mechanisms like the Hippo pathway and EMT [41]. Cells attach to the ECM through various receptors, including integrins, which play a prominent role in promoting epithelial differentiation and cell development [36, 37]. Loss of integrin subunits, such as α6 and α2, can lead to tumor progression. The integrin activity and function rely on substances like syndecans, which bind to ECM proteins like collagen and laminin.

Solid tumors consist of large extracellular matrix deposits and account for up to 60 % of the tumor mass. The presence of large collagen deposits and a high percentage of fibroblast infiltration contribute to chemotherapy resistance and poor patient prognosis.

Exosomes / Экзосомы

Exosomes are microvesicles ranging in size from 30 to 200 nm. Their contents depend on the source cell and include protein, RNA, DNA, and lipids. In TME, exosomes are involved in interaction between tumor and stromal cells. TME exosomes play a crucial role in promoting inflammation, tumor progression, neoangiogenesis, and metastasis. Hypoxia enhances exosome production and facilitates stromal cell-to-TAF conversion.

Growth factors / Факторы роста

Tumor microenvironment contains various growth factors, such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and VEGF, which down modulate activity of anti-tumor T-cells [50]. Leukocytes and TME factors, such as TGF-β, GM-CSF, and PDGF, stimulate tumor growth, enhance angiogenesis, and interfere with signaling molecule release. TME protects tumor stem cells by regulating the activity of signaling molecules and immune cells. TME components secrete cytokines, growth factors, and chemokines that promote tumor cell migration.

Tumor acidosis / Опухолевый ацидоз

Mutations and modifications of genes primarily drive tumor growth. It is, however, known that metabolic reprogramming also plays a role in this event [54]. Metabolic reprogramming is a multilayered phenomenon that involves interplay between tumor cells and the surrounding stroma. Presently, there is marked interest in understanding the metabolic adaptations that occur during TME acidosis. Acidosis is a critical factor in tumor progression [54] because it affects tumor behavior, determines the rate of metastasis and invasion, and regulates immune surveillance mechanisms.

Consequently, tumor acidosis represents an important therapeutic target and is no longer considered a mere

side effect of tumor growth. Tumor acidosis is associated with extracellular accumulation of lactic acid and hypoxia [54]. Tumor cells metabolic activity leads to a markedly accumulated H^+ level in TME. The disorganized nature of the tumor vasculature prevents the effective and timely elimination of H^+ ions from the extracellular environment resulting in development of tumor hypoxia and a shift in glycolytic metabolism. Decreasing pH in TME enhances tumor cell motility and alters cytoskeletal dynamics that affect macrophage and fibroblast polarization and activity. Alkalinization of intratumoral pH level promotes increased cell migration involving actin-binding proteins. Conversely, extracellular acidification leads to activated proteases and intercellular interactions. Tumor areas with the lowest pH have been shown to have peak rates of tumor invasion, and vice versa.

According to available data, lysosomal-associated membrane protein 2 (LAMP2) has been found to enhance tumor cell survival in acidic conditions [54]. LAMP2 plays a crucial role in protecting lysosomal membranes from proteolysis during carcinogenesis. The increased TME acidity triggers expression of autophagy regulator 5 (ATG5) in preinvasive tumor cells. Furthermore, cells exposed to a low pH environment for extended period exhibit higher level of autophagy biomarkers such as ATG5 and BCL-2. However, the mechanisms underlying such changes have not yet been fully analyzed.

Tumor microbiome / Опухолевый микробиом

Microbiomes are a source of various metabolites that systemically and locally promote carcinogenesis. They affect disease progression and may determine response to therapy. Currently, the relationship between tumor phenotypes and tumor-colonizing microbial species have been extensively studied. Microbiota deeply impacts on the effectiveness of immunotherapy [50]. The effect of intestinal microbiota on cancer development depends on its crosstalk with human immune system and TME components. The tumor microbiota in TME influences xenobiotics biotransformation and metabolism [50], which account for the rate of tumor cell growth and spread *in vivo*. Assessing fecal microbiota transplantation in *Clostridium difficile* infection suggests a success in the treatment of complex cancer cases [55].

Effect of tumor on microenvironment / Влияние опухоли на микроокружение

Cells within TME interact with each other and with tumor cells, affecting tumor invasion, growth, and metastasis. TME remains an important battleground between host immune system and tumor. The wide range of TME cellular interactions determines host tolerance and tumor response.

Mesenchymal cells play an important role in the interaction between tumors and TME [56]. This stromal cell type influences tumor biology by acting on its ability to differentiate into pericytes and TAFs [43, 49]. Peptide signaling molecules, stromal cell-derived factor 1 (SDF-1), monocyte chemoattractant protein 1 (MCP-1), leucine-37 (LL-37), TGF-β [17, 32] as well as nitric oxide (NO) and exosomes are released by tumor cells and facilitate mesenchymal cell recruitment and destruction.

Tumor cells activate fibroblasts, promoting cancer progression [48]. Fibroblasts can be activated via vascular endothelial growth factor A (VEGF-A) signaling. Thus, stromal-activated fibroblasts play an important role in tumor growth and can be used to treat various cancer types.

Targeting tumor microenvironment as a new therapeutic approach / Влияние на микроокружение опухоли как новый терапевтический подход

The investigation of TME holds promise for developing novel therapeutic antitumor strategies. Currently, surgical procedures, chemotherapy, and radiation therapy are the most widely employed treatment options in cancer patients. However, selective depletion of TME regulatory T-cells can enhance function and vaccine production of induced memory CD8+ T-cells in cancer patients [16, 20]. Furthermore, in the case of Hodgkin lymphoma, T-regs have been found to improve patient survival by directly impeding tumor cell division and growth [57].

The current focus in the field is to regulate protumor activity of TME cells, including NK- and NKT-cells. Additionally, the functionality of mesenchymal cells presents a prominent target for developing novel therapeutic strategies. The regulation of these functions can be utilized to enhance tumor immunosurveillance. The efforts to investigate such areas hold great promise for development of effective and innovative cancer therapies.

Tumor acidosis may be targeted therapeutically by neutralizing the acidic environment applying buffers and suppressing hydrogen ion production.

Immune checkpoint inhibitors are a new and important approach for treating various cancer types, which target programmed death 1 (PD-1) on healthy cells and programmed death ligand 1 (PD-L1) on tumor cells. Tumor cells express PD-L1, which activates PD-1 and suppresses the immune response of PD-1-expressing cells. However, PD-1 and PD-L1 inhibitors prevent the interaction between PD-L1 and its cognate receptors assisting to preserve immune responses [52]. These inhibitors have been clinically tested in melanomas,

renal cell carcinoma, non-small cell lung cancer, colon cancer, and bladder cancer [55]. Immunotherapy using checkpoint inhibitors has been shown to reduce tumor size and provide durable responses with low toxicity.

Dendritic cells activation by vaccination has been successfully used in the treatment of prostate cancer. The "Provenge" protocol is based on monocyte collection from prostate cancer patients followed by monocyte, differentiation into DCs, activation with prostatic acid phosphatase (PAP) antigen, and subsequently inoculated back to the patients.

Integrins are cell membrane receptors for diverse ECM proteins that affect differentiation, proliferation, and survival of tumor cells [58]. Integrins and their effectors are among the most promising markers and targets for tumor therapy. Integrin antagonists, such as the avβ3 and avβ5 integrin antagonists cilengitide, successfully block tumor progression and demonstrate high antitumor efficacy.

Analogies have been drawn between inflammation/wound healing and tumor growth due to activation of oncogenic mutations, altered immune cell function, and the initiation of angiogenesis. Apart from providing a physical scaffold promoting tumor growth, TME comprises a range of growth factors, including chemokines and angiogenic factors, that interact with various cell surface receptors.

Several studies indicate that mutations in the genes associated with the TGF-β family can contribute to tumor development. Mutations in the genes encoding transforming growth factor beta receptor type II (TGFBR2), activin receptor type 2A (ACVR2A) and SMAD4 receptor can influence tumor development [55]. Activin and TGF-β are crucial TME components and play a prominent role in regulating cell differentiation, migration, proliferation, and apoptosis. TGF-β triggers activin secretion by tumor stromal cells, which in turn promotes metastasis in epithelial cells.

It was previously believed that primary activin-related function is to stimulate release of follicle-stimulating hormone by the pituitary gland. However, recent studies suggest that it also plays a key role in inflammation, immunity, fibrosis, and angiogenesis. Activin is a crucial regulator of carcinogenesis and regeneration [59]. Animal models have demonstrated that upregulated activin expression results in formation of larger tumors and cancer cachexia [54].

Antiangiogenic therapy is aimed at targeting the VEGF/VEGF-R signaling axis. Types of antiangiogenic therapy include neutralizing antibodies against VEGF-A (bevacizumab); decoy receptors for VEGF-A or B (aflibercept); tyrosine kinase inhibitors (sorafenib); and neutralizing antibodies, which block VEGF binding to cognate receptor (ramucirumab). Monotherapy with antiangiogenic drugs is not effective enough, and greater success is achieved by combination with other drugs.

It has been found that certain cells and substances are present in all tumor types, even though TME composition can vary. Therefore, some treatment options may be effective for all tumor types in the future. Recent studies have shown that immunotherapy with CTLA4 antibodies can effectively treat advanced cancer.

Thromboinflammation and tumor microenvironment / Тромбовоспаление и микроокружение опухоли

The concept of "thrombus inflammation" was introduced in 2004. It describes the interplay between hemostatic and inflammatory responses that occur in various pathophysiological conditions such as sepsis, disseminated intravascular coagulation, stroke, cancer, etc. Thromboinflammation is represented by mutual interactions and reciprocal activation between endothelial cells, subendothelium, leukocytes, platelets, as well as reactions of innate immunity, complement cascade, coagulation, and fibrinolysis. The crosstalk between thrombosis and inflammation stems from an cardinal response to infectious agents and tissue damage. In some invertebrates, "clotting" occurs in the hemolymph being supported by hemocytes, the precursors of vertebrate platelets. The impact of bacteria on hemocytes or hemolymph leads to rapid hemolymph coagulation, detaining pathogens and limiting further spread. Later, this early cardinal response became more specialized. Altogether, a role for hemostasis, inflammation, and immunity also became differentiated.

In addition to cardiovascular diseases and complications, the role of thromboinflammation in cancer progression has been proven. In this field, tumors are treated as non-healing wounds. In this scenario, platelets are intimately involved in a vicious cycle of activating tumor cells, which in turn activate platelets. Mutual activation entails the development of cancer-associated thrombosis, activation of neutrophils along with release of neutrophil extracellular traps as well as strengthens proinflammatory microenvironment promoting tumor growth and metastasis.

NETs components have been found to be highly effective in combating tumors. Myeloperoxidase (MPO), for instance, has been shown to be harmful to melanoma cells. In case of MPO deficiency, the likelihood of tumor relapses and progression increases [60]. NETs histones have the ability to damage tumor vasculature, destroy epithelial and tumor cells, attract dendritic cells to the tumor, and exert antiangiogenic properties. However, NETs proteases can also promote metastasis

by destroying the extracellular matrix components. The matrix metalloproteinase 9 (MMP-9) released from NETs blocks tumor cell apoptosis, facilitating migration, invasion, and metastasis [61, 62]. NETs bearing DNA strands attached to the vascular endothelium may capture tumor cells from the bloodstream. After 48 hours, micrometastases begin to be detected in the liver [63].

There has been a long-standing hypothesis stating that the interaction between neutrophils and platelets plays a role in ischemia-reperfusion injury, even before the term thrombus inflammation was coined [64]. The focus has been put on the von Willebrand factor (vWF) and its role in the thromboinflammatory response. Studies showed that vWF concentration increases in the blood plasma of individuals with malignant growth, proportional to disease stage. The interaction between vWF, tumor cells, platelets, and endothelial cells contributes to hematogenous dissemination and the formation of metastatic foci. This is thought to be a consequence of the deficiency or dysfunction of ADAMTS-13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13), the vWF-degrading protease activity, which regulates platelet-tumor adhesive interactions in the metastatic process [65]. There is ongoing debate on the anti- or prometastatic vWF role. Some studies suggested that vWF plays a protective role against tumor spread, as vWF-deficient mice exhibited an increased number of lung metastases. However, another study found that vWF promoted the formation of pulmonary metastases through a hematogenous route in mouse models. Interestingly, the lack of Weibel-Palade bodies and dysregulated secretion of prometastatic factors were observed in vWF-deficient mice, which may activate prometastatic potential.

In cancer patients, the vWF concentration is higher and the ADAMTS-13 concentration is lower than in the general population, and such changes depend on the disease stage. A relationship has been identified between vWF concentration, ADAMTS-13 activity, and the risk of thrombosis in cancer patients [66]. vWF level is higher in those patients who developed thrombosis within 6 months. It has been shown that patients with tumor progression had significantly higher vWF concentration, but lower ADAMTS-13 activity [67].

Approximately 5 % of patients with idiopathic thrombosis exhibit malignancies within a year following the thrombotic episode. Conversely, hypercoagulation is detected in cancer patients at the time of disease diagnosis. In comparison to the general population, cancer patients exhibit higher hypercoagulability level and the incidence of genetic thrombophilia [68]. These findings suggest a relationship between hemostasis dysregulation and tumor growth, suggesting about a plausible role for hemostasis gene polymorphisms and mutations in cancer initiation. A study by R. Pihusch et al. showed that prothrombin mutation is a risk factor for gastrointestinal malignancies. [69]. The mechanism behind this is prothrombin activation resulting in formation of thrombin that interacts with the proteinase-activated receptor 1 (PAR-1), ensuring tumor cell survival, proliferation, and adhesion [70]. C.Y. Vossen et al. noted about the carcinogenic role of factor V Leiden mutation and prothrombin mutation [71]. Furthermore, E.C. de Haas et al. demonstrated that the plasminogen activator inhibitor-1 (PAI-1) 4G/4G genotype is linked to an increased risk of early disease relapse and decreased survival during platinum-containing chemotherapy for testicular cancer [72]. PAI-1 enhances tumor neoangiogenesis and blocks endothelial and tumor cell apoptosis, thereby promoting tumor progression [73]. A study on breast cancer revealed a relationship between tissue factor pathway inhibitor (TFPI) polymorphisms and tumor size, subtypes, and the presence of lymph node metastases. TFPI regulates the activity of tissue factor (TF), which triggers the extrinsic coagulation pathway. Oncogene-induced tumor TF expression promotes cell proliferation and invasion, angiogenesis, and metastasis. TFPI exhibits antimetastatic properties, and its upregulated expression correlates with a better prognosis in breast cancer patients. Considering the role of the hemostatic system in carcinogenesis, genetic markers of hereditary thrombophilia may serve as prognostic markers for tumor progression [74].

The role for antiphospholipid antibodies (APLAs) in interaction between immune system, hemostasis, and inflammatory reactions cannot be ignored. However, the APLAs prevalence in the general population is not fully clarified due to the lack of population-wide studies. In a prospective study with healthy subjects, 10 % of individuals had circulating APLAs, whereas 1 % had lupus anticoagulant (LA) [75]. In cancer patients, the circulation of APLAs level varies from 1.4 to 74 % [76]. It is believed that APLAs play a role in the oncological process by causing immune-mediated thrombosis in response to tumor antigens, immunotherapy, or a systemic inflammatory response [77]. During tumor growth, APLAs production increase due to excessive tumor cell proliferation and aberrant apoptosis [77]. The autoantibody production is triggered by the externalization of phosphatidylserine to cell outer membrane during apoptosis, which leads the recognition of surface epitopes consisting mainly of phospholipids and β_2-glycoprotein 1 upon removal of dying cells. Cancer patients may also develop catastrophic antiphospholipid syndrome (CAPS), which can lead to

lethal outcome due to thrombosis and multiple organ failure. Study data reveal that 16 % of patients with CAPS have cancer, mainly lymphomas and leukemia [78].

Conclusion / Заключение

Tumor cells exist in close interaction with the microenvironmental constituents, being part of the whole organism. TME plays a critical role in tumor cell existence and survival. Dynamic and reciprocal interactions between tumor cells and related environment play a crucial role in tumorigenesis, tumor progression and metastasis. The level of the current science allows not only to investigate TME composition and evaluate this crosstalk, but also in the future to develop new diagnostic tools and treatment strategies for oncological diseases by affecting tumor microenvironment.

ARTICLE INFORMATION	ИНФОРМАЦИЯ О СТАТЬЕ
Received: 30.01.2024. **Revision received:** 22.02.2024.	**Поступила:** 30.01.2024. **В доработанном виде:** 22.02.2024.
Accepted: 26.02.2024. **Published:** 28.02.2024.	**Принята к печати:** 26.02.2024. **Опубликована:** 28.02.2024.
Author's contribution	**Вклад авторов**
All authors contributed equally to the article.	Все авторы внесли 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 authors declare no funding.	Авторы заявляют об отсутствии финансовой поддержки.
Provenance and peer review	**Происхождение статьи и рецензирование**
Not commissioned; externally peer reviewed.	Журнал не заказывал статью; внешнее рецензирование.

References / Литература:

1. LeBleu V. Imaging the tumor microenvironment. *Cancer J*. 2015;21(3):174–8. https://doi.org/10.1097/PPO.0000000000000118.
2. Del Prete A., Schioppa T., Tiberio L. et al. Leukocyte trafficking in tumor microenvironment. *Curr Opin Pharmacol*. 2017;35:40–7. https://doi.org/10.1016/j.coph.2017.05.004.
3. Desai A., Small E.J. Treatment of advanced renal cell carcinoma patients with cabozantinib, an oral multityrosine kinase inhibitor of MET, AXL and VEGF receptors. *Future Oncol*. 2019;15(20):2337–48. https://doi.org/10.2217/fon-2019-0021.
4. Mantovani A., Allavena P., Sica A., Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–44. https://doi.org/10.1038/nature07205.
5. Torre L.A., Bray F., Siegel R.L. et al. Global cancer statistics, 2012. *CA Cancer J Clin*. 2015;65(2):87–108. https://doi.org/10.3322/caac.21262.
6. Hanahan D., Coussens L.M. Accessories to the crime: functions of cells recruited to the tumor microenvironment. *Cancer Cell*. 2012;21(3):309–22. https://doi.org/10.1016/j.ccr.2012.02.022.
7. Hinshaw D.C., Shevde L.A. The tumor microenvironment innately modulates cancer progression. *Cancer Res*. 2019;79(18):4557–66. https://doi.org/10.1158/0008-5472.CAN-18-3962.
8. Pottier C., Wheatherspoon A., Roncarati P. et al. The importance of the tumor microenvironment in the therapeutic management of cancer. *Expert Rev Anticancer Ther*. 2015;15(8):943–54. https://doi.org/10.1586/14737140.2015.1059279.
9. Angell H., Galon J. From the immune contexture to the Immunoscore: the role of prognostic and predictive immune markers in cancer. *Curr Opin Immunol*. 2013;25(2):261–7. https://doi.org/10.1016/j.coi.2013.03.004.
10. Wang T., Niu G., Kortylewski M. et al. Regulation of the innate and adaptive immune responses by Stat-3 signaling in tumor cells. *Nat Med*. 2004;10(1):48–54. https://doi.org/10.1038/nm976.
11. Maimela N.R., Liu S., Zhang Y. Fates of CD8+ T cells in tumor microenvironment. *Comput Struct Biotechnol J*. 2019;17:1–13. https://doi.org/10.1016/j.csbj.2018.11.004.
12. Lv L., Pan K., Li X.-d. et al. The accumulation and prognosis value of tumor infiltrating IL-17 producing cells in esophageal squamous cell carcinoma. *PloS One*. 2011;6(3):e18219. https://doi.org/10.1371/journal.pone.0018219.
13. Plitas G., Rudensky A.Y. Regulatory T cells in cancer. *Annu Rev Cancer Biol*. 2020;4(1):459–77. https://doi.org/10.1146/annurev-cancerbio-030419-033428.
14. Curiel T.J., Coukos G., Zou L. et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. *Nat Med*. 2004;10(9):942–9. https://doi.org/10.1038/nm1093.
15. Fozza C., Longinotti M. T-cell traffic jam in Hodgkin's lymphoma: pathogenetic and therapeutic implications. *Adv Hematol*. 2011;2011:501659. https://doi.org/10.1155/2011/501659.
16. Koreishi A.F., Saenz A.J., Persky D.O. et al. The role of cytotoxic and regulatory T-cells in relapsed/refractory Hodgkin lymphoma. *Appl Immunohistochem Mol Morphol*. 2010;18(3):206–11. https://doi.org/10.1097/PAI.0b013e3181c7138b.
17. Gomes A.Q., Martins D.S., Silva-Santos B. Targeting γδ T lymphocytes for cancer immunotherapy: from novel mechanistic insight to clinical application. *Cancer Res*. 2010;70(24):10024–7. https://doi.org/10.1158/0008-5472.CAN-10-3236.
18. Tanaka M., Iwakiri Y. The hepatic lymphatic vascular system: structure, function, markers, and lymphangiogenesis. *Cell Mol Gastroenterol Hepatol*. 2016;2(6):733–49. https://doi.org/10.1016/j.jcmgh.2016.09.002.
19. Milne K., Köbel M., Kalloger S.E. et al. Systematic analysis of immune infiltrates in high-grade serous ovarian cancer reveals CD20, FoxP3 and TIA-1 as positive prognostic factors. *PloS One*. 2009;4(7):e6412. https://doi.org/10.1371/journal.pone.0006412.
20. Andreu P., Johansson M., Affara N.I. et al. FcRγ activation regulates inflammation-associated squamous carcinogenesis. *Cancer Cell*. 2010;17(2):121–34. https://doi.org/10.1016/j.ccr.2009.12.019.
21. Mauri C., Bosma A. Immune regulatory function of B cells. *Annu Rev Immunol*. 2012;30:221–41. https://doi.org/10.1146/annurev-immunol-020711-074934.
22. Horikawa M., Minard-Colin V., Matsushita T., Tedder T. F. Regulatory B cell production of IL-10 inhibits lymphoma depletion during CD20 immunotherapy in mice. *J Clin Invest*. 2011;121(11):4268–80. https://doi.org/10.1172/JCI59266.
23. Sharonov G.V., Serebrovskaya E.O., Yuzhakova D.V. et al. B cells, plasma cells and antibody repertoires in the tumour microenvironment. *Nat Rev*

Immunol. 2020;20(5):294–307. https://doi.org/10.1038/s41577-019-0257-x.
24. Marcus A., Gowen B. G., Thompson T.W. et al. Recognition of tumors by the innate immune system and natural killer cells. *Adv Immunol*. 2014;122:91–128. https://doi.org/10.1016/B978-0-12-800267-4.00003-1.
25. Qian B.-Z., Pollard J.W. Macrophage diversity enhances tumor progression and metastasis. *Cell*. 2010;141(1):39–51. https://doi.org/10.1016/j.cell.2010.03.014.
26. Condeelis J., Pollard J.W. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. *Cell*. 2006;124(2):263–6. https://doi.org/10.1016/j.cell.2006.01.007.
27. Wang S.-C., Hong J.-H., Hsueh C., Chiang C.-S. Tumor-secreted SDF-1 promotes glioma invasiveness and TAM tropism toward hypoxia in a murine astrocytoma model. *Lab Invest*. 2012;92(1):151–62. https://doi.org/10.1038/labinvest.2011.128.
28. Franklin R.A., Liao W., Sarkar A. et al. The cellular and molecular origin of tumor-associated macrophages. *Science*. 2014;344(6186):921–5. https://doi.org/10.1126/science.1252510.
29. Gabrilovich D.I., Ostrand-Rosenberg S., Bronte V. Coordinated regulation of myeloid cells by tumours. *Nat Rev Immunol*. 2012;12(4):253–68. https://doi.org/10.1038/nri3175.
30. Meredith M.M., Liu K., Darrasse-Jeze G. et al. Expression of the zinc finger transcription factor zDC (Zbtb46, Btbd4) defines the classical dendritic cell lineage. *J Exp Med*. 2012;209(6):1153–65. https://doi.org/10.1084/jem.20112675.
31. Nozawa H., Chiu C., Hanahan D. Infiltrating neutrophils mediate the initial angiogenic switch in a mouse model of multistage carcinogenesis. *Proc Natl Acad Sci U S A*. 2006;103(33):12493–8. https://doi.org/10.1073/pnas.0601807103.
32. Youn J.-I., Gabrilovich D.I. The biology of myeloid-derived suppressor cells: the blessing and the curse of morphological and functional heterogeneity. *Eur J Immunol*. 2010;40(11):2969–75. https://doi.org/10.1002/eji.201040895.
33. Erler J.T., Bennewith K.L., Cox T.R. et al. Hypoxia-induced lysyl oxidase is a critical mediator of bone marrow cell recruitment to form the premetastatic niche. *Cancer Cell*. 2009;15(1):35–44. https://doi.org/10.1016/j.ccr.2008.11.012.
34. Granot Z., Henke E., Comen E.A. et al. Tumor entrained neutrophils inhibit seeding in the premetastatic lung. *Cancer Cell*. 2011;20(3):300–14. https://doi.org/10.1016/j.ccr.2011.08.012.
35. Walker C., Mojares E., del Río Hernández A. Role of extracellular matrix in development and cancer progression. *Int J Mol Sci*. 2018;19(10):3028. https://doi.org/10.3390/ijms19103028.
36. Nieman K.M., Kenny H.A., Penicka C.V. et al. Adipocytes promote ovarian cancer metastasis and provide energy for rapid tumor growth. *Nat Med*. 2011;17(11):1498–503. https://doi.org/10.1038/nm.2492.
37. Alitalo K. The lymphatic vasculature in disease. *Nat Med*. 2011;17(11):1371–80. https://doi.org/10.1038/nm.2545.
38. Swartz M.A., Lund A.W. Lymphatic and interstitial flow in the tumour microenvironment: linking mechanobiology with immunity. *Nat Rev Cancer*. 2012;12(3):210–9. https://doi.org/10.1038/nrc3186.
39. Erez N., Truitt M., Olson P. et al. Cancer-associated fibroblasts are activated in incipient neoplasia to orchestrate tumor-promoting inflammation in an NF-κB-dependent manner. *Cancer Cell*. 2010;17(2):135–47. https://doi.org/10.1016/j.ccr.2009.12.041.
40. Xing F., Saidou J., Watabe K. Cancer associated fibroblasts (CAFs) in tumor microenvironment. *Front Biosci*. 2010;15(1):166–79. https://doi.org/10.2741/3613.
41. Korneev K.V., Atretkhany K.-S. N., Drutskaya M. S. et al. TLR-signaling and proinflammatory cytokines as drivers of tumorigenesis. *Cytokine*. 2017;89:127–35. https://doi.org/10.1016/j.cyto.2016.01.021.
42. Shiga K., Hara M., Nagasaki T. et al. Cancer-associated fibroblasts: their characteristics and their roles in tumor growth. *Cancers*. 2015;7(4):2443–58. https://doi.org/10.3390/cancers7040902.
43. Li B., Wang J. H.-C. Fibroblasts and myofibroblasts in wound healing: force generation and measurement. *J Tissue Viability*. 2011;20(4):108–20. https://doi.org/10.1016/j.jtv.2009.11.004.
44. Kraman M., Bambrough P.J., Arnold J.N. et al. Suppression of antitumor immunity by stromal cells expressing fibroblast activation protein-α. *Science*. 2010;330(6005):827–30. https://doi.org/10.1126/science.1195300.
45. Armulik A., Genové G., Betsholtz C. Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. *Dev Cell*. 2011;21(2):193–215. https://doi.org/10.1016/j.devcel.2011.07.001.
46. Cooke V.G., LeBleu V.S., Keskin D.N et al. Pericyte depletion results in hypoxia-associated epithelial-to-mesenchymal transition and metastasis mediated by met signaling pathway. *Cancer Cell*. 2012;21(1):66–81. https://doi.org/10.1016/j.ccr.2011.11.024.
47. Turley S.J., Cremasco V., Astarita J.L. Immunological hallmarks of stromal cells in the tumour microenvironment. *Nat Rev Immunol*. 2015;15(11):669–82. https://doi.org/10.1038/nri3902.
48. McAndrews K.M., McGrail D.J., Ravikumar N., Dawson M.R. Mesenchymal stem cells induce directional migration of invasive breast cancer cells through TGF-β. *Sci Rep*. 2015;5(1):16941. https://doi.org/10.1038/srep16941.
49. Lam P.Y. Biological effects of cancer-secreted factors on human mesenchymal stem cells. *Stem Cell Res Ther*. 2013;4(6):138. https://doi.org/10.1186/scrt349.
50. Hu Y., Li D., Wu A. et al. TWEAK-stimulated macrophages inhibit metastasis of epithelial ovarian cancer via exosomal shuttling of microRNA. *Cancer Lett*. 2017;393:60–7. https://doi.org/10.1016/j.canlet.2017.02.009.
51. Farnie G., Sotgia F., Lisanti M.P. High mitochondrial mass identifies a sub-population of stem-like cancer cells that are chemo-resistant. *Oncotarget*. 2015;6(31):30472–86. https://doi.org/10.18632/oncotarget.5401.
52. Feig C., Jones J.O., Kraman M. et al. Targeting CXCL12 from FAP-expressing carcinoma-associated fibroblasts synergizes with anti-PD-L1 immunotherapy in pancreatic cancer. *Proc Natl Acad Sci U S A*. 2013;110(50):20212–7. https://doi.org/10.1073/pnas.1320318110.
53. Henke E., Nandigama R., Ergün S. Extracellular matrix in the tumor microenvironment and its impact on cancer therapy. *Front Mol Biosci*. 2020;6:160. https://doi.org/10.3389/fmolb.2019.00160.
54. Vaupel P., Mayer A. Hypoxia in tumors: pathogenesis-related classification, characterization of hypoxia subtypes, and associated biological and clinical implications. *Adv Exp Med Biol*. 2014;812:19–24. https://doi.org/10.1007/978-1-4939-0620-8_3.
55. Elinav E., Garrett W.S., Trinchieri G., Wargo J. The cancer microbiome. *Nat Rev Cancer*. 2019;19(7):371–6. https://doi.org/10.1038/s41568-019-0155-3.
56. Hofer H.R., Tuan R.S. Secreted trophic factors of mesenchymal stem cells support neurovascular and musculoskeletal therapies. *Stem Cell Res Ther*. 2016;7(1):131. https://doi.org/10.1186/s13287-016-0394-0.
57. Altman J.B., Benavides A.D., Das R., Bassiri H. Antitumor responses of invariant natural killer T cells. *J Immunol Res*. 2015;2015:652875. https://doi.org/10.1155/2015/652875.
58. Keely P.J. Mechanisms by which the extracellular matrix and integrin signaling act to regulate the switch between tumor suppression and tumor promotion. *J Mammary Gland Biol Neoplasia*. 2011;16(3):205–19. https://doi.org/10.1007/s10911-011-9226-0.
59. Guan J., Chen J. Mesenchymal stem cells in the tumor microenvironment. *Biomed Rep*. 2013;1(4):517–21. https://doi.org/10.3892/br.2013.103.
60. Metzler K.D., Fuchs T.A., Nauseef W.M. et al. Myeloperoxidase is required for neutrophil extracellular trap formation: implications for innate immunity. *Blood*. 2011;117(3):953–9. https://doi.org/10.1182/blood-2010-06-290171.
61. Acuff H.B., Carter K.J., Fingleton B. et al. Matrix metalloproteinase-9 from bone marrow-derived cells contributes to survival but not growth of tumor cells in the lung microenvironment. *Cancer Res*. 2006;66(1):259–66. https://doi.org/10.1158/0008-5472.CAN-05-2502.
62. Pahler J.C., Tazzyman S., Erez N. et al. Plasticity in tumor-promoting inflammation: impairment of macrophage recruitment evokes a compensatory neutrophil response. *Neoplasia*. 2008;10(4):329–40. https://doi.org/10.1593/neo.07871.

63. Cools-Lartigue J., Spicer J., McDonald B. et al. Neutrophil extracellular traps sequester circulating tumor cells and promote metastasis. *J Clin Invest*. 2013;123(8):3446–58. https://doi.org/10.1172/JCI67484.
64. Romson J.L., Hook B., Rigot V. et al. The effect of ibuprofen on accumulation of indium-111-labeled platelets and leukocytes in experimental myocardial infarction. *Circulation*. 1982;66(5):1002–11. https://doi.org/10.1161/01.cir.66.5.1002.
65. Goh C.Y., Patmore S., Smolenski A. et al. The role of von Willebrand factor in breast cancer metastasis. *Transl Oncol*. 2021;14(4):101033. https://doi.org/10.1016/j.tranon.2021.101033.
66. Price L.C., Wort S.J. Earlier diagnosis and international registries may improve outcomes in pulmonary tumour thrombotic microangiopathy. *Eur Respir J*. 2016;47(2):690–1. https://doi.org/10.1183/13993003.01736-2015.
67. Farge D., Bounameaux H., Brenner B. et al. International clinical practice guidelines including guidance for direct oral anticoagulants in the treatment and prophylaxis of venous thromboembolism in patients with cancer. *Lancet Oncol*. 2016;17(10):e452–e466. https://doi.org/10.1016/S1470-2045(16)30369-2.
68. Tinholt M., Viken M.K., Dahm A.E. et al. Increased coagulation activity and genetic polymorphisms in the F5, F10 and EPCR genes are associated with breast cancer: a case-control study. *BMC Cancer*. 2014;14:845. https://doi.org/10.1186/1471-2407-14-845.
69. Pihusch R., Danzl G., Scholz M. et al. Impact of thrombophilic gene mutations on thrombosis risk in patients with gastrointestinal carcinoma. *Cancer*. 2002;94(12):3120–6. https://doi.org/10.1002/cncr.10590.
70. Tavares V., Pinto R., Assis J. et al. Dataset of GWAS-identified variants underlying venous thromboembolism susceptibility and linkage to cancer aggressiveness. *Data Brief*. 2020;30:105399. https://doi.org/10.1016/j.dib.2020.105399.
71. Vossen C.Y., Hoffmeister M., Chang-Claude J.C. et al. Clotting factor gene polymorphisms and colorectal cancer risk. *J Clin Oncol*. 2011;29(13):1722–7. https://doi.org/10.1200/JCO.2010.31.8873.
72. de Haas E.C., Zwart N., Meijer C. et al. Association of PAI-1 gene polymorphism with survival and chemotherapy-related vascular toxicity in testicular cancer. *Cancer*. 2010;116(24):5628–36. https://doi.org/10.1002/cncr.25300.
73. Duffy M.J., McGowan P.M., Harbeck N. et al. uPA and PAI-1 as biomarkers in breast cancer: validated for clinical use in level-of-evidence-1 studies. *Breast Cancer Res*. 2014;16(4):428. https://doi.org/10.1186/s13058-014-0428-4.
74. Tavares V., Pinto R., Assis J. et al. Venous thromboembolism GWAS reported genetic makeup and the hallmarks of cancer: Linkage to ovarian tumour behaviour. *Biochim Biophys Acta Rev Cancer*. 2020;1873(1):188331. https://doi.org/10.1016/j.bbcan.2019.188331.
75. Vila P., Hernandez M., Lopez-Fernandez M., Batlle J. Prevalence, follow-up and clinical significance of the anticardiolipin antibodies in normal subjects. *Thromb Haemost*. 1994;72(8):209–13.
76. Vassalo J., Spector N., de Meis E. et al. Antiphospholipid antibodies in critically ill patients with cancer: a prospective cohort study. *J Crit Care*. 2014;29(4):533–8. https://doi.org/10.1016/j.jcrc.2014.02.005.
77. Abdel-Wahab N., Tayar J.H., Fa'ak F. et al.. Systematic review of observational studies reporting antiphospholipid antibodies in patients with solid tumors. *Blood Adv*. 2020;4(8):1746–55. https://doi.org/10.1182/bloodadvances.2020001557.
78. Cervera R., Rodríguez-Pintó I., Colafrancesco S. et al. 14th international congress on antiphospholipid antibodies task force report on catastrophic antiphospholipid syndrome. *Autoimmun Rev*. 2014;13(7):699–707. https://doi.org/10.1016/j.autrev.2014.03.002.

About the authors:

Victoria O. Bitsadze – MD, Dr Sci Med, Professor of RAS, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, 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.

Ekaterina V. Slukhanchuk – MD, PhD, Associate Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow Russia. E-mail: ekaterina@ginekologhirurg.ru. ORCID: https://orcid.org/0000-0001-7441-2778. Scopus Author ID: 57217824907. WOS Researcher ID: AAW-3812-2021.

Antonina G. Solopova – MD, Dr Sci Med, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, 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.

Jamilya Kh. Khizroeva – MD, Dr Sci Med, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, 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.

Fidan E. Yakubova – MD, Clinical Resident, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-8882-1588.

Esmira A. Orudzhova – MD, Head of Antenatal Outpatient Care Center, Maternity Hospital No. 1 – Branch of Vorokhobov City Clinical Hospital No. 67, Moscow, Russia.

Natalia D. Degtyareva – Student, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002- 8100-0189.

Elena S. Egorova – MD, PhD, Associate Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-4556-5449. Scopus Author ID: 5720982859.

Nataliya A. Makatsariya – MD, PhD, Associate Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0002-2541-3843. Researcher ID: F-8406-2017.

Natalia V. Samburova – MD, PhD, Associate Professor, Department of Pathophysiology, Institute of Biodesign and Modeling of Complex Systems, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0000-4564-8439. Scopus Author ID: 57208129705.

Vladimir N. Serov – MD, Dr Sci Med, Professor, Academician of RAS, Chief Researcher, Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia; President of the Russian Society of Obstetricians and Gynecologists, Moscow, Russia. ORCID: https://orcid.org/0000-0003-2976-7128.

Lev A. Ashrafyan – MD, Dr Sci Med, Professor, Academician of RAS, Honored Doctor of the Russian Federation, Director of the Institute of Oncogynecology and Mammology, Deputy Director of Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia. ORCID: https://orcid.org/0000-0001-6396-4948. Scopus Author ID: 57194173388.

Zamilya D. Aslanova – MD, Postgraduate Student, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0003-1070-7336.

Arina V. Lazarchuk – Student, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0000-0003-2136-1641.

Ekaterina S. Kudryavtseva – Student, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia. ORCID: https://orcid.org/0009-0004-6250-325X.

Alina E. Solopova – MD, Dr Sci Med, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Leading Researcher, Department of Radiation Diagnostics, Kulakov National Medical Research Center for Obstetrics, Gynecology and Perinatology, Moscow, Russia. ORCID: https://orcid.org/0000-0003-4768-115X. Scopus Author ID: 24460923200. Researcher ID: P-8659-2015.

Daredzhan L. Kapanadze – MD, PhD, Director, Center of Pathology of Pregnancy and Hemostasis, Tbilisi, Georgia.
Jean-Christophe Gris – MD, Dr Sci Med, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, 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; Foreign Member of RAS, Moscow, Russia. ORCID: https://orcid.org/0000-0002-9899-9910. Scopus Author ID: 7005114260. Researcher ID: AAA-2923-2019.
Ismail Elalamy – MD, Dr Sci Med, Professor, Department of Obstetrics, Gynecology and Perinatal Medicine, 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.
Cihan Ay – MD, PhD, Professor, Clinical Unit of Hematology and Hemostasiology, Department of Medicine I, University of Vienna, Vienna, Austria. ORCID: https://orcid.org/0000-0003-2607-971. Scopus Author ID: 55356863800.
Alexander D. Makatsariya – MD, Dr Sci Med, Academician of RAS, Professor, Head of the Department of Obstetrics, Gynecology and Perinatal Medicine, Filatov Clinical Institute of Children's Health, Sechenov University, Moscow, Russia; Vice-President of the Russian Society of Obstetricians and Gynecologists (RSOG); Honorary Doctor of the Russian Federation; Emeritus Professor of the University of Vienna. ORCID: https://orcid.org/0000-0001-7415-4633.

Сведения об авторах:
Бицадзе Виктория Омаровна – д.м.н., профессор РАН, профессор кафедры акушерства, гинекологии и перинатальной медицины 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.
Слуханчук Екатерина Викторовна – к.м.н., доцент кафедры акушерства, гинекологии и перинатальной медицины 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. E-mail: ekaterina@ginekologhirurg.ru. ORCID: https://orcid.org/0000-0001-7441-2778. Scopus Author ID: 57217824907. WOS Researcher ID: AAW-3812-2021.
Солопова Антонина Григорьевна – д.м.н., профессор кафедры акушерства, гинекологии и перинатальной медицины 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.
Хизроева Джамиля Хизриевна – д.м.н., профессор кафедры акушерства, гинекологии и перинатальной медицины 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.
Якубова Фидан Эльчин кызы – клинический ординатор кафедры акушерства, гинекологии и перинатальной медицины 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/0000-0002-8882-1588.
Оруджова Эсмира Афлатуновна – зав. центром амбулаторной медицинской помощи женской консультации, Родильный дом № 1 – филиал ГБУЗ «Городская клиническая больница № 67 имени Л.А. Ворохобова Департамента здравоохранения города Москвы», Москва, Россия.
Дегтярева Наталья Дмитриевна – студент 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/0000-0002-8100-0189.
Егорова Елена Сергеевна – к.м.н., доцент кафедры акушерства, гинекологии и перинатальной медицины 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/0000-0002-4556-5449. Scopus Author ID: 5720982859.
Макацария Наталия Александровна – к.м.н., доцент кафедры акушерства, гинекологии и перинатальной медицины 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/0000-0002-2541-3843. Researcher ID: F-8406-2017.
Самбурова Наталья Викторовна – к.м.н., доцент кафедры патофизиологии Института цифрового биодизайна и моделирования живых систем ФГАОУ ВО Первый Московский государственный медицинский университет имени И.М. Сеченова Министерства здравоохранения Российской Федерации (Сеченовский Университет), Москва, Россия. ORCID: https://orcid.org/0000-0000-4564-8439. Scopus Author ID: 57208129705.
Владимир Николаевич Серов – д.м.н., профессор, академик РАН, главный научный сотрудник ФГБУ «Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени академика В.И. Кулакова» Министерства здравоохранения Российской Федерации, Москва, Россия; президент Российского общества акушеров-гинекологов, Москва, Россия. ORCID: https://orcid.org/0000-0003-2976-7128.
Ашрафян Лев Андреевич – д.м.н., профессор, академик РАН, заслуженный врач Российской Федерации, директор Института онкогинекологии и маммологии, зам. директора ФГБУ «Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени академика В.И. Кулакова» Министерства здравоохранения Российской Федерации, Москва, Россия. ORCID: https://orcid.org/0000-0001-6396-4948. Scopus Author ID: 57194173388.
Асланова Замиля Джамалидиновна – аспирант кафедры акушерства, гинекологии и перинатальной медицины 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/0000-0003-1070-7336.
Лазарчук Арина Владимировна – студент 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/0000-0003-2136-1641.
Кудрявцева Екатерина Сергеевна – студент 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/0009-0004-6250-325X.
Солопова Алина Евгеньевна – д.м.н., профессор кафедры акушерства, гинекологии и перинатальной медицины 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; ведущий научный сотрудник отдела лучевой диагностики ФГБУ «Национальный медицинский исследовательский центр акушерства, гинекологии и перинатологии имени академика В.И. Кулакова» Министерства здравоохранения Российской Федерации, Москва, Россия. ORCID: https://orcid.org/0000-0003-4768-115X. Scopus Author ID: 24460923200. Researcher ID: P-8659-2015.

Капанадзе Дареджан Левановна – к.м.н., директор Центра патологии беременности и гемостаза, Тбилиси, Грузия.
Гри Жан-Кристоф – д.м.н., профессор кафедры акушерства, гинекологии и перинатальной медицины 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; иностранный член РАН, Москва, Россия. ORCID: https://orcid.org/0000-0002-9899-9910. Scopus Author ID: 7005114260. Researcher ID: AAA-2923-2019.
Элалами Исмаил – д.м.н., профессор кафедры акушерства, гинекологии и перинатальной медицины 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.
Ай Джихан – д.м.н., профессор, клиническое подразделение гематологии и гемостазиологии, медицинское отделение I, Венский университет, Вена, Австрия. ORCID: https://orcid.org/0000-0003-2607-971. ScopusAuthor ID: 55356863800.
Макацария Александр Давидович – д.м.н., профессор, академик РАН, зав. кафедрой акушерства, гинекологии и перинатальной медицины 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; вице-президент Российского общества акушеров-гинекологов (РОАГ); Заслуженный врач Российской Федерации; Почетный профессор Венского Университета. ORCID: https://orcid.org/0000-0001-7415-4633. Scopus Author ID: 57222220144. Researcher ID: M-5660-2016.

2024 • Vol. 18 • № 1
Obstetrics, Gynecology and Reproduction