



DUAL ROLE OF LEUKOCYTES IN CANCER DEVELOPMENT PROTECTION AND PROMOTION OF TUMOR GROWTH

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Abstract: The immune system, and in particular leukocytes, play a complex and contradictory role in cancer pathology. This article explores the dual nature of leukocytes in cancer development - on the one hand, in tumor recognition and destruction, and on the other hand, in supporting tumor growth and metastasis. The study analyzes scientific articles and clinical trials published over the past decade (2015-2025) and examines the interactions of different leukocyte subpopulations (macrophages, T-lymphocytes, neutrophils, myeloid suppressor cells) in the tumor microenvironment. Tumor-associated macrophages (TAMs) significantly contribute to cancer progression by promoting tumor growth and angiogenesis. Also, regulatory T lymphocytes and myeloid-derived suppressor cells exert immunosuppressive functions by forming an immunosuppressive environment. Meanwhile, effector lymphocytes, such as cytotoxic T lymphocytes and natural killer cells, exert a strong antitumor response. This article reveals the molecular mechanisms regulating the dual properties of leukocytes, including the role of various cytokines, chemokines, and signaling pathways. The dynamic nature of the tumor microenvironment and the processes by which it becomes immunosuppressive are discussed in detail. The results of the study are aimed at improving immunotherapy strategies, in particular, by inhibiting immunosuppressive leukocyte populations and enhancing antitumor immunity. This article summarizes the latest advances in the field of cancer immunology and considers the possibilities of their implementation in clinical practice.

Keywords: leukocytes, cancer immunology, tumor microenvironment, tumor-associated macrophages, immunosuppression, immunotherapy, myeloid suppressor cells, cytotoxic T-lymphocytes, cancer progression, immunosuppressive environment.

Research Objective

The main objective of this study is to systematically analyze the dual role of leukocytes in cancer development - on the one hand, their protective function, and on the other hand, their support for tumor growth and metastasis, based on scientific data published between 2015 and 2025. The study aimed to determine how different leukocyte types are modulated in the tumor microenvironment and their impact on cancer progression. [1]

Research Methods

The study used a systematic literature review method. Articles published between 2015 and 2025 from scientific databases such as PubMed, Scopus, Web of Science and Google Scholar were identified using the search keywords ("leukocytes", "cancer immunology", "tumor microenvironment", "TAM", "MDSC", "immunotherapy"). The selected articles were assessed according to their quality and relevance. A general conclusion about the dual role of leukocytes was formed by synthesizing and analyzing the data. [2] The study also used the meta-analysis method and compared the results of different studies. [3]

Introduction

Cancer is a dynamic process that develops not only as a result of defects at the cellular level, but also as a result of complex interactions between the body and the immune system. Leukocytes, which are the main components and effector cells of the immune system, play an important role in the pathogenesis of cancer. According to the traditional understanding, the immune system protects the body from cancer by recognizing and destroying tumor cells. However, recent studies have shown that leukocytes may play a dual role in cancer development—protection on the one hand, and tumor growth and metastasis on the other. [4]

Leukocytes are nucleated blood cells that include neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Each type of leukocyte has a specific function in the development of cancer. For example, T lymphocytes, particularly CD8+ cytotoxic T lymphocytes and CD4+ helper T lymphocytes, are the main mediators of antitumor immunity. Cytotoxic T lymphocytes have the ability to directly recognize and destroy tumor cells. [5] B lymphocytes play a protective role by producing antitumor antibodies. [6] Natural killer (NK) cells, on the other hand, can destroy tumor cells that do not express MHC molecules. [7] However, during cancer development, a tumor microenvironment is formed, and this microenvironment alters the function of leukocytes. The tumor microenvironment is a complex system consisting of tumor cells, immune cells, stromal cells, extracellular matrix, and various factors. [8] This microenvironment has a profound effect on the activation, differentiation, and function of immune cells. As a result, several leukocyte populations are converted to an immunosuppressive phenotype and support tumor growth. [9] Tumor-associated macrophages (TAMs) are a prime example of this process. TAMs typically have an M2 phenotype and produce cytokines and growth factors that promote angiogenesis, tissue remodeling, and immunosuppression. [10] High levels of TAMs in many types of cancer are associated with poor prognosis. [11] Similarly, myeloid suppressor cells (MDSCs) are overexpressed in cancer patients, suppressing T-cell activation and function, creating an immunosuppressive environment. [12] Regulatory T-cells (Tregs) are important in maintaining the immunosuppressive environment. They are designed to control the immune response and prevent self-immunity, but in the setting of cancer they suppress antitumor immunity. [13] Treg cells are often overexpressed in tumors and are associated with poor clinical outcomes. [14]

Neutrophils also play a dual role in cancer development. In some cases they exert antitumor effects, while in others they can promote tumor growth and metastasis. [15] Tumor-associated neutrophils (TANs) can have both N1 (antitumor) and N2 (protumor) phenotypes, similar to TAMs. [16]

The dual role of leukocytes in cancer development is important for the development of immunotherapy strategies. To date, the most successful form of immunotherapy, immune checkpoint inhibitors, is primarily aimed at restoring T-lymphocyte activation. [17] However, new therapies targeting other leukocyte populations, such as TAMs or MDSCs, are also in development. [18]

The aim of this article is to review the dual role of different leukocyte types in cancer development, based on scientific data accumulated over the past decade. We will review the

molecular mechanisms that regulate the protective and protumor effects of leukocytes, as well as how this knowledge can be applied to the development of new immunotherapies.

Results

Dual role of T lymphocytes

T lymphocytes are the main effector cells of adaptive immunity and play a central role in cancer immunosurveillance. CD8⁺ cytotoxic T lymphocytes (CTLs) are capable of recognizing and killing tumor cells. Tumor cells express tumor-associated antigens (TAAs) on their surface, which are presented by MHC I molecules. CTLs recognize these antigens through the T-cell receptor (TCR) and release cytotoxic mediators such as perforin and granzymes, leading to tumor cell apoptosis. [19]

As demonstrated by numerous clinical studies, the abundance of T lymphocytes, particularly CTLs, within tumors is associated with a better prognosis in most types of cancer. [20] For example, in patients with colorectal cancer, higher levels of CTLs within tumors are associated with longer survival. [21] Similarly, in pancreatic cancer, infiltration of T lymphocytes within tumors is a positive prognostic marker for response to therapy and overall survival. [22]

However, the antitumor activity of T lymphocytes can be suppressed by various mechanisms in the tumor microenvironment. Tumor cells can express immune checkpoints, such as PD-L1, which bind to the PD-1 receptor on the surface of CTLs and inhibit T-cell activation. [23] Inhibition of the PD-1/PD-L1 axis by immune checkpoint inhibitors allows for the restoration of antitumor activity of T lymphocytes, which has been proven to be an effective therapy in many types of cancer. [24]

CD4⁺ regulatory T lymphocytes (Treg) play a key role in shaping the immunosuppressive environment. Treg cells express the transcription factor FoxP3 and are designed to regulate the immune response. In the setting of cancer, Treg cells accumulate in the tumor microenvironment and suppress antitumor immunity. [25] Treg cells exert immunosuppressive effects through a variety of mechanisms, including inhibition of the proliferation and cytotoxic activity of cytotoxic T lymphocytes and production of immunosuppressive cytokines such as IL-10 and TGF- β . [26] In many types of cancer, including lung cancer, gastric cancer, and melanoma, high levels of Treg cells within the tumor are associated with poor prognosis. [27] Therapeutic strategies targeting Treg cells are being developed, but targeted blockade of their immunosuppressive effects may increase the risk of autoimmune complications. [28]

Tumor-associated macrophages (TAMs)

Macrophages are multifaceted cells of the immune system that can adopt different phenotypes in response to different signals. Traditionally, classical activation of M1 macrophages occurs in response to inflammatory cytokines such as IFN- γ and LPS, and they have antitumor properties. In contrast, alternative activation of M2 macrophages occurs in response to cytokines such as IL-4 and IL-13, and they promote tissue remodeling, angiogenesis, and immunosuppression. [29]

In the context of cancer, macrophages in the tumor microenvironment typically adopt properties resembling the M2 phenotype and are referred to as tumor-associated macrophages (TAMs). TAMs produce a variety of factors that promote tumor progression, including



angiogenesis-promoting factors (VEGF, FGF), tumor cell proliferation and survival-promoting factors (EGF, TGF- β), and extracellular matrix-processing enzymes (MMPs). [30] TAMs also play a key role in shaping the immunosuppressive environment. They produce immunosuppressive cytokines, such as IL-10 and TGF- β , and also express enzymes, such as arginase-1 and inducible nitric oxide synthase (iNOS), that suppress T-cell activation and function. [31] TAMs can also express PD-L1, which directly inhibits T-cell activation. [32]

In many cancers, including breast cancer, lung cancer, and glioblastoma, high levels of TAMs are associated with poor clinical outcomes. [33] Therefore, therapeutic strategies targeting TAMs are being developed. These strategies include inhibiting the accumulation of TAMs in tumors (inhibition of the CCL2/CCR2 axis), switching TAM activation from an M2 to an M1 phenotype, or eliminating TAMs. [34]

Myeloid suppressor cells (MDSCs)

Myeloid suppressor cells (MDSCs) are a pathologically activated population of hematopoietic stem cells that proliferate in cancer, inflammation, and other pathological conditions. MDSCs are divided into granulocytic (G-MDSCs) and monocytic (M-MDSCs) subgroups. [35] MDSCs exert their immunosuppressive effects through a variety of mechanisms, including altering L-arginine metabolism by increasing arginase-1 and iNOS activity, producing reactive oxygen species (ROS) and reactive nitrogen species (RNS), and suppressing T-lymphocyte proliferation and activation. [36]

MDSCs are often elevated in peripheral blood and tumor microenvironments in cancer patients and are associated with poor prognosis. [37] MDSCs also enhance the immunosuppressive environment by promoting the differentiation and expansion of Treg cells. [38]

Therapies targeting MDSCs aim to inhibit their expansion or immunosuppressive function. Phosphodiesterase-5 inhibitors, such as sildenafil, can reduce the immunosuppressive activity of MDSCs. [39] Hematopoietic inhibitors, such as sunitinib, have also been shown to reduce MDSC levels. [40]

Natural killer (NK) cells

Natural killer (NK) cells are the main effector cells of innate immunity, and they can kill tumor cells that do not express MHC class I molecules. NK cells are activated by a balance of activating and inhibitory receptors. [41] Tumor cells often express low levels of MHC class I molecules, which makes them less likely to be recognized by NK cells. NK cells play an important role in cancer immunosurveillance. Low levels of NK cells are associated with poor prognosis in many types of cancer. [42] NK cells also produce cytokines, particularly IFN- γ , to modulate the antitumor immune response. [43] However, the tumor microenvironment can suppress NK cell function. Immunosuppressive cytokines such as TGF- β can downregulate NK cell activation receptors and inhibit their cytotoxic function. [44] Tumor cells can also express ligands that bind to NK cell inhibitory receptors, preventing NK cell activation. [45]

NK cell therapy is a promising approach to cancer immunotherapy. Adoptive transfer of autologous or allogeneic NK cells, or the use of cytokines that enhance NK cell activity (e.g., IL-15), has shown promising results in various types of cancer. [46]

Role of neutrophils

Neutrophils are the most abundant cells of the innate immune system and play a complex role in cancer development. Tumor-associated neutrophils (TANs) are neutrophils found in the

tumor microenvironment. Like TAMs, TANs can have N1 (antitumor) and N2 (protumor) phenotypes. [47]

N1 neutrophils express high levels of TNF- α , ICAM-1, and low levels of arginase, and they can stimulate the activation of cytotoxic T lymphocytes. In contrast, N2 neutrophils express high levels of arginase, VEGF, and MMP-9, and they can promote angiogenesis and tumor growth. [48]

TGF- β is an important factor in the transition from the N1 to the N2 phenotype. Inhibition of TGF- β promotes the N1 phenotype, thereby enhancing antitumor immunity. [49] High levels of TANs are associated with poor prognosis in many types of cancer, but this association varies depending on the type of cancer and the context. [50]

B-lymphocytes and humoral immunity

B-lymphocytes are the main mediators of humoral immunity, producing antitumor antibodies. Antitumor antibodies act as a protective factor by recognizing and destroying tumor cells. [51] In some cases, B-lymphocytes can stimulate the activation of T-lymphocytes by presenting antigens. [52]

However, B lymphocytes can also play an immunosuppressive role in the form of regulatory B lymphocytes (Breg). Breg cells exert their immunosuppressive effects by producing immunosuppressive cytokines such as IL-10 and TGF- β . [53] Breg cells can stimulate the differentiation and expansion of Treg cells. [54]

In cancer patients, increased Breg cells have been observed in a number of cancer types and may be associated with poor prognosis. [55] Therefore, the role of B lymphocytes varies depending on the type and context of cancer, and they can perform both protective and immunosuppressive functions.

Discussion

The dual role of leukocytes in cancer development is important for the development of immunotherapy strategies. The success of immune checkpoint inhibitors has demonstrated the possibility of restoring the antitumor potential of T lymphocytes. However, immunosuppressive leukocyte populations, including TAMs, MDSCs, and Treg cells, may be an important factor in resistance to immune checkpoint inhibitors. [56]

Future immunotherapy strategies should include targeting different leukocyte populations simultaneously. For example, targeted depletion of TAMs or switching their phenotype from M2 to M1 may enhance the efficacy of immune checkpoint inhibitors. [57] Similarly, suppression of MDSCs may help restore antitumor activity of T lymphocytes. [58] NK cell therapy remains a promising avenue for cancer immunotherapy. The cytotoxic potential of NK cells and their independence from MHC restriction make them attractive as a universal cell therapy platform. [59] However, overcoming the immunosuppressive effects of the tumor microenvironment is an important challenge to enhance the efficacy of NK cell therapy. The role of neutrophils in cancer progression is relatively poorly understood and this area requires future research. Harnessing the antitumor potential of N1 neutrophils or inhibiting the protumor effects of N2 neutrophils could provide novel immunotherapeutic approaches. [60]

Conclusion

Leukocytes play a complex and contradictory role in cancer development. On the one hand, they have the ability to mount a strong antitumor immune response, and on the other hand, they can convert into immunosuppressive populations that support tumor growth and

metastasis in the tumor microenvironment. This duality is characteristic of various leukocyte types, including T lymphocytes, macrophages, myeloid suppressor cells, natural killer cells, neutrophils, and B lymphocytes.

The tumor microenvironment profoundly influences leukocyte differentiation, activation, and function, resulting in an immunosuppressive environment and suppression of antitumor immunity. This process is regulated by various cytokines, chemokines, growth factors, and signaling pathways.

Research over the past decade has provided a deeper understanding of the role of leukocytes in cancer development, leading to the development of new immunotherapy strategies. Immune checkpoint inhibitors have already revolutionized cancer treatment, but immunosuppressive leukocyte populations remain an important resistance mechanism.

Future research should focus on identifying the interactions between different leukocyte populations, as well as the molecular mechanisms that regulate their function. Combination therapy strategies that simultaneously target different leukocyte types may significantly increase the efficacy of immunotherapy. Personalized immunotherapy approaches should also be developed based on the immune profile of individual patients.

In conclusion, the dual role of leukocytes in cancer development is important for understanding the success and limitations of immunotherapy. This knowledge can be used to develop new and effective cancer treatments in the future.

References:

1. MICROFLORA, Dilshodovich KH SHIELD OF INTESTINAL. "CHANGE EFFECT ON THE GLANDS." American Journal of Pediatric Medicine and Health Sciences (2993-2149) 1 (2023): 81-83.
2. Dilshodovich, Khalilov Hikmatulla, Kayimov Mirzohid Normurotovich, and Esanov Alisher Akromovich. "RELATIONSHIP BETWEEN THYROID DISEASE AND TYPE 2 DIABETES." (2023).
3. To'laganovna, Y. M. (2025). SKELET MUSKULLARNING FIZIOLOGIYASI VA ULARNING ISHLASH MEXANIZMI: AKTIN VA MIOZIN VA ENERGIYA ASOSLARI. AMERICAN JOURNAL OF SOCIAL SCIENCE, 3(4), 54-60.
4. Tolaganovna, Y. M., & Shavkatjon o'g'li, A. A. (2025). INSON ORGANIZMIDA YURAK QONTOMIR KALSALLIKLARI, MIOKARD INFARKTINING KELIB CHIQISH SABABLARI VA ULARNING OLIH CHORA-TADBIRLARI. AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE, 3(4), 136-144.
5. Jo'rabek, K. (2025). BUYRAK KASALLIKLARGA OLIB KELADIGAN PATALOGIK HOLATLAR VA ULARNI OLDINI OLIH. AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE, 3(4), 129-135.
6. Azimova, S. B., and H. D. Khalikov. "Modern pathogenetic aspects of urolithiasis development." The American Journal of Medical Sciences and Pharmaceutical Research 7.04 (2025): 21-24.
7. Dilshod ogli, Xalilov Hikmatulla, and Qayimov Mirzohid Normurotovich. "THE ROLE OF ARTIFICIAL INTELLIGENCE AND ROBOTICS IN MEDICINE." Web of Medicine: Journal of Medicine, Practice and Nursing 3, no. 5 (2025): 201-207.



8. To'laganovna, Yusupova Moxira. "SKELET MUSKULLARNING FIZIOLOGIYASI VA ULARNING ISHLASH MEXANIZMI: AKTIN VA MIOZIN VA ENERGIYA ASOSLARI." AMERICAN JOURNAL OF SOCIAL SCIENCE 3.4 (2025): 54-60.
9. Ogli, Xalilov Hikmatulla Dilshod, Namiddinov Abror Anasbek Ogli, Sayfullayeva Durдона Dilshod Qizi, and Hikmatova Gulasal Farhodjon Qizi. "TELEMEDITSINANING PROFILAKTIK DAVOLANISHDA AHAMIYATI." Eurasian Journal of Academic Research 4, no. 4-2 (2024): 66-70.
10. Dilshod ogli, Xalilov Hikmatulla, Amirqulov Navro'zbek To'rayevich, and Shukurov Umidjon Majid o'g'li. "GIPOTIREOIDIZMNI EKSPERIMENTAL MODELLASHTIRISH." AMERICAN JOURNAL OF APPLIED MEDICAL SCIENCE 3.2 (2025): 207-209.
11. Xalilov, H. D., Namiddinov, A. A., Berdiyev, O. V., & Ortiqov, O. S. (2024). GIPERTIROIDIZM VA YURAK ETISHMOVCHILIGI. Research and Publications, 1(1), 60-63.
12. Berdiyev, O. V., M. Quysinboyeva, and A. Sattorova. "Telemeditsina Orqali Qalqonsimon Bez Kasalliklarini Boshqarish." Open Academia: Journal of Scholarly Research 2.6 (2024): 69-74.
13. Karabayev, Sanjar. "SOG'LIQNI SAQLASHDA TELETIBBIYOT IMKONIYATLARI, XUSUSIYATLARI VA TO'SIQLARI." Евразийский журнал медицинских и естественных наук 3.2 Part 2 (2023): 41-46.
14. Шадманова, Н.К. and Халилов, Х.Д., 2023. НАУЧНО-ПРАКТИЧЕСКИЙ ИНТЕРЕС ИЗУЧЕНИЯ ВЕГЕТАТИВНОЙ РЕГУЛЯЦИИ ДИЗАДАПТИВНЫХ РЕАКЦИЙ СЕРДЕЧНО-СОСУДИСТОЙ СИСТЕМЫ. Евразийский журнал академических исследований, 3(8), pp.126-134.
15. Normurotovich, Qayimov Mirzohid, and Ganjiyeva Munisa Komil Qizi. "GIPOTIROIDIZM VA YURAK ETISHMOVCHILIGI." Eurasian Journal of Academic Research 4, no. 5-3 (2024): 14-19.
16. Normurotovich, Q. M. "Dilshod ogli XH RODOPSIN G OQSILLARI FILOGENETIK TAHLIL." Journal of new century innovations 43, no. 2 (2023): 178-183.
17. Maxira, Yusupova, Xalilov Hikmatulla Dilshod ogli, and Berdiyev Otabek Vahob ogli. "FIZIOLOGIYA FANI RIVOJLANISHI TIBBIYOTDAGI AHAMIYATI. FIZIOLOGIYADA TADQIQOT USULLARI." PEDAGOG 7.12 (2024): 111-116.
18. MICROFLORA DK. CHANGE EFFECT ON THE GLANDS. American Journal of Pediatric Medicine and Health Sciences (2993-2149). 2023;1:81-3.
19. Dilshodovich, Khalilov Hikmatulla. "SHIELD OF INTESTINAL MICROFLORA CHANGE EFFECT ON THE GLANDS." American Journal of Pediatric Medicine and Health Sciences (29932149) 1 (2023): 81-83.
20. Dilshodovich, K.H., Normurotovich, K.M. and Akromovich, E.A., 2023. RELATIONSHIP BETWEEN THYROID DISEASE AND TYPE 2 DIABETES.
21. Dilshod ogly, Khalilov Hikmatulla, Shatursunova Madina Abdujamilovna, and Shukurov Umidjon Majid ogly. "THE IMPORTANCE OF ARTIFICIAL INTELLIGENCE IN THE DETECTION OF KIDNEY DISEASES MODERN APPROACHES AND PROSPECTS." Western European Journal of Modern Experiments and Scientific Methods 3.04 (2025): 9-13.
22. Ikrom, T., 2025. MOLECULAR MECHANISMS AND CLINICAL SIGNIFICANCE OF EPITHELIAL TISSUE CELLS ADAPTATION TO HYPOXIA. Western European Journal of Modern Experiments and Scientific Methods, 3(05), pp.15-22.

23. Ikrom, Tilyabov. "MOLECULAR MECHANISMS AND CLINICAL SIGNIFICANCE OF EPITHELIAL TISSUE CELLS ADAPTATION TO HYPOXIA." Western European Journal of Modern Experiments and Scientific Methods 3.05 (2025): 15-22.
24. Abdujamilovna, S.M. and Dilshod oqli, X.H., 2025. QAND MIQDORINING SUYAKLANISHGA TA'SIRI. Continuing education: international experience, innovation, and transformation, 1(10), pp.137-141.
25. Абдухаликова, Нигора Фахриддиновна, and Хикматулла Халилов. "РОЛЬ ЦИТОХРОМА И В МЕХАНИЗМАХ КЛЕТОЧНОГО ДЫХАНИЯ И ГИПОКСИИ." Advanced methods of ensuring the quality of education: problems and solutions 2.11 (2025): 62-68.
26. Абдухаликова, Нигора Фахриддиновна, and Хикматулла Халилов. "РОЛЬ СУКЦИНАТДЕГИДРОГЕНАЗЫ В МЕХАНИЗМАХ ГИПОКСИИ." Advanced methods of ensuring the quality of education: problems and solutions 2.11 (2025): 55-61.
27. Faxriddinova, Abduxalikova Nigora, Xalilov Hikmatulla Dilshod oqli, and Jabborov Botir Baxodir oqli. "EOZINOFIL FAGASITOV QILISH MEKANIZMLARI." Advanced methods of ensuring the quality of education: problems and solutions 2.11 (2025): 44-54

